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Au(I) Catalyzed Manipulation of Propargylic Alcohols:

A New Route Towards the Synthesis of Indole Alkaloids

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1. Introduction

1.1 Gold Catalysis

The use of [Au(I)] complexes in organic reactions has undergone a marked development over last years, featuring unique properties in terms of π-acidity and functional group tolerance. These features combined with the soft acidity of cationic [Au(I)] complexes provide unique catalytic properties to [Au(I)] and [Au(III)] for homogeneous organic transformations.

Experimental and theoretical tools have been extensively adopted to elucidate gold catalysis and involvement of relativistic effects turned out to be prominent in Au-chemistry.[1]

1.2 Relativistic effects

Schröedinger's equation (1926) can correctly predict the atomic orbital energy levels for hydrogen but is unable to account for the fine structure of the hydrogen atomic spectrum, in which the bands are split.

Although accounting for spin as a perturbation of the Schrödinger equation corrects for this, in systems in which electrons move at speeds approaching the speed of light (c) a more general relativistic consideration is required.

In 1928 Dirac developed a new equation taking special relativity into account, permitting solutions to systems in which electrons move at significant velocities. The term 'relativistic effects' therefore refers to any phenomenon resulting from the need to consider velocity as significant relative to the speed of light.

One basic consequence of the special theory of relativity is that mass increases towards infinity as a body's velocity approaches c, which can be expressed mathematically as $m = m_0/[1 - (v/c)^2]$, where m is the corrected mass, m_0 is non-relativistic (rest) mass, and v is velocity.

For a given atom, the average radial velocity of the 1s electrons is $V_r = Z$, where Z is the atomic number. The expression v/c can therefore be calculated as Z/137 (137 atomic units (a.u.) = c).

For example, in Hg, $Z = 80$ and v/c for the 1s electrons is $80/137 = 0.58$; that is, the 1s electrons have a radial velocity that is 58% of c.

There are three major phenomena that result from relativistic effects:[2,3] the first can easily be rationalized by considering the equations above.

In non-relativistic calculations, $c = \infty$ and v/c therefore approaches 0, so no mass correction need be applied to the particles under consideration. In situations in which c is considered to be 137 a.u.,

the mass of an electron will increase considerably. Because the Bohr radius of an electron orbiting a nucleus is inversely proportional to the mass of the electron, this increase in mass corresponds to a decrease in radius. This relativistic contraction of the 1s orbital also applies to all other s and p orbitals. Thus, the electrons are closer to the nucleus and have greater ionization energies.

Practically, this contraction is only significant for elements in which the 4f and 5d orbitals are filled.

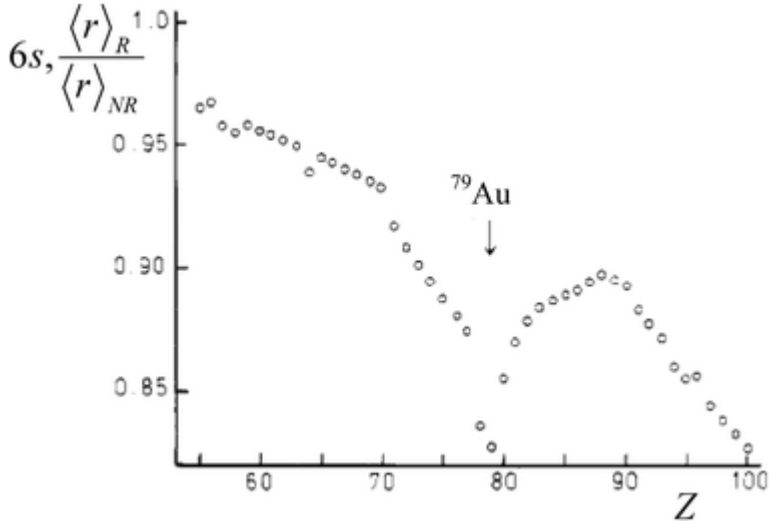


Figure 1.1 *Calculated relativistic contraction of the 6s orbital. The relativistic and non-relativistic atomic radii were determined computationally. Notably, Pt, Au and Hg are markedly influenced.*

The second manifestation of relativistic effects is indirect; electrons occupying the d and f orbitals are better shielded by the electrons in the contracted s and p orbitals and therefore see a weaker nuclear attraction.

The third effect of a relativistic treatment is spin–orbit coupling, which accounts for the fine splitting in the hydrogen atomic spectrum noted above.

Relativistic effects are crucial to understanding the electronic structure of heavy elements; consideration of other phenomena, such as the lanthanide contraction, are insufficient.[4,5]

Among the experimental observations conventionally explained by relativistic effects is the colour of Au. The golden colour is due to excitation of the 5d electrons to the Fermi level, which occurs with a bandgap of 2.38 eV; blue visible light is therefore absorbed.

In silver, by contrast, the bandgap is much larger and no visible light is absorbed. The smaller bandgap in Au is due to the relativistic contraction of the 6s and 6p orbitals and the expansion of the 5d orbitals.

1.3 Main characteristics of Au complexes

In Au complexes, the relativistic contraction of the 6s orbital results in a stronger ligand-Au bond energy. Another important phenomenon due to the distortion from the expected electronic structure, is the aurophilicity,[6] that represents the tendency for Au-Au interactions to be stabilizing on the order of hydrogen bonds.

[Au(I)] complexes generally adopt a linear, bicoordinate geometry.[7,8] The practical consequence of the limited coordination geometry in [Au(I)] complexes is the general need to abstract only one ligand from the neutral complex to obtain the cation catalytic species.

Additionally organo-aurate(I) species are not particularly nucleophilic relative to, for example, [Cu(I)] complexes. Indeed, theoretical studies indicate that Au 5d electrons are held with great energy than that Cu 3d electrons, due to the decreased energy repulsion between electrons caused by the diffuse 5d orbitals. This results in a less nucleophilicity of the metal species and in a low tendency of these species to undergo oxidative addition.[9] In fact, experimental studies report that reductive elimination from [$LR_3Au(III)$] complexes are disfavoured.[10,11]

Therefore [Au(I)] species are relatively stable to oxygen and consequently tolerant towards air and moisture. We can conclude that the apparent redox stability of [Au(I)] complexes under ambient conditions allows for the development of new modes of reactivity not involving the traditional oxidative addition/reductive elimination cycles so prevalent in late transition-metal catalysis.

1.4 Alkynophilicity

Many investigations concerning the reactivity of Au complexes emphatized the propensity of both [Au(III)] and [Au(I)] complexes to activate alkynes towards nucleophilic addition.[12] Early investigations showed a wide array of nucleophiles that could be added to alkynes in an intermolecular[13,14] or intramolecular[15] manner using [Au(I)] or [Au(III)] complexes.

In the presence of [Au(I)] or [Au(III)] salts, alkynes react as a basic Lewis donor, donating electrons to the electron deficient metal and behaving as a π-ligand.

This type of coordination between the alkyne and the metal can be explained by the Dewar-Chatt-Duncanson model. The *p* orbitals of the alkyne interact with the *d* orbitals of the metal in two different ways: 1) a σ-symmetric donation from the filled orbitals of the π-system of the alkyne towards an empty *d* orbital of the metal (L→M); 2) a π-symmetric back donation of electron density from a filled d orbital of the metal to an empty π* orbital of the alkyne (M→L). The alkyne has a second occupied π orbital perpendicular to the equatorial plane which may be engaged in another M-L bond (Figure 1.2).

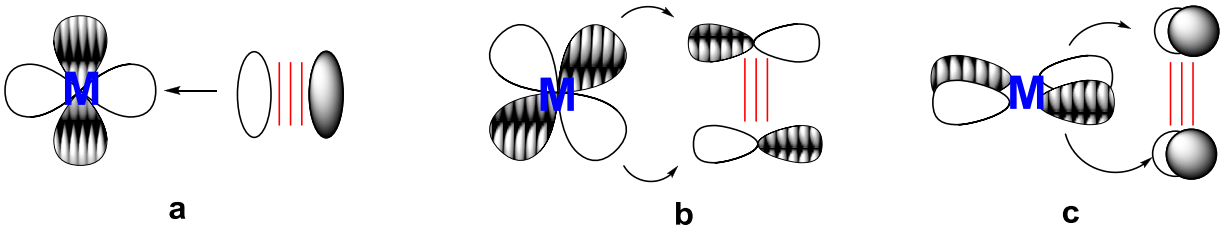


Figure 1.2. *a) σ-donation (L→M), b) π-retrodonation (M→L), c) π⊥ retrodonation (M→L).*

The Dewar-Chatt-Duncanson model predicts an elongation of the triple bond by transfer of the electron density into the antibonding π* orbitals, consequently the alkyne becomes more electrophilic and more prone for the nucleophilic attack on the unsatured C-C bond.

In 1998, Teles demonstrated the utility of cationic phosphine [Au(I)] species in catalyzing the hydration of alkynes.[16]

R_3PAuX (X = trifluoromethanesulphonate or other week coordinating counterions) species, formed in situ by the abstraction of Cl from R_3PAuCl with AgX or by protonolysis of R_3PAuCH_3 with acids, were shown to be superb catalysts for a series of C-C bond forming reactions including Conia-ene (Figure 1.3)[17] hydroarylation reactions[18,19] as well as carbon-heteroatom bond forming reactions.[20,21,22]

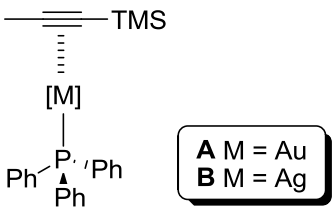
Figure 1.3. *General example of a gold(I)-catalyzed Conia-ene reaction.*

Because [Au(I)L_1] is a large, diffuse cation that shares positive charge with the phosphine ligand, one might expect orbital rather than charge interactions to dominate in binding a second ligand. Thus, phosphine-[Au(I)] may be considered a 'soft' Lewis acid, preferentially activating 'soft' electrophiles, such as π-systems.

The rationalizing of the superior π-acidity in cationic [Au(I)] complexes, respect to other metals of Group 11, may be achieved also by the isolation and characterization of cationic phosphine Au and Ag π–complexes.

A comparative analysis with density functional theory calculations reveled that σ-donation from the alkyne π bond to the metal center is the most important bonding interaction for both gold and silver (Table 1.4). However, the magnitude of this interaction is significantly larger for the gold complex (56.6 vs 38.5 kcal/mol for Ag).

Table 1.4*. Natural bond order orbital interactions energies*

Parameter	Energy (Kcal/mol)	
		
	Gold complex **A**	*Silver complex* **B**
π→M	56.6	38.5
π→M	13.3	6.4
Difference	43.3	32.1

This interaction is primarily responsible for augmenting the electrophilicity of the coordinated alkyne. Interestingly, back-donation from gold to π* of the coordinated alkyne is also larger in magnitude (13.3 vs 6.4 kcal/mol for Ag).

While this interaction is expected to decrease the electrophilicity of the coordinated alkyne, it suggests that back-donation from gold may be important for other aspects of gold(I) catalysis such as its capability to promote organic reaction through carbenoid intermediates.

Studies on [Au(I)]–ethylene and [Au(I)]–ethyne bonding indicated that Au–alkyne complexes have a lower LUMO for the addition of a nucleophile than that of analogous Au–alkene complex;[23,24] this is potentially the source of the 'alkynophilicity' observed in [Au(I)]-catalyzed reactions.

Bibliography

[1]. McKelvey, D. R. *J. Chem. Educ*. **1983**, *60*, 112–116.

[2]. Pyykko, P., Desclaux, J.P., *Acc. Chem. Res*. **1979**, *12*, 276–281.

[3]. Pyykko, P. *Chem. Rev*. **1988**, *88*, 563–594.

[4]. Norrby, L. J. *J. Chem. Educ*. **1991**, *68*, 110–113.

[5]. Bagus, P. S., Lee, Y. S. & Pitzer, K. S. *Chem. Phys. Lett*. **1975**, *33*, 408–411.

[6]. Scherbaum, F., Grohmann, A., Huber, B., Kruger, C. Schmidbaur, H. *Angew.Chem.Int.Ed.* **1988**, *27*, 1544–1546.

[7]. Carvajal, M. A., Novoa, J. J. & Alvarez, S. *J.Am.Chem.Soc.*, **2004**, *126*, 1465–1477.

[8]. Schwerdtfeger, P., Hermann, H. L. & Schmidbaur, H. *Inorg. Chem*., **2003**, *42*, 1334–1343.

[9]. Nakanishi, W., Yamanaka, M. & Nakamura, E., *J.Am.Chem.Soc.,* **2005**, *127*,1446–1453.

[10].Komiya, S. & Kochi, J. K. *J.Am.Chem.Soc.,***1976**, *98*, 7599–7607.

[11]. Komiya, S., Albright, T. A., Hoffmann, R. & Kochi, J. K. *J.Am.Chem.Soc.,* **1976**, *98*, 7255–7265.

[12]. Hashmi, A. S. K. *Gold Bull*. **2004**, *37*, 51–65.

[13]. Fukuda, Y., Utimoto, K. & Nozaki, M. *Heterocycles*, **1987**, *25*, 297–300.

[14]. Hashmi, A. S. K., Schwarz, L., Choi, J.-H. & Frost, T. M. *Angew. Chem*. *Int. Ed.*, **2000**, *39*, 2285–2288.

[15]. Fukuda, Y. & Utimoto, K., *J. Org. Chem*. **1991**, *56*, 3729–3731.

[16]. Teles, J. H., Brode, S. & Chabanas, M. *Angew. Chem. Int. Ed*. **1998**, *37*, 1415–1418.

[17]. Kennedy-Smith, J. J., Staben, S. T. & Toste, F.D. *J.Am.Chem.Soc.,* **2004**, *126*, 4526–4528.

[18]. Staben, S. T., Kennedy-Smith, J. J. & Toste, F. D. *Angew. Chem. Int. Ed*., **2004**, *43*, 5350–5352.

[19]. Reetz, M. T. & Sommer, M., *Eur. J. Org. Chem*. **2003**, 3485–3496.

[20]. Nevado, C. & Echavarren, A. M. *Chem. Eur. J*., **2005**, *11*, 3155–3164.

[21]. Ferrer, C. & Echavarren, A. M. *Angew. Chem. Int. Ed*., **2006**, *45*, 1105–1109.

[22]. Antoniotti, S., Genin, E., Michelet, W. & Genet, J. P. *JACS*., **2005**, *127*, 9976–9977.

[23]. Hartwig, R., *J. Phys. Chem*., **1996**, *100*, 12253–12260.

[24]. Nechaev, M., Rayon, V., Frenking, G., *J. Phys. Chem. A*, **2004**, *108*, 3134–3142.

.2. Hydroarylation of Alkynes: New perspectives in gold catalysis

2.1 Hydroarylation of alkynes

Substituted styrenes and vinylic compounds, which can be obtained from hydroarylation of alkynes, are very useful and versatile intermediates used in organic synthesis. The most powerful synthetic method of this class of compounds is the Mirozoki-Heck reaction which involves the coupling reaction of organic halides or triflates with alkenes.[1,2] However, the use of new methodologies of aromatic C-H bond activation, followed by C-C bond formation, constitutes attractive and environmentally benign alternatives due to the greater synthetic availability. Many examples of late transition metal catalyzed hydroarylations of alkynes have been reported. For example Trost developed the Pd-catalyzed hydroarylation of ethyl propiolates with electron rich phenols (Figure 2.1).[3] In this synthesis the use of $Pd(OAc)_2$ and trifluoroacetic acid (TFA) is necessary to afford *cis*-aryl substituted alkenes **5** in regio- and stereoselective manner.

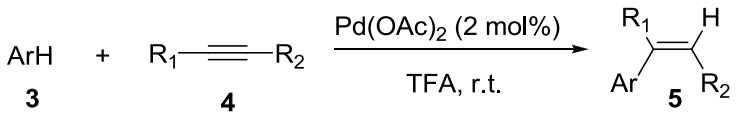
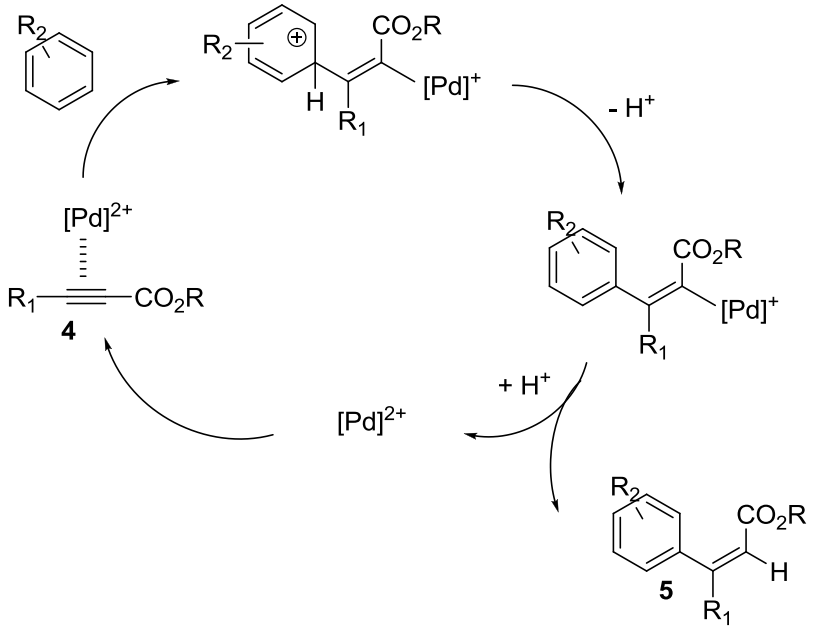


Figure 2.1. *Pd Catalyzed arylation of alkynes.*

A recent mechanistic report by Tunge and Foresee suggests that the $Pd(OAc)_2$-catalyzed reaction proceeds via electrophilic aromatic substitution (Scheme 2.2).[4]



Scheme 2.2.*. Mechanism hypothesized for the Pd-catalyzed arylation of alkynes*

Shirakawa reported that metal triflates (*i.e.* $Sc(OTf)_3$, $In(OTf)_3$ and $Zr(OTf)_4$) catalyzed alkenylation of arenes with phenyl substituted alkynes to give 1,1-diarylalkenes **7** (Figure 2.3).[5]
The reaction probably proceeds via a Friedel-Crafts type mechanism through an alkenyl cation intermediate.

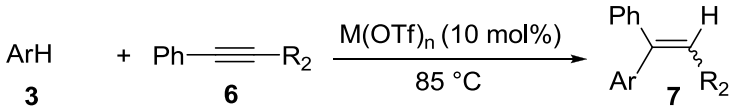
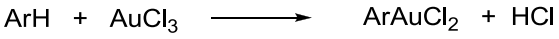


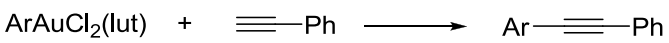
Figure 2.3. *$M(OTf)_n$ catalyzed alkenylation of arenes*

Reetz and Sommers pioneered the use of gold catalysis in this process.
They were interested in the capability of gold salts such as $AuCl_3$ to afford ready auration of aromatic compounds with formation of aryl-gold compounds (Scheme 2.4).[6]



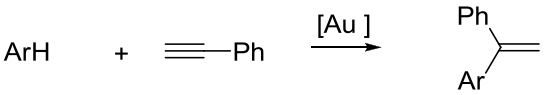
Scheme 2.4 *Au(III)-mediated auration of aromatic compounds.*

Compounds such as $ArAuCl_2$ are dimeric in nature and can be disaggregated by complexation with ligands (such as PPh_3, SR_2, lutidine, etc) in monomeric form of the type $[ArAuCl_2(L)]$.
The lutidine adduct has shown to undergo stoichiometric coupling with phenylacetylene to obtain the product in nearly quantitative yields (Scheme 2.5).[7]



Scheme 2.5 *Au(III)-Ar stochiometric coupling with phenyl-acetilene.*

Because of the formation of an alkynyl-aryl-[Au(III)] specie, which undergoes reductive elimination to give the coupling product, Reetz and Sommers started searching the appropriate oxidant agent to close the catalytic cycle but in catalytic reactions hydroarylated product was observed (Scheme 2.6).

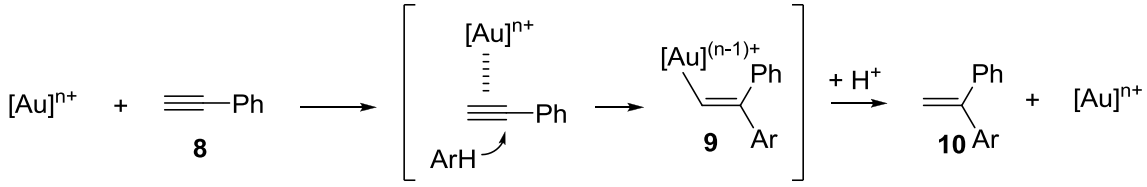


Scheme 2.6 *[Au]-catalyzed arylation of alkynes.*

The synthetic results reported in their work can be viewed as a gold catalyzed nucleophilic addition reaction of alkynes. Although cationization of $AuCl_3$ or AuCl complexes by [Ag(I)] or other Lewis acids is required, auration of the arene seems unlikely in view of the known stoichiometric reaction of arylgold compounds with alkynes, which give arylacetylenes. Therefore, activation of the alkyne by Au-π complexation is involved.

In the specific case of the phenylacetylene (*i.e.* electron-rich alkyne), the authors proposed that the π-Au complex would undergo an electrophilic aromatic substitution to form a vinyl-Au intermediate **9**.

The simultaneously released H^+ would protonate this intermediate, setting free the product **10** as well as regenerating the salt catalyst (Scheme 2.7).

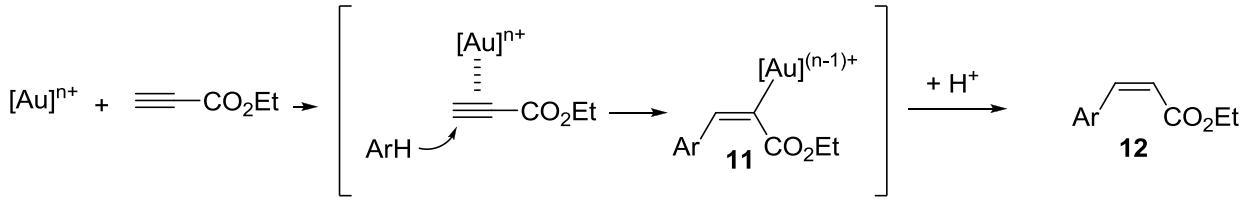


Scheme 2.7 *Mechanism of [Au(III)]- catalyzed arylation of alkynes.*

On the contrary, for electron-poor alkynes (i.e. ethyl propiolate), it is accepted that the catalytic active species have to be a cationic ligand-stabilized [Au(I)] complex L-Au^+ rather than an Au salt.

The cationic gold complex coordinates to the alkyne, and nucleophilic attack of the arene from the opposite side leads to the formation of a vinylgold intermediate which is stereospecifically protonated with final formation of the (*Z*)-olefin.

On the basis of this assumption a plausible mechanism for the reaction of acetylene–carboxylic-acid ester ith arenes can be formulated as shown below (Scheme 2.8).



Scheme 2.8 *Mechanism of [Au(III)] catalyzed arylation of electron-deficient alkynes.*

In conclusion, [Au(I)] and [Au(III)]-catalyzed reactions provide high regioselectivity in the hydroarylation of terminal alkynes and in both cases regioselectivity is dominated by electronic factors. Particularly, while in the first case the Ar-H follows a "Markovnikov" addition, in the second case a gold-catalyzed Micheal addition reaction is involved.[8]

Bibliography

[1]. Mizoroki, T., Mori, K., Ozaki, A.; *Bull. Chem. Soc. Jpn*. **1971**, *44*, 581-581.

[2]. (a) Heck, R. F.; Noller, Jr., J. P.; *J. Org. Chem*. **1972**, *37*, 2320-2322. (b) Heck, R. F. *Acc. Chem. Res*. **1979**, *12*, 146-151. (c) Tsuji, J. Palladium Reagents and Catalysts, John Wiley & Sons: Chichester, **1995**, pp. 168.

[3]. (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **1996**, *118*, 6305-6306. (b) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc*. **2003**, *125*, 4518-4526.

[4]. Tunge, J. A. & Foresee, N. L. *Organometallics*, **2005**, *24*, 6440-6444.

[5]. Tsuchimoto, T., Maeda, T., Shirakawa, E., Kawakami, Y., *Chem. Commun*. **2000**, 1573-1574.

[6]. Kharasch, M.S., Isbell, H.S., *J. Am. Chem. Soc*. **1931**, *53*, 3053-3059.

[7]. De Graaf, P.W.J., Boersma, J., Van der Kerk, G.J.M., *J. Organomet. Chem*. **1976**, *105*, 399-406.

[8]. Reetz, M. T. & Sommer, M., *Eur. J. Org. Chem*. **2003**, 3485–3496.

3. Classical reactivity of Propargylic alcohols in Gold Catalysis

3.1 Propargylic alcohols in gold catalysis

It is now well recognized that [Au(I)] and [Au(III)]-based catalyst systems are exceptional π acids that activate alkynes, allenes, and alkenes towards a variety of reactions.[1] Some of the most common modes of reactivity involve additions to π systems (alkyne hydration, olefin addition, etc.), rearrangements (e.g., propargyl Claisen), isomerization reactions (enyne cycloisomerization), and combinations thereof.[2,3]

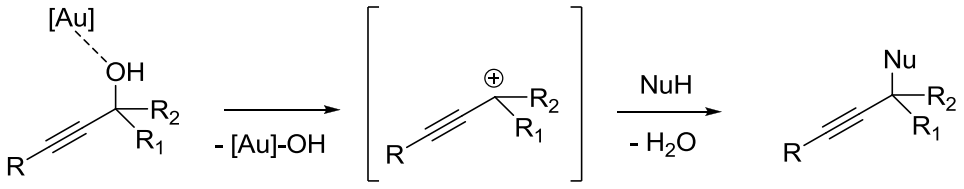
Propargylic alcohols are readily available by a variety of methods and constitute important key intermediates for the preparation of complex structures found in molecules of biological interest. Gold catalysis, due to its functional group tolerability represents an extraordinary tool for synthetic chemists to exploit the double functionality of propargylic alcohols (the insatured triple bond and the nucleophilic hydroxyl moiety) to develop new synthetic methodologies towards highly functionalized molecules.

In this section we report the classical mode of activation of propargylic alcohols via gold catalysis.[4]

3.2 Dehydrative nucleophilic substitution of propargylic alcohols

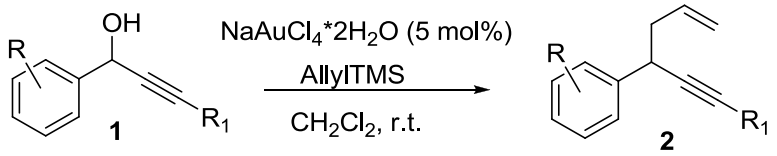
These reactions generally have several practical advantages because low catalyst loadings are typically employed under mild conditions and water is the only byproduct.

Mechanistically, dehydrative transformations may follow either cationic or noncationic pathways, depending on the Lewis acidity of the gold catalyst and the nature of the substrate (Scheme 3.1.)



Scheme 3.1 *Gold catalyzed dehydrative nucleophilic substitution of propargylic alcohol*

Campagne *et al.*[5] reported the nucleophilic substitutions of the benzylic-propargylic alcohols **1** (Scheme 3.2) with allyl trimethylsilane in the presence of catalytic amounts of $NaAuCl_4*2H_2O$ to form the benzylic 1,5-enynes **2**.

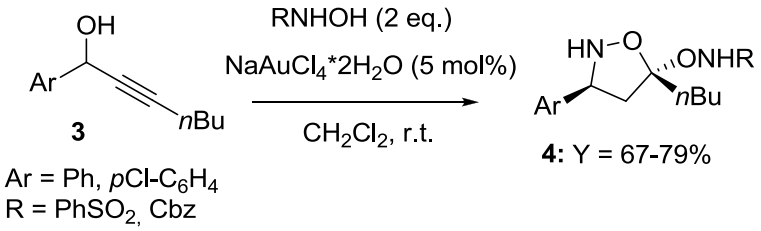


Scheme 3.2 *[Au(III)] catalyzed nucleophilic substitution of propargylic alcohols.*

The reactions work best with electron-donating substituents, which help in generating a stable carbocation, and with diminished yields when mildly deactivating groups are present on the aromatic ring and no reaction occurring with *p*-NO_2.

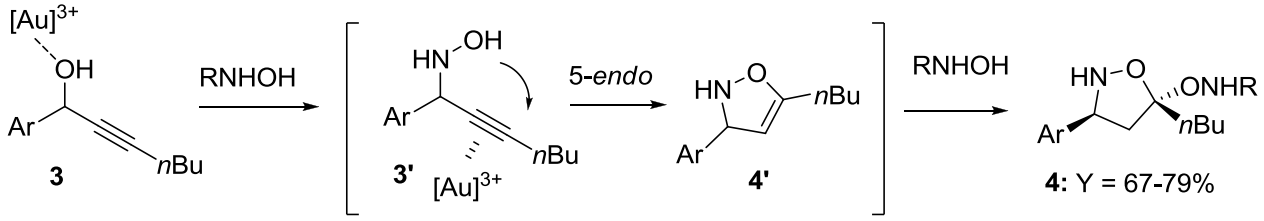
Friedel–Crafts reactions can also be performed under the same conditions with electron-rich aromatic nucleophiles such as anisoles. Heteroatom nucleophiles such as alcohols, thiols, and amines also function well in these reactions to yield substitution products under these conditions.

Campagne again[6] recently reported a cascade reaction sequences initiated by a Au-catalyzed additions of N-protected hydroxyamines to propargylic alcohols **3** (Scheme 3.3).



Scheme 3.3*. Gold(III) catalyzed synthesis of isoxazolidine scaffolds.*

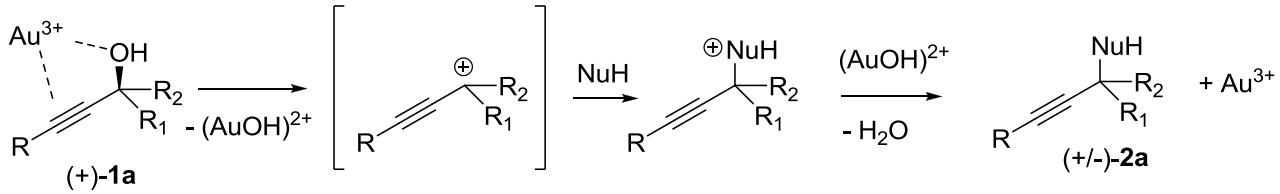
The 2,3- dihydroisoxazoles **4** are obtained by nucleophilic substitution of the hydroxylamines on the propargylic alcohols **3**, followed by 5-*endo* cyclizations of the hydroxy groups onto the alkyne moieties in **3'**. Addition of a second equivalent of the hydroxylamine to **3'** provides **4** as single diastereomer (Scheme 3.4.).



Scheme 3.4 *Mechanism of the diastereoselctive synthesis of isoxazolidine scaffolds.*

The mechanism is proposed with [Au(III)] acting as a Lewis acid (Scheme 3.4). This is supported by the fact that the presence of the alkyne moiety is not necessary, since substitution reactions of non-propargylic benzyl and allylic alcohols also proceed.

Further evidence for a cationic mechanism was obtained when use of chiral propargylic alcohols (generically shown as **1a**) yielded **2a** as racemic mixtures (Scheme 3.5).



Scheme 3.5 *[Au(III)] promotes racemization of enantiomerically enriched propargylic alcohols.*

3.3 Annulation reactions

The development of gold-catalyzed reactions for the synthesis of carbocycles and heterocycles has flourished over the past 10 years[7,8,9] and continues to address new synthetic challenges. The use of unsaturated alcohols for the formation of both aromatic and nonaromatic rings has been explored. These substrates are easily activated by gold complexes and are also readily prepared from common starting materials. Whereas the reactions of propargyl alcohols shown in Section 3.1 demonstrate substitution of acyclic systems, ring-forming reactions are also possible, with both carbocycles and heterocycles being readily formed.

The benzannulation of the 3-hydroxy-1,5-enynes **5a** (Figure 3.6.) to form the tetrahydronaphthalenes **6a** has been described by Barriault[10] and can be carried out under mild conditions as is illustrated by catalyst optimization studies.

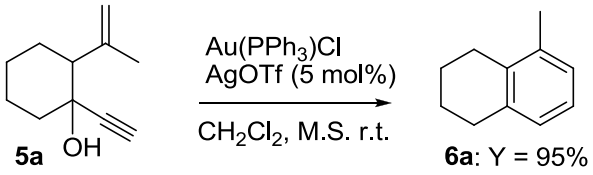
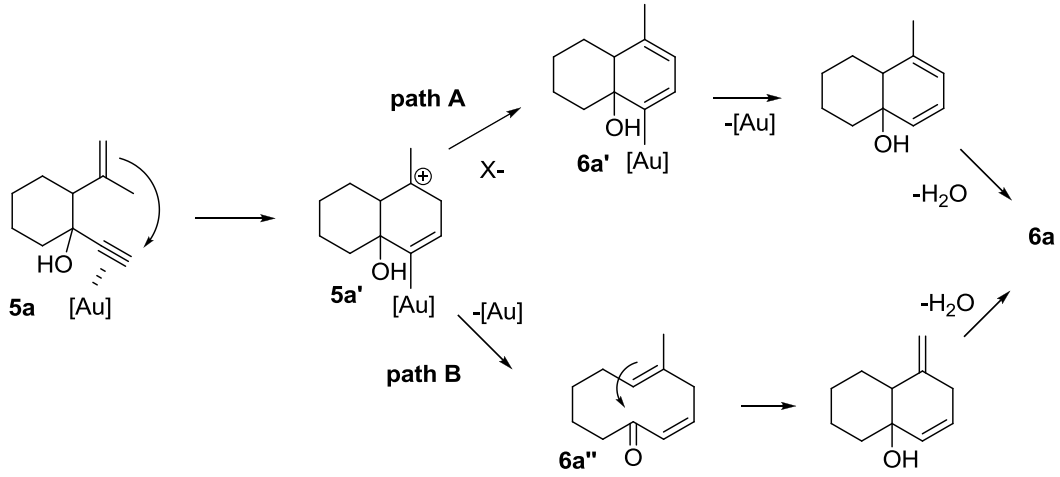


Figure 3.6 *[Au(I)]- catalyzed benzannulation of 1,5-enynes.*

The proposed mechanism involves the carbocation **5a'** followed either by deprotonation and loss of water to form **6a'** (path A, Scheme 3.7) or by ring-expansion to form the 10-membered ring **6a''** with proteodeauration and subsequent conversion to **6a** (path B, Scheme 3.7).



Scheme 3.7 *Two different mechanistic pathways for the annulation of 1,5 enynes.*

Similar reactivity was described by Hashmi[11] who reported the Au-catalyzed preparation of the benzofurans **8** from the β-ethynyl-β-hydroxyfurans **7** in moderate to high yields (Figure 3.8).

A related transformation for the synthesis of benzo[*b*]furans from 3-silyloxy-1,5-enynes was also developed by the same group in 2011.[12]

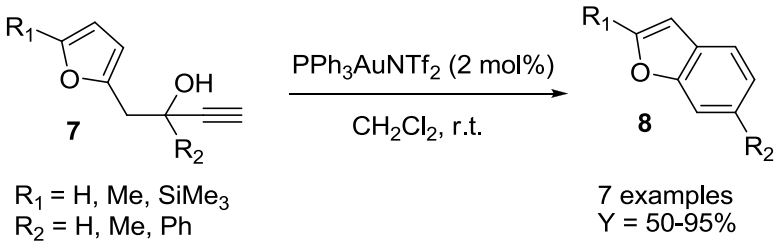


Figure 3.8 *[Au(I)]-catalyzed synthesis of benzofurans.*

3.4. Spiro-ketalization reactions.

The annulation reactions described above use carbon nucleophiles, but propargylic alcohols have also been found to react with heteroatom nucleophiles, leading to a variety of products. This strategy has been used for the formation of unsaturated spiroketals.

Metal-catalyzed formation of spiroketals from acetylenic diols is challenging because of the formation of mixtures of **10** and **11**.[13] Cyclizations of propargyl triols **12** are advantageous because they are typically selective for the formation of single regioisomers **13**.[14] The olefin can thus be placed in the desired position simply by using the appropriate propargylic alcohol (Figure 3.9).

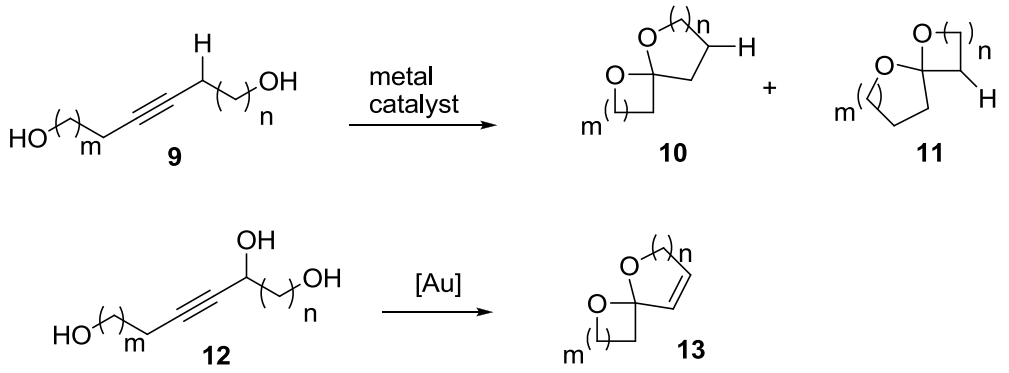


Figure 3.9 *Stereoselective ketalization by means of Gold catalysis.*

In studies on substrate scope, these transformations showed good to excellent yields and proved to be highly tolerant of substitution.

Examples include varying ring sizes – [5.5], [5.6], and [6.6] – , the facile formation of highly substituted spiroketals and also of the trisubstituted olefins (Figure 3.10).

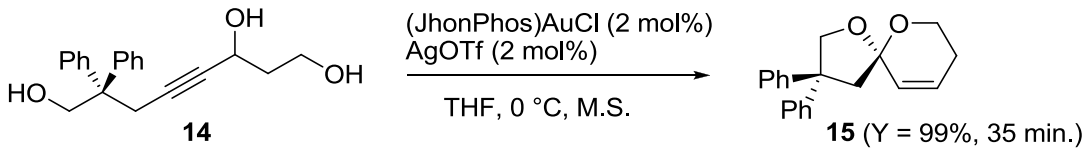
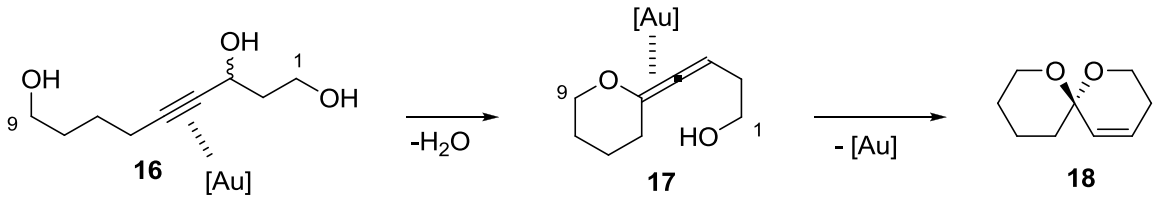


Figure 3.10 *[Au(I)]-catalyzed spiro-ketalization of propargylic alcohols.*

The initial hypothesis for how these compounds might have been formed involved dehydrative cyclization of **16** to provide the allenol **17** followed by Au-catalyzed addition of the terminal C1 alcohol to the activated allene, leading to the spiroketal **18**. It was demonstrated that either of the

two primary alcohols (C1 or C9) in **16** might initially cyclize and that **18** could be formed from the resulting intermediate **17** (Scheme 3.11).



Scheme 3.11 *Mechanism of the [Au(I)]-catalyzed spiro-ketalization.*

3.5. Synthesis of Heteroaromatics

The observation that the C1 alcohol can add to the alkyne at C5 prompted study of systems lacking the C9 alcohol. Concurrently, Akai[15] and Aponick[16] reported the gold-catalyzed preparation of five-membered aromatic heterocycles from heteroatom-substituted propargylic alcohols In the presence of [Au(I)] catalysts, the propargylic alcohols **19** rapidly underwent reaction to form the heterocycles **20** (Figure 3.12).

The substrate scope was explored with substituted diols, to give a variety of furans in excellent yields.

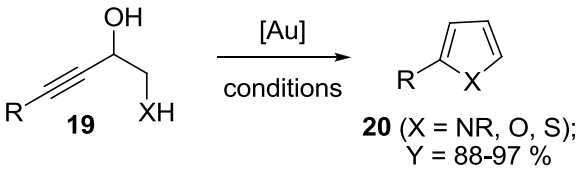


Figure 3.12. *General scope of the [Au(I)]-catalyzed synthesis of heterocycles.*

3.6. Conclusions

We envisioned several [Au(I)]/[Au(III)] catalyzed transformation of propargylic alcohols in which dehydrative nucleophilic substitutions of the hydroxyl moiety occurred. This led to several transformation in which functionalized molecules were synthesized in high yields, high chemoselective and releasing H_2O as only stoichiometric by-product.

Bibliography

[1]. A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev*. **2011**, *111*, 1657–1712.

[2]. A. S. K. Hashmi*, Chem. Rev*. **2007**, *107*, 3180–3211.

[3]. E. Jiménez- Núñez, A. M. Echavarren, *Chem. Rev*. **2008**, *108*, 3326–3350.

[4]. B. Berenger, A., Aponick, *Eur. J. Org. Chem*. **2011**, 6605–6617.

[5]. M. Georgy, V. Boucard, J.-M. Campagne*, J. Am. Chem. Soc*. **2005**, *127*, 14180–14181.

[6]. O. Debleds, C. Dal Zotto, E. Vrancken, J.-M. Campagne, P. Retailleau, *Adv. Synth. Catal*. **2009**, *351*, 1991–1998.

[7]. D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev*. **2008**, *108*, 3351-3387.

[8]. J. Muzart, *Tetrahedron* **2008**, *64*, 5815-5820.

[9]. M. Rudolph, A. S. K. Hashmi, *Chem. Commun*. **2011**, *47*, 6536–6544.

[10]. (a) C. M. Grisé, L. Barriault, *Org. Lett*. **2006**, *8*, 5905–5908; (b) C. M. Grisé, E. M. Rodrigue, L. Barriault, *Tetrahedron* **2008**, *64*, 797–808.

[11]. A. S. K. Hashmi, M. Wölfle, *Tetrahedron* **2009**, *65*, 9021–9029.

[12]. A. S. K. Hashmi, W. Yang, F. Rominger, *Angew. Chem. Int. Ed*. **2011**, *50*, 5762–5765.

[13]. For leading references on transition-metal-catalyzed spiroketalization, see: a) K. Utimoto, *Pure Appl. Chem*. **1983**, *55*, 1845–1852; b) B. Liu, J. K. De Brabander, *Org. Lett*. **2006**, *8*, 4907–4910; c) Y. Li, F. Zhou, C. J. Forsyth, *Angew. Chem. Int. Ed.* **2007**, *46*, 279–282; d) A. Dieguez-Vazquez, C. C. Tzschucke, W. Y. Lam, S. V. Ley, *Angew. Chem. Int. Ed*. **2008**, *47*, 209–212.

[14]. A. Aponick, C.-Y. Li, J. A. Palmes, *Org. Lett*. **2009**, *11*, 121– 124.

[15]. M. Egi, K. Azechi, S. Akai, *Org. Lett*. **2009**, *11*, 5002–5005.

[16]. A. Aponick, C.-Y. Li, J. Malinge, E. Finco Marques, *Org. Lett*. **2009**, *11*, 4624–4627.

4. Propargylic alcohols in the synthesis of indoline alkaloids.

4. Propargylic alcohols in the synthesis of indoline alkaloids

4.1 Introduction

The indole presents a structure found commonly in numerous research area such pharmaceuticals, fragrances, agrochemicals, pigments and material sciences.[1]

Indole chemistry started to receive great attention by the 50's when alkaloid reserpine[2] was introduced as one of the first drugs for the treatment of disease of the central nervous system (CNS). In the 60's the discovery of vincristine, an efficient antitumoral drug based on a dimer of the alkaloid (-)-vindoline, propelled further the indole chemistry.

Among all the alkaloids containing or deriving from indole ring, indolines are highly prominent.

The indoline substructure is considered a privileged scaffold and is found in a wide variety of common natural products.

A range of natural polycylic indolines has been summarized (Figure 4.1).

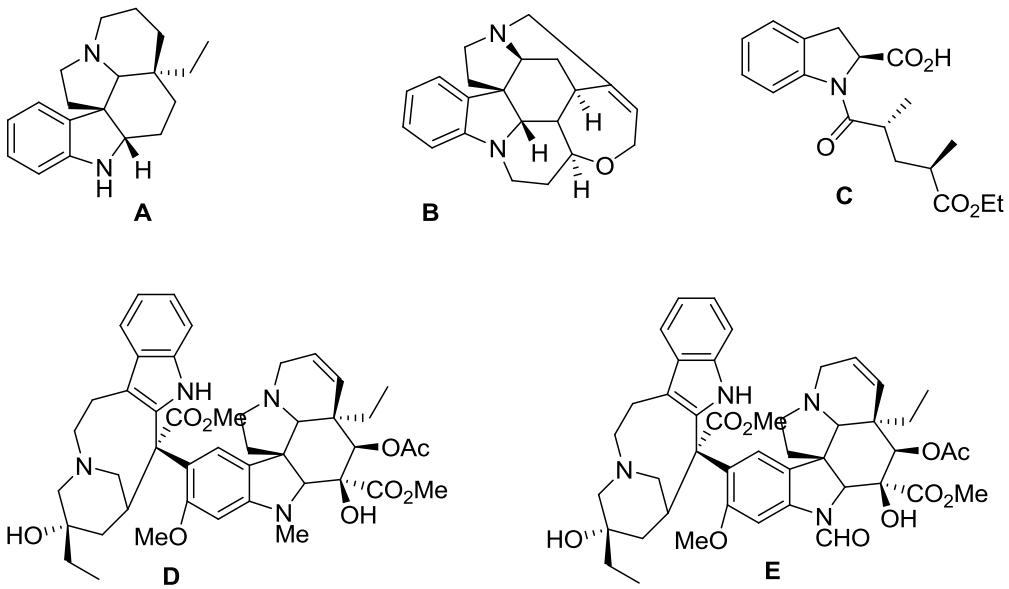


Figure 4.1. *Examples of biological active polycyclic indoline alkaloids*

Aspidospermidine **A**, the aspidosperma alkaloid, is the skeleton included in two of the most potent anti-cancer agent vinblastine **D** and vinblastine **E**.[3]

Vinblastine is a vinca alkaloid and is an *anti*-microtubule drug used for the treatment of certain kind of cancer, including Hodgkin's lymphoma.

Strycnine **B** is a very toxic alkaloid extracted from Strychnos Nux Vomica tree which acts as a blocker or antagonist at the inhibitory glycine receptor (GlyR), a ligand gated chloride channel in spinal cord and the brain and causes convulsions and eventually death through asphyxia or sheer exhaustion.

Pentopril **C** is a member of a series of 1-glutarylindoline-2(*S*)-carboxylic acid derivatives. It acts as ACE (angiotensin-converting enzyme) inhibitor, adopted in the treatment of hypertension.[4]

Numerous efforts have been made to develop new protocols for the synthesis and functionalization of indole cores in order to obtain new molecules with potential pharmacophoric effects and particularly indolines.

4.2 Gold catalyzed reaction of indoles with alkynes. State of art

Hydroarylation of alkynes catalyzed by electrophilic transition metal complexes (particular gold catalysis) is a valuable synthetic method for the synthesis of alkenyl arenes and heteroarenes.

Over the past years particular attention has been devoted towards the possibility to extend this catalytic methodology to alkynyl-based indoles in order to discover new approaches for bioactive indole and indoline alkaloids.

Echavarren was the first to report a [Au(I)] or [Au(III)] catalyzed methodology for the annulation of seven-membered rings on indoles by cyclization with alkynes.[5]

Here substrate **1** was found a pertinent precursor in the presence of cationic gold complexes to give azepino-[4,5-*b*] indoles **2** while the more electrophilic $AuCl_3$ leads to indolazocines **2'** (Figure 4.2).

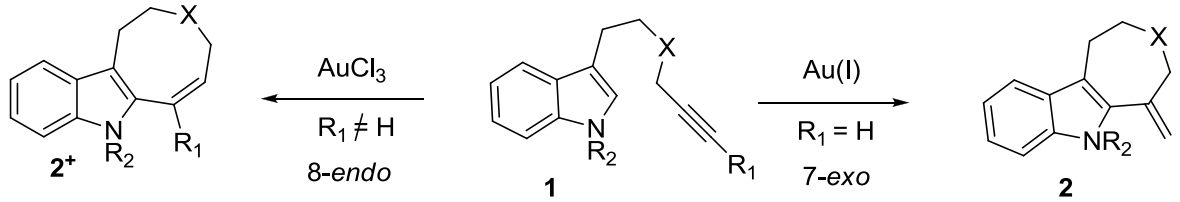


Figure 4.2 *Au-controlled regioselectivity in indole alkaloids.*

The unprecedented regiocontrol in this type of cyclizations appeared to be function of the oxidation state of the catalyst.

The indoloazocine subunit is present in several indole and indoline alkaloids such as *deoxyisoaustamide*, *okaramine* N and *lundurine* (Figure 4.3).

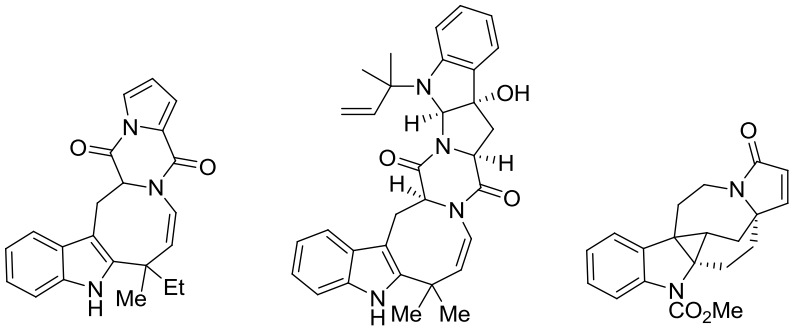


Figure 4.3 *Indoloazocine derivated indole alkaloids.*

In studying this reactivity Echavarren tested a new [Au(I)] cationic complex bearing bulky phosphane ligand (Figure 4.4).

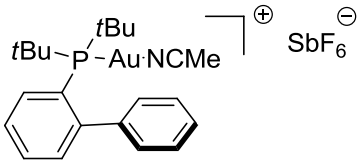


Figure 4.4 *Silver-free gold catalyst developed by the Echavarren Group.*

This complex is a white, air stable solid readily prepared from the corresponding gold chloride complex and allows to perform the reactions in the absence of [Ag(I)] salts.

Other important applications in the synthesis of highly functionalized indole-based compounds starting from alkynyl indoles were developed by Liu **(**Figure 4.5). [6]

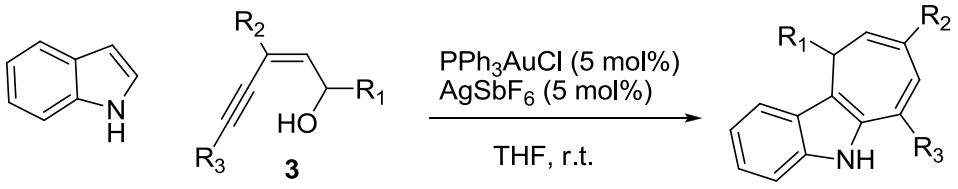
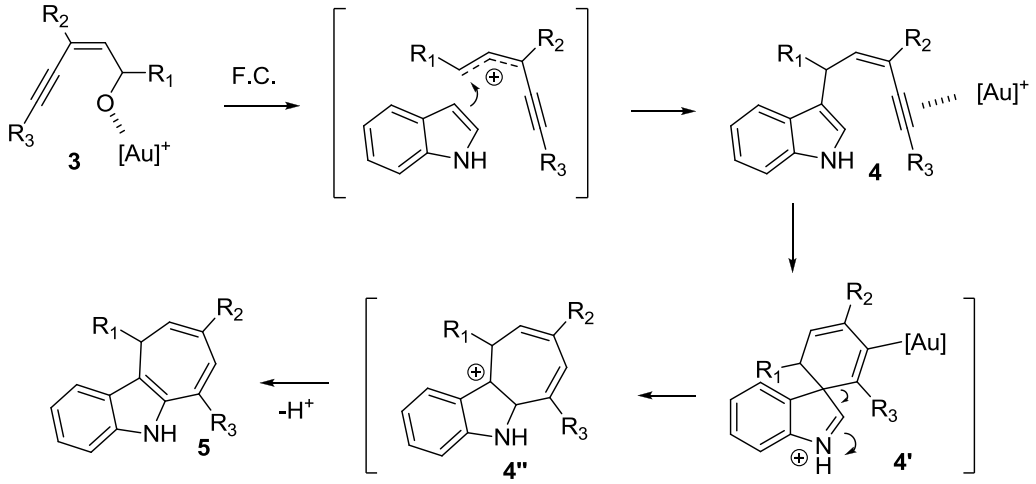


Figure 4.5 *[Au(I)]-catalyzed alkylation of indoles with (Z)-enynols.*

In the first case, by using (Z)-enynols it was possible to realize a tandem cyclization in which both Friedel-Crafts (FC) and hydroarylation reactions were performed in the same reaction vessel.
The reaction was initiated by the [Au^+]-assisted C-O bond clevage of enynol **3**, resulting in the formation of an allylic cation intermediate, which undergoes the FC reaction with indole to generate indole eneyne **4** (Scheme 4.6).



Scheme 4.6 *Mechanism reported: [Au(I)] assisted C-O cleavage and F.C. reaction with indole.*

Then indole-enyne **4** enters into the hydroarylation sequence which generates dihydrocyclohepta[*b*]indole framework. The resulting products are of considerable interest as they are present as key structural subunits in indole alkaloids such as ambiguine, silicine and caulersin (Figure 4.7)

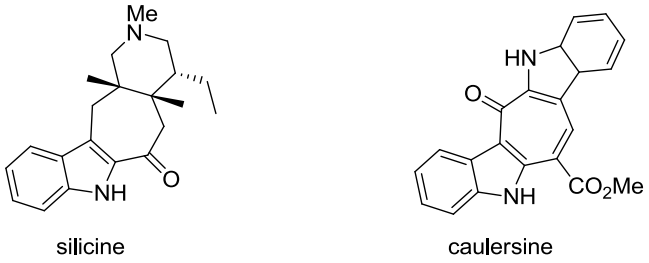


Figure 4.7 *Structure of silicne and caulersine alkaloids.*

Interistingly, Hashmi[7] reported the first gold-catalyzed 3,2-carbonyl shift in alkynyl-substituted indole-3-carboxamides opening an highly efficient and regioselective access to azepino-[3,4-*b*]indol-1-ones. They envisioned that a 3,2-shift of the acylamino substituent in derivatives of indole-3-carboxylic acid would be a highly desirable entry to the pharmaceutically important indoloazepinones.[8]

In order to achieve this, alkyne-substituted indole-3-carboxamide (**6a**, Ar = 2-thiophene) was used as the model substrate (Figure 4.8).

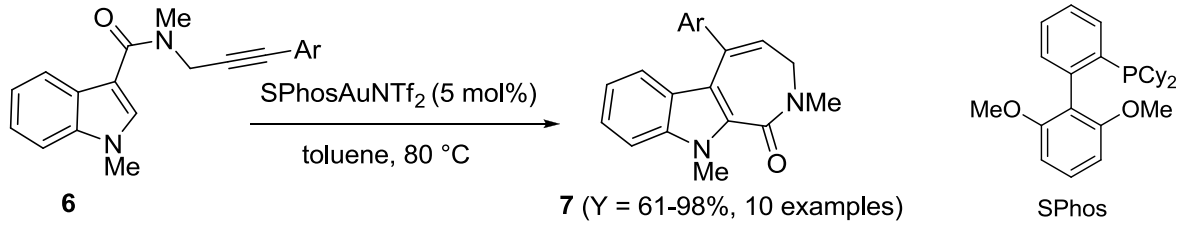
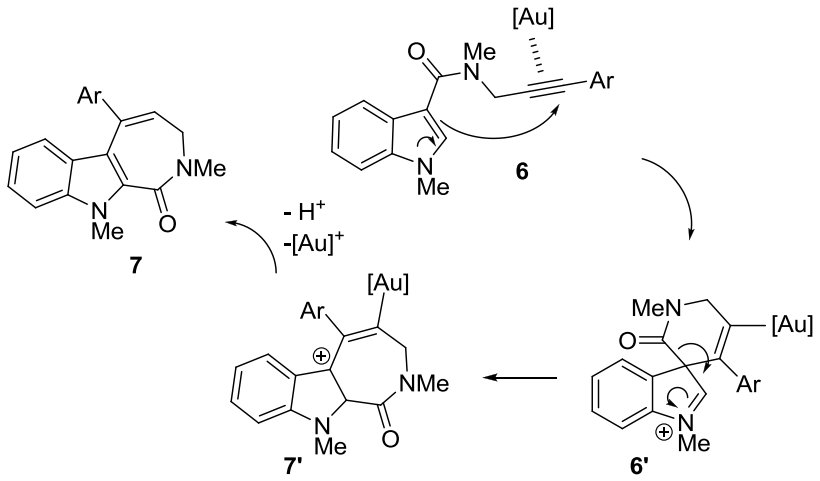


Figure 4.8 *Alkynyl-substituted indole-3-carboxamides leading to azepino[3,4-b]indol-1-ones*

Mechanistically, after the initial π-coordination to the alkyne **6**, the spirocyclic cationic intermediate **6'** is formed by the electrophilic *ipso*-attack of the activated alkyne to the most nucleophilic position of the indole system (Scheme 4.9).



Scheme 4.9 *Mechanism reported for [3,2]- acylamino shift of indoles.*

At this stage the migration of the acylammino group is preferred to a migration of the vinyl substituent, which delivers intermediate **7'**. Finally, elimination of a proton and protodeauration of **7'** resulted in the product **7** and restored the active species.

The second example reported by Liu in this field, involves the use of a cationic gold (I) complex to synthesize tetracyclic indolines via tandem cyclization (Figure 4.9).[9]

Starting from the alkynyl indole **8** containing a secondary alcohol and $PPh_3AuCl/AgOTf$ as catalyst the tetracyclic indoline was obtained as a single regio and diastoisomer.

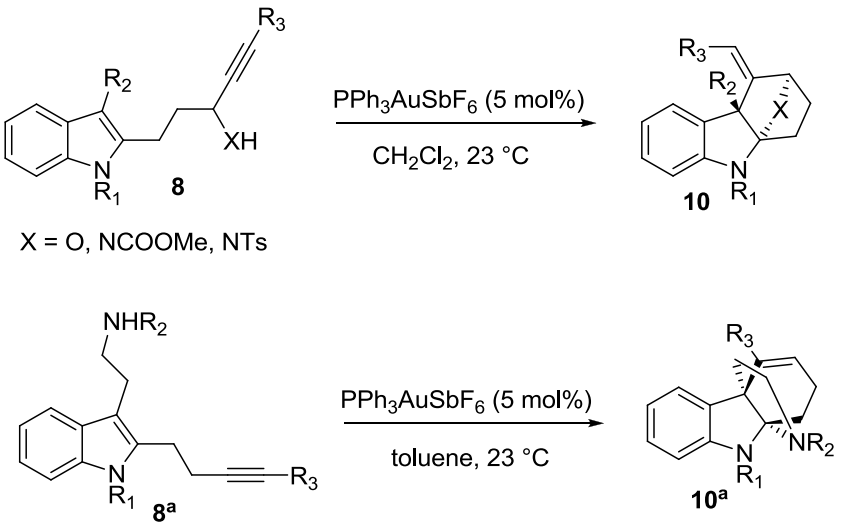
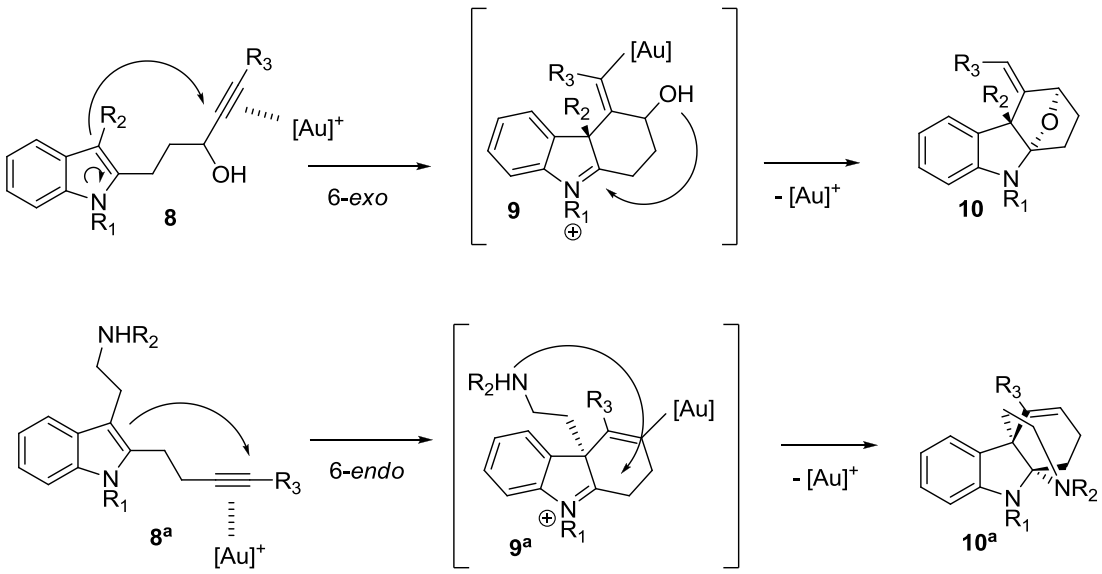


Figure 4.9 *[Au(I)]-catalyzed indoline synthesis*

Here the presence of a nucleophilic group (the secondary alcohol) is fundamental. A gold catalyst may selectively activate the triple bond of the alkynyl indoles and promote the *exo* or *endo* cyclization (first cyclization step). The resulting iminium ions **9** and **9**[a] can be susceptible to a nucleophilic attack by the nucleophile leading to a second cyclization step that would lead to **10** and **10**[a] (Scheme 4.10.).



Scheme 4.10. *Mechanisim hypothesized for the [Au(I)]promoted indoline synthesis.*

Another very interesting example was reported by Zhang (Figure 4.11).[10]

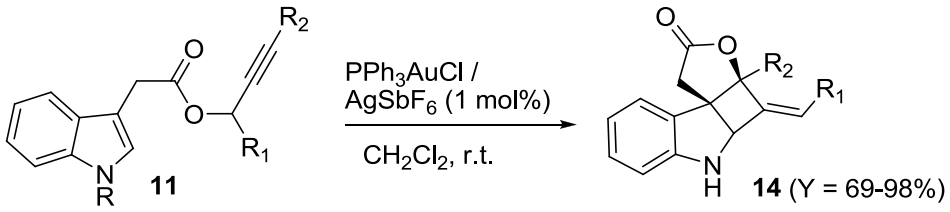
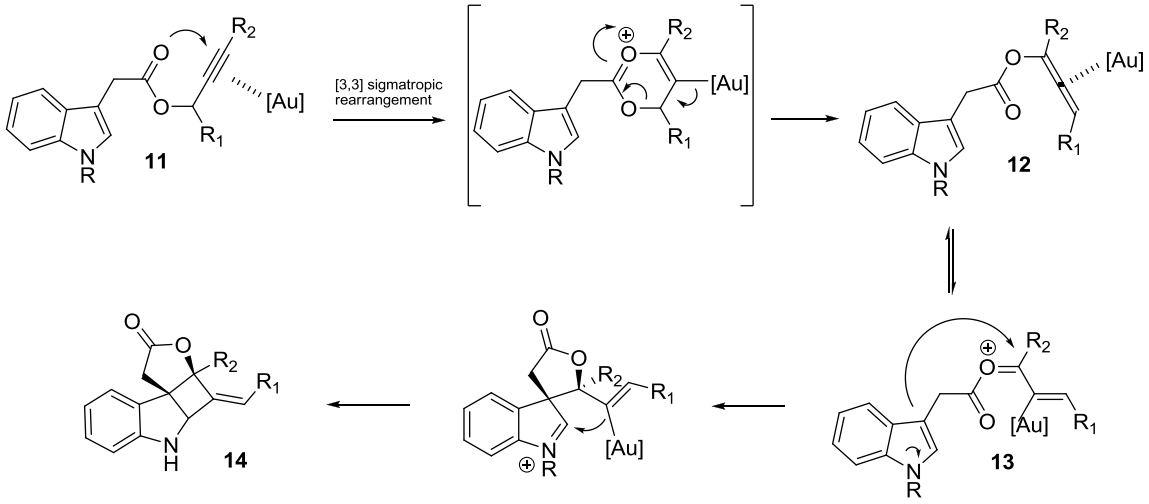


Figure 4.11. *Au-catalyzed 3,3-rearrangement-[2+2]-cycloadditions of propargylic esters.*

In this case using indole-based propargylic carboxylate of type **11**, a gold catalyst was able to promote the well known reactivity of a [3,3]-sigmatropic rearrangement in order to obtain intermediate **10**. Then, again an equilibrium was established between **12** and **13** by the gold catalyst which promoted the addition of the nucleophilic C3 of the indole to the oxonium to generate an alkenyl-gold intermediate which finally trapped the imminium to generate a 2,3-fused tetracyclic indoline of type **14** (Scheme 4.12).



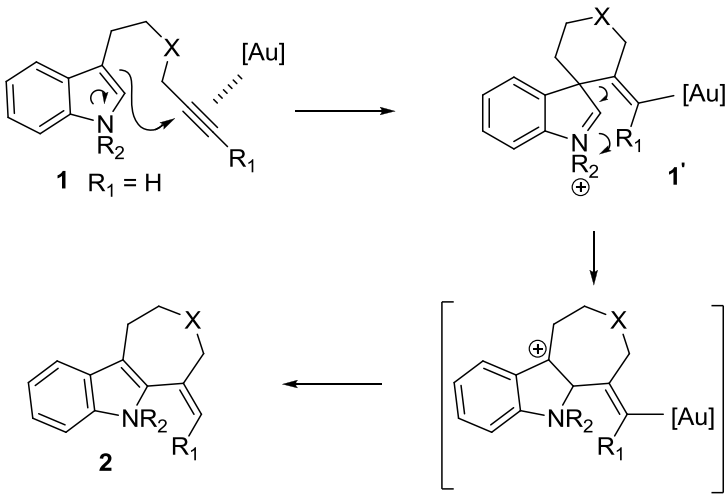
Scheme 4.12 *Mechanism reported for the [Au(I)]-catalyzed synthesis of indolines.*

4.3 Stereoselective synthesis of tetracyclic indolines.

At the begging of my investigation our goal was to develop a new metal catalyzed cascade reaction in order to achieve a new methodology for the synthesis of structurally complex indoline alkaloids. Indoline alkaloids, as we previously seen, are prominent molecular motifs in naturally occurring compounds displaying distinct pharmacological properties.[11] These compounds are commonly constituted by polycyclic fused molecular architectures featuring quaternary stereocenters.[12]

The use of gold catalysis for its high functional group tolerability and the high selectivity in the activation of unsatured hydrocarbons would constitute a perfect tool for the design of a cascade process in which an atom/step economical synthesis of structurally complex polycyclic indolines would be achieved.

One of the most effective example reported in literature involving the use of gold (I) catalysis for the transformation of the indole core using π-activated alcohols as electrophilic patterns, was reported by Echavarren (Scheme 4.13).



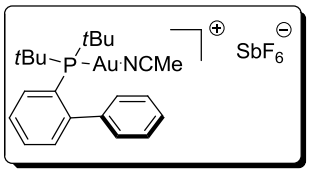


*Figure **4.13a***

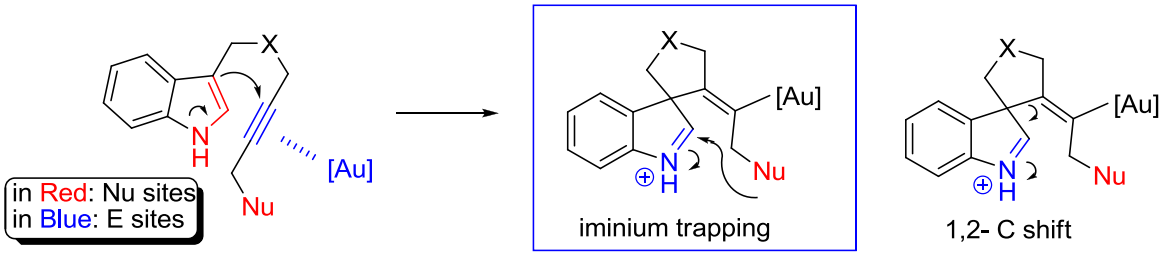
Scheme 4.13 *Mechanism of the Au(I) catalyzed hydroindolination of alkynes.*

The use of the phosphine based, silver-free gold(I) complex (Figure 4.13a) gave rise to an hydroindolination reaction in which a new family of C2-C3 connected rings was achieved.

In the reactivity developed, it was hypothesized that the first step would occur at the more nucleophilic C3 carbon in order to generated a transient spiro-immonium specie **1'** (Scheme 4.13) able to undergo a 1,2-carbon shift and generate indole **2** after the final protoauration step.

Our working hypothesis relied on the possibility to use a well-designed acyclic precursor with a pre-installed nucleophilic moiety in order to trap the transient electrophilic spiro-iminium transient,

avoiding at the same time the rearomatization of the indole core and heading to the synthesis of a tetracyclic indoline (Scheme 4.14)



Scheme 4.14 *Working hypothesis for the [Au(I)] catalyzed synthesis of tetracyclic indolines.*

This could be envisioned as a straightforward synthetic methodology for *furoindolines*, which are frequently existing structural fragments in natural products (Figure 4.15).

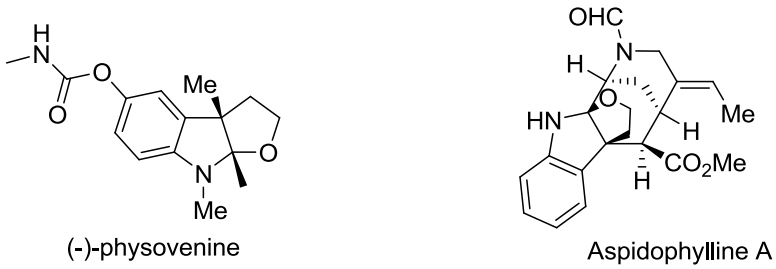
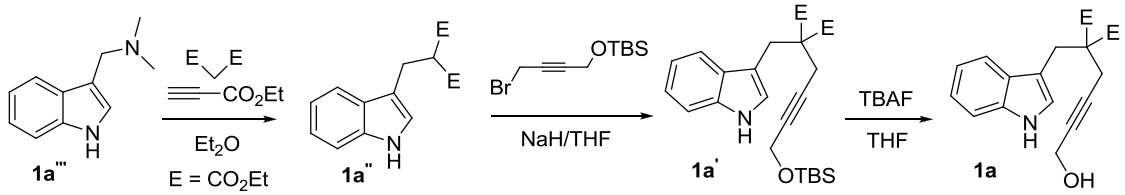


Figure 4.15 *Naturally occurring furoindolines.*

Moreover, substituted furoindolines with a quaternary carbon center at the C3 position represent a synthetic challenge and still mainly rely their synthesis on the Fischer methodology so a one-pot methodology results to be very interesting from a synthetic point of view.

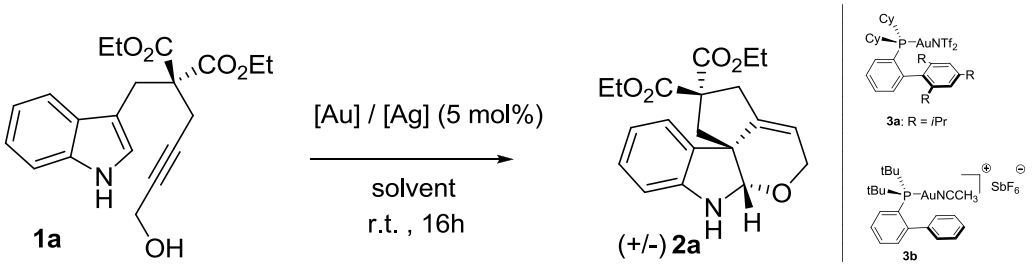
At the outset of our investigation we identified on the unprotected (-NH) indole alcohol **1a** our model substrate. The synthesis of the acyclic precursor was achieved in three simple synthetic passages starting from gramine **1a**''' (Scheme 4.16)



Scheme 4.16 *Synthetic tree for the synthesis of propargylic alcohol **1a**.*

With the model substrate in our hands, we enterprized a screening of metal catalysts with π-acidity properties. Delightly, the use of [Au(III)] and [Au(I)] opened access to a new class of tetracyclic indolines, *Dihydropyranil indolines* of type **2**.[14]

The results are reported in Table 4.17.



entry	[Au]	[Ag]	solvent	Yield[b] (%)
1[a]	$AuCl_3$		Toluene	10
2	$AuCl_3$	AgOTf	Toluene	33
3	PPh_3AuCl	AgOTf	CH_2Cl_2	45
4	$[(PPh_3Au)_3O]BF_4$		CH_2Cl_2	72
5	IMesAuCl	AgOTf	CH_2Cl_2	55
6	**3a**		CH_2Cl_2	60
7	**3b**		CH_2Cl_2	74
8	**3b**		Toluene	72
9	**3b**		MeOH	61
10	**3b**		$MeNO_2$	63
11	**3b**[c]		Toluene	56
12	**3b**[d]		CH_2Cl_2	80
13	PPh_3AuCl	$AgSbF_6$	CH_2Cl_2	68
14	$[dppf(AuCl)_2]$	$AgSbF_6$	CH_2Cl_2	31

a All the reactions were carried out under nitrogen conditions at room temperature, unless otherwise specified. b Isolated yield after flash chromatography. In all cases, compound 2a was obtained as a single diastereoisomer (1H-NMR and LC-analysis). c Under reflux. d 10 mol% of the catalyst was used at rt. *I*Mes = 1,3-bis(2,4,6-trimethylphenyl)- imidazol-2-ylidene.

Table 4.17 *Optimization of the catalytic system.*

Early screening experiments with different gold sources revealed that cationic gold(I) catalysts displayed greater competence with respect to [Au(III)] analogues (entries 1 and 2), in providing the tetracyclic fused indoline **2a** (yields up to 33%).

This trend can be tentatively ascribed to poisoning phenomena exerted by the aminic nitrogen atom of **2a** on the most electrophilic [Au(III)] species. Among the gold(I) π-acids scrutinized (entries 3–7), the well-defined silver-free complex **3b** (5 mol%)[15] was elected as the catalyst of choice providing **2a** with high 5-*exo*-dig regiochemistry and an excellent diastereomeric ratio (yield=74%, dr > 50:1).

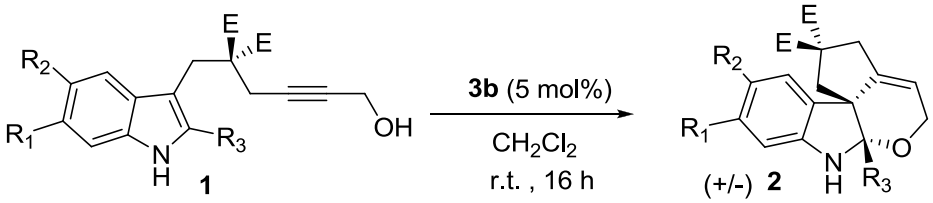
Among the solvents examined (MeOH, toluene, $MeNO_2$ and DCM, entries 7–10), CH_2Cl_2 proved to be the reaction media of choice.

Moreover, partial decomposition of the starting compound was recorded under forced conditions (toluene, reflux, entry 11) while higher loadings of **3b** (i.e. 10 mol%) did not significantly impact the isolated yield of **2a** (80%, entry 12, Table 4.15.).

Then, the role of the counterion as well as the phosphine ligand was further investigated through experimental controls carried out with preformed gold complexes [PPh_3AuCl] and [$dppf(AuCl)_2$] in the presence of $AgSbF_6$ (entries 13 and 14). Here, while entry 13 proved unambiguously the superiority of SbF_6 with respect to OTf counterion in terms of chemical yield (entry 13 vs 3), dinuclear cationic gold species [$dppf(AuSbF_6)_2$] led to **2a** in lower extent (yield = 31%).

In all these cases the regiochemistry of the hydroindolination proceedeed through a 5-*exo*-dig pathway and with high diastereoisomeric ratio (> 50:1).

The scope of this cascade process has been explored subjecting a wide number of propagyl acyclic derivatives **1** to the classical optimized catalytic system. The results are collected in Table 4.18:



entry	$R_1/R_2/R_3$	E	(+/-)-**2**	Yield (%)
1	H/H/H	CO_2Me	**2b**	75
2	H/H/H	CO_2tBu	**2c**	70
3	H/H/H	CO_2tBu	**2c**	81
4	H/Me/H	CO_2Et	**2d**	70
5	H/MeO/H	CO_2Et	**2e**	86
6	H/Cl/H	CO_2Me	**2f**	75
7	H/Cl/H	CO_2Et	**2g**	75
8	H/Br/H	CO_2Et	**2h**	75
9	Cl/H/H	CO_2Et	**2i**	78
10	H/H/Me	CO_2Et	**2j**	59

a All the reactions were carried out under nitrogen conditions at room temperature. b Isolated yield after flash chromatography. In all cases, compounds **2** were isolated as a single diastereoisomer (^{1}H-NMR and LC-analysis). c In the presence of 10 mol% of the catalyst.

Table 4.18 *General scope of the synthesis of tetracyclic indolines.*

Firstly, the malonyl tethering unit did not exhibit a marked influence on the final chemical output, and the corresponding dihydropyranyl indolines **2b**,**c** were isolated in comparable yields (70–81%, entries 1–3). Good yields (up to 78%) were also obtained in the presence of electron-withdrawing groups located at the C(5)- and C(6)- positions of the indolyl ring (entries 6–9).

Contrarily, indole compounds carrying electron-donating groups (i.e. **1d**,**e**) proved to be more reluctant toward the cascade cyclization. However by increasing the catalyst loading to 10 mol%, indolines **2d**,**e** were isolated in high chemical yields (70–86%, entries 4 and 5). Moreover, also 2-methylindole derivative **1j** proved to be a suitable precursor for compound **2j**, with the simultaneous formation of two consecutive quaternary stereocenters in a diastereomerically defined manner (yield = 59%, entry 10).

The structure of **2** was unimbigously determined by subjecting substrate **2c** to X-ray analysis (Figure 4.19).

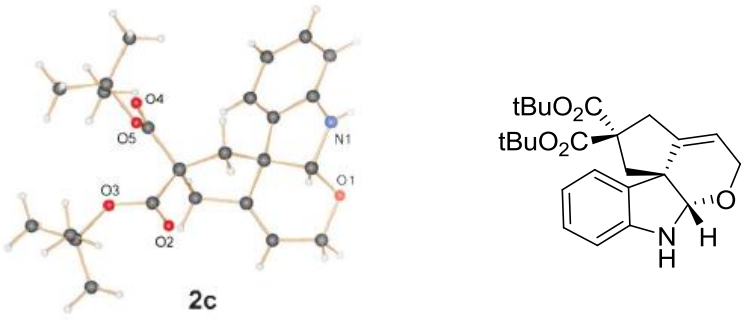


Figure 4.19 *X-ray structure of indoline* ***2c****.*

Subsequentely the scope of this methodology has been shifted to the possibility of synthesizing different tetracyclic indolines with a tryptamine-based scaffold.

Starting from the commercially available tryptamines we were able to synthesized indole-based propargylic alcohols of type **4a** following the sequence reported in Figure 4.20

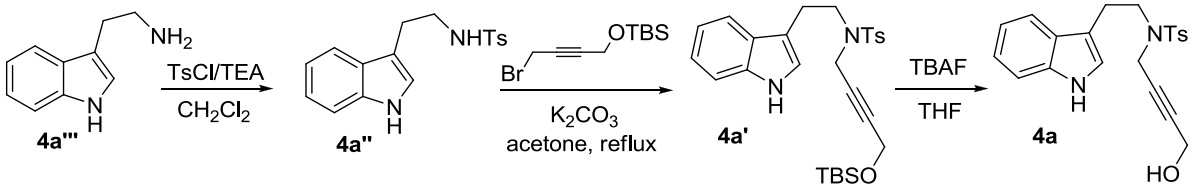
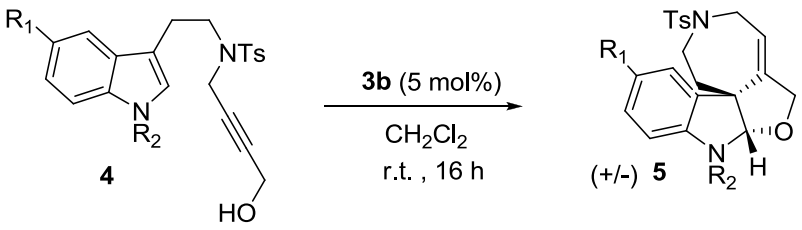


Figure 4.20 *Synthetic tree for the synthesis of tryptamine derivated propargylic alcohols* ***4a****.*

A range of tryptamine derivatives **4b-d** was also prepared.

Subjecting these acyclic precursors to the classical optimized catalytic conditions we realized surprisingly the synthesis of a new class of tetracyclic indolines **5**.

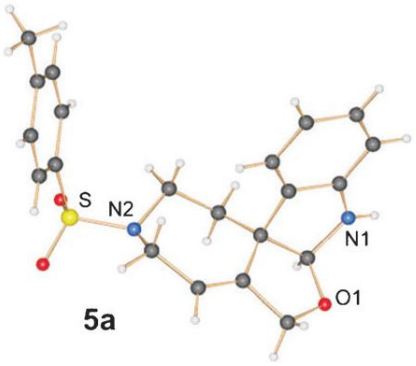
Both EDG and EWG groups on the indole scaffold were efficiently supported by gold catalysis (Table 4.21).



Entry	R_1/R_2	(+/-)-5	Yield (%)
1	H/H	**5a**	76
2	Cl/H	**5b**	60
3	MeO/H	**5c**	52
4	H/Me	**5d**	53

Table 4.21 *Scope of the synthesis of furoindolines* ***5****.*

Interestingly in this case the hydroindolination step proceeded with opposite regiochemistry (7-*endo*-dig) opening access to a new class of tetracyclic indolines, *furoindolines*. Even in this case an X-ray analysis of **5a** (left) out any doubt about the structures of the synthesized products.



A temptative explanation of the regiochemistry inversion recorded has been rationalized in term of intrinsic molecular requisites of the precursors (Figure 4.22)

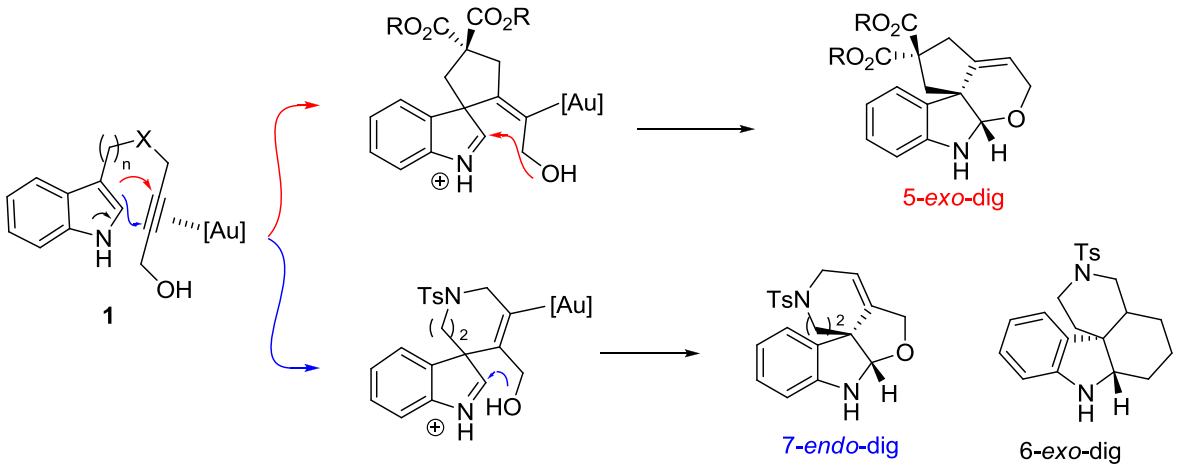


Figure 4.22 *Regiochemical pathways in the synthesis of tetracyclic indolines.*

Starting from indole based propargylic alcohol of type **1**, the limited length of the side arm (n=1) allows a proper overlapping between the C3 of the indole and the internal Csp of the alkyne exclusively opening access to a 5-*exo* regiochemistry (*dihydropyranil indolines).*

Indole based propargylic alcohols of type **4** have a longer flexible side arm so both regiochemical pathways are hypothetically accessible. But even in this case only, one of the two possible regioisomers was isolated, namely the 7-*endo*-dig one.

The explanation is still a matter of doubt because for the Baldwin rules, both the cyclization modes are plausible.

The role of the tethering unit has been ruled out because when we synthesized the propargylic alcohol of type **4e** (n=2) featuring the malonyl as tethering unit, again a complete 7-*endo*-dig regiochemistry was recovered although with poor yields (Figure 4.23).

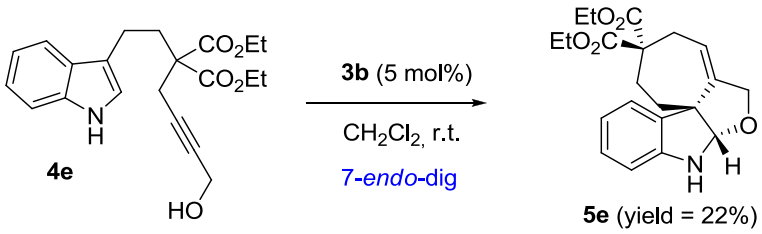


Figure 4.23 *Role of the tethering unit in the synthesis of tetracyclic indolines.*

Conclusions 4.4.

In this section we described a stereoselective protocol for the synthesis of highly functionalized tetracyclic indolines. Dihydropyranylindolines and furoindolines present a scaffold found in molecules with interesting biological activity. Commercially available gold catalyst was able to promote a cascade process with high yields, high atom economy (100%) and complete diastereo- and regioselection. Interestingly, changing the nature of the acyclic precursors led to the possibility to tune the regioselection shifting from a 5-*exo*-dig pathway (opening access to the family of dihydropiranylindolines) to the 7-*endo*-dig (heading to the synthesis of furoindolines).

4.5 Enantioselective gold(I) catalysis with dinuclear phosphines.

In the new millennium homogeneous gold(I) catalysis has featured an exponential growth in interest, with particular applications in the electrophilic manipulation of unactivated unsaturated hydrocarbons.

Most recently, the unique π-acidity of gold(I) species has found fascinating applications also in enantioselective organic transformations, opening new horizons in the manipulation of scarcely functionalized π-systems. However, the linear coordination mode combined with the intrinsic "outer-sphere" reaction channels usually displayed by cationic [Au(I)] centers forces chemical events to occur far away from the chiral organic ligand.

These considerations have presented several barriers to the full development of enantioselective gold catalysis, that have only recently found convincing solutions (Figure 4.24)

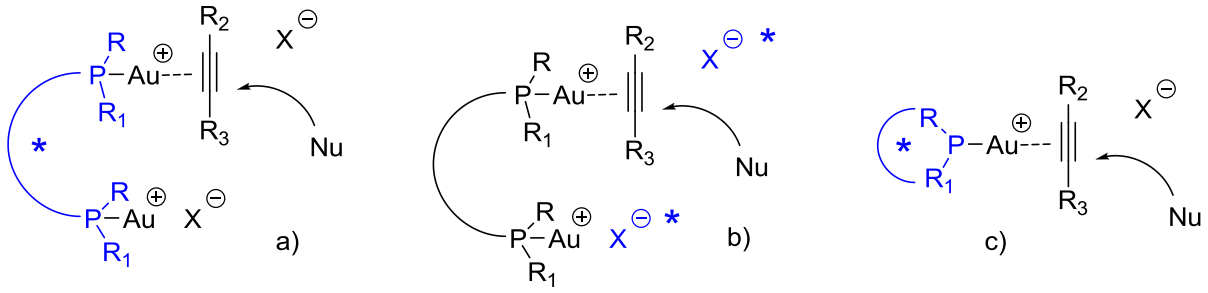


Figure 4.24 *Strategies in asymmetric gold catalysis: a) Chiral dinuclear gold complexes; b) Chiral counterion catalysis; c) Chiral monodenate ligand approach.*

Despite the pioneering work on the enantioselective Au(I)- catalyzed aldol condensation reported in the mid-1980s, the field remained virtually silent for more than a decade before its further development.

Among the main approaches currently utilized in asymmetric gold catalysis, the use of cationic dinuclear phosphine- based gold complexes, featuring axially chiral C2- symmetric scaffolds (i.e., BINAP, SEGPHOS, or BIPHEP ligands), dominates recent reports.

Complexes of general formula [P-P($AuX)_2$], with X = non-coordinating counterion, routinely involve chiral phosphines carrying large aromatic groups on the phosphorus substituents in order to overcome the challenging linear coordination mode of the metal center.

These scaffolds are expected to establish secondary interactions such as π-π and π-Au(I) stacking, which would allow rigid chiral pockets around the metal center to be realized. Although the intrinsic roles of the two gold atoms during catalysis are still a matter of debate, aurophilic contacts

are often invoked to stabilize reaction intermediates or to determine optimal tridimensional geometric arrangements in the catalyst-substrate adducts.
Despite this, reaction mechanisms are commonly depicted with only one gold center coordinating to the π-system in the stereochemical event.

4.6. Enantioselective hydroindolination of π-alcohols.

Very few example of enantioselective gold catalyzed hydroindolination of π-activated alcohols are reported in literature. Widenhoefer firstly succeded in performing the first enantioselective intramolecular hydroarylation of 2-(allenyl)-indoles to generate substituted polycylic indole derivatives.[14]
In this case, reaction of 2-(Y-allenyl)-indole **1A** with a catalytic 1:2 mixture of [(*S*)-DTBM-MeOBiphep$(AuCl)_2$] and $AgBF_4$ in toluene at -10 °C led to the isolation of tetrahydrocarbazole **2A** with good yields and high enantioselection (Figure 4.25)

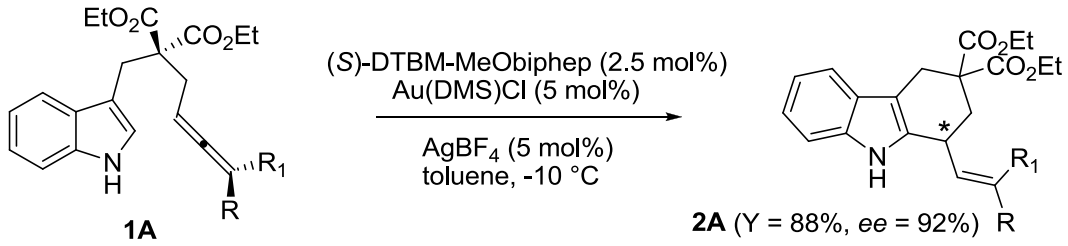


Figure 4.25 *[Au(I)]- catalyzed enantioselective hydroindolination of allenes.*

Activation of allenes is more challenging with respect to hydroarylation of alkynes due to their low reactivity. In this case, the nucleophilic attack, which generates a Csp3 stereocenter at the terminal carbon atom of a π-allene gold(I) complex and so stereocontrol is dominated by the presence of a chiral ligand.

More recently, Bandini described the first example of enantioselective gold catalyzed hydroindolynation of allylic alcohols (Figure 4.26).[15]

Starting from a specifically designed indolyl-allylic alcohol (*Z*)-**1B**, 1-vinyl-tetrahydrocarbazoles **2B** were synthesized in highly enantioselective manner.

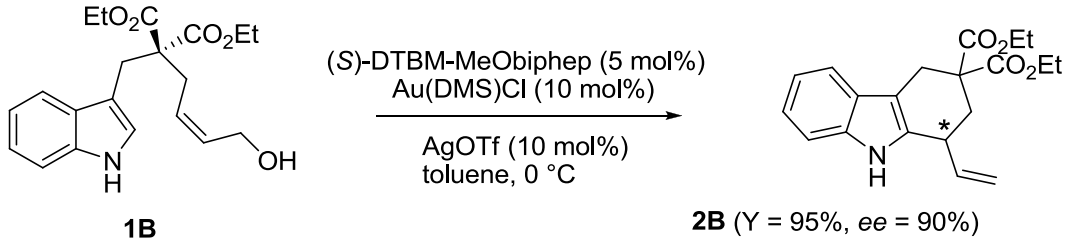
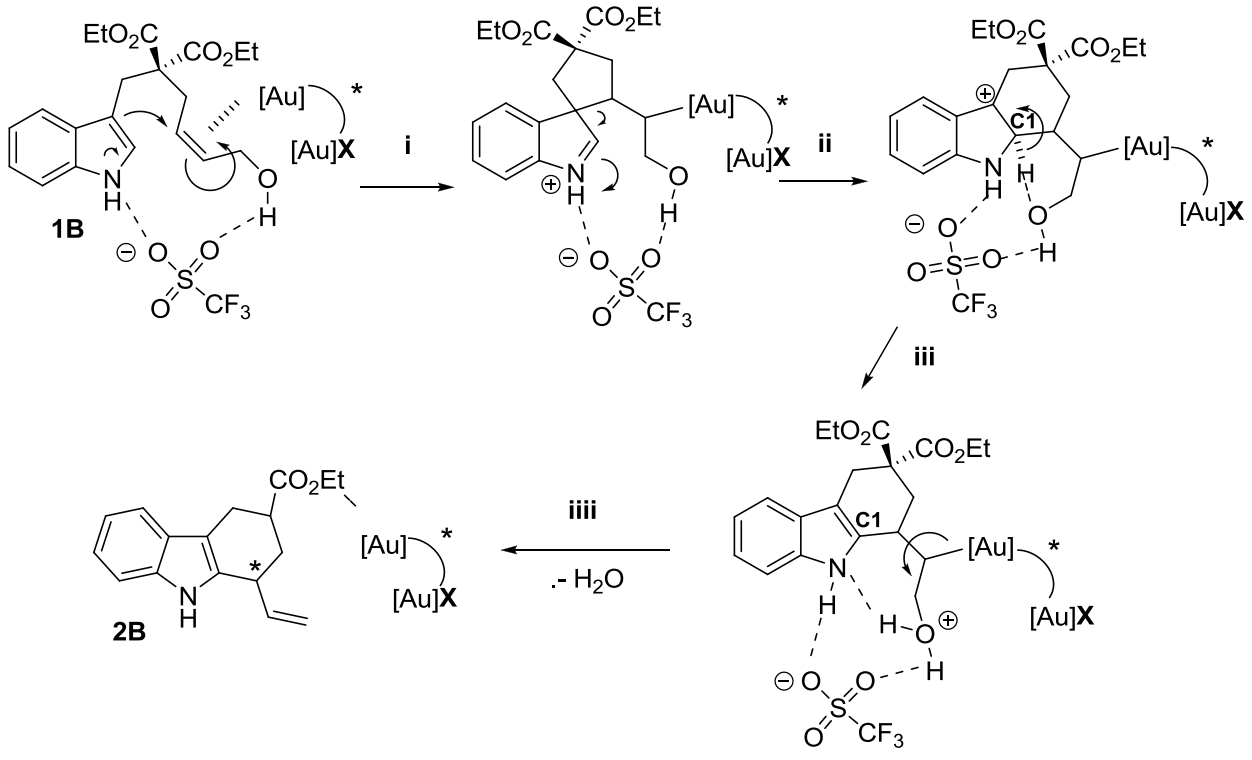


Figure 4.26 *[Au(I)) catalyzed enantioselective hydroindolinaton of allylic alcohols.*

The mechanism of this reactivity has been deeply investigated by using a combined experimental-computational DFT approach.[16] Some results obtained with the two model systems can be summarized as follows (Scheme 4.26):



Scheme 4.26 *Mechanism hypothesized for the Au(I) catalyzed hydroindolination of allylic alcohols.*

(1) The favored mechanism is a stepwise SN2' type mechanism based on indole-auration of the C −C double bond (outer-sphere-like), rearomatization of the indole moiety, and subsequent β-elimination of [Au(I)]-H_2O.

(2) The triflate counterion has been demonstrated to play a pivotal role several times along the reaction coordinate. First of all, this ion exerts a sort of "folding effect" which forces the two reactive sites of the starting adduct to move closer, adopting the right orientation to react (U-turn-type geometry). This is achieved by means of two rather strong H-bonds involving the indole NH bond, the allylic hydroxyl group, and two triflate oxygen atoms (**i**).

This hypothesis has been confirmed by additional experimental results on modified reacting systems where the above-described H-bonds cannot be established (Figure 4.27).

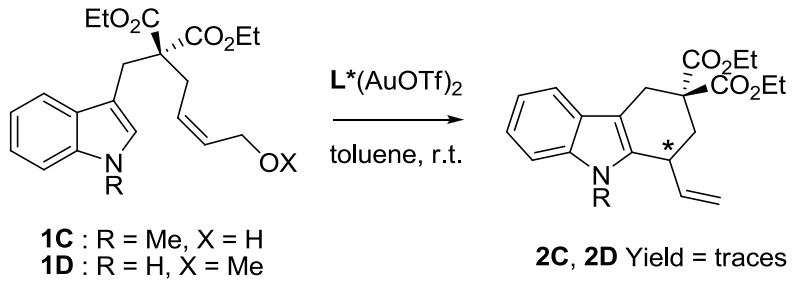


Figure 4.27 *Experimental studies on the role of hydrogen bonding*

The negatively charged triflate ion plays an additional important role in "assisting" the proton transfer from C1 (C(2) indole position, Scheme 4.26, **iii**) to the allylic hydroxyl oxygen and, thus, restoring the aromatic character of the pyrrolyl ring (**ii**). The triflate ion strongly interacts with the hydroxyl hydrogen and enhances the basicity of the hydroxyl oxygen. The role of the triflate counterion is once again crucial in the third reaction step (**iii**), where the releasing of one molecule of water is helped by the persisting strong hydrogen bond between this ion and the oxonium intermediate

4.7. Enantioselective protocol for the synthesis of tetracyclic indolines.

The chemical output obtained by exploiting this cascade reaction led us to make some interesting consideration.

Compounds **A** and **B** present two consecutive stereogenic centers and the possibility to achieve an enantioselective protocol intrigued us even because, as we previously saw, although examples of enantioselective gold catalyzed hydroindolination of π-systems (such allenes), and π-activated alcohols are reported in literature, no example of gold catayzed hydroindolination of akynes are known so far.

4.8. Results and discussion

At the outset of the present investigation we envisioned that, as the overall stereochemistry of the final product (A or B) is essentially ruled by the initial gold-triggered regioselective hydroindolination of the triple bond, the use of chiral gold complexes could theoretically open access to the unprecedented enantioselective gold-catalyzed synthesis of indolines carrying all-carbon quaternary stereocenters at the C(3) position (Figure 4.28).[17]

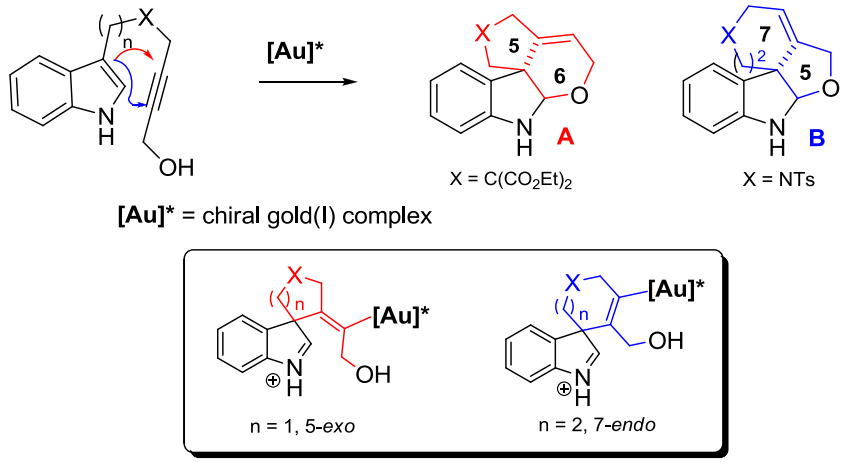


Figure 4.28 *Working hypothesis of the enantioselective synthesis of tetracyclic indolines.*

Aiming to discover the optimal reaction parameters, we first underwent a screening of reaction conditions (namely, ligands, solvent, gold counterions, and temperature) by selecting **1a** as a readily available and synthetically flexible model acyclic precursor.

A range of chiral C2-symmetrical bis-phosphine ligands (Figure 4.29.) (**L1-6**, 5 mol %) was initially tested in the cascade reaction by preparing in situ the corresponding cationic binuclear gold complexes of the general formula $L(AuSbF_6)_2$ (entries 1-6,Table 4.30). [18]

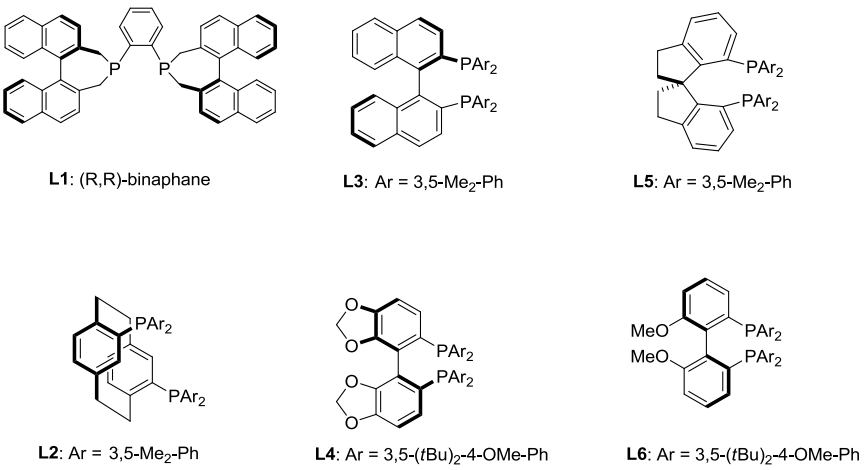
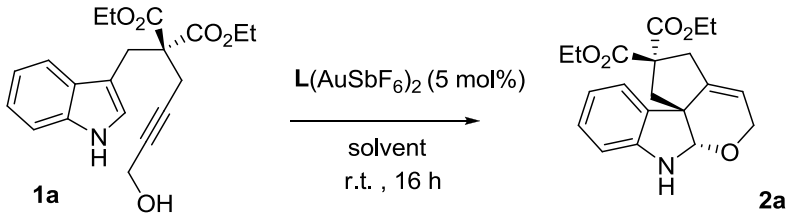


Figure 4.29 *Commercially available Chiral biphosphine ligands.*

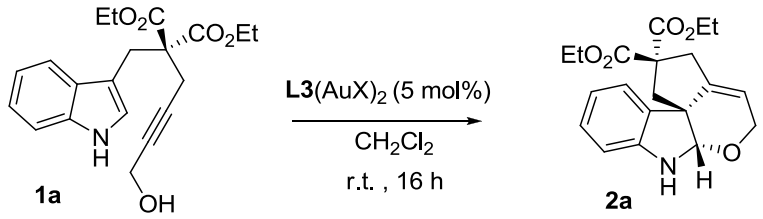


Entry	**L**	Solvent / T°C	Yield (%)	*ee* (%)
1	(*R,R*)-**L1**	Benzene / 25° C	21	46 (+)
2	(*S*)-**L2**	--	26	20
3	(*R*)-**L3**	CH_2Cl_2 / 25°C	65	56
4	(*S*)-**L4**	--	36	14
5	(*R*)-**L5**	Benzene / 25°C	61	0
6	(*S*)-**L6**	--	65	18

Table 4.30 *Optimization of the catalytic system: Ligand*

As reported in this table the best ligand was found to be **L3** ((*R*)-xylyl-binap) that was able to promote this transformation with good yield (65%) and promising *ee* (56%).

In the presence of **L3** we considered different counterions in order to improve the catalytic system (Table 4.31).

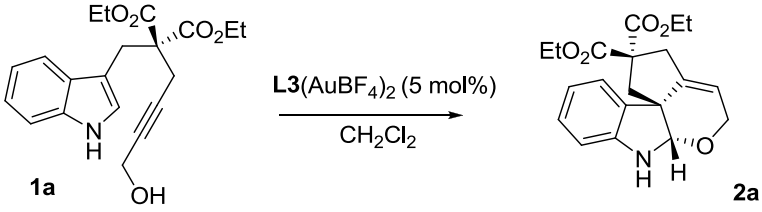


Entry	AgX	Yield (%)	*ee* (%)
7	AgOTf	59	72
8	$AgNTf_2$	80	27
9	$AgBF_4$	60	74
10	$AgPF_6$	70	70
11	Ag(*p*NB)*	traces	-

*= *para*-nitrobenzoate

Table 4.31 *Optimization of the catalytic system: Counterion.*

Here, while the use of *para*-NO_2-benzoate (*p*NBn) did not promote the reaction at all, the addition of AgOTf and $AgBF_4$ provided **2a** in comparable yield (60%) and *ee* up to 74% (entry 9).At the end of this survey we can see that the use of $AgBF_4$ resulted to be the best in term of stereoselection (*ee* = 74%) and moderate yield (60%). For this reason finally, we tried to modify some reaction conditions by lowering the temperature of the reaction and by adding molecular sieves in order to get some improvements (Table 4.32).

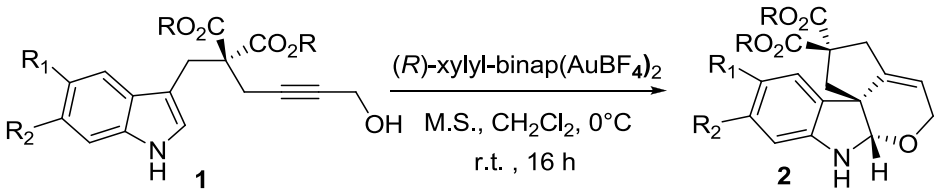


Entry	T(°C)	M.S. (Å)	Time (h)	Yield (%)	*ee* (%)
12	0	4	4	89	86
13	0	5	16	72	82

Table 4.32 *Final optimization of the catalytic system for the synthesis of dihydropyranylindolines.*

Gratifingly by lowering the temperature at 0 °C and in the presence of M.S. (4 Å) good yield (89%) and higher enantioselection (84%) was obtained.

Encouraged by the results obtained in the standard cascade reaction assays, we verified the generality of the method by subjecting a series of N(H)-free indole propargylic alcohols **1b-i** to standard cyclization conditions, and the results are summarized in Table 4.33.

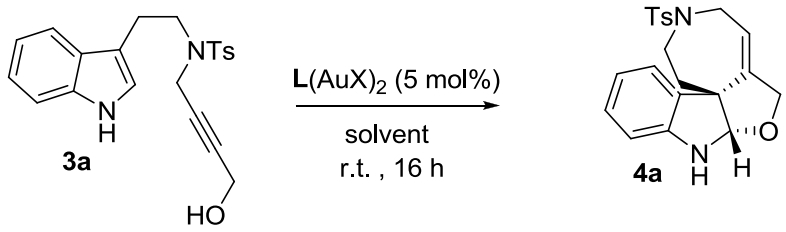


entry	1	$R/R_1/R_2$	Yield (%)	*ee* (%)
1	**1b**	Me/H/H	65	87
2	**1c**	tBu/H/H	60	76
3	**1dd**	tBu/MeO/H	51	77
4	**1e**	Et/MeO/H	50	76
5	**1f**	Me/Cl/H	58	83
6	**1g**	Et/Cl/H	70	75
7	**1h**	Et/Br/H	75	81
8	**1i**	Et/H/Cl	67	84

Table 4.33 *Scope of the enantioselective protocol for the synthesis of dihydropyranylindolines.*

In the presence of 5 mol% of (*R*)-[**L3**$(AuBF_4)_2$], satisfactory yields (50-75%) were obtained over a range of indole substitutions as well as malonyl tethering units. In all cases, the corresponding tetracyclic indolines **2b-i** were isolated with excellent chemo- and diastereoselectivity (>50:1).
Finally, the scope of the reaction was expanded further proving the competence of readily accessible alcohols **3** as acyclic precursors in the present gold-catalyzed process.

Interestingly,optimal results were recorded by subjecting model substrates **3a** to reaction conditions involving (*S*)-DTBM-segphos(AuOTf)$_2$ as the chiral catalyst (5 mol %) and benzene as the solvent (Table 4.34).



entry	L	AgX	Solvent	Yield (%)	*ee* (%)
1	**L3**	AgOTf	CH_2Cl_2 -toluene (1:4)	50	60
2	**L2**	--	--	35	58
3	**L5**	--	--	42	28
4	**L4**	--	--	52	38
5	**L4**	--	--	50	68
6	**L6**	--	--	65	32
7	**L4**	$AgBF_4$	--	50	24
8	**L4**	AgOTs	--	55	52
9	**L4**	AgOTf	CH_2Cl_2	80	34
10	**L4**	--	Benzene	62	85

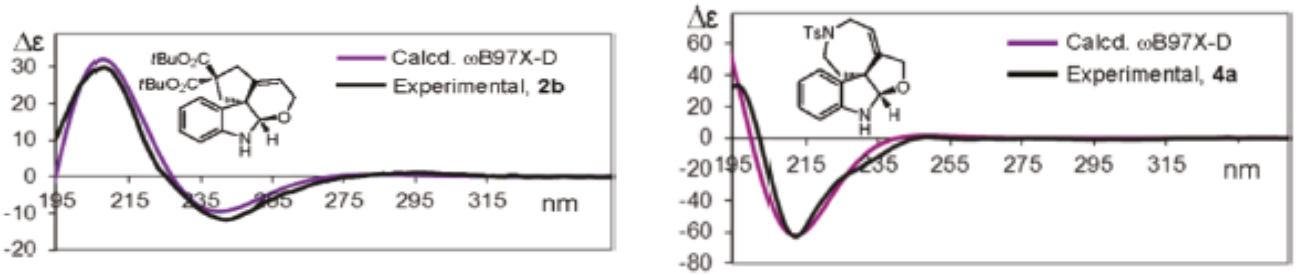
Table 4.34 *Optimization of the catalytic system: Ligand and counterion*

This enantioselective protocol was proved to be competent also for a substituted tryptamine-based propargylic alcohol **3b** generating a tetracylic indoline with good yields (67%) and good enantiomeric excess (82%) (Figure 4.35).

Figure 4.35 *Enantioselective synthesis of furoindolines.*

In particular, even using chiral gold(I) catalysts, tryptamine derivatives **3a,b** underwent cyclization via a preferential 7-*endo*-dig regiochemical pathway leading to tetracyclic furoindolines **4**, carrying a fused azasubstituted unsaturated seven-membered cycle.

In collaboration with Prof. A. Mazzanti (University of Bologna) we also succeded in the determination of the absolute configuration of the indolines **2b** and **4a** via simulation of their electronic circular dichroism spectra and $[\alpha]_D$ values by means of the TD-DFT approach.[20] The ECD spectra calculated for the 7a*R*,12b*S* absolute configuration of **4a** and for the 6a*R*,11b*R* configuration for **2b** showed very good agreement with the experimental spectra of the major enantiomers (Figure 4.36).



Also the calculated $[\alpha]_D$ values matched well with the experimental signs and values, thus enforcing the reliability of the assignment.

Figure 4.36 *TD-DFT simulations of the electronic circular dichroism spectra of compounds* ***2b*** *and* ***4a****. The black traces correspond to the experimental spectra. The purple lines show the simulations obtained assuming the* ***7a****R,****12b****S configuration for* ***4a*** *and the* ***6a****R,****11b****R configuration for* ***2b****.*

Conclusions 4.9

In conclusion, in this section we reported the first example of [Au(I)] catalyzed enantioselective hydroindolynation of propargylic alcohols as a synthetic cascade route towards the preparation of tetracyclic indolines, *dihydropyranylindolines* and *furoindolines*.

The ready availability of the acyclic precursors, the mild reaction conditions, and the good levels of regio-, diastereo-, and enantioselectivity nominate the protocol as a rapid entry to stereodefined polycyclic indoline alkaloids.

Bibliography

[1]. a) R. J. Sundberg in The Chemistry of Indoles, Academic Press, New York, **1970**; b) R. K. Brown in Indoles (Ed.: W. J.Houlihan), Wiley-Interscience, New York, **1972**.

[2]. F.-R. Chen, J. Huang, *Chem. Rev*. **2005**, *105*, 4671-4706.

[3]. M.Toczko,C.Heathcock. *J.Org.Chem*.,**2000**, *65*, 2642-2645.

[4] .F.Goodman,G.Weiss, *Cardiovascular Drug Rew*. **2002**, *3*(19).

[5]. Echavarren A.M, Ferrer C., *Chem. Eur. J*., **2007**, *13*, 1358-1373.

[6]. Y. Lu, X. Du, X. Jia, Y. Liu,' *Adv.Synth.Cat*., **2009**, *351*, 1517-1522.

[7]. A. S. K. Hashmi, W. Yang, F. Rominger, *Adv. Synth. Catal*. **2012**, *354*, 1273 – 1279

[8]. Hymenialdisine as well as paullone derivatives selectively inhibit different kinases and cytokines: a) J.-G. Parmentier, B. Portevin, R. M. Golsteyn, A. Pierr, J. Hickman, P. Gloanec, G. De Nanteuil, *Bioorg. Med. Chem. Lett*. **2009**, *19*, 841–844; b) N. Dessalew, P. V. Bharatam, *Biophys. Chem*. **2007**, *128*, 165–175; c) V. Sharma, J. J. Tepe, *Bioorg. Med. Chem. Lett*. **2004**, *14*, 4319–4321; d) Y. Wan, W. Hur, C. Y. Cho, Y. Liu, F. J. Adrian, O. Lozach, S. Bach, T. Meijer, N. S. Gray, *Chem. Biol*. **2004**, *11*, 247–259; e) C. Schultz, A. Link, M. Leost, D. W. Zaharevitz, R. Gussio, A. A. Sausville, L. Meijer, C. J. Kunick, *J. Med. Chem*. **1999**, *42*, 2909–2919.

[8]. Y Liu, W Xu, X Wang, *Org. Lett.*, **2010**, *12*, 1448–1451.

[9]. L. Zhang, *J. Am. Chem. Soc.,* **2005***, 127,* 16804–16805.

[10]. (a) T. Hudlicky´ and J. W. Reed, *The Way of Synthesis: Evolution of Design and Methods for Natural Products*, WILEY-VCH, Weinheim, **2007**, 759–842; (b) D. Liu, G. Zhao and L. Xiang, *Eur. J. Org. Chem*., **2010**, 3975, and references therein.

[11]. For representative examples see: (a) T. Matsuura, L. E. Overman and D. J. Poon, *J. Am. Chem. Soc.*, **1998**, *120*, 6500; (b) T. Sunazuka, T. Hirose, T. Shirahata, Y. Harigaya, M. Hayashi, K. Komiyama and S. Omura, *J. Am. Chem. Soc.*,**2000**, *122*, 2122; (c) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao and D. W. C. MacMillan, *Proc. Natl. Acad. Sci. U. S. A*., **2004**, *101*, 5842; (d) A.

Steven and L. E. Overman, *Angew. Chem., Int. Ed*., **2007**, *46*, 5488; (e) S. B. Jones, B. Simmons and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2009**, *131*, 13606; (f) L. M. Repka, J. Ni and S. E. Reisman, *J. Am. Chem. Soc*., **2010**, *132*, 14418; (g) S. Lucarini, F. Bartoccini, F. Battistoni, G. Diamantini, G. Piersanti, M. Richi and G. Spadoni, *Org. Lett*., **2010**, *12*, 3844; (h) Q.-F. Wu, H. He, W.-B. Liu and S.-L. You, *J. Am. Chem. Soc*., **2010**, *132*, 11418; (i) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou and X. Zhang, *J. Am. Chem. Soc*. **2010**, *132*, 8909.

[12]. T. Sunazuka, K. Yoshida, N. Kojima, T. Shirahata, T. Hirose, M. Handa, D. Yamamoto, Y. Harigaya, I. Kuwajimaa and S. Omura, *Tetrahedron Lett.*, **2005**, *46*, 1459-1463.

[13]. G. Cera, P. Crispino, M. Monari, M. Bandini, *Chem. Commun.* **2011**, *47*, 7803-7805.

[14]. (a) C. Nieto-Oberhuber, S. Lopez and A. M. Echavarren, *J. Am. Chem. Soc*., **2005**, *127*, 6178; (b) E. Herrero-Gomez,C. N. Oberhuber, S. Lopez, J. Benet-Buchholz and A. M. Echavarren, *Angew. Chem., Int. Ed*., **2006**, *45*, 5455.

[15]. C. Liu, R. Widenhofer, *Org. Lett.*, **2007**, *9*, 1935–1938.

[16]. M. Bandini, A. Eichholzer; *Angew. Chem. Int. Ed*. **2009**, *48*, 9533-9537.

[17]. M. Bandini, A. Bottoni, M. Chiarucci , G. Cera , and G. Miscione *J. Am. Chem. Soc.*, **2012**, *134*, 20690–20700.

[18]. G. Cera, M. Chiarucci, A. Mazzanti, M. Mancinelli, M. Bandini, *Org. Lett*. **2012**, *14*, 1350-1353;

[19]. Chiral mononuclear gold complexes based on phosphoramidite ligands were also tested, furnishing 2a only in traces. For related references, see: Teller, H.; Flugge, S.; Goddard, R.; Furstner, A. *Angew. Chem., Int. Ed*. **2010**, *49*, 1949.

[20]. (a) Bringmann, G.; Bruhn, T.; Maksimenka, K.; Hemberger, Y. *Eur. J. Org. Chem*. **2009**, 2717. (b) Crawford, T. D.; Tam, M. C.; Abrams, M. L. *J. Chem. Phys.* **2007**, *111*, 12057-12067.

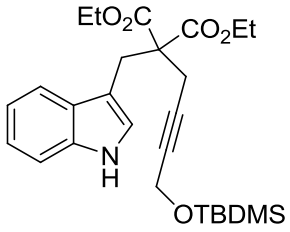
Supporting Information

General Methods. 1H-NMR spectra were recorded on Varian 200 (200 MHz), Varian 400 (400 MHz) spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, pd = pseudo duplet, t = triplet, pt = pseudo triplet, q = quartet, pq = pseudo quartet, br = broad, bs = broad singlet, m = multiplet), coupling constants (Hz). 13C-NMR spectra were recorded on a Varian 200 (50 MHz), Varian 400 (100 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: 77.0 ppm). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. They are reported as: *m/z* (rel. intense). LC-electrospray ionization mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 240-400 mesh silica gel. Elemental analyses were carried out by using a EACE 1110 CHNOS analyzer.

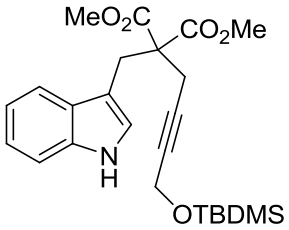
Materials. All reactions were carried out under inert gas and under anhydrous conditions, if not further specified. Anhydrous solvents were supplied by Fluka in Sureseal® bottles and used without any further purification. Targeted tosyl-tryptamines were synthesized in variable yields (50-86%), from the commercially available tryptamines, following conventional protocols. tryptamines/TsCl/TEA (1/1.2/2), CH2Cl2, rt,4 h.1 2-(1*H*-indol-3ylmethyl)-malonic acid dialkyl esters were synthesized as previously described.2 Propargylic bromide **A** was synthesized from monoprotected butyn-1,4-diol following a conventional protocol. In a three-necked round bottomed flask, equipped with a dropping funnel, under nitrogen atmosphere, 10 mmol of monoprotected butyn-1,4-diol and 11 mmol of NBS were dissolved in 25 ml of DCM. At the same time, 11 mmol of PPh3 were dissolved in 15 ml of DCM in the adding funnel and then the solution dropped at 0 °C. The suspension was allowed to warm up to r.t. and stirred for 2 hs. DCM was then removed under vacuum. The crude was then treated with 30 ml of pentane and stirred for 1 h. Afterwards the organic layer was filtered with a Gooch funnel and pentane removed under vacuum to afford propargylic bromide **A** with yields greater than 90% and NMR purity > 95%.

Synthesis of indolyl propargylic silyl ethers 1a'-j'

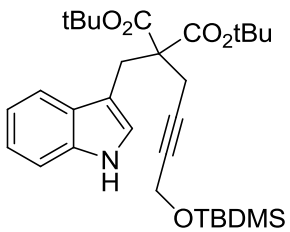
To a solution of 2-(2,5-disubstituted-1*H*-indole-3-ylmethyl) malonic acid dialkyl ester (1eq.) in THF, NaH (60% suspension in mineral oil, 2 eq.) was added at 0 °C. The suspension was stirred for 30 min at 0 °C, then **2** (1.2 eq) was added drop-wise. The reaction was warmed up to room temperature and stirred for 3 h. After extractive work-up (H_2O/EtOAc) the organic layer was separated, dried with Na2SO4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography. Compounds **1f'**, **1g'** and **1i'** were not isolated and deprotected as reaction crudes.



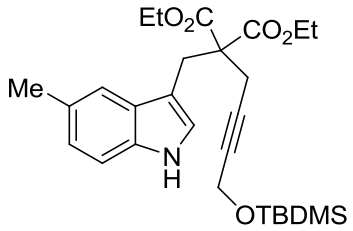
1a': Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 8:2). Yield = 77%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.15 (s, 6H); 0.92 (s, 9 H); 1.23 (t, J = 7.2 Hz, 6H); 2.83 (s, 2H); 3.57 (s, 2H); 4.12-4.21 (m, 4H); 4.46 (s, 2H); 7.07-7.18 (m, 3H); 7.33 (d, J = 8.4 Hz, 1H); 7.67 (d, J = 7.6 Hz, 1H); 8.08 (s, 1H). LC-MS: 472 (M+1). 494 (M+Na).



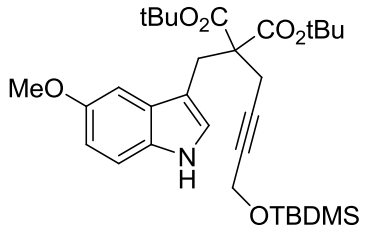
1b': Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 8:2). Yield = 48%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.02 (s, 6H); 0.96 (s, 9H); 2.86 (s, 2H); 3.66 (s, 2H); 3.67 (s, 6H); 4.43 (t, J = 2.0 Hz , 2H); 6.99 (d, J = 2.0, Hz, 1H); 7.10 (ddd, J1 = 18.0 Hz, J2 = 8.0, Hz, J3 = 1.2 Hz, 2H); 7.28 (d, J = 8.0 Hz, 1H); 7.59 (d, J = 8.0 Hz, 1H); 8,31 (s, 1H). LC-MS: 444 (M+1), 466 (M+Na).



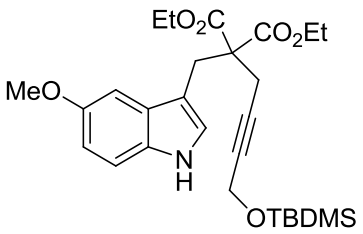
1c': Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 8:2). Yield = 56%. ^{1}H-NMR (400 MHz,$CDCl_3$) δ: 0.10 (s, 6H); 0.87 (s, 9H); 1.43 (s, 9H); 2.75 (s, 2H); 3.47 (s, 2H); 4,36 (s, 2H); 7.05 (s, 1H); 7.09 (pt, J = 6.8 Hz, 1H); 7.16 (pt, J = 7.2 Hz, 1H); 7.32 (d, J = 8.0 Hz, 1H); 7.79 (d, J = 8.0 Hz, 1H); 8.10 (s,1H). LC-MS: 550 (M+Na).



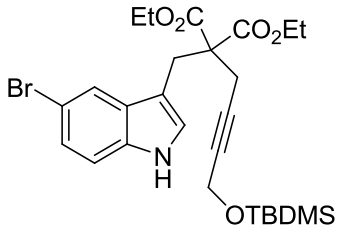
1d': Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 8:2). Yield = 58%. ^{1}H-NMR (400 MHz,$CDCl_3$) δ: 0.13-0.15 (m, 6H); 0.92-0.94 (m, 9H); 1.23-1.27 (m, 6H); 2.83 (t, J = 2.0 Hz, 2H); 3.55 (s, 2H); 4.12-4.21 (m, 4H); 4.38 (s, 2H); 6.99 (dd, J1 = 8.4 Hz, J2 = 1.6 Hz, 1H); 7.03 (d, J = 2.4 Hz, 1H); 7.16 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H); 7.97 (s, 1H). LC-MS 486 (M); 509 (M+ Na).



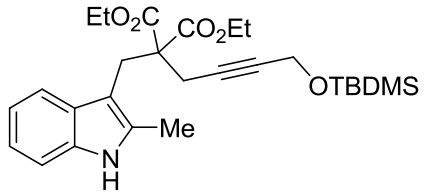
1dd'. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 8:2). Yield = 65%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.13 (s, 6H); 0.92 (s, 9H); 1.44 (s, 18H); 2.78 (t, J = 2.4 Hz, 2H); 3.45 (s, 2H); 3.88 (s, 3H); 4.35 (t, J = 2Hz, 2H); 6.83 (m, 1H); 6.99 (d, J = 2.4 Hz, 1H); 7.19 (d, J = 8.8 Hz, 1H); 7.31 (d, J = 2.4 Hz, 1H); 8.04 (s, 1H). LC-MS: 444 (M+1). 466 (M+Na). Anal. calcd for (C31H47NO6Si: 557.79): C, 66.75; H, 8.49; N: 2.51. Found: C, 66.68; H, 8.41; N: 2.33.



1e'. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 8:2). Yield = 60%. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.13 (s, 6H); 0.90 (s, 9H); 1.26 (t, J = 7.2 Hz, 6H); 2.85 (s, 2H); 3.54 (s, 2H); 3.86 (s, 3H); 4.17 (q, J = 7.2 Hz, 4H); 4.35 (s, 2H); 6.83 (d, J = 8.8 Hz, 1H); 7.01 (d, J = 2.8 Hz, 1H); 7.19-7.27 (m, 2H); 7.95 (s, 1H). LC-MS: 502 (M+1).



1h'. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 8:2). Yield = 46%. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.14 (s, 6H); 0.91 (s, 9H); 1.27 (t, J = 7.2 Hz, 6H); 2.81 (s, 2H); 3.53 (s, 2H); 4.17 (q, J = 7.2 Hz, 4H); 4.39 (s, 2H); 7.10 (d, J = 2.4 Hz, 1H); 7.23-7.27 (m, 2H); 7.75 (d, J = 2.0 Hz, 1H); 8.13 (s, 1H). LC-MS: 552 (M+1), 573 (M+Na).

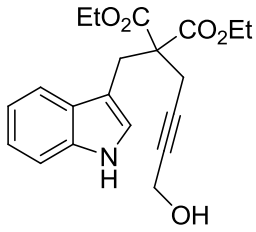


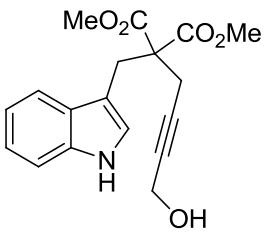
1j'. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 8:2). Yield = 30%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.15 (s, 6H); 0.92 (s, 9H); 1.22 (t, J = 7.2 Hz, 6H); 2.40 (s, 3H); 2.81 (s, 3H); 3.51 (s, 2H); 4.15 (q, J = 7.2 Hz, 4H); 4.37 (t, J = 2.0 Hz, 2H); 7.01-7.10 (m, 2H); 7.22 (d, J = 8.4 Hz, 1H); 7.60 (d, J = 7.6 Hz, 1H); 7.80 (s, 1H). LC-MS: 486 (M+1).

Synthesis of indolyl propargylic alcohols 1a-j.

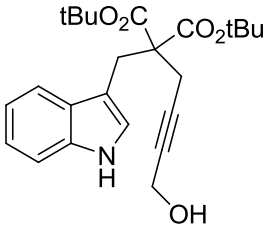
In a one-necked round bottom flask, the desired silyloxy compound **1'** was dissolved in 10 ml of reagent grade THF and then TBAF (1 eq.) was added at the reaction mixture. After stirring for 2-3 h, the reaction was monitored by TLC analysis and judged complete. After extractive work-up (H2O/AcOEt), the collected organic layers were dried over anhydrous Na2SO4 and concentrated under vacuum. The crude was purified by flash-chromatography.

1a. Yellow solid. Flash chromatography (CH2Cl2:MeOH = 95:5). Yield = 80%. Mp: 80- 82 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.2 Hz, 6H); 2.82 (s, 2H); 3.57 (s, 2H); 4.10-4.29 (m, 4H); 4.30 (s, 2H); 7.03 (d, J = 2.0 Hz,1H); 7.11 (ddd, J1 = 18.6 Hz, J2 = 8.0 Hz, J3 = 1.2 Hz, 2H); 7.32 (d, J = 1.2 Hz, 1H); 7.64 (d, J = 8.0 Hz, 1H); 8.28 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9(2C), 23.1, 27.3, 50.9, 58.2, 61.6(2C), 81.4, 82.0, 109.4, 111.1, 118.7, 119.3, 121.9, 123.6, 128.0, 135.8, 170.3(2C). LC-MS: 340 (M-H2O); 358 (M+1); 380 (M+Na). Anal. calcd for (C20H23NO5: 357.40): C, 67.21; H, 6.49; N: 3.92. Found: C, 67.15; H, 6.50; N: 3.88.

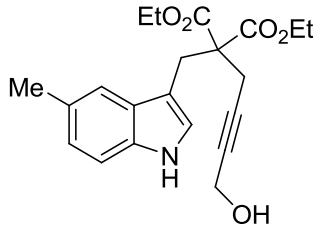




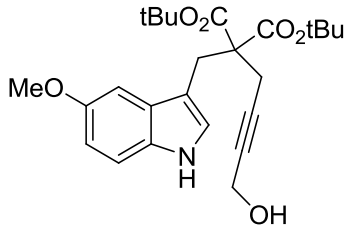
1b. Viscous yellow oil. Flash chromatography (DCM:MeOH = 95:5). Yield = 90%. ^{1}H-NMR (400 MHz,$CDCl_3$) δ: 2.86 (s, 2H); 3.56 (s, 2H); 3.67 (s, 6H); 4.27 (t, J = 2.0 Hz, 2H); 7.00 (d, J = 2.0 Hz, 1H); 7.10 (ddd, J1 = 18.0 Hz, J2 = 8.0 Hz, J3 = 1.2 Hz, 2H); 7.28 (d, J = 8.0 Hz, 1H); 7.59 (d, J = 8.0 Hz ,1H); 8,31 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.1, 27.5, 51.0, 52.7, 52.8(2C), 81.1, 82.1, 109.1, 111.1, 118.6, 119.4, 121.9, 123.6, 127.9, 135.8, 170.7(2C). LC-MS: 330 (M+1); 352 (M+Na). Anal. calcd for (C18H19NO5: 329.35): C, 65.64; H, 5.81; N: 4.25. Found: C, 65.55; H, 5.70; N: 4.10.



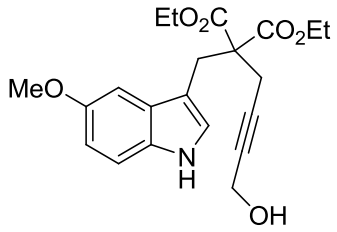
1c. White solid. Flash chromatography (DCM:MeOH = 95:5). Yield = 72%. Mp: 117-119 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 18H); 2.76 (s, 2H); 3.48 (s, 2H); 4,28 (s, 2H); 7.04 (s, 2H); 7.13 (ddd, J1 = 17.0 Hz, J2 = 8.0 Hz, J3 = 1.2 Hz, 2H); 7.31 (dd, J = 8.0 Hz, J_2 = 1.2 Hz, 1H); 7.77 (d, J = 8.0 Hz, 1H); 8.13 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.2, 26.7, 27.8(6C), 51.3, 52.8, 81.6(2C), 81.8, 82.2, 110.1, 110.9, 119.3, 121.9(2C), 123.2, 128.4, 135.7, 169.5(2C). LC-MS: 302 (M-CO2*t*Bu); 436 (M+Na). Anal. calcd for (C24H31NO5: 413.51): C, 69.71; H, 7.56; N: 3.39. Found: C, 69.68; H, 7.43; N: 3.25.



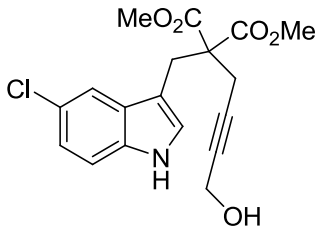
1d. Yellow amorphous solid. Flash chromatography (DCM:MeOH = 95:5). Yield = 91%. ^{1}HNMR (400 MHz,$CDCl_3$) δ: 1.26 (t, J = 7.2 Hz, 6H); 2.44 (s, 3H); 2.83 (t, J = 2.0 Hz, 2H); 3.55 (s, 2H); 4.12-4.24 (m, 4H); 4.31 (s, 2H); 6.99-7.01 (m, 2H); 7.22 (d, J = 8.4 Hz, 1H); 7.45 (s, 1H); 7.96 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.1(2C), 21.6, 23.2, 27.4, 51.3, 58.2, 61.8 (2C), 81.6, 82.2, 108.9, 110.9, 118.6, 123.6, 123.8, 128.4, 128.6, 134.3, 170.5(2C). LC-MS: 372 (M+1), 394 (M+Na). Anal. calcd for (C21H25NO5: 371.43): C, 67.91; H, 6.78; N: 3.77. Found: C, 67.80; H, 6.66; N: 3.85.



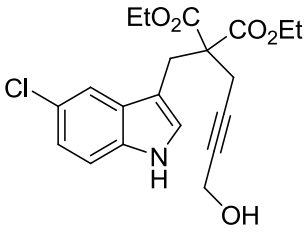
1dd. White solid. Flash chromatography (*c*Hex:AcOEt = 7:3). Yield = 82%. Mp: 146 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 18); 2.74 (t, J = 2.0 Hz, 2H); 3.44 (s, 2H); 3.87 (s, 3H); 4.28 (s, 2H); 6.83 (dd, J1 = 9.2 Hz, J2 = 2.4 Hz, 1H); 6.98 (d, J = 2.0 Hz, 1H); 7.20 (d, J = 9.2 Hz, 1H); 7.31 (d, J = 2.4 Hz, 1H); 8.06 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.1, 26.8, 27.8 (6C), 51.1, 55.9, 59.4, 81.7, 81.8 (2C), 82.3, 101.3, 109.8, 111.6, 112.1, 123.9, 129.0, 130.9, 153.9, 169.5 (2C). LC-MS: 446 (M+Na). Anal. calcd for (C25H33NO6: 443.53): C, 67.70; H, 7.50; N: 3.16. Found: C, 67.61; H, 7.58; N: 3.12



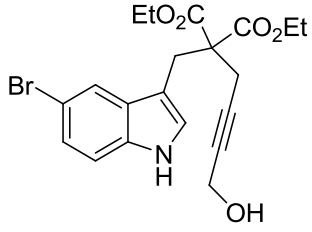
1e. Viscous orange oil. Flash chromatography (DCM:MeOH = 95:5). Yield = 45%. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.2 Hz, 6H); 2.8 (s, 2H); 3.53 (s, 2H); 3.86 (s, 3H); 4.16 (q, J = 7.2 Hz, 4H); 4.30 (s, 2H); 6.83 (dd, J1 = 8.4 Hz, J2 = 2.4 Hz, 1H); 6.97 (d, J = 2.4 Hz, 1H); 7.20 (dd, J1 = 5.8 Hz, J2 = 2.8 Hz 2H); 8.10 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.1, 30.9, 51.1, 55.8, 58.5, 60.4, 61.6(2C), 81.7, 82.0, 100.9, 109.4, 111.7, 112.2, 124.1, 128.7, 131.0, 154.0, 170.2(2C). LC-MS: 388 (M+1), 410 (M+Na). Anal. calcd for (C21H25NO6: 387.43): C, 65.10; H, 6.50; N: 3.62. Found: C, 65.01; H, 6.45; N: 3.70.



1f. Viscous yellow oil. Flash chromatography (DCM:MeOH = 95:5). Yield = 51% .^{1}HNMR (400 MHz, $CDCl_3$) δ: 2.80 (t, J = 2.0 Hz, 2H); 3.54 (s, 2H); 3.74 (s, 6H); 4.33 (t, J = 2.4 Hz, 2H); 7.07 (d, J = 2.4 Hz, 1H); 7.13 (d, J = 2.0 Hz, 1H); 7.26 (d, J = 2.0 Hz, 1H); 7.62 (d, J = 2.0 Hz, 1H); 8.10 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.1, 27.3, 51.3, 52.8, 58.0(2C), 81.3, 82.3, 109.4, 112.1, 118.5, 122.4, 124.9, 125.4, 134.2, 159.0, 170.4(2C). LC-MS: 364 (M+1), 386 (M+Na). Anal. calcd for (C18H18ClNO5: 363.79): C, 59.43; H, 4.99; N: 3.85.Found: C, 59.27; H, 5.06; N: 3.66.

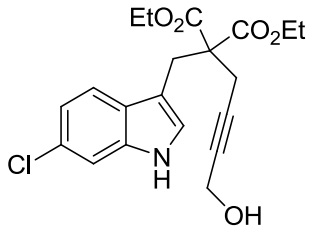


1g. White solid. Flash chromatography (DCM:MeOH = 95:5). Yield = 60%. Mp = 107-109°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.26 (t, J = 7.2 Hz, 6H); 2.79 (t, J = 2.0 Hz, 2H); 4.12 (s, 2H); 4.12-4.24 (m, 4H); 4.33 (dt, J1 = 4.0 Hz, J2 = 2.0 Hz, 2H), 7.08 (d, J = 2.4 Hz, 1H), 7.12 (dd, J1 = 8.8 Hz, J2 = 2.0 Hz, 1H); 7.14 (s, 1H); 7.26 (d, J = 2.8 Hz, 1H); 7.65 (d, J = 2.0 Hz, 1H); 8.12 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0(2C), 23.0, 27.1, 51.3, 57.9, 61.8(2C), 81.5, 82.2, 112.1, 118.5, 122.3, 124.8, 125.3, 129.2, 132.0, 134.1, 170.1(2C). LC-MS: 392 (M+1), 414 (M+Na). Anal. calcd for (C20H22ClNO5: 391.85): C, 61.30; H, 5.66; N: 3.57. Found: C, 61.19; H, 5.70; N: 3.40.

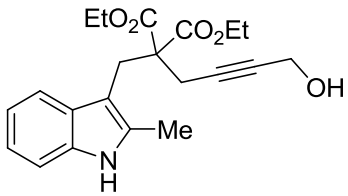


1h. Yellow solid. Flash chromatography (DCM:MeOH = 95:5). Yield = 74%. Mp = 124-126 °C. 1H-NMR (400 MHz, $CDCl_3$) δ: 1.27 (t, J = 7.2 Hz, 6H); 2.79 (s, 2H); 3.53 (s, 2H); 4.12- 4.22 (m, 4H); 4.33 (s, 2H); 7.05 (d, J = 2.4 Hz, 1H); 7.22 (dd, J1 = 20.8 Hz, J2 = 8.0 Hz, 2H); 7.79 (s, 1H); 8.24 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9(2C),

22.9, 27.0, 51.2, 57.8, 61.8(2C), 81.3, 82.2, 109.2, 112.5, 112.7, 121.6, 124.7, 124.7, 129.8, 134.4, 170.1(2C). LCMS: 436 (M), 437(M+1), 438 (M+2). Anal. calcd for (C20H22BrNO5: 436.30): C, 55.06; H, 5.08; N: 3.21. Found: C, 55.11; H, 5.12; N: 3.10.



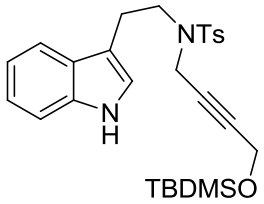
1i. Viscous white oil. Flash chromatography (DCM:MeOH = 95:5). Yield = 60%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.2 Hz, 6H); 2.81 (t, J = 1.6 Hz, 2H), 3.53 (s, 2H); 4.12-4.24 (m, 4H); 4.31 (s, 2H); 7.04 (d, J = 2.0 Hz, 1H); 7.07 (dd, J1 = 8.4 Hz, J2= 1.6 Hz, 1H); 7.33 (d, J = 1.6 Hz, 1H); 7.56 (d, J = 8.0 Hz, 1H); 8.12 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0(2C), 23.1, 27.2, 51.3, 58.1, 61.7(2C), 81.4, 82.1, 109.9, 111.0, 119.8, 120.3, 124.1, 126.7, 128.0, 136.2, 170.1(2C). LC-MS: 414 (M+Na). Anal. calcd for (C20H22ClNO5: 391.85): C, 61.30; H, 5.66; N: 3.57. Found: C, 61.33; H, 5.75; N: 3.51.



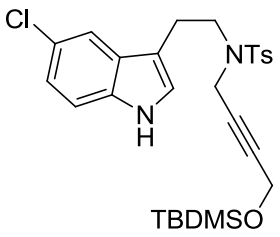
1j. Viscous orange oil. Flash chromatography (DCM:MeOH = 95:5). Yield = 74%. ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.15 (t, J = 7.2 Hz, 6H); 2.27 (s, 3H); 2.73 (s, 3H); 3.44 (s, 2H); 4.12 (q, J = 7.2 Hz, 4H); 4.22 (s, 2H); 6.96-7.00 (m, 2H); 7.13 (d, J = 8.0 Hz, 1H); 7.50 (d, J = 8.0 Hz, 1H); 7.85 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.0, 13.9(2C), 23.1, 26.8, 51.2, 58.6, 61.6(2C), 81.9, 82.0, 105.5, 110.0, 118.3, 119.1, 121.1, 129.3, 133.6, 135.2, 170.5(2C). LC-MS: 371 (M+1); 394 (M+Na). Anal. calcd for (C21H25NO5: 371.43): C, 67.91; H, 6.78; N: 3.77. Found: C, 67.95; H, 6.70; N: 3.67.

Synthesis of indolyl alcohols 4.

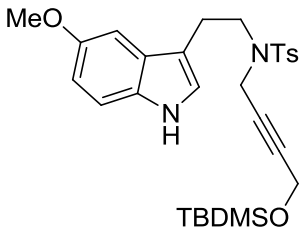
In a Schlenk tube equipped with a magnetic stirring bar, (4-bromo-but-2-ynyloxy)-*tert*-butyl-dimethyl-silane **A** (1.2 eq.), was added to the corresponding *N*-tosyl tryptamine (1 eq.), K_2CO_3 (2 eq.) dissolved in 5 ml of acetone. The reaction mixture was stirred at 60 °C for 12 h, and then quenched with water. The aqueous layer was extracted with ethyl acetate (3× 15 ml). The combined organic layers were dried with Na2SO4 and the solvents evaporated under vacuum. The residue was purified by flash-chromatography.



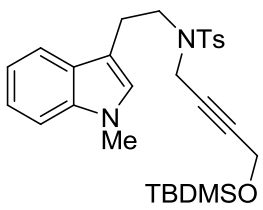
4a'. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 80:20). Yield = 50%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.05 (s, 6H); 0.87 (s, 9H); 2.40 (s, 3H); 3.08 (t, J = 7.6 Hz, 2H); 3.51 (t, J = 7.6 Hz, 2H); 4.08 (s, 2H); 4.20 (s, 2H); 7.10-7.24 (m, 5H); 7.37 (d, J = 8.1 Hz, 1H); 7.62 (d, J = 7.6 Hz, 1H); 7.73 (d, J = 8.0 Hz, 2H); 8.01 (s, 1H). LC-MS: 497 (M+1).



4b'. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 80:20). Yield = 35%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.05 (s, 6H); 0.87 (s, 9H); 2.41 (s, 3H); 3.02 (t, J = 7.2 Hz, 2H); 3.48 (t, J = 7.2 Hz, 2H); 4.11 (t, J = 2.0 Hz, 2H); 4.19 (t, J = 2.0 Hz, 2H); 7.15 (pt, J = 2.0 Hz, 2H); 7.26-7.28 (m, 4H); 7.52 (d, J = 2.0 Hz, 1H); 7.33 (d, J = 8.0 Hz, 1H); 8.07 (s, 1H). LC-MS: 533 (M+1).

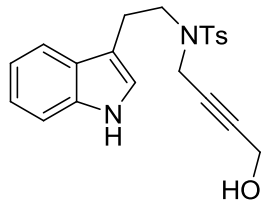


4c'. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 90:10). Yield = 37%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.048 (s, 6H); 0.88 (s, 9H); 2.40 (s, 3H); 3.31 (t, J = 8.4 Hz, 2H); 3.49 (t, J = 8.4 Hz, 2H); 3.88 (s, 3H); 3.96 (t, J = 2.0 Hz, 2H); 4.18 (t, J = 2.0 Hz, 2H); 6.87 (dd, J1 = 8.4 Hz, J2 = 2.4 Hz, 1H); 7.07 (dd, J1 = 8.4 Hz, J2 = 2.4 Hz, 1H); 7.24- 7.28 (m, 3H); 7.72 (d, J = 7.2 Hz, 2H); 7.92 (br, 1H). LC-MS: 527 (M+1), 549 (M+Na).

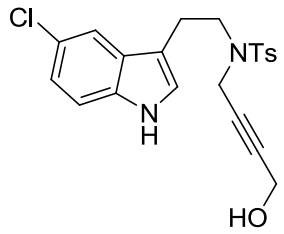


4d'. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 91:9). Yield = 44%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.048 (s, 6H); 0.88 (s, 9H); 2.40 (s, 3H); 3.06 (t, J = 7.2 Hz, 2H); 3.49 (t, J = 7.2 Hz, 2H); 3.75 (s, 3H); 4.08 (t, J = 2.0 Hz, 2H); 4.21 (t, J = 2.0 Hz, 2H); 6.94 (s, 1H); 7.09-7.13 (m, 1H); 7.22-7.31 (m, 5H); 7.60 (d, J = 8.0 Hz, 2H); 7.71 (d, J = 8.0 Hz, 2H). LC-MS: 533 (M+Na).

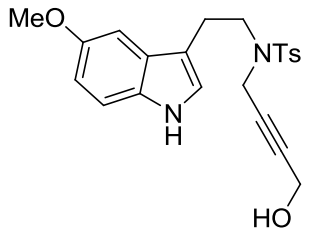
The cleavage of the silyl protecting group was performed in analogy to the previously described method for **1'**.



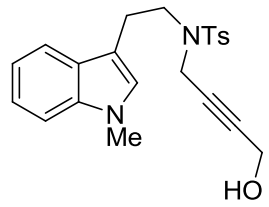
4a. White solid. Flash-chromatography (DCM:MeOH = 95:5). Yield: 70%. Mp = 109-111 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H); 2.99 (t, J = 7.6 Hz, 2H); 3.43 (t, J = 7.6 Hz, 2H); 3.90 (s, 2H); 4.08 (s, 2H); 7.00-7.13 (m, 5H); 7.28 (d, J = 7.2 Hz, 1H); 7.52 (d, J = 7.2 Hz, 1H); 7.64 (dd, J1 = 6.6 Hz, J2 = 2.0 Hz, 2H); 8.01 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.5, 24.4, 37.1, 47.1, 50.7, 78.8, 83.7, 111.2, 112.3, 118.6, 119.4, 122.1, 122.3, 127.2, 127.8(2C), 129.4(2C), 135.9, 136.2, 143.5. LC-MS: 383 (M+1),405 (M+Na). Anal. calcd for ($C_{21}H_{22}N_2O_3S$: 382.48): C, 65.95; H, 5.80; N: 7.32. Found: C, 65.88; H, 5.89; N: 7.22.



4b. Pale yellow wax. Flash-chromatography (DCM:MeOH = 95:5). Yield: 60%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.41 (s, 3H); 2.99 (t, J = 8.0 Hz, 2H); 3.48 (t, J = 8.0 Hz, 2H); 4.05 (s, 2H); 4.16 (s, 2H); 7.11 (s, 1H); 7.13 (d, J = 2.0 Hz, 1H); 7.26-7.28 (m, 3H); 7.51 (d, J = 1.6 Hz, 1H); 7.71 (d, J = 8.0 Hz, 2H); 8.27 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.6, 24.2, 37.1, 46.9, 50.9, 78.8, 84.1, 112.2, 112.4, 118.2, 122.5, 123.9, 125.3, 127.9 (2C), 128.5, 129.6 (2C), 134.6, 135.9, 143.7. LC-MS: 439 (M+Na). Anal. calcd for ($C_{21}H_{21}ClN_2O_3S$: 416.92): C, 60.50; H, 5.08; N: 6.72. Found: C, 60.41; H, 5.00; N: 6.85.



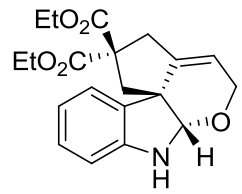
4c. Yellow viscous oil. Flash-chromatography (*c*Hex:EtOAc = 60:40). Yield: 71%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H); 3.04 (t, J = 8.0 Hz, 2H); 3.50 (t, J = 8.0 Hz, 2H); 3.87 (s, 3H); 4.00 (s, 2H); 4.19 (s, 2H); 6.87 (dd, J1 = 8.4 Hz, J2 = 2.4 Hz, 1H); 7.06 (d, J = 2.4 Hz, 1H); 7.14 (d, J = 2.4 Hz, 1H); 7.25-7.27 (m, 3H); 7.73 (d, J = 8.0 Hz, 2H); 8.00 (br, 1H). ^{13}CNMR (100 MHz, $CDCl_3$) δ: 21.4, 24.4, 37.1, 46.8, 50.6, 56.1, 78.6, 84.0, 101.4, 111.6, 111.9, 111.9, 123.2, 127.7(2C), 129.4(2C), 131.5, 135.9, 143.5, 153.8. LC-MS: 413 (M+1), 435 (M+Na). Anal. calcd for (C22H24N2O3S: 412.50): C, 64.06; H, 5.86; N: 6.79. Found: C, 64.15; H, 5.79; N: 6.71.



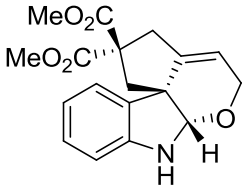
4d. White wax. Flash-chromatography (DCM:MeOH = 95:5). Yield: 43%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.41 (s, 3H); 3.07 (t, J = 7.2 Hz, 2H); 3.50 (t, J = 7.2 Hz, 2H); 3.76 (s, 3H); 3.99 (s, 2H); 4.19 (t, J = 1.6 Hz, 2H); 6.96 (s, 1H); 7.11 (ddd, J1 = 8.0 Hz, J2 = 7.2 Hz, J3 = 1.2 Hz, 1H); 7.23-7.51 (m, 4H); 7.60 (d, J = 8.0 Hz, 1H); 7.73 (dd, J1 = 6.8 Hz, J2 = 2.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 24.3, 29.7, 37.1, 47.2, 50.8, 78.9, 83.7, 109.3 110.7, 118.7, 118.9, 121.7, 127.0, 127.7, 127.9, 129.3(2C); 136.0, 137.0, 143.5. LC-MS: 397 (M+1). Anal. calcd for (C22H24N2O3S: 396.50): C, 66.64; H, 6.10; N: 7.07. Found: C, 66.55; H, 6.01; N: 7.15

General procedure for the gold-catalyzed diastereoselective domino cyclization.

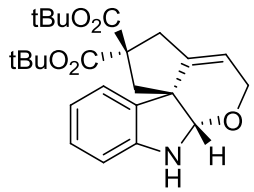
In a 10 ml two-necked round bottomed flask, substrate **1/4** (0.2 mmol) was dissolved 1.0 ml of dry, followed by theaddition of catalyst **3b** (5 mol%). The mixture was stirred overnight at rt, then the crude directly charged into a plug ofsilica for flash-chromatography purification.



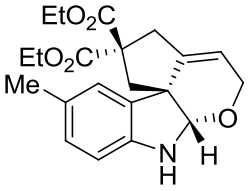
2a. White wax. Flash chromatography (*c*Hex:AcOEt = 7:3). Yield = 74%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.18-1.21 (m, 6H); 2.37 (d, J = 14.4 Hz, 1H); 2.89 (d, J =14.0 Hz, 1H); 3.03 (d, J = 15.2 z, 1H); 3.62 (dd, J1 = 15.3 Hz, J2 = 3.6 Hz, 1H); 4.08 (s, 2H); 4.18-4.37 (m, 4H); 4.97 (s, 1H); 5.71 t, J = 3.6 Hz, 1H); 6.68 (d, J = 8.0 Hz, 1H); 6.73 (pt, J = 8.0 Hz, 1H); 7.06 (dd, J1 = 14.4 Hz, J2 = 7.5 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.0, 41.0, 45.1, 52.3, 57.8, 1.1, 61.8, 61.9, 93.4, 109.6, 119.3, 19.6, 123.2, 127.9, 135.0, 137.5, 148.4, 171.5, 171.7. LC-MS: 358 (M+1); 380 (M+23). Anal. calcd for (C20H23NO5: 7.40): C, 67.21; H, 6.49; N: 3.92. Found: C, 7.40; H, 6.31; N: 3.92.



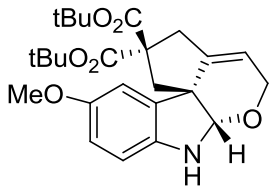
2b. Pale yellow oil. Flash chromatography (*c*Hex:AcOEt = 6:4). Yield = 75%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ2.41 (d, J = 14.4 Hz, 1H); 2.87 (d, J = 14.0 Hz, 1H); 3.05 (d, J = 15.6 Hz, 1H); 3.63 (dd, J1 = 15.6 Hz, J2 = 3.2 Hz, 1H); 3.71 (s, 3H); 3.76 (s, 3H); 4.08 (dd, J1 = 5.2 Hz, J2 = 2.8 Hz, 2H); 4.96 (s, 1H); 5.72 (d, J = 2.8 Hz, 1H); 6.66 (d, J = 0.8 Hz, 1H); 6.74 (t, J = 6.4 Hz, 1H); 7.03-7.07 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 41.0, 45.1, 52.3, 53.0, 53.1, 61.1, 93.3, 109.6, 119.4, 119.6, 123.1, 127.9, 134.8, 137.3, 148.4, 156.3, 171.9, 172.2. LC-MS: 330 (M+1), 352 (M+Na).Anal. calcd for (C18H19NO5: 329.36): C, 65.64; H, 5.81; N: 4.25. Found: C, 65.60; H, 5.96; N: 4.19.



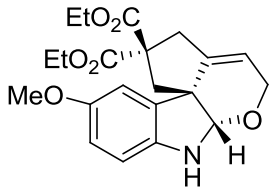
2c. White solid. Flash chromatography (*c*Hex:AcOEt = 85:15). Yield = 81%. Mp = 155-157 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (s, 9H); 1.41 (s, 9H); 2.25 (d, J = 14.0 Hz, 1H); 2.82 (d, J = 14.0 Hz, 1H); 2.91 (d, J = 15.2 Hz, 1H); 3.55 (dd, J1 = 15.2 Hz, J2 = 2.4 Hz, 1H); 4.08 (s, 2H); 4.95 (s, 1H); 5.67 (t, J = 2.4 Hz, 1H); 6.71 (dt; J1 = 15.2 Hz, J2 = 8.0 Hz, 2H); 7.01-7.10 (m, 2H). ^{13}CNMR (100 MHz, $CDCl_3$) δ: 27.7(3C), 27.8(3C), 40.8, 44.9, 52.3, 59.1, 61.2, 81.6, 93.4, 109.6, 118.8, 119.6, 123.3, 127.7, 135.2, 137., 170.5, 170.9. LC-MS: 414 (M+1); 436 (M+Na). Anal. calcd for (C24H31NO5: 412.51): C, 69.71; H, 7.56; N: 3.39. Found: C, 69.75; H, 7.44; N: 3.21.



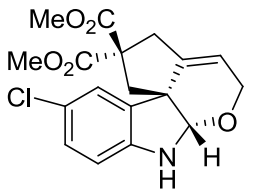
2d. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 7:3). Yield = 70%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.20 (t, J = 7.2 Hz, 6H); 2.31 (d, J = 14.0 Hz, 1H); 2.89 (d, J = 14.0, Hz, 1H); 3.02 (d, J = 15.6 Hz, 1H); 3.61 (dd, J1 = 15.6 Hz, J2 = 2.0 Hz, 1H); 3.73 (s, 3H); 4.13-4.93 (m, 4H); 4.24 (s, 2H); 4.90 (s, 1H); 5.70 (t, J = 2.0 Hz, 1H); 6.61 (d, J = 1.6 Hz, 2H); 6.73 (pt, J = 1.6 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.0, 20.9, 41.1, 44.9, 52.3, 57.9, 61.3, 61.7, 61.8, 93.6, 109.4, 119.3, 123.9, 128.2, 128.9, 135.3, 137.6, 146.0, 171.4, 171.7. LC-MS: 372 (M+1), 394 (M+Na). Anal. calcd for (C21H25NO5: 371.43): C, 67.91; H, 6.78; N: 3.77. Found: C, 67.83; H, 6.69; N: 3.60.



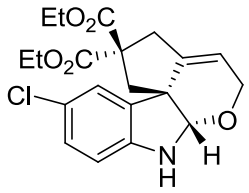
2dd.Pale pink solid. Mp = 128 °C. Flash chromatography (*c*Hex:AcOEt = 6:4). Yield = 51%.^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.43 (s, 9H); 1.44 (s, 9H); 2.2 (d, J = 14.0 Hz, 1H); 2.80 (d, J = 13.6 Hz, 1H); 2.88 (d, J = 16.0 Hz, 1H); 3.57 (dd, J1 = 16.0 Hz, J2 = 3.2 Hz, 1H); 3.73 (s, 3H); 4.10 (d, J = 1.6 Hz, 2H); 4.88 (s, 1H); 5.66 (d, J = 2.4 Hz, 1H); 6.10 (d, J = 1.2 Hz, 2H); 6.76 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.7 (3C), 27.8 (3C), 40.7,44.5, 52.9, 55.8, 58.9, 61.6, 81.6, 81.7, 94.0, 110.2, 110.3, 112.9, 118.9, 136.5, 137.3, 141.9, 153.9, 170.6, 170.9. LC-MS: 447. Anal. calcd for (C25H33NO6: 443.53): C, 67.70; H, 7.50; N: 3.16. Found: C, 67.55; H, 7.48; N: 3.22.



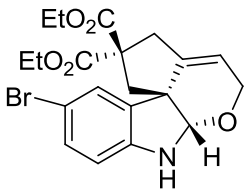
2e. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 7:3). Yield = 45%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.20 (t, J = 7.2 Hz, 6H); 2.31 (d, J = 14.0 Hz, 1H); 2.89 (d, J = 14.0 Hz, 1H); 3.02 (d, J = 15.6 Hz, 1H); 3.61 (dd, J1 = 15.6 Hz, J2 = 2.0 Hz, 1H); 3.73 (s, 3H); 4.12-4.22 (m, 4H); 4.24 (s, 2H); 4.90 (s, 1H); 5.70 (t, J = 2.0 Hz, 1H); 6.61 (d, J = 1.6 Hz, 2H); 6.73 (pt, J = 1.6 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.0, 40.9, 44.6, 52.8, 55.9, 57.7, 61.5, 61.8, 61.9, 93.9, 110.1, 110.4, 112.7, 119.3, 136.3, 137.1, 142.0, 153.9, 171.4, 171.7. LC-MS: 388 (M+1). Anal. calcd for (C21H25NO6: 387.43): C, 65.10; H, 6.50; N: 3.62. Found: C, 65.23; H, 6.41; N: 3.78.



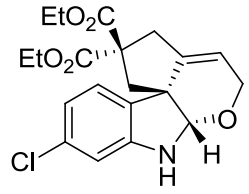
2f. White wax. Flash chromatography (*c*Hex:AcOEt = 6:4). Yield = 75%.^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.38 (d, J = 14.0 Hz, 1H); 2.85 (d, J = 14.0 Hz, 1H); 3.08 (d, J =15.6 Hz, 1H); 3.57 (dt, J1 = 16.0 Hz, J2 = 2.8 Hz, 1H); 3.76 (s, 6H); 4.08 (t, J = 2.8 Hz, 2H); 4.93 (s, 1H); 5.74 (t, J = 2.8 Hz, 1H); 6.59 (d, J = 8.0 Hz, 1H); 7.01 (d, J = 10.4 Hz, 1H); 7.27 (d, J = 3.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.9, 40.9, 44.9, 52.5, 53.1, 61.4, 65.8, 93.5, 110.4, 119.9, 123.6, 124.1, 127.7(2C), 136.7, 147.9 , 171.7, 172.2. LC-MS: 364 (M+1); 386 (M+Na). Anal. calcd for (C18H18ClNO5: 363.79): C, 59.43; H, 4.88; N: 3.85. Found: C, 59.33; H, 4.97; N: 3.73.



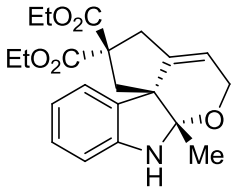
2g. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 7:3). Yield = 75%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.27 (t, J = 7.2 Hz, 6H); 2.36 (d, J = 14.4 Hz, 1H); 2.87 (d, J = 14.0 Hz, 1H); 3.06 (d, J = 15.6 Hz, 1H); 3.56 (dd, J1 = 15.6 Hz, J2 = 2.8 Hz, 1H); 4.07-4.09 (m, 2H); 4.17-4.25 (m, 4H); 4.93 (s, 1H); 5.73 (dd, J1 = 5.4 Hz, J2 = 2.4 Hz, 1H); 6.58-6.60 (m, 1H); 6.99-7.02 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.0, 40.9, 44.8, 52.5, 57.8, 61.4, 61.9, 62.0, 93.5, 110.4(2C), 119.8, 123.6, 124.1, 127.7, 136.9, 147.1, 171.2, 171.6. LC-MS: 414 (M +Na). Anal. calcd for (C20H22ClNO5: 391.85): C, 61.30; H, 5.66; N: 3.57. Found: C, 61.21; H, 5.54; N: 3.45.



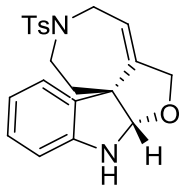
2h. White solid. Flash chromatography (*c*Hex:AcOEt = 7:3). Yield = 75%. Mp = 155-157 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.2 Hz, 6H); 2.36 (d, J = 14.4 Hz, 1H); 2.86 (d, J = 14.4 Hz, 1H); 3.06 (d, J = 15.6 Hz, 1H); 3.55 (dd, J1 = 15.6 Hz, J2 = 2.4 Hz, 1H); 4.08 (s, 2H); 4.17-4.26 (m, 4H); 4.93 (s, 1H); 5.73 (s, 1H); 6.55 (dd, J1 = 6.4 Hz, J2 = 2.0 Hz, 1H); 7.15 (dd, J1 = 7.2 Hz, J2 = 2.0 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.0, 40.9, 42.7, 44.8, 52.5, 57.8, 61.3, 61.9, 93.4, 111.0, 119.8,m126.4, 130.5, 136.9, 137.2, 147.6, 169.2, 171.2, 171.6. LC-MS: 436 (M); 437 (M+1); 438 (M+2). Anal. calcd for (C20H22BrNO5: 436.30): C, 55.06; H, 5.08; N: 3.21. Found: C, 55.17; H, 4.99; N: 3.12.



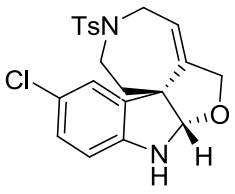
2i. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 6:4). Yield = 78%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.27 (t, J = 7.2 Hz, 6H); 2.33 (d, J = 14.0 Hz, 1H); 2.87 (d, J = 14.8 Hz, 1H); 3.02 (d, J = 15.6 Hz, 1H); 3.58 (dd, J1 = 15.8 Hz, J2 = 2.8 Hz, 1H); 4.06 (s, 2H); 4.12-4.22 (m, 4H); 4.97 (s, 1H); 5.72 (d, J = 2.8 Hz, 1H); 6.65 (s, 1H); 6.68 (d, J = 8.0 Hz, 1H); 6.96 (d, J = 8.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0, 14.1, 40.8, 45.0, 51.8, 57.7, 61.1(2C), 61.9, 93.5, 109.8, 119.3, 119.5, 124.0, 133.6, 135.6, 137.2, 149.7, 171.4, 171.6. LC-MS: 414 (M+Na). Anal. calcd for (C20H22ClNO5: 391.85): C, 61.30; H, 5.66; N: 3.57. Found: C, 61.35; H, 5.73; N: 3.46.



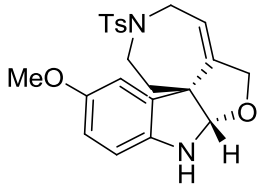
2j. Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 7:3). Yield = 58%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.20 (t, J = 7.2 Hz, 6H); 1.53 (s, 3H); 2.36 (d, J = 14.0 Hz, 1H); 2.94 (d, J = 14.0 Hz, 1H); 3.02 (d, J = 15.6 Hz, 1H); 3.62 (d, J = 16.0 Hz, 1H); 4.03 (d, J = 16.0 Hz, 1H); 4.13-4.26 (m, 5H); 5.62 (pt, J = 3.8 Hz, 1H); 6.64 (d, J = 8.0 Hz, 1H); 6.70 (pt, J = 7.2 Hz, 1H); 7.01-7.08 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.0, 18.8, 40.7, 42.8, 54.6, 57.1, 60.9, 61.8(2C), 95.2, 109.7, 117.5, 119.5, 123.2, 127.6, 136.8, 137.4, 147.4, 171.7, 172.0. LC-MS: 371 (M+1); 394 (M+Na). Anal. calcd for (C21H25NO5: 371.43): C, 67.91; H, 6.78; N: 3.77. Found: C, 67.85; H, 6.59; N: 3.71.



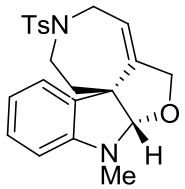
5a. White solid. Flash-chromatography (*c*Hex:AcOEt = 7:3). Yield: 76%. Mp = 109-111 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.85 (dt, J1 = 12.6 Hz, J2 = 3.6 Hz, 1H); 2.00 (td, J1 = 12.0 Hz, J2 = 4.0 Hz, 1H); 2.34 (s, 3H); 3.27 (dt, J1 = 12.6 Hz, J2 = 3.6 Hz, 1H); 3.53 (td, J1 = 12.0 Hz, J2 = 4.0 Hz, 1H); 3.77 (dd, J1 = 16.4 Hz, J2 = 4.0 Hz, 1H); 4.10 (dd, J1 = 16.4 Hz, J2 = 5.6 Hz, 1H); 4.21 (s, 2H); 5.05 (s, 1H); 5.68 (t, J = 5.6 Hz, 1H); 6.61 (d, J = 7.6 Hz, 1H); 6.74 (pt, J = 7.6 Hz, 1H); 7.06 (pt, 8.0 Hz, 1H); 7.19-7.28 (m, 2H); 7.41 (d, J = 7.6 Hz, 1H); 7.63(d, J = 8.0 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.5, 29.7, 32.6, 45.5, 59.1, 72.2, 100.9, 109.7, 117.5, 119.6, 126.6, 127.3(2C), 128.9, 129.4, 129.8(2C), 136.1, 143.5, 146.5, 148.5. LC-MS: 383 (M+1), 405 (M+Na). Anal. calcd for (C21H22N2O3S: 382.48): C, 65.95; H, 5.80; N: 7.32. Found: C, 65.88; H, 5.69; N: 7.22.



5b.White solid. Flash-chromatography (*c*Hex:AcOEt = 7:3). Yield: 60 % Mp = 100-103 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.94 (dt, J1 = 14.0 Hz, J2 = 3.6 Hz, 1H); 2.07 (dd, J1 = 14.0 Hz, J2 = 4.8 Hz, 1H); 2.46 (s, 3H); 3.38 (dt, J1 = 9.6 Hz, J2 = 4.0 Hz, 1H); 3.58 (dt, J1 = 12.8 Hz, J2 = 2.8 Hz, 1H); 3.88 (dd, J1 = 15.2 Hz, J2 = 4.8 Hz, 1H); 4.14-4.19 (m, 1H); 4.29-3.30 (m, 2H); 4.73 (s, 1H); 5.15 (s, 1H); 5.77-5.80 (m, 1H); 6.60 (d, J = 8.0 Hz, 1H); 7.09 (dd, J1 = 8.0 Hz, J2 = 1.6 Hz, 1H); 7.35 (d, J = 7.6 Hz, 2H); 7.46 (d, J = 2.0 Hz, 1H); 7.72 (d, J = 7.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.5, 23.3, 32.6, 45.4, 45.6, 55.1, 59.1, 72.2, 73.5, 79.4, 86.7, 101.2, 110.5, 118.3, 126.7, 127.3(2C), 128.8, 129.8(2C), 131.4, 143.6, 147.1. LC-MS: 417 (M+1), 439 (M+Na). Anal. calcd for (C21H21ClN2O3S: 416.92): C, 60.50; H, 5.08; N: 6.72. Found: C, 60.41; H, 5.19; N: 6.62.

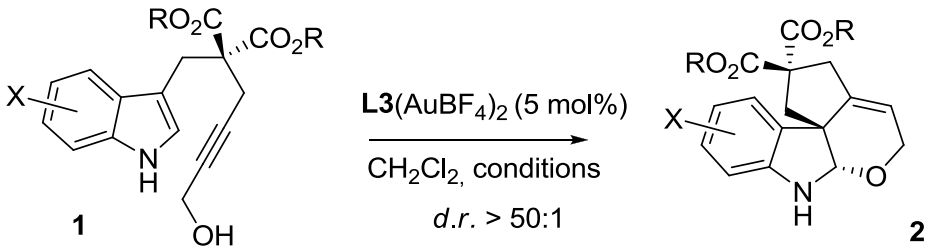


5c. White solid. Flash-chromatography (*c*Hex:AcOEt = 65:35). Yield: 52%. Mp = 72-74 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.99 (dq, J1 = 14.0 Hz, J2 = 3.2 Hz, 1H); 2.01 (dd, J1 = 7.2 Hz, J2 = 5.2 Hz, 1H); 2.46 (s, 3H); 3.05-3.15 (m, 1H); 3.19 (dp, J1 = 14.0 Hz, J2 = 7.2 Hz, 1H); 3.51 (dd, J1 = 8.0 Hz, J2 = 5.2 Hz, 1H); 3.68-3.72 (m, 1H); 3.82 (s, 3H); 4.21 (m, 2H); 5.23 (s, 1H); 5.67-5.69 (m, 1H); 6.61 (d, J = 8.8 Hz, 1H); 6.67 (dd, J1 = 8.8 Hz, J2 = 6.4 Hz, 1H); 6.85 (s, 1H); 7.35 (d, J = 7.6 Hz, 2H); 7.70 (d, J = 7.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.5, 26.9, 32.1, 45.3, 45.4, 56.1, 72.2, 101.6, 110.6, 112.3, 115.2, 117.9, 127.4(2C), 129.6, 129.8(2C), 142.3, 143.6, 146.1, 154.1. LC-MS: 413 (M+1), 435 (M+Na). Anal. calcd for (C22H24N2O3S: 412.50): C, 64.06; H, 5.86; N: 6.79. Found: C, 64.00; H, 5.85; N: 6.85.



5d. White solid. Flash-chromatography (*c*Hex:AcOEt = 8:2). Yield = 53%. Mp = 160-162 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.85 (dt, J1 = 14.0 Hz, J2 = 3.6 Hz, 1H); 1.98 (td, J1 = 11.6 Hz, J2 = 3.6 Hz, 1H); 2.38 (s, 3H); 2.88 (s, 3H); 3.26-3.29 (m, 1H); 3.54 (td, J1 = 12.4 Hz, J2 = 4.0 Hz, 1H); 3.78 (dd, J1 = 16.4 Hz, J2 = 4.0 Hz, 1H); 4.09-4.13 (m, 2H); 4.17-4.21 (m, 1H); 4.92 (s, 1H); 5.66 (t, J = 4.8 Hz, 1H); 6.41 (d, J = 7.6 Hz, 1H); 6.67 (pt, J = 7.6 Hz, 1H); 7.10 (t, J = 7.6 Hz, 1H); 7.27 (d, J = 7.6 Hz, 1H); 7.35 (d, J = 6.4 Hz, 1H); 7.63 (d, J = 8.0 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 24.3, 26.7, 37.1, 47.2, 50.8, 54.1, 78.9, 83.7, 109.3, 110.7, 118.6, 118.9, 121.7, 127.0, 127.6, 127.9(2C), 129.3(2C), 136.7, 140.0, 143.4. LC-MS: 397 (M+1). Anal. calcd for (C22H24N2O3S: 396.50): C, 66.64; H, 6.10; N: 7.07. Found: C, 66.41; H, 6.00; N: 7.01.

General procedure for the catalytic enantioselective synthesis of (6a*R*,11b*R*)-alkyl 3,5,6a,7-tetrahydrocyclopenta[3,4]pyrano[2,3-*b*]indole-2,2(1H)-dicarboxylate 2



To a flamed two-necked round bottom flask, connected to the line of inert gas, were added in sequence 1 mL of anhydrous CH2Cl2, (*R*)-xylyl-binap (2.1 mg, 5 mol%, **L3**), and AuCl·DMS (1.6 mg, 10 mol%). After stirring for 30 min the volatiles were removed under vacuum ad the flask left under vacuum for 30 min. The flask was covered with an aluminium foil, then CH2Cl2 (1 mL). After 15 min stirring, 1.1 mg of AgBF4 followed by the desired he indolyl alcohol **1** (0.05 mmol). After stirring the reaction crude in the dark for the indicated time and temperatures (see below), the crude was directly charged into a column for flash chromatographic purification.

(6a*R*,11b*R*)-**2a**. White wax. Flash chromatography (*c*Hex:AcOEt = 7:3). Yield = 89% (eluent: *c*-Hex:AcOEt = 80:20). *Ee* = 86%. $[\alpha]_D$ = -35.7° (*c* = 0.7, CH_2Cl_2, *ee* = 84%). Chiral HPLC: OD-H column, *n*Hex:IPA = 90:10, flow = 1.0 mL/min, 40 °C, Rt(6*S*,11*S*) = 20.2 min, Rt(6*R*,11*R*) = 21.1 min. Anal. calcd for (C20H23NO5: 357.40): C, 67.21; H, 6.49; N: 3.92. Found: C, 67.40; H, 6.31; N: 3.92.

(6a*R*,11b*R*)-**2b**. Pale yellow oil. Flash chromatography (*c*Hex:AcOEt = 6:4). Yield = 60%. *Ee* = 76%. $[\alpha]_D$ = -45.8 (*c* = 0.8, $CHCl_3$, *ee* = 76%). Chiral HPLC: OD-H column, *n*Hex:IPA = 90:10, flow = 0.5 mL/min, 40 °C, Rt(6a*R*,11b*R*) = 18.2 min, Rt(6a*S*,11b*S*) = 20.8 min. Anal. calcd for (C18H19NO5: 329.36): C, 65.64; H, 5.81; N: 4.25. Found: C, 65.60; H, 5.96; N: 4.19.

(6a*R*,11b*R*)-**2c**. White solid. Flash chromatography (*c*Hex:AcOEt = 85:15). Yield = 65%. *Ee* = 87%. %. $[\alpha]_D$ = -47.4° (*c* = 1.4, CH_2Cl_2 , *ee* = 76%). Chiral HPLC: OD-H column, *n*Hex:IPA = 95:5, flow = 0.5 mL/min, 40 °C, Rt(6*S*,11*S*) = 13.3 min, Rt(6*R*,11*R*) = 14.0 min. Anal. calcd for (C24H31NO5: 412.51): C, 69.71; H, 7.56; N: 3.39. Found: C, 69.75; H, 7.44; N: 3.21.

(6a*R*,11b*R*)-**2dd**. Pale pink solid. Mp = 128 °C. Flash chromatography (*c*Hex:AcOEt = 6:4). Yield = 51%. %. *Ee* = 77%. $[\alpha]_D$ = -16.1 (*c* = 0.5, $CHCl_3$, *ee* = 77%). Chiral HPLC: OD-H column, *n*Hex:IPA = 90:10, flow = 0.5 mL/min, 40 °C, Rt(6a*S*,11b*S*) = 5.8 min, Rt(6a*R*,11b*R*) = 6.5 min.

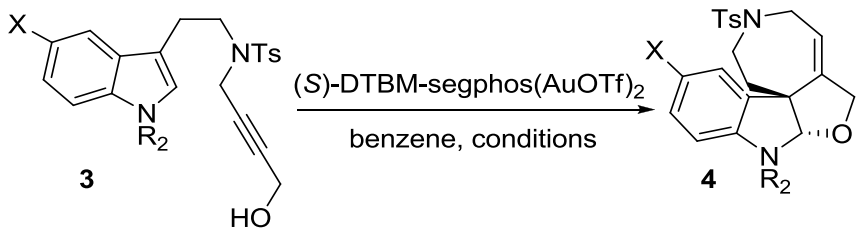
(6a*R*,11b*R*)-**2e.** Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 7:3). Yield = 50%. *Ee* = 76%. $[\alpha]_D$ = -29.2 (*c* = 0.6, $CHCl_3$, *ee* = 70%). Chiral HPLC: IA column, *n*Hex:IPA = 85:15, flow = 0.7 mL/min, 40 °C, Rt(6a*R*,11b*R*) = 18.8 min, Rt(6a*S*,11b*S*) = 23.6 min. Anal. calcd for (C21H25NO6: 387.43): C, 65.10; H, 6.50; N: 3.62. Found: C, 65.23; H, 6.41; N: 3.78.

(6a*R*,11b*R*)-**2f.** White wax. Flash chromatography (*c*Hex:AcOEt = 6:4). Yield = 58%. *Ee* = 83%. $[\alpha]_D$ = -14.4 (*c* = 1.0, $CHCl_3$, *ee* = 82%). Chiral HPLC: OD-H column, *n*Hex:IPA = 90:10, flow = 0.7 mL/min, 40 °C, Rt(6a*S*,11b*S*) = 21.8 min, Rt(6a*R*,11b*R*) = 22.9 min. Anal. calcd for (C18H18ClNO5: 363.79): C, 59.43; H, 4.88; N: 3.85. Found: C, 59.33; H, 4.97; N: 3.

(6a*R*,11b*R*)-**2h.** White solid. Flash chromatography (*c*Hex:AcOEt = 7:3). Yield = 75%. *Ee* = 81%. $[\alpha]_D$ = -33.1 (*c* = 0.4, $CHCl_3$, *ee* = 68%). Chiral HPLC: IA column, *n*Hex:IPA = 70:30, flow = 1.0 mL/min, 40 °C, Rt(6a*R*,11b*R*) = 9.1 min, Rt(6a*S*,11b*S*) = 13.1 min. Anal. calcd for (C20H22BrNO5: 436.30): C, 55.06; H, 5.08; N: 3.21. Found: C, 55.17; H, 4.99; N: 3.12.

(6a*R*,11b*R*)-**2i.** Viscous yellow oil. Flash chromatography (*c*Hex:AcOEt = 6:4). Yield = 67%. *Ee* = 84%. $[\alpha]_D$ = -21.5 (*c* = 0.2, $CHCl_3$, *ee* = 84%). Chiral HPLC: OJ column, *n*Hex:IPA = 80:20, flow = 0.5 mL/min, 40 °C, Rt(6a*S*,11b*S*) = 27.6 min, Rt(6a*R*,11b*R*) = 41.2 min. Anal. calcd for (C20H22ClNO5: 391.85): C, 61.30; H, 5.66; N: 3.57. Found: C, 61.35; H, 5.73; N: 3.46.

General procedure for the catalytic enantioselective synthesis of the (7a*S*,12b*R*)-3-tosyl-2,4,6,7a,8-hexahydro-1H-azepino[4',5':3,4]furo[2,3-b]indole-4.



To a flamed two-necked round bottom flask, connected to the line of inert gas, were added in sequence 1 mL of anhydrous CH2Cl2, (*S*)-DTBM-segphos (2.8 mg, 5 mol%), and AuCl·DMS (1.5 mg, 10 mol%). After stirring for 30 min the volatiles were removed under vacuum and the flask left under vacuum for 30 min. After covering the flask with an aluminium foil, anhydrous benzene was added (1 mL) followed by 20 mg of activated 4Å MS. After 15 min stirring, 1.3 mg of AgOTf was added and the reactor cooled to 10 °C. Finally, the indolyl alcohol **3** (19 mg, 0.05 mmol) was added at once, and the mixture was gently stirred at the same temperature overnight. The crude was directly charged into a column for flash chromatographic purification.

(7a*S*,12b*R*)-4a. White solid. Reaction time: 16 h, reaction temperature: 25 °C. Flash-chromatography (*c*Hex:AcOEt = 7:3). Yield: 62%. *Ee* = 85%. $[\alpha]_D$ = -65.8° (*c* = 1.8, $CHCl_3$, *ee* = 80%). Chiral HPLC: IA column, *n*Hex:IPA = 65:35, flow = 0.6 mL/min, 40 °C, Rt(7*S*,12*R*) = 27.0 min, Rt(7*R*,12*S*) = 31.1 min. Anal. calcd for (C21H22N2O3S: 382.48): C, 65.95; H, 5.80; N: 7.32. Found: C, 65.88; H, 5.69; N: 7.22.

(7a*S*,12b*R*)-4b.White solid. Reaction time: 16 h, reaction temperature: 25 °C. Flash-chromatography (*c*Hex:AcOEt = 7:3). Yield: 67%. *ee* = 82%. $[\alpha]_D$ = -97.7 (*c* = 0.5, $CHCl_3$, *ee* = 68%). Chiral HPLC: IA column, *n*Hex:IPA = 70:30, flow = 0.7 mL/min, 40 °C, Rt(7*S*,12*R*) = 18.1 min, Rt(7*R*,12*S*) = 28.6 min. Anal. calcd for (C21H21ClN2O3S: 416.92): C, 60.50; H, 5.08; N: 6.72. Found: C, 60.41; H, 5.19; N: 6.62

5. Gold Catalyzed synthesis and functionalization of [1,2-*a*]azepino-indoles

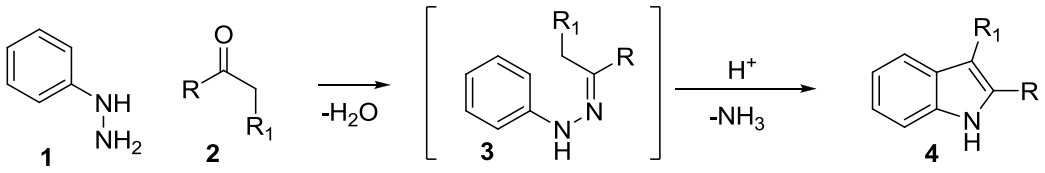
5.1 Synthesis and functionalization of indole cores

Indole is one of the most abundant heteroaromatic compound found in nature, and is ranked third (after benzene and pyridine) amongst the most prevalent architectures found in bioactive molecules. In this context, nevertheless well established classical procedures like the Fisher indole synthesis, the diversity of indoles as well as their biological and pharmaceutical relevance, is still motivating academic and industrial researchers to look for new and improved synthesis for indole derivatives.[1]

More recently, especially transition metal catalysis has become a powerful tool synthetic tool for the indole synthesis. For example, with the aid of catalysis the formation of C-N bonds via addition of nitrogen-containing nucleophiles across C-C unsaturated bonds can be easily realized. More specifically, the electrophilic activation of alkynes in the presence of late transition metal complexes and subsequent intramolecular as well as intermolecular addition reactions has become a popular strategy to prepare functionalized indoles. In this context, it is not surprising even to note an increase of activity in the development of sustainable methods not only for the synthesis but also for a further functionalization of the indolyl core.

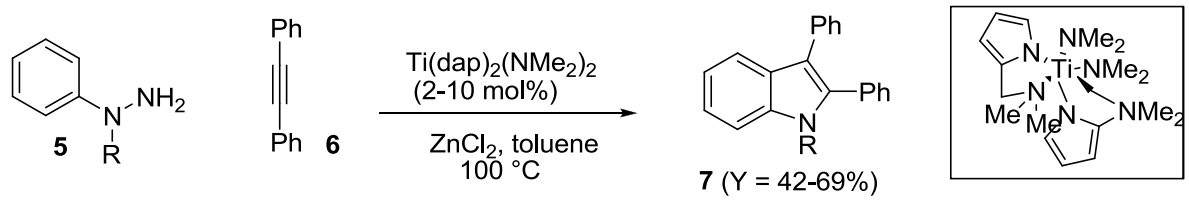
5.2. Indole synthesis: Electrophilic activation of alkynes.

Since its discovery in 1883, the Fischer indole reaction has remained an essential method for the synthesis of a variety of indoles via cyclization of N-arylhydrazones **3** generated by the condensation of arylhydrazines **1** with ketones **2** (Scheme 5.1).



Scheme 5.1 *Fischer indole synthesis.*

More recently the catalytic hydrohydrazination has become a feasible method for its synthesis as reported by Odom which described the first catalytic procedure (Scheme 5.2).[2]



Scheme 5.2 *Titanium catalyzed Fisher indole synthesis.*

Notably, the arylhydrazones obtained underwent further Fischer indole reaction by in situ addition of $ZnCl_2$ to provide N-alkyl- and N–arylindoles **7** in high yields.

Another attractive methodology for the one pot synthesis of 2,3-disubstituted indoles is the so-called Larock heteroannulation process.

In 1991, Larock reported this useful method for the preparation of indoles for the first time.[3]

Here a palladium-catalyzed heteroannulation of internal alkynes with N-protected *o*-iodo-anilines **8** gave the corresponding derivative **10** (Figure 5.3).

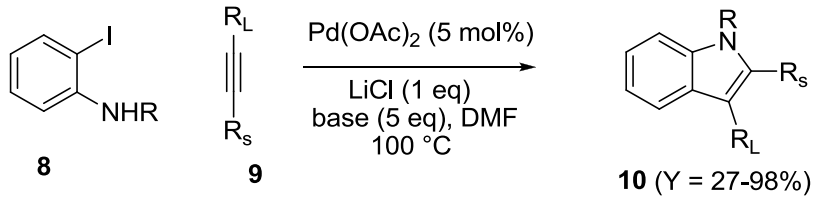
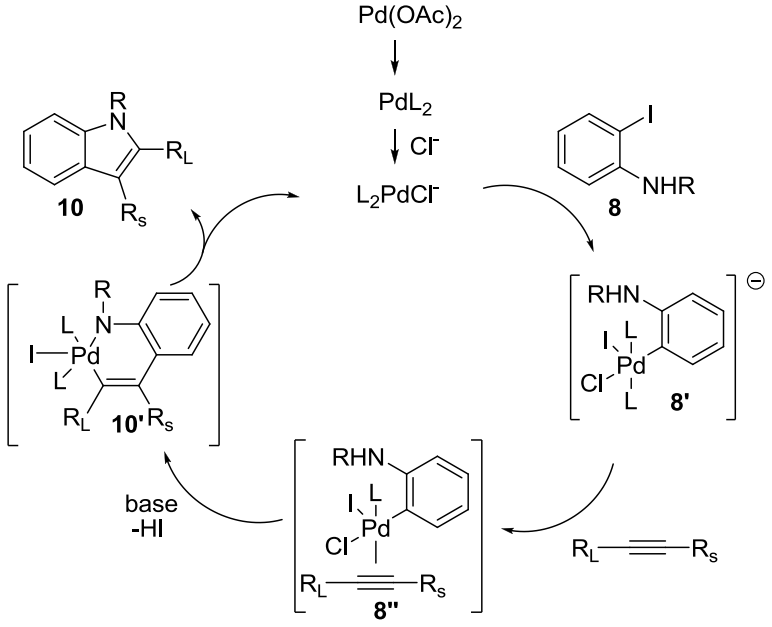


Figure 5.3. *The Larock heteroannulation for the synthesis of 2,3-disubstituted indoles.*

The cyclization is regioselective with unsymmetrical alkynes, wherein the more sterically hindered group (R_L) of the alkyne is recovered in the 2-position of the indole.

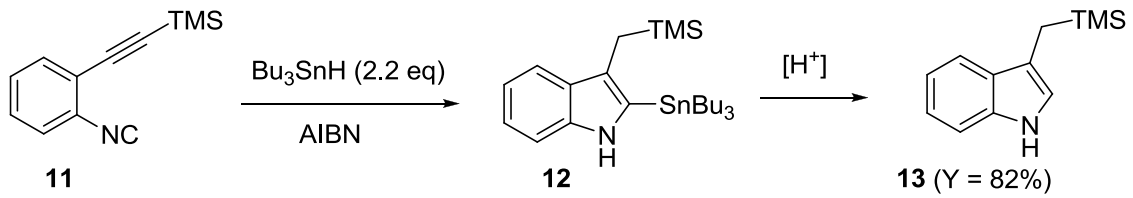
The reaction involves the reduction of $Pd(OAc)_2$ to an active Pd(0) species. Oxidative addition of Pd(0) to the aryl iodide and coordination of the alkyne to the palladium centre gave the aryl-Pd intermediate **8''**(Scheme 5.4).



Scheme 5.4 *Mechanism for the Larock heteroannulation.*

Then, the more sterically demanding group (R_L) is inserted away from the sterically encumbered aryl group. Subsequent regioselective *syn*-insertion into the aryl-Pd bond, nitrogen displacement of the halide in the resulting vinylic Pd intermediate to form a six-membered palladacycle **10'**, and reductive elimination leads the indole **10** with regeneration of the active catalyst.

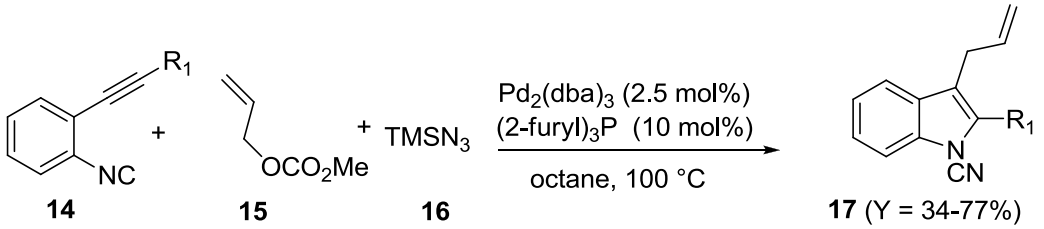
Isocyanides provide an additional nitrogen source as starting material for the synthesis of the indole skeleton. Based on the Fukayama isonitrile-alkene free-radical coupling reaction, the group of Rainier developed an analogous alkyne-iso-nitrile free-radical reaction for the synthesis of indoles (Scheme 5.5).[4]



Scheme 5.5. *Synthesis of indoles from o-alkynylaryl isocyanides via radical cyclization.*

Starting from aryl isocyanides **11** having a suitably positioned alkyne, 5-*exo*-dig radical cyclization provided the indolenine intermediate **12**. The resulting 2-stannylindole can be destannylated by acidic work-up to afford the 3-substituted indole **13**.

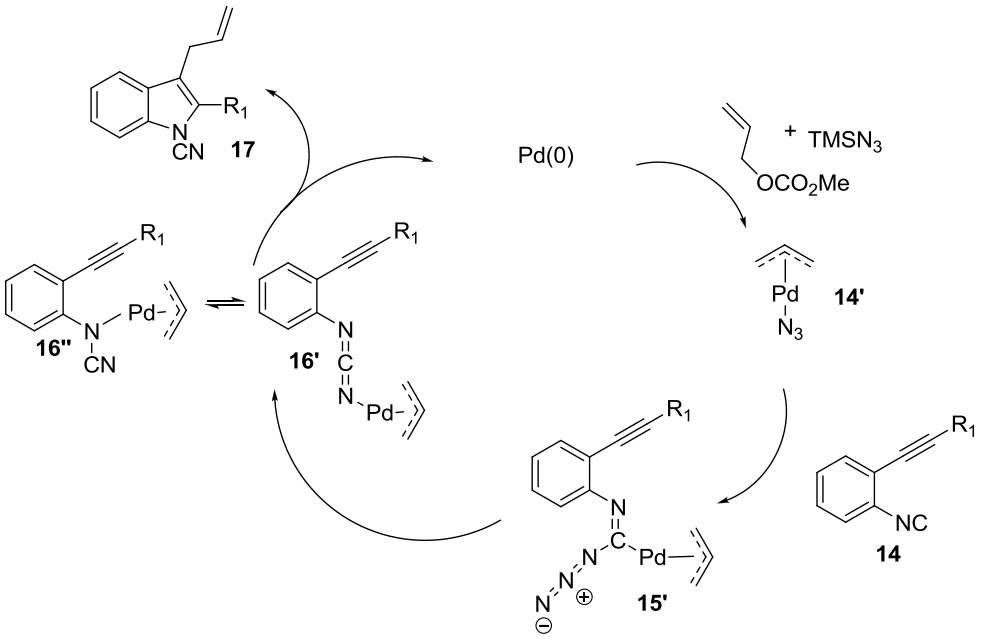
Moreover, *o*-alkynylphenyl isocyanides have been employed for the synthesis of various substituted N-cyanoindoles via coupling of aryl isocyanides **14**, allylmethyl carbonate, and trimethylsilyl azide **16** (Scheme 5.6).[4b]



Scheme 5.6. *Multicomponent coupling reaction for the synthesis of N-cyanoindoles.*

The proposed mechanism for this multicomponent coupling reaction is shown in Scheme 5.7. Initially, π-allylpalladium azide **14'** is formed through the reaction of Pd(0) with allyl methyl carbonate **15** and $TMSN_3$ **16**. Then, reaction with the isocyanide **14** generates the π-allylpalladium intermediate **15'**.

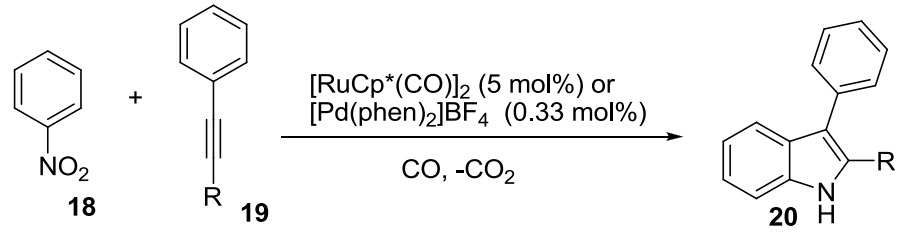
Release of N2 followed by 1,2-migration provides the palladium-carbodiimide complex **16'** via a π-allylpal- ladium mimic of the Curtius rearrangement.



Scheme 5.7. *Proposed mechanism for the synthesis of N –cyanoindoles.*

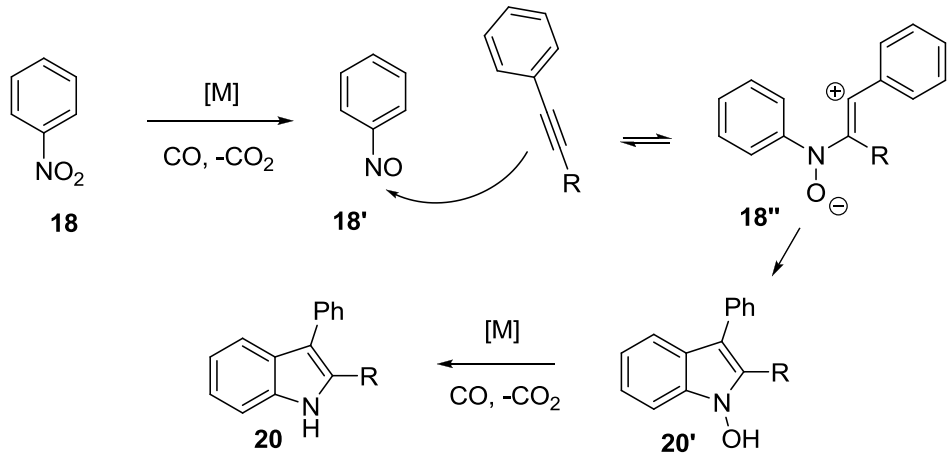
The palladium-carbodiimide complex **16'** is in equilibrium with the palladium-cyanamide complex **16''**. Finally, The N –cyanoindoles **17** are formed through insertion of the alkyne moiety into the Pd-N bond of **16''** followed by reductive elimination of Pd(0).

A very interesting approach was developed Nicholas and Penoni reported a $[RuCp^*(CO)_2]_2$ - catalyzed cycloaddition reaction of nitroarenes **18** with alkynes **19** to give indoles **20** at high temperature (Scheme 5.7).[5] Although the reaction proceeded with excellent regioselectivity, the yields of the corresponding indoles were only moderate until a more reactive catalyst, palladium phenanthroline complex $[Pd(phen)_2]BF_4$ was developed for this transformation by Regaini.[6]



Scheme 5.7. *Ruthenium- and palladium-catalyzed reaction of nitroarenes with alkynes.*

Mechanistically, the catalytic reduction of nitroarene **18** with CO, initially produces nitrosoarene **18'** and CO2 as stoichiometric by-product (Scheme 5.8).



Scheme 5.8. *Mechanism for the reaction of alkynes with nitrosoarenes generated from nitroarenes.*

The nitrosoarene interacts reversibly with the alkyne to intermediate **18''**. Cyclization gives the corresponding N hydroxyindole **20'** which is reduced in a last step to the indole **20** in the presence of CO and the catalyst. The radical character of the intermediate adduct explains the need for an aryl group on the alkyne, wherein the aryl ring stabilizes charges or a radical in the α-position.

5.3. Indole synthesis: cyclization of ortho-alkynyl aniline derivatives.

The transition metal-catalyzed hydroamination of *o*-alkynylaniline derivatives has become an established approach for the preparation of 2-substituted indoles. This method usually requires two steps: 1) introduction of the alkynyl moiety to give arene through Sonogashira reactions and 2) a subsequent cyclization reaction (Figure 5.9) Throughout the last decade numerous examples have been reported for indole syntheses from o-alkynylaniline derivatives, including basic conditions, ammonium fluoride-mediated reactions, and transition metal-catalyzed reactions.

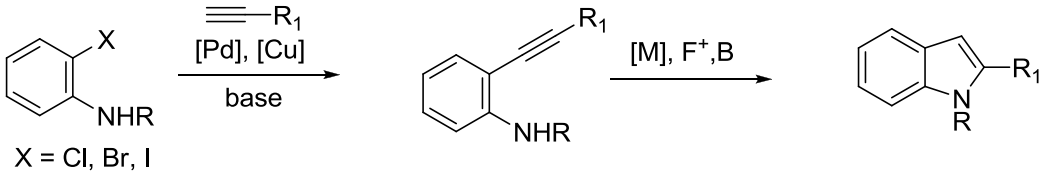


Figure 5.9. *Metal, base and fluorine mediated hydroamination of o-alkynyl-anilines.*

It is well established that transition metal salts with π-acidity are able to activate the triple bond of an alkyne towards the addition of a nucleophilic amine mojety in order to synthesize an N-protected indole core with a substituent on the C2.

In this field, palladium complexes are amongst the most frequently used transition metal reagents for the ring closing reaction of *o*-alkynyl anilines. In the past years the work concentrated on the synthesis of 2,3-disubstituted indoles **23** via palladiumcatalyzed reactions of aryl iodides, bromides, and triflates with o-alkynyltrifluoroacetanilides **21**. For example, Cacchi and co-workers published an extension of this procedure to aryl chlorides **22** (Figure 5.10).[7]

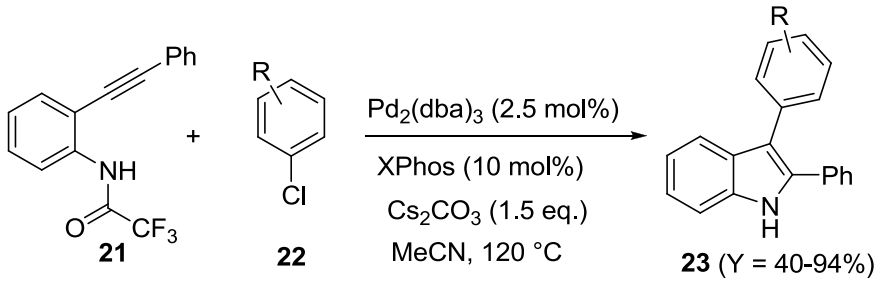


Figure 5.10. *Reaction of o-alkynyltrifluoroacetanilides with aryl chlorides.*

Nishizawa reported a cyclization reaction of *o*-alkynyl anilines using catalytic amounts of a [Hg(II)] salt. In agreement with the traditional work on alkyne activation, the reaction is initiated by π-complexation of the alkyne **24** with $Hg(OTf)_2$ (Figure 5.11).[8]

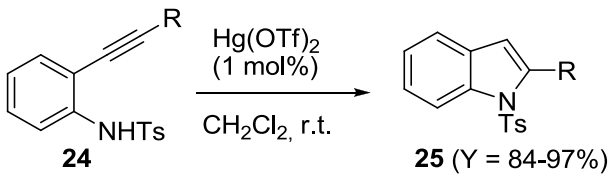


Figure 5.11 *$Hg(OTf)_2$-catalyzed indole cyclization.*

In spite of using $Hg(OTf)_2$ in catalytic amounts, the use of such toxic metals should be avoided in state-of-the-art organic synthesis.

As previously mentioned, gold catalysis arose to prominence in the last decade as a proven tool for the electrophilic activation of unsatured C-C bonds.

Hence, Marinelli reported the cyclization of o-alkynyl anilines in presence of $NaAuCl_4*H_2O$ using the ionic liquid [bmim]BF_4 as a potential environmentally benign reaction medium.[9]

With respect to gold catalysts, it is noteworthy that Li and co-workers developed a double hydroamination reaction of *o*-alkynylanilines **26** with terminal alkynes **27** leading to N-vinylindoles **28** (Figure 5.12).[10]

After optimization, the best result is obtained at room temperature without any solvent in the presence of an $AuCl_3$/AgOTf mixture.

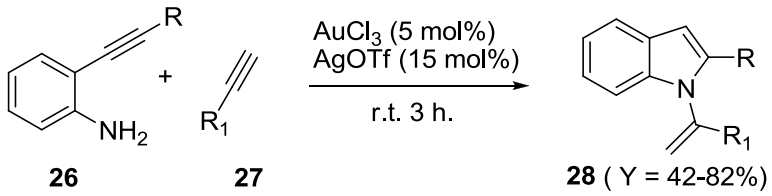
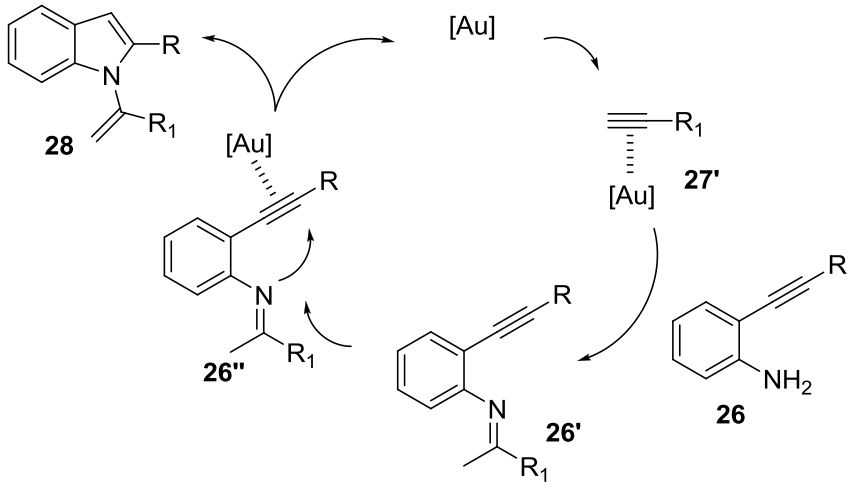


Figure 5.12 *Gold-catalyzed synthesis of N-vinylindoles.*

The proposed mechanism for the [Au(III)]-catalyzed double hydroamination involves the initial activation of alkyne **27** by [Au(III)] to generate intermediate **27'**. This reacts further with **26** to yield the first hydroamination product **26'**. Subsequently, the alkyne is again activated by [Au(III)] and produces intermediate **26''** via nucleophilic addition of the imine nitrogen.

After protonation at the C-3 position of the indole the final product **28** is formed and the catalyst is regenerated (Scheme 5.13).



Scheme 5.13 *Mechanistic proposal for the synthesis of N-vinylindoles by gold catalysis.*

However, catalytic methods that simultaneously address synthesis and derivatization of indoles are still far from common.[11] Some leading metal-assisted examples deal principally with the construction of the pyrrolyl ring with a final C3-functionalization through alkylations[12] or cross-coupling reactions.[13]

In this field the use of gold catalysis in the conversion of *o*-alkynyl anilines into indoles remains largely unexplored.

Arcadi described in a pioneristic work that a [Au(III)] salt in EtOH or EtOH-water mixture can lead to indoles in a very easy fashion starting from *o*-alkynyl-anilines.[14]

After that, many [Au]-catalytic methodologies for the one pot synthesis and functionalization of indole cores starting from ready available *o*-alkynyl-anilines were described.

5.4. State of the art.

With the evidence that gold catalyst were effective in promoting the coniugate addition reaction of indoles to α,β-enones **31**, Arcadi again reported a one-pot procedure for the sequential cyclization/ coniugate addition reaction of *o*-alkynyl-anilines **29** (Figure 5.14).[15]

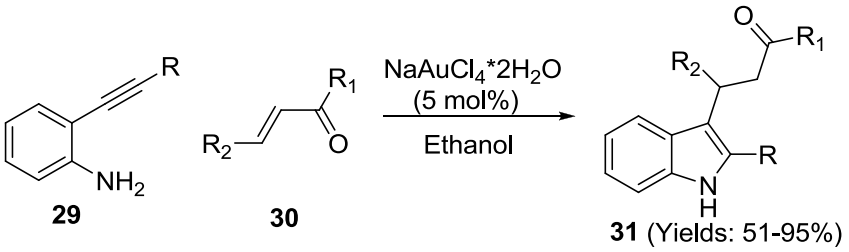
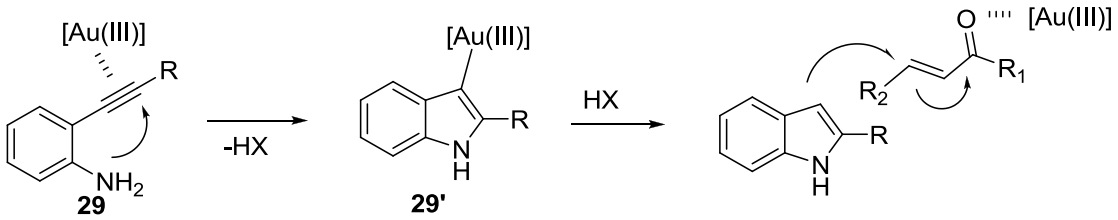


Figure 5.14. *[Au(III)]-catalyzed tandem hydroamination-Micheal addition.*

In this case unprotected anilines **29** performed chemoselectively in the Micheal-addition, preventing a gold-catalyzed competitive aza-Michael reaction with α,β-enones.
Mechanistically, [Au(III)] salt in this case is able to promote the first hydroamination step leading to the indole nucleus and then, after acidic protodeauration can behave as a Lewis acid (LA) activating the ketone moiety towards the α,β addition (Scheme 5.15).



Scheme 5.15 *Mechanism hypothisized for the tandem hydroamination-Micheal addition*

Waser developed a one-pot process in which it was possible to synthesize the indole ring and then to achieve the direct alkynylation starting from *o*-alkynyl-anilines **32** (Figure 5.16).[16]

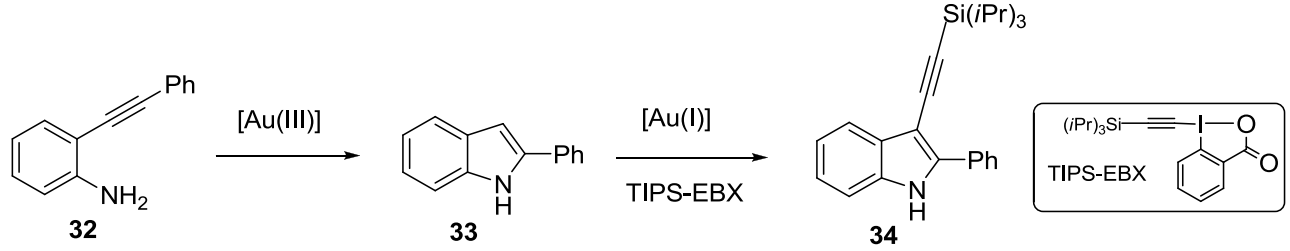
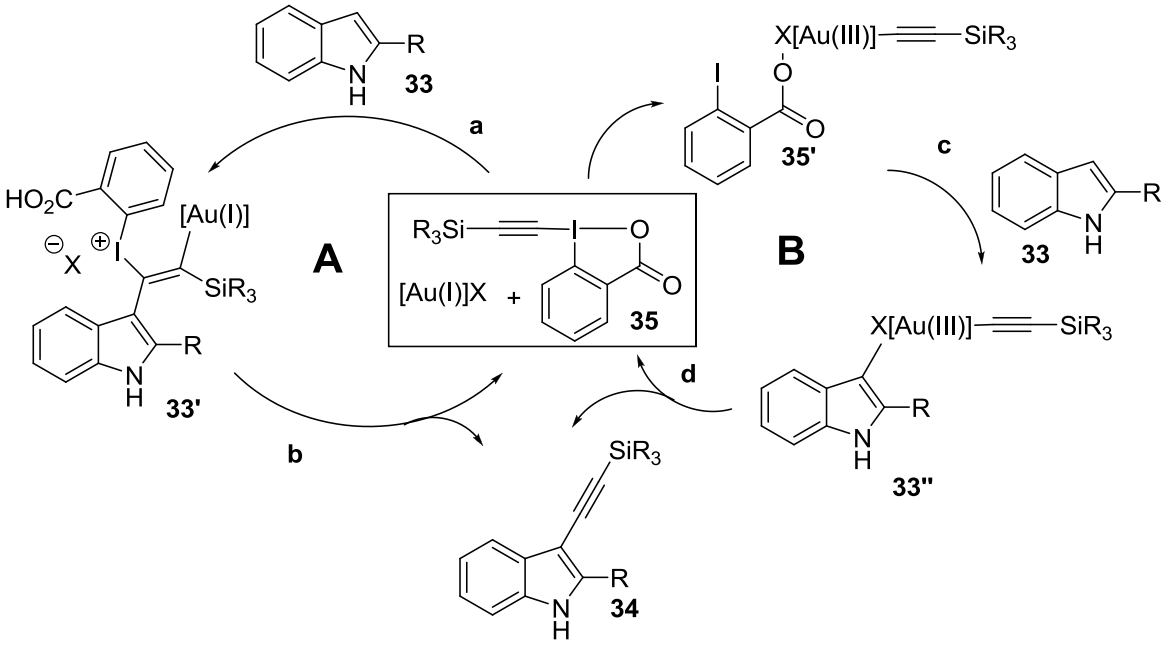


Figure 5.16 *[Au(I))/[Au(III)] tandem hydroamination/alkynylination sequence*

Two different type of different gold catalysts were employed in this transformation: $NaAuCl_4*2H_2O$ to promote the hydroamination of the triple bond and generate the indole and AuCl to catalyze the akynylation of the commercial available benziodioxolone TIPS-EBX. Mechanistically, for the alkynylation step two hypothesis were considered: path **A)** a gold mediated addition of the indole to the triple bond of the benzodioxolone **35**, to generate vinyl intermediate **33'**(**a**) which is able to generate product **34** after β-elimination (**b**) (Scheme 5.17).



Scheme 5.17. *Mechanism hypothesized for the gold mediated alkynylation.*

Differently, pathway **B** involves the oxidation of [Au(I)] to [Au(III)] by means of benzodioxolne **35** to produce a gold(III)-acetylene complex **35'**, followed by indole metalation (**c)** to give **33''** and final reductive elimination (**d**).

Furthermore, Ono described an atom-economical synthetic method for the generation of fused indoles **37**, using a gold-catalyzed cascade cyclization of diynes **36** through an intramolecular cascade 5-*endo*-dig cyclization followed by a 6- or 7- *endo*-dig cycloisomerization (Figure 5.18).[17]

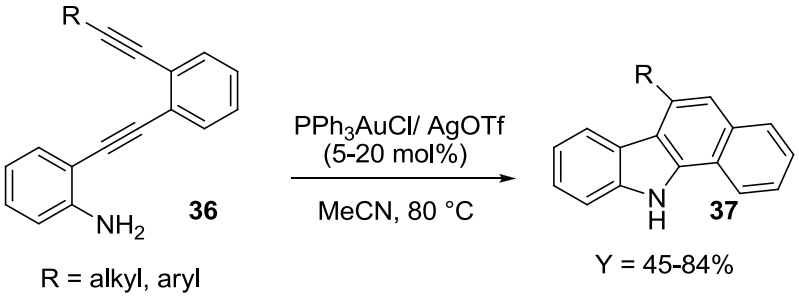


Figure 5.18 *[Au(I))-catalyzed dienynes cyclization towards indole synthesis*

This protocol was found to be very efficient towards the synthesis of a family of annulated carbazoles which showed good antifungal activity against *T.mentagrophytes* and *T. Rubrum.*

This methodology has been ascertained also for the synthesis of 7-membered-ring azepino- or oxepino [3,4-*b*]-indoles and cyclo-hepta-[*b*]-indole derivatives which are attractive drug templates.

Three dyine derivatives were synthesized and subjected to the catalytic system and the results are shown in the table below (Figure 5.18).

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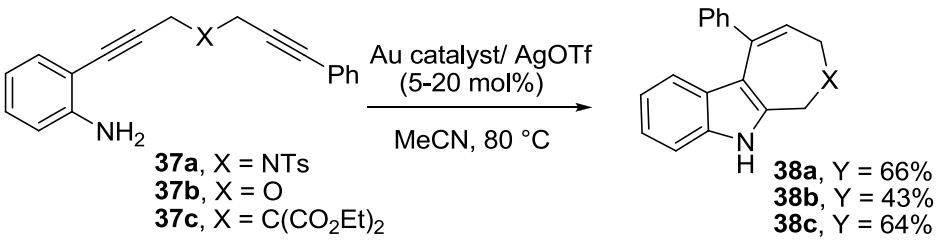
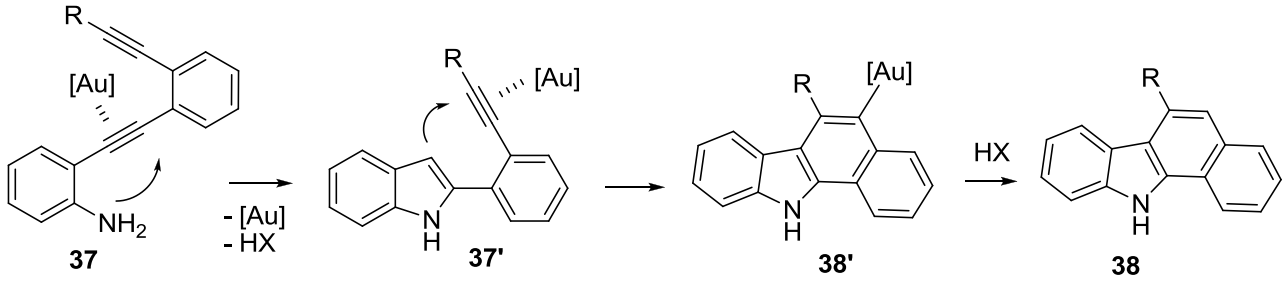


Figure 5.18 *Scope of the [Au(I)] catalyzed cyclization of dienynes.*

From a mechanistic point of view high alkynophilicity phosphine based gold complexes activated the alkyne between the two arene promoting a 5-*endo*-dig cyclization generating the indole ring **38** (Scheme 5.19).



Scheme 5.19. *Mechanism for the [Au(I)] catalyzed cyclization of dienynes.*

This is followed by proto-deauration to give the first cyclization product **37'**. Further activation of the second alkyne by the gold catalyst to synthesize **38** would lead to 6-*endo*-dig cyclization at the C-3 position of the indole and subsequent rearomatization to give arylgold intermediate **38'**. Finally, proto-deauration of **38'** would produce fused carbazole **38** by regenerating the active catalyst.

More recently Chan described the suitability of aniline-based propargylic alcohol as patterns to develop a versatile approach for indole synthesis (Figure 5.20).[18]

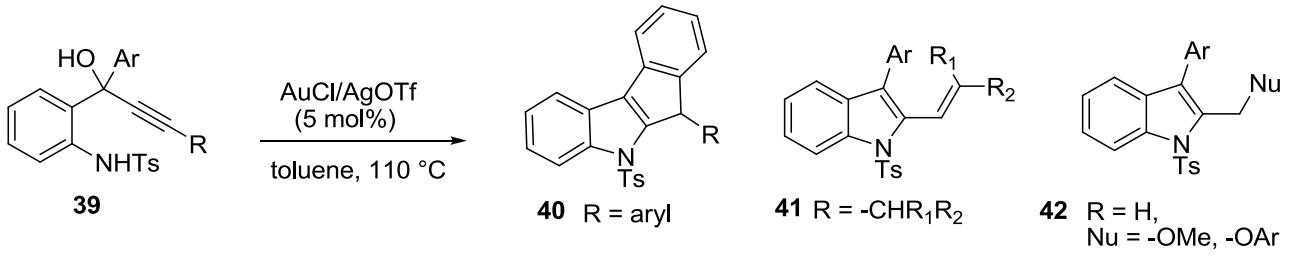
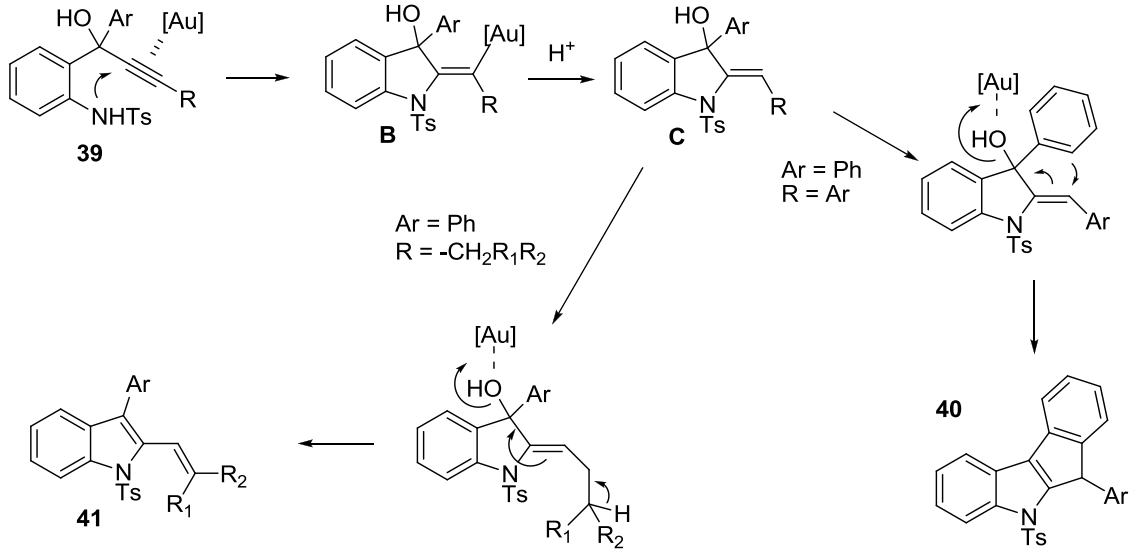


Figure 5.20 *[Au(I)]-catalyzed synthesis of indoles starting from tosylamino-propargylic alcohols.*

Gold catalyst promoted the hydroamination of the triple bond to generate intermediate **C** whose fate depended on the nature of the substituents R and Ar (Scheme 5.21). In presence of Ar = Ph a Friedel-Crafts event would be promoted by a sigma interaction between the gold catalyst and the hydroxylic moiety to led to **40**.

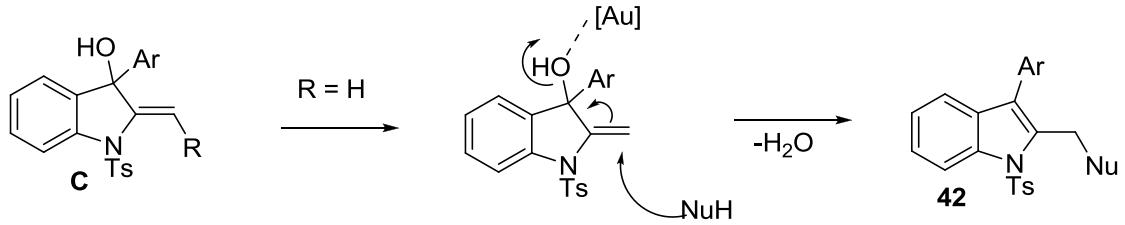
On the other hand, for R = $CH_2R_1R_2$ a rapid rearrangement led to 2-vinyl-indoles of type **41**.



Scheme 5.21 *Mechanism for the synthesis of indole **40** and **41.***

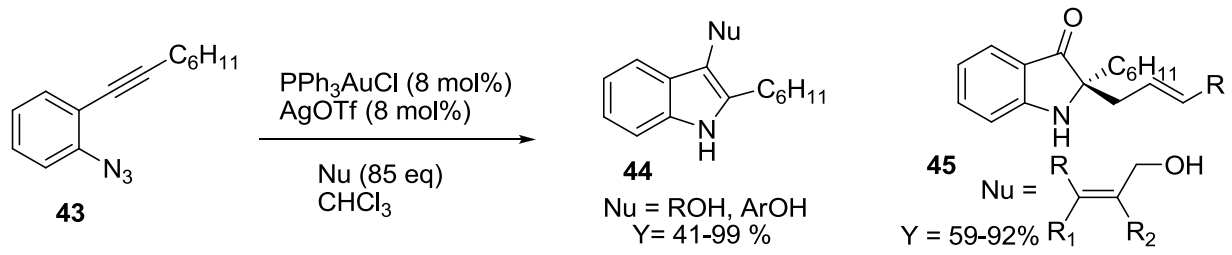
On the other hand, a more reactive primary vinyl gold species formed when R = H would be prone to a more rapid protodeauration/1,3-allylic alcohol isomerization process (1,3-AAI) and provide the (1H-indol-2-yl)methanol product **42**.

In the presence of a strong nucleophile, preferential SN2' substitution would be expected to give the 2-alkyl-1 H-indole adduct (Scheme 5.22).



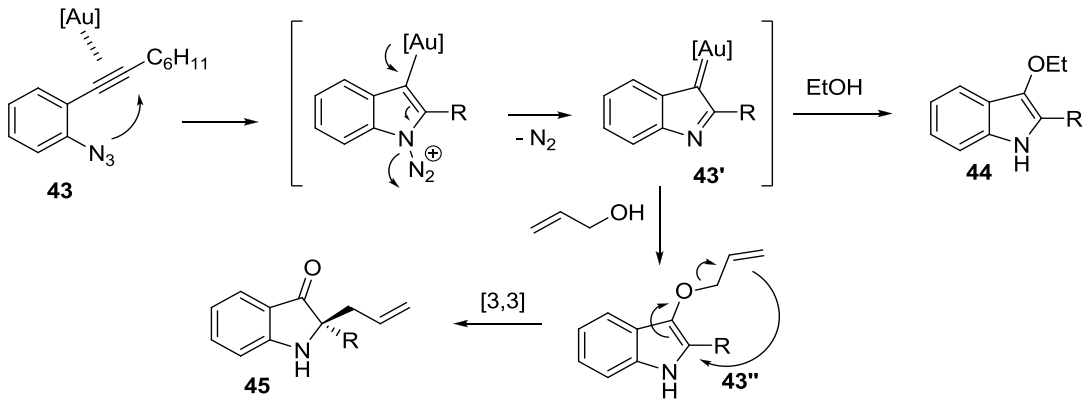
Scheme 5.22 *Mechanism fo the synthesis of indole* ***42****.*

Another very interesting example reported in literature was described by Gagosz and co-workers in studying the reactivity of 2-alkynyl-arylazides for the synthesis of pseudoindoxyl and indolyl frameworks (Scheme 5.23).[19]



Scheme 5.23 *Gold catalyzed transformation of ortho-alkynyl-arylazides: Synthesis of indoxylil and indolyl frameworks.*

Starting from readily available acyclic precursors, gold(I) catalyst was able to promote the first hydroamination step of the azide moiety onto the activated alkyne in order to generate an hypothetical electrophilic α-imino-gold carbene intermediate **43'**, that would be a suitable site for the addition of a nucleophilic specie in order to generate functionalized indoles (Scheme 5.24).



Scheme 5.24 *Different chemoselectivity for the α-imino-gold carbene intermediate* ***43'****.*

This kind of intermediate in presence of nucleophiles such as phenols and alcohols, undergoes a nucleophilic substitution leading to a 1,2 di-substituted indole rings; while in presence of an allylic alcohol, intermediate **43''** undergoes a [3,3]-Claisen rearrangement opening access to a class of pseudo-indoxyl alkaloids. [20]

As we can see, all these reactivities involved the synthesis and the functionalization of the indole core in the 2 and 3 position and all the cascade reactions developed in these previous works, proved to be competent only in the synthesis of C2-C3 connected ring to the indole system.
In literature only two examples are reported involing the possibility of synthesis and then functionalization of the indole core generating an N1-C2 connected membered ring.
Zhang again proved gold(I) carbene complexes to be competent in the formation of cyclic-ketone fused indoles from N-(2-alkynylphenyl)lactams (Figure 5.25).[21]

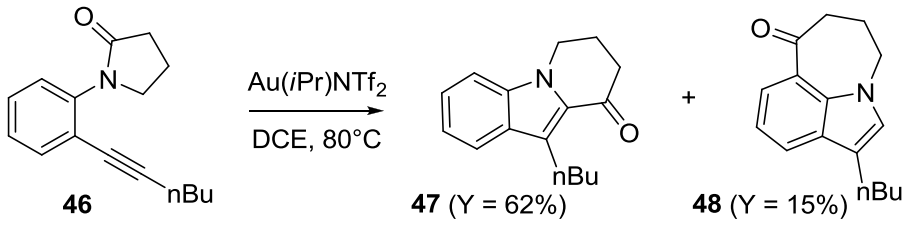
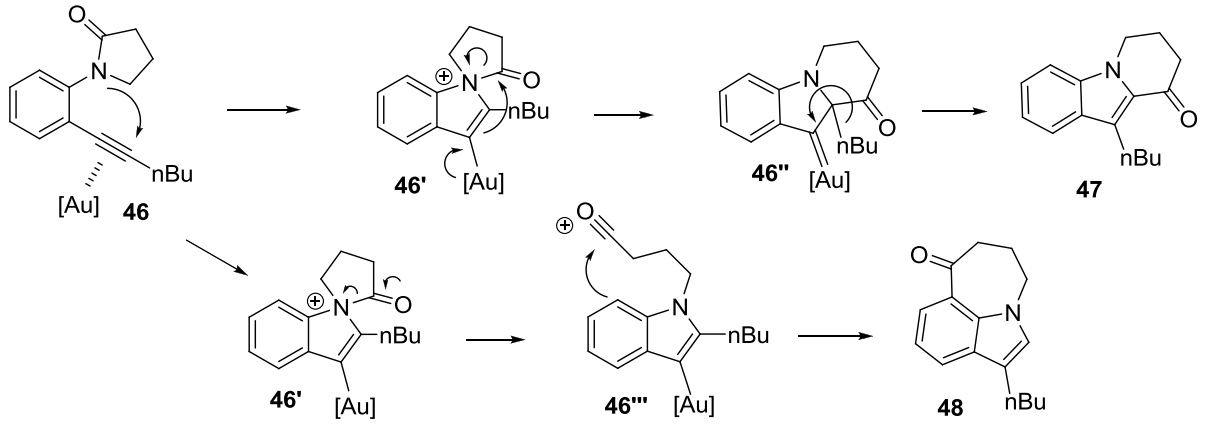


Figure 5.25 *Au(I)-catalyzed synthesis and annulation of N-(2-alkynylphenyl)lactams.*

After a gold promoted 5-*endo*-cyclization leading to indolyl intermediate **46'**, two distinct pathways could led to different chemical outputs (Scheme 5.26).
In the first case the indolyl iminium would results in a 1,2-acyl migration to intermediate **46''** and finally to a 1,2-shift of the alkyl group onto the metalcarbenoid moiety resulting in a cyclic-ketone-indole **47**.



Scheme 5.26 *Mechanistic pathways for the Au(I)-catalyzed synthesis of indoles.*

Alternatively, the 1,2-acyl migration could proceed stepwise via the acylium intermediate **46'''** (route b). Interestingly, this reaction can be viewed as an intramolecular insertion of one end of the C-C triple bond into the lactam amide bond with concurrent 1,2-migration of the substituent on the triple bond.

The last example was reported by Iwasawa in which a gold(III) salt was able to promote a [3+2] cycloaddition of metal-containing azomethine ylides generated by an *endo*-cyclization of an alkynyl imine (Figure 5.27).[22]

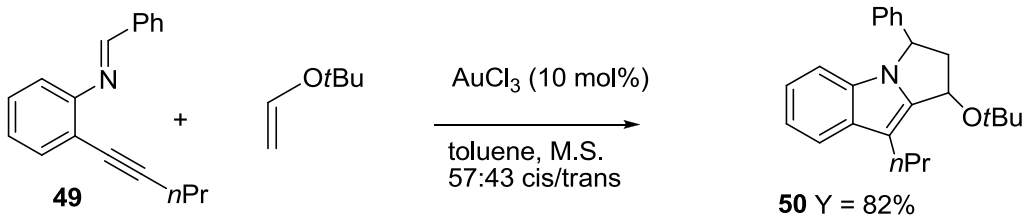
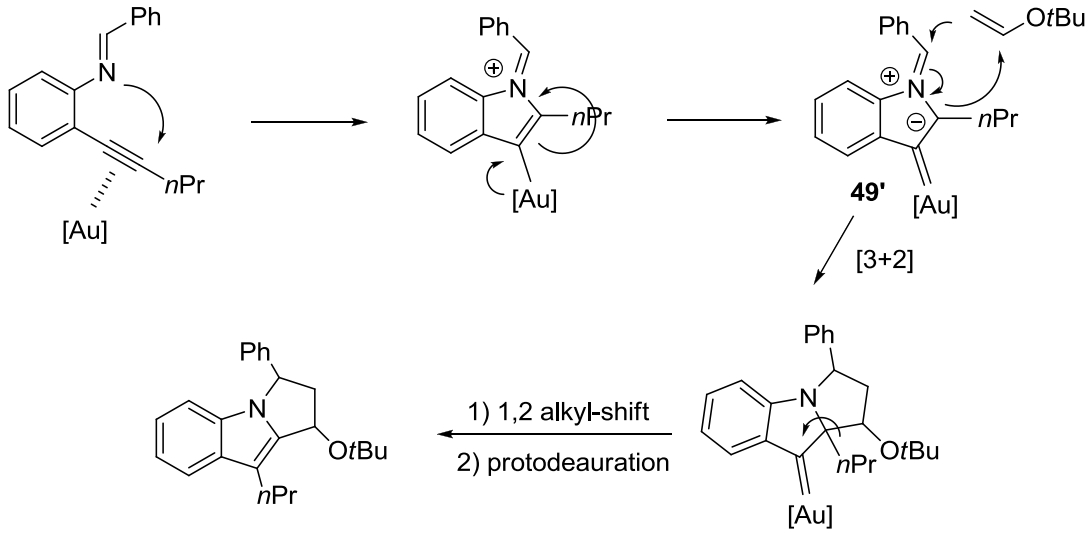


Figure 5.27 [*Au(I)]-catalyzed synthesis and [3+2]-cycloaddition.*

Electrophilic activation of the internal alkyne moiety by these metals induces the nucleophilic, 5-*endo*-mode of cyclization of the imino nitrogen onto the alkyne moiety to generate the corresponding metal-containing azomethine ylides **49'**(Scheme 5.28).



Scheme 5.28 *Mechanism of the [Au(I)]-catalyzed synthesis and [3+2] cycloaddition.*

Successive [3+2]-cycloaddition and 1,2-alkyl migration give tricyclic indole with regeneration of the catalyst. The internal alkyne protocol affords a highly efficient method for the preparation of 3-substituted tricyclic indole skeletons such as mitomycins.

5.5. Results and discussion

Since our goal was to develop new methodologies involving the use of propargylic alcohols as patterns in cascade reactions, we thought about the possibility to develop a new process in which both synthesis and functionalization of the indole was realized with two consecutive cyclization events. At the outset of this investigation, we thought that readily available 2-(propargylic alcohol)-anilines (**1a**) could be a suitable acyclic precursors to develop a cascade process.

This substrate is readily available by means of two synthetic step starting from commercial 2-iodo-aniline as shown in the Figure 5.17.

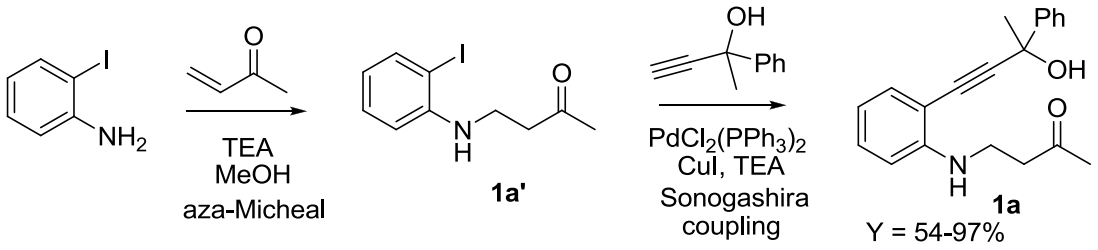


Figure 5.17 *Synthetic tree of the synthesis of model substrate* ***1a****.*

Intermediate **1a'** was obtained by a previously reported aza-Micheal protocol using different types or alkyl or aryl- vinyl ketones and finally our model subtrate was synthesized by a classical Sonogashira coupling with $PdCl_2(PPh_3)_2$ (2% of loading) and CuI (2% of loading) as catalysts.

Preliminarly our working hypothesis relied on the electrophilicity of the triple bond of the propagylic alcohol (upon metal or acid activation), which is able to undergo the addition of the amine moiety in order to generate an indole core (Figure 5.18).

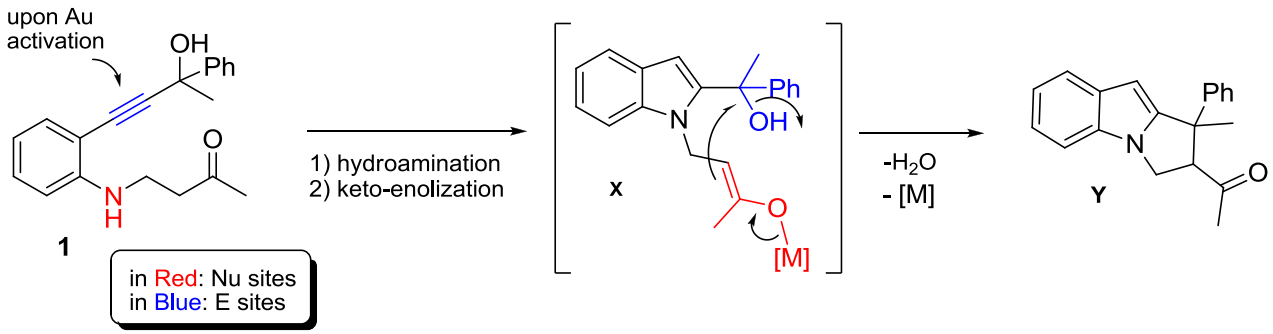


Figure 5.18 *Working hypothesis for a [Au(I)]-catalyzed synthesis and annulation of indole cores.*

Interestingly, we know metals with π-acidity, are able to promote the keto-enolic tautomerization of a pre-installed ketone moiety in order to generate a nucleophile that could be theoretically trapped

by a tertiary alcohol via a SN1 substitution to get the final synthesis of a 5-membered N1-C2 connected ring **Y** with two consecutive stereocenters.

However, when we subjected substrate **1a** to a cationic gold carbene complex in toluene, at reflux, we obtained the synthesis of a complete different chemical ouput (Figure 5.19).

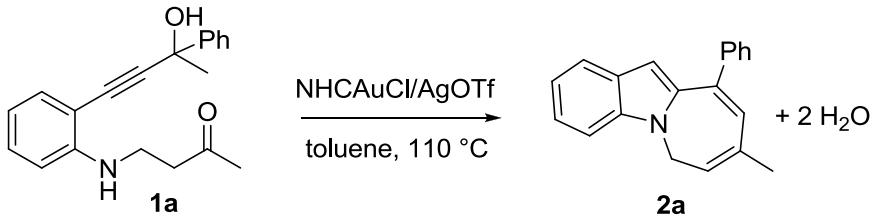


Figure 5.19 *Generation of azepino-indole* ***4a*** *catalyzed by (NHC)AuOTf complex.*

The chemical outcome can be rationalized through the reaction machinery depicted in Figure 5.20.

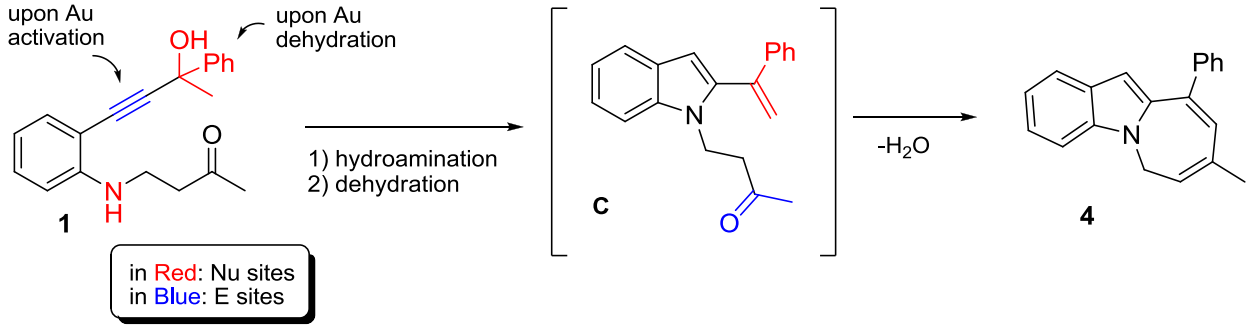


Figure 5.20*. Mechanistic hypothesis for the synthesis of azepinoindole* ***4****.*

In fact, propargylic alcohol behaves as a nucleophile after the synthesis of the indolyl nucleus. The dehydration of the tertiary alcohol would led to intermediate **C**, a nucleophilic 2-vinyl-indole able to attack the electrophilic ketone leading to the second cyclization with the formation of a seven-membered N1-C2 connected ring **4**.

Interestingly **4**, formally a [1,2-*a*]-azepino indole presents a structure which has displayed fascinating pharmacological activities, such as acting in the inhibition of HCV NS5B polymerase (A; Figure 5.21)[23] and as modulators for CNS neurotransmitter receptors (B) (Figure 5.21).[24]

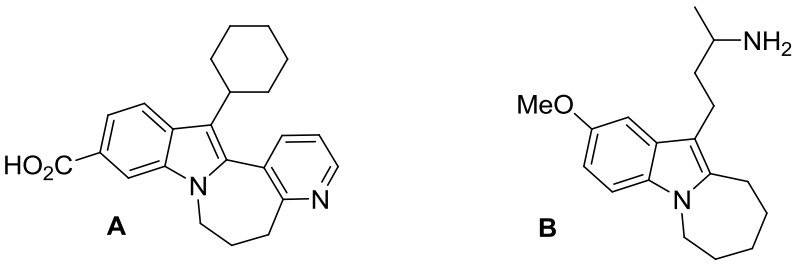
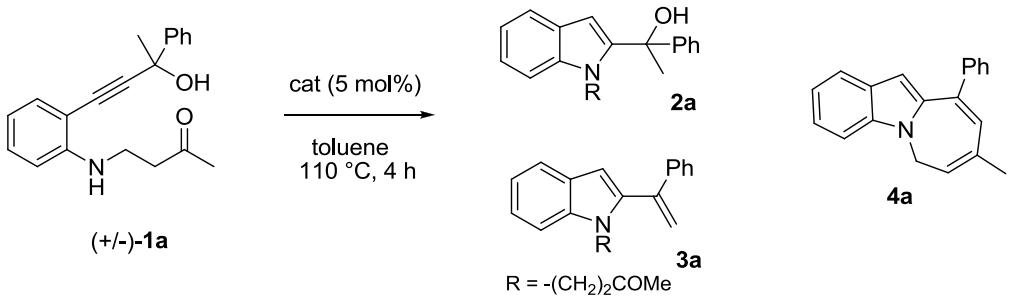


Figure 5.21. *Azepino indole framework in biological active molecules.*

Although the metal-catalyzed synthesis of 6H-azepino-[1,2-*a*]-indole derivatives has recently been documented,[25] stepwise synthetic sequences starting from a preformed indolyl nucleus are generally necessary to build up the fused seven-membered polycyclic system.[26]

At this stage we started a survey of reaction conditions to identify the optimal catalytic system for the one-pot synthesis of the [1,2-*a*]-azepino indoles (Table 5.22):



entry	Cat	2a (%)	3a (%)	4a (%)
1	$InOTf_3$			
2	$FeCl_3$			
3	AgOTf		23	
4	TfOH			
5	$Au(PPh_3)NTf_2$	64	36	
6	$(AuNTf_2)_2$dppf	15		
7	$[(AuPPh_3)_3O]BF_4$	35		
8	$AuCl_3$			
9	**6**		98	
10	**7**		90	
11	Au(*I*Pr)Cl/$AgBF_4$		35	34
12	Au(*I*Pr)Cl/AgOTs		76	23
13	Au(*I*Pr)Cl/$AgSbF_6$			89
14	Au(*I*Pr)Cl/AgOTf			96
15	Au(*I*Pr)OH/TfOH			68
16	Au(*I*Ad)Cl/AgOTf		61	traces
17	Au(*It*Bu)Cl/AgOTf		57	traces

Table 5.22. *Optimization table for the catalytic synthesis of [1,2-a]-azepinoindoles.*

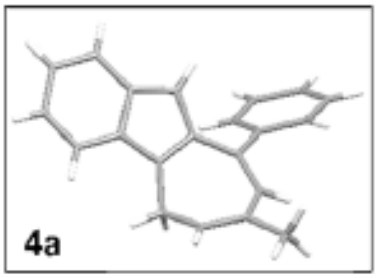
Among the metal species utilized (entries 1–3,5) gold(I) showed the highest catalytic activity. However, indolyl-alcohol **2a** and 2-vinyl-indole **3a** were obtained exclusively in the presence of phosphine-based gold(I) complexes (entries 5–7). The use of an N-heterocyclic carbene (NHC)-bearing system, [Au(*I*Pr)Cl]/$AgBF_4$ (5 mol%; *I*Pr=1,3-di(isopropylphenyl)imidazol-2-ylidene),

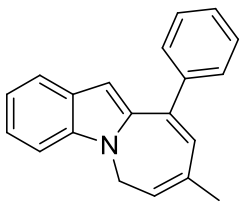
in refluxing toluene for 4 h, provided the desired 8-methyl-10-phenyl-6H-azepino-[1,2-*a*]-indole (**4a**) in 34% yield (Table 1, entry 11).

As the use of [Au(NHC)] systems is becoming more widespread in organic synthesis,[14] and as the synthetic routes to a series of congeners have been reported, we envisioned the possibility of increasing the chemical yield of the reaction sequence by examining the role of the counterion (entries 12–14). Among these, AgOTf (Tf=trifluoromethanesulfonyl) provided **4a** in nearly quantitative yield (96%, entry 14). Gold catalysis proved essential in this transformation, as the decomposition of **1a**, along with the modest formation of **3a**, was observed to occur to a varying degree when the reaction was conducted using AgOTf or TfOH (5 mol%) in the absence of gold.

The silver-free [Au(*I*Pr)(OH)]/TfOH system (5 mol%) promoted the gold-catalyzed cascade sequence in 68% yield, whereas attempts to carry out the reaction at lower temperatures or catalyst loadings led to a significant erosion in the yield of the desired product. Different N-heterocyclic carbene/gold complexes, such as [Au(*I*Ad)Cl] (*I*Ad=1,3-di(adamantyl)imidazol-2-ylidene and [Au(*I*tBu)Cl)] (*I*tBu=1,3-di(tert-butyl)imidazol-2-ylidene), were also tested, but modest results were obtained compared to those obtained with the [Au(*I*Pr)Cl] congener (entries 17–18).

To unequivocally establish the atom connectivity present in **4a**, its structure was determined by single-crystal X-ray analysis.





After optimizing the reaction conditions, the generality of the method was next explored by subjecting a series of alkynyl anilines **1b**–**p** to the cascade ring-closing procedure.

The results are summarized in Table 5.23.

Entry[a]	$R/R_1/R_2$	$Ar(R_3)/X$	**4**	Yield (%)[b]
1	H/Me/Me	*p*-FC_6H_4/H	**4b**	94
2	H/Me/Me	*p*-BrC_6H_4/H	**4c**	88
3	H/Me/Me	*p*-MeC_6H_4/H	**4d**	64
4	H/Me/Me	Ph/ *p*-F	**4e**	93
5	H/Me/Me	*p*-FC_6H_4/ *p*-F	**4f**	59
6[c]	H/Me/Me	*p*-$NO_2C_6H_4$/H	**4g**	92
7	H/Ph/Me	Ph/H	**4i**	75
8	Me/Me/Me	Ph/H	**4j**	65
9[d]	H/Et/Me	Ph/H	**4k**	48
10	H/Me/Me	*m*-MeC_6H_4/H	**4k**	78
11	H/*p*-ClC_6H_4/Me	Ph/H	**4l**	59
12	H/Me/Me	Ph/ *p*-Me	**4m**	70
13[e]	H/Me/CD_3	Ph/H	[H]-**4a**	82
14	H/Me/Me	Me/H	**4n**	70
15[f]	H/Me/Me	Et/H	**4o**	55[g]
16[f]	H/Me/Me	*i*Pr/H	**4p**	50

[a] All reactions were carried out under a nitrogen atmosphere. [b] Yield of isolated product after flash chromatography. [c] Reaction time of 1 h. [d] A mixture of compounds derived from the final endo and exo dehydration event was obtained (see the Supporting Information).
[e] [H]-**4a**/[D]-**4a** >25:1 by NMR spectroscopy. [f] With 10 mol% of catalyst.
[g] A 6:1 mixture of isomers was obtained (see the Supporting Information).

Table 5.24. *Scope for the synthesis of [1,2-a]-azepinoindoles.*

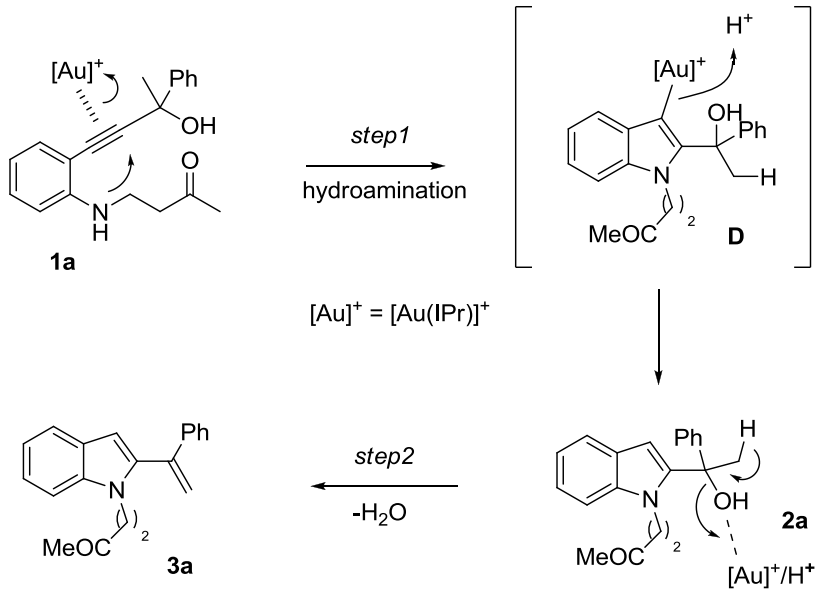
Structural modifications were performed at several positions on the molecule: 1) on the aniline ring, 2) on the ketone chain, and 3) on the propargylic alcohol substituents. As long as aryl tertiary alcohols were involved, the process proved to be highly selective towards substituents on the aromatic framework. Electron-withdrawing substituents on the aryl groups were well tolerated and lead to the corresponding azepinoindoles **4b**,**c**,**f**,**g** in good yields (59–94%; Table 5.23, entries 1,2,5,6). Analogously, *p*-tolyl and *m*-tolyl derivatives **1d** and **1i** smoothly underwent the double ring-closing process (64–78% yield, entries 3 and 10). With regards to the aniline chain, the

introduction of a methyl unit at the β-position of the ketone group did not significantly affect the reaction (**4j**, 65%, entry 8).

Analogously, substrates **1h** and **1l**, which bear an aromatic substituent on the carbonyl group (R_1=Ph, *p*-ClC_6H_4), performed well under the optimized conditions, leading to **4h** and **4l** in 75% and 59%, respectively (entries 7 and 11). When R_1=Et (**1k**) was employed in the reaction sequence, an inseparable mixture of azepinoindole isomers (see the Supporting Information for details) was obtained in 48% overall yield. Finally, the introduction of electron-donating and electron-withdrawing substituents onto the aniline ring was tolerated (59-93% yield; **4e**–**f**,**m**) and bis(alkyl)-substituted tertiary propargylic alcohols (**1n**–**p**) also proved to be competent precursors, providing the corresponding tricyclic compounds **4n**–**p** in good yields (entries 14–16).

The present cascade sequence leads to several mechanistic questions. For example, gold(I) species could exert both π- and σ-acidity at different point during the reaction. Moreover, the potential for co-catalysis by the Brønsted acids formed in situ (such as TfOH when AgOTf is used) cannot be ruled out. Interestingly, the identification of compounds **2** and **3** as reaction intermediates facilitated the mechanistic investigation and allowed for the monitoring of individual reaction steps. First, the hydroamination of the triple bond was found to proceed by gold catalysis (Scheme 5.22, step 1). This is supported by the unsatisfactory chemical outcomes when the reaction was carried out in the presence of AgOTf or TfOH, (entries 3–4, Table 5.23).

At this stage, the reaction sequence could proceed through a protodeauration of the 3-[Au]-indolyl species **D** and subsequent dehydration (Scheme 5.24, step 2).[27,28]



Scheme 5.24. *Mechanistic insights into step 1 (hydroamination of indole) and step 2 (dehydration to vinyl-indole **3a**).*

The most interesting aspect about this reactivity, to our knowledge, was the last cyclization step, the condensation of vinyl-indole **3a** on the carbonyl unit in order to afford the seven membered ring. This process could be in principle promoted by the activation of the carbonyl unit by means of a Lewis acid (LA) or a Bronsted acid according to the classical reactivity of a Prins reaction. Anyway there were experimental observation that didn't fit adequately to this type of activation. First of all treating **3a** with catalytic amount (5 mol% in refluxing toluene or 15% at r.t.) of TfOH, only small amounts of product **4a** were recovered (22% of yield).

Then, a [Au(I)]/LA-type assisted mechanism does not properly explain the unique reactivity observed with Au-NHC species when compared to more electrophilic phosphine-based gold complexes.

Finally, the quantitative proton/deuterium exchange observed with the deuterated alcohol [D_3]-**1a** (Table 2, entry 13) suggested possible interactions of the vinylindole intermediate with the Au(I)-NHC catalyst.

To get more insight in the final chemical event we decided to follow the reaction step-by step synthesizing each intermediates raising the temperature of the reaction (Figure 5.25).

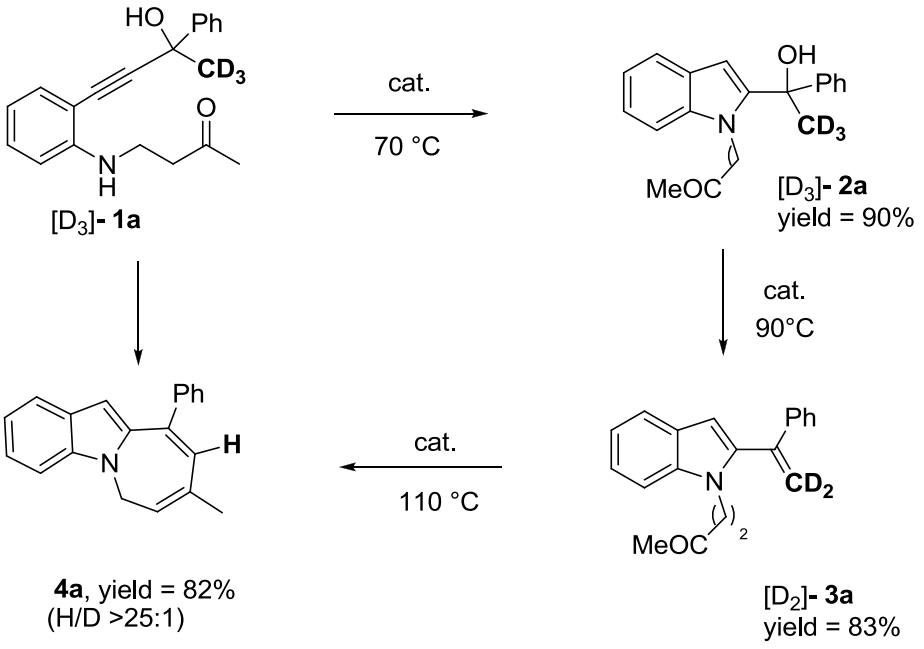


Figure 5.25. *Deuterium labelling experiment and monitoring of deuterium incorporation in the chemical events into the synthesis of azepino-indoles.*

It was found that the catalyst generated by the addition of AgOTf to Au(*I*Pr)Cl was able to catalyze the selective transformation of [D_3]-**1a** to [D_3]-**2a** and from [D_3]-**2a** to [D_2]-**2a**.

When the reaction were conducted respectively to 70 °C and 90 °C. But finally when D_2-**3a** was refluxed in toluene with the same catalyst system, H-**4a** was exclusively isolated in 82% of yield and with complete proton/deuterium exchange.[29]

This finding clearly suggested such a kind of interaction between the electrophilic NHC-Au(I) complex and the electron-rich double bond of the vinyl-indole **3a**.

As a further proof of this interaction we decided to synthesize a deuterated vinyl-indole with no electrophilic moiety but an alkyl group (a *n*-butyl group) in order to avoid any kind of interaction between any hypothetical nucleophilic species (generated by the interaction of the NHCAu with the vinyl-indole) and the electrophilic ketone moiety.

So we decided to run this experiment by using the same catalyst optimized for the cascade reaction by using water as external electrophile in order to highlight a D/H exchange as a proof of a nucleophilic NHCAu(I)-vinyl specie (Figure 5.26)

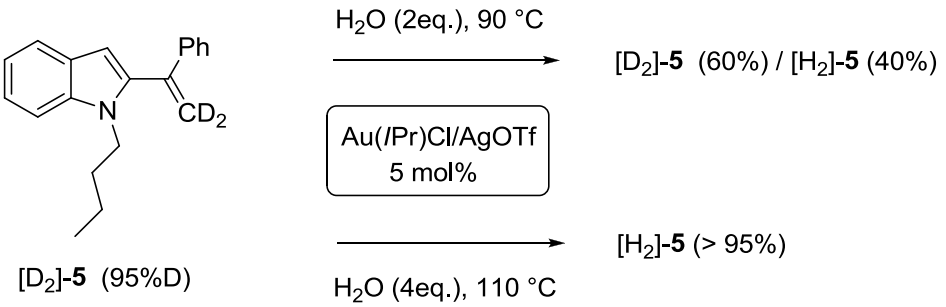


Figure 5.26. *Deuterium experiments to prove the interaction between vinyl-indole [D_2]-**5** and NHCAu(I) complex.*

As we can see from this experiment, when we subjected [D_2]-**5** to the classical catalytic system, in toluene at 90 °C with 2 equivalent of water as external nucleophile, we recovered 40 % of protodeuterated compound [H_2]-**5**. And, according to our previous hypothesis, subjecting D_2-**5** to the classical catalytic conditions (catalyst, refluxing toluene) a nearly quantitative generation of a gold-vinyl specie was recovered by trapping with 4 equivalents of water (used in great excess to avoid phenomena of evaporation).

In this way, by highlighting this new nucleophilic specie not only we justified the phenomenon of protodeuteration recovered for acyclic precursor D_2-**1a** but we also rationalized the last chemical event, the condensation of the vinyl-indole specie onto the ketone moiety.

We can finally suggest from the experimental evidences that the cationic NHCAu(I) adduct might insert into the electron-rich double bond to generate a nucleophilic vinyl gold specie **E**. This would led to the intramolecular condensation with the ketone moiety that finally would produce **4a** upon dehydration and 1,3-proton-transfer/protodeauration (Figure 5.27).[30]

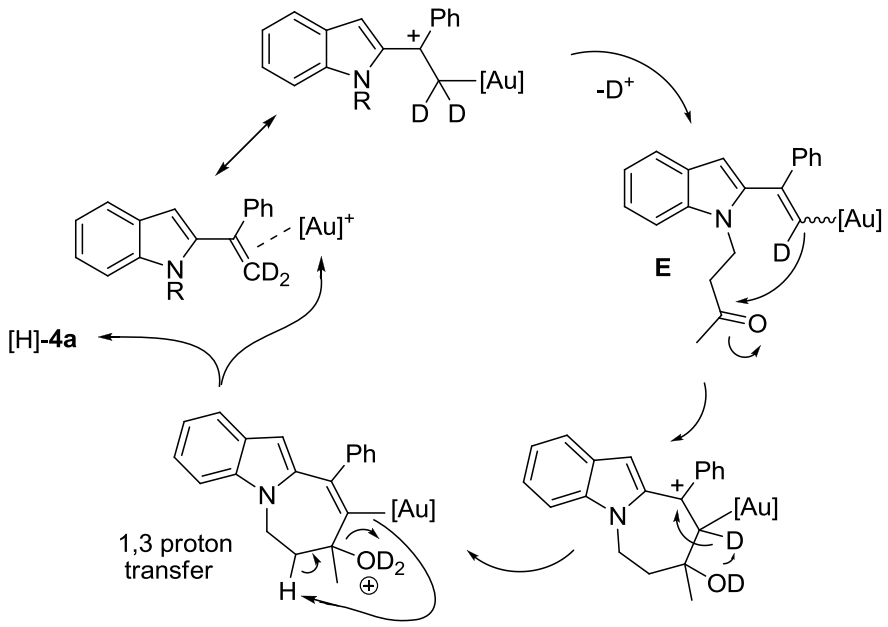


Figure 5.27. *Mechanistic hypothesis of the last annulation step for the synthesis of azepinoindoles.*

An alternative mechanistic explanation, the hypothetical C-H activation process of the C3 leading to the generation of a nucleophilic 3-gold-indolyl derivative, was found to be unlikely. This kind of process is decribed to happen only in presence of strongly electron-deficient of arenes (pKa < 31 and in presenxe of Ag_2O). [31]

Moreover, when H_2-**5** was treated with [Au(*I*Pr)(OTf)] ([D_8]-toluene, reflux) activation of the C3-H position of the indole core was never observed by NMR spectroscopy.

The possibility to achieve a further functionalization step of the azepino-indole **4a** was enviosened by subjecting the acyclic precursor **1a** to the classical catalytic conditions and after completion, adding several Micheal acceptors in order to promote a C3-functionalization (Figure 5.28).

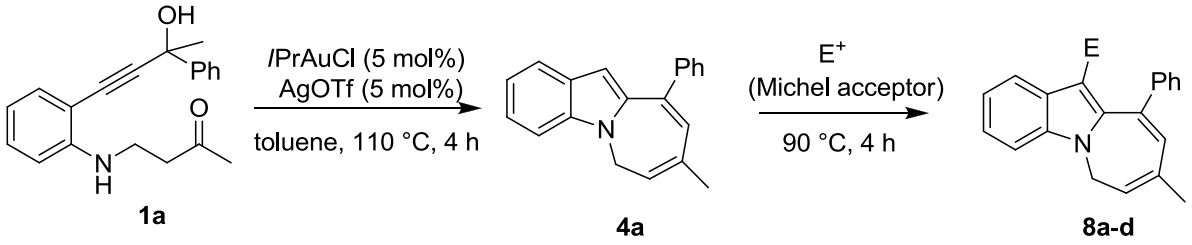


Figure 5.28. *[Au(I)]-assisted functionalization of azepino-indole* ***4a****.*

We reported several examples for the synthesis of highly functionalized azepino-indoles in which the presence of the [Au(I)]-carbene specie co-catalyzed the Micheal-addition of several electrophilic species such as methyl-vinyl-ketone (**8a**), nitro-styrene (**8b**), N-ethyl-malimide (**8c**) and finally (E)-dibenzyl diazene-1,2-dicarboxylate (**8d**) (Figure 5.29).

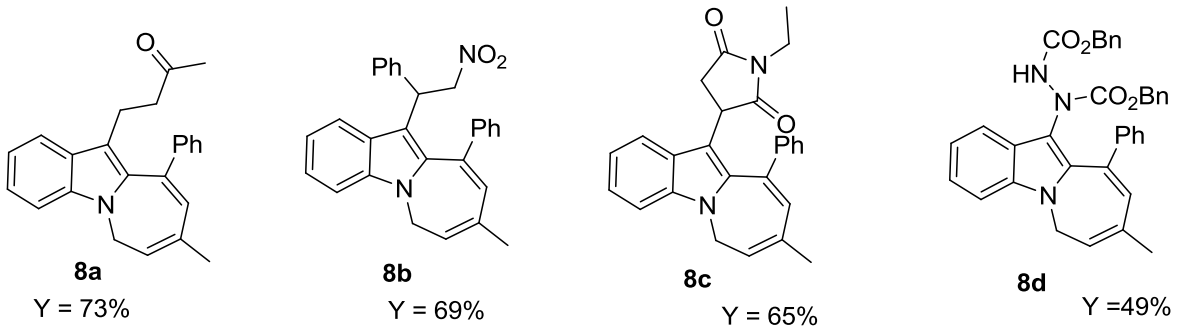


Figure 5.29. *Library of C3-alkylated azepino-indoles* ***8a-d****.*

Conclusions 5.6.

In this section we reported an unprecedented gold catalyzed *de novo* synthesis of a new class of [1,2-*a*] azepino-indoles, starting from readily available aniline-based propargylic alcohols. A broad scope for this reaction was reported, highlighting the excellent chemoselectivity for this transformation. Respect to other protocols for the step-by-step synthesis of azepino-indoles reported in literature, the synthetic availability of the acyclic precursors, the high chemical yields and the production of water as only stochiometric by-product, makes this protocol unique and of great interest from a synthetic point of view. Experimental evidences, suggested the key role of an unprecedented gold-vinyl specie in the final ring closing event.

Bibliography

[1]. K. Kruger, A. Tillack, M. Beller, *Adv. Synth. & Cat*., **2008**, *350*, 2153-2167.

[2]. C. Cao, Y. Shi, A. L. Odom, *Org. Lett.* **2002**, *4*, 2853 –2856.

[3]. R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689 – 6690.

[4]. a) J. D. Rainier, A. R. Kennedy, E. Chase, *Tetrahedron Lett.* **1999**, *40*, 6325 – 6327; b) J. D. Rainier, A. R. Kennedy, *J. Org. Chem.* **2000**, *65*, 6213 – 6216.

[5]. A. Penoni, K. M. Nicholas, *Chem. Commun.* **2002**, *5*, 484 – 485.

[6]. F. Ragaini, A. Rapetti, E. Visentin, M. Monzani, A. Caselli, S. Cenini, *J. Org. Chem.* **2006**, *71*, 3748 – 3753.

[7]. S. Cacchi, G. Fabrizi, A. Goggiamani, *Adv. Synth.Catal.* **2006**, *348*, 1301 – 1305.

[8]. T. Kurisaki, T. Naniwa, H. Yamamoto, H. Imagawa, M. Nishizawa, *Tetrahedron Lett.* **2007**, *48*, 1871 – 1874.

[9]. I. Ambrogio, A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, *Synlett,* **2007**, 1775 – 1779.

[10]. Y. Zhang, J. P. Donahue, C.-J. Li, *Org. Lett.* **2007**, *9*, 627 – 630.

[11]. J. Barluenga, F. Rodriguez, F. J. Façans, *Chem. Asian J*., **2009**, *4*, 1036.

[12]. For some recent leading examples using [Au], see: a) A. Praveen, K. Karthikeyan, P.T.Perumal, *Tetrahedron* **2009**, *65*, 9244; b) X. Zeng, R. Kinjo, B. Donnadieu, G. Bertrand, *Angew. Chem. Int. Ed*. **2010**, *49*, 942; c) B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang, L. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 8358; d) P. Kothandaraman, S. Reddy Mothe, S. Si Min Toh, P.W. H. Chan, *J. Org. Chem*. **2011**, *76*, 7633.

[13]. For some representative examples, see: a) D. Bouyssi, N. Monteiro, G. Balme, *Beilstein J. Org. Chem*. **2011**, *7*, 1387, and references therein; b) Y. Oda, N. Matsuyama, K. Hirano, T. Satoh, M. Miura, *Synthesis* **2012**, 1515.

[14]. A. Arcadi, G. Bianchi, F. Marinelli, *Synthesis*, **2008**, *4*, 210-218.

[15]. M. Alfonsi, A. Arcadi, M. Aschi, G. Bianchi, F. Marinelli *J. Org. Chem.*, 2005, 70, 2265–2273.

[16]. J. P. Brand, C. Chevalley, J. Waser, *Beilstein J. Org. Chem.* **2011,** *7,* 565–569.

[17]. K. Hirano, Y. Inaba, N. Takahashi, M. Shimano, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.*, **2011**, *76*, 1212–1227.

[18]. P. Kothandaraman, W. Rao, S. J. Foo, P.W.H. Chan, *Angew. Chem. Int.,* **2010***, 27,* 4723-4727.

[19]. A. Wetzel, F. Gagosz, *Angew. Chem. Int. Ed.*, **2011**, *50*, 7354.

[20]. For austamide, see: a) P. S. Steyn, *Tetrahedron* **1971**, *12*, 3331; for aristotelone, see: b) V. Zabel, W. H. Watson, M. Bittner, M. Silva, *J. Chem. Soc. Perkin Trans*. **1980** , 2842; for fluorocarp-amine, see: c) H. Takayama, M. Kurihara, S. Subhadhirasakul, M. Kitajima, N. Aimi, S. Sakai, *Heterocycles*, **1996** , *42*, 87.

[21]. G. Li, X. Huang, L. Zhang, *Angew. Chem. Int.,* **2008***, 2,* 352-355.

[22]. H.Kusama , Y.Miyashita, J. Takaya , N. Iwasawa, *Org. Lett.*, **2006**, 8, 289–292.

[23]. a) T.W. Hudyma, X. Zheng, F. He, M. Ding, C. P. Bergstrom, P.Hewawasam, S.W. Martin, R. G. Gentles, *WO2007/092000A1*, **2007**; b) M. Ding, F. He, M. A. Poss, K. L. Rigat, Y.-K. Wang, S. B. Roberts, D. Qiu, R. A. Fridell, M. Gao, R. G. Gentles, *Org.Biomol. Chem*. **2011**, *9*, 6654;

[24]. a) D. R. Adams, J. J. Bently, J. R. A. Roffey et al., PTC *WO 00/12510A1*, **2000**; b) M.D. Ennis, R. L. Hoffman, N. B. Ghazal, R. M. Olson, C. S. Knauer, C. L. Chio, D. K. Hyslop, J. E. Campbell, L.W. Fitzgerald, N. F. Nichols, K. A. Svensson, R. B. McCall, C. L. Haber, M. L. Kageyc, D. M. Dinhc, *Bioorg. Med. Chem. Lett*. **2003**, *13*, 2369.

[25]. a) H. Kusama, Y. Suzuki, J. Takaya, N. Iwasawa, *Org. Lett.* **2006**, *8*, 895; b) K. Cariou, B. Ronan, S. Mignani, L. Fensterbank, M. Malacria, *Angew. Chem.Int. Ed.* **2007**, *46*, 1881.

[26]. For some representative examples, see: a) V. Aureggi, M. Davoust, K. M. Gericke, M. Lautens, *Synlett* **2009**, 1004; b) S. Pozzi, J. Habermann, M. de R. Rico Ferreira, F. Narjes, *Synlett* **2009**, 1395; c) P. A. Suryavanshi, V. Sridharan, J. Carlos Mendez, *Org. Biomol. Chem.* **2010**, *8*, 3426; d) L. Huang, M. Shi, *Chem. Commun.* **2012**, *48*, 4501.

[27].A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger*, Adv. Synth. Catal*., **2010**, *352*, 971.

[28]. Refluxing **2a** in toluene for a few hours in the absence of acid sources led to the quantitative recovery of unreacted alcohol.

[29]. When [D_2]-**3a** was reacted in the presence of TfOH (5 mol%) at r.t., [D]-**4a** was isolated in 25%, whereas refluxing conditions led to decomposition of the starting material.

[30]. G. Cera, S. Piscitelli, M. Chiarucci, G. Fabrizi, A. Goggiamani, R. S. Ramón, S. P. Nolan, M. Bandini, *Angew.Chem.In.Ed.* **2012**, *51*, 9891-9895.

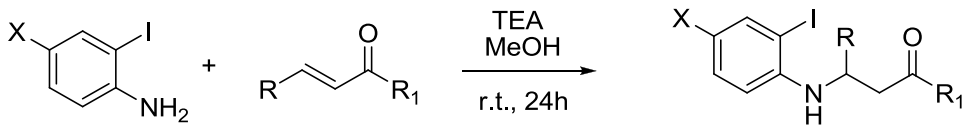
[31]. P. Lu, T. C. Boorman, A. M. Z. Slawin, I. Larrosa, *J. Am. Chem. Soc*. **2010**, *132*, 5580.

Supporting Informations

General Methods. ^{1}H-NMR spectra were recorded on Varian 200 (200 MHz), Varian 400 (400 MHz) spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, pd = pseudo duplet, t = triplet, pt = pseudo triplet, q = quartet, pq = pseudo quartet, br = broad, bs = broad singlet, m = multiplet), coupling constants (Hz). ^{13}C-NMR spectra were recorded on a Varian 200 (50 MHz), Varian 400 (100 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: 77.0 ppm). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. They are reported as: m/z (rel. intense). LC-electrospray ionization mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 240-400 mesh silica gel. Elemental analyses were carried out by using a EACE 1110 CHNOS analyzer. Separation via preparative HPLC was performed on a Agilent Technologies MSD 1100 liquid chromatograph using a Zorbax Eclipse SDB-C18 column (21.2 x 150 mm) with acetonitrile and milliQ-H_2O as eluents.

Synthesis of 4-(2-iodo-phenylamino)-butan-2ones.

Compounds **3a-e** were obtained via classic Michael addition in accordance with the previously described procedure. [1]



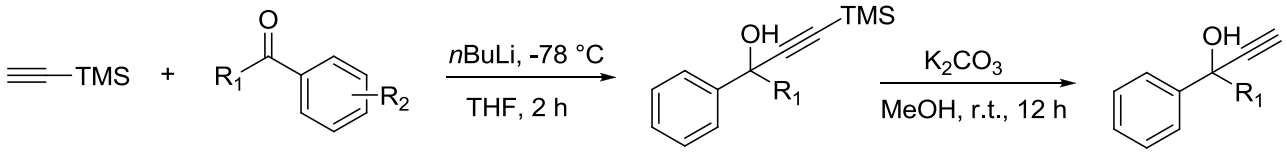
3a: X = H, R = H, R_1 = Me **3k**: X = H, R = H, R_1=Et

3e: X = F, R = H, R_1 = Me **3h**: X = H, R = H, R_1 = Ph

3j: X = H, R = Me, R_1 =Me **3l**: X = H, R = H, R_1 = (pCl)Ph

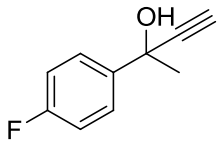
1] Sole, D.; Bonjoch, J.; *J.Am.Chem.Soc.*, **2003**, *125*, 1587

Synthesis of 2-aryl-but-3-yn-2ols (2b-2D_3a)

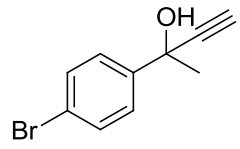


In a three necked round bottomed flask, under nitrogen atmosphere, a solution of BuLi 2.5 M in hexanes (1.2 eq) was added dropwise to a stirred solution of trimethylsilylacetylene (1.2 eq) in THF at -78 °C. After being stirred ad that temperature for 30 min, a solution of the desired ketone (1 eq) in THF (0.2mM) was added to the suspension over a period of 10 min, and the reaction allowed to reach room temperature. The reaction was judged complete by TLC analysis (2 h). After extractive work-up [NH_4Cl(sat)/Et_2O] the organic layers were collected, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was then dissolved in methanol and placed in a two-necked round bottomed flask under anhydrous conditions and then 1.2 eq of K_2CO_3 were added and the reaction stirred overnight. After extractive work-up (brine/AcOEt) the organic-layers were

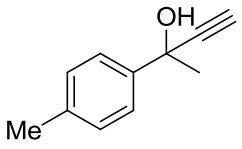
collected, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was finally purified by flash-chromatography (c-Hex:AcOEt=85:15).



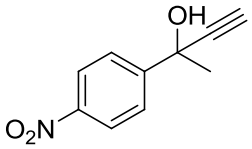
2b. Viscous yellow oil. Yield: 60%. ^{1}H-NMR (200 MHz, $CDCl_3$), δ: 1.76 (s, 3H); 2.69 (s, 2H); 7.04 (pt, J = 8.8 Hz, 2H); 7.63 (dd, J_1 = 4.4 Hz, J_2 = 9.2 Hz, 2H). GC-MS: 149 (M-Me).



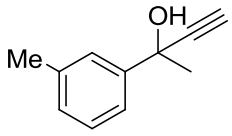
2c. Viscous pale yellow oil. Yield: 58%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.72 (s, 3H); 2.57 (s, 1H); 2.65 (s, 1H); 7.43 (dd, J_1 = 2.8 Hz, J_2 = 8.4 Hz, 1H); 7.49 (dd, J_1 = 2.8 Hz, J_2 = 8.4 Hz, 1H); 7.56 (dd, J_1 = 3.2 Hz, J_2 = 8.4 Hz, 1H); 7.76 (dd, J_1 = 4 Hz, J_2 = 8.4 Hz, 1H). GC-MS: 211 (M-Me).



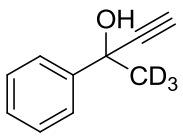
2d. Viscous orange oil. Yield: 57%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.77 (s, 3H); 2.34 (s, 3H); 2.40 (s, 1H); 2.56 (s, 1H); 7.16 (d, J = 8.0 Hz, 1H); 7.24 (d, J = 7.6 Hz, 1H); 7.54 (d, J = 8.4 Hz, 1H); 7.84 (d, J = 8.4, 1H). GC-MS: 160 (M); 145 (M-Me).



2g. Viscous red oil. Yield: 65%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.80 (s, 3H); 2.60 (s, 1H); 2.75 (s, 1H); 7.84 (d, J = 9.2 Hz, 2H); 8.23 (d, J = 8.8 Hz, 2H). GC-MS: 176 (M-Me).

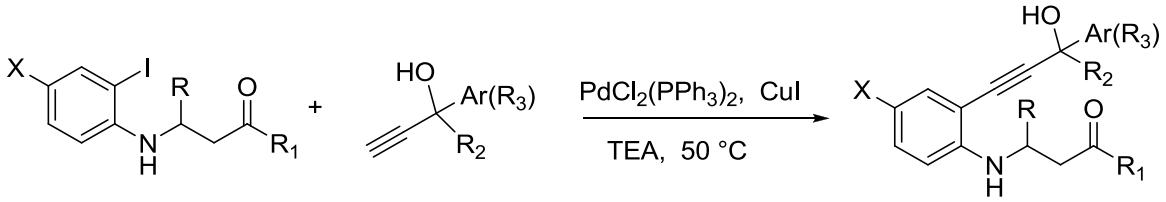


2i. Viscous orange oil. Yield: 61%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.77 (s,3H); 2.38 (s, 3H); 2.65 (s, 1H); 7.10 (d, J = 7.6 Hz, 1H); 7.25-7.27 (m, 1H); 7.44 (d, J = 10.8 Hz, 2H). GC-MS: 145 (M-Me).

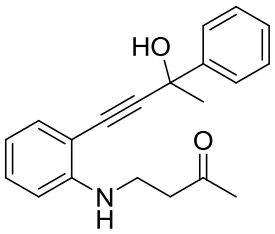


D_3-**2a**. Viscous white oil. Yield: 55%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 2.64 (s, 1H); 2.94 (bs, 1H); 7.27 (pt, J = 7.6 Hz, 1H); 7.34 (pt, J = 8.4 Hz, 1H); 7.42 (pt, J = 8.0 Hz, 1H); 7.63 (d, J = 9.6 Hz, 1H); 7.91 (d, J = 9.6, 1H). GC-MS: 131 (M-CD_3).

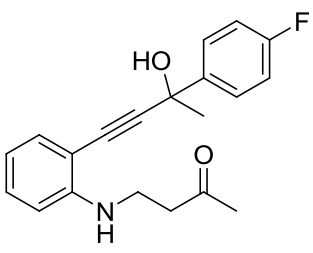
Synthesis aniline-propargylic alcohols 1a-o



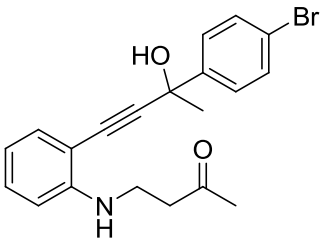
In a Schlenk tube, under nitrogen atmosphere, iodo-aniline derivative (1 eq), 2-arylbut-3-yn-2-ol (1.3 eq), $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (2 mol%) were added to 5 ml of TEA and the reaction heated to 50 °C until completion (monitored by TLC analysis). After extractive work-up with a saturated solution of NH_4Cl and DCM, the crude was purified by flash-chromatography (9:1 cHex:AcOEt 6:4 cHex:AcOEt).



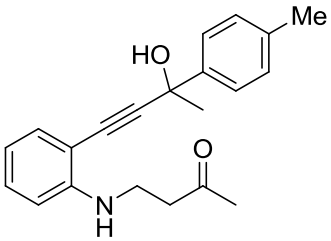
1a. Viscous orange oil. Yield: 90%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.92 (s, 3H); 2.10 (s, 3H); 2.68 (t, J = 6.4 Hz, 2H) 3.41 (t, J = 6.4 Hz, 2H); 3.69 (s, 1H); 4.91 (s, 1H); 6.21 (d, J = 8.4 Hz, 1H); 6.57 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H); 7. 19 -7.23 (m, 1H); 7.31-7.37 (m, 2H); 7.39 (td, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 2H); 7.75 (d, J = 5.6 Hz, 1H); 7.77 (d, J = 1.2 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.1, 33.4, 38.0, 42.3, 70.2, 81.1, 98.9, 107.5, 109.7, 116.5, 124.9 (2C), 127.4, 128.2 (2C), 129.9, 131.9, 145.8, 148.6, 208.4. LC-MS: 308 (M+1), 330 (M+Na). Elem. Anal. ($C_{20}H_{21}NO_2$, MW: 307.39) calc. C, 78.15; H, 6.89; N, 4.56; found: C, 78.00; H, 6.71; N, 4.61.



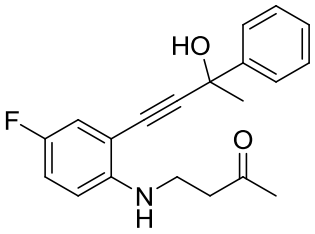
1b. Viscous yellow oil. Yield: 90%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ:1.89 (s, 3H), 2.18 (s, 3H); 2.74 (t, J = 6.4 Hz, 2H); 3.16 (s, 1H); 3.47 (t, J = 6Hz, 2H); 5.31 (s, 1H); 6.62 (dd, J_1 = 7.6 Hz, J_2 =6.4 Hz, 1H); 6.67 (m, 1H); 7.05-7.10 (m, 1H); 7.21 (dt, J_1 = 7.6 Hz, J_2 =1.6 Hz, 1H); 7.30 (dd, J_1 = 7.2 Hz, J_2 = 1.2Hz, 1H); 7.71-7.74 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.9, 33.4, 37.8, 42.1, 69.6, 81.1, 98.6, 107.3, 109.6, 116.4, 126.7, 126.8, 129.9, 131.8, 141.7 (2C); 148.5, 160.7, 163.1, 208.6. LC-MS: 326 (M+1); 348 (M+Na). Elem. Anal. ($C_{20}H_{20}FNO_2$, MW: 325.38) calc. C, 73.83; H, 6.20; N, 4.30; found: C, 73.60; H, 6.21; N, 4.44.



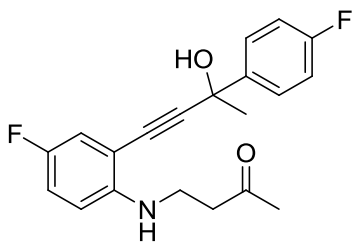
1c. Viscous yellow oil. Yield: 60 %.^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.87 (s, 3H); 2.11 (s, 3H); 2.70 (t, J = 6.4 Hz, 2H); 3.42 (t, J = 6.4 Hz, 2H); 6.61 (d, J = 8.4 Hz, 1H); 6.46 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H); 7.20 (dt, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H); 7.27-7.30 (m, 1H); 7.50 (dd, J_1 = 6.6 Hz, J_2 = 2Hz, 2H); 7.61 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.2, 33.4, 38.0, 42.2, 69.8, 81.4, 98.3, 107.3, 109.8, 116.6, 121.3, 126.9 (2C), 130.1, 131.2 (2C), 131.9, 145.0, 148,7, 208.7. LC-MS: 387 (M+1), 409 (M+Na). Elem. Anal. ($C_{20}H_{20}BrNO_2$, MW: 386.28) calc. C, 62.17; H, 5.22; N, 3.63; found: C, 62.02; H, 5.30; N, 3.61.



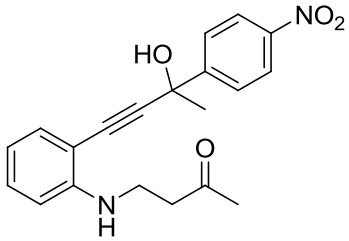
1d. Viscous red oil. Yield: 54%.^{1}H-NMR (200 MHz, $CDCl_3$), δ: δ: 1.94 (s, 3H); 2.17 (s, 3H); 2.42 (s, 3H); 2.76 (t, J = 6.2 Hz, 2H); 3.48 (t, J = 6.2 Hz, 2H); 6.69-6.71 (m, 2H); 7.23-7.27 (m, 4H); 7.68 (d, J = 8 Hz, 2H); LC-MS: 321 (M+1), 344 (M+Na). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.0, 30.2, 33.3, 38.1, 42.4, 70.2, 81.0, 99.0, 107.6, 109.7, 116.5, 124.9 (2C), 128.9 (2C), 129.9, 131.9, 137.2, 143.0, 148.7, 208.3. LC-MS: 322 (M+1), 344 (M+Na). Elem. Anal. ($C_{21}H_{23}NO_2$, MW: 321.41) calc. C, 78.47; H, 7.21; N, 4.36; found: C, 78.45; H, 7.15; N, 4.29.



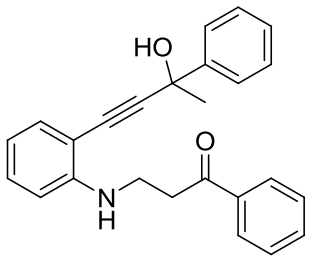
1e. Viscous yellow oil. Yield: 69 %. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.87 (s, 3H); 2.07 (s, 3H); 2.65 (t, J = 6.0 Hz, 2H); 3.40 (t, J = 6.0 Hz, 2H); 6.32 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H); 6.89 (dt, J_1 = 6.4 Hz, J_2 = 3.2 Hz, 1H); 6.99 (dd, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H); 7.28 (dd, J_1 = 6.0 Hz, J_2 = 2.4 Hz, 1H); 7.36-7.38 (m, 2H); 7.71 (dd, J_1 = 5.0 Hz, J_2 = 1.2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.2, 33.6, 38.8, 42.2, 70.2, 80.2, 99.6, 108.4, 110.9, 116.9, 118.1, 124.9 (2C), 127.6, 128.2 (2C), 145.6, 153.3, 155.6, 208.6. LC-MS: 326 (M+1). Elem. Anal. ($C_{20}H_{20}FNO_2$, MW: 325.38) calc. C, 73.83; H, 6.20; N, 4.30; found: C, 73.45; H, 6.31; N, 4.21.



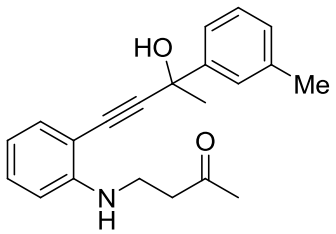
1f. Viscous yellow oil. Yield: 98%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.42 (s, 3H); 1.86 (s, 3H); 2.67 (t, J = 6.0 Hz, 2H); 3.34 (t, J = 6.0 Hz, 2H); 6.51 (m, 1H); 6.90 (pt, J = 8.8 Hz, 1H); 6.98 (dd, J_1 = 8.4 Hz, J_2 = 3.2 Hz, 1H); 7.03 (dt, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 2H); 7.65-7.69 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.2, 33.4, 38.7, 42.2, 69.7, 80.3, 99.3, 108.2, 111.0, 114.8 (2C); 115.0 (2C); 117.0, 117.8, 141.4, 145.5, 153.3, 163.4, 208.8. LC-MS: 343 (M+1), 365 (M+Na). Elem. Anal. ($C_{20}H_{19}F_2NO_2$, MW: 343.37) calc. C, 69.96; H, 5.58; N, 4.08; found: C, 69.90; H, 5.45; N, 4.00.



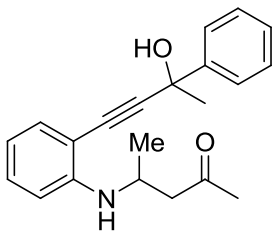
1g. Viscous red oil. Yield: 98%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.90 (s, 3H); 2.12 (s, 3H); 2.73 (t, J = 6-0 Hz, 2H); 3.42 (t, J = 6.0 Hz, 2H); 3.96 (s, 1H); 5.05 (s, 1H); 6.62 (pt, J = 8.0 Hz, 1H); 6.65 (d, J = 6.4 Hz, 1H); 7.21 (dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H); 7.27 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H); 7.90 (dd, J_1 = 11.6 Hz, J_2= 2.8 Hz, 2H); 8.21 (dd, J_1 = 11.4 Hz, J_2 = 2.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.3, 33.6, 38.1,42.2, 69.9, 82.1, 97.4, 107.1, 109.9, 116.7, 123.5 (2C), 126.1 (2C), 130.3, 132.0, 147.2, 148.7, 153.0, 209.2. LC-MS: 353 (M+1), 375 (M+Na). Elem. Anal. ($C_{20}H_{20}N_2O_4$, MW: 352.38) calc. C, 68.17; H, 5.72; N, 7.95; found: C, 68.20; H, 5.65; N, 7.88.



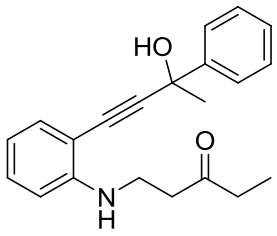
1h. Viscous white oil. Yield: 72%. ^{1}H-NMR (200 MHz, $CDCl_3$), δ: 1.90 (s, 3H); 3.18 (t, J = 6.2 Hz, 2H); 3.57 (t, J = 6.2 Hz, 2H); 6.26 (pt, J = 8.0 Hz, 2H); 7.15-7.43 (m, 7H); 7.51 (d, J = 6.8 Hz, 1H); 7.74 (d, J = 8.8 Hz, 2H); 7.85 (d, J = 8.4 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 33.4, 37.5, 38.5, 70.4, 81.3, 98.9, 107.6, 109.7, 116.5, 124.8, 125.0 (2C), 127.5, 128.0 (2C), 128.2, 128.3, 128.6, 130.0, 132.0, 133.4, 136.4, 145.9, 148.8, 199.5. LC-MS: 370 (M+1), 392 (M+Na). LC-MS: 370 (M+1), 392 (M+Na). Elem. Anal. ($C_{25}H_{23}NO_2$, MW: 369.46) calc. C, 81.27; H, 6.27; N, 3.79; found: C, 81.20; H, 6.18; N, 3.65



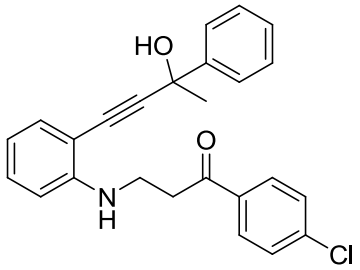
1i. Viscous red oil. Yield: 78 %. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.88 (s, 3H); 2.10 (s, 3H); 2.38 (s, 3H); 2.70 (t. J = 6.0 Hz, 2H); 3.42 (t, J = 6.0 Hz, 2H); 6.59- 6.62 (m, 2H); 7.10 (d, J = 7.2 Hz, 1H); 7.18 (t, J = 7.2 Hz, 1H); 7.26- 7.29 (m, 2H); 7.52 (d, J = 8.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.5, 30.3, 33.4, 38.2, 42.5, 70.4, 81.2, 99.0, 107.7, 109.8, 116.6, 122.1, 125.6, 128.2, 128.3, 130.0, 132.0, 137.9, 145.8, 148.8, 208.3. LC-MS: 322 (M+1). Elem. Anal. ($C_{21}H_{23}NO_2$, MW: 321.41) calc. C, 78.47; H, 7.21; N, 4.36; found: C, 78.40; H, 7.12; N, 4.21.



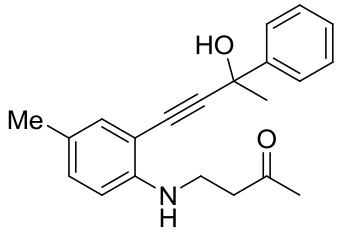
1j. Viscous orange oil. Yield: 68%. ^{1}H-NMR (200 MHz, $CDCl_3$), δ:1.21 (t, J = 7.2 Hz, 3H); 1.90 (d, J = 4.4 Hz, 3H); 2.08 (s, 3H), 2.49-2.53 (m, 1H); 2.67 (ddd, J_1 = 16.4 Hz, J_2= 14.0 Hz, J_3 = 4.8Hz, 1H); 2.72 (s, 1H); 3.93 (dd, J_1 = 12.4 Hz, J_2 = 6.4 Hz, 1H); 4.78 (s, 1H); 6.61 (pt, J =4.8 Hz, 1H); 6.63 (d, J = 7.6 Hz, 1H); 7.18 (pt, J = 7.6 Hz, 1H); 7.28-7.31 (m, 2H); 7.38 (pt, J = 5.6 Hz, 2H); 7.73-7.75 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$), δ: 20.6, 30.9, 33.3, 45.0, 49.2, 70.3, 81.3, 99.0, 107.5, 110.1, 116.4, 124.9, 127.5, 128.2 (2C), 130.0 (2C); 131.9, 145.9, 147.9, 208.4. LC-MS:322 (M+1), 344 (M+Na). Elem. Anal. ($C_{21}H_{23}NO_2$, MW: 321.41) calc. C, 78.47; H, 7.21; N, 4.36; found: C, 78.55; H, 7.31; N, 4.30.



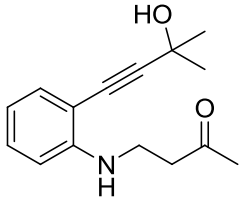
1k. Viscous yellow oil. Yield: 97%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.01 (t, J = 7.6 Hz, 3H); 1.92 (s, 3H); 2.39 (q, J = 7.6 Hz, 2H); 2.68 (t, J = 6.4 Hz, 2H); 3.43 (t, J = 6.4 Hz, 2H); 6.62-6.68 (m, 2H); 7.21 (dt, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H); 7.31 (d, J = 2.4 Hz, 1H); 7.33 (dd, J_1 = 5.6 Hz, J_2 = 1.2 Hz, 1H); 7.40 (pt, J = 5.2 Hz, 2H); 7.76 (d, J = 4.8 Hz, 1H); 7.78 (d, J = 5.6 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 7.6, 33.4, 36.2, 38.2, 41.0, 70.3, 81.2, 98.9, 107.6, 109.7, 116.5, 124.9 (2C), 127.4, 128.2 (2C), 129.9, 131.9,145.8, 148.7, 211.3. LC-MS: 322 (M+1), 344 (M+ Na). Elem. Anal. ($C_{21}H_{23}NO_2$, MW: 321.41) calc. C, 78.47; H, 7.21; N, 4.36; found: C, 78.45; H, 7.25; N, 4.31



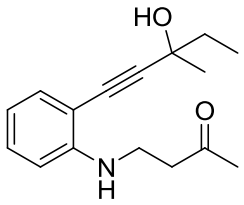
1l. Viscous orange oil. Yield: 60%. ^{1}H-NMR (200 MHz, $CDCl_3$), δ: 1.89 (s, 3H); 3.18 (t, J = 6.4 Hz, 2H); 3.61 (t, J= 6.4 Hz, 2H); 6.64-6.67 (m, 2H); 7.20 (dt, J_1 = 8Hz, J_2 = 1.6 Hz, 1H); 7.29-7.31 (m, 2H); 7.37-7.40 (m, 4H); 7.73 (d, J = 1.2 Hz, 2H); 7.79 (dd, J_1 = 6.8 Hz, J_2 = 1.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 33.4, 37.6, 38.5, 70.5, 81.4, 98.9, 109.7, 116.7, 124.8, 125.0 (2C), 127.6, 128.3, 128.4, 128.9 (2C); 129.5 (2C), 130.1, 132.1, 134.8, 140.0, 145.9, 148.7, 198.3. LC-MS: 386 (M-H_2O), 426 (M+Na). Elem. Anal. ($C_{25}H_{22}ClNO_2$, MW: 403.90) calc. C, 74.34; H, 5.49; N, 3.47; found: C, 74.41; H, 5.29; N, 3.41.



1m. Viscous orange oil. Yield: 65%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ =1.91 (s, 3H) 2.06, (s, 3H); 2.12 (s, 3H); 2.75 (t, J = 6.0 Hz, 2H); 3.21 (s, 1H); 3.44 (t, J = 5.8 Hz, 2H); 4.81 (bs, 1H); 6.57 (d, J = 8.3 Hz, 1H); 7.04 (d, J = 8.3 Hz, 1H); 7.33 (t, J = 7.3 Hz, 1H); 7.41 (t, J = 7.6 Hz, 2H); 7.76 (d, J = 7.0 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.2, 30.3, 33.5, 38.7, 42.6, 70.4, 81.5, 98.6, 107.8, 110.3, 125.1, 126.0, 127.6, 128.3, 130.7, 132.3, 146.0, 146.7, 208.5. LC-MS: 321 (M+1).

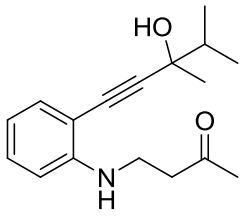


1n. Viscous orange oil. Yield: 64%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 6H) 2.20, (s, 3H), 2.78 (t, J = 6.0 Hz, 2H), 2.89 (s, 1H), 3.48 (t, J = 6.0 Hz, 2H), 5.00 (bs, 1H); 6.60-6.67 (m, 2H), 7.16-7.31 (m, 2H). ^{13}C-NMR (100 MHz, CDCl3): δ 30.4, 31.6 (2C), 38.2, 42.6, 65.6, 78.5, 100.2, 107.8, 110.0, 116.6, 130.0, 131.9, 148.5, 208.6. LC-MS: 268 (M+ Na).

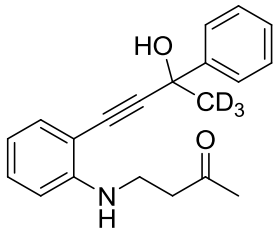


1o. Viscous orange oil. Yield: 61%. ^{1}H-NMR (200 MHz, $CDCl_3$), δ: 1.10 (t, J = 7.6 Hz, 3H); 1.59 (s, 3H); 1.81 (q, J = 7.6 Hz, 2H); 2.13 (s, 3H); 2.71 (t, J = 6.4 Hz, 2H); 3.42 (t, J = 6.4 Hz, 2H); 4.93 (s, 1H); 6.59 (dd, J_1 = 13.6 Hz, J_2 = 7.6 Hz, 2H), 7.16 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H); 7.23 (dd, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 9.1, 29.3, 30.1, 36.4, 37.9,

42.3, 68.9, 79.4, 99.0, 107.7, 109.4, 116.3, 129.5, 131.8, 148.3, 208.4. LC-MS: 260 (M+1); 282 (M+Na). Elem. Anal. ($C_{16}H_{21}NO_2$, MW: 259.34) calc. C, 70.10; H, 8.16; N, 5.40; found: C, 70.00; H, 8.05; N, 5.35.

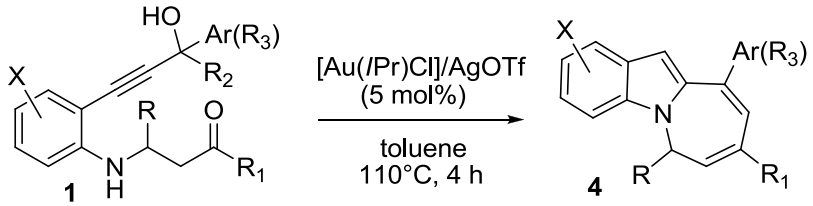


1p. Viscous red oil. Yield: 75%.^{1}H-NMR (200 MHz, $CDCl_3$), δ: 1.07 (d, J_2 = 6.8 Hz, 3H); 1.11(d, J = 6.8 Hz, 3H), 1.57 (s, 3H); 1.92 (m, 1H); 2.17 (d, J = 2.8 Hz, 3H), 2.76 (t, J = 6.4 Hz, 2H); 3.46 (t, J = 6.4 Hz, 2H); 6.61-6.64 (m, 2H); 7.18 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H); 7.25 (dd, J_1 = 7.6 Hz, J_2 =2.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 17.2, 17.6, 26.9, 29.8, 37.7, 38.5, 42.1, 71.7, 79.9, 97.8, 107.5, 109.2, 116.1, 129.2, 131.5, 148.0, 207.8. LC-MS: 273 (M+1). Elem. Anal. ($C_{17}H_{23}NO_2$, MW: 273.37) calc. C, 74.69; H, 8.48; N, 5.12; found: C, 74.55; H, 8.35; N, 5.13.

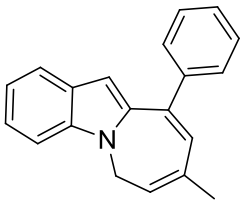


D_3-**1a**. Viscous yellow oil. Yield: 73%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 2.13 (s, 3H); 2.72 (t, J = 6.0 Hz, 2H); 3.16 (s,1H); 3.45 (t, J = 6.0 Hz, 2H); 5.00 (s, 1H); 6.61-6.67 (m, 2H); 7.21 (t, J = 7.6 Hz, 1H); 7.32 (d, J = 6.8 Hz, 2H); 7.38 (t, J = 7.2 Hz, 2H); 7.75 (d, J = 7.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.1, 30.5, 38.4, 42.7, 70.4, 81.5, 99.1, 107.8, 110.0, 116.8, 125.2, 127.7 (2C), 128.5 (2C), 130.2, 132.2, 146.1, 149.0, 208.6. LC- MS: 311 (M+1), 333 (M+Na

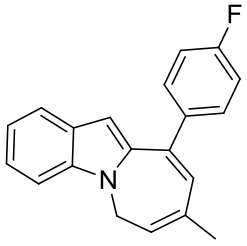
Catalytic synthesis of azepinoindoles 4a-o



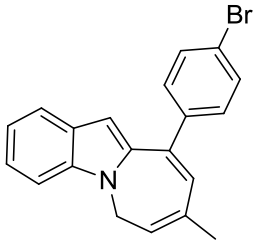
In a Schlenck tube, under nitrogen atmosphere and in absence of light, [Au(iPr)Cl] (5 mol%) was dissolved in 0.5 ml of anydrous toulene; then AgOTf (5 mol%) was added to generate the gold catalytic specie in situ. After stirring 20 min in the dark, the acyclic precursor was dissolved in further 0.5 ml of toluene and added to the reaction mixture.Then, the Schlenck tube was placed in a pre-warmed bath at 110 °C and the reaction stirred for additional 4 hours. After completation (TLC analysis), toluene was removed under reduced pressure and the crude purified by flash-chromatography (95:5 cHex:AcOEt).



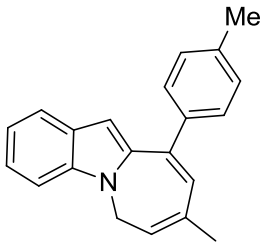
4a. Yellowish solid. m.p.: 110-115 °C. Yield: 96%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.85 (s, 3H); 4.56 (d, J = 8.0 Hz, 2H); 5.75 (t, J = 7.2 Hz, 1H); 6.14 (s, 1H); 6.19 (s, 1H); 6.96 (t, J = 7.2 Hz, 1H); 7.13 (dt, J_1 = 7.6 Hz, 1H); 7.27-7.31 (m, 5H); 7.43-7.46 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.8, 50.0, 102.9, 108.9, 119.4, 120.9, 121.9, 122.7, 127.8, 128.0 (2C), 128.1 (2C), 129.2 (2C), 135.2, 138.2, 139.7, 140.0, 142.4. LC-MS: 272 (M+1). Elem. Anal. ($C_{20}H_{17}N$, MW: 271.36) calc. C, 88.52; H, 6.31; N, 5.16; found: C, 88.35; H, 6.21; N, 5.05.



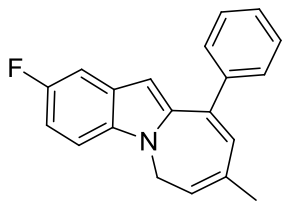
4b. Pale yellow solid. m.p.: 103-110 °C. Yield: 94%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.96 (s, 3H); 4.67 (d, J = 6.8 Hz, 2H); 5.87 (t, J = 6.8 Hz, 1H); 6.21 (s, 1H); 6.25 (s, 1H); 7.16-7.19 (m, 3H); 7.24 (pt, J = 7.8 Hz, 1H); 7.41 (d, J = 8.4 Hz, 1H); 7.51 (dd, J_1 = 8.6 Hz, J_2 = 5.4 Hz, 2H); 7.54 (d, J = 8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.8, 41.0, 102.9, 108.9, 114.8, 115.2 (2C); 119.5, 120.9, 122.1, 122.8, 127.8, 128.0, 130.7, 130.9, 135.3, 137.1, 139.9. LC-MS: 290 (M+1).



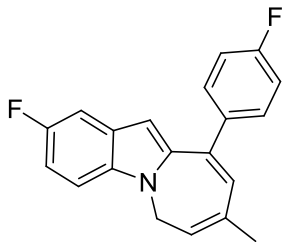
4c. Red solid. m.p: 128-132 °C. Yield: 88%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.95 (s, 3H); 4.66 (d, J = 6.4 Hz, 2H); 5.88 (t, J = 6.0 Hz, 1H); 6.22 (s, 1H); 6.26 (s, 1H); 7.07 (pt, J = 8.0 Hz, 1H); 7.24-7.27 (m, 1H); 7.39-7.43 (m, 3H); 7.51-7.54 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.8, 41.0, 102.9, 108.9, 119.6, 120.9, 122.0, 122.1, 123.1, 127.8, 128.2, 130.8 (2C), 131.2 (2C), 135.3, 137.0, 139.1, 139.9, 141.3.LC-MS : 351 (M+1). Elem. Anal. ($C_{20}H_{16}BrN$, MW: 350.25) calc. C, 68.58; H, 4.60; N, 4.00; found: C, 68.39; H, 4.55; N, 3.95.



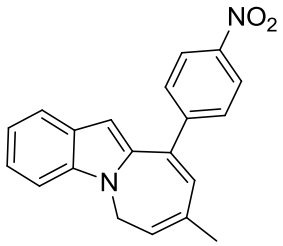
4d. Orange solid. m.p.:128-132 °C. Yield: 64%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.96 (s, 3H); 2.43 (s, 3H); 4.68 (d, J = 6.4 Hz, 2H); 5.86 (t, J = 6.4 Hz, 1H); 6.26 (s, 1H); 6.29 (s, 1H); 7.07 (pt, J = 7.6 Hz, 1H); 7.20-7.25 (m, 3H); 7.41 (d, J = 8.4 Hz, 1H); 7.45 (d, J = 7.6 Hz, 2H); 7.54 (d, J = 8.4 Hz, 1H); ^{13}C-NMR (100MHz, $CDCl_3$) δ: 21.2, 22.8, 41.0, 102.8, 108.9, 119.4, 120.8, 121.8, 122.5, 127.6, 127.8, 128.8 (2C), 129.0 (2C), 137.8, 138.2, 139.5, 139.8, 140.1. LC-MS: 286 (M+1). Elem. Anal. ($C_{21}H_{19}N$, MW: 285.38) calc. C, 88.38; H, 6.71; N, 4.91; found: C, 88.45; H, 6.76; N, 4.86.



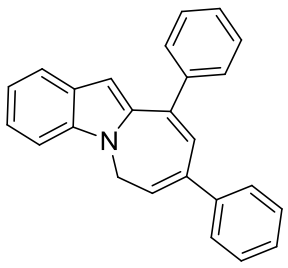
4e. Pale orange solid. m.p.: 137-142 °C. Yield: 93%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.97 (s, 3H); 4.65 (d, J = 6.4 Hz, 2H); 5.86 (t, J = 6.4 Hz, 1H); 6.19 (s, 1H); 6.32 (s, 1H); 6.98 (dt, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H); 7.16 (dd, J_1 =9.8 Hz, J_2 = 2.4 Hz, 1H); 7.31 (dd, J_1 = 9.0 Hz, J_2 = 4.4 Hz, 1H); 7.38-7.41 (m, 3H); 7.52 (d, J = 2.4 Hz, 1H); 7.54 (pt, J = 2Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ: 22.8, 41.3, 102.6, 105.1, 105.3, 109.6, 110.3, 110.6, 122.7, 127.9, 128.6 (2C); 129.1 (2C); 131.9, 138.1, 140.1, 141.0, 142.1, 158.8. LC-MS: 290 (M+1). Elem. Anal. ($C_{20}H_{16}FN$, MW: 289.35) calc. C, 83.02; H, 5.57; N, 4.84; found: C, 82.95; H, 5.61; N, 4.89.



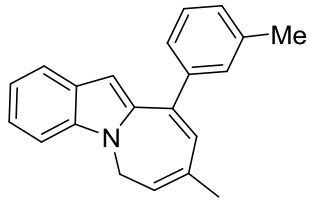
4f. White solid. m.p.: 138-144 °C. Yield: 59%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.96 (s, 3H); 4.64 (d, J = 6.4 Hz, 2H); 5.86 (t, J = 6.4 Hz, 1H); 6.16 (s, 1H); 6.98 (dt, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H); 7.09 (pt, J = 8.9 Hz, 2H); 7.17 (dd, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 1H); 7.31 (dd, J_1 = 9.4 Hz, J_2 = 4.4 Hz, 2H); 7.49-7.52 (m, 2H); ^{13}C -NMR (100 MHz, $CDCl_3$), δ: 22.7, 41.3, 102.6, 105.1, 109.6, 109.7, 110.7, 114.9 (2C); 115.2 (2C); 122.8, 128.5, 130.7, 130.8, 132.0, 137.0, 138.1, 140.0, 161.5.LC-MS: 294 (M+1). Elem. Anal. ($C_{19}H_{13}F_2N$, MW: 293.31) calc. C, 77.80; H, 4.47; N, 4.78; found: C, 77.85; H, 4.55; N, 4.71.



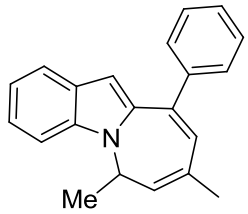
4g. Orange solid. m.p: 96-104 °C. Yield: 92%. ^{1}H-NMR (400Hz, $CDCl_3$), δ: 1.97 (s, 3H); 4.68 (d, J = 6.4 Hz, 2H); 5.88 (t, J = 6.8 Hz, 1H); 6.24 (s, 1H); 6.30 (s, 3H), 7.07 (pt, J = 7.2 Hz, 1H); 7.23 (pt, J = 7.2 Hz, 1H); 7.39-7.42 (m, 4H); 7.54-7.56 (m, 2H). ^{13}C -NMR (100 MHz, $CDCl_3$), δ: 26.9, 42.4, 98.9, 107.6, 109.9, 116.7, 123.3, 123.6, 126.0, 126.2, 127.5 (2C), 128.2, 128.3, 130.1, 132.0, 132.8, 133.1, 143.2, 148.9. LC-MS: 339 (M+Na). Elem. Anal. ($C_{20}H_{16}N_2O_2$, MW: 316.35) calc. C, 75.93; H, 5.10; N, 8.86; found: C, 75.85; H, 5.15; N, 8.78.



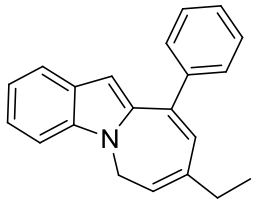
4h. Orange solid. m.p: 175-180 °C. Yield: 70%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 4.82 (d, J = 6.4 Hz, 2H); 6.27 (t, J = 6.4 Hz, 1H); 6.29 (s, 1H); 6.64 (s, 1H); 7.04 (t, J = 7.2Hz, 1H); 7.19-7.23 (m, 1H); 7.30-7.37 (m, 6H); 7.42 (d, J = 6.8 Hz, 3H), 7.52 (d, 7.6 Hz, 1H); 7.58-7.61 (m,2H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ: 40.1, 103.3, 108.9, 119.6 (2C), 121.0, 122.1, 123.3, 126.0, 126.9 (2C), 127.8 (2C), 127.9, 128.2 (2C), 128.3 (2C), 129.2 (2C), 139.5, 140.1, 142.5, 144.2. LC-MS: 334 (M+1). Elem. Anal. ($C_{25}H_{19}N$, MW: 333.43) calc. C, 90.06; H, 5.74; N, 4.20; found: C, 90.15; H, 5.66; N, 4.18.



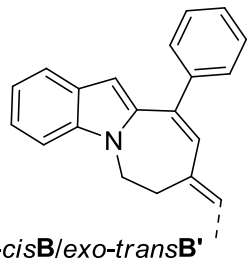
4i. Red solid. m.p.: 98-106 °C. Yield: 78%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.83 (s, 3H); 2.27 (s,3H); 4.54 (d, J = 6.4 Hz, 2H); 5.73 (s, 1H); 6.12 (s, 1H); 6.15 (s, 1H); 6.93 (pt, J = 6.8 Hz, 1H); 7.06-7.10 (m, 2H); 7.13-7.17 (m, 2H); 7.21 (d, J = 8.8 Hz, 1H); 7.28 (d, J = 8.8 Hz, 1H); 7.41 (d, J = 7.2 Hz, 1H).^{13}C -NMR (100 MHz, $CDCl_3$), δ: 22.8, 26.9, 41.0, 102.9, 108.9, 119.4, 120.9, 121.9, 122.6, 126.3, 127.9 (2C), 128.7 (2C), 129.9, 135.2, 137.6, 138.3, 139.8, 140.1, 142.4. LC-MS: 286 (M+1). Elem. Anal. ($C_{21}H_{19}N$, MW: 285.38) calc. C, 88.38; H, 6.71; N, 4.91; found: C, 88.35; H, 6.55; N, 4.98.



4j. Yellow solid. m.p.: 135-139 °C. Yield: 65%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 1.54 (d, J = 6.4 Hz, 3H); 1.96 (s, 3H); 5.33 (q, J = 7.2 Hz, 1H); 5.93 (d, J = 7.2 Hz, 1H); 6.13 (s, 1H); 6.27 (s, 1H); 7.07 (dd, J_1 = 7.6 Hz, J_2 = 6.8 Hz, 2H); 7.22 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 2H); 7.41- 7.45 (m, 2H); 7.51-7.53 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 17.9, 24.0, 48.5, 105.3, 108.8, 119.6, 120.8, 121.9, 127.2 (2C), 127.8, 128.0 (2C), 128.1 (2C), 128.8 (2C), 135.6, 136.1, 136.9, 142.7. LC-MS: 286 (M+1); Elem. Anal. ($C_{21}H_{19}N$, MW: 285.38) calc. C, 88.38; H, 6.71; N, 4.91; found: C, 88.36; H, 6.88; N, 4.7.

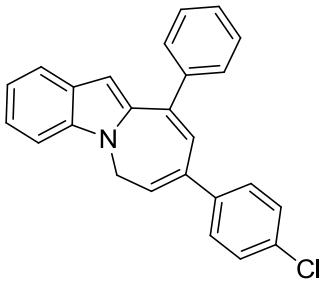


endo-**A**

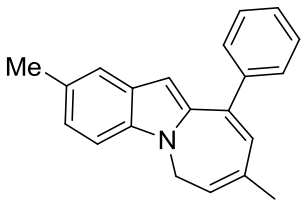


exo-cis-**B**/*exo-trans*-**B'**

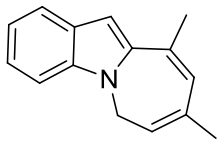
4k. Yellowish oil. Yield: 48%. Isolated as a mixture of inseparable regioisomers [*endo*-**A**, *exo-cis*-**B**, *exo-trans*-**B^{I}**]. ^{1}H-NMR (400 MHz, $CDCl_3$, diagnostic signals) δ: 1.12 (t, J = 6.8 Hz, 3H, A); 1.83 (t, J = 7.2 Hz, 3H, B); 2.27 (q, J = 6.8 Hz, 2H, A); 2.80-2.82 (m, 2H, B); 4.37-4.41 (m, 2H, B); 4.70 (d, J = 6.8 Hz, 2H, 2H); 5.58-5.60 (m, 1H, B); 5.78-5.80 (m,1H, B^{I}); 5.86 (t, J = 6.8 Hz, 1H, A); 6.13 (s, 1H, B); 6.16 (s, 1H, B^{I}); 6.24 (s, 1H, A); 6.29 (s, 1H, B); 6.32 (s, 1H, B^{I}); 6.54 (s, 1H; A). LC-MS: 286 (M+1) (B/B^{I}); 286 (M+1) (A).



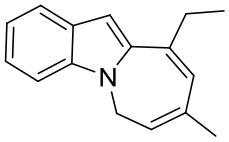
4l. Orange oil. Yield: 59%.^{1}H-NMR (400 MHz, $CDCl_3$), δ: 4.85 (d, J = 6.8 Hz, 2H); 6.28 (t, J = 7.2 Hz, 1H); 6.31 (s, 1H); 6.58 (s, 1H); 7.07 (pt, J = 7.2 Hz, 1H); 7.24 (pt, J = 7.2 Hz, 1H); 7.32 (dd, J_1 = 7.4 Hz, J_2 = 1.6 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H); 7.38-7.42 (m, 4H); 7.44 (s, 1H); 7.54 (d, J = 11.0 Hz, 1H); 7.58-7.60 (m, 2H).^{13}C-NMR (100 MHz, $CDCl_3$, diagnostic signals) δ: 40.9, 103.4, 108.9, 119.6, 120-9, 122.2, 123.5, 125.2, 128.1 (2C), 128.2 (2C), 128.5 (2C), 129.1 (2C), 133.7, 135.3, 139.2, 140.5, 142.2, 143.1, 145.8. LC-MS: 368 (M+1). Elem. Anal. ($C_{25}H_{18}ClN$, MW: 367.87) calc. C, 81.62; H, 4.93; N, 3.81; found: C, 81.70; H, 4.88; N, 3.75.

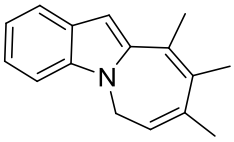


4m. Yellowish solid. m.p.:130-135 °C. Yield: 70%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.96 (s, 3H); 2.42 (s, 3H); 4.65 (d, J = 6.4 Hz, 2H); 5.85 (t, J = 6.4 Hz, 1H); 6.15 (s, 1H); 6.27 (s, 1H); 7.05 (dd, J_1 = 8.6 Hz, J_2 = 1.2 Hz, 1H); 7.27 (d, J = 5.2Hz, 1H); 7.30 (s, 1H); 7.39 (dd, J_1 = 5.2 Hz, J_2 = 3.2Hz, 3H); 7.54 (dd, J_1 = 6.4 Hz, J_2 = 4Hz, 2H). ^{13}C -NMR (100 MHz, $CDCl_3$), δ: 22.8, 29.7, 41.1, 102.4, 108.6, 120.3, 122.6, 123.7, 127.8, 127.9, 128.1 (2C); 128.6, 129.2 (2C); 129.5, 133.8, 138.3, 139.7, 139.9, 142.4.LC-MS: 285 (M+1). LC-MS: 286 (M+1). Elem. Anal. ($C_{21}H_{19}N$, MW: 285.38) calc. C, 88.38; H, 6.71; N, 4.91; found: C, 88.51; H, 6.65; N, 4.82.

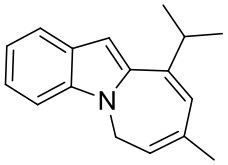


4n. Yellow solid. m.p.: 98-105 °C. Yield: 70%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.89 (s, 3H); 2.37 (s, 3H); 4.52 (d, J = 6.4 Hz, 2H); 5.80 (t, J = 6.4 Hz, 1H); 6.08 (s,1H); 6.61 (s,1H); 7.11 (pt, J = 7.2Hz, 1H); 7.26 (pt, J = 7.2 Hz, 1H); 7.39 (d, J = 8.0 Hz, 1H); 7.64 (d, J = 8.0 Hz,1H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ: 23.8, 29.7, 40.9, 99.5, 108.9, 119.3 (2C); 120.6, 121.4, 121.7 (2C); 127.4 (2C); 132.3, 139.8. LC-MS: 210 (M+1). Elem. Anal. ($C_{15}H_{15}N$, MW: 209.23) calc. C, 86.08; H, 7.22; N, 6.69; found: C, 86.15; H, 7.30; N, 6.60.


C

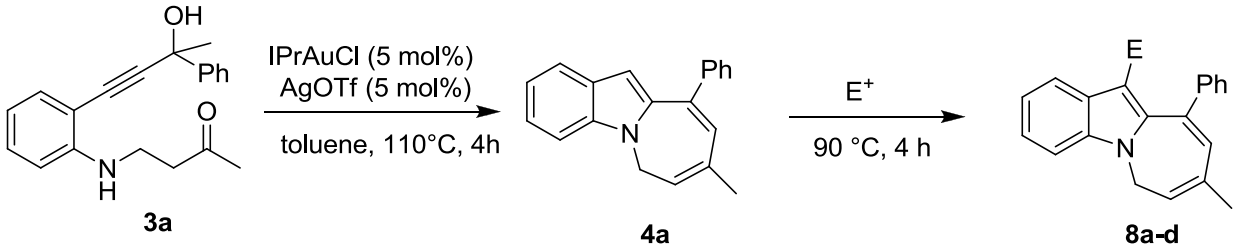

D

4o.Viscous brownish oil. Yield: 55% (6:1 C/D). ^{1}H-NMR (400 MHz, $CDCl_3$, only signals of isomer C are described), δ: 1.24 (t, J = 7.6 Hz, 3H); 1.86 (s, 3H); 2.69 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 2H); 4.48 (d, J = 6.4 Hz, 2H); 5.78 (t, J = 6.8 Hz, 1H); 6.04 (s, 1H); 6.58 (s, 1H); 7.07 (t, J = 6.8 Hz, 1H); 7.20 (dt, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 1H); 7.36 (d, J = 8.0 Hz,1H); 7.60 (d, J = 8,0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$ diagnostic signals of C), δ: 14.8, 22.8, 30.7, 40.9, 99.0, 109.0, 119.4, 120.7, 121.6, 121.8, 126.0, 128.2, 135.3, 139.1, 139.9, 151.1. LC-MS: 224 (M+1) Elem. Anal. ($C_{16}H_{17}N$, MW: 223.31) calc. C, 86.05; H, 7.67; N, 6.27; found: C, 86.00; H, 7.55; N, 6.15.

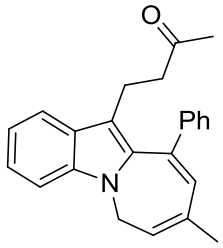


4p.Viscous brownish oil. Yield: 50%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.26 (d, J = 6.4 Hz, 6H); 1.87 (s, 3H); 3.05-3.10 (m, 1H); 4.46 (d, J = 6.8 Hz, 2H); 5.78 (t, J = 6.8 Hz, 1H); 6.02 (s, 1H); 6.59 (s, 1H); 7.06 (t, J = 7.2 Hz, 1H); 7.19 (t, J = 7.2 Hz, 1H); 7.36 (d, J = 8.0 Hz, 1H); 7.60 (d, J = 8.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ: 23.3 (2C); 29.8, 34.1, 40.8, 98.5, 108.9, 119.4 (2C); 120.7, 121.5, 122.1, 123.8, 124.8, 128.2, 139.9, 144.0. LC-MS: 238 (M+1). Elem. Anal. ($C_{17}H_{19}N$, MW: 237.34) calc. C, 86.03; H, 8.07; N, 5.90; found: C, 86.13; H, 8.00; N, 5.85.

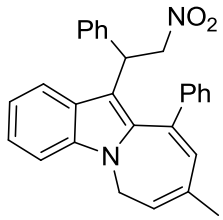
Catalytic *C3*-functionalization of azepinoindoles.



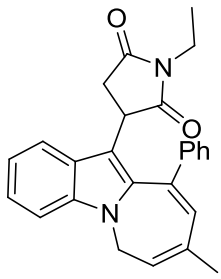
In a Schlenck tube, under nitrogen atmosphere and in absence of light, [Au(*I*Pr)Cl] (5 mol%) was dissolved in 0.5 ml of anydrous toulene; then AgOTf (5 mol%) was added to generate the gold catalytic specie in situ. After stirring 20 min in the dark, the acyclic precursor was dissolved in further 0.5 ml of toluene and added to the reaction mixture.Then, the Schlenck tube was placed in a pre-warmed bath at 110 °C and the reaction stirred for additional 4 hours. After completation, the temperature was lowered at 90°C and the Micheal acceptors (1.5 eq.) added in the tube.The reaction stirred over-night and after completation (TLC analysis), toluene was removed under reduced pressure and the crude purified by flash-chromatography (95:5 cHex:AcOEt).



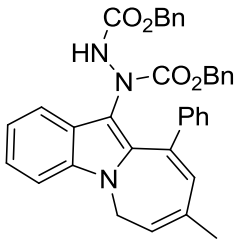
8a. Orange oil. Yield : 73 %. ^{1}H-NMR (400Hz, $CDCl_3$), δ: 1.83 (s, 3H); 1.91 (s, 3H); 2.37 (dt, J_1 = 2.8 Hz, J_2 = 8 Hz, 2H); 2.45 (dt, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 2H); 4.61 (d, J = 6.8 Hz, 2H); 5.83 (t, J = 6.8 Hz, 1H); 6.39 (s, 1H); 7.06 (pt, J = 8 Hz, 1H); 7.22 (pt, J = 8 Hz, 1H); 7.35 (m, 4H); 7.45 (dd, J_1 = 2 Hz, J_2 = 7.6 Hz, 2H); 7.52 (d, J = 8 Hz, 1H); ^{13}C-NMR (100MHz, $CDCl_3$) δ: 19.3, 22.1, 29.5, 40.7, 44.0, 108.8, 111.8, 118.89, 118.9, 121.9, 124.4, 127.0, 127.9, 128.0, 128.2, 128.3, 128.5, 131.0, 134.2, 134.5, 138.2, 140.1, 142.3, 208.7. LC-MS: 342 (M+1), 364 (M+Na); t_r = 12.323.



8b. Orange oil. Yield : 69%.^{1}H-NMR (400Hz, $CDCl_3$), δ: 1.95 (s, 3H); 4.55 (dd, J_1 = 5.6 Hz, J_2 = 14 Hz, 1H); 4.63 (t, J = 8 Hz, 1H); 4.75 (dd, J_1 = 7.6 Hz, J_2 = 13.2 Hz, 2H); 5.02 (dd, J_1 = 8 Hz, J_2 = 12.4 Hz, 1H); 5.86 (t, J = 6.8 Hz, 1H); 6.54 (s, 1H); 7.02 (m, 3H); 7.16 (m, 3H); 7.23 (m, 4H); 7.32 (d, J = 8 Hz, 1H); 7.43 (m, 3H); ^{13}C-NMR (100MHz, $CDCl_3$) δ: 21.8, 26.9, 40.2, 40.8, 78.5, 109.4, 119.5, 120.2, 121.8, 124.5, 126.6, 126.8, 127.2 (2C), 127.9 (2C), 128.0, 128.3 (2C), 128.6 (2C), 132.6, 134.8, 136.3, 137.5, 139.4, 140.4, 141.9. LC-MS: 421 (M+1), 443 (M+Na); t_r = 13.642.



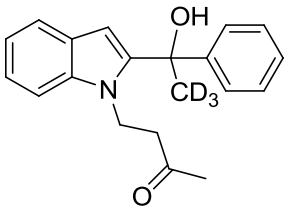
8c. Orange oil. Yield : 65 %.^{1}H-NMR (400Hz, $CDCl_3$), δ: 1.22 (t, J = 6.8 Hz, 3H); 1.95 (s, 3H); 2.52 (dd, J_1 = 9.2 Hz, J_2 = 18.4 Hz, 1H); 2.69 (dd, J_1 = 6.8 Hz, J_2 = 18.4 Hz, 1H); 3.58 (m, 3H); 4.5 (dd, J_1 = 6 Hz, J_2 = 14.4 Hz, 1H); 4.76 (dd, J_1 = 7.2 Hz, J_2 = 14.4 Hz, 1H); 5.87 (t, J = 6.8 Hz, 1H); 6.49 (s, 1H); 7.04 (m, 1H); 7.22 (m, 1H); 7.30 (d, J = 7.6 Hz, 1H); 7.33-7.53 (m, 6H). LC-MS: 397 (M+1), 419 (M+Na); t_r = 11.337.



8d. Orange oil. Yield : 49 %.^{1}H-NMR (400Hz, $CDCl_3$), δ: 1.86 (s, 3H); 1.91 (s, 3H); 2.39 (dt, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 2H); 2.47 (dt, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 2H); 4.64 (d, J = 6.4 Hz, 2H); 5.86 (t, J = 6.8 Hz, 1H); 7.08 (pt, J = 7.6 Hz, 1H); 7.25 (pt, J = 8 Hz, 1H); 7.38 (m, 4H); 7.47 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 2H); 7.54 (d, J = 8.4 Hz, 1H); ^{13}C-NMR (100MHz, $CDCl_3$) δ: 19.3, 22.0, 29.5, 40.7, 44.0, 108.8, 111.9, 118.9, 118.95, 121.9, 122.9, 124.4, 127.9, 128.0, 128.2, 128.5, 131.0, 134.2, 134.5, 138.2, 138.24, 140.0, 142.3, 208.7. LC-MS: 343 (M+1), 365 (M+Na); t_r = 12.423.

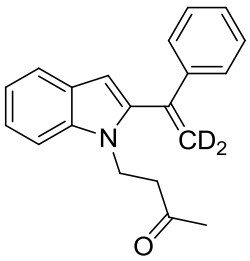
Control experiment with deuterated compound D_3-1a. (Scheme 2).

D_3-2a was obtained by stirring D_3-1a in toluene at 70 °C under classical conditions.



D_3-**2a**. Yellowish oil. Yield: 90%. ^{1}H-NMR (200 MHz, $CDCl_3$), δ: 1.89 (s, 3H); 2.65-2.68 (m, 2H); 4.14-4.17 (m, 1H); 4.43-4.45 (m, 1H); 6.70 (s, 1H); 7.29-7.31 (m, 7H); 7.65 (dd, J_1 = 13.2 Hz, J_2 = 3.2 Hz, 1H). LC-MS: 311 (M+1); 333 (M+Na).

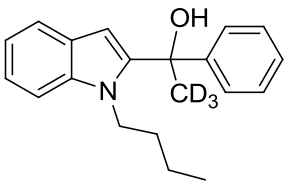
D_2-**3a** was obtained by stirring *D_3*-**2a** in toluene at 90 °C under classical conditions.



D_2-**3a**. Reddish oil. Yield: 83%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.88 (s, 3H); 2.49 (t, J = 7.6 Hz, 2H); 4.02 (t, J = 7.6 Hz, 2H); 6.54 (s, 1H); 7.08 (dt, J_1 = 8Hz, J_2 = 1.2 Hz, 1H); 7.16 (dt, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 1H); 7.21 (d, J = 8.0 Hz, 1H); 7.19-7.21 (m, 5H); 7.58 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H). LC-MS: 292 (M+1), 314 (M+Na).

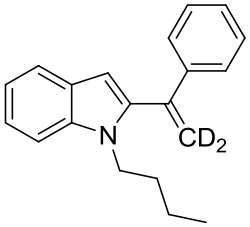
Control experimental C_{sp2}-D/H exchange reaction catalyzed by [Au(IPr)Cl] /AgOTf.

D_3-**5**[1] was synthesized by a classical Sonogashira cross-coupling between N-butyl-2-iodo-aniline and *D_3-2*-phenylbut-3-yn-2-ol *D_3*-**2a**.



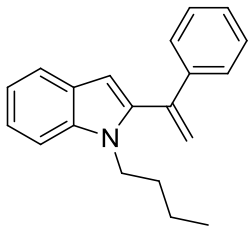
D_3-**5**[1]. Red viscous oil. Yield: 72%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 0.96 (t, 7.2 Hz, 3H); 1.38-1.47 (m, 2H); 1.57-1.65 (m, 2H); 3.14-3.18 (m, 2H); 6.61 (d, J = 8.4 Hz, 1H); 6.64 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H); 7.23 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H); 7.34-7.36 (m, 2H); 7.41 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 2H); 7.76 (dd, J_1= 8.6 Hz, J_2 = 3.2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ:13.8, 20.2, 31.4, 43.1, 70.4, 81.8, 98.5, 106.4, 109.5, 115.9, 124.9 (2C); 127.7, 128.4 (2C); 130.2, 132.1, 145.8, 149.3.LC-MS: 297 (M+1).

D$_2$-**5** was synthesized by subjecting *D*$_3$-**5**[1] to cat **2** in toluene at 110 °C until completion consumption of the starting material. The crude was the purified by chromatography column c-Hex-AcOEt 99:1.



D$_2$-**5**. Orange viscous oil. Yield: 95%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 0.78 (t, J = 7.6 Hz, 3H); 1.13 (q, J= 7.6 Hz, 2H);1.51 (q, J = 7.6 Hz, 2H); 3.78 (t, J = 7.6 Hz, 2H); 6.58 (s,1H); 7.13 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H); 7.20-7.28 (m, 3H); 7.31-7.38 (m, 4H); 7.64 (d, J = 7.6 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ:13.6, 20.0, 31.8, 43.9, 103.2, 109.7, 119.5, 120.5, 120.6, 121.5, 125.3, 126.9, 127.9, 128.1, 128.2, 128.4, 129.0, 137.3, 140.0, 141.5. LC-MS: 278 (M+1).

The exchange reaction was performed in a Schlenk tube under air, in which Au(*i*Pr)Cl (5 mol%) was dissolved in toluene and then AgOTf (a tip of spatula) was added to generate the cationic gold catalytic specie. After 20 minutes stirring, *D*$_2$-**5** and 2-4 eq. of water were added in sequence. The Schlenk tube was sealed and allowed to warm to 90-110 °C for 4 hs. Different degrees of protodeuteration were recorded according the temperature and the equivalents of water by ^{1}H-NMR**.**



H$_2$-**5.** Yellow oil.^{1}H-NMR (400 MHz, $CDCl_3$), δ: 0.8 (t, J = 7.2 Hz, 3H); 1.45 (q, J = 7.2 Hz, 2H); 1.14-1.18 (m, 2H); 3.80 (t, J = 7.2 Hz, 2H); 5.56 (d, J = 1.6 Hz, 1H); 5.80 (d, J = 1.6 Hz, 1H); 6.60 (s, 1H); 7.15 (pt, J = 6.8 Hz, 1H); 7.22 (pt, J = 6.8 Hz, 1H); 7.33-7.38 (m, 6H); 7.66 (d, J = 7.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ:13.6, 20.0, 31.8, 43.9, 103.2, 109.7, 118.1, 119.5, 120.6, 121.5, 126.9, 127.9, 128.1, 128.4 (2C); 137.3, 140.1, 140.6, 141.7. LC-MS: 276 (M+1).

6. Gold catalyzed synthesis of [1,2-*a*]-pyrido- and [4,3-*a*]-oxazino-indoles

6.1 Propargylic alcohols in the synthesis of [1,2-*a*]-pyrido- and [4,3-*a*]-oxazino-indoles.

Amazed by the synthetic flexibility of aniline-based tertiarty propargylic alcohols we got involved in the study of new reactivity in order to develop new gold catalyzed cascade reaction for the synthesis and functionalization of the indole cores. In the previous work, a single gold catalyst was able to promote the hydroamination step in intermediate **1**, in order to synthesize the indole ring. A Lewis/Bronsted acid activation was able to induce the dehydration of the alcohol generating a vinyl-indole specie **C**. Only later the formation of an unprecedented gold-vinyl specie would led to the attack to the ketone to generate the azepino indole scaffold **4**.

Our idea was to try to invert the reactivity of propargylic intermediate **D**, designing an acyclic precursor **5**, with a pre-installed nucleophilic moiety, that could attack the alcohol intermediate *via* a dehydrative nucleophilic substitution (Figure 6.1).

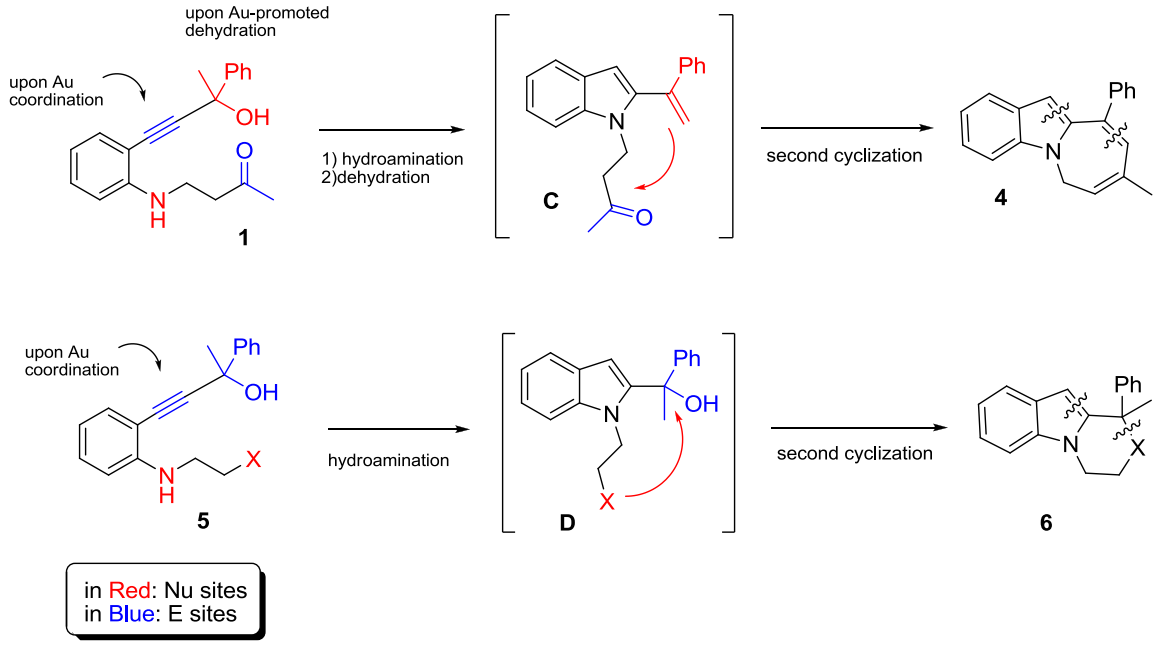


Figure 6.1. *Mechanistic hypothesis for the inversion of reactivity of propargylic alcohols.*

In fact, when allowed to react in the presence of mild metal bifunctional π/σ acids, the alcoholic group of a propargylic alcohol can exert either nucleophilic or electrophilic character, depending on the chemical surrounding.[1]

Again Gold catalysis appeared, to our hypothesis, a proven tool to promote a cascade process involving a first hydroamination step and a final FC event.

In fact, several example of catalytic [Au(I)]/[Au(III)] dehydrative Friedel-Crafts reactions are reported in literature.

6.2 [Au]-catalyzed dehydrative nucleophilic substitution of benzylic alcohols.

In contrast with the allylic and propargylic substrates that also involve aryl substitution described in Chapter 5, dehydrative SN1 reactions are possible with non-allylic or nonpropargylic arylic alcohols too. Beller *et al*. accomplished C–C bond-formation through a gold-catalyzed Friedel–Crafts-type benzylation of *o*-xylene with the benzylic alcohols (Figure 6.2).[2]

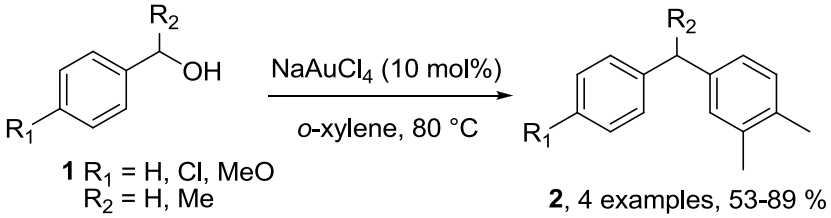


Figure 6.2 *[Au(III)]-catalyzed FC reaction of electron-rich aromatic rings.*

The same strategy was described by Medio-Simón for the synthesis of the unsymmetrical benzylic ethers **4** from the benzylic alcohols **3** and saturated alcohols that were used as solvents (Figure 6.3).[3]

This methodology is compatible with the use of primary, secondary, and tertiary aliphatic alcohols as nucleophiles and gives moderate to high yields. The reactions proceed under relatively mild conditions and give moderate to good yields with activating or deactivating groups on the benzylic moiety.

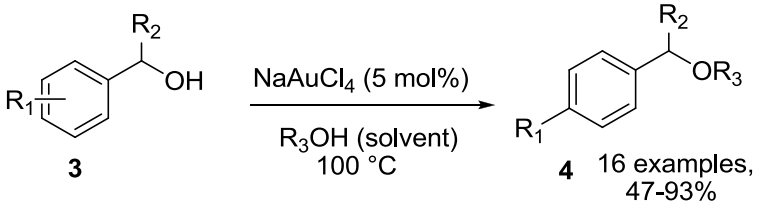
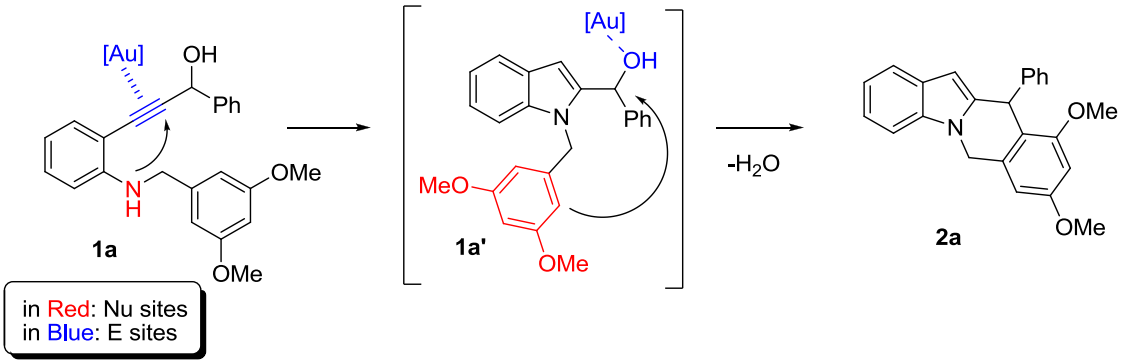


Figure 6.3 *[Au(III)]-catalyzed etherification of benzylic alcohols.*

6.3 Results and discussion

Intrigued by the possibility to study another approach towards the synthesis and functionalization of the indole core, we designed an acyclic precursor with a nucleophilic moiety preinstalled on the aniline framework, namely an electron-rich aromatic ring. To our hypothesis, subjecting intermediate **1a** to a [Au(I)] catalyst, it was possible to promote a hydroindolination step and then a Friedel-Crafts (FC) reaction onto the activated benzylic alcohol (Scheme 6.4).



Scheme 6.4 *Design of a [Au(I)]-catalyzed cascade hydroamination/FC reaction sequence*

Delightly, when we treated intermediate **1a** to several [Au(I)] complexes it was possible to isolate a dihydroindole[1,2-*b*]-isoquinoline derivative **2a**.[4] Such a kind of molecular architectures are of considerable pharmacological relevance because they represent *C*-analogues of tryptanthrin, a cytotossic drug (Figure 6.5).[5]

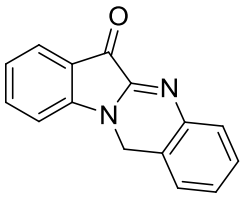
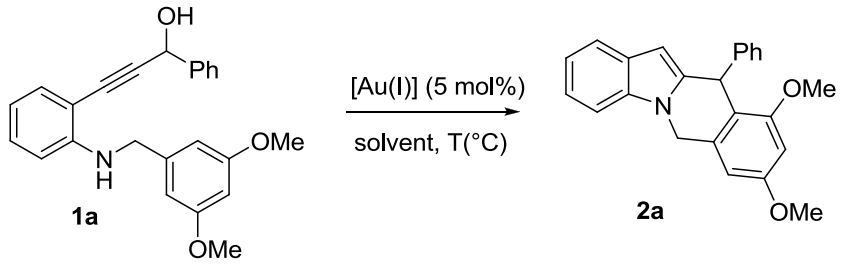


Figure 6.5. *tryptanthrin: a Potent Inhibitors of Indoleamine 2,3-Dioxygenase with Therapeutic Activity in Lewis Lung Cancer (LLC) Tumor*

Our model substrate **1a** was subjected to a survey of reaction conditions: gold catalysts, solvents and temperature in order to find the best catalytic conditions for this transformation (Table 6.5).

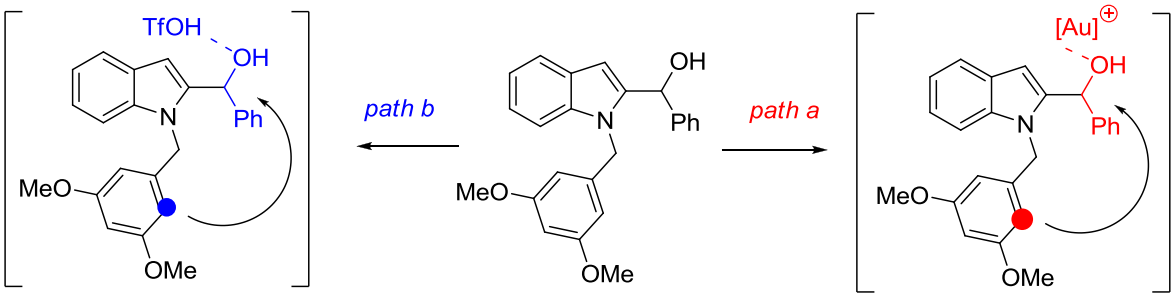


entry	[Au(I)]/AgX	Solvent	Temperature (°C)	Yield (%)
1	[JhonPhosAu](SbF$_6$)(CH$_3$CN)	DCE	60	-
2	PPh$_3$AuCl/AgPNB[a]	DCE	60	-
3	PPh$_3$AuNTf$_2$	toluene	60	40
4	*I*PrAuCl/AgBF$_4$	CH$_2$Cl$_2$	25	35
5	*I*PrAuCl/AgOTf	toluene	60	50
6	*I*PrAuCl/AgOTf	toluene	90	66

(a) AgPNB= Ag-*p*-nitro-benzoate.

Table 6.5 *Optimization table for the synthesis of indole[1,2-b]indole.*

The best catalytic conditions for this transformation resulted in the use of a NHCAu(I) complex, *I*PrAuCl cationized with AgOTf in toluene at 90 °C (entry 6), providing indole-isoquinoline **2a** with 66 % of yields. More coordinating counterions PNB (entry 2), NTf$_2$, (entry 3) and BF$_4$ (entry 4), proved to be less competent in promoting the last cyclization step. The role of OTf resulted to be fundamental in the last dehydrative FC step (the annulation step). This could be probably due to an improved electrophilicity of tha Au(I) specie (*path a*) or to the generation of catalytic amounts of a strong Bronsted acid (HOTf) that *co*-catalyzed the FC step (*path b*, Scheme 6.6).



Scheme 6.6 *Mechanistic hypothesis for the FC reaction onto the benzylic alcohol.*

We reported two further examples concerning the synthesis of indole-[1,2-*b*]-isoquinolines starting from acyclic precursor with an EDG and an EWG on the *para* position of benzylic alcohols (Figure 6.7).

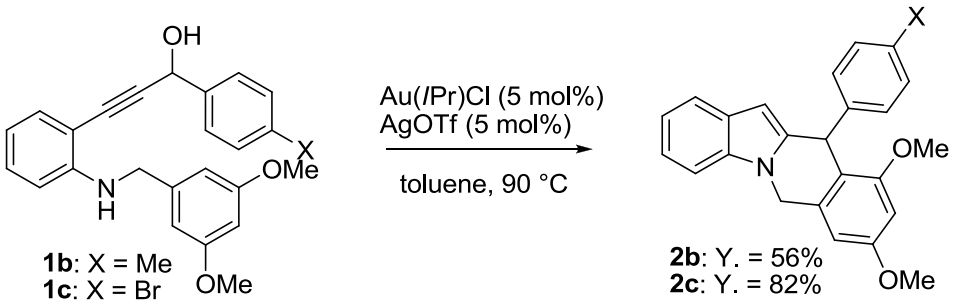


Figure 6.7 *Scope for the synthesis of indole[1,2-b]-isoquinolines.*

The presence of an EWG as a bromide activates the benzylic alcohols towards the FC reaction; this resulted in better yields (**2c**, 82%) respect to a group bearing a more EDG (*i.e.* Me) which leads to the synthesis of the indole-isoquinoline with poorer yields (**2b**, 56%).

Amazed by the discovery of the modulating properties of propargylic alcohols derivates, we get more insight into the possibility to develop a cascade reaction for the synthesis of indoles with more interesting biological activities.

In designing an amine-diol of type **1d** as acyclic precursors, we would open access to a very important class of compounds, the oxazino-[4,3-*a*]-indoles which have attracted growing attention due to their peculiar activity as ligands for 5-HT_2C receptor, antidepressant, and 5-HT_4 receptor antagonists (Figure 6.8).[6]

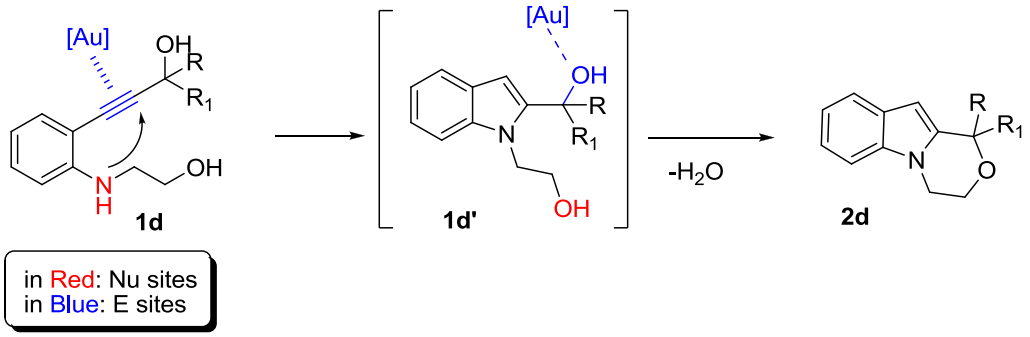
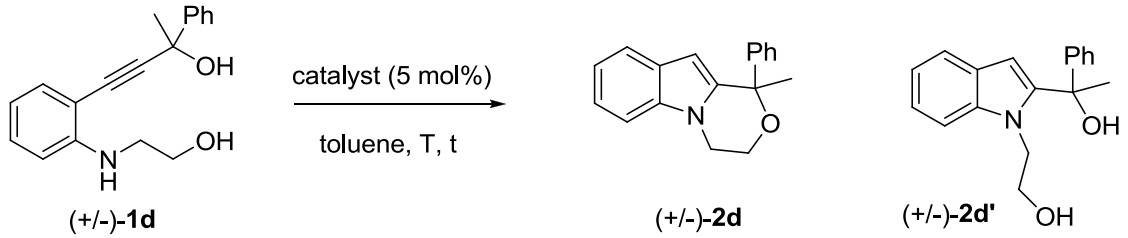


Figure 6.8 *Mechanistic hypothesis for the [Au(I)]-catalyzed synthesis of [4,3-a]-oxazinoindoles.*

The choice of unprotected amine diol **1d** as model substrate, again, significantly restricted the class of potentially useful promoting agents.

While Brønsted acids would presumably form the unreactive corresponding ammonium salts, conventionals Lewis acids could either be irreversibly deactivated by coordination to the hard heteroatoms or would lead to decomposition of the starting material if propargylic carbocations are formed before the hydroamination of the C-C triple bond takes place. Consequently, π-acid late-transition metal species, particularly [Au(I)] complexes appeared to be the promoters of choice for the titled transformation. In Table 6.9, we summarize some of the results obtained during the optimization of the catalytic system, choosing **1d** as the model substrate.



(+/-)-**1d** (+/-)-**2d** (+/-)-**2d'**

entry	Catalyst	T(°C)/ time (h)	Yield 2d/2d' (%)
1	$HNTf_2$	25/3.5	-/-
2	*p*TsOH	25/3.5	-/-
3	$AgNTf_2$	25/3.5	9/-
4	$In(OTf)_3$	25/3.5	-/-
5	$(PPh_3)_2PdCl_2$	25/3.5	-/-
6	$AuCl_3$/AgOTf	25/3.5	16/-
7	PPh_3AuNTf_2	25/3.5	-/11
8	Au*I*PrCl/$AgNTf_2$	25/3.5	55/-
9	[JhonPhosAu](MeCN)(SbF_6)	25/17.5	-/57
10	$XPhosAuNTf_2$	25/3.5	71/-
11	[XPhosAuCl]/AgOTf	25/3.5	62/-
12	[XPhosAuCl]/AgOTs	25/3.5	33/-
13	[XPhosAuCl]/$AgSbF_6$	25/3.5	-/24
14	[XPhosAuCl]/$AgBF_4$	25/3.5	-/25
15	$XPhosAuNTf_2$	50/3.5	92/-
16	$XPhosAuNTf_2$	50/48	76/-

[a] All the reactions were carried out under nitrogen atmosphere in anhydrous toluene with 5 mol% loading of catalyst, unless otherwise specified. [b] Yields of produce isolated after flash chromatography. [c] Substantial decomposition of 1a was observed. [d] Starting material 1a was recovered untouched. [e] XPhosAuCl was formed in situ. [f] With 1 mol% of $XPhosAuNTf_2$, JhonPhos=

(2-biphenyl)di-tert-butylphosphine, XPhos=dicyclohexyl[2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine, IPr=1,3-bis(diisopropylphenyl) imidazol-2-ylidene.

Table 6.9 *Optimization table for the synthesis of [4,3-a]-oxazino-indoles.*

As expected, organic Brønsted acids such as $HNTf_2$ and *p*TsOH were not efficient, leading to rapid decomposition of **1d** (Table 6.9, entries 1,2). $AgNTf_2$ furnished **2d** but in unsatisfactory manner (yield = 9%, Table 6.9, entry 3).

Some improvements were recorded in the presence of $AuCl_3$/AgOTf (5 mol%), which led to **2d** in 16% yield along with the recovery of untouched **1d** (Table 6.9, entry 4). This finding prompted us to investigate less heterophilic [Au(I)] species.

Well-defined silver-free Gagosz complex [PPh_3AuNTf_2] and [JhonPhosAu] showed some aptitude in triggering the initial 5-*endo*-dig cyclization (**2d'**, 11% and 57%, respectively), but the second ring-closing event was not promoted at all (Table 6.9, entries 5, 7).

To our delight, cationic gold carbene species [Au*I*PrCl]/$AgNTf_2$ and commercially available [$XPhosAuNTf_2$] provided **2d** in 55% and 71% yield, respectively, at room temperature after 3.5 h reaction time (Table 6.9, entries 6, 8).

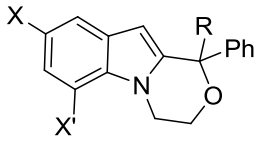
The role of the counterion was then investigated, and control experiments (Table 1, entries 11–14) clearly show the superior efficiency of NTf_2 in comparison to OTf, OTs, and SbF_6.

Finally, we were pleased that the reaction at 50 °C in the presence of silver-free [$XPhosAuNTf_2$] (5mol%) gave quantitative conversion within 3.5 h, providing **2d** in 92% yield (Table 6.9, entry 13).[7]

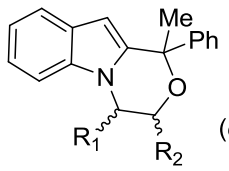
The loading of the catalyst was also reduced to 1 mol%; in this case longer reactiontime was required (48 h) but synthetically useful yield (76%) was still obtained (Table 6.9, entry 14).

Having established the optimal reaction conditions, we examined the generality of the methodology in terms of substrate scope. A range of tertiary and secondary propargylic alcohols (**1e**–**u**) were synthesized and subjected to the double ring-closing process under the assistance of [$XPhosAuNTf_2$] (5 mol%, toluene, 50 °C).

A collection of tricyclic and tetracyclic products is summarized in Figure 6.10.

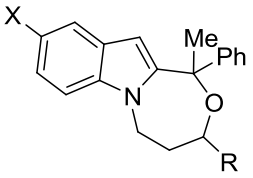


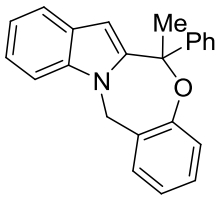
2e, X = F, X' = H, R = Ph, Y = 84%
2f, X = Me, X' = H R = Ph, Y = 81%
2g, X = Me, X' = H, R = Me, Y = 83%
2h, X = H, X' = H, R = *i*Pr, Y = 53%
2i, X = H, X' = H, R = nC_9H_{19}, Y = 96%
2j, X = H, X' = H, R = $(CH_2)_2CO_2Et$ Y = 71%
2k, X = Me, X' = Me, R = Ph, Y = 80%



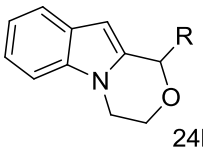
(*d.r.* = 1:1)

2l, R_1 = H, R_2 = Me, Y = 67%
2m, R_1 = Ph, R_2 = H, Y = 98%
2n, $R_1 = R_2 = C_4H_8$, Y = 96%





2r, Y =77% (24h)



24h, 100°C

2s, R = *p*Me-Ph, Y = 70%
2t, R = Ph, Y = 82%
2u, R = *p*MeO-Ph, Y = 56%

2o, X = H, R = H, Y =56% (24h)
2p, X = Me, R = Me, Y = 92% (24h, *d.r.* = 1:1.9)
2q, X =CN, R = Me, Y = 69% (100°C, 24h, *d.r.* = 1:1)[a]

Figure 6.10 *Scope of the reaction (reaction conditions: XPhosAuNTf$_2$ (5 mol%), toluene, 50 °C, 3.5 h, unless otherwise specified). All substrates were obtained as racemic mixtures. [a]: IPrAuCl/AgNTf$_2$ (5 mol%) as the catalyst.*

A range of oxazinoindoles (**2e**–**k**) were obtained in good to excellent yields (53–96%). In particular, aliphatic (**2g**–**j**) and aromatic groups (**2e**, **f**, **k**,) on the carbynol carbon atom were adequately tolerated along with electron-withdrawing electron-donating groups on the aniline ring.

Moreover, the oxazinyl ring was also substituted with aryl and alkyl groups, leading to compounds **2l**–**n** in good yields (67– 98%).

Important building blocks in medical chemistry such as tetrahydro-[1,4]-oxazepino [4,3-*a*]indoles, featuring a seven-membered ring fused at the N(1)/C(2) positions (**2o**–**r**), were also accessible through the present protocol in good yield (53–92%).

Finally, we explored the gold-catalyzed cascade reaction with secondary propargylic alcohols. Despite the higher reaction temperature required (100 °C), the corresponding targeted compounds **2s**–**u** were obtained in reasonable yields (56–82%).

While substrate **1z** was recovered unreacted because probably the less reactivity of primary alcohol respect to secondary and tertiary alcohol (Figure 6.11).

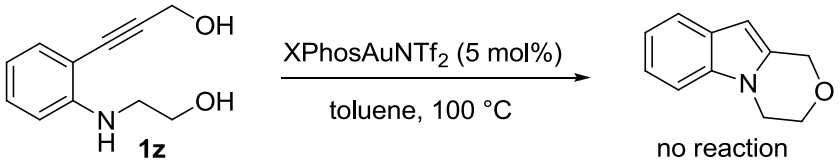
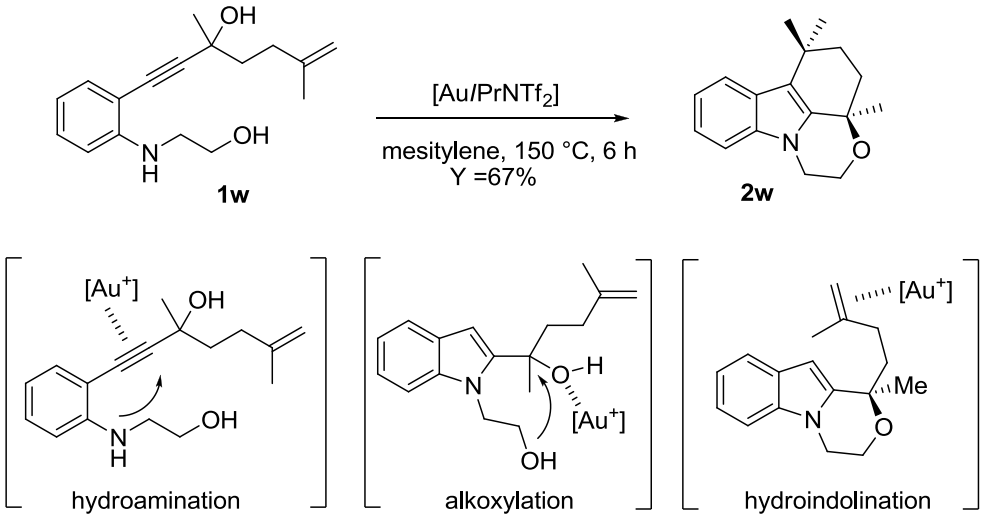


Figure 6.11 *Unreactive substrate **1z**.*

The synthetic potential of the present methodology was underlined further by the realization of a triple-cascade reaction using **1w** as starting material.

The use of 5 mol% [Au(*I*Pr)NTf_2] led to the one-pot regioselective 5-*endo*-dig hydroamination of the C-C triple bond, alkoxylation of the carbynol carbon atom, and 6-*exo*-trig hydroindolination of the olefin in satisfying yield (69%, Scheme 6.12). The three consecutive gold-assisted ring-closing events (*i.e.*, hydroamination, alkoxylation, hydroindolination) open an efficient access to tetracyclic indolyl scaffolds of type **2w**, featuring concomitant N(1), C(2) and C(3) functionalization.



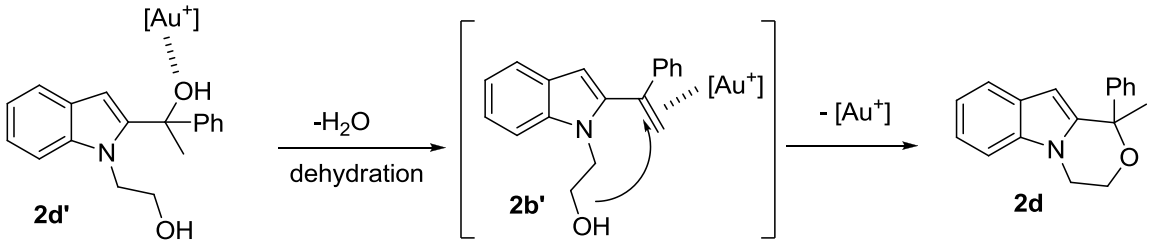
Scheme 6.12 *[Au(I)]-catalyzed triple cascade reaction for the synthesis of highly functionalized indoles.*

Finally even in this case we get more insights into a mechanistic rationalization of this chemical transformation. Particularly, using some catalyst it was possible to isolate the indole intermediate **2d'** generated by the gold-triggered formation of the indolyl core (5-*endo*-dig hydroamination of the triple bond).

At this stage we hypothesized two different mechanistic pathway.

In the first case, [Au(I)] could behave as a Lewis acid promoting the dehydration of the tertiary alcohol intermediate **2d'** providing vinyl indole **2b'** (Scheme 6.13).

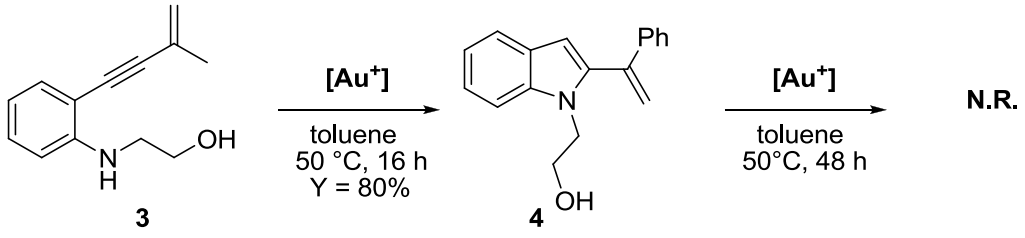
Then again, [Au(I)] catalyst would be able to activate the double bond and promote the attack of the hydroxyle onto the alkene generating the oxazino indole.



Scheme 6.13 *Mechanistic hypothesis: LA activation of alcohol* ***2d'*** *and activation of the alkene by [Au(I)] catalyst.*

This hypothesis was refused when the probe ene-yne compound **3** was subjected to gold catalysis, to synthesize cyclized 2-vinyl indole **4** that was isolated in 80% yield (Scheme 6.14).

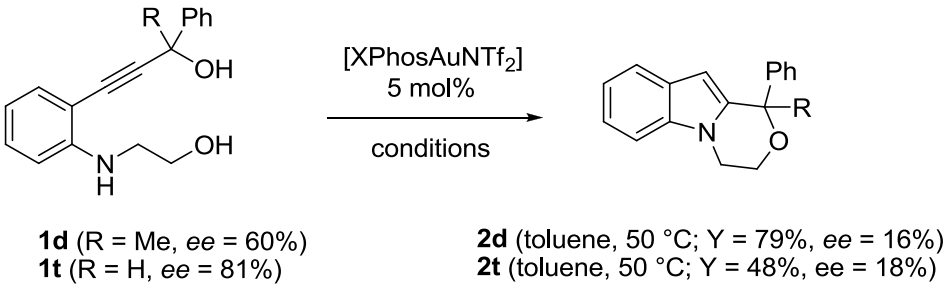
Interestingly, compound **4** was recovered untouched even after prolonged reaction (48 h), thus demonstrating the unfeasibility of the gold-catalyzed hydroalkoxylation of the electron-rich carbon–carbon double bond.



Scheme 6.14 *Experimental evidence for a [Au(I)] activation of the alkene.*

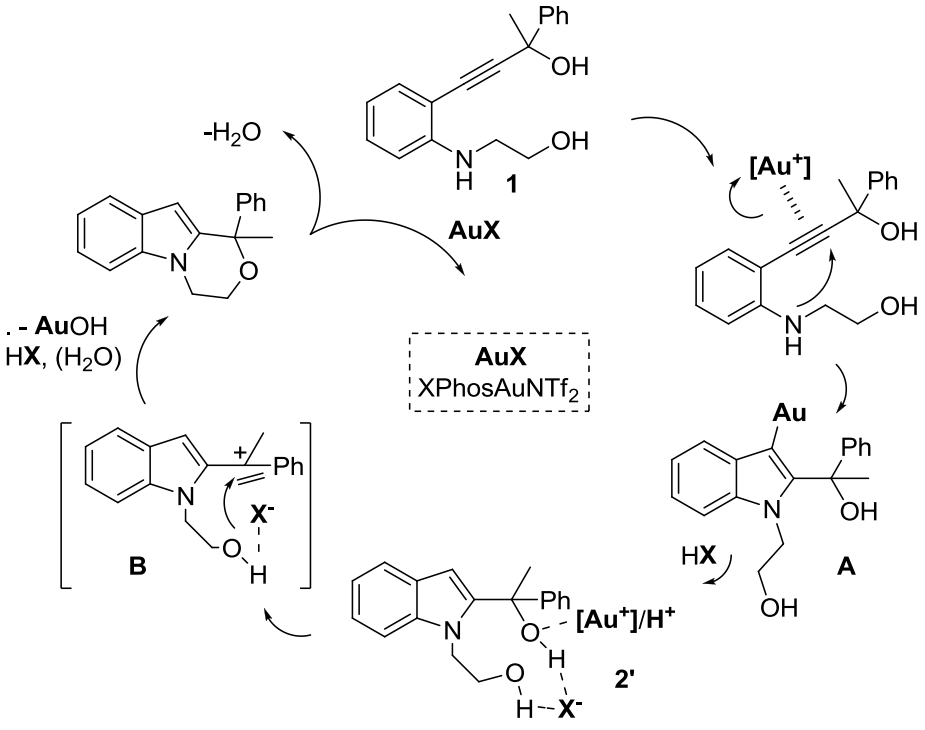
For the second hypothesis we thought about a SN1 type mechanism. So enantiomerically enriched alcohols **1d** (*ee* = 60%) and **1t** (*ee* = 81%, see the Supporting Information) were allowed to react in the presence of [XPhosAuNTf$_2$] (5 mol%).

Unexpectedly, under optimal conditions (*i.e.*, toluene, 50 °C), significant but not complete racemization was recorded in both cases (Scheme 6.15).[8,9]



Scheme 6.15 *Partial racemization recovered in the [Au(I)]-assisted SN1 reaction of* ***1d****.*

This evidence can be rationalized with a "not-pure" SN1-type mechanism[10] in the presence of ion pairs of type **B** (Scheme 6.16). Accordingly, we recently reported on the "folding effect" played by the counterion in the enantioselective gold-catalyzed alkylation of indoles with allylic alcohols. Here, the negatively charged species (*i.e.*, OTf) binds simultaneously to the acidic protons of the substrate. Analogous situation could be envisioned in the present C-O bond-forming process (see intermediate **2'**), with direct impact of the gold counterion on the geometry of the incoming electrophilic center.



Scheme 6.16 *Mechanism hypothisized for the cascade process for [4,3-a]-oxazinoindoles.*

To confirm the presence of ion pairing in the C-O bondforming event, a highly coordinating solvent (*i.e.*, THF) was utilized, leading to the desired product in lower yield (39%) and to complete racemization (Figure 6.17). This speculative interpretation is also in agreement with the decreasing reactivity trend recorded with the propargylic alcohols (tertiary > secondary > primary) that also tends to exclude a mixed SN1–SN2 reaction profile.[11]

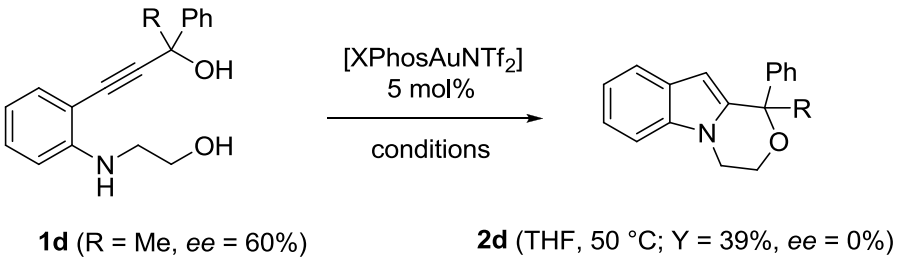


Figure 6.17 *Solvent effect in leds to racemization of enantioenriched alcohol* ***1d****.*

6.4 Conclusions.

In conclusion in this section, we envisioned the chemical flexibility of aniline-based propargylic alcohols in the synthesis of polycylic fused indole cores. The use of pre-installed nucleophilic moieties such as electron-rich arenes or simple primary alcohols opened access to indole[1,2-*b*]-isoquinolines or [4,3-*a*]–oxazino-indoles. A single [Au(I)] catalyst was able to promote a *hydroamination*/*dehydrative nucleophilic substitution* cascade sequence synthesizing highly functionalized indole architectures with high chemoselectivity and producing water as only stoichiometric by-product.

Bibliography

[1]. E. B. Bauer, *Synthesis* **2012**, 1131 – 1151.

[2]. K. Mertins, I. Iovel, J. Kischel, A. Zapf, M. Beller, *Adv. Synth.Cat.* **2006**, *348*, 691–695.

[3]. A. B. Cuenca, G. Mencha, G. Asensio, M. Medio-Simón, *Chem. Eur. J.* **2008**, *14*, 1518–1523.

[4]. G.Cera, M. Bandini, *unpublished results*.

[5]. Bergman, J.; Lindström , J.-O.; Tilstam, U. *Tetrahedron*, **1985**, *41*, 2879 and references cited therein.

[6]. a) C. A. Demerson, G. Santroch, L. G. Humber, *J. Med. Chem*. **1975**, *18*, 577 –580; b) C. Farina, S. Gagliardi, P. Misiano, P. Celestini, F. Zunino, PCT Int. Appl., *WO 200510521 3A2 20051110*, **2005**.

[7]. M. Chiarucci, E. Matteucci, G. Cera, G. Fabrizi, M. Bandini**,** *Chem. Asian J.* **2013**, *8*, 1776-1779.

[8]. For a recent review on gold-catalyzed chiral transfer and memory effects, see: N. T. Patil, *Chem. Asian J*. **2012**, *7*, 2186 – 2194.

[9]. At the present it is not possible to discriminate between partial inversion or retention of configuration.

[10]. a) I. P. Beletskaya, *Russ. Chem. Rev*. **1975**, *44*, 1067 –1090; b) J. M. Harris, *Prog. Phys. Org. Chem*. **1974**, *11*, 89– 173; c) D. J. Raber, J. M. Harris, P. v. R. Schleyer in Ions and Ion Pairs in Organic Reactions, Vol. 2 (Ed.: M. Szwarc), Wiley, New York, **1974**, pp. 247 – 374.

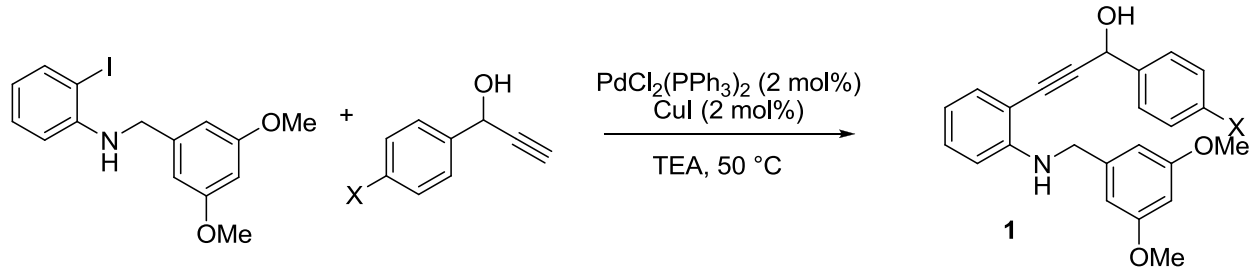
[11]. R. A. Sneen, *Acc. Chem. Res*. **1973**, *6*, 46– 53.

Supporting Information

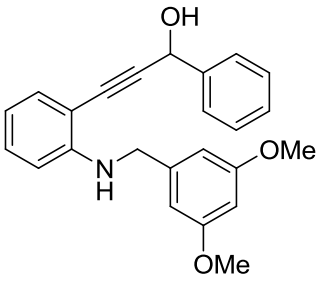
General Methods.

1H-NMR spectra were recorded on Varian 200 (200 MHz), Varian 400 (400 MHz) spectrometers. Chemical shifts arereported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, , t = triplet, q = quartet, p = pseudo, b = broad, m = multiplet), coupling constants (Hz). 13C-NMR spectra were recorded on a Varian 200 (50 MHz), Varian 400 (100 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett- Packard 5971 with GC injection. They are reported as: m/z (rel. intense). LC-electrospray ionization mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 240-400 mesh silica gel. Anhydrous THF and DCM were distilled respectively from sodium-benzophenone and P2O5 prior to use; Other anhydrous solvents were supplied by Fluka or Sigma Aldrich in Sureseal® bottles and used without any further purification. Analytical high performance liquid chromatography (HPLC) was performed on a liquid chromatograph equipped with a variable wave-length UV detector (deuterium lamp 190-600 nm), using a Daicel ChiracelTM AD and Daicel ChiralpakTM IB column (0.46 cm I.D. x 25 cm Daicel Inc). HPLC grade isopropanol and n-hexane were used as the eluting solvents. Commercially available chemicals were purchased from Sigma Aldrich, Stream and TCI and used without any further purification. Elemental analyses were carried out by using a EACE 1110 CHNOS analyzer. Optical rotations were determined in a 1 ml cell with a path length of 10 mm (NaD line). Melting points were determined with Bibby Stuart Scientific Melting Point Apparatus SMP 3 and are not corrected.

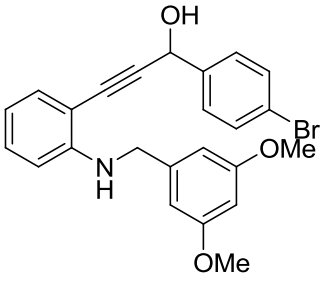
General procedures for the catalytic synthesis of 3-(2-(3,5-dimethoxybenzylamino)phenyl)-1-phenylprop-2-yn-1-ols.



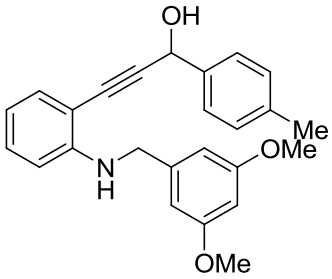
In an oven dried Schlenk tube, under nitrogen atmosphere, N-alkyl-2-iodoaniline 6 (2 mmol, 1 eq.) and alkyne 7 (2.4 mmol, 1.2 eq.) were dissolved in 4 ml of TEA. $(PPh_3)_2PdCl_2$ (0.04 mmol, 0.02 eq.) and CuI (0.04 mmol, 0.02 eq.) were added in sequence and the reaction mixture was heated at 50 °C until complete consumption of the starting material (TLC, 1-16 h). The reaction mixture was diluted with water (5 ml) and extracted with ethyl acetate (3 x 10 ml). The organic layer was dried over Na_2SO_4 and the volatiles were removed under vacuum. The residue was purified with silica-gel flash chromatography using cyclohexane and ethyl acetate mixture as eluting solvents.



1a: Orange oil . Yield =78 %. Flash chromatography *c*-Hex:AcOEt = 7:3. 1H-NMR (CDCl3, 400 MHz) δ: 3.74 (s, 6H); 4.20 (s, 2H); 5.65 (s, 1H); 6.39 (t, J = 2.4 Hz, 1H); 6.51-6.56 (m, 3H); 6.67 (t, J = 7.2 Hz, 1H); 7.12-7.18 (m, 3H); 7.32 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H); 7.45 (d, J = 8Hz, 2H). 13C-NMR (CDCl3, 100 MHz) δ:21.2, 26.9, 47.9, 55.3, 63.1, 83.3, 95.1, 99.1, 105.0 (2C), 106.9, 110.2, 116.7, 126.6 (2C), 129.4 (2C), 130.2, 132.3, 138.0, 138.2, 141.7, 148.7, 161.1 (2C). ESI-MS (m/z): 352 $[M\text{-}OH]^+$.

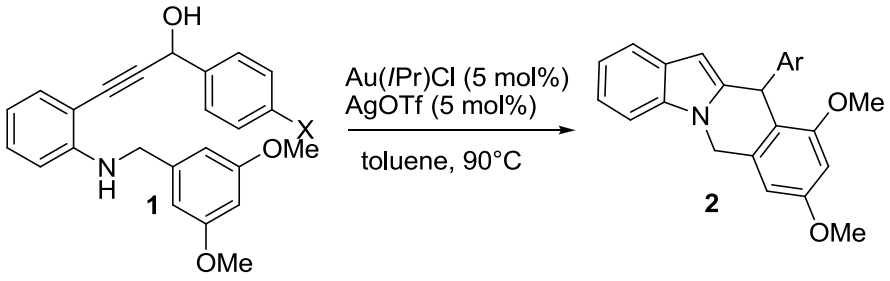


1b: Brown oil. Yield =82 %. Flash chromatography *c*-Hex:AcOEt = 7:3. 1H-NMR (CDCl3, 400 MHz) δ: 2.34 (s, 3H); 3.74 (s, 6H); 4.20 (s, 2H); 5.67 (s, 1H); 6.38 (t, J = 2.4 Hz, 1H); 6.51-6.56 (m, 3H); 6.64 (t, J = 7.2 Hz, 1H); 7.12-7.17 (m, 3H); 7.31 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H); 7.45 (d, J = 8Hz, 2H). 13C-NMR (CDCl3, 100 MHz) δ:21.2, 26.9, 47.9, 55.3, 65.1, 83.3, 95.1, 99.1, 105.1 (2C), 106.9, 110.1, 116.6, 126.6 (2C), 129.4 (2C), 130.2, 132.3, 138.0, 138.2, 141.7, 149.1, 161.1 (2C). ESI-MS (m/z): 367 $[M\text{-}OH]^+$.

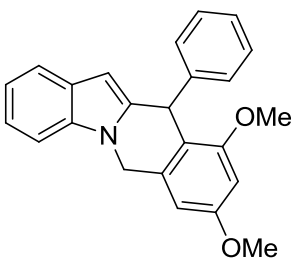


1c: Orange oil. Yield =74 %. Flash chromatography *c*-Hex:AcOEt = 7:3. 1H-NMR (CDCl3, 400 MHz) δ: 3.74 (s, 6H), 4.26 (s, 2H), 4.95 (s, 1H), 5.62 (s, 1H), 6.38 (t, J = 2.4 Hz, 1H); 6.48 (d, J = 2.4 Hz, 2H), 6.55 (d, J = 8.0 Hz, 1H); 6.29 (dt, J1 = 8.6 Hz, J2 = 2.4 Hz, 1H), 7.17 (dt, J1 = 7.4 Hz, J2 = 2.4 Hz, 1H), 7.29 (dd, J1 = 7.4 Hz, J2 = 2.4 Hz, 1H); 7.37-7.42 (m, 4H). 13C-NMR (CDCl3, 100 MHz) δ: 26.9, 47.9, 55.3, 64.5, 83.8, 94.4, 99.0, 105.2 (2C), 106.5, 110.2, 116.7, 122.3, 128.3 (2C), 130.5, 131.7, 132.4, 139.8, 141.5, 149.1, 161.1 (2C). ESI-MS (m/z): 432 $[M\text{-}OH]^+$.

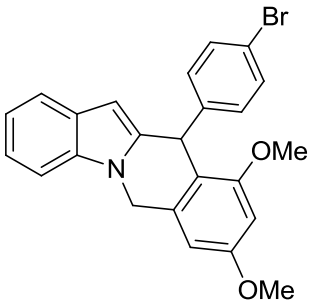
General procedure for the catalytic synthesis of indole[1,2-b]quinolines.



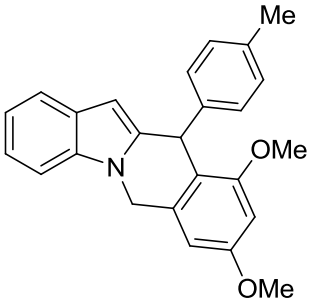
In an oven dried Schlenk tube, under nitrogen atmosphere gold catalyst was added (0.0025 mmol, 5 mol%) in 0.5 ml of anhydrous toluene and then the active specie generated by adding the silver salt (0.0025 mmol, 5 mol%). After half an hour of stirring, **1** (0.05 mmol, 1 eq.) was dissolved in 0.5 ml of anhydrous toluene and added to the reaction mixture. The reaction was heated at the desired temperature until complete consumption of the starting material (TLC, 3-24 hours). The crude reaction mixture was directly purified with silica-gel flash chromatography (cHex:EtOAc = 95:5).



2a: Orange oil. Yield = %. Flash chromatography *c*-Hex:AcOEt = 95:5. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.79 (s, 3H); 3.83 (s, 3H); 5.07 (d, J = 15.6 Hz, 1H); 5.27 (d, J = 15.6 Hz, 1H); 5.76 (s, 1H); 6.42 (d, J = 4.8 Hz, 2H); 6.50 (s, 1H); 6.98 (d, J = 7.6 Hz, 2H); 7.09 (t, J = 7.6 Hz, 1H); 7.18 (t, J = 7.6 Hz, 1H); 7.24-7.27 (m, 3H); 7.37 (d, J = 8.4 Hz, 1H); 7.56 (d, J = 8.0 Hz, 1H).

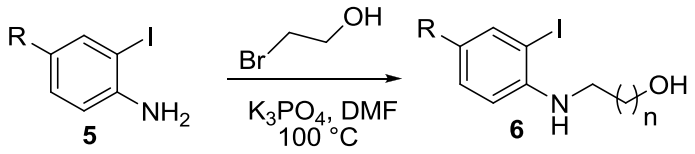


2b: Orange oil. Yield = %. Flash chromatography *c*-Hex:AcOEt = 95:5. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ:3.80 (d, J = 1.6 Hz, 3H); 3.83 (d, J = 1.6 Hz, 3H); 5.11 (d, J = 16.0 Hz, 1H); 5.283 (d, J = 15.2 Hz, 1H); 5.83 (s, 1H); 6.44 (d, J = 4.8 Hz, 2H); 6.51 (s, 1H); 7.07 -7.19 (m, 7H), 7.24 (d, J = 1.6 Hz, 1H); 7.36-7.38 (d, J = 7.6 Hz, 1H); 7.47 (d, J = 7.6 Hz, 1H).

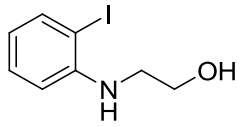


2c: Orange oil. Yield = %. Flash chromatography *c*-Hex:AcOEt = 95:5. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.21 (s, 3H); 3.81 (s, 3H); 3.83 (s, 3H); 5.08 (d, J = 15.6 Hz, 1H); 5.27 (d, J = 15.6 Hz, 1H); 5.79 (s, 1H); 6.43 (d, J = 2.8 Hz, 2H); 6.49 (d, J = 2.0 Hz, 1H); 6.95 (dd, J_1 = 19.4 Hz, J_2 = 8.4 Hz, 2H); 7.06-7.09 (m, 1H), 7.16 (dt, J_1 = 7.2 Hz, J_2 = 0.4 H, 1H),7.24-7,32 (m, 2H), 7.36 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H).

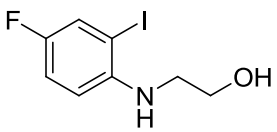
General procedures for the catalytic synthesis of (2-iodophenyl)amino alcohols 6.



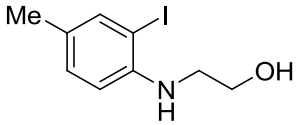
In an oven dried screw-capped Schlenk tube under nitrogen atmosphere the desired 2-iodoaniline 5 (5 mmol, 1 eq.) and K_3PO_4 (10 mmol, 2 eq.) were suspended in 3 ml of anhydrous DMF and 2-bromoethanol was added (10 mmol, 2 eq.). The brown suspension was stirred at 100 °C for 24 hours, then the reaction mixture was diluited with water (20 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude reaction mixture was concentrated under reduced pressure and purified with silica-gel flash chromatography using cyclohexane and ethyl acetate mixture as eluting solvents.



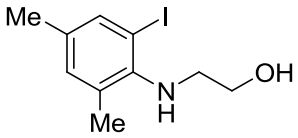
6a: from 2-iodoaniline (5a) and 2-bromoethanol. Brown oil. Yield = 90%. Flash chromatography *c*Hex:AcOEt = 9:1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.6 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 6.64 (d, J = 7.6 Hz, 1H), 6.49 (t, J = 7.6 Hz, 1H), 4.48 (bs, 1H), 3.85 (t, J = 4.8 Hz, 2H), 3.32 (t, J = 4.8 Hz, 2H), 1.79 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.2, 139.2, 129.4, 119.1, 111.0, 85.9, 61.1, 46.3. ESI-MS (m/z): 264 $[M+H]^+$.



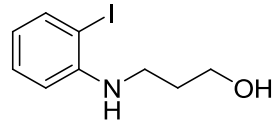
6b: from 4-fluoro-2-iodoaniline (5b) and 2-bromoethanol. Brown oil. Yield = 55%. Flash chromatography *c*Hex:AcOEt = 9:1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 7.6 Hz, J = 3.0 Hz, 1H), 6.96-6.88 (m, 1H), 6.47 (dd J = 9.0 Hz, J = 4.8 Hz, 1H), 3.46 (t, J = 5.6 Hz, 2H), 3.22 (t, J = 5.6 Hz, 2H). ESI-MS (m/z): 326, 282 $[M+H]^+$.



6c: from 2-iodo-4-methylaniline (5c) and 2-bromoethanol. Brown oil. Yield = 63%. Flash chromatography *c*Hex:AcOEt = 9:1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 4.30 (bs, 1H), 3.87 (t, J = 4.0 Hz, 2H), 3.35 (t, J = 4.0 Hz, 2H), 2.23 (s, 3H), 1.86 (bs, 1H).13C-NMR (100 MHz, CDCl3) δ 145.0, 139.4, 130.0, 128.7, 111.0, 86.1, 61.1, 46.6, 19.8.

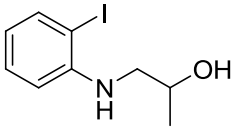


6h: 2-iodo-4,6-dimethylaniline and 2-bromoethanol. Brown oil. Yield = 65%. Flash chromatography cHex:AcOEt = 9:1. 1H-NMR (400 MHz, CDCl3): δ 7.46 (s, 1H), 6.94 (s, 1H), 4.46 (bs, 2H), 3.80 (t, J = 5.1 Hz, 2H), 3.12 (t, J = 5.1 Hz, 2H), 2.33, (s, 3H), 2.24 (s, 3H). 13C-NMR (100 MHz, CDCl3) δ 148.7, 134.1, 130.5, 127.5 , 126.0, 111.9, 79.5, 60.8, 45.8, 31.5, 20.2.

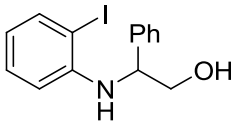


6g: In an oven dried screw-capped Schlenk tube under nitrogen atmosphere 2-iodoaniline (5 mmol, 1 eq.) and K_3PO4 (10 mmol, 2 eq.) were suspended in 3 ml of anhydrous DMF and 3-chloropropanol was added (10 mmol, 2 eq.) followed by NaI (1 mmol, 0.2 eq.). The brown suspension was stirred at 100 °C for 24 hours, then the reaction mixture was diluited with water (20 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude reaction mixture was concentrated under reduced pressure and purified with silica-gel flash chromatography (cHex:AcOEt = 7:3) to afford the product as a brown oil in 26% yield. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.66 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.22 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.61 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.45 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 3.85 (t, J = 6.0 Hz, 2H), 3.33 (t, J = 6.0 Hz, 2H), 1.95 (quint, J = 6.0 Hz, 2H). ESI-MS (m/z): 278 [M+H]+.

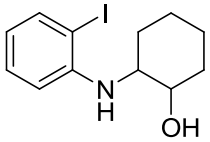
In a round bottom flask under air atmosphere 2-iodoaniline (2 mmol, 1 eq.) was dissolved in the proper epoxide and LiBr (0.4 mmol, 0.2 eq.) was added. The reaction mixture was stirred at room temperature or 100 °C until satisfactory conversion of the starting material was obtained (TLC, 24-36 h). The volatiles were removed under reduced pressure and the residue was purified with silica-gel flash chromatography using cyclohexane and ethyl acetate mixture as eluting solvents.



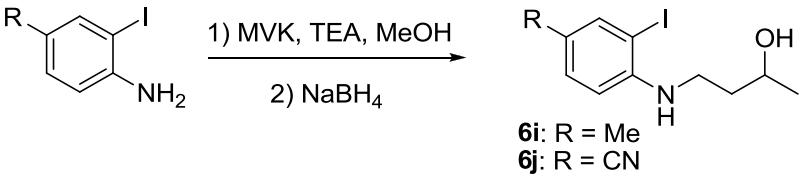
6d: from 2-iodoaniline and propylene oxide, 36 hours at room temperature. Brown oil. Yield = 86%. Flash chromatography cHex:AcOEt = 95:5. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.68 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.21 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.62 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H),6.47 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 4.11-4.05 (m, 1H), 3.27 (dd, J = 12.8 Hz, J = 3.6 Hz, 1H), 3.09 (dd, J = 12.8 Hz, J = 8.4 Hz, 1H), 1.30 (d, J = 6.0 Hz, 3H). ESI-MS (m/z): 278 $[M+H]^+$.



6e: from 2-iodoaniline and styrene oxide, 36 hours at rt. Brown oil. Yield = 80%. Flash chromatography cHex:AcOEt = 95:5. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.60 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.33-7.18 (m, 5H), 6.96 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.35 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.29 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 4.47 (dd, J = 6.8 Hz, J = 4.0 Hz, 1H), 3.89 (dd, J = 11.2 Hz, J = 4.0 Hz, 1H), 3.74 (dd, J = 11.2 Hz, J = 6.8 Hz, 1H). ESI-MS (m/z): 340 $[M+H]^+$.

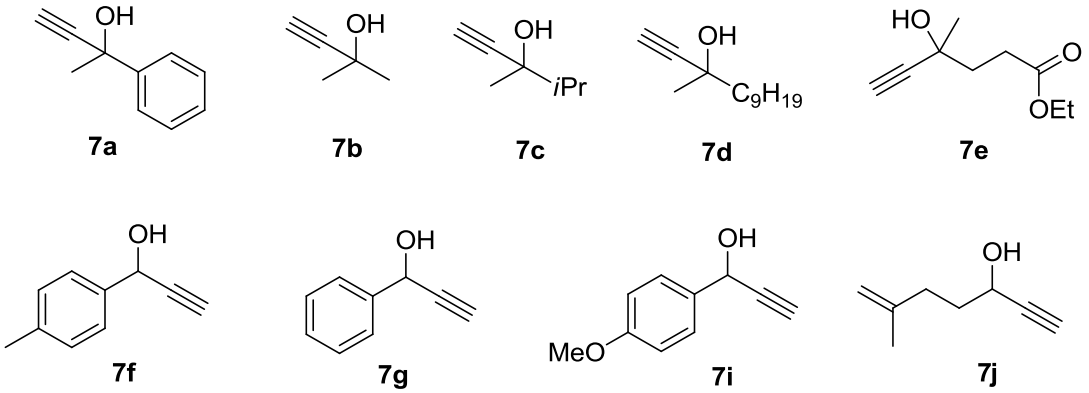


6f: from 2-iodoaniline and cyclohexene oxide, 24 hours at 100 °C. Brown oil. Yield = 68%. Flash chromatography cHex:AcOEt = 95:5. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.68 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.21 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.79 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.50 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 3.36-3.26 (m, 1H), 3.21 (ddd, J = 11.2 Hz, J = 9.2 Hz, J = 4.0 Hz, 1H), 2.18-2.05 (m, 2H), 1.79-1.72 (m, 2H), 1.48-1.14 (m, 4H). ESI-MS (m/z): 335 $[M+H_2O]^+$, 318 $[M+H]^+$.



In a round bottom flask under air atmosphere the proper iodoaniline (2 mmol, 1 eq.) was dissolved in 4 ml of methanol and TEA (4 mmol, 2 eq.) and methyl vinyl ketone (4 mmol, 2 eq.) were added. The reaction was stirred at room temperature until complete consumption of the starting material (TLC, 24 hs). The volatiles were removed under reduced pressure and the residue was re-dissolved in 4 ml of methanol and $NaBH_4$ (6 mmol, 3 eq.) was added portionwise. After complete consumption of the ketone (TLC, 1 h) the reaction was quenched with water and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude product was filtered throw a short pad of silica-gel and used directly for the Sonogashira coupling.

Synthesis of terminal alkynes 7.



Substrates **7a-d** and **7g** are commercially available and were purchased by TCI. **7f** and **7h** were prepared according to a literature known procedure. In an oven dried three-necked round bottom flask the proper aldehyde (11 mmol, 1 eq.) was dissolved in 30 ml of anhydrous THF. The solution was cooled to -78 °C and ethynylmagnesium chloride (0.5 M in THF, 13.2 mmol, 1.2 eq.) was added dropwise. The reaction mixture was stirred at room temperature for 4 hours and then quenched with saturated NH_4Cl solution (20 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organic layers were washed with brine and then dried over Na_2SO_4. The organic solvent was removed under reduced pressure to afford the desired product in synthetic useful purity.

7f: Yield = 98%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, J = 7.6 Hz, 2H), 7.22 (d, J = 7.6 Hz, 2H), 5.45 (d, J = 5.2 Hz, 1H), 2.68 (d, J = 1.6 Hz, 1H), 2.39 (s, 3H), 2.31 (d, J = 5.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 138.4, 137.2, 129.4 (2C), 126.6 (2C), 83.7, 74.7, 64.3, 21.2.

7h: Yield 95%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 5.43 (d, J = 5.2 Hz, 1H), 3.84 (s, 3H), 2.69 (d, J = 2.0 Hz, 1H), 2.28 (d, J = 5.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 159.8, 132.4, 128.1 (2C), 114.0 (2C), 83.7, 74.6, 64.0, 55.3.

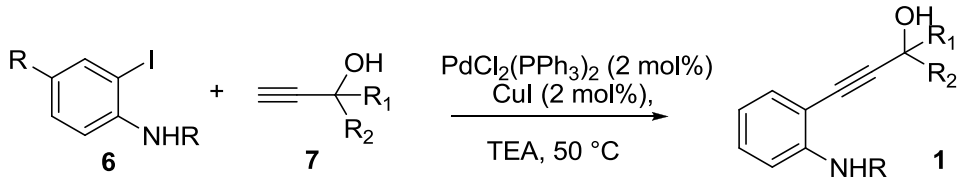
7e and **7i** were synthesized according to the following procedure: In an oven dried three-necked round bottom flask ethynyltrimethylsilane (2.4 mmol, 1.2 eq.) was dissolved in 2.5 ml of anhydrous THF. The solution was cooled at -78 °C and BuLi (2.5 M in THF, 2.4 mmol, 1.2 eq.) was added dropwise. The solution was stirred for 15 minutes and then a solution of the proper ketone (2 mmol, 1 eq.) in 2 ml of THF was slowly added. The solution was warmed at room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl solution (5 ml) and extracted with

ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine and then dried over Na_2SO_4. The organic solvent was removed under reduced pressure and the crude product was dissolved in 4 ml of methanol and K_2CO_3 (2.4 mmol, 2 eq.) was added. The reaction mixture was stirred at room temperature for 4 hours and then diluted with water (5 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the crude product was purified by silica-gel flash chromatography cyclohexane and ethyl acetate mixture as eluting solvents.

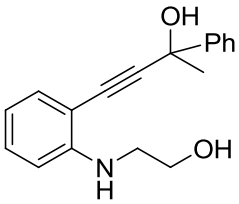
7e: Clear oil. Yield = 20%. Flash chromatography c-Hex:AcOEt = 95:5. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 4.13 (q, J = 7.2 Hz, 2H), 2.66-2.54 (m, 2H), 2.45 (s, 1H), 2.03-1.95 (m, 2H), 1.51 (s, 3H), 1.25 (t, J = 7.2 HZ, 3H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 174.0, 86.8, 73.7, 71.8, 67.2, 37.9, 30.0, 26.8, 14.1. GC-MS (m/z): 125 (10) $[M\text{-}EtO]^+$, 109 (50), 69 (53),53 (100).

7i: Clear oil. Yield = 26%. Flash chromatography c-Hex:AcOEt = 9:1. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 4.72 (s, 2H), 2.45 (s, 1H), 3.00-2.21 (m, 2H), 1.77-1.67 (m, 5H), 1.50 (s, 3H). GC-MS (m/z, for the TMS-protected 7i): 195 (20) $[M\text{-}Me]^+$, 177 (20), 123 (25), 99 (50), 73 (100), 55 (40).

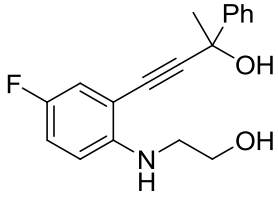
General procedure for the Sonogashira coupling. Synthesis of 1.



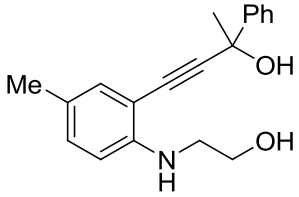
In an oven dried Schlenk tube, under nitrogen atmosphere, N-alkyl-2-iodoaniline 6 (2 mmol, 1 eq.) and alkyne 7 (2.4 mmol, 1.2 eq.) were dissolved in 4 ml of TEA. $(PPh_3)_2PdCl_2$ (0.04 mmol, 0.02 eq.) and CuI (0.04 mmol, 0.02 eq.) were added in sequence and the reaction mixture was heated at 50 °C until complete consumption of the starting material (TLC, 1-16 h). The reaction mixture was diluted with water (5 ml) and extracted with ethyl acetate (3 x 10 ml). The organic layer was dried over Na_2SO_4 and the volatiles were removed under vacuum. The residue was purified with silica-gel flash chromatography using cyclohexane and ethyl acetate mixture as eluting solvents.



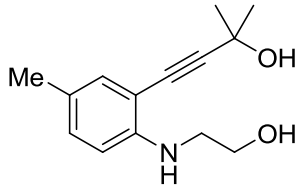
1d: from 6a and 2-phenylbut-3-yn-2-ol 3 (7a). Brown oil. Yield = 98%. Flash chromatography *c*-Hex:AcOEt = 8:2. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, J = 7.6 Hz, 2H), 7.36-7.33 (m, 3H), 7.29 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.68 (t, J = 8.0 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 4.95 (bs, 1H), 4.75 (bs, 1H), 3.71-3.64 (m, 2H), 3.18 (bs, 2H), 1.85 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.9, 145.6, 131.9, 129.9, 128.2 (2C), 127.5, 125.0 (2C), 116.6, 109.9, 107.3, 98.6, 81.2, 70.2, 60.5, 45.1, 33.2. ESI-MS (m/z): 304 $[M+Na]^+$, 264 $[M-OH]^+$. Anal. calcd for (C18H19NO2: 281.35): C, 76.84; H, 6.81; N, 4.98; Found: C, 76.73, H, 6.67, N, 4.87.



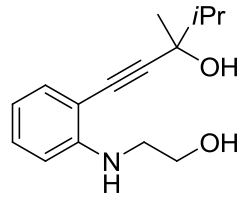
1e: from 6b and 2-phenylbut-3-yn-2-ol (7a). Brown oil. Yield = 78%. Flash chromatography *c*-Hex:AcOEt = 7:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, J = 7.2 Hz, 2H), 7.29-7.19 (m, 3H), 6.97 (dd, J = 8.8 Hz, J = 2.8 Hz, 1H), 6.84 (dt, J = 8.8 Hz, J = 2.8 Hz, 1H), 6.37 (dd, J = 8.8 Hz, J = 4.8 Hz, 1H), 4.96 (bs, 1H), 3.64-3.54 (m, 2H), 3.04 (t, J = 4.8 Hz, 2H), 1.76 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 154.4 (d, JC-F = 233 Hz), 145.6 (d, JC-F = 2 Hz), 145.4, 128.2 (2C), 127.6, 124.9 (2C), 117.9, (d, JC-F = 23 Hz), 116.7 (d, JC-F = 22 Hz), 110.9 (d, JC-F = 8 Hz), 108.1 (d, JC-F = 9 Hz), 99.4, 80.4, 70.2, 60.5, 45.7, 33.2. ESI-MS (m/z): 282 $[M-OH]^+$. Anal. calcd for (C18H18FNO2: 299.34): C, 72.22; H, 6.06; N, 4.68; Found: C, 72.11, H, 6.00, N, 4.55.



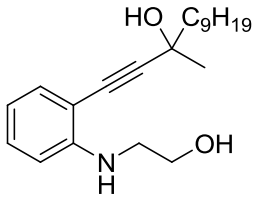
1f: from 6c and 2-phenylbut-3-yn-2-ol (7a). Brown oil. Yield = 88%. Flash chromatography c-Hex:AcOEt = 7:3. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 7.2 Hz, 2H), 7.25-7.43 (m, 3H), 7.17 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.53 (d, J = 8.0 Hz, 1H), 5.06 (bs, 1H), 3.75 (bs, 1H), 3.73 (t, J = 4.8 Hz, 2H), 3.23 (t, J = 4.8 Hz, 2H), 2.24 (s, 3H), 1.87, (s, 3H), 1.12 (bs, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 147.0, 145.8, 132.3, 130.8, 128.3 (2C), 127.6, 126.0, 125.0 (2C), 110.5, 107.6, 98.6, 81.7, 70.5, 61.1 45.8, 33.4, 20.2. ESI-MS (m/z): 318 $[M+Na]^+$, 278 $[M-OH]^+$. Anal. calcd for (C19H21NO2: 295.38): C, 77.26; H, 7.17; N, 4.74; Found: C, 77.35, H, 7.09, N, 4.85.



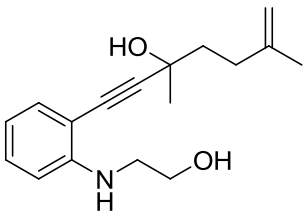
1g: from 6c and 2-methylbut-3-yn-2-ol (7b). Brown oil. Yield = 90%. Flash chromatography *c*-Hex:AcOEt = 7:3. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.46 (bs, 2H), 3.52 (t, J = 4.8 Hz, 2H), 3.25 (t, J = 4.8 Hz, 2H), 2.71 (bs, 1H), 2.21 (s, 3H), 1.61 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.7, 132.1, 130.5, 126.0, 110.5, 107.9, 99.9, 78.7, 65.6, 60.8, 45.8, 31.5 (2C), 20.2. ESI-MS (m/z): 465, 256 $[M+Na]^+$, 234 $[M+H]^+$, 216 [M-OH]+. Anal. calcd for (C14H19NO2: 233.31): C, 72.07; H, 8.21; N, 6.00; Found: C, 71.98, H, 8.34, N, 6.13.



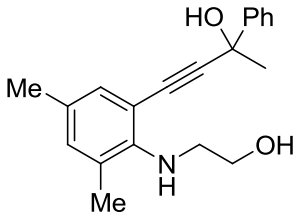
1h: from 6a and 3,4-dimethylpent-1-yn-3-ol (7c). Brown oil Yield = 74%. Flash chromatography *c*-Hex:AcOEt = 8:2. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.26 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.17 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.63 (t, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 3.84 (t, J = 4.8 Hz, 2H), 3.32 (t, J = 4.8 Hz, 2H), 1.90 (sept, J = 6.8 Hz, 1H), 1.54 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.8, 131.9, 129.7, 116.6, 109.9, 107.8, 98.3, 80.4, 72.1, 60.8, 45.5, 38.9, 31.9, 17.9, 17.7. ESI-MS (m/z): 270 [M+Na]+, 248 $[M+H]^+$, 230 $[M-OH]^+$. Anal. calcd for (C15H21NO2: 247.33): C, 72.84; H, 8.56; N, 5.66; Found: C, 72.76, H, 8.41, N, 5.85.



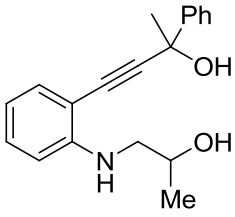
1i: from 6a and 3-methyldodec-1-yn-3-ol (7d). Brown oil. Yield = 62%. Flash chromatography [c]-Hex:AcOEt = 9:1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.18 (dt, J = 7.6 Hz, J = 1.2 Hz, 1H), 6.64 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 3.85 (t, J = 5.2 Hz, 2H), 3.33 (t, J = 5.2 Hz, 2H), 1.78-1.72 (m, 2H), 1.58 (s, 3H), 1.36-1.25 (m, 14H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.7, 131.7, 129.8, 116.7, 110.0, 107.8, 99.3, 79.7, 68.8, 61.0, 45.6, 43.8, 31.2, 29.8, 29.7, 29.6, 29.5, 29.3, 24.9, 22.7, 14.1. ESI-MS (m/z): 332 $[M+H]^+$, 314 $[M-OH]^+$. Anal. calcd for (C21H33NO2: 331.49): C, 76.09; H, 10.03; N, 4.23; Found: C, 76.01, H, 10.13, N, 4.34.



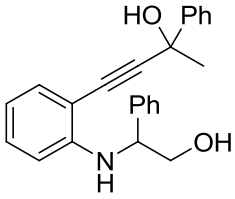
1j: from 6a and ethyl 4-hydroxy-4-methylhex-5-ynoate (7e). Brown oil. Yield 26%. Flash chromatography c-Hex:AcOEt = 8:2. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.23 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.61 (t, J = 7.6 Hz, 1H), 6.58 (d, J = 7.6 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.86 (t, J = 5.2 Hz, 2H), 3.30 (t, J = 5.2 Hz, 2H), 2.72-2.58 (m, 2H), 2.16-2.04 (m, 2H), 1.60 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.5, 149.0, 132.0, 130.0, 116.5, 109.9, 107.2, 97.8, 80.6, 67.9, 60.9, 60.8, 45.4, 38.3, 30.5, 30.3, 14.0. ESI-MS (m/z): 328 $[M+Na]^+$, 306 $[M+H]^+$, 288 [M-OH]+. Anal. calcd for (C17H23NO4: 305.37): C, 66.86; H, 7.59; N, 4.59; Found: C, 66.78, H, 7.48, N, 4.68.



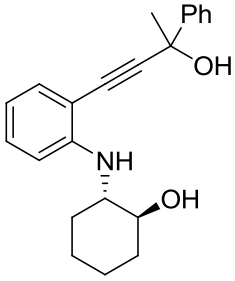
1k: from 6h and 2-phenylbut-3-yn-2-ol (7a). Brown oil. Yield = 91%. Flash chromatography cHex:AcOEt = from 8:2 → 6:4. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, J = 7.6 Hz, 2H), 7.38-7.28 (m,3H), 7.10 (s, 1H), 6.92 (s, 1H), 3.66-3.63 (m, 2H), 3.21-3.20 (m, 2H), 2.25 (s, 3H), 2.23 (s, 3H), 1.85 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.1 (2C), 132.7, 130.9, 130.4, 129.3, 128.2 (2C), 127.4, 125.0 (2C), 114.5, 97.4, 82.5, 70.0, 61.7, 50.4, 36.5, 20.4, 18.4. ESI-MS (m/z): 310 $[M+H]^+$, 292 $[M-OH]^+$; Anal. calcd for (C20H23NO2: 309.40): C, 77.64; H, 7.49; N, 4.53; Found: C, 77.55, H, 7.55, N, 4.59.



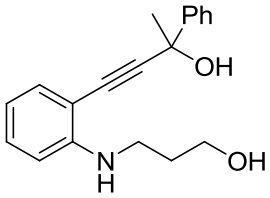
1l: from 6d and 2-phenylbut-3-yn-2-ol (7a). Brown oil. Yield = 92%. Flash chromatography c- Hex:AcOEt = 9:1. ^{1}H-NMR (400 MHz, $CDCl_3$, mixture of diastereoisomers, diagnostic signals) δ 7.73 (d, J = 8.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, 2H), 7.34-7.29 (m, 2H), 7.03 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.67 (t, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 4.04-3.96 (m, 1H), 3.25 (dt, J = 12.8 Hz, J = 2.8 Hz, 1H), 3.04 (ddd, J = 12.8 Hz, J = 8.0 Hz, J = 2.0 Hz, 1H), 1.89 (s, 3H), 1.22 (dd, J = 6.0 Hz, J = 2.0 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, mixture of diastereoisomers, diagnostic signals) δ 149.0, 145.6, 131.8, 129.9, 128.1 (2C), 127.5, 125.0 (2C), 116.5, 110.0, 107.4, 98.8, 81.3, 70.3, 66.2, 50.4, 33.3, 20.7. ESI-MS (m/z): 318 $[M+Na]^+$, 278 $[M-OH]^+$.



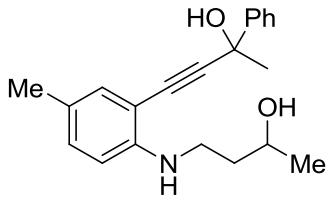
1m: from 6e and 2-phenylbut-3-yn-2-ol (7a). Brown oil. Yield = 84%. Flash chromatography cHex:AcOEt = 8:2. ^{1}H-NMR (400 MHz, $CDCl_3$, mixture of diastereoisomers, diagnostic signals) δ 7.78 (dd, J = 7.6 Hz, J = 1.6 Hz, 2H), 7.40-7.25 (m, 9H), 7.04 (t, J = 7.6 Hz, 1H), 6.62 (t, J = 7.6 Hz, 1H), 6.38- 6.35 (m, 1H), 4.53-4.50 (m, 1H), 3.92-3.87 (m, 1H), 3.75-3.66 (m, 1H), 1.93 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, mixture of diastereoisomers, diagnostic signals) δ 148.3, 145.8, 139.8, 131.8, 129.9, 128.8 (2C), 128.4 (2C), 127.7, 127.6, 126.6 (2C), 125.0 (2C), 116.9, 111.4, 107.7, 99.1, 81.6, 70.5, 67.3, 59.5, 33.4. ESI-MS (m/z): 380 $[M+Na]^+$, 358 $[M+H]^+$, 340 $[M-OH]^+$.



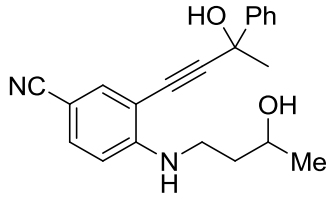
1n: from 6f and 2-phenylbut-3-yn-2-ol (7a). Brown oil. Yield = 96%. Flash chromatography cHex:AcOEt = from 8:2 ⏲6:4. ^{1}H-NMR (400 MHz, $CDCl_3$, mixture of diastereoisomers, diagnostic signals) δ 7.73 (d, J = 8.0 Hz, 1.5H), 7.62 (d, J = 8.0 Hz, 0.5H), 7.42-7.31 (m, 4H), 7.19 (dt J = 8.0 Hz, J = 1.6 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 8.0 Hz, 1H), 3.36-3.24 (m, 1H), 3.20-3.14 (m, 1H), 2.06- 2.03 (m, 2H), 1.89 (s, 3H), 1.76-1.65 (m, 2H), 1.42-1.24 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$, mixture of diastereoisomers, diagnostic signals) δ 149.0, 145.9, 132.1, 130.0, 128.3 (2C), 127.6, 124.9 (2C), 117.2, 111.6, 108.2, 99.1, 81.5, 74.4, 70.3, 59.7, 33.3, 33.2, 33.0, 24.7, 24.1. ESI-MS (m/z): 358 $[M+Na]^+$, 318 $[M-OH]^+$, 236.



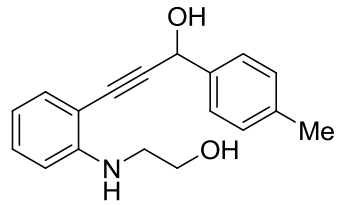
1o: from 6g and 2-phenylbut-3-yn-2-ol (7a). Brown oil. Yield = 88%. Flash chromatography *c*-Hex:AcOEt 8:2. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 2H) 7.41-7.29 (m, 4H), 7.21 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.64 (t J = 8.0 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 3.78 (t, J = 5.6 Hz, 2H), 3.30 (t, J = 6.0 Hz, 2H), 1.92-1.83 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.3, 146.0, 131.8, 130.0, 128.2 (2C), 127.5, 125.0 (2C), 116.2, 109.6, 107.1, 98.2, 81.5, 70.2, 65.7, 49.4 33.4, 31.1. ESI-MS (m/z): 318 [M+Na]+, 296 $[M+H]^+$, 278 $[M-OH]^+$. Anal. calcd for (C19H21NO2: 295.38): C, 77.26; H, 7.17; N, 4.74; Found: C, 77.43, H, 8.8.33, N, 4.71.



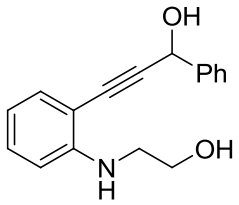
1p: from 6i and 2-phenylbut-3-yn-2-ol (7a). Brown oil. Yield = 81%. Flash chromatography cHex:AcOEt = from 8:2 → 6:4. ^{1}H-NMR ($CDCl_3$, 400 MHz, mixture of diastereoisomers) δ 7.75 (d, J = 7.6 Hz, 2H), 7.40-7.33 (m, 3H), 7.29 (s, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.55 (d, J = 7.6 Hz, 1H), 4.58 (bs, 1H), 3.69 (m, 1H), 3.27-3.18 (m, 2H), 2.58 (s, 3H), 1.88 (s, 3H), 1.72-1.69 (m, 2H), 1.15 (d, J = 6.0 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.4, 146.2, 132.2, 130.7, 128.2 (2C), 127.5, 125.6 (2C), 125.2, 110.3, 107.5, 98.5, 81.8, 70.2, 67.6, 41.7, 37.3, 33.6, 23.7, 21.1. ESI-MS (m/z): 346 [M+Na]+, 324 $[M+H]^+$, 306 $[M-OH]^+$.



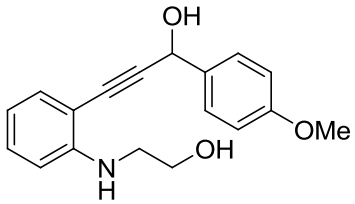
1q: from 6j and 2-phenylbut-3-yn-2-ol (7a). Brown oil. Yield = 71%. Flash chromatography cHex:AcOEt = from 8:2 → 6:4. ^{1}H-NMR (DMSO-d6, 400 MHz, mixture of diastereoisomers) δ 7.66 (d, J = 8.0 Hz, 2H), 7.60 (s,1H), 7.56 (d, J = 8.4 Hz, 1H), 7.40-7.36 (m, 2H), 7.31-7.29 (m, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.25 (bs, 1H), 6.06 (m, 1H), 4.69 (t, J = 4.8 Hz, 1H), 3.78 (m, 1H), 3.33- 3.29 (m, 2H), 1.74 (s, 3H), 1.85-1.76 (m, 2H), 1.10 (d, J = 5.2 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d6) δ 152.1, 147.0, 135.7, 134.3, 128.5 (2C), 127.6, 125.4 (2C), 120.0, 110.0, 107.2, 101.7, 96.6, 78.3, 69.0, 64.8, 37.9, 33.9, 31.4, 22.5. ESI-MS (m/z): 357 $[M+Na]^+$, 317 $[M-OH]^+$.



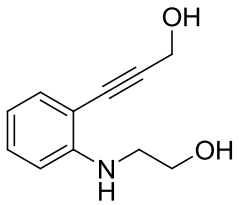
1s: from 6a and 1-(p-tolyl)prop-2-yn-1-ol (7f). Brown oil. Yield = 76%. Flash chromatography c-Hex:AcOEt 8:2. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.50 (m, 2H), 7.25-7.35 (m, 1H), 7.07-7.24 (m, 3H), 6.49-6.71 (m, 2H), 5.67 (s, 1H), 5.13 (bs, 1H), 4.13 (t, J = 6.8 Hz, 1H), 3.78 (bs, 2H), 3.28 (bs, 1H), 2.81 (bs, 1H), 2.37, (s, 3H), 1.55 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.1, 138.1, 137.9, 132.2, 132.0, 130.1, 129.3, 126.8, 116.6 (2C), 109.9, 107.4, 95.1, 83.3, 64.9, 61.0, 45.5, 31.6. LC-MS (m/z): 304 $[M+Na]^+$, 264 $[M-OH]^+$. Anal. calcd for (C19H19NO2: 281.35): C, 76.84; H, 6.81; N, 4.98; Found: C, 76.81, H, 6.71, N, 4.81.



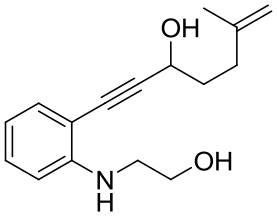
1t: from 6a and 1-phenylprop-2-yn-1-ol (7g). Brown oil. Yield 83%. Flash chromatography cHex:AcOEt = 8:2. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.62-7.52 (m, 2H) 7.42-7.26 (m, 4H), 7.20 (dt, J = 7.2 Hz, J = 1.6 Hz, 1H), 6.65 (dt J = 7.2 Hz, J = 1.0 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 5.66 (s, 1H), 4.85 (bs, 2H), 3.71 (t, J = 5.2 Hz, 2H), 3.21 (t, J = 5.2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 149.0, 140.7, 132.1, 130.1, 128.5 (2C), 128.2, 126.7 (2C), 116.6, 109.9, 107.3, 94.9, 83.2, 64.9, 60.8, 45.3. ESI-MS (m/z): 250 $[M-OH]^+$, 268 $[M+H]^+$, 290 $[M+Na]^+$. Anal. calcd for (C17H17NO2: 267.32): C, 76.38; H, 6.41; N, 5.24; Found: C, 76.24, H, 6.71, N, 5.12.



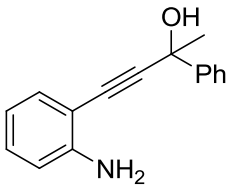
1u: from 6a and 1-(4-methoxyphenyl)prop-2-yn-1-ol (7h). Brown oil. Yield = 78%. Flash chromatography cHex:AcOEt = 8:2. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.53 (s, 2H), 7.26-7.35 (m, 1H), 7.21 (t, J = 8.0 Hz, 1H), 6.92 (d, , J = 8.0 Hz, 2H), 6.58-6.71 (m, 2H), 5.67 (s, 1H), 4.99 (bs, 1H), 3.83 (s, 3H), 3.75-3.86 (m, 2H), 3.31 (t, J = 5.2 Hz, 2H), 2.66, (bs, 1H), 1.80 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.7, 149.1, 133.1, 132.2, 130.2, 128.2 (2C), 116.7, 114.0 (2C), 109.5, 107.3, 95.1, 83.2, 64.8, 61.1, 55.3, 45.6. LC-MS (m/z): 320 $[M+Na]^+$, 280 $[M-OH]^+$. Anal. calcd for (C18H19NO3: 297.35): C, 72.71; H, 6.44; N, 4.71; Found: C, 72.65, H, 6.41, N, 4.68.



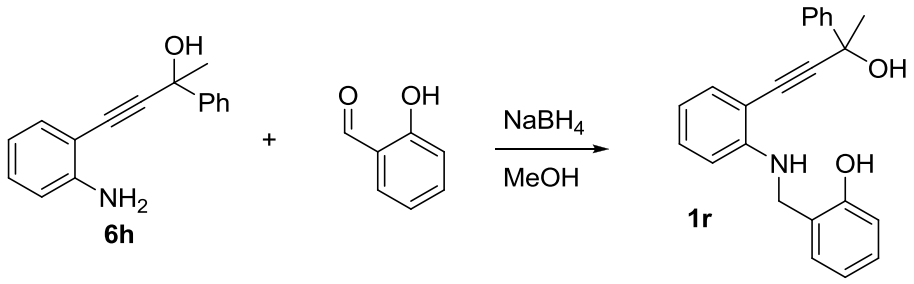
1z: from 6a and propargyl alcohol. Brown oil. Yield 72%. Flash chromatography cHex:AcOEt = 8:2. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.22 (d, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.17 (dt, J = 7.6 Hz, J =1.6 Hz, 1H), 6.62 (t, J = 7.6 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 6.46 (s, 2H), 3.81 (t, J = 5.2 Hz, 2H), 3.28 (t, J = 5.2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.9, 132.1, 130.0, 116.6, 109.9, 107.4, 93.3, 82.0, 60.8, 51.2, 45.5. ESI-MS (m/z): 214 $[M+Na]^+$, 192 $[M+H]^+$. Anal. calcd for (C11H13NO2: 191.23): C, 69.09; H, 6.85; N, 7.32; Found: C, 69.16, H, 6.95, N, 7.55.



1w: from 6a and 3,6-dimethylhept-6-en-1-yn-3-ol (7i). Brown oil. Yield = 79%. Flash chromatography c-Hex:AcOEt = from 8:2→6:4. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.26 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.18 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.64 dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 4.75 (s, 2H), 3.84 (t, J = 5.2 Hz, 2H), 3.30 (t, J = 5.2 Hz, 2H), 2.38 - 2.22 (m, 2H), 1.97-1.84 (m, 2H), 1.77 (s, 3H), 1.60 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 148.8, 145.7, 131.9, 129.8, 116.7, 110.0, 109.9, 107.6, 98.7, 80.1, 68.7, 60.9, 45.4, 41.6, 33.1, 29.9, 22.7. ESI-MS (m/z): 296 $[M+Na]^+$, 274 $[M+H]^+$, 256 $[M-OH]^+$. Anal. calcd for (C17H23NO2: 273.37): C, 74.69; H, 8.48; N, 5.12; Found: C, 74.55, H, 8.31, N, 5.01.



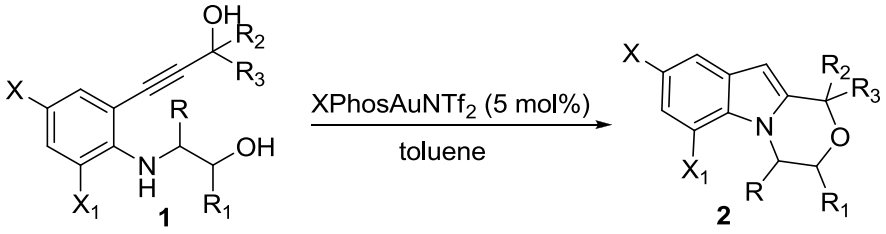
6h: from 2-iodoaniline (5a) and 2-phenylbut-3-yn-2-ol (7a). Brown oil Yield 98%. Flash-chromatography ^{c}Hex:AcOEt = 8:2. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.41-7.38 (m, 2H), 7.35-7.31 (m, 2H), 7.14 (t, J = 8.0 Hz, 1H), 6.73-6.69 (m, 2H), 1.90 (s, 3H). ^{13}C- NMR (100 MHz, $CDCl_3$) δ 147.9, 145.7, 132.3, 129.9, 128.4, 128.3 (2C), 127.7, 124.9 (2C), 117.9, 114.4, 98.1, 81.6, 70.5, 33.5. GC-MS (m/z): 219 (100), $[M-H_2O]^+$, 204 (36), 189 (10), 165 (15), 105 (31), 89 (45).



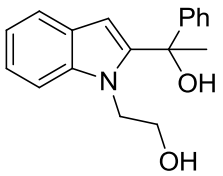
In an oven dried two-necked round bottom flask, equipped with a reflux condenser, under nitrogen atmosphere 6h (1 mmol, 1 eq.) and salicylaldehyde (1.1 mmol, 1.1 eq.) were dissolved in 4 ml of anhydrous methanol and heated at reflux for 4 hour. The solution was then cooled at 0 °C and $NaBH_4$ (2 mmol, 2 eq.) was added. The reaction mixture was stirred at room temperature for 2 hours and then quenched with water (5 ml). Methanol was removed under reduced pressure and the aqueous phase was extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude reaction mixture was purified with silica-gel flash chromatography (cHex:AcOEt = 7:3).

Brown oil. Yield = 90%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.66 (dd, J = 8.0 Hz, J = 1.6 Hz, 2H), 7.37 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.31-7.14 (m, 6H), 6.89-6.78 (m, 4H), 4.39 (d, J = 1.6 Hz, 2H), 1.85 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 155.7, 148.6, 145.4, 131.1, 130.0, 128.9, 128.8, 128.3 (2C), 127.6, 124.7 (2C), 123.4, 120.2, 118.8, 116.3, 112.4, 109.4, 99.0, 81.1, 70.4, 46.7, 33.2. ESI-MS (m/z): 366 [M+Na]+, 346, 344 $[M+H]^+$, 326 $[M-OH]^+$. Anal. calcd for (C23H21NO2: 343.42): C, 80.44; H, 6.16; N, 4.08; Found: C, 80.31, H, 6.09, N, 4.16.

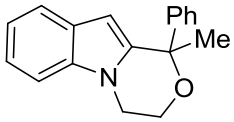
General procedure for the catalytic synthesis of oxazino[4,3-a]indole.



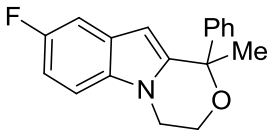
In an oven dried two-necked round bottom flask, under nitrogen atmosphere 1 (0.05 mmol, 1 eq.) was dissolved in 1 ml of anhydrous toluene and the gold catalyst was added (0.0025 mmol, 5 mol%). The reaction mixture was heated at the desired temperature until complete consumption of the starting material (TLC, 3-24 hours). The crude reaction mixture was directly purified with silica-gel flash chromatography (cHex:EtOAc = 95:5).



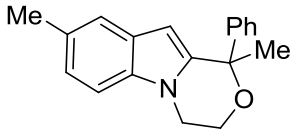
(+/-)-**2d'**.^{1}H-NMR (CD_3CN, 400 MHz) δ 7.62 (d, J = 7.6 Hz, 1H), 7.36-7.31 (m, 5H), 7.28-7.24 (m, 1H), 7.17 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.09 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 6.72 (s, 1H), 4.98 (bs, 1H), 4.03 (ddd, J = 15.2 Hz, J = 5.2 Hz, J = 4.0 Hz, 1H), 3.93 (ddd, J = 15.2 Hz, J = 8.8 Hz, J = 5.6 Hz, 1H), 3.62 (ddd, J = 10.8 Hz, J = 8.8 Hz, J = 5.6 Hz, 1H), 3.42 (ddd, J = 10.8 Hz, J = 5.2 Hz, J = 4.0 Hz, 1H), 3.33 (bs, 1H), 1.93 (s, 3H). ^{13}CNMR (CD_3CN, 100 MHz) δ 148.9 145.8, 138.7, 129.2 (2C), 128.1, 127.7, 125.9 (2C), 122.6, 121.5, 120.4, 110.9, 101.6, 73.4, 60.9, 46.8, 33.6. ESI- MS (m/z): 304 $[M+Na]^+$, 282 $[M+H]^+$, 264 $[M-OH]^+$.



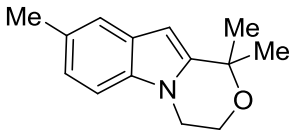
(+/-)-**2d**: white solid (mp = 135-141 °C). Yield = 92%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 7.6 Hz, 1H), 7.46 (dd, J = 8.0 Hz, J = 1.2 Hz, 2H), 7.33-7.27 (m, 4H), 7.24 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.19 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 6.49 (s, 1H), 4.13-4.05 (m, 2H), 4.02-3.98 (m, 1H), 3.93-3.86 (m, 1H), 1.93 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 144.3, 138.2, 136.3, 128.2 (2C), 127.7, 127.6, 126.4 (2C), 121.3, 120.4, 120.2, 108.9, 99.3, 78.0, 59.2, 41.6, 31.4. GC-MS (m/z): 263 (40) $[M]^+$, 248 (100) $[M\text{-}Me]^+$, 186 (30), 105 (60), 77 (70). Chiral HPLC analysis: AD column nHex:i-PrOH 98:2. Flow: 0.7 ml/min, 40°C, λ = 214 nm. tR (minor) = 9.18 min; tR (major) = 10.09 min. Anal. calcd for (C18H17NO: 263.33): C, 82.10; H, 6.51; N, 5.32; Found: C, 82.21, H, 6.66, N, 5.38.



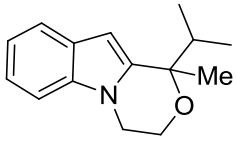
(+/-)-**2e**: white solid (mp = 159-162 °C). Yield = 84 %. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, J = 8.0 Hz, 2H), 7.34-7.28 (m, 4H), 7.20 (dd, J = 8.8 Hz, J = 4.4 Hz, 1H), 6.97 (td, J = 8.8 Hz, J = 2.4 Hz, 1H), 6.45 (s, 1H), 4.10-4.05 (m, 2H), 3.98-3.84 (m, 2H), 1.91 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 158.4 (d, JC-F = 233 Hz), 144.1, 140.0, 132.9, 128.3 (2C), 127.9 (d, JC-F = 10 Hz), 127.7, 126.3 (2C), 109.6 (d, JC-F = 16 Hz), 109.4, 105.3 (d, JC-F = 23 Hz), 99.4, (d, JC-F = 4 Hz), 77.9, 59.1, 41.7, 31.3. GC-MS (m/z): 281 (35) $[M]^+$, 266 (100) $[M\text{-}Me]^+$, 204 (25), 105 (25), 77 (20). Anal. calcd for (C18H16FNO: 281.32): C, 76.85; H, 5.73; N, 4.98; Found: C, 76.76, H, 5.61, N, 4.88.



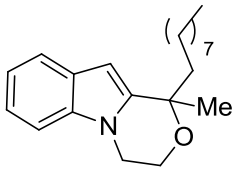
(+/-)-**2f**: white solid (mp = 134-137 °C). Yield = 81%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.46-7.42 (m, 3H), 7.33-7.28 (m, 3H), 7.20 (d, J = 8.4 Hz, 1H), 7.06 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H), 6.40 (s, 1H), 4.10-4.03 (m, 2H), 3.98-3.84 (m, 2H), 2.49 (s, 3H), 1.91 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 144.4, 138.3, 134.8, 129.5, 128.2 (2C), 127.9, 127.6, 126.4 (2C), 122.9, 120.1, 108.7, 98.9, 78.0, 59.2, 41.7, 31.3, 21.5. GC-MS (m/z): 277 (40) $[M]^+$, 262 (100) $[M\text{-}Me]^+$, 200 (25), 156 (25), 105 (50), 77 (60). Anal. calcd for (C19H19NO: 277.36): C, 82.28; H, 6.90; N, 5.05; Found: C, 82.12, H, 6.71, N, 4.91.



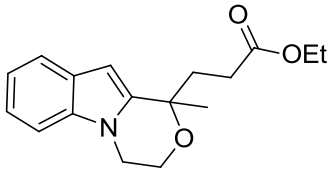
(+/-)-**2g**: white solid (mp = 88-91 °C). Yield = 83%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.60 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.01 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H), 6.13 (s, 1H), 4.17 (pt, J = 5.2 Hz, 2H), 4.03 (pt, J = 5.2 Hz, 2H), 2.45 (s, 3H), 1.64 (s, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 141.6, 129.3, 128.1, 122.3, 119.8, 108.4, 95.0, 73.3, 59.0, 41.6, 29.6 (2C), 21.4. GC-MS (m/z): 215 (45) $[M]^+$, 200 (100) $[M\text{-}Me]^+$, 158 (20). Anal. calcd for (C14H17NO: 215.29): C, 78.10; H, 7.96; N, 6.51; Found: C, 78.22, H, 8.01, N, 6.32.



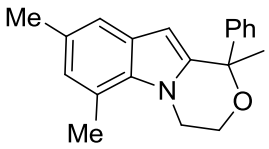
(+/-)-**2h.** Clear oil. Yield = 53%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.18 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.12 (td, J = 7.6 Hz, J = 0.8 Hz, 1H), 6.18 (s, 1H) 4.20-4.16 (m, 1H), 4.08-3.99 (m, 3H), 2.11 (sept, J = 6.8 Hz, 1H), 1.55 (s, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 140.3, 135.5, 127.8, 120.5, 120.1, 119.8, 108.6, 96.4, 78.3, 59.1, 41.8, 38.5, 24.6, 17.3, 16.7. GC-MS (m/z): 229 (10) $[M]^+$, 186 (100) $[M\text{-}iPr]^+$, 144 (25), 115 (15). Anal. calcd for (C15H19NO: 229.32): C, 78.56; H, 8.35; N, 6.11; Found: C, 78.32, H, 8.41, N, 6.20.



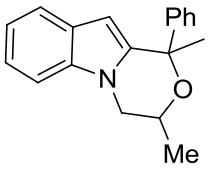
(+/-)-**2i**: clear oil. Yield = 96%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.18 (td, J = 7.6 Hz, J = 0.8 Hz, 1H), 7.12 (td, J = 7.6 Hz, J = 0.8 Hz, 1H), 6.18 (s, 1H) 4.20- 4.11 (m, 2H), 4.08-4.05 (m, 2H), 1.97-1.82 (m, 2H), 1.59 (s, 3H), 1.29-1.24 (m, 14H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 141.1, 135.5, 127.9, 120.6, 120.1, 119.9, 108.6, 95.8, 75.8, 59.0, 42.7, 31.8, 29.9, 29.6, 29.5, 29.3, 27.4, 26.9, 23.7 22.7, 14.1. ESI-MS (m/z): 314 $[M+H]^+$. Anal. calcd for (C21H31NO: 313.24): C, 80.46; H, 9.97; N, 4.47; Found: C, 80.62, H, 10.01, N, 4.42.



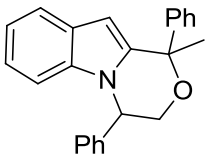
(+/-)-**2j**: clear oil. Yield = 71%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.19 (dt, J = 8.0 Hz, J =1.6 Hz, 1H), 7.12 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.20 (s, 1H), 4.17-4.02 (m, 6H), 2.48-2.41 (m, 1H), 2.34-2.17 (m, 3H), 1.62 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 173.6, 139.5, 135.6, 127.9, 120.9, 120.3, 120.0, 108.7, 96.1, 75.2, 60.3, 59.0, 41.5, 37.7, 29.3, 27.4, 14.1. ESI-MS (m/z): 310 $[M+Na]^+$, 288 $[M+H]^+$. Anal. calcd for (C17H21NO: 287.15): C, 71.06; H, 7.37; N, 4.87; Found: C, 71.02, H, 7.29, N, 4.91.



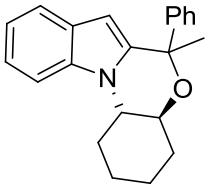
(+/-)-**2k**. Sticky solid. Yield 75%. ^{1}H -NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, J = 6.8 Hz, 2H), 7.38-7.34 (m, 4H), 6.84 (s, 1H), 6.46 (s, 1H), 4.50-4.38 (m, 2H), 4.07-3.92 (m, 2H), 2.76 (s, 3H), 2.50 (s, 3H), 1.97 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 144.8, 140.2, 138.6, 129.5, 128.7, 128.1 (2C), 127.5, 126.4 (2C), 126.1, 120.9, 118.0, 100.1, 78.0, 59.6, 45.2, 31.4, 21.1, 19.7. GC-MS (m/z): Anal. calcd for (C20H21NO: 291.16): C, 82.44; H, 7.26; N, 4.81; Found: 5 C, 82.32, H, 7.38, N, 4.73.



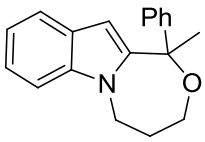
(+/-)-**2l**: clear oil; Yield = 67%, *dr* = 1:1.2. ^{1}H-NMR ($CDCl_3$, 400 MHz, mixture of diastereoisomers) δ: 7.68 (d, J = 7.2 Hz, 1Hmajor), 7.58 (d, J = 7.2 Hz, 2Hmajor), 7.54 (d, J = 8.0 Hz, 1Hminor), 7.45 (dd, J = 8.4 Hz, J = 1.2 Hz, 2Hminor), 7.35-7.16 (m, 6Hminor + 5Hmajor), 7.10 (t, J = 7.2 Hz, 1Hmajor), 6.51 (s, 1Hminor), 6.17 (s, 1Hmajor), 4.41-4.31 (m, 1Hmajor), 4.20 (dd, J = 11.6 Hz, J = 2.4 Hz, 1Hmajor), 4.03 (dd, J = 10.8 Hz, J = 3.6 Hz, 1Hminor), 4.00-3.92 (m, 1Hminor), 3.77 (t, J = 11.6 Hz, 1Hmajor), 3.66 (t, J = 10.8 Hz, 1Hminor), 2.03 (s, 3Hmajor),1.91 (s, 3Hminor), 1.50 (d, J = 6.0 Hz, 3Hmajor), 1.38 (d, J = 6.0 Hz, 3Hminor). ^{13}C-NMR ($CDCl_3$, 100 MHz, mixture of diastereoisomers) δ (major): 144.9, 140.3, 136.1, 128.1 (2C), 128.0, 127.4, 125.8 (2C), 121.0. 120.4, 120.0, 108.7, 97.9, 77.1, 66.0, 47.8, 27.4, 19.3. δ (minor): 146.5, 137.8, 135.4, 128.2 (2C), 127.9, 127.5, 126.1 (2C), 121.2, 120.4, 120.2, 109.0, 99.1, 77.2, 64.6, 47.8, 32.0, 19.1. GC-MS (m/z): 277 (50) $[M]^+$, 262 (90) $[M-Me]^+$, 217 (20), 200 (30), 158 (20), 105 (100), 77 (65), 51 (30).



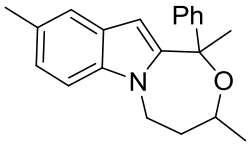
(+/-)-**2m**: sticky solid. Yield = 98%, *dr* = 1:1. ^{1}H-NMR ($CDCl_3$, 400 MHz, mixture of diastereoisomers) δ: 7.68 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.52-7.47 (m, 4H), 7.36-7.23 (m, 12H), 7.17-7.15 (m, 2H), 7.12- 7.04 (m, 3H), 7.01 (t, J = 8.0 Hz, 1H),6.93-6.90 (m, 3H), 6.59 (s, 2H), 6.55 (d, J = 8.4 Hz, 1H), 5.33 (dd, J = 10.8 Hz, J = 5.6 Hz, 1H), 5.24 (d, J = 3.6 Hz, 1H), 4.16 (dd, J = 12.0 Hz, J = 3.6 Hz, 1H), 4.03 (dd, J = 12.4 Hz, J = 5.6 Hz, 1H), 3.92 (d, J = 12.0 Hz, 1H), 3.62 (dd, J = 12.4 Hz, J = 10.8 Hz, 1H), 2.02 (s, 3H), 1.98 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz, mixture of diastereoisomers) δ 144.4, 144.1, 140.9, 139.3, 138.3, 138.0, 136.6 135.6, 128.9 (2C), 128.6 (2C), 128.4 (2C), 128.3, 128.2 (2C), 128.1, 127.9, 127.8, 127.7, 127.6, 127.1 (2C), 126.5 (2C), 126.4 (2C), 126.0 (2C), 121.5, 121.2, 120.4, 120.3 (2C), 120.2, 112.0, 110.4, 100.2, 99.5, 78.3, 77.2, 67.0, 66.2, 58.5, 55.7, 32.0, 31.4. GC-MS (m/z): 339 (30) $[M]^+$, 324 (60) $[M\text{-}Me]^+$, 218 (25), 204 (20), 105 (100) 77 (65).



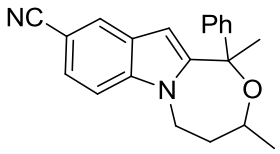
(+/-)-**2n**: white solid (mp = 134-141 °C). Yield = 96%, *dr* = 1:1.3. ^{1}H-NMR ($CDCl_3$, 400 MHz, mixture of diastereoisomers) δ 7.68-7.66 (m, 1H), 7.60-7.57 (m, 2H), 7.55-7.53 (m, 3H), 7.48 (d, J = 7.6 Hz, 2H), 7.32-7.27 (m, 5H), 7.23 (d, J = 7.6 Hz, 1H), 7.18-7.15 (m, 2H), 7.14-7.05 (m, 2H), 6.51 (s, 1Hmajor), 6.24 (s, 1Hminor), 4.06 (ddd, J = 11.6 Hz, J = 9.2 Hz, J = 4.0 Hz, 1Hminor), 3.97 (ddd, J = 11.6 Hz, J = 9.6 Hz, J = 3.2 Hz, 1Hmajor), 3.87 (ddd, J = 11.2 Hz, J = 9.2 Hz, J = 4.0 Hz, 1Hminor), 3.46 (ddd, J = 11.6 Hz, J = 9.6 Hz, J = 3.6 Hz, 1Hmajor), 3.24 (bd, J = 11.2 Hz, 1Hminor), 3.12 (bd, J = 11.6 Hz, 1Hmajor), 2.05 (s, 3Hminor), 1.86 (s, 3Hmajor), 1.96-1.89 (s, 2H), 1.82-1.80 (m, 2H), 1.72- 1.64 (m, 3H), 1.56-1.48 (m, 3H), 1.41-1.26 (m, 4H). ^{13}C-NMR ($CDCl_3$, 100 MHz, mixture of diastereoisomers) δ 147.1, 145.1, 142.0, 139.5, 136.4, 135.6, 128.7, 128.6, 128.2 (2C), 128.1 (2C), 127.4, 127.2, 126.1 (2C), 125.7 (2C), 121.0, 120.7, 120.6, 120.4, 119.7, 119.3, 112.3, 111.9, 100.3, 99.2, 78.9, 77.1, 75.8, 74.4, 59.7 (2C), 32.7, 31.5, 31.1, 29.9, 29.4, 27.6, 24.6, 24.5, 24.3, 24.2. GC-MS (m/z): 317 (50) $[M]^+$, 302 (90) $[M\text{-}Me]^+$, 240 (40), 217 (40), 144 (30), 105 (100), 77 (80).



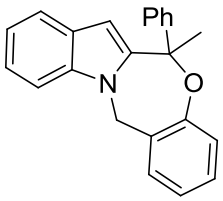
(+/-)-**2o**: white solid (mp = 129-133 °C). Yield = 53%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J = 8.0 Hz, 1H), 7.35-7.09 (m, 8H), 6.68 (s, 1H), 4.37 (dt, J = 14.4 Hz, J = 4.0 Hz, 1H), 3.99 (dt, J = 13.2 Hz, J = 5.6 Hz, 1H), 3.86 (dt, J = 13.2 Hz, J = 5.6 Hz, 1H), 3.76 (dt, J = 14.4 Hz, J = 7.2 Hz, 1H), 1.97 (s, 3H), 1.89-1.83 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.8, 142.7, 137.0, 128.3 (2C), 127.3, 127.1, 126.6 (2C), 121.7, 120.7, 119.4, 108.8, 102.8, 80.0, 64.5, 42.2, 31.8, 30.0. GC-MS (m/z): 277 (95) $[M]^+$, 262 (100) $[M\text{-}Me]^+$, 234 (90), 217 (35), 200 (35), 172 (40), 154 (30), 77 (80). Anal. calcd for (C19H19NO: 277.36): C, 82.28; H, 6.90; N, 5.05; Found: C, 82.10, H, 6.79, N, 4.98.



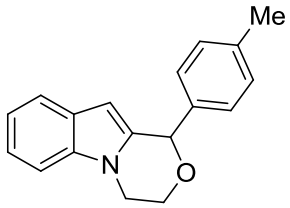
(+/-)-**2p**: sticky solid. Yield = 92%. *dr* = 1:1.9. ^{1}H-NMR ($CDCl_3$, 400 MHz, mixture of diastereoisomers) δ 7.43 (s, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.32-7.24 (m, 3H), 7.21-7.15 (m, 5H), 7.09- 7.02 (m, 4H), 7.56 (s, 2H), 4.38 (dd, J = 14.8 Hz, J = 4.0 Hz, 1H), 4.12 (dd, J = 14.0 Hz, J = 6.0 Hz, 1H), 4.07-4.03 (m, 1H), 3.92 (ddd, J = 14.0 Hz, J = 12.4 Hz, J = 5.2 Hz, 1H), 3.76-3.70 (m, 1H), 3.61 (pt, J = 12 Hz, 1H), 2.48 (s, 3H), 2.46 (s, 3H), 2.00 (s, 3H), 1.88 (s, 3H), 1.84-1.57 (m, 4H), 1.29 (d, J = 6.0 Hz, 6H). ^{13}C-NMR ($CDCl_3$, 50 MHz, mixture of diastereoisomers) δ 145.6, 143.3, 143.2, 142.1, 135.4, 134.7, 128.4, 128.3, 128.2 (2C), 127.7 (2C), 127.5, 127.2, 126.8 (2C), 126.6 (2C), 125.3 (2C), 123.0 (2C), 120.2, 120.0, 108.5, 108.0, 101.9, 101.1, 80.0, 78.7, 71.5, 67.8, 42.9, 39.8, 36.8, 36.4, 33.1, 30.0, 26.7, 22.8, 22.2, 21.1. GC-MS (m/z): 305 (55) $[M]^+$, 290 (100) $[M\text{-}Me]^+$, 248 (100), 186 (30), 115 (25), 77 (20), 55 (25).



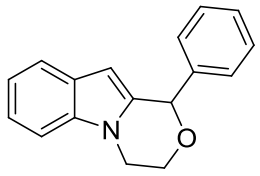
(+/-)-**2q**: sticky solid. Yield = 69%. *dr* = 1:1. ^{1}H-NMR ($CDCl_3$, 400 MHz, mixture of diastereoisomers) δ 7.99 (s, 1H), 7.98 (s, 1H), 7.44-7.22 (m, 12H), 7.01 (d, J = 6.4 Hz, 2H), 6.73 (s, 1H), 6.72 (s, 1H), 4.41 (dd, J = 14.4 Hz, J = 5.2 Hz, 1H), 4.16-3.98 (m, 3H), 3.76-3.65 (m, 2H), 2.01 (s, 3H), 1.93-1.78 (m, 2H), 1.90 (s, 3H), 1.73-1.66 (m, 2H), 1.33 (d, J = 6.0 Hz, 3H), 1.30 (d, J = 6.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz, mixture of diastereoisomers) δ 145.1, 144.9, 142.2, 142.1, 137.9 (2C), 128.6 (2C), 128.0 (2C), 127.8, 127.1, 127.0, 126.6 (2C), 126.4, 126.2, 126.0, 125.3 (2C), 124.7, 124.6, 120.7 (2C), 109.8, 109.3, 103.3 (2C), 102.4, 102.3, 79.7, 78.7, 71.5, 68.0, 43.4, 40.3, 36.5, 36.3, 30.0, 26.8, 22.8, 22.3. GC-MS (m/z): 316 (65) $[M]^+$, 301 $[M\text{-}Me]^+$, 281 (10),259 (100), 242 (20)229 (15), 197 (45), 179 (15), 165 (10), 147 (10), 129 (10), 10 5 (30), 91 (40), 77 (25), 55 (30).



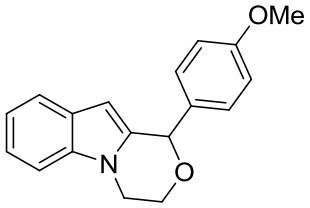
(+/-)-**2r**: white solid (mp = 135-139 °C). Yield = 77%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.30-7.19 (m, 7H), 7.14-7.03 (m, 3H), 6.85 (t, J = 7.6 Hz, 1H), 6.79 (s, 1H), 4.88 (d, J = 15.2 Hz, 1H), 4.74 (d, J = 15.2 Hz, 1H), 2.16 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 155.4, 145.2, 140.4, 137.0, 129.2, 129.0, 128.5 (2C), 127.4, 127.1, 125.3 (2C), 124.2, 122.1, 121.4, 121.3, 121.0, 119.6, 108.8, 102.7, 81.1, 46.6, 31.8. GC-MS (m/z): 325 (30) $[M]^+$, 310 (30) $[M\text{-}Me]^+$, 230 (10), 189 (15), 176 (10), 152 (10), 107 (55), 78 (100), 52 (40). Anal. calcd for (C23H19NO: 325.40): C, 84.89; H, 5.89; N, 4.32; Found: C, 84.78, H, 5.81, N, 6.20.



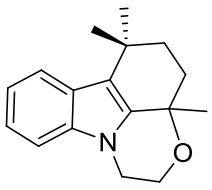
(+/-)-**2s**: white solid (mp = 195-199 °C). Yield = 70%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, J = 7.2 Hz, 1H), 7.35 (pt, J = 7.6 Hz, 3H), 7.22 (pt, J = 7.6 Hz, 3H), 7.12 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 5.96 (s, 1H), 5.87 (s,1H), 4.47-4.44 (m, 1H), 4.23-4.16 (m, 3H), 2.39 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 138.4, 136.7, 136.4, 136.2, 129.1 (2C), 128.2 (2C), 127.7, 121.2, 120.4, 120.1, 108.7, 98.7, 77.3, 63.6, 41.7, 25.3. GC-MS (m/z): 263 (90) $[M]^+$, 248 (10) $[M\text{-}Me]^+$, 235 (30), 218 (50), 205 (20), 190 (20), 169 (20), 143 (40), 119 (50), 91 (100). Anal. calcd for (C18H17NO: 263.33): C, 82.10; H, 6.51; N, 5.32; Found: C, 82.01, H, 6.31, N, 5.21.



(+/-)-**2t**: sticky solid. Yield = 82%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, J = 7.6 Hz, 1H), 7.49-7.46 (m, 2H), 7.40-7.33 (m, 3H), 7.34 (d, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 5.96 (s, 1H), 5.91 (s,1H), 4.48-4.40 (m, 1H), 4.26-4.15 (m, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 142.9, 139.6, 136.2, 128.6, 128.4 (2C), 128.2 (2C), 127.8, 121.3, 120.5, 120.2, 108.7, 98.8, 77.6, 63.7, 41.7. GCMS (m/z): 249 (100) $[\bullet M]^+$, 218 (45), 172 (30), 105 (25) 77 (30). Chiral HPLC analysis: IB column nHex:i-PrOH 90:10. Flow: 0.7 ml/min, 40°C, λ = 230 nm. tR (minor) = 9.92 min; tR (major) = 13.32 min. Anal. calcd for (C17H15NO: 249.31): C, 81.90; H, 6.06; N, 5.62; Found: C, 81.76, H, 6.10, N, 5.78.

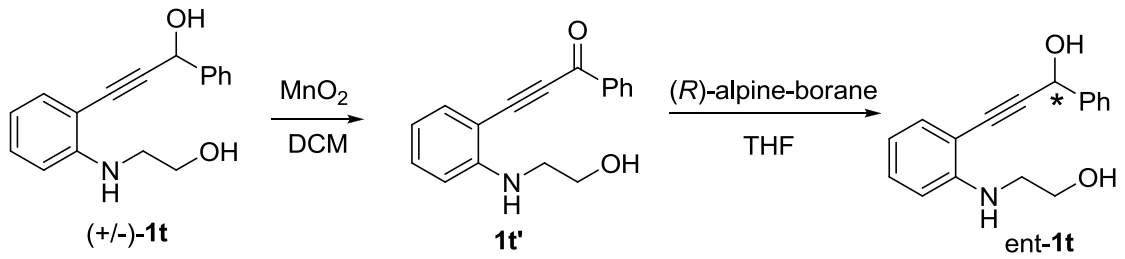


(+/-)-**2u**: white solid (mp = 177-180 °C). Yield = 56%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 5.95 (s, 1H), 5.85 (s,1H), 4.45-4.39 (m, 1H), 4.23-4.14 (m, 3H), 3.84 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 159.9, 136.6, 136.3, 131.9, 129.7 (2C), 127.8, 121.3, 120.5, 120.1, 113.8 (2C), 108.7, 98.8, 77.2, 63.6, 55.3, 41.7. GC-MS (m/z): 279 (100) $[M]^+$, 263 (20), 248 (65), 218 (35), 204 (35), 154 (30), 135 (70), 108 (40), 77 (30). Anal. calcd for (C18H17NO2: 279.33): C, 77.40; H, 6.13; N, 5.01; Found: C, 77.24, H, 6.10, N, 5.24.



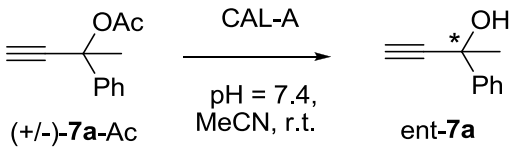
(+/-)-**2w**: clear oil. Yield = 69%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.19 (dt, J = 8.0 Hz, J = 1.2 Hz, 1H), 7.13 (dt, J = 8.0 Hz, J = 1.2 Hz, 1H), 4.50 (ddd, J = 12.0 Hz, J = 10.4 Hz, J = 4.0 Hz, 1H), 4.09 (ddd, J = 11.6 Hz, J = 4.0 Hz, J = 2.8 Hz, 1H), 3.99 (ddd, J = 12.0 Hz, J = 5.2 Hz, J = 2.8 Hz, 1H), 3.76 (ddd, J = 11.6 Hz, J = 10.4 Hz, J = 5.2 Hz, 1H), 2.00-1.91 (m, 2H), 1.89-1.86 (m, 1H), 1.83-1.79 (m, 1H), 1.67 (s, 3H), 1.52 (s, 3H), 1.36 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 140.0, 136.7, 127.3, 121.0, 120.2, 119.8, 117.1, 110.1, 71.9, 59.2, 43.6, 38.4, 34.7, 32.4, 30.7, 28.8, 24.4. GC-MS (m/z): 255 (20) $[M]^+$, 240 (100) $[M\text{-}Me]^+$, 210 (10), 194 (10), 180 (10), 168 (10), 154 (10). Anal. calcd for (C17H21NO: 255.35): C, 79.96; H, 8.29; N, 5.49; Found: 5 C, 79.81, H, 8.16, N, 5.21.

Synthesis of enantiomerically enriched substrates.



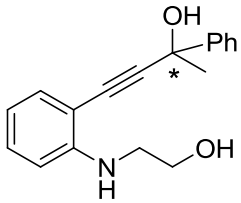
1t': in a 25 ml round bottom flask (+/-)-1q (0.2 mmol, 1 eq.) was dissolved in 7 ml of DCM and activated MnO2 (2 mmol, 10 eq.) was added. The reaction mixture was stirred at room temperature until complete consumption of the starting material (2 hours, TLC). The solution was then filtered through a short pad of Celite and concentrate under reduced pressure. The 1u: in a 25 ml round bottom flask (+/-)-1q (0.2 mmol, 1 eq.) was dissolved in 7 ml of DCM and activated MnO2 (2 mmol, 10 eq.) was added. The reaction mixture was stirred at room temperature until complete consumption of the starting material (2 hours, TLC). The solution was then filtered through a short pad of Celite and concentrate under reduced pressure. The crude reaction mixture was purified with silica-gel flash chromatography (cHex:AcOEt = 8:2) affording the product as a brown oil in 68% yield. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.19 (d, J = 7.6 Hz, 2H), 7.64-7.43 (m, 4H), 7.39-7.24 (m, 1H), 6.78-6.61 (m, 2H), 3.92 (t, J = 5.2 Hz, 2H), 3.41 (m, 2H). ^{13}C-NMR ($CDCl_3$, 50 MHz) 177.9, 151.4, 136.9, 134.3, 133.9, 130.1, 129.5 (2C), 128.7 (2C), 116.6, 110.2, 103.7, 94.0, 92.2, 60.9, 45.4. ESI-MS (m/z): 288 $[M+Na]^+$, 266 $[M+H]^+$.

ent-**1t**: In an oven dried two-necked round bottom flask under nitrogen atmosphere ketone 1u (0.2 mmol, 1 eq.) was dissolved in 3 ml of anhydrous THF and the solution was cooled at 0 °C. (R)-alpine borane (0.5 M THF solution, 1 mmol, 2 eq.) was added dropwise and the solution was stirred at room temperature until satisfactory conversion of the starting material was achieved (TLC, 24 hours). The reaction mixture was quenched with 0.5 M NaOH solution (5 ml) and stirred at room temperature for 1.5 hours. The aqueous solution was extracted with AcOEt (3x 5 ml). The combined organic layers were washed with 1M HCl, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude reaction mixture was purified with silica-gel flash chromatography (*c*Hex:AcOEt = 6:4) to afford the product as a brown oil in 35% yield and 81% *ee*. = -8.1° (c = 0.57, CHCl3). Chiral HPLC analysis: AD column nHex:i-PrOH 70:30. Flow: 0.5 ml/min, 40°C, λ = 230 nm. tR (minor) = 7.39 min; tR (major) = 8.01 min.



Enantiomerically enriched alcohol ent-**7a** was prepared according to a modified literature procedure 2 by enzymatic kinetic resolution of racemic ester **7a**-Ac.

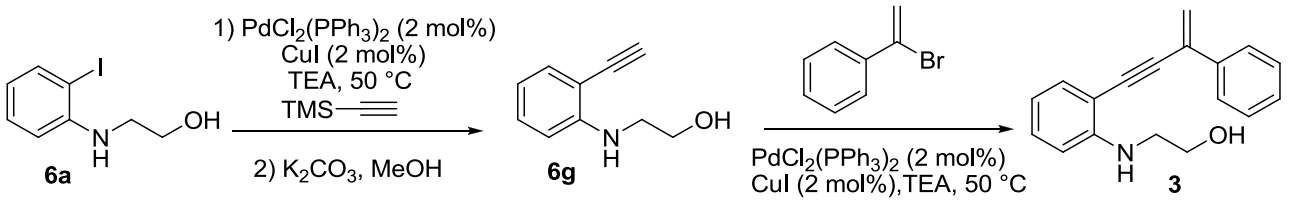
In screw-capped vial ester **7a**-Ac was dissolved in 0.5 ml MeCN and diluited with 5 ml of phosphate buffer at pH 7.4. Lipase A from C. Antarctica was added (20 mg, 5.72 U/mg). The suspension was shaken at room temperature for a week and then the aqueous solution was extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the mixture of alcohol and ester was purified with silica-gel flash chromatography (*c*Hex:AcOEt = 9:1) to afford the pure alcohol as a clear oil in 8% yield and 60 % *ee*. = + 2.3 (c = 0.97, CHCl3). Chiral HPLC analysis: AD column nHex:i-PrOH 98:2. Flow: 0.5 ml/min, 40°C, λ = 214 nm. tR (minor) = 19.95 min; tR (major) = 20.91 min.

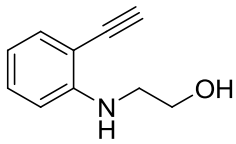


ent-**1d** was synthesized from 6a and ent-7a according to the general procedure for the Sonogashira coupling. = + 23.6 (c = 0.51, CHCl3). Chiral HPLC analysis: AD column *n*Hex:i-PrOH 80:20. Flow: 0.7 ml/min, 40°C, λ = 214 nm. tR (major) = 8.28 min; tR (minor) = 8.83 min.

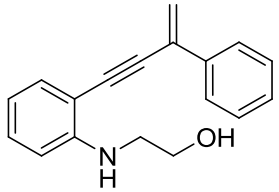
Control experiments evidence for SN1-mechanism via intimate ion-pairs.

Synthesis of enyne 4.



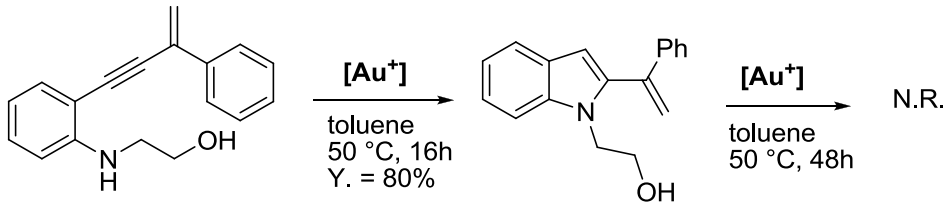


In an oven dried Schlenk tube, under nitrogen atmosphere, N-alkyl-2-iodoaniline 6a (1 mmol, 1 eq.)and trimethylsilylacetylene (1.2 mmol, 1.2 eq.) were dissolved in 2 ml of TEA. $(PPh_3)_2PdCl_2$ (0.04 mmol, 0.02 eq.) and CuI (0.04 mmol, 0.02 eq.) were added in sequence and the reaction mixture was heated at 50 °C until complete consumption of the starting material (TLC, 3 hours). The reaction mixture was diluited with water (5 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was dissolved in methanol (5 ml) and K_2CO_3 (1.5 mmol, 1.5 eq.) was added. After 3 hours at room temperature the reaction mixture was diluited with water (5 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine and dried over Na_2SO_4. The volatiles were removed under reduced pressure and the crude product was purified with silica-gel flash chromatography (cHex:AcOEt = 8:2) to afford the product as a brown oil in overall 44% yield. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.54 (d J = 7.6 Hz, 1H), 7.19 (t, J = 7.6 Hz. 1H), 6.62-6.59 (m, 2H), 3.81 (t, J = 5.2 Hz, 2H), 3.42 (s, 1H), 3.38 (t, J = 5.2 Hz, 2H)



Compound **3** was synthesized from 6g and α-bromostyrene according to the general procedure for the Sonogashira coupling. Brown oil. Yield = 33%. Flash chromatography *c*Hex:AcOEt = 8:2. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.65 (d, J = 7.6 Hz, 2H), 7.35-7.24 (m, 4H), 7.17-7.10 (m, 1H), 6.63-6.55 (m, 2H), 5.88 (s, 1H), 5.67 (s, 1H), 3.75 (t, J = 5.2 Hz, 2H), 3.28 (t, J = 5.2 Hz, 2H). ESI-MS (m/z): 286 $[M+Na]^+$, 264 $[M+H]^+$.

When the probe ene-ino compound **3** was subjected to gold catalysis only partially cyclized 2-vinyl indole **4** was isolated in 80% yield. Interestingly, compound 4 was recovered untouched even under prolonged reaction conditions (48 h), proving the unfeasibility of the gold catalyzed hydroalkoxylation of the electron-rich carbon-carbon double bond **([Au$^+$]:** XPhosAuNTf$_2$).



4: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.27-7.21 (m, 4H), 7.19-7.15 (m, 1H), 7.07 (t, J = 7.6 Hz, 2H), 6.56 (s, 1H), 5.76 (s, 1H), 5.51 (s, 1H), 3.93 (t, J = 6.0 Hz, 2H), 3.60 (t, J = 6.0 Hz, 2H).

7. Merging Synthesis and Enantioselective functionalization of Indole Cores.

7.1 Merging Synthesis and Enantioselective functionalization of Indole Cores.

At the end of our investigation on the development of new gold catalyzed cascade reactions using propargylic alcohols as precursors we discovered interestingly that, catalytic synthesis and enantioselective functionalization of the indole derivatives seemed to proceed on parallel routes, but no examples of merging these reactivities, under the direction of a single chiral promoting agent, have been reported. Undoubtedly, providing reliable solutions to this still open issue will deeply impact crucial aspects of modern organic synthesis: step, redox, and atom economy in alkaloid chemistry.

7.2 Electrophylic activation of Allylic alcohols.

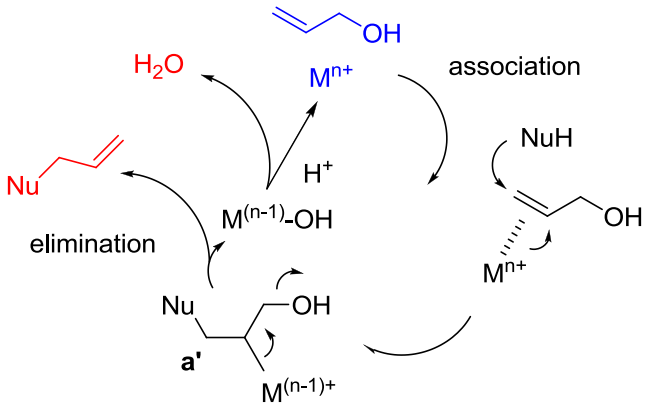
Catalytic asymmetric allylic alkylation is a well-established synthetic protocol for the synthesis of complex molecular architectures in a stereo-defined manner.[1] The well-established Tsuji–Trost-type nucleophilic substitution of activated allylic fragments is among the most potent stereoselective tool for the functionalization of stabilized 'soft' as well as unstabilized 'hard' carbon- and heteroatom-based nucleophiles.[2] In the last decade, several developments in this field, concerned the replacement of conventional activated leaving group such as acetates, carbonates, phosphates, and halides with more synthetically reliable alcohols.[3] These brought several advantages into the field that are related to step economy (most of the aforementioned leaving groups are obtained from alcohols), cost efficiency (alcohols are largely available at reasonable prices), and environmental impact (water would result as the only stoichiometric by-product of the catalytic transformation).

On the other hand, alcohols are, by far, the more poorly reactive electrophilic species, with the resulting need for high loading of catalysts, high reaction temperatures, and/or addition of external activators. Neverthless, 'softer' transition metal species with marked π-acid character have been shown to promote allylic alkylation methodologies via conventional electrophilic activation of the carbon–carbon double bond, under η^2-complexation pathway.

In this direction, the isohypsic nature of [Au(I)] and [Hg(II)] salts/complexes, their unique carbophilicity and moderate heterophilicity makes these metals candidates for promoters of allylic alkylation reactions in the presence of scarcely reactive alcohols.[4]

In principle, the late-transition-metal-assisted reaction can occur through a concerted or stepwise mechanistic event.

More frequently it involves the initial addition of the nucleophilic species to the olefin unit leading to a β-hydroxy organometallic intermediate **a'**, with the subsequent β-elimination to restore the carbon–carbon double bond (Scheme 7.1).



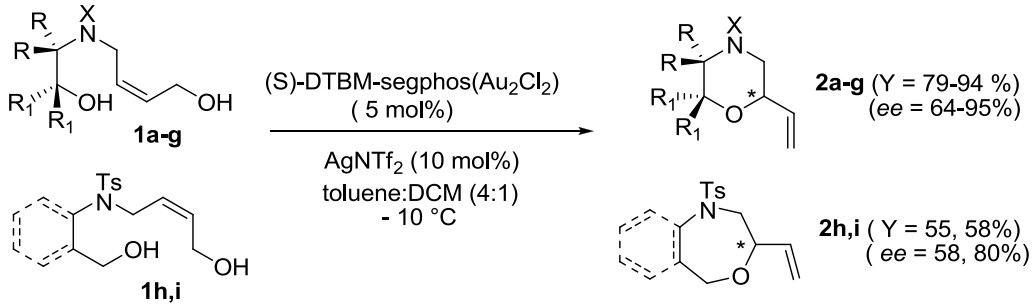
Scheme 7.1. *Mechanism for the nucleophilic addition to activated allylic alcohols.*

It should be emphasized that concomitant metal–oxygen coordination cannot be ruled out *a priori* (*i.e.* σ-Lewis acid mediated mechanism) even if the poor oxophilicity of late-transition-metal species should favor the η^2-[M/olefin] interaction.[5]
In this context, it is not surprising that gold catalysis gained a prominent role in the activation of allylic alcohols.
Moreover, mild conditions and the high functional-group tolerance, allowed a more efficient development of enantioselective protocols for the synthesis of complex molecular architectures.

7.3 Enantioselective Gold Catalyzed alkylation of allylic alcohols.

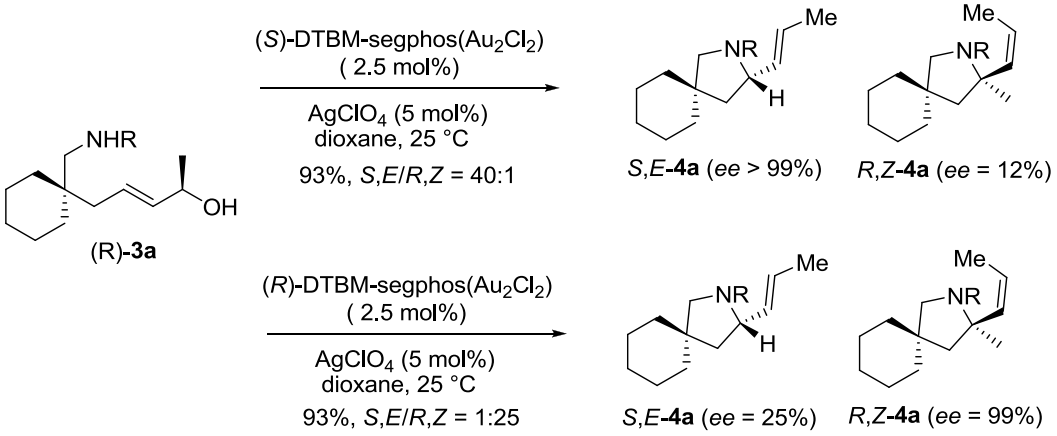
In this field Bandini pioneered reporting, as previous mentioned, the first example of enantioselective gold(I) catalyzed alkylation of indoles with allylic alcohols. Recently, the same group reported a gold(I) catalyzed enantioselective oxalkylation of allylic alcohols[6] to synthesize highly functionalized morpholines for which catalytic steroeselective synthesis still remains relatively unexplored.[7] This reactivity was deeply explored from a mechanistic point of view shading lights on the role of the configuration of the allylic alcohol **1**.

Particularly, subjecting diastereoisomeric (*Z*)- and (*E*)-**1a** (R, R_1 = H, X = NTs) to the optimum conditions inversion of stereoinduction was observed in the morpholine **2a** with the same catalyst indicating (*R*)-DTBM-segphos/(*Z*)-**1a** as the matched stereochemical combination.[8] Moreover, this inversion calls for a tight anchoring of the C=C double bond to the dinuclear catalyst with a prominent role of the hydroxyl group orientation (Scheme 7.2).[9]



Scheme 7.2. *Enantioselective [Au(I)]-catalyzed oxalkylation of allylic alcohols for the synthesis of enantioenriched morpholines.*

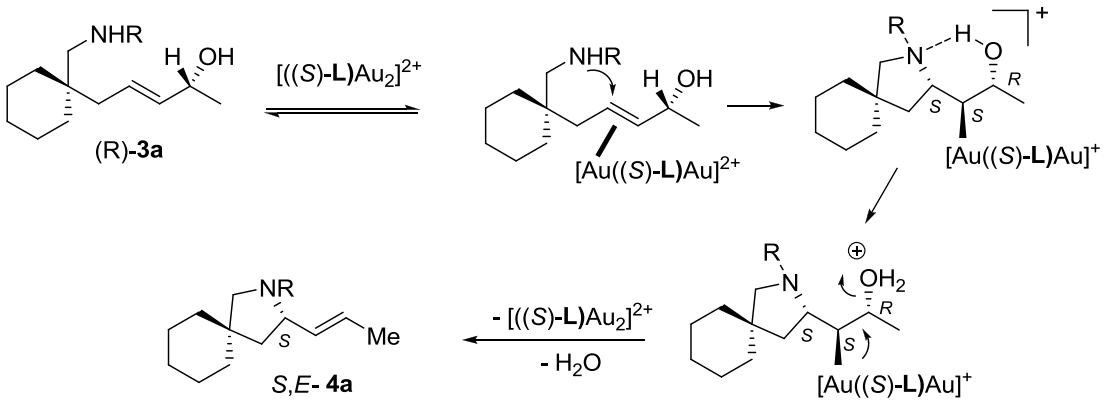
Widenhofer reported the first example of enantioselective gold catalyzed dehydrative ammination of allylic alcohols with carbamates (Scheme 7.3).[10]



Scheme 7.3. *Enantioselective [Au(I)]- catalyzed amination of allylic alcohols.*

Mechanistically, we can see that asymmetric induction is determined solely by the catalyst configuration (*S*→*S*; *R*→*R*) and that *E*/*Z* selectivity is determined by the stereochemical relationship between the incipient N-bound stereocenter and the extant O-bound stereocenter (*S*/*R*→*E*; *R*/*R*→*Z*).

This resulted to be consistent with the net *syn* displacement of the hydroxy group by the attacking carbamate nucleophile (Scheme 7.4).

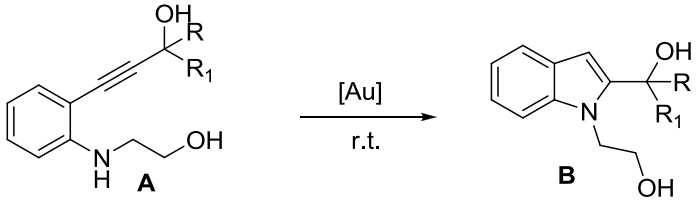


Scheme 7.4. *Mechanism proposed for the syn displacement of the hydroxyle.*

The net *syn* displacement of the hydroxyl group by the nitrogen nucleophile, which was also documented for the amination of allylic alcohols catalyzed by achiral mono(gold) complexes, is consistent with a mechanism involving π-complexation of gold to the C=C bond followed by *anti*-addition of the nucleophile and *anti*-elimination of the hydroxy group, perhaps facilitated by an intramolecular N-H-O hydrogen bond.

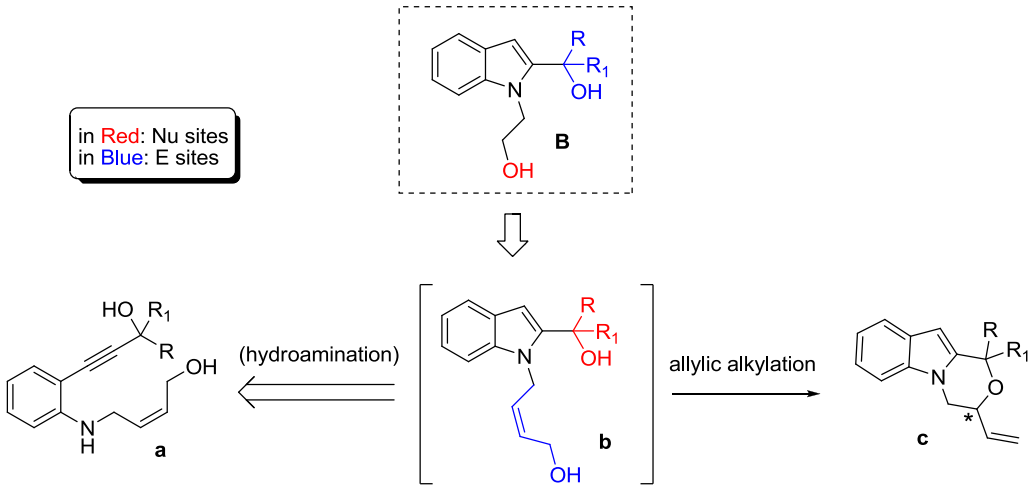
7.4 Synthesis and enantioselective functionalization of indole cores: Results and discussion

The interest of our group in the use of allylic alcohols as electrophilic patterns in developing stereoselective transformation and the high flexibility of aniline-based propargylic alcohols led us to investigate onto the development of a cascade process in which, starting from readily available acyclic precursors, was possible not only to synthesize the indole ring but also to achieve an enantioselective functionalization of the polycylic system. In a previous work, starting from alkynyl diols of type **A**, we were able to synthesize an indolyl intermediate of type **B** with achiral gold species (Scheme 7.5).



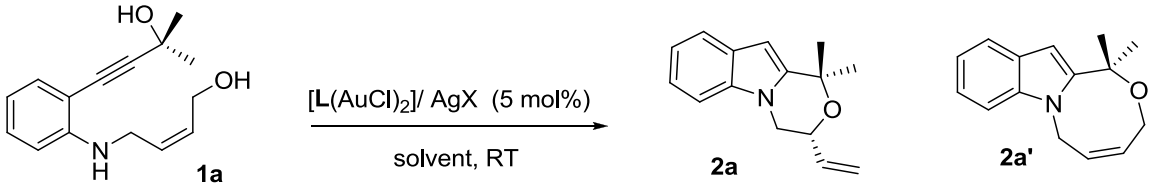
Scheme 7.5. *Designing a [Au(I)]-cascade sequence for the synthesis and enantioselective functionalization of indoles: synthesis of the indole core.*

The structure of the indolyl-diol intermediate **B**, in combination with the aptitude of chiral gold complexes in promoting stereoselective allylic alkoxylation reactions, inspired the possibility to replace the CH_2CH_2OH group of **A** with an allylic alcohol unit at the aniline nitrogen atom.This observation led us towards the synthesis of acyclic precursors in which the propargylic unit could allow the preliminary hydroamination step to afford the synthesis of the indole core leading to a suitable intermediate for a metal catalyzed allylic alkoxylation (Scheme 7.6).[11]



Scheme 7.6 *Designing a [Au(I)]-cascade sequence: enantioselective functionalization*

This last chemical event would open access to the synthesis of polycyclic indoles [4,3-*a*]-oxazino indoles **c** in a stereochemically defined manner. It has to be emphasized that such a late-stage stereodifferentiating event in a gold-catalyzed asymmetric domino process is somehow unusual, [12] and the choice for a particularly robust and functional-group-tolerant catalytic system will be mandatory. We decided substrate **1a** as a model substrate and then we tested a range of chiral dinuclear phosphine- based gold complexes (Table 7.7).



entry	L	X[b]	solvent	**2a**/**2a'**[b]	Yield (%) **2a**+**2a'**	*ee* (%)[b]
1	**L1**	NTf_2	Tol/CH_2Cl_2	-[d]	.	-
2	**L2**	NTf_2	Tol/CH_2Cl_2	95:5	46	4
3	**L3**	NTf_2	Tol/CH_2Cl_2	80:20	77	11 (-)
4	**L4**	NTf_2	Tol/CH_2Cl_2	>95:5	49	50
5	**L5**	NTf_2	Tol/CH_2Cl_2	>95:5	77[e]	54 (-)
6	**L6**	NTf_2	Tol/CH_2Cl_2	>95:5	60[f]	47 (-)
7	**L7**	NTf_2	Tol/CH_2Cl_2	>95:5	79[f]	48 (-)
8	**L8**	NTf_2	Tol/CH_2Cl_2	>95:5	77	58
9	**L9**	NTf_2	Tol/CH_2Cl_2	>95:5	64[f]	72
10	**L9**	NTf_2	Tol/CH_2Cl_2	80:20	47[g]	65
11	**L9**	ClO_4	Tol/CH_2Cl_2	20:80	58[f]	5
12	**L9**	OTs	Tol/CH_2Cl_2	60:40	72	11 (-)
13	**L9**	SbF_6	Tol/CH_2Cl_2	45:55	45[f]	63
14	**L9**	OTf	Tol/CH_2Cl_2	>95:5	70[f]	55
15	**L9**	NaBArF	Tol/CH_2Cl_2	85:15	83	9 (-)

[a] All of the reactions were carried out under nitrogen for 24 h. Standard conditions require toluene/CH_2Cl_2 4:1 as the reaction media and room temperature. [b] Determined by chiral HPLC. [c] Yields of isolated product after flash chromatography. [d] No reaction. [e] Reaction time 2 h. [f] Reaction time 4 h. [g] With (*E*)-**1a**. [h] Reaction time 1 h, with (*R*)-L9. [i] Reaction time 16 h at 0 °C, with (R)-L9. L: L1=(*R*)-binaphane; L2=(*R*)-diop, L3=(*R*)-Tol-binap, L4=(*S*)-3,5-xylyl-phanephos, L5=(*R*)-xylyl-SDP; L6=(*S*)-DTBM-MeO-biphep; L7=(*S*)-3,5-xylyl-MeO-biphep; L8=(*R*)-3,5-(iPr)2-4-NMe2-MeObiphep; L9=(*S*)-DTBM-segphos.

Table 7.7 *Optimization of the catalytic system fot the synthesis of oxazino-indoles: Ligand effect.*

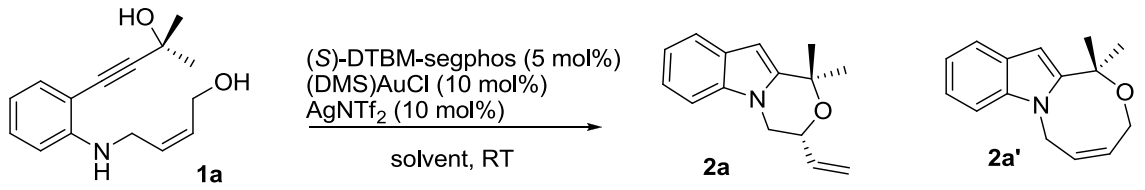
A range of commercially available *C2*-symmetric chiral biphosphines (**L1**–**L9**) were tested (entries 1–9) in the presence of $AgNTf_2$ as the halide scavenger and toluene/CH_2Cl_2 (4:1) as the reaction media. Interestingly, the formation of the oxazino-indole **2a** was always preferred with respect to oxazocino[4,3-*a*]-indole derivative **2a'**, providing clear evidence of the preferred intramolecular allylic alkylation with respect to the dehydrative alkoxylation of the tertiary alcohol.

Among them, promising results in terms of enantioselectivity and reaction rate were recorded with DTBM-segphos (**L9**) as the chiral ligand (5 mol%). In particular, after 4 h reaction time, **2a** was obtained in 64% yield, 95:5 **2a**/**2a'** ratio, and 72% *ee* (entry 9).

Moreover, the impact of the counterion over the stereochemical profile of the process was investigated (entries 11–15).

Bis(trifluoromethansulfonamide) emerged as the anion of election, while comparable results in terms of stereodiscrimination were obtained also in the presence of SbF_6 (63% *ee*, entry 13), accompanied by poor chemoselectivity (**2a**/**2a'** = 45:55). Finally, inversion of stereoinduction was recorded when OTs and BArF were employed (entries 12, 15).

Then, a range of reaction media was assessed, indicating toluene as the solvent of choice (Table 7.8).



Entry	solvent	time	Yield(%) [a]	**2a**/**2a'**[b]	*ee* (%) [a,b]
1	$MeNO_2$	24	-	-	-
2	THF	24	-	-	-
3	Dioxane	24	93	0/100	-
4	MTBE	2	86	50/50	50 (-)
5	DCM	4	98	20/80	49 (-)
6	Benzene	3	88	> 95:5	55 (-)
7	Anisole	16	90	60/40	36 (-)
8	*p*Cl-C_6H_5	22	98	35/65	51 (-)
9	*p*CF_3-C_6H_5	16	27	80/20	59 (-)
10	*p*F-C_6H_5	2	75	> 95:5	69 (-)
11	Xylene	4	66	> 95:5	74 (-)
12	Tol:*n*Hept. 4:1	4	80	> 95:5	48 (-)
13	Toluene	4	58	> 95:5	74 (-)
14[c]	Toluene	2	63	> 95:5	72 (-)
15[d]	Toluene	2	54	> 95:5	58 (-)
16[e]	Toluene	1	72	> 95:5	85 (-)
17[e,f]	Toluene	16	72	> 95:5	87 (-)

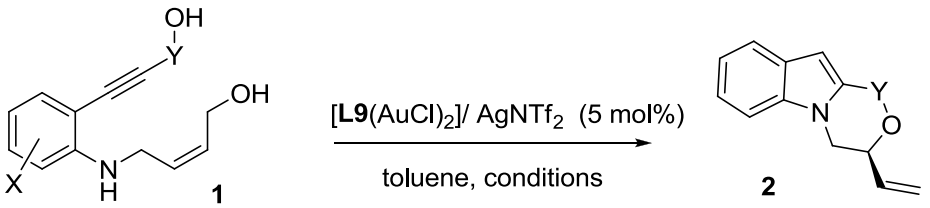
[a]: Isolated product after flash chromatography (**2a**+**2a'**). [b]: Determined by hiral HPLC analysis. [c]: AgCl removed by filtration. [d]: 5 mol% of $AgNTf_2$. [e]: 15 mol% of $AgNTf_2$. [f]: Reaction carried out at 0 °C. [g]: Brand new (DMS)AuCl.

Table 7.8. *Optimization of the catalytic system fot the synthesis of oxazino-indoles: Solvent effect*

Delightfully, **2a** was obtained selectively (**2a**/**2a'** > 95:5) in 72% yield and with enantiomeric excess up to 87% at 0 °C (entry 17). Notably, the importance of the C=C configuration over the whole reaction profile was finally investigated by subjecting (*E*)-**1a** to optimal reaction conditions ([DTBM-segphos($AuNTf_2$)$_2$], toluene/CH_2Cl_2, r.t.).

Interestingly, almost complete inversion of stereoinduction in the presence of the same enantiomer of the chiral ligand (65% *ee*, entry 10) was recorded, providing a clear insight into the SN2'-type mechanism of the final allylic alkylation ring closure.[12] Last but not least, a range of acid–base additives and water scavengers were ested without any significant improvements in terms of both chemical as well as optical reaction outcome.

Then, with the optimal reaction conditions in hand, the scope of the procedure was evaluated by subjecting a range of diols (**1b**–**q**) to the [Au(I)]-catalyzed cascade process (Table 7.9).



entry	Y	X	Cond. [°C]/[h]	2	Yield (%)	*ee* (%)
1	cHex	H	0/24	**2b**	72	84
2	cHept	H	0/22	**2c**	94	78
3	$C(nC_4H_7)_2$	H	25/7	**2d**	72	84
4	CH_2	H	25/24	**2e**	88	85
5	$C(C_2H_5)_2$	H	25/4	**2f**	71	82
6	4-pyranyl	H	25/7	**2g**	74	86
7	4-(NTs)piperidyl	H	25/4	**2h**	62	95
8	$C(Me)_2$	6-Cl	25/2	**2i**	61	82
9	$C(Me)_2$	5-CF_3	25/4	**2j**	84	86
10	$C(Me)_2$	5,7-$(Me)_2$	25/4	**2k**	93	90
11	4-(NTs)piperidyl	6-Cl	25/24	**2l**	84	90
12	4-(NTs)piperidyl	5-F	25/2	**2m**	78	96
13	4-(NTs)piperidyl	5-CF3	25/24	**2n**	62	95
14	4-(NTs)piperidyl	5-Me	25/5	**2o**	82	94
15	4-(NTs)piperidyl	5,7-(Me)2	25/24	**2p**	60	98
16	fluorenyl	H	25/92	**2q**	30	84

Table 7.9. *Scope for the synthesis and enantioselective functionalization of oxazino-indoles.*

Substituents were placed both on the alkynyl chain (Y) and inthe aniline ring (X), providing a good level of functionalgroup tolerance.

Generally, the presence of an alkyl group at the propargylic position increased the reaction rate in comparison to the unsubstitued propargylic derivative **1e** (entry 4).

A classic Thorpe–Ingold[13] effect could be account to rationalize this behavior.

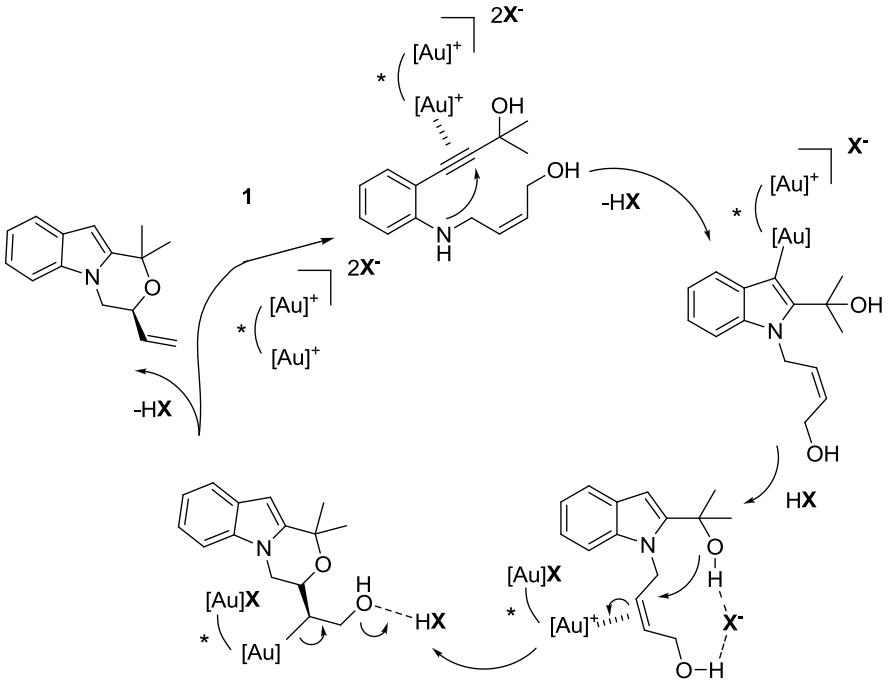
Good to high enantiomeric excesses were routinely obtained with both cyclic as well as acyclic R-groups (78–90% *ee*). Interestingly, when N-tosyl pypirindone was chosen as the "tethering unit" X (**1h**, entry 7) the double ring-closing processes worked smoothly, providing **2h** in decent yield (62%) and excellent 95% *ee*.

Then several anilines (**1i**–**p**) comprising substitutions at the benzenoid ring were explored. In all cases, the targeted oxazino-indoles were obtained in satisfactory yields (61– 93%) and excellent stereocontrol (up to 98% *ee*). Finally, the biaryl substituted fluorenyl diol **1q** was reacted under optimal reaction parameters. A prolonged reaction time (92 h) provided the corresponding polycyclic scaffold **2q** in modest yield (30%) but appreciable stereocontrol (entry 16).

From a mechanistic point of view, the present [Au(I)]-catalyzed cascade process can be rationalized as depicted in Scheme 7.10.

In particular, the initial activation of the alkynyl unit by the chiral gold complex triggered the hydroaminative cycle followed by the protodeauration step.[14]

The resulting indolyl diol **C** can enter the stereoselective alkoxylation cycle (cycle II), which, based on recent mechanistic investigations on related transformations,[15] is described as comprising a stepwise SN2'-type process (that is, anti-alkoxyauration of the C=C, anti-elimination [Au]-OH sequence).



Scheme 7.10. *Mechanistic prediction for the synthesis and enantioselective functionalization*

Interestingly, reverse alkoxylation leading the tricyclic indole derivative **2'** became competitive or predominant to the allylating step only in highly coordinating solvents (such as dioxane, Figure 7.11) .

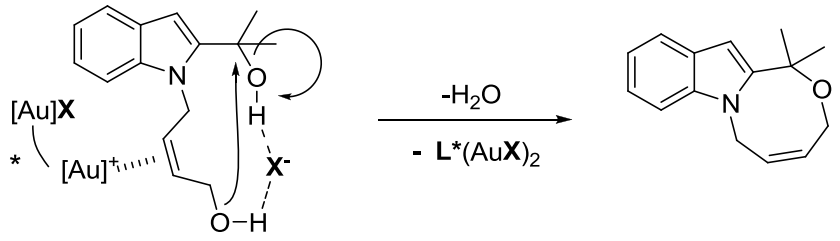
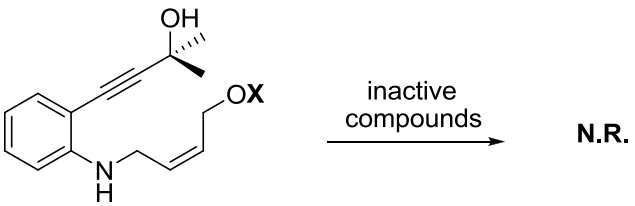


Figure 7.11. *Solvent effect inverting the chemoselectivity of hydroxylic and allylic moiety.*

To shed some light on the proposed mechanism, the following experimental controls were carried out. First, the crucial role of the leaving hydroxy group on the overall process was ascertained by reacting under best conditions the corresponding OTBDMS and OCO_2Et derivatives of model substrate **1a** (Scheme 7.12).

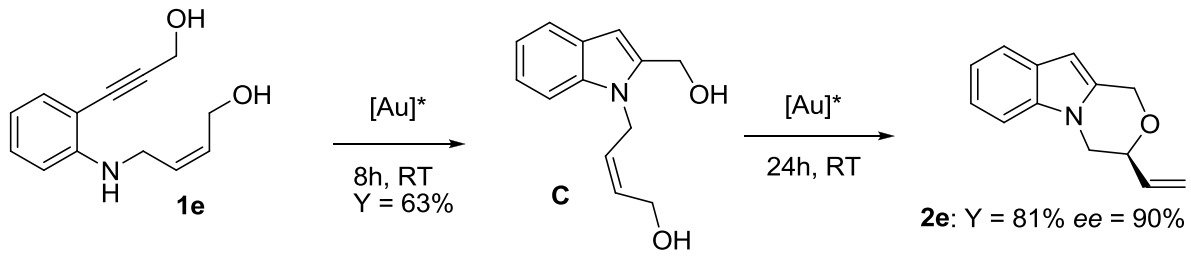
In the case of the silyl-ether, the complete consumption of the precursor led to a complex mixture of unknown compounds. On the contrary, ethylcarbonate underwent exclusively the initial C-N bond forming event (yield = 87%, RT, 16 h), demonstrating the complementarity of the gold-catalyzed allylic alkylations with respect to Pd-catalyzed Tsuji–Trost-like processes.[16, 17]



Scheme 7.12. *Mechanistic studies: behaviour of functionalized allylic alcohols.*

Finally, we unambiguously confirmed the role of diol **C** as the molecular conjunction of the two catalytic cycles by stopping the cascade reaction of **1e** after 8 h (C was isolated in 63% yield).

Then, indolyl diol **C** was reacted in the presence of DTBM-segphos($AuNTf_2$)$_2$ (5 mol%), leading to **2e** with stereoinduction (yield = 81%, 90% *ee*), which is comparable to the one-pot procedure (Table 2, entry 4, 85% *ee*; Scheme 7.14).



Scheme 7.14. *Mechanistic studies: Role of diol* ***C*** *in the enantioselective ring closure event.*

7.4. Conclusions.

In this section we reported an unprecedented gold-catalyzed cascade sequence to access substituted [4,3-*a*]-oxazino-indoles in high enantiomeric excess, exploiting simultaneously the synthetic flexibility of aniline-based allylic/propargylic alcohols.

Interestingly, the use of a single chiral gold(I)-complex assisted both synthesis of the pyrrolyl core and the subsequent enantioselective allylic alkoxylation, delivering water as the only stoichiometric by-product.

Bibliography

[1]. (a) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003; and references therein. (b) Trost, B. M.; Crawley, M. L. *Top. Organomet. Chem.* **2012**, *38*, 321.

[2]. (a) Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, **2000**, 593. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis I-III*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**, 833. (e) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, 1641. (f) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427. (g) Hartwig, J. F. *Allylic Substitution*; University Science Books: Sausalito CA, **2010**. For the pioneering investigation in the field see: (h) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1650.

[3] For reviews on the topic: (a) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501. (b) Bandini, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 994. (c) Emer, E.; Sinisi, R.; Guiteras Capdevila, M.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, 647. (d) Biannic, B.; Aponick, A. *Eur. J. Org. Chem.* **2011**, 6605.

[4] Muzart, J. *Eur. J. Org. Chem.* **2007**, 3077; and references therein.

[5]. Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.

[6]. M. Bandini, M. Monari, A. Romaniello, M. Tragni, *Chem.Eur.J.* **2010**, *16*, 14272-14277.

[7]. M. L. Leathen, B. R. Rosen, J. P. Wolfe, *J. Org. Chem*. **2009**, *74*, 5107 – 5110, and references therein. See also: a) H. Ito, Y. Ikeuchi, T. Taguchi, Y. Hanzawa, M. Shiro*, J. Am. Chem. Soc*. **1994**, *116*, 5469 – 5470; b) M. K. Ghorai, D. Shukla, K. Das, *J. Org. Chem*. **2009**, *74*, 7013 – 7022.

[8]. Opposite behavior was documented in the Tsuji–Trost-type approach for the preparation of **4a**.

[9]. Z olefins have been demonstrated to bind more tightly to cationic gold(I) complexes containing sterically demanding phosphine ligands than that the corresponding E isomers, see: T. J. Brown, M. G. Dickens, R. A. Widenhoefer, *Chem. Commun*. **2009**, 6451 –6453.

[10]. P. Mukherjee, R. A.Widenhoefer; *Angew. Chem. Int. Ed*. **2012**, *51*, 1405.

[11]. M. Chiarucci, R. Mocci, L.-D. Syntrivanis, G. Cera, A. Mazzanti, M. Bandini, *Angew.Chem.Int.Ed.* **2013**, *52*, 10850-10853.

[12]. C. C. J. Loh, D. Enders, *Chem. Eur. J*. **2012**, *18*, 10212, and references therein.

[13] R. M. Beesley, C. K. Ingold, J. F. Thorpe, J. *Chem. Soc. Trans*. **1915**, *107*, 1080.

[14]. H. V. Adcock, P.W. Davies, *Synthesis* **2012**, 3401, and references therein.

[15]. a) M.Bandini, A. Bottoni, M. Chiarucci, G. Cera, G. Miscione, *J. Am. Chem. Soc*. **2012**, *134*, 20690; b) M. Chiarucci, M. di Lillo, A. Romaniello, P. G. Cozzi,G. Cera, M. Bandini, *Chem. Sci*. **2012**, *3*, 2859.

[16]. a) B. M. Trost, D. L. Van Vranken, *Chem. Rev*. **1996**, *96*, 395; b) B. M. Trost, M. L. Crawley, *Chem. Rev*. **2003**, *103*, 2921.

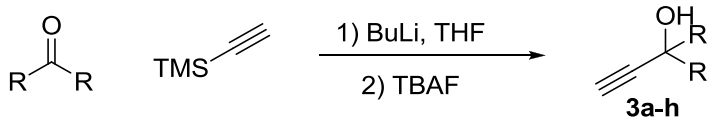
[17]. S. Porcel, V. Lopez-Carrillo, C. Garcia-Yerba, A. M. Echavarren, *Angew. Chem. Int. Ed*. **2008**, *47*, 188

Supporting Informations

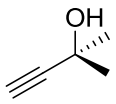
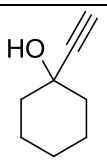
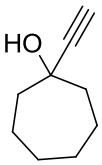
General Methods.

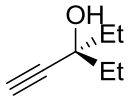
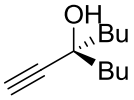
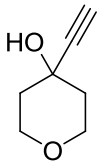
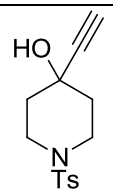
1H-NMR spectra were recorded on Varian 200 (200 MHz), Varian 400 (400 MHz) and Varian 600 (600 MHz) spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, sext = sextet, sept = septet, p = pseudo, b = broad, m = multiplet), coupling constants (Hz). 13C-NMR spectra were recorded on a Varian 200 (50 MHz), Varian 400 (100 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. They are reported as: m/z (rel. intense). LC-electrospray ionization mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 240-400 mesh silica gel. Anhydrous THF and DCM were distilled respectively from sodium-benzophenone and P2O5 prior to use. Other anhydrous solvents were supplied by Fluka or Sigma Aldrich in Sureseal® bottles and used without any further purification. Analytical high performance liquid chromatography (HPLC) was performed on a liquid chromatograph equipped with a variable wave-length UV detector (deuterium lamp 190-600 nm), using a Daicel ChiracelTM AD, OD, OD-H, and Phenomenex Lux®- 5u-CELLULOSE-3 column (0.46 cm I.D. x 25 cm Daicel Inc). HPLC grade isopropanol and n-hexane were used as the eluting solvents. Commercially available chemicals were purchased from Sigma Aldrich, Stream and TCI and used without any further purification. Elemental analyses were carried out by using a EACE 1110 CHNOS analyzer. Optical rotations were determined in a 1 ml cell with a path length of 10 mm (NaD line). Melting points were determined with Bibby Stuart Scientific Melting Point Apparatus SMP 3 and are not corrected.

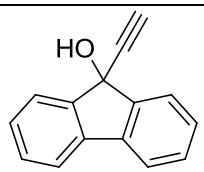
Synthesis of propargylic-alcohols.



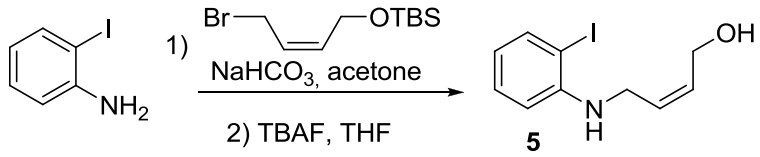
In an oven dried three-necked round bottom flask ethynyltrimethylsilane (2.4 mmol, 1.2 eq.) was dissolved in 2.5 ml of anhydrous THF. The solution was cooled at 0 °C and nBuLi (2.5 M in THF, 2.4 mmol, 1.2 eq.) was added drop-wise. The solution was stirred for 15 minutes and then a solution of the proper ketone (2 mmol, 1 eq.) in 2 ml of THF was slowly added. The solution was warmed at room temperature and stirred overnight. The reaction was quenched with saturated NH4Cl solution (5 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine and then dried over Na_2SO_4. The organic solvent was removed under reduced pressure and the crude product was dissolved in 4 ml of THF and TBAF (1.2 mmol, 1.2 eq.) was added. The reaction mixture was stirred at room temperature for 4 hours and then diluted with water (5 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the crude product was purified by silica-gel flash chromatography using cyclohexane and ethyl acetate mixture eluting solvents.

Propargylic alcohol	**Structure**	**Analytical data**
3a		Commercially available
3b		Commercially available
3c		Clear oil. Yield: 51%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.47 (s, 1H), 2.03 (dd, J = 13.6 Hz, J = 7.6 Hz, 2H), 1.96 (bs, 1H), 1.88-1.82 (m, 2H), 1.68-1.54 (m, 8H). ^{13}C-NMR ($CDCl_3$, 100

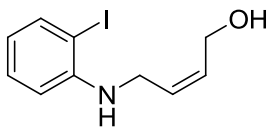
		MHz) δ 88.8, 71.6, 71.2, 42.9 (2C), 28.0 (2C), 22.0 (2C). GC-MS (m/z): 137 (5), 123 (15), 95 (40), 68 (70), 53 (100).
3d		Commercially available
3e		Clear oil. Yield 20 %. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.44 (s, 1H), 1.68-1.63 (m, 4H), 1.53-1.46 (m, 4H), 1.36 (psext, J = 7.2 Hz, 4H), 0.94 (t J = 7.2 Hz, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 87.0, 72.1, 71.1, 41.6 (2C), 26.9 (2C), 22.8 (2C), 14.1 (2C).
3f		Sticky solid. Yield 48 %. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.84 (dt J = 12.0 Hz, J = 4.4 Hz, 2H), 3.60 (ddd, J = 12.0 Hz, J = 9.2 Hz, J = 2.8 Hz, 2H), 3.48 (bs, 1H), 2.51 (s, 1H), 1.90-1.85 (m, 2H), 1.74 (ddd J = 13.2 Hz, J = 9.2 Hz, J = 4.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 86.4, 72.8, 65.1, 64.4 (2C), 39.5 (2C GC-MS (m/z): 180 $[M-H_2O]^+$ (80), 68 (100).
3g		Sticky solid. Yield 70%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, J = 8.0 Hz, 2H), 7.31(d, J = 8.0 Hz, 2H), 3.25-3.21 (m, 2H), 3.09-3.05 (m, 2H), 2.44 (s, 1H), 2.43 (s, 3H), 1.99-1.97 (m, 2H), 1.89-1.84 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.5, 129.9, 129.7 (2C), 127.5 (2C), 85.7, 73.2, 65.1, 42.6 (2C), 30.1 (2C), 21.5 (2C). ESI-MS (m/z): 302 $[M+Na]^+$, 280 $[M+H]^+$, 262 $[M-OH]^+$.

3h		White solid. Yield 76%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, J = 7.6 Hz, 2H), 7.63 (d, J = 7.6 Hz, 2H), 7.44-7.36 (m, 4H), 2.69 (bs, 1H), 2.48 (s, 1H). ESI-MS (m/z): 189 $[M\text{-}OH]^+$.

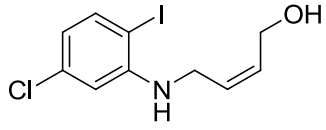
General procedures for the allylation of 2-iodoaniline.



In a Schlenk tube the proper 2-iodoaniline (2 mmol, 1 eq.) was dissolved in 8 ml of acetone and allyl bromide (2.4 mmol, 1.2 eq.), $NaHCO_3$ (7.4 mmol, 3.7 eq.) and water (2 ml) were added in sequence. The reaction mixture was stirred at 70 °C until complete consumption of the bromide (4-8 hs, GC). The solution was then cooled at rt, diluted with water (10 ml) and extracted with AcOEt (3 x 15 ml). The combined organic layers were dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The crude product was dissolved in 10 ml of THF and TBAF (2.6 mmol 1.3 eq.) was added at 0°C. The reaction mixture was stirred at rt for 2-4 hs and then diluted with water (15 ml). The aqueous layer was extracted with AcOEt (3 x 15 ml) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified with silica-gel flash chromatography using cyclohexane-AcOEt mixture as eluting solvent.

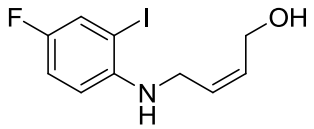


(Z)-**5a**: Brown oil, yield = 43%. Flash chromatography cHex:AcOEt = 9:1→7:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.68 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H), 7.23 (dt, J = 8.0 Hz, J = 1.2 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.49 (t, J = 8.0 Hz, 1H), 5.87-5.81 (m, 1H), 5.76-5.70 (m, 1H), 4.32 (d, J = 6.4 Hz, 2H), 3.87 (d, J = 6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 146.9, 139.0, 131.7, 129.4, 128.8, 119.1, 110.8, 85.6, 58.6, 41.4. ESI-MS (m/z): 290 $[M+H]^+$. IR (nujol): ν 3199(m), 2865(s), 1665(m), 1581(s), cm-1. Anal. calcd for (C10H12INO: 289.00): C, 41.54; H, 4.18, N, 4.84; Found: C, 41.51, H, 4.10, N, 4.71.

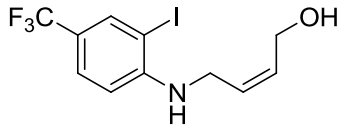


(Z)-**5b**: Brown solid, mp = 47-49 °C, yield = 40%. Flash chromatography cHex:AcOEt = 8:2→7:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.54 (d, J = 8.0 Hz, 1H), 6.52 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 5.84-5.81 (m, 1H), 5.69-5.66 (m, 1H), 4.31-4.28 (m, 2H), 3.83-3.81 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 147.8, 139.4, 135.5, 132.1, 128.0, 118.7, 110.6, 82.4, 58.5, 41.3. ESI-MS (m/z): 324, 326

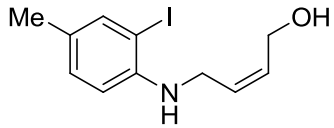
[M+H]$^+$. IR (nujol): ν 3196(m), 1641(m), 1578(s), cm-1. Anal. calcd for (C10H11ClINO: 322.96): C, 37.12; H, 3.43, N, 4.33; Found: C, 37.01, H, 3.31, N, 4.21.



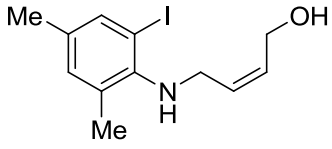
(Z)-**5c**: Brown oil, yield = 58%. Flash chromatography cHex:AcOEt = 9:1→ 7:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.43 (dd, J = 8.0 Hz, J = 2.8 Hz, 1H), 6.98 (ddd, J = 8.8 Hz, 8.0 Hz, J = 2.8 Hz, 1H), 5.50 (dd, J = 8.8 Hz, J = 4.8 Hz, 1H), 5.85-5.80 (m, 1H), 5.74-5.68 (m, 1H), 4.31 (d, J = 6.4 Hz, 2H), 3.83 (d, J = 6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 154.9 (d, J = 238.0 Hz), 143.8, 131.9, 128.7, 125.6 (d, J = 25.0 Hz), 115.8 (d, J = 21.2 Hz), 110.6 (d J = 6.8 Hz), 84.1, 58.7, 42.1. ESI-MS (m/z): 308 [M+H]$^+$. IR (nujol): ν 3185(m), 2853(s), 1653(m), 1598(s), cm-1. Anal. calcd for (C10H11FINO: 306.99): C, 39.11; H, 3.36, N, 4.56; Found: C, 39.15, H, 3.41, N, 4.59.



(Z)-**5d**: Brown oil, yield = 33%. Flash chromatographicHex:AcOEt = 9:1→ 7:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.88 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 5.88-5.82 (m, 1H), 5.70-5.64 (m, 1H), 4.60 (bs, 1H), 4.31 (d, J = 5.6 Hz, 2H), 3.91 (t, J = 5.6 Hz, 2H), 1.79 (bs, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 149.3, 136.0 (q, J = 3.8 Hz), 132.2, 127.9, 126.7 (q, J = 3.8 Hz), 125.0, 122.3, 83.7, 58.6, 41.1. ESI-MS (m/z): 258 [M+H]$^+$. IR (nujol): ν 3175(m), 2865(s), 1655(m), cm-1. Anal. calcd for (C11H11F3INO: 356.98): C, 37.00; H, 3.10, N, 3.92; Found: C, 37.09, H, 3.21, N, 3.81.

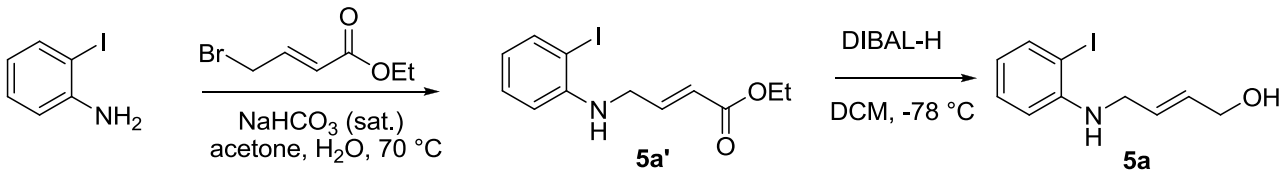


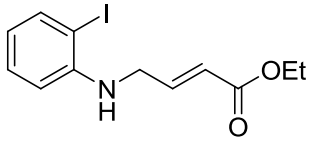
(Z)-**5e**: Brown oil, yield = 35%. Flash chromatography cHex:AcOEt = 8:2→ 7:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, J = 4.0 Hz, 1H), 7.03 (dd, J = 4.0, 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.81-5.82 (m, 1H), 5.73-5.74 (m, 1H), 4.29-4.31 (m, 2H), 3.83 (d, J = 5.4 Hz, 2H), 2.22 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 144.5, 139.5, 131.7, 131.6, 130.0, 129.1, 128.7, 110.9, 58.7, 41.8, 19.8. ESI-MS (m/z): 304 [M+H]$^+$. IR (nujol): ν 3200(m), 2901(s), 1680(m), 1588(s), cm-1. Anal. calcd for (C11H14INO: 303.01): C, 43.58; H, 4.66, N, 4.62; Found: C, 43.51, H, 4.71, N, 4.51.



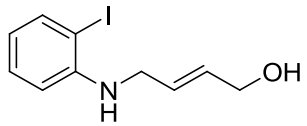
(Z)-**5f**: Brown oil, yield = 54%. Flash chromatography cHex:AcOEt = 8:2 →7:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.45 (s, 1H), 6.94 (s, 1H), 5.78-5.81 (m, 2H), 4.19 (t, J = 2.0 Hz, 2H), 3.59 (t, J = 2.0 Hz, 2H), 2.35 (s, 3H), 2.19 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 144.8, 137.2, 134.5, 132.5, 131.7, 131.5, 129.2, 96.4, 58.4, 45.4, 19.7, 19.5. ESI-MS (m/z): 318 $[M+H]^+$. IR (nujol): ν 3195(m), 2864(s), 1670(m), 1598(s), cm-1. Anal. calcd for ($C_{12}H_{16}INO$: 317.03): C, 45.44; H, 5.08, N, 4.42; Found: C, 45.31, H, 5.16, N, 4.31.

Synthesis of alcohol (*E*)-5a.



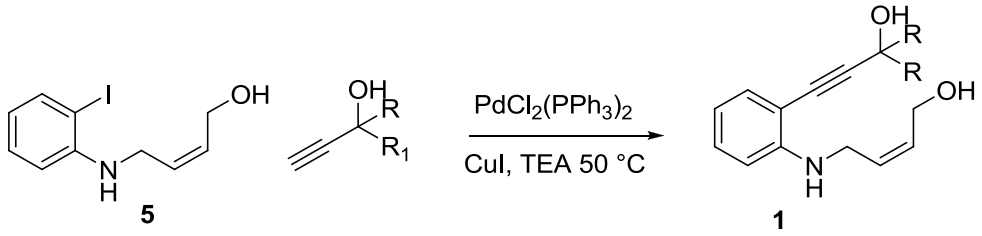


(*E*)-**5a'**: In a Schlenk tube 2-iodoaniline (2 mmol, 1 eq.) was dissolved in 8 ml of acetone and (E)-ethyl bromocrotonate (2.4 mmol, 1.2 eq., technical grade), $NaHCO_3$ (7.4 mmol, 3.7 eq.) and water (2 ml) were added in sequence. The reaction mixture was stirred at 80 °C until complete consumption of 2-iodoaniline (6 hs, TLC). The solution was then cooled at rt, diluted with water (10 ml) and extracted with AcOEt (3 x 15 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, and the volatiles were removed under reduced pressure. The crude product was purified with silica-gel flash chromatograp (cHex:AcOEt 9:1) to afford the pure product as a brown oil in 85% yield. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.67 (dd, J = 8.0, Hz, J = 1.6 Hz, 1H), 7.19 (dt J = 8.0 Hz, J = 1.2 Hz, 1H), 7.06- 6.98 (m, 1H), 6.49-6.45 (m, 2H), 6.01 (dt, J = 15.6 Hz, J = 2.0 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.00 (dd, J = 4.8 Hz, J = 2.0 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 166.0, 144.5, 141.5, 139.8, 129.4, 121.9, 119.2, 110.7, 85.3, 60.4, 44.8, 14.1. GC-MS (m/z): 331 (10) $[M]^+$, 302 (10) $[M-Et]^+$, 258 (10), 232 (10) 130 (100), 104 (20), 91 (25), 77 (20). IR (neat): ν 3320(s), 2950(m), 2981(s), 1695(s), cm-1. Anal. calcd for (C10H10INO2: 302.98): C, 39.63; H, 3.33, N, 4.62; Found: C, 39.72, H, 3.21, N, 4.61.

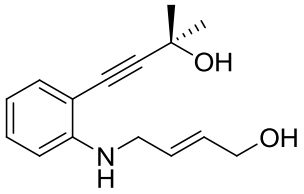


(*E*)-**5a**: In an oven dried two necked under nitrogen atmosphere ester (E)-5a' (1 mmol, 1 eq.) was dissolved in anhydrous DCM (2 ml). The solution was cooled at -78 °C and then DIBAL-H (1.2 mmol, 1,2 eq., 1.0 M solution in toluene) was added. The reaction was stirred at room temperature until complete consumption of the starting material (TLC, 4 hs) and then quenched with water (2 ml). The solution was diluted with DCM (5 ml) and a saturated solution of Rochelle salt was added. The emulsion was vigorously stirred until clear phase separation and then the aqueous layer was extracted with DCM (3 x 10 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified with silica-gel flash chromatography (cHex:AcOEt 9:1→7:3) to afford the pure product as a brown oil in 60% yield. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.67 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.20 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.56 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.46 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 5.92-5.80 (m, 2H),4.33 (bs, 1H), 4.16 (d, J = 4.8 Hz, 2H), 3.83 (d, J = 4.4 Hz, 2H), 1.80 (bs, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 146.8, 139.0, 131.2, 129.3, 127.7, 118.8, 110.8, 85.4, 62.8, 45.4. ESI-MS (m/z): 290 $[M+H]^+$. IR (neat): ν 3389(s), 3036(m), 2858(s), 1701(w), 1594(s), 1313(m), cm-1. Anal. calcd for (C10H12INO: 289.00): C, 41.54; H, 4.18, N, 4.84; Found: C, 41.66, H, 4.02, N, 4.70.

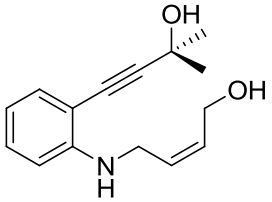
General procedure for the Sonogashira coupling.



In an oven dried Schlenk tube, under nitrogen atmosphere, **5** (2 mmol, 1 eq.) and the desired propargylic alcohol **3a**-**h** (2.4 mmol, 1.2 eq.) were dissolved in 4 ml of TEA. $(PPh_3)_2PdCl_2$ (0.04 mmol, 0.02 eq.) and CuI (0.04 mmol, 0.02 eq.) were added in sequence and the reaction mixture was heated at 50 °C until complete consumption of the starting material (TLC, 1-16 h). The reaction mixture was diluted with water (5 ml) and extracted with ethyl acetate (3 x 10 ml). The organic layer was dried over Na_2SO_4 and the volatiles removed under vacuum. The residue was purified with silica-gel flash chromatography using cyclohexane and ethyl acetate mixture as eluting solvents.

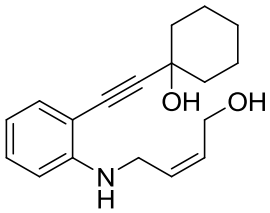


(*E*)-**1a**: Reaction conditions: 2 hs, 50 °C. Yield = 98%. Brown oil. Flash chromatography cHex:AcOEt = 6:4→ 3:7. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.24 (dd J = 8.0 Hz, J = 1.2 Hz, 1H), 7.16 (dt, J = 8.0 Hz, J = 1.2 Hz, 1H), 6.61 (t, J = 8.0 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 5.90-5.77 (m, 2H), 4.11 (d, J = 4.4 Hz, 2H), 3.80 (d, J = 4.4 Hz, 2H), 1.62 (s, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.5, 132.0, 130.8 129.7, 128.2, 116.4, 109.9, 107.2, 100.0, 78.6, 65.6, 62.6, 44.7, 31.6 (2C). ESI-MS (m/z): 268 [M+Na]+, 246 $[M+H]^+$, 228 $[M\text{-}OH]^+$. Anal. calcd for (C15H19NO2: 245.14): C, 73.44; H, 7.81, N, 5.71; Found: C, 73.32, H, 7.75, N, 5.65.

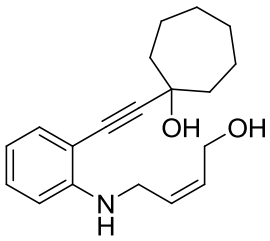


(Z)-**1a**: Reaction conditions: 2 hs, 50 °C. Yield = 98%. Brown oil. Flash chromatography cHex:AcOEt = 6:4→ 4:6. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.26 (dd J = 7.6 Hz, J = 1.6 Hz, 1H), 7.20 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.65 (t, J = 7.6 Hz, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.86-5.73 (m, 2H), 4.29 (d, J = 6.4 Hz, 2H), 3.85 (d, J = 6.0 Hz, 2H), 1.63 (s, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.5, 132.0,

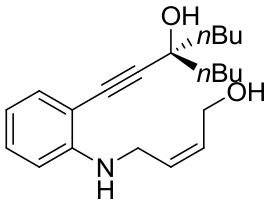
131.7, 129.9, 129.3, 116.9, 110.0, 107.5, 100.1, 78.7, 65.7, 58.6, 40.8, 31.7 (2C). ESI-MS (m/z): 246 $[M+H]^+$. IR (neat): ν 3385(s), 2961(m), 2215(s), 1706(m), 1510(m) cm-1. Anal. calcd for (C15H19NO2: 245.14): C, 73.44; H, 7.81, N, 5.71; Found: C, 73.51, H, 7.70, N, 5.62.



(Z)-**1b**: Reaction conditions: 1 h, 50 °C. Yield = 95%. Brown oil. Flash chromatography cHex:AcOEt = 6:4→ 4:6 ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.28 (dd, J = 7. 6 Hz, J = 1.2 Hz, 1H), 7.19 (dt, J = 7.6 Hz, J = 1.2 Hz, 1H), 6.65 (dt, J = 7.6 Hz, J = 1.2 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 5.85-5.79 (m, 1H), 5.77-5.71 (m, 1H), 4.28 (d, J = 6.4 Hz, 2H), 3.84 (d, J = 6.0 Hz, 2H), 2.01- 1.99 (m, 2H), 1.76-1.58 (m, 8H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.5, 132.0, 131.8, 129.8, 129.0, 116.8, 109.9, 107.7, 99.0, 80.8, 69.3, 58.4, 40.8, 40.1 (2C), 25.2, 23.5 (2C). ESI-MS (m/z): 286 $[M+H]^+$. IR (nujol): ν 3385(s), 2951(m), 2211(s), 1566(m), 1515(m), 1441(s) cm-1. Anal. calcd for (C18H23NO2: 285.17): C, 75.76; H, 8.12, N, 4.91; Found: C, 75.64, H, 8.04, N, 4.82.

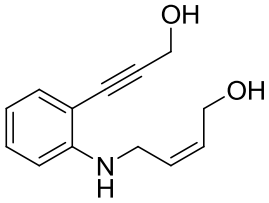


(*Z*)-**1c**: Reaction conditions: 2 hs, 50 °C. Yield = 67%. Brown oil. Flash chromatography cHex:AcOEt = 6:4 → 4:6. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.27 (dd, J = 7. 6 Hz, J = 1.6 Hz, 1H), 7.19 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.65 (t, J = 7.6 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 5.84-5.78 (m, 1H), 5.76-5.70 (m, 1H), 4.27 (d, J = 7.6 Hz, 2H), 3.82 (d, J = 6.4 Hz, 2H), 2.11 (dd, J = 14.0 Hz, J = 7.6 Hz, 2H), 1.95-1.89 (m, 2H), 1.71-1.58 (m, 8H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.6, 132.0, 131.8, 129.8, 129.8, 116.8, 109.9, 107.8, 100.1, 80.1, 74.5, 58.4, 43.3, 40.8 (2C), 27.9 (2C), 22.4 (2C). ESI-MS (m/z): 322 $[M+Na]^+$, 300 $[M+H]^+$, 282 $[M-OH]^+$. IR (nujol): ν 3365(s), 2213(s), 1703(m), 1461(s), cm-1. Anal. calcd for (C19H25NO2: 299.19): C, 76.22; H, 8.42, N, 4.48; Found: C, 76.14, H, 8.31, N, 4.40.

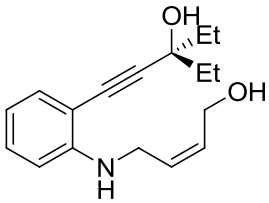


(Z)-**1d**: Reaction conditions: 4 hs, 50 °C. Yield = 85%. Brown oil. Flash chromatography cHex:AcOEt = 6:4→ 4:6. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.27 (dd J = 7.6 Hz, J = 1.6 Hz, 1H), 7.20 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.65 (t, J = 7.6 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 5.86-5.80 (m, 1H), 5.77-5.71 (m, 1H), 4.29 (d, J = 6.4 Hz, 2H), 3.84 (d, J = 6.0 Hz, 2H), 1.80-1.68 (m, 4H), 1.55 (psept J = 7.2 Hz, 4H), 1.38 (psext, J = 7.2 Hz, 4H), 0.95 (t, J = 7.2 Hz, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.6, 132.1, 131.8, 129.8, 128.9, 116.8, 109.8, 107.6, 98.4, 80.8, 71.8, 58.5, 41.9, 40.8 (2C), 26.7

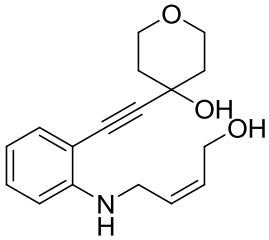
(2C), 22.9 (2C), 14.1 (2C). ESI-MS (m/z): 353 $[M+Na]^+$, 330 $[M+H]^+$, 312 $[M-OH]^+$. IR (neat): ν 3397(s), 2959(m), 2214(s), 1700(m), 1576(m), 1513(m), 1454(s) cm-1. Anal. calcd for (C21H31NO2: 329.24): C, 76.55; H, 9.48, N, 4.25; Found: C, 76.41, H, 9.40, N, 4.12.



(*Z*)-**1e**: Reaction conditions: 4 hs, 50 °C. Yield = 62%. Brown oil. Flash chromatography cHex:AcOEt = 6:4→ 4:6. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.28 (d J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 6.65 (t, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 5.85-5.71 (m, 2H), 4.53 (s, 2H), 4.29 (d, J = 6.4 Hz, 2H), 3.85 (d, J = 6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.7, 132.3, 131.6, 130.1, 129.3, 116.8, 109.9, 107.3, 93.3, 82.2, 58.4, 51.6, 40.7. ESI-MS (m/z): 256 $[M+K]^+$, 240 $[M+Na]^+$, 218 $[M+H]^+$. IR (neat): ν 3392(s), 2950(m), 2213(s), 1555(w) cm-1. Anal. calcd for (C13H15NO2: 217.11): C, 71.87; H, 6.96, N, 6.45; Found: C, 71.77, H, 6.81, N, 6.31.

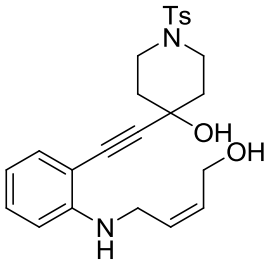


(Z)-**1f**: Reaction conditions: 8 hs, 50 °C. Yield = 52%. Brown oil. Flash chromatography cHex:AcOEt = 6:4→ 4:6. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.28 (dd J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.65 (t, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 5.86-5.82 (m, 1H), 5.78-5.74 (m, 1H), 4.30 (d, J = 6.4 Hz, 2H), 3.85 (d, J = 6.4 Hz, 2H), 1.83-1.73 (m, 4H), 1.11 (t, J = 7.2 Hz, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.6, 132.1, 131.8, 129.8, 129.0, 116.7, 109.8, 107.6, 97.8, 81.0, 72.8, 58.5, 40.7, 34.5 (2C), 88 (2C). ESI-MS (m/z): 274 $[M+H]^+$, 256 $[M-OH]^+$. IR (neat): ν 3390(s), 2961(m), 2213(s), 1581(m), 1510(m) cm-1. Anal. calcd for (C17H23NO2: 273.17): C, 74.69; H, 8.48, N, 5.12; Found: C, 74.51, H, 8.32, N, 5.04.

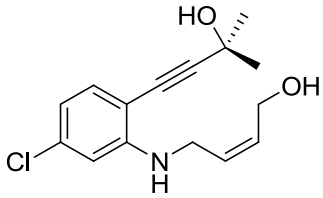


(*Z*)-**1g**: Reaction conditions: 4 hs, 50 °C. Yield = 78%. Clear oil. Flash chromatography cHex:AcOEt = 6:4→ 4:6. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.28 (dd J = 7.6 Hz, J = 1.6 Hz, 1H), 7.22 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 6.62 (d, J = 7.6 Hz, 1H), 5.86-5.80 (m, 1H), 5.78-5.72 (m, 1H), 4.28 (d, J = 6.4 Hz, 2H), 3.94 (dt, J = 12.0 Hz, J = 4.0 Hz, 2H), 3.84 (d, J = 6.0 Hz, 2H), 3.71 (ddd, J = 12.0 Hz, J = 9.2 Hz, J = 2.8 Hz, 2H), 3.50 (bs, 3H), 2.05-2.01 (m, 2H), 1.90 (ddd, J = 13.2 Hz, J = 9.2 Hz, J = 4.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.3, 132.1, 131.9, 130.1, 128.8, 117.1, 110.3, 107.3, 97.6, 81.5, 66.3, 64.9 (2C), 58.4, 40.8, 40.1 (2C). ESI-MS (m/z): 310 $[M+Na]^+$, 288 $[M+H]^+$, 270 [M-OH]+. IR (neat): ν 3385(s), 2965(m),

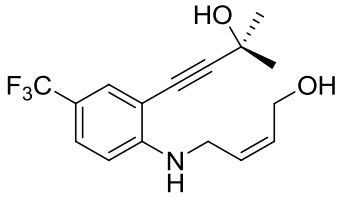
2215(s), 1569(m) cm-1. Anal. calcd for (C17H21NO3: 287.15): C, 71.06; H, 7.37, N, 4.87; Found: C, 70.89, H, 7.19, N, 4.85.



(*Z*)-**1h**: Reaction conditions: 5 hs, 50 °C. Yield = 69%. Pale brown solid, mp = 130- 132 °C. Flash chromatography cHex:AcOEt = 1:1→ 0:1. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.17 (dt, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.02 (dd, J = 7.6 Hz, J = 1.2 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 6.54 (d, J = 7.6 Hz, 1H), 5.79-5.73 (m, 1H), 5.69-5.63 (m, 1H), 4.22 (d, J = 6.8 Hz, 2H), 3.77 (d, J = 6.4 Hz, 2H), 3.26-3.23 (m, 2H), 3.08-3.04 (m, 2H), 2.41 (s, 3H), 2.06-2.00 (m, 2H), 1.94- 1.88 (m, 2H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 148.5, 143.6, 133.1, 132.0, 131.6, 130.2, 129.7 (2C), 129.1, 127.6 (2C), 116.7, 110.0, 106.7, 96.9, 81.8, 65.8, 58.3, 43.0 (2C), 40.6, 38.4 (2C), 21.5. ESI-MS (m/z): 479 $[M+K]^+$, 463 $[M+Na]^+$, 441 [M+H]+. IR (nujol): ν 3316(s), 1698(m), 1515(s), 1310(m) cm-1. Anal. calcd for (C24H28N2O4S: 440.18): C, 65.43; H, 6.41, N, 6.36; Found: C, 65.29, H, 6.49, N, 6.29.

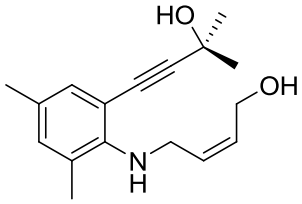


(*Z*)-**1i**:. Reaction conditions: 2 hs, 50 °C. Yield = 98%. Clear oil. Flash chromatography cHex:AcOEt = 6:4 → 4:6. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.14 (d J = 8.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.54 (s, 1H), 5.84-5.80 (m, 1H), 5.74-5.70 (m, 1H), 4.27 (d, J = 6.4 Hz, 2H), 3.80 (d, J = 6.4 Hz, 2H), 1.61 (s, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 149.3, 135.7, 132.7, 131.9, 128.5, 116.6, 109.8, 105.8, 100.6, 77.8, 65.7, 58.3, 40.5, 31.5 (2C). ESI-MS (m/z): 304, 302 $[M+Na]^+$, 282, 280 $[M+H]^+$. Anal. calcd for (C15H18ClNO2: 279.10): C, 64.40; H, 6.49, N, 5.01; Found: C, 64.21, H, 6.58, N, 5.11.

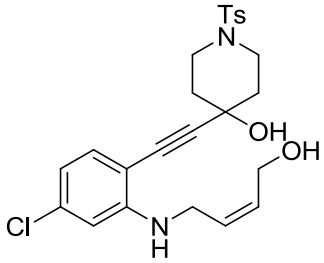


(*Z*)-**1j**: Reaction conditions: 4 hs, 50 °C. Yield = 68%. Brown oil. Flash chromatography cHex:AcOEt = 1:1. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.50 (s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 5.89-5.83 (m, 1H), 5.77-5.71 (m, 1H), 4.31 (d, J = 6.4 Hz, 2H), 3.89 (d, J = 5.2 Hz, 2H), 1.65 (s, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 150.5, 132.0, 129.2, (d, J = 8.4 Hz), 128.8,

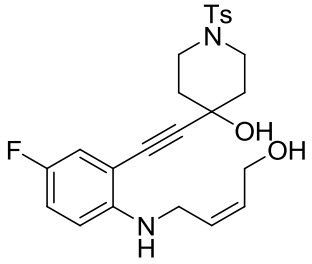
126.8 (d, J = 8.4 Hz), 118.5, 110.0, 108.9, 100.9, 77.4, 65.7, 58.5, 40.4, 31.5 (2C). ESI-MS (m/z): 336 $[M+Na]^+$, 314 $[M+H]^+$, 296 $[M-OH]^+$. Anal. calcd for (C16H18F3NO2: 313.13): C, 61.34; H, 5.79, N, 4.47; Found: C, 61.41, H, 5.61, N, 4.31.



(*Z*)-**1k**. Reaction conditions: 1 hs, 50 °C. Yield = 65%. Clear oil. Flash chromatography cHex:AcOEt = 6:4 →1:1. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.03 (s, 1H), 6.91 (s, 1H), 5.79-5.77 (m, 2H), 4.22 (d, J = 4.4 Hz, 2H), 3.75 (d, J = 5.6 Hz, 2H), 2.26 (s, 3H), 2.21 (s, 3H), 1.60 (s, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 145.6, 132.4, 131.9, 131.5, 130.6, 129.2, 125.2, 115.2, 98.5, 79.7, 65.3, 58.3, 45.2, 31.4 (2C), 20.3, 18.3. ESI-MS (m/z): 296 $[M+Na]^+$. IR (nujol): ν 3376(s), 2218(m), 1653(m), 1616(m), 1516(s), 1158(s), cm-1. Anal. calcd for (C17H23NO2: 273.17): C, 74.69; H, 8.48, N, 5.12; Found: C, 74.81, H, 8.33, N, 5.00.

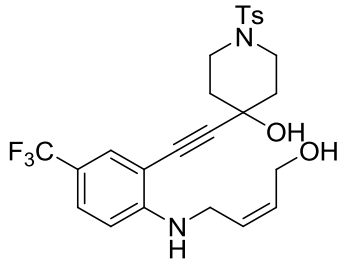


(*Z*)-**1l**. Reaction conditions: 4 hs, 50 °C. Yield = 62%.pale brown solid, mp = 220-222 °C. Flash chromatography cHex:AcOEt = 1:1→ 0:1. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 6.55 (s, 1H), 5.89-5.82 (m, 1H), 5.75- 5.69 (m, 1H), 4.29 (d, J = 6.8 Hz, 2H), 3.80 (d, J = 6.0 Hz, 2H), 3.23-3.15 (m, 4H), 2.44 (s, 3H), 2.11-2.05 (m, 2H), 1.99-1.93 (m, 2H). ^{13}C-NMR (DMSO-d6, 50 MHz) δ 145.0, 143.5, 139.0, 130.0, 128.3, 128.2 (2C), 127.7, 125.2 (2C), 123.0, 122.8, 110.7, 104.7, 100.4, 94.5, 74.7, 59.4, 52.6, 38.2 (2C), 33.2 (2C), 16.5. ESI-MS (m/z): 497, 499 $[M+Na]^+$, 475, 477 $[M+H]^+$. IR (nujol): ν 3325(s), 2217(s), 1706(w) cm-1. Anal. calcd for (C24H27ClN2O4S: 474.14): C, 60.69; H, 5.73, N, 5.90; Found: C, 60.53, H, 5.66, N, 5.81.

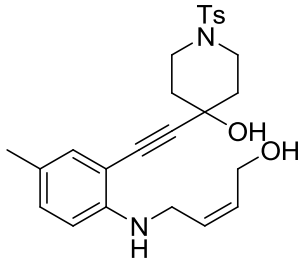


(*Z*)-**1m**: Reaction conditions: 7 hs, 50 °C. Yield = 79%. Pale brown solid, mp = 133-137 °C. Flash chromatography cHex:AcOEt = 1:1. ^{1}H-NMR (DMSOd6, 400 MHz) δ 7.64 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.00 (dt, J = 8.8 Hz, J = 2.8 Hz, 1H), 6.73 (dd, J = 8.8 Hz, J = 2.8 Hz, 1H), 6.52 (dd, J = 8.8 Hz, J = 4.8 Hz, 1H), 5.74 (s, 1H), 5.64-5.58 (m, 1H), 5.39-5.34 (m, 1H), 5.06 (t, J = 6.0 Hz, 1H), 4.75 (t, J = 5.2 Hz, 1H), 4.08 (t, J = 5.2 Hz, 2H), 3.77 (t, J = 6.0 Hz, 2H), 3.05-2.94 (m, 4H), 2.39 (s, 3H), 1.99-1.92 (m, 2H), 1.82-1.76 (m, 2H). ^{13}C-NMR (DMSO-d6, 50 MHz) δ 153.9 (d, J = 230.6 Hz), 146.3, 144.4, 133.2, 132.9, 132.1, 130.5 (2C),

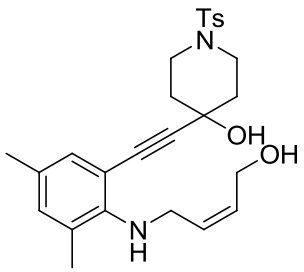
128.6 (2C), 118.1 (d, J = 23.5 Hz), 117.4 (d, J = 23.0 Hz), 111.6 (d, J = 7.8 Hz), 107.2 (d, J = 9.1 Hz), 99.7, 80.2, 67.9, 64.8, 57.8, 43.5 (2C), 38.5 (2C), 21.7. ESIMS (m/z): 481 $[M+Na]^+$, 458 $[M+H]^+$. IR (nujol): ν 3319(s), 2212(s), 1595(w), 1506(s), 1305(m) cm-1. Anal. calcd for (C24H27FN2O4S: 458.17): C, 62.86; H, 5.94, N, 6.11; Found: C, 62.77, H, 5.87, N, 6.02.



(*Z*)-**1n**: Reaction conditions: 2 hs, 50 °C. Yield = 95%, pale brown solid, mp = 122-124 °C. Flash chromatography cHex:AcOEt = 1:1. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 1H), 7.30 (s, 1H), 6.57 (d, J = 8.4 Hz, 1H), 5.86-5.80 (m, 1H), 5.72-5.66 (m, 1H), 4.97 (bs, 1H), 4.26 (d, J = 6.4 Hz, 2H), 3.85 (d, J = 6.0 Hz, 2H), 3.31-3.26 (m, 2H), 3.11-3.06 (m, 2H), 2.41 (s, 3H), 2.28 (s, 1H), 2.09-2.05 (m, 2H), 1.98-1.93 (m, 2H), 1.83 (bs, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 150.5. 143.9, 133.0, 132.0, 129.7 (2C), 129.1 (d, J = 3.8 Hz), 128.5, 127.6 (2C), 127.1 (d J = 3.8 Hz), 118.4, 118.1, 109.0, 106.2, 97.7, 80.6, 65.9, 58.4, 42.9 (2C), 40.3, 38.4 (2C), 21.4. ESI-MS (m/z): 509 $[M+H]^+$. IR (nujol): ν 3321(s), 2210(s), 1700(m), 1652(m), 1376(m) cm-1. Anal. calcd for (C25H27F3N2O4S: 508.16): C, 59.04; H, 5.35, N, 5.51; Found: C, 58.96, H, 5.21, N, 5.50.

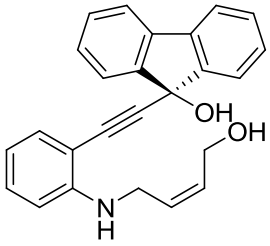


(*Z*)-**1o**: Reaction conditions: 3 hs, rt. Yield = 61%. Pale yellow solid, mp = 142-145 °C. Flash chromatography cHex:AcOEt = 7:3→4:6. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.99 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 6.92 (d, J = 1.6 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 5.81-5.75 (m, 1H), 5.72- 5.66 (m, 1H), 4.23 (d, J = 6.4 Hz, 2H), 3.76 (d, J = 6.4 Hz, 2H), 3.27-3.22 (m, 2H), 3.14-3.09 (m, 2H), 2.42 (s, 3H), 2.17 (s, 3H), 2.08-2.02 (m, 2H), 1.96-1.89 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 146.4, 143.5, 133.3, 132.3, 130.9, 129.6 (2C), 129.3, 128.6, 127.6 (2C), 126.2, 110.5, 106.9, 96.7, 81.9, 65.7, 58.3 42.9 (2C), 41.0, 38.5 (2C), 21.5, 20.1. ESI-MS (m/z): 455 $[M+H]^+$. IR (nujol): ν 3312(s), 2216(s), 1708(m), 1642(m), 1375(m) cm-1. Anal. calcd for (C25H30N2O4S: 454.19): C, 66.05; H, 6.65, N, 6.16; Found: C, 65.91, H, 6.48, N, 6.00.



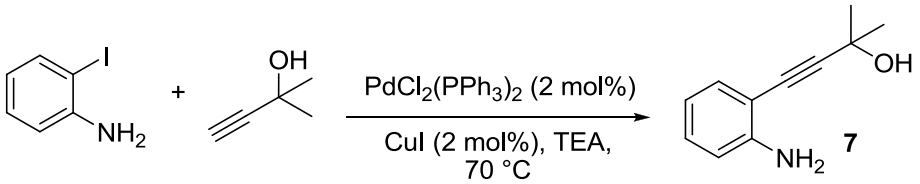
(*Z*)-**1p**:. Reaction conditions: 3 hs, rt. Yield = 30%. Pale brown solid, mp = 65-69 °C. Flash chromatography cHex:AcOEt = 6:4 →4:6. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.92 (s, 1H), 6.86 (s, 1H), 5.79-5.69 (m, 2H), 4.20 (d, J = 4.4 Hz, 2H), 3.69 (d, J = 5.6 Hz, 2H), 3.24-3.13 (m, 4H), 2.43 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 2.07-2.01 (m, 2H), 1.95-1.89 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 145.3,

143.4, 133.3, 132.0, 131.8, 130.7, 129.7 (2C), 129.4, 128.6, 128.4, 127.6 (2C), 114.9, 95.6, 82.6, 65.1, 58.7, 45.4, 42.8 (2C), 38.3 (2C), 21.5, 20.3, 18.0. ESI-MS (m/z): 469 $[M+H]^+$. IR (nujol): ν 3365(s), 2215(s) cm-1.Anal. calcd for (C26H32N2O4S: 468.21): C, 66.64; H, 6.88, N, 5.98; Found: C, 66.41, H, 6.75, N, 5.87.

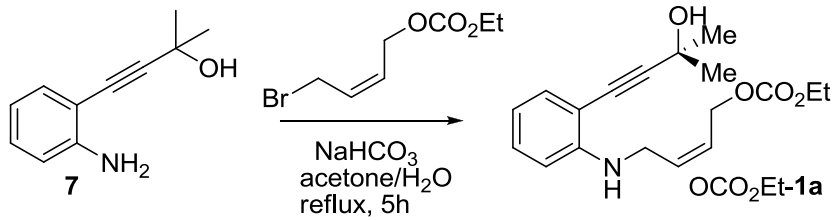


(*Z*)-**1q**: Reaction conditions: 5 hs, 50 °C. Yield = 90%. Sticky solid, mp = 82-84 °C. Flash chromatography cHex:AcOEt = 1:1. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, J = 7.2 Hz, 2H),7.61 (d, J = 7.2 Hz, 2H), 7.38 (t, J = 7.2 Hz, 2H), 7.33 (t, J = 7.2 Hz, 2H), 7.21 (d, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 6.51 (d, J = 7.6 Hz, 1H), 5.76-5.70 (m, 1H), 5.63-5.57 (m, 1H), 4.16 (d, J = 6.4 Hz, 2H), 3.70 (d, J = 6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 149.1, 147.3 (2C), 138.9 (2C), 132.0, 131.7, 130.1, 129.5 (2C), 128.7, 128.5 (2C), 124.2 (2C), 120.1 (2C), 116.6, 109.8, 106.9, 95.4, 79.8, 75.1, 58.3, 40.6. ESI-MS (m/z): 390 $[M+Na]^+$, 350 $[M-OH]^+$. IR (neat): ν 3350(m), 2959(m), 2216(m), 1700(m), 1653(m), 1570(w), 1376(s) cm-1. Anal. calcd for (C25H21NO2: 367.16): C, 81.72; H, 5.76, N, 3.81; Found: C, 81.69, H, 5.71, N, 3.69.

Synthesis of OCO2Et-1a.

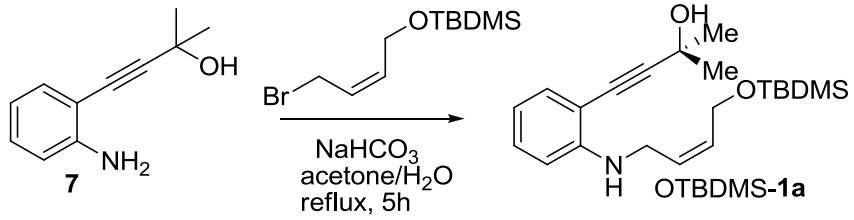


In an oven dried Schlenk tube, under nitrogen atmosphere, ortho-iodoaniline (1.8 mmol, 1 eq.) and the propargylic alcohol (2.4 mmol, 1.3 eq.) were dissolved in 4 ml of freshly distilled TEA. $(PPh_3)_2PdCl_2$ (2 mol%) and CuI (2 mol%) were added in sequence and the reaction mixture was heated at 70 °C until complete consumption of the starting material (TLC, 4 h). The reaction mixture was diluted with water (5 ml) and extracted with ethyl acetate (3 x 10 ml). The organic layer was dried over Na2SO4 and the volatiles removed under vacuum. The residue was purified with silica-gel flash chromatography using cyclohexane and ethyl acetate mixture as eluting solvents.Yield = 83%. Brown sticky oil. Flash chromatography cHex:AcOEt = 7:3→ 6:4. ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.86 (dd, J = 2.0, 8.0 Hz, 1H), 7.72 (dt, J = 2.0, 8.0 Hz, 1H), 7.29-7.31 (m, 2H), 4.78 (br, 2H). 2.26 (s, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 147.6, 132.1, 129.6, 117.9, 114.3, 107.4, 99.4, 78.7, 65.7, 31.7(2C). ESI-MS (m/z): 158 ($M-H_2O$).



Alkylation of aminol **7** (1.4 mmol) was carried out as previously described in the presence of (Z)-bromo-allyl carbonate (equimolar amount to 7). Yield = 56%. Pale brown oil. Flash chromatography cHex:AcOEt = 9:1. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.27 (dd, J = 2.0, 7.2 Hz, 1H), 7.18 (dt, J = 2.0, 7.6 Hz, 1H), 6.65 (dt, J = 1.2, 7.2 Hz, 1H), 6.60 (d, J = 9.2 Hz, 1H), 5.81-5.87 (m, 1H), 5.71-5.78 (m, 1H), 4.77 (d, J = 6.4 Hz, 2H), 4.23 (q, J = 5.6 Hz, 2H), 3.91 (d, J = 6.0 Hz, 2H), 1.65 (s, 6H), 1.26-1.33 (m, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 155.1, 148.3, 132.1, 129.8, 126.3, 126.0, 116.7, 109.6, 107.3, 100.1, 78.5, 65.6, 64.2, 63.2, 40.6, 31.6(2C), 14.2. ESI-MS (m/z): 300 (M-H2O), 318 $(M+H)^+$, 340 $(M+Na)^+$. IR (neat): ν 3402(s), 1982(s), 2219(m), 1734(s), 1653(m), 1576(s), 1266(s) cm-1. Anal. calcd for (C18H23NO4: 317.16): C, 68.12; H, 7.30, N, 4.41; Found: C, 68.00, H, 7.18, N, 4.51.

Synthesis of OTBDMS-1a.

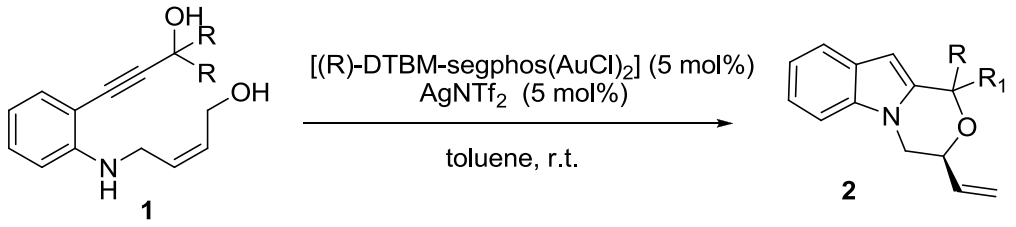


Mono-alkylation of the ortho-propargylaniline was carried out as previously described.

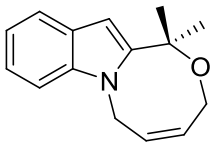
OTBDMS-**1a** was obtained via Sonogashira cross-coupling in 50% yield after flash chromatography (cHex:AcOEt = 9:1). Yellow viscous oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.23-7.25 (m, 1H), 7.16 (dt, J = 2.0, 7.6 Hz, 1H), 6.63 (dt, J = 2.0, 7.6 Hz 1H), 6.56 (d, J = 8.0 Hz, 1H), 5.69-5.72 (m, 1H), 5.56-5.60 (m, 1H), 4.30 (dd, J = 0.8 Hz, 1.6 Hz, 2H), 3.83 (d, J = 6.0 Hz, 2H), 1.62 (s, 6H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.5, 132.3, 132.2, 129.9, 127.6,

116.5, 109.7, 107.0, 99.9, 78.7, 65.7, 59.5, 40.9, 31.7, 25.9(3C), 18.3, -5.2(2C). ESI-MS (m/z): 360 $(M+H)^+$. IR (neat): ν 3404(s), 3075(m), 3025(m), 2929(s), 2857(m), 2219(m), 1922(w), 2219(m), 1652(s), 1603(s), 1559(s) cm-1. Anal. calcd for (C21H33NO2Si: 359.23): C, 70.15; H, 9.25, N, 3.90; Found: C, 70.00, H, 9.41, N, 3.80.

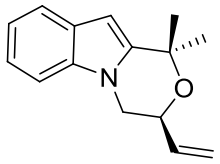
General procedure for the enantioselective gold-catalyzed cascade reaction.



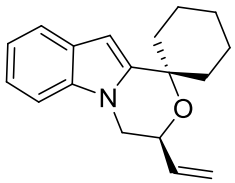
In an oven dried two-necked round bottom flask (*R*)-DTBM-segphos (2.5 μmol, 5 mol%), was dissolved in 0.5 ml of anhydrous DCM and [Au(DMS)Cl] (5 μmol, 10 mol%) was added. The solution was stirred for 10 minutes and then the volatiles were removed leaving the complex that was dried under vacuum for an extra 20 minutes. The complex was dissolved in anhydrous toluene (0.5 ml) and then $AgNTf_2$ (5 μmol, 10 mol%) was added in the dark followed by a solution of the desired substrate (1) in 0.5 ml of toluene. The reaction was stirred at the desired temperature until complete consumption of the acyclic precursor. Then, the reaction mixture was directly charged at the top of a short pad of silica-gel for chromatographic purification.



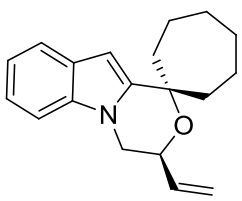
Oxazocino[4,3-*a*]indole **2a'**: Flash chromatography cHex:AcOEt = 97:3. White wax. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.45 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.11 (t J = 7.6 Hz, 1H), 6.99 (t J = 7.6 Hz, 1H), 6.36 (s, 1H), 6.00-5.96 (m, 1H), 5.49 (dt, J = 10.8 Hz, J = 3.6 Hz, 1H), 4.57 (bs, 2H), 4.16 (bs, 2H), 1.67 (s, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 144.9, 137.2, 132.6, 127.8, 126.2, 121.4, 120.2, 119.6, 108.9, 100.1, 76.6, 62.3, 40.8, 25.5 (2C) (methyl signal was not detected under the experimental conditions). GC-MS (m/z): 227 (20) $[M]^+$, 212 (20) $[M-Me]^+$, 200 (15), 182 (40), 168 (100), 154 (50), 128 (30), 115 (40), 102 (20), 89 (40), 77 (25), 53 (25). Anal. calcd for (C15H17NO: 227.30): C, 79.26; H, 7.54, N, 6.16; Found: C, 79.19, H, 7.67, N, 6.09.



(*S*)-**2a**: Reaction conditions: 16 hs, 0 °C. Yield = 73%, clear oil. *ee* = 87%. [α]D = +77 ° (c = 0.31, $CHCl_3$). Flash chromatography cHex:AcOEt = 97:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz,, 1H), 7.13 (t, J = 8.0 Hz, 1H), 6.23 (s, 1H), 6.04 (ddd, J = 17.2 Hz, J = 10.4 Hz, J = 6.0 Hz, 1H), 5.52 (dt, J = 17.2 Hz, J = 1.2 Hz, 1H), 5.37 (dt, J = 10.4 Hz, J = 1.2 Hz, 1H), 4.67-4.62 (m, 1H), 4.16 (dd, J = 11.2 Hz, J = 3.2 Hz, 1H), 3.76 (t, J = 11.2 Hz, 1H), 1.69 (s, 3H), 1.66 (s, 3H) ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 141.3, 135.4, 135.3, 128.1, 120.8, 120.2, 120.1, 118.1, 108.7, 95.4, 73.8, 69.3, 46.0, 31.3, 28.5. GC-MS (m/z): 227 $[M]^+$ (45), 212 $[M-Me]^+$ (60), 170 (100), 154 (65), 128 (35), 115 (40), 103 (15), 89 (30), 77 (20). HPLC: AD, nHex:iPrOH 90:10, flow = 0.5 ml/min, 40 °C. tR: 7.20 min (minor), 8.15 min (major). IR (nujol): ν 1575(m), 1441(s), 1309(m) cm-1. Anal. Calcd for (C15H17NO: 227.30): C, 79.26; H, 7.54, N, 6.16; Found: C, 79.12, H, 7.45, N, 6.11.

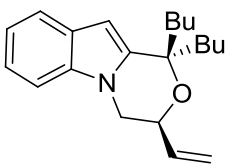


(*S*)-**2b**. Reaction conditions: 7 hs rt. Yield = 72%, clear oil. *ee* = 84%, [α]D = +38.5° (c = 0.34, $CHCl_3$). Flash chromatography cHex:AcOEt = 97:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.18 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.11 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.23 (s, 1H), 6.06 (ddd, J = 17.2 Hz, J = 10.8 Hz, J = 5.2 Hz, 1H), 5.56 (dt, J = 17.2 Hz, J = 1.2 Hz, 1H), 5.36 (dt, J = 10.8 Hz, J = 1.2 Hz, 1H), 4.60-4.56 (m, 1H), 4.16 (dd, J = 11.6 Hz, J = 3.2 Hz, 1H), 3.73 (t, J = 11.6 Hz, 1H), 2.29 (d, J = 13.6 Hz, 1H), 2.02-1.86 (m, 3H), 1.79-1.54 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 142.1, 135.6, 135.4, 128.1, 120.7, 120.2, 119.9, 117.1, 108.6, 95.4, 74.4, 68.0, 46.2, 39.7, 35.6, 25.5, 21.6, 21.4. GC-MS (m/z): 267 $[M]^+$ (100), 224 (100), 196 (35), 182 (70), 168 (65), 154 (35), 130 (30), 115 (30), 89 (20), 55 (40). IR (nujol): ν 1700(w), 1535(m), 1456(s), 1312(m) cm-1. HPLC: OD, nHex:iPrOH 90:10, flow = 0.5 ml/min, 40 °C. tR: 8.77 min (major), 9.81 min (minor). Anal. calcd for (C18H21NO: 267.37): C, 80.86; H, 7.92, N, 5.24; Found: C, 80.75, H, 7.78, N, 5.15

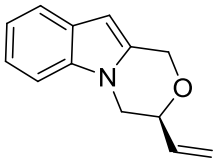


(*S*)-**2c**. Reaction conditions: 22 hs, 0 °C. Yield = 94%, white wax. *ee* = 78%. [α]D = +90.1° (c = 0.33, $CHCl_3$). Flash chromatography cHex:AcOEt = 97:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz,

1H), 7.18 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.26 (s, 1H), 6.04 (ddd, J = 17.2 Hz, J = 10.8 Hz, J = 5.2 Hz, 1H), 5.57 (d, J = 17.2 Hz, 1H), 5.36 (t, J = 10.8 Hz, 1H), 4.60- 4.57 (m, 1H), 4.15 (dd, J = 11.2 Hz, J = 3.2 Hz, 1H), 3.73 (t, J = 11.2 Hz, 1H), 2.24 (dd, J = 10.8 Hz, J = 8.0 Hz, 1H), 2.11-2.06 (m, 2H), 1.98 (dd, J = 14.8 Hz, J = 10.0 Hz, 1H), 1.88-1.58 (m, 8H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.1, 135.7, 135.4, 128.1, 120.8, 120.2, 119.9, 117.3, 108.7, 95.2, 78.1, 68.3, 46.1, 43.6, 39.0, 29.4, 29.3, 22.4, 21.9. GC-MS (m/z): 281 $[M]^+$ (100), 224 (100), 196 (30), 168 (70), 144 (35), 115 (25), 55 (40). IR (nujol): ν 2953(m), 1596 (w), 1545(m), 1461(s), 1310(m) cm-1. HPLC: OD-H, nHex:iPrOH 99:1, flow = 0.5 ml/min, 40 °C. tR: 14.09 min (major), 17.76 min (minor). Anal. calcd for (C19H23NO: 281.39): C, 81.10; H, 8.24, N, 4.98; Found: C, 81.15, H, 8.09, N, 4.79.

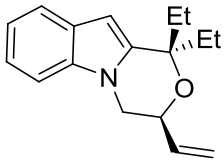


(*S*)-**2d**. Reaction conditions: 7 hs, rt. Yield = 72%, clear oil. *ee* = 84%. [α]D = +31.6° (c = 0.45, $CHCl_3$). Flash chromatography cHex:AcOEt = 97:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.18 (dt, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.12 (dt, J = 7.6 Hz, J = 1.2 Hz, 1H), 6.17 (s, 1H), 6.03 (ddd, J = 16.4 Hz, J = 10.8 Hz, J = 5.6 Hz, 1H), 5.51 (d, J = 16.4 Hz, 1H), 5.35 (d, J = 10.8 Hz, 1H), 4.57-4.53 (m, 1H), 4.14 (dd, J = 11.2 Hz, J = 3.2 Hz, 1H), 3.72 (t, J = 11.2 Hz, 1H), 2.03-1.96 (m, 2H), 1.85-1.72 (m, 2H), 1.54-1.38 (m, 3H), 1.37-1.20 (m, 5H), 0.91 (t, J = 7.2 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 140.0, 135.5, 135.4, 128.2, 120.5, 120.2, 119.9, 117.7, 108.6, 95.9, 78.6, 69.4, 46.1, 41.0, 40.1, 25.9, 25.8, 23.1, 22.9, 14.1, 14.0. GC-MS (m/z): 311 $[M]^+$ (20), 254 (100), 236 (15), 170 (30), 85 (20), 57 (40). HPLC: OD, nHex:iPrOH 90:10, flow = 0.5 ml/min, 40 °C. tR: 7.97 min (major), 11.05 min (minor). Anal. calcd for (C21H19NO: 311.46): C, 80.98; H, 9.38, N, 4.50; Found: C, 81.06, H, 9.52, N, 4.39.

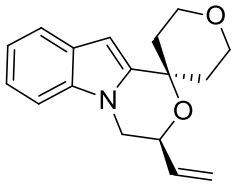


(*S*)-**2e**: Reaction conditions: 24 hs, rt. Yield = 88%, white solid, mp = 110-112 °C. *ee* = 85%. [α]D = +31.9 ° (c = 0.34, $CHCl_3$, *ee* = 74%). Flash chromatography cHex:AcOEt = 97:3 9:1. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz,, 1H), 7.13 (t, J = 8.0 Hz, 1H), 6.24 (s, 1H), 6.04 (ddd, J = 17.2 Hz, J = 10.4 Hz, J = 5.6 Hz, 1H), 5.53 (d, J = 17.2 Hz, 1H), 5.39 (d, J = 10.4 Hz, 1H), 5.18 (d, J = 14.8 Hz, 1H), 5.01 (d, J = 14.8 Hz, 1H), 4.49-4.44 (m, 1H), 4.20 (dd, J = 11.2 Hz, J = 3.2 Hz, 1H), 3.80 (t, J = 11.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 136.0, 134.8, 132.5, 128.2, 121.0, 120.3, 120.1, 118.2, 108.5, 95.7, 74.8, 64.5, 46.1. GC-MS (m/z): 199 $[M]^+$ (20), 170 (20), 143 (100), 115 (30). IR (nujol): ν 1698(w), 1539(m), 1440(s), 1310(m) cm-1. HPLC: AD,

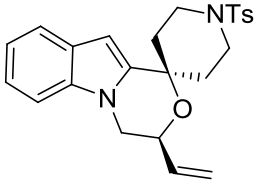
nHex:iPrOH 90:10, flow = 0.5 ml/min, 40 °C. tR: 9.72 min (minor), 10.57 min (major). Anal. calcd for (C13H13NO: 199.25): C, 78.36; H, 6.58, N, 7.03; Found: C, 78.12, H, 6.51, N, 7.21



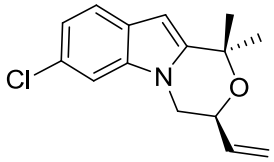
(*S*)-**2f**: Reaction conditions: 4 hs, rt. Yield = 71%, clear oil. *ee* = 82%. [α]D = +44.1° (c = 0.36, $CHCl_3$). Flash chromatography cHex:AcOEt = 97:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.18 (s, 1H), 6.04 (ddd, J = 17.2 Hz, J = 10.4 Hz, J = 5.6 Hz, 1H), 5.52 (d, J = 17.2 Hz, 1H), 5.36 (dt, J = 10.4 Hz, J = 1.2 Hz, 1H), 4.57-4.52 (m, 1H), 4.15 (dd, J = 11.2 Hz, J = 3.2 Hz, 1H), 3.73 (t, J = 11.2 Hz, 1H), 2.11-1.99 (m, 2H), 1.89-1.73 (m, 2H), 1.02 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 139.5, 135.5, 135.4, 128.2, 120.6, 120.2, 119.9, 117.7, 108.6, 96.0, 78.9, 69.4, 46.1, 33.1, 32.5, 8.2, 8.0. GC-MS (m/z): 255 (40) $[M]^+$, 226 (100) $[M\text{-}Et]^+$, 170 (70), 57 (70). HPLC: AD, nHex:iPrOH 90:10, flow = 0.5 ml/min, 40 °C. tR: 7.14 min (minor), 7.50 min (major). Anal. calcd for (C17H21NO: 255.35): C, 79.96; H, 8.29, N, 5.49; Found: C, 79.81, H, 8.11, N, 5.41.



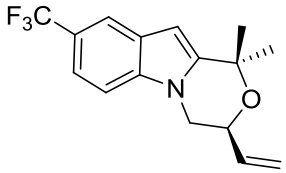
(*S*)-**2g**: Reaction conditions: 3 hs, rt. Yield = 74%, white solid, mp = 88-90 °C. *ee* = 86%. [α]D = + 48.1° (c = 0.41, $CHCl_3$). Flash chromatography cHex:AcOEt = 97:3 9:1. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.28 (s, 1H), 6.06 (ddd, J = 17.2 Hz, J = 10.4 Hz, J = 4.8 Hz, 1H), 5.57 (d, J = 17.2 Hz, 1H), 5.39 (d, J = 10.4 Hz, 1H), 4.60-4.55 (m, 1H), 4.19 (dd, J = 11.6 Hz, J = 3.2 Hz, 1H), 4.01 (dt, J = 11.6 Hz, J = 2.4 Hz, 1H), 3.93-3.85 (m, 3H), 3.76 (t, J = 11.6 Hz, 1H), 2.30 (ddd, J = 13.6 Hz, J = 12.4 Hz, J = 5.2 Hz, 1H), 2.19-2.15 (m, 1H), 2.30 (ddd, J = 14.8 Hz, J = 11.6 Hz, J = 6.4 Hz, 1H), 1.89 (dd, J = 13.6 Hz, J = 2.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 140.1, 135.3, 134.9, 127.9, 121.1, 120.3, 120.1, 117.4, 108.6, 95.9, 72.0, 68.6, 63.4, 63.3, 46.1, 40.0, 35.8. GC-MS (m/z): 269 $[M]^+$ (100), 196 (30), 168 (60), 144 (30), 116 (20). HPLC: AD, nHex:iPrOH 90:10, flow = 0.5 ml/min, 40 °C. tR: 11.16 min (minor), 13.95 min (major). Anal. calcd for (C75H19NO2: 269.34): C, 75.81; H, 7.11, N, 5.20; Found: C, 75.75, H, 7.00, N, 5.28.



(*S*)-**2h**: Reaction conditions: 4 hs, rt. Yield = 62%, white solid, mp = 78-80 °C. *ee* = 95%. [α]D = +29.0° (c = 0.5, $CHCl_3$). Flash chromatography cHex:AcOEt = 9:1→ 7:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.20 (s, 1H), 5.90 (ddd, J = 17.2 Hz, J = 10.4 Hz, J = 4.8 Hz, 1H), 5.28 (d, J = 17.2 Hz, 1H), 5.24 (d, J =10.4 Hz, 1H), 4.48-4.43 (m, 1H), 4.14 (dd, J = 11.6 Hz, J = 3.2 Hz, 1H), 3.77-3.65 (m, 3H), 2.88 (dt, J = 12.4 Hz, J = 2.8 Hz, 1H), 2.73 (dt, J = 12.4 Hz, J = 2.8 Hz, 1H), 2.48 (s, 3H), 2.30-2.24 (m, 2H), 2.06- 1.96 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.4, 139.1, 135.4, 134.7, 133.6, 129.6 (2C), 127.9, 127.7 (2C), 121.3, 120.5, 120.3, 117.2, 108.7, 96.1, 71.7, 68.5, 46.0, 41.9, 41.8, 38.8, 34.5, 21.5. IR (nujol): ν 3397(m), 1456(m), 1080(w), cm-1. ESI-MS (m/z): 445 $[M+Na]^+$, 423 $[M+H]^+$. HPLC: OD, nHex:iPrOH 70:30, flow = 1.0 ml/min, 40 °C. tR: 13.10 min (major), 17.54 min (minor). Anal. calcd for (C24H26N2O3S: 422.54): C, 68.22; H, 6.20, N, 6.63; Found: C, 68.10, H, 6.11, N, 6.45.

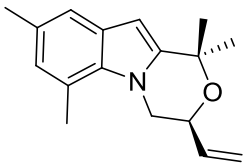


(*S*)-**2i**: Reaction conditions: 2 hs, rt. Yield = 62%, pale yellow oil. *ee* = 82%. [α]D = +75.0° (c = 0.40, $CHCl_3$). Flash chromatography cHex:AcOEt = 97:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, J = 8.4 Hz, 1H), 7.27 (s, 1H), 7.08 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 6.19 (s, 1H), 6.02 (ddd, J = 17.2 Hz, J = 10.4 Hz, J = 5.6 Hz, 1H), 5.50 (d, J = 17.2 Hz, 1H), 5.37 (d, J = 10.4 Hz, 1H), 4.65-4.60 (m, 1H), 4.09 (dd, J = 11.2 Hz, J = 3.2 Hz, 1H), 3.72 (t, J = 11.2 Hz, 1H), 1.67 (s, 3H), 1.64 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 142.1, 135.9, 135.2, 126.8, 126.6, 121.0, 120.7, 118.1, 108.9, 95.6, 73.7, 69.2, 46.1, 31.3, 28.5. ESI-MS (m/z): 262, 264 $[M+H]^+$. HPLC: OD, nHex:iPrOH 90:10, flow = 0.5 ml/min, 40 °C. tR: 8.39 min (minor), 11.44 min (major). Anal. calcd for (C15H16ClNO: 261.75): C, 68.83; H, 6.16, N, 5.35; Found: C, 68.75, H, 6.05, N, 5.21.

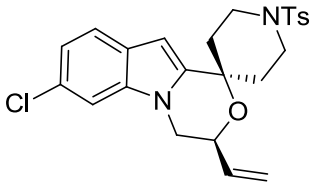


(*S*)-**2j**: Reaction conditions: 3 hs, rt. Yield = 84%, clear oil. *ee* = 86%. [α]D = +59.0° (c = 0.33, $CHCl_3$). Flash chromatography cHex:AcOEt = 97:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.84 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 6.31 (s, 1H), 6.03 (ddd, J = 17.2 Hz, J = 10.8 Hz, J = 6.0 Hz, 1H), 5.53 (dt, J = 17.2 Hz, J = 1.6 Hz, 1H), 5.39 (dt, J = 10.8 Hz, J = 1.6 Hz, 1H), 4.68-4.63

(m, 1H), 4.19 (dd, J = 11.6 Hz, J = 3.2 Hz, 1H), 3.79 (t, J = 11.6 Hz, 1H), 1.71 (s, 3H), 1.67 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.2, 136.6, 135.1, 127.5, 122.6, 122.3, 118.2, 117.9 (d, J = 4.2 Hz), 117.6 (d, J = 3.5 Hz), 108.9, 96.4, 73.7, 69.2, 46.2, 31.3, 28.4. GC-MS (m/z): 295 (60) $[M]^+$, 280 (100) $[M\text{-}Me]^+$, 238 (60), 198 (20), 154 (20). IR (nujol): ν 3381(w), 1581(m), 1431 (s), 1300(m) cm-1. HPLC: LUX-CEL-3 (OJ-H), nHex:iPrOH 95:5, flow = 0.5 ml/min, 40 °C. tR: 12.8 min (major), 16.8 min (minor). Anal. calcd for (C16H19NO: 241.33): C, 79.63; H, 7.94, N, 5.80; Found: C, 79.52, H, 7.85, N, 5.65.

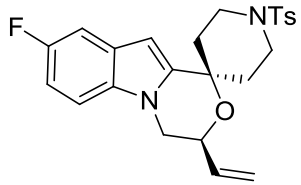


(*S*)-**2k**: Reaction conditions: 4 hs, rt. Yield = 93%, white solid, mp = 116-118 °C. *ee* = 90%. [α]D = +116.0 ° (c = 0.48, $CHCl_3$). Flash chromatography cHex:AcOEt = 95:5.1H-NMR ($CDCl_3$, 400 MHz) δ 7.16 (s, 1H), 6.69 (s, 1H), 6.10 (s, 1H), 6.00 (ddd, J = 17.2 Hz, J = 10.8 Hz, J = 6.0 Hz, 1H), 5.47 (d, J = 13.2 Hz, 1H), 5.33 (pt, J = 10.8 Hz, 1H), 4.58-4.54 (m, 1H), 4.00 (t, J = 11.2 Hz, 1H), 2.68 (s, 3H), 2.36 (s, 3H), 1.64 (s, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 145.4, 132.2, 131.8, 131.4, 130.5, 129.1, 128.9, 98.3, 65.2, 58.4, 45.1, 31.2, 29.5, 20.5, 18.2. ESI-MS (m/z): 256 $[M+H]^+$. HPLC: AD, nHex:iPrOH 93:7, flow = 0.5 ml/min, 40 °C. tR: 7.0 min (minor), 7.9 min (major). IR (nujol): ν 3305(w), 1595(m), 1456 (s), 1305(m), cm-1. Anal. calcd for (C17H21NO: 255.35): C, 79.96; H, 8.29, N, 5.49; Found: C, 79.81, H, 8.05, N, 5.55.

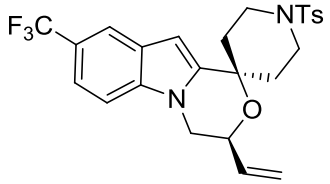


(*S*)-**2l**: Reaction conditions: 24 hs, rt. Yield = 84%, white solid, mp = 212-214 °C. *ee* = 96%. [α]D = +25.3° (c = 0.69, $CHCl_3$). Flash chromatography cHex:AcOEt = 9:1→ 7:3.^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 6.17 (s, 1H), 5.88 (ddd, J = 17.6 Hz, J = 10.8 Hz, J = 4.8 Hz, 1H), 5.27 (dt, J = 17.6 Hz, J = 1.2 Hz, 1H), 5.24 (dt, J = 10.8 Hz, J = 1.2 Hz, 1H), 4.46-4.41 (m, 1H), 4.07 (dd, J = 11.6 Hz, J = 3.2 Hz, 1H), 3.77-3.70 (m, 2H), 3.65 (t, J = 11.6 Hz, 1H), 2.86 (dt, J = 12.4 Hz, J = 2.4 Hz, 1H), 2.71 (dt, J = 12.4 Hz, J = 2.4 Hz, 1H), 2.47 (s, 3H), 2.29-2.21 (m, 2H), 2.01-1.93 (m, 2H). ^{13}CNMR ($CDCl_3$, 100 MHz) δ 143.5, 139.9, 135.9, 134.4, 133.6, 129.6 (2C), 127.7 (2C), 127.3, 126.4, 121.3, 120.9, 117.4, 108.8, 96.3, 71.7, 68.4, 46.1, 41.9, 41.7, 38.7, 34.5, 21.5. ESI-MS (m/z): 479 $[M+Na]^+$, 457 $[M+H]^+$. IR (nujol): ν 3382(m), 2932(w), 1700(m), 1653(m), 1503(m) cm-1. HPLC: OD, nHex:iPrOH 80:20, flow = 1.0 ml/min, 40 °C. tR:

10.82 min (minor), 18.44 min (major). Anal. calcd for (C24H25ClN2O3S: 456.98): C, 63.08; H, 5.51, N, 6.13; Found: C, 63.19, H, 5.42, N, 6.02.

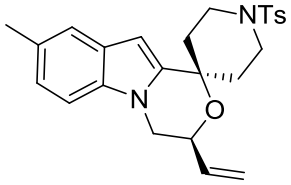


(*S*)-**2m**: Reaction conditions: 2 hs, rt. Yield = 78%, white solid, mp = 139-142 °C. *ee* = 96%. [α]D = +15.4° (c = 0.72, $CHCl_3$). Flash chromatography cHex:AcOEt = 9:1 7:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.19 (dd, J = 9.6 Hz, J = 2.4 Hz, 1H), 7.12 (dd, J = 8.8 Hz, J = 4.4 Hz, 1H), 6.90 (dt, J = 8.8 Hz, J = 2.4 Hz, 1H), 6.13 (s, 1H), 5.86 (ddd, J = 17.6 Hz, J = 10.8 Hz, J = 5.2 Hz, 1H), 5.25 (dt, J = 17.6 Hz, J = 1.6 Hz, 1H), 5.21 (dt, J = 10.8 Hz, J = 1.6 Hz, 1H), 4.44-4.39 (m, 1H), 4.07 (dd, J = 11.2 Hz, J = 3.2 Hz, 1H), 3.74-3.67 (m, 2H), 3.64 (t, J = 11.2 Hz, 1H), 2.84 (dt, J = 12.4 Hz, J = 2.4 Hz, 1H), 2.69 (dt, J = 12.4 Hz, J = 2.4 Hz, 1H), 2.45 (s, 3H), 2.26-2.19 (m, 2H), 1.99-1.92 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 159.4, 143.5, 140.7, 134.5, 133.6, 132.1, 129.6 (2C), 128.1 (d, J = 10.0 Hz), 127.7 (2C), 117.3, 109.6 (d, J = 26.1 Hz), 109.2 (d, J = 9.8 Hz), 105.3 (d, J = 23.5 Hz), 96.2 (d, J = 4.6 Hz), 71.7, 68.5, 46.0, 41.8, 41.7, 38.7, 34.4, 21.5. ESI-MS (m/z): 441 $[M+H]^+$. IR (nujol): ν 3385(m), 1665(m), 1441(s), 1371(s) cm-1. HPLC: OD, nHex:iPrOH 80:20, flow = 0.5 ml/min, 40 °C. tR: 21.66 min (major), 23.53 min (minor). Anal. calcd for (C24H25FN2O3S: 440.53): C, 65.43; H, 5.72, N, 6.63; Found: C, 65.38, H, 5.70, N, 6.52.

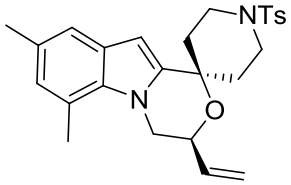


(*S*)-**2n**: Reaction conditions: 18 hs, rt. Yield = 62%, white solid, mp = 180-186 °C. *ee* = 95%. [α]D = +26.2° (c = 0.31, $CHCl_3$). Flash chromatography cHex:AcOEt = 9:1→ 7:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.88 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.4 Hz, 1H), 6.29 (s, 1H), 5.90 (ddd, J = 17.2 Hz, J = 10.4 Hz, J = 4.8 Hz, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.26 (d, J = 10.4 Hz, 1H), 4.48-4.45 (m, 1H), 4.17 (dd, J = 11.6 Hz, J = 3.2 Hz, 1H), 3.78-3.69 (m, 3H), 2.88 (dt, J = 12.0 Hz, J = 2.4 Hz, 1H), 2.73 (dt, J = 12.0 Hz, J = 2.4 Hz, 1H), 2.48 (s, 3H), 2.32-2.24 (m, 2H), 2.06-1.96 (m, 2H). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 143.5, 141.0, 136.7, 134.3, 133.6, 129.6 (2C), 127.7 (2C), 127.2, 125.2 (q, J = 270.0 Hz), 122.7 (q, J = 32.0 Hz), 118.2 (d, J = 4.3 Hz), 118.0 (d, J = 3.6 Hz), 117.5, 108.9, 97.1, 71.8, 68.4, 46.2, 41.8, 41.7, 38.8, 34.5, 21.5. ESI-MS (m/z): 513 $[M+Na]^+$, 491 $[M+H]^+$. IR (nujol): ν 3371(m), 1700(w), 1651(m), 1456(s), 1378(s) cm-1. HPLC: OD, nHex:iPrOH 80:20, flow = 1.0 ml/min, 40 °C. tR:

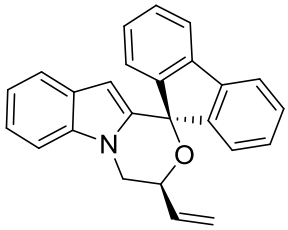
9.53 min (minor), 10.71 min (major). Anal. calcd for (C25H25F3N2O3S: 490.54): C, 61.21; H, 5.14, N, 5.71; Found: C, 61.34, H, 5.65, N, 5.69.



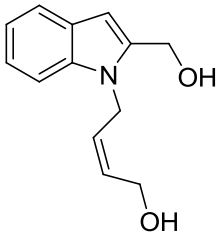
(*S*)-**2o**: Reaction conditions: 5 hs, rt. Yield = 82%, white solid, mp = 192-194 °C. *ee* = 94%. [α]D = +14.0° (c = 0.61, $CHCl_3$). Flash chromatography cHex:AcOEt = 8:2. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 8.0 Hz, 2H), 7.37- 7.29 (m, 3H), 7.14 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.10 (s, 1H), 5.88 (ddd, J = 17.2 Hz, J = 10.8 Hz, J = 4.8 Hz, 1H), 5.26 (d, J = 17.2 Hz, 1H), 5.23 (d, J = 10.8 Hz, 1H), 4.45-4.42 (m, 1H), 4.10 (dd, J = 11.6 Hz, J = 2.8 Hz, 1H), 3.75-3.69 (m, 2H), 3.65 (t, J = 11.6 Hz, 1H), 2.87 (dt, J = 12.4 Hz, J = 2.4 Hz, 1H), 2.71 (dt, J = 12.4 Hz, J = 2.4 Hz, 1H), 2.47 (s, 3H), 2.44 (s, 3H), 2.28-2.22 (m, 2H), 2.01-1.94 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.4, 139.1, 134.7, 133.8, 133.6, 129.6 (2C), 129.5, 128.1, 127.7 (2C), 122.9, 120.1, 117.1, 108.3, 95.6, 71.7, 68.5, 46.0, 41.9, 41.8, 38.7, 34.5, 21.5, 21.4. ESI-MS (m/z): 437 $[M+H]^+$. IR (nujol): ν 3371(m), 1652(m), 1456(s), 1378(s) cm-1. HPLC: AD, nHex:iPrOH 80:20, flow = 0.7 ml/min, 40 °C. tR: 18.55 min (minor), 28.33 min (major). Anal. calcd for (C25H28N2O3S: 436.57): C, 68.78; H, 6.46, N, 6.42; Found: C, 68.54, H, 6.38, N, 6.55.



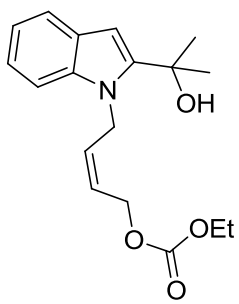
(*S*)-**2p**: Reaction conditions: 24 hs, rt. Yield = 62%, white solid, mp = 198-200 °C. *ee* = 98%. [α]D = +9.0 ° (c = 0.24, CHCl3). Flash chromatography cHex:AcOEt = 9:1→ 7:3. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.18 (s, 1H), 6.71 (s, 1H), 6.08 (s, 1H), 5.80-5.90 (m, 1H), 5.20-5.27 (m 2 H), 4.54 (dd, J = 7.2 Hz, 3.2 Hz, 1H), 4.36-4.40 (m, 1H), 3.94 (t, J = 7.2 Hz, 1H), 3.67-3.78 (m, 1H), 2.86 (dt, J = 9.6 Hz, 2.0 Hz, 1H), 2.72 (dt, J = 9.6 Hz, 2.0 Hz, 1H), 2.66 (s, 3H), 2.47 (s, 3H), 2.37 (s, 3H), 2.02-2.28 (m, 1H), 1.94- 2.01 (m, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.4, 139.4, 134.8, 133.8, 133.3, 129.6 (2C), 129.5, 128.8, 127.7 (2C), 126.0, 120.4, 118.0, 117.1, 96.6, 71.8, 69.0, 46.0, 41.9, 41.8, 39.2, 34.5, 21.5, 21.0, 19.7. ESI-MS (m/z): 451 $[M+H]^+$, 473 $[M+Na]^+$. IR (nujol): ν 3397(m), 1718(w), 1596(m), 1378(s), cm-1. HPLC: AD, nHex:iPrOH 80:20, flow = 0.7 ml/min, 40 °C. tR: 11.94 min (minor), 14.76 min (major). Anal. calcd for (C26H30N2O3S: 450.59): C, 69.30; H, 6.71, N, 6.22; Found: C, 69.12, H, 6.77, N, 6.12.



(*S*)-**2q**. Reaction conditions: 92 hs, rt. Yield = 30%, white solid, mp = 189-192 °C. *ee* = 84%. [α]D = + 43.0° (c = 0.14, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.66 (t J = 8.4 Hz, 2H), 7.55-7.50 (m, 2H), 7.45-7.39 (m, 4H), 7.28-7.22 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.10 (t J = 7.6 Hz, 1H), 6.03 (ddd, J = 17.2 Hz, J = 10.8 Hz, J = 6.0 Hz, 1H), 5.85 (s, 1H), 5.47 (d, J = 17.2 Hz, 1H), 5.33 (d, J = 10.8 Hz, 1H), 5.28-5.23 (m, 1H), 4.51 (dd, J = 11.6 Hz, J = 3.2 Hz, 1H), 4.09 (t, J = 11.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 148.3, 148.2, 140.0, 139.9, 135.0, 129.6, 129.4, 129.1, 128.4, 128.3, 127.7, 125.6, 125.1, 121.2, 120.7, 120.4, 120.3, 119.9, 118.5, 108.8, 104.4, 97.8, 83.5, 71.7, 46.4. ESI-MS (m/z): 350 [M+H]+. IR (nujol): ν 3101(m), 1451(s), 1376(m), cm-1. HPLC: AD, nHex:iPrOH 80:20, flow = 0.5 ml/min, 40 °C. tR: 12.08 min (major), 15.89 min (minor). Anal. calcd for (C25H19NO: 349.42): C, 85.93; H, 5.48; Found: C, 85.80, H, 5.51.



C. Reaction conditions: 10 hs, rt. Yield = 63%, viscous yellow oil. Flash chromatography cHex:AcOEt = 1:1. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.62 (d J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.26 (dt, J = 2.0, 7.2 Hz, 1H), 7.12 (dt, J = 2.0, 7.2 Hz, 1H), 6.48 (s, 1H), 5.79- 5.82 (m, 1H), 5.68-5.78 (m, 1H), 4.97 (d J = 6.0 Hz, 2H), 4.82 (s, 2H), 4.30 (d, J = 6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 138.0, 130.3, 128.2, 127.6, 122.3, 121.0, 120.6, 119.8, 109.3, 102.5, 58.0, 57.5, 40.8. ESI-MS (m/z): 200 [M+H], 218 (M+H_2O), 223 (M+Na). Anal. calcd for (C13H14NO: 200.11): C, 77.97; H, 7.05; N, 6.99; Found: C, 77.81, H, 6.95; N, 6.81.



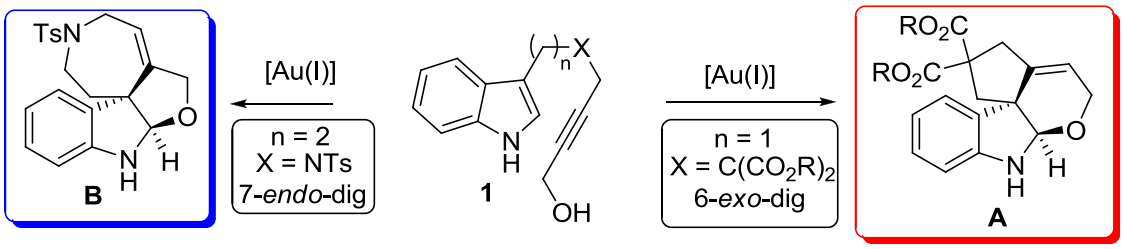
D. Reaction conditions: 16 hs, rt. Yield = 87%, viscous yellow oil. Flash chromatography cHex:AcOEt = 75:25. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.57 (d J = 4.4 Hz, 1H), 7.23 (d, J = 4.4 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.39 (s, 1H), 5.73-5.77 (m, 1H), 5.61-5.64 (m, 1H), 5.30 (d, J = 4.4 Hz, 2H), 4.24 (q, J = 4.4 Hz, 2H), 1.78 (d, J = 4.4 Hz, 1H), 1.74 (s, 6H), 1.32 (t, J = 4.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 155.2, 144.9, 137.7, 131.6, 127.2, 124.4, 121.9, 120.6, 119.8, 109.6, 99.1, 69.9, 64.2, 63.2, 43.1, 30.9(2C), 14.4. ESI-MS (m/z): 318 [M+H], 240 (M+Na). IR (neat): ν 3502(s), 2980(s), 1739(s), 1456(m), 1374(m), 1259(s)

cm-1. Anal. calcd for (C18H23NO4: 317.16): C, 68.12; H, 7.30; N, 4.41; Found: C, 68.13, H, 7.17; N, 4.29.

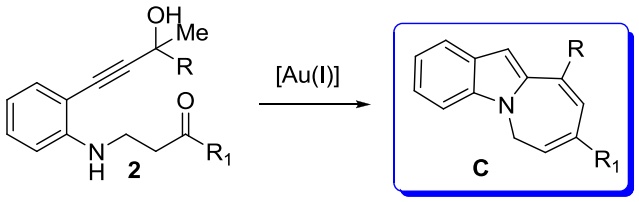
Conclusion

In this work we presented several aspects regarding the possibility to use readily available propargylic alcohols as acyclic precursors to develop new stereoselective [Au(I)]-catalyzed cascade reactions for the synthesis of highly complex indole architectures.

The use of indole-based propargylic alcohols of type **1** in a stereoselective [Au(I)]-catalyzed hydroindolynation/immiun trapping reactive sequence opened access to a new class of tetracyclic indolines, *dihydropyranylindolines* **A** and *furoindolines* **B**. An enantioselective protocol was futher explored in order to synthesize this molecules with high yields and *ee*.

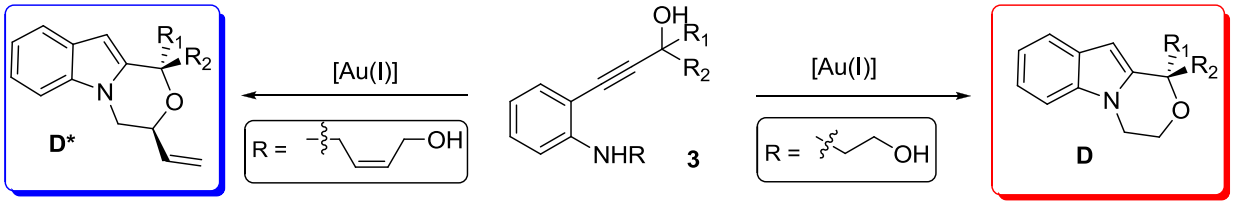


The suitability of propargylic alcohols in [Au(I)]-catalyzed cascade reactions was deeply investigated by developing cascade reactions in which was possible not only to synthesize the indole core but also to achieve a second functionalization. Aniline based propargylic alcohols **2** were found to be modular acyclic precursors for the synthesis of *[1,2-a] azepinoindoles* **C**.



In describing this reactivity we additionally reported experimental evidences for an unprecedented NHCAu(I)-vinyl specie which in a chemoselective fashion, led to the annulation step, synthesizing the N1-C2-connected seven membered ring.

The chemical flexibility of propargylic alcohols was further explored by changing the nature of the chemical surrounding with different preinstalled N-alkyl moiety in propargylic alcohols of type **3**.



Particularly, in the case of a primary alcohol, [Au(I)] catalysis was found to be prominent in the synthesis of a new class of *[4,3-a]-oxazinoindoles* **D** while the use of an allylic alcohol led to the first example of [Au(I)] catalyzed synthesis and enantioselective functionalization of this class of molecules (**D***).

With this work we established propargylic alcohols as excellent acyclic precursor to developed new [Au(I)]-catalyzed cascade reaction and providing new catalytic synthetic tools for the stereoselective synthesis of complex indole/indoline architectures.