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TITOLO TESI

"Active bis-ferrocene molecules as unit for molecular computation"

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I dedicate a special brackets the boys of Alicante, I have suffered their share of the research group in the two months spent in Spain

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ABSTRACT

Traditional logic gates are rapidly reaching the limits of miniaturization. Overheating of these components is no longer negligible. A new physical approach to the machine was proposed by Prof. C S. Lent "Molecular Quantum cellular automata". Indeed the quantum-dot cellular automata (*QCA*) approach offers an attractive alternative to diode or transistor devices. Th units encode binary information by two polarizations without corrent flow. The units for QCA theory are called QCA cells and can be realized in several way. Molecules can act as QCA cells at room temperature. In collaboration with STMicroelectronic, the group of Electrochemistry of Prof. Paolucci and the Nananotecnology laboratory from Lecce, we synthesized and studied with many techniques surface-active chiral bis-ferrocenes, conveniently designed in order to act as prototypical units for molecular computing devices. The chemistry of ferrocene has been studied thoroughly and found the opportunity to promote substitution reaction of α ferrocenyl alcohols with various nucleophiles without the aid of Lewis acid as catalysts. The only interaction between water and the two reagents is involve in the formation of a carbocation specie which is the true reactive species. We have generalized this concept to other benzyl alcohols which generating stabilized carbocations. Carbocation describe in Mayr's scale were fondametal for our research. Finally, we used these alcohols to alkylate in enantioselective way aldehydes via organocatalysis.

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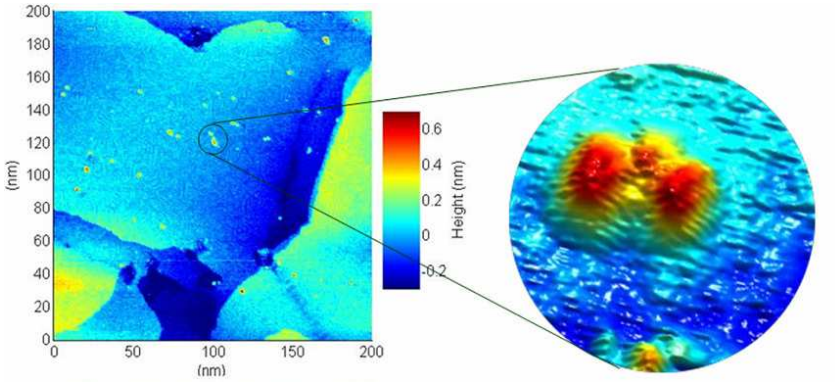
LIST OF ABBREVIATIONS

AcCN	acetonitrile
ACOEt	ethyl acetate
Bn	benzyl
BPY	2,2'-Bipyridine
BOC	tert-butyl carbamate
Bu_4NF	tetrabutylammoniofluride
DME	dimethoxyetane
DMF	ceric (IV) ammonium nitrate
CA	chronoamperometry
CAN	dimethylformamide
CV	cyclic voltammetry
DBSA	dodecylbenzenesulfonic acid
DCM	dichloromethane
DFT	density functional theory
DMSO	dimethylsulfoxide
d.r.	diasteromeric ratio
(*E*)	Electrophilic parameter in Mayr's scale
EIS	Electrochemical Impedance Spectroscopy
ESI-MS	detector electrospray ionization mass spectrometry
EtOH	ethyl alcohol
Et_3N	triethylamina
e.e.	enantiomeric excess
Et_2O	Diethylether
Fc	Ferrocene fragment
Fc^+	ferrocenium fragment
FC	Friedel-Crafts reaction
FET	field effect transistor
GC	gas chromatography
HCl	hydrochloric acid
HOMO	highest occupied molecular orbital
IprOH	isopropanol

KH	potassium hydride
LUMO	lowest unoccupied molecular orbital
MEO	6-mercaptoexan-1-ol
MeOH	Methanol
MeMgBr	Methyl magnesium bromide
N	Nucleophilicity in Mayr's scale
NBS	N-Bromosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
OLED	Organic Light Emitting Diode
OTf	trifluoromethansulfonate
Ph	phenyl
PTSA	Para-toluenesulfonic acid
PPHOS	phosphine ferrocene ligands
QCA	Quantum cellular automata
RT	Room temperature
SAM	self assemble monolayer
SCE	saturated calomel electrode
SOMO	singly occupied molecular orbital
STM	scanning tube microscopy
***t*BuOK**	kallium tert-butoxide
T°C	temperature in Celsius degree
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TS	tosyl group
TM	retention time of the major pick in a chromatogram
tm	retention time of the minor pick in a chromatogram

Chapter 1

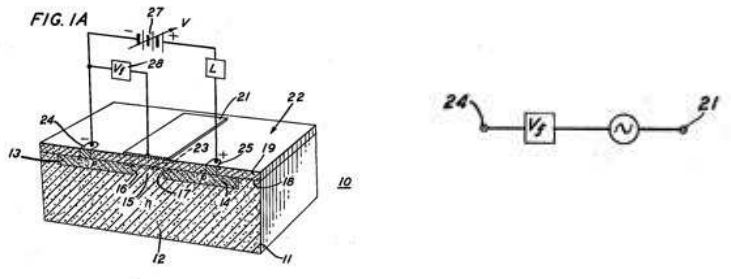
Surface-active Chiral ferrocene compounda as QCA Units for Molecular Computing Devices



Introduction

Computers dating back to those composed of electromechanical relay switches have relied on encoding binary information in the *"on"* or *"off"* state of a current switch. Field-effect transistors (FETs)[1] are the foundation of present digital logic technologies such as complementary metal oxide semiconductors. Despite vast improvements in integrated circuit fabrication technology over the past three decades, the role played by the FET has remained that of a current switch, much like the mechanical relays used by Konrad Zuse in the 1930s.

Figure 1 Field effect transistor prototype, patent of 1963.



By adhering to strict scaling rules, FETs have maintained acceptable performance despite tremendous reductions in size, permitting the microelectronics industries to make phenomenal increases in device density and computational power.[2]

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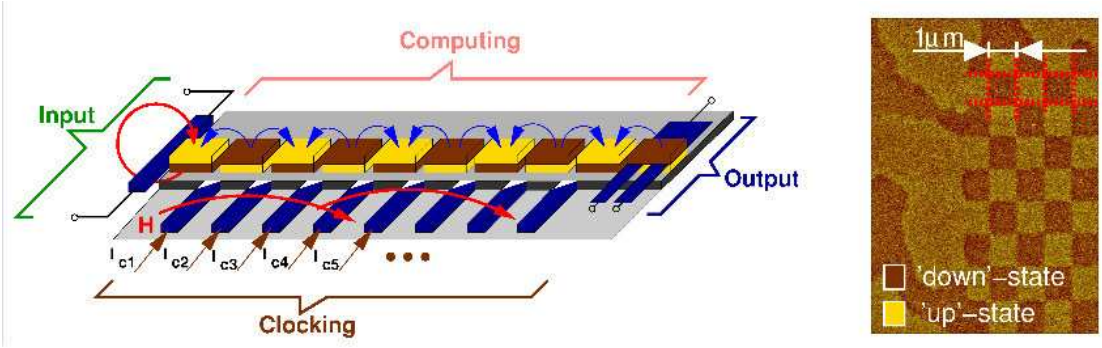
[1] For FETs details see: Kahng, Dawon, "Electric Field Controlled Semiconductor Device," U. S. Patent No. *3,102,230* (Filed 31 May 31, **1960**, issued August 27, **1963**).

[2] I. Amlani, A. O. Orlov, G. Toth, G. H. Bernstein, C. S. Lent, G. L. Snider, *Science* **1999**, *284*, 289.

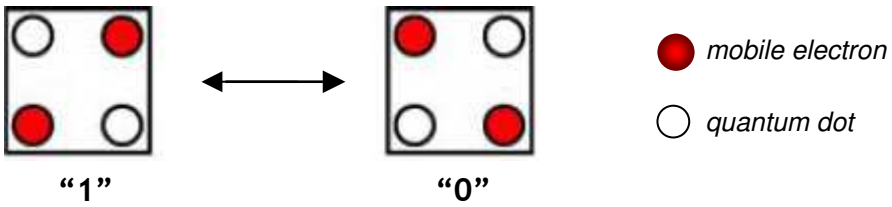
By approaching the quantum nanostructure limits fundamental effects will make further scaling difficulties as unacceptable power dissipation and short-channel effects, which lead to performance degradation. Achievement of ever higher levels of integration in microelectronics eventually will require a shift from the field-effect transistor (FET) based paradigm to a revolutionary approaches to computing. [3]

Figure 2 Logic gate by Field-coupled nanomagnets[4]



The approach must be compatible with the inherent properties of nanostructures, as it should exploit the effects that accompany small sizes. New frontiers in nanoscale computing devices have been developed. **Q**uantum-dot **C**ellular **A**utomata[5] *(QCA)* is an alternative vision to binary computing since no current flow is required to encode binary information. Conventional transistors and current switches will be outclass. Binary code "bit" is represented in QCA approch through the charge configuration in the cell. Two different polarizations are symbolized in Figure 3:

Figure 3. Schematic rappresentation of a four-dot *QCA* cell in two possible states.



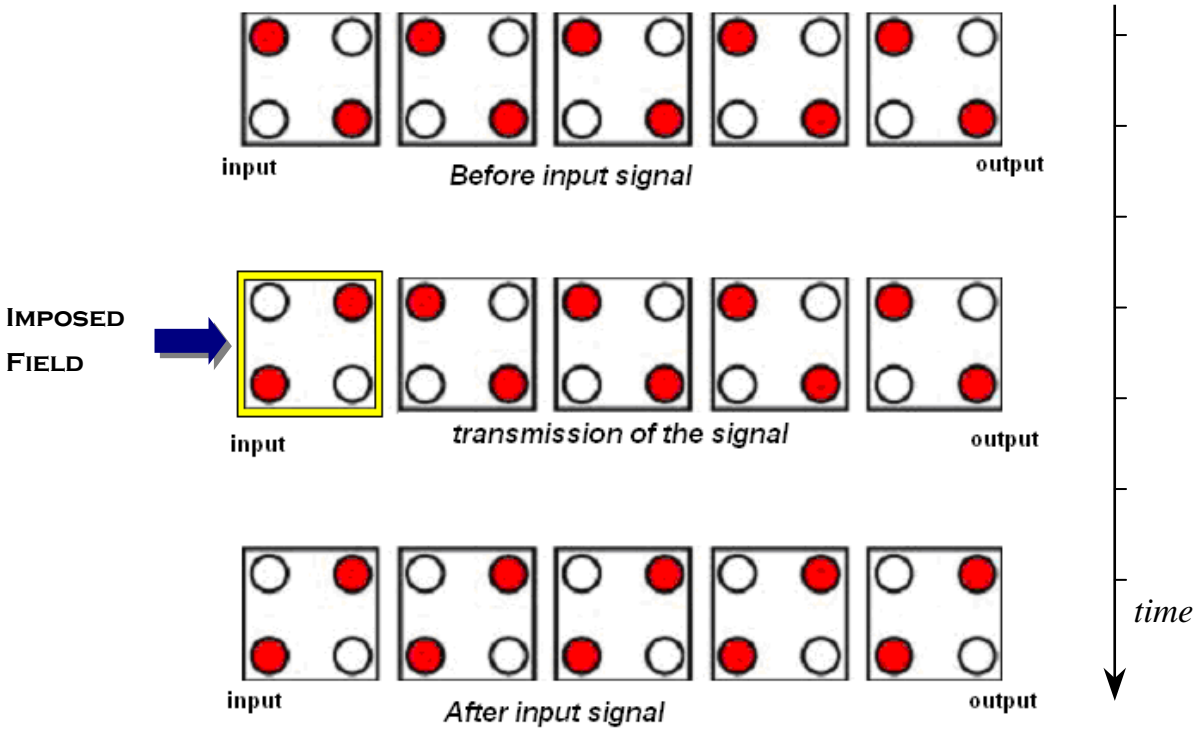
[3] A. O. Orlov, I. Amlani, G. H. Bernstein, C. S. Lent, G. L. Snider, *Science* **1997**, *277*, 928.
[4] for more detail see: http://www.lte.ei.tum.de/homes/mbech/nanomagnete/
[5] C. S. Lent, P. D.Tougaw, *Proceed. of the IEEE*, **1997**, *85*, 541.

Overview on Quantum Cell Automata

The cell shown in Figure 3 contain four quantum dots and two mobile electrons, which will occupy antipodal sites in the square due to coulomb repulsions but the electrons have to be well localized on individual dots to obtain a QCA cell. This condition is satisfy if energy barriers are sufficiently high.

The second requirement is the change of the *charge configuration* due to an external signal (input) through electron tunneling between neighboring sites (dots) of the cell. The compensating positive charge is fixed and immovable.[6] In binary logic only two charge configurations need to copy "0" and "1 codes. Isolated cells have two energetically equivalent arrangements of the extra electrons but in a QCA binary wire (more cells side by side, Figure 4) only one arragement is promoted due to coulomb force among neighbour cells.

Figure 4. Cells arranged in a line all take on the same configuration.



The left-most cell shown in Figure 4 is fixed with a polarization representing the input. The ground state configuration of the remaining free cells changes and each cell polarizes in the same way as the input cell. This cell-cell interaction is the basis of QCA device operation. On this basis logic gates may be realized as shown in Figure 5.

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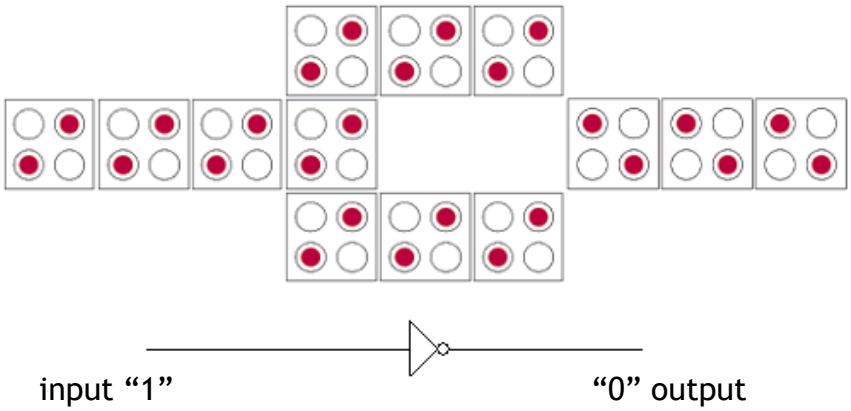
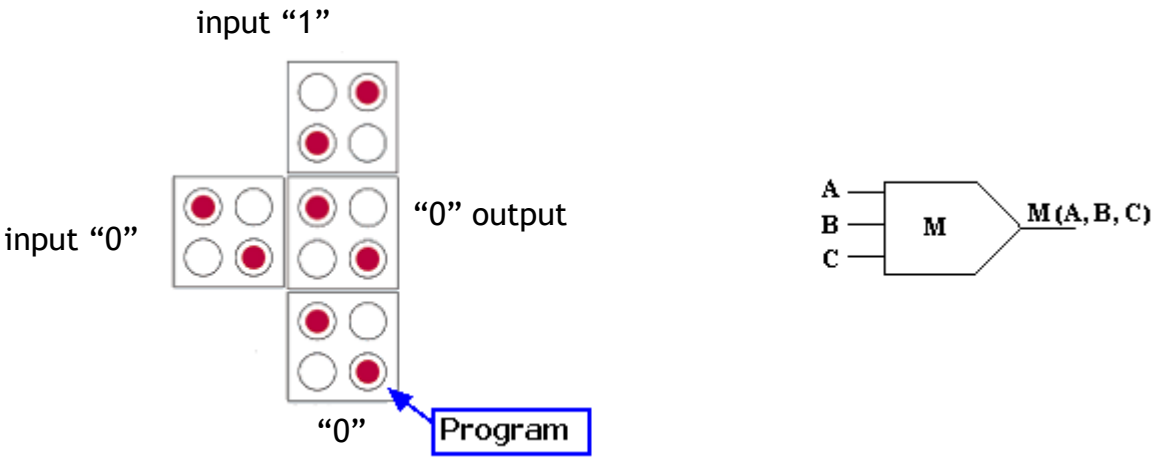
[6] C.S. Lent, P. D. Tougaw, *J. Appl. Phys.* **1994**, *75*, 4077.

Figure 5. Fundamental QCA devices

- The inverter uses diagonal anti-voting behavior to invert the signal



- The majority logic gate and its logical symbol



A detailed discussion of QCA characteristics can be found in ref. *5*.

To carry out QCA opearation the state energy difference of the two polarizations must be greater than the thermal energy k_BT. C. S. Lent and co-workers submited several metal-dots QCA devices (50 nm scale dots and tunnel junctions) to cryogenic temperatures to satisfy this requirement.[2,3] Although those experiments proved their theory, a pratical QCA logic gates establishment is actually remote.

Molecolar Quantum Cellular automata

Until now molecular electronic devices are commonly realized to improve traditional diode or transistor devices at nanoscale levels. Indeed the molecular quantum-dot cellular automata (*QCA*) approach offers an attractive alternative to molecular diode or transistor devices. Moreover molecular QCA cells should have state energy difference of two polarizations greater than the thermal energy at room temperature. Indeed the energy difference scales inversely with size and at the molecular level[7,8] QCA devices can be contracted so that a single molecule behave as a QCA cell. Quantum dots are set up by redox centers within the molecule and molecular bonds form tunneling paths. Among the several methods to realize QCA logic gates, the use of molecules have many advantages.
First of all molecules furnish QCA cells of uniform size, which have high device density[9] in the range of 10^{11}–10^{14} devices cm^{-2}. Finally the intrinsic bistability of the charge configuration results in dipole or quadrupole fields which couple strongly to the state of neighboring molecules.[10] Remarkable is the possibility that the QCA devices encode information without corrent flow, enhancing logic operations with ultra-low power dissipation.[11]

Design and Synthesis of Molecular (QCA) cells

Molecules or supramolecular systems act as cells only in solid state and pratical linkers are required. Another requirement is the setting and reading signals as input/output.
On equal terms, neutral species are preferred to ionic species due to their counterions. However, many of the benefits of QCA architectures derive from the ability to have clocked control of the effective tunnel barriers between dots, which must be little conjugated in order to avoid charge delocalization, however, tunneling must be possible within a cell under the biasing action of its neighbors, to permit state switching.
On the basis of experience with the metal-dot works, the first step was to establish the basic character of a nonlinear, bistable interaction between molecules, on which the fundamental device performance depends. Charge distribution during Molecular QCA operations have to respond in a nonlinear way to the Coulombic perturbation produced by

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[7] C. S. Lent, B. Isaksen, M. Lieberman, *J. Am. Chem. Soc.* **2003**, *125*, 1056; for other molecules can allow QCA tecnology, see also: ref 10 and *18*.

[8] C. S. Lent, B. Isaksen, *IEEE Trans. Electron Devices **2003**, 50,* 1890.

[9] C. S. Lent, *Science* **2000**, *288*, 1597; by comparison with "no QCA" molecular memory patterned at 10^{11} bits cm^{-2} see: J. E. Green, J. W. Choi, A. Boukai, Y. Bunimovich, E. Johnston-Halperin, E. Delonno, Y. Luo, B. A. Sheriff, K. Xu, Y. S. Shin, H.-R. Tseng, J. F. Stoddart, J. R. Heath, *Nature* **2007**, *445*, 414.

[10] Y. Lu, C. S. Lent *J. Comput. Electron. 4*, **2005**, 115.

[11] C. S. Lent, M. Liu, Y. Lu, *Nanotech.* **2006**, *17,* 4240.

the neighboring molecule polarization changing. Finally a single-molecule implementation of a QCA cell requires a molecule in which charge is localized on specific sites and can tunnel between those sites.

Ferrocene is interesting candidate as quantum dot

A well known prototypical 3d metallocene as ferrocene respond to molecular QCA requirements that consists of two cyclopentadienyl rings bonded to the opposite ends of a transition-metal, iron atom, at the centre. This bonding involves the overlap of n*s*, (n-1)d, and np orbitals of the metal with molecular orbital of each aromatic cyclopentadienyl ring. Since its discovery in 1951 by Pauson and Kealy[12], ferrocene and its derivatives has been subject of extensive study/research due to their unique structural, spectroscopic and electrochemical properties.[13] Ferrocene undergoes a one-electron oxidation at a low potential, around 0.5 V (depends by solvent media[14]) in reversible way. (Table 1)

Table 1 Formal Potentials *(V)* for the Ferrocene/Ferrocenium Couple.[15a]

■ Connelly, *Chem. Rev.* **1996,** *96*, 879.

Solvent	$[NBu_4][PF_6]$[15b]	$[NEt_4][PF_6]$[15c]	$[NBu_4][ClO_4]$[15d]
nitromethane	0.35	0.31	0.34
nitrobenzene		0.37	
propylene carbonate	0.38	0.36	0.34
MeCN	0.40	0.38	0.38
DMSO		0.43	0.45
DMF	0.45	0.46	0.47
CH_2Cl_2	0.46		0.48
acetone	0.48	0.46	0.50
glyme	0.51		
THF	0.56		0.53
others			
H_2O (0.1M NaF)	0.16V[15e]		
MeCN (0.2 M $Li[ClO_4]$)	0.31V[15f]		

[12] *T. J. Kealy, P. L. Pauson,* Nature ***1951***, 168, *1039*.

[13] a) A. H. Schafer, C. Seidel, L. Chi, H. Fuchs, *Comm. Adv. Mater*. **1998**, *10*, 839; b) A. Pugh, M. W. Lufaso, M. Zeller, T. R. Wagner, L. S. Curtin, *Jour. Organometallic Chem.* **2006**, *691*, 680.

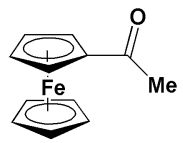
[14] For reviews on chemical redox agents see: N. G. Connelly, W. E. Geiger, *Chem. Rev*. **1996,** *96*, 879.

[15] a) Supporting electrolyte concentration, 0.1 M. b) Data from W.E Geiger's laboratory, University of Vermont; c) J. P. Chang, E. Y. Fung, J. C. Curtis, *Inorg. Chem* **1986**, *25*, 4233; d) D. Chang, T. Malinski, A. Ulman, K. M. Kadish, Inorg, Chem, 1984, 23, 817; e) A. M. Bond, E. A. McLennan, R. S. Stojanovic, F. G. Thomas, *Anal. Chem.* **1987**, *59*, 2853; f) T. Kuwana, D. E. Bublitz, G. Hoh, *J. Am. Chem. Soc*. **1960**, *82*, 5811.

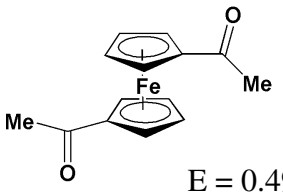
Oxidation of ferrocene gives a stable cation called ferrocenium.[16] Substituents on the cyclopentadienyl ligands alters the redox potential in the expected way:

- Formal potential obtained in CH_2Cl_2 Connelly, *Chem. Rev.* **1996,** *96*, 880.

  a) electron withdrawing group shift the potential in the anodic direction:

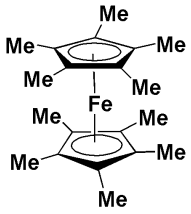


E = 0.27



E = 0.49

  b) electron donating groups shift the potential in the cathodic direction:



E = -0.59

Ferrocene derivatives exhibiting multiple ferrocene groups, with a prospect of producing mixed-valent states, are being actively explored for application as molecular diodes.[17]

Ferrocene fragments within molecular QCA cells

Less than seven years ago Lent[18] reported a quite interesting molecule containing unsymmetrical mixed-valence complex *trans*-Ru-$(dppm)_2(C{\equiv}CFc)Cl$, dppm= methylbis (diphenylphosphane), Fc= $(\eta^5\text{-}C_5H_5)Fe(\eta^5\text{-}C_5H_4)$.[19] The molecule was then supported in its corresponding oxidized form to a silicon surface through a binding linker as shown in Figure 6.

---

[16] T.-Y. Dong, L.-S. Chang, I.-M. Tseng, S.-J. Huang, *Langmuir*, **2004**, *20*, 4471.

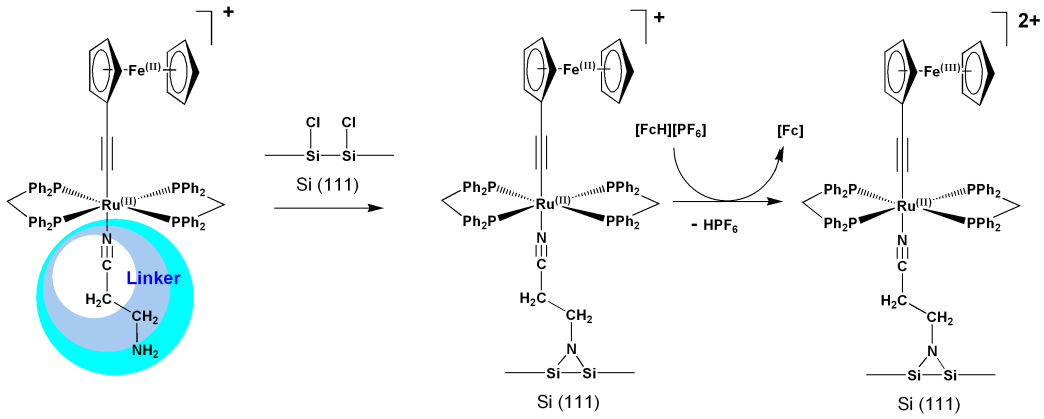
[17] C. Engtrakul, L. R. Sita, *Nano Lett*. **2001**, *1*, 541.

[18] H. Qi, S. Sharma, Z. Li, G. L. Snider, A. O. Orlov, C. S. Lent, T. P. Fehlner, *J. Am. Chem. Soc*. **2003**, *125*, 15250.

[19] Z. Li, T. P. Fehlner, *Inorg. Chem*. **2003**, *42*, 5715.

Figure 6 Mixed-valence complex Ru^{II} Fe^{III} on surface

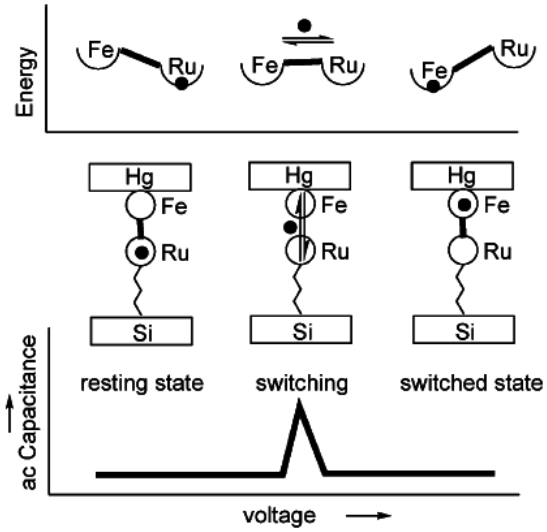
■ Lent, *J. Am. Chem. Soc.* **2003**, *125*, 15254.



Under an electric field **Fe(II)-Ru(III)** and the **Fe(III)-Ru(II) cations** exchange an electron between the Fe and Ru sites at the potential where metal well energies are equalized, that is, switching of the two-dot QCA cell, as shown in Figure 7. The design of complex *trans*-Ru-$(dppm)_2(C{\equiv}CFc)(NCCH_2H_2NH_2)][PF_6]$ for surface attachment was driven by several considerations, based on the compatibility with the synthetic chemistry necessary to build up the dinuclear complex.

Figure 7 Schematic representation of the experiment.

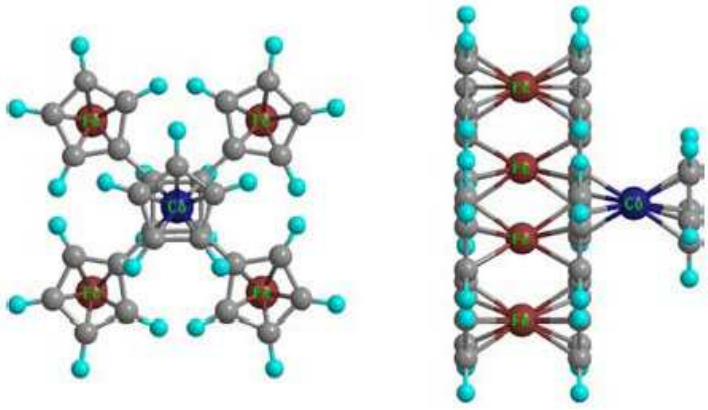
■ Lent, *J. Am. Chem. Soc.* **2003**, *125*, 15251



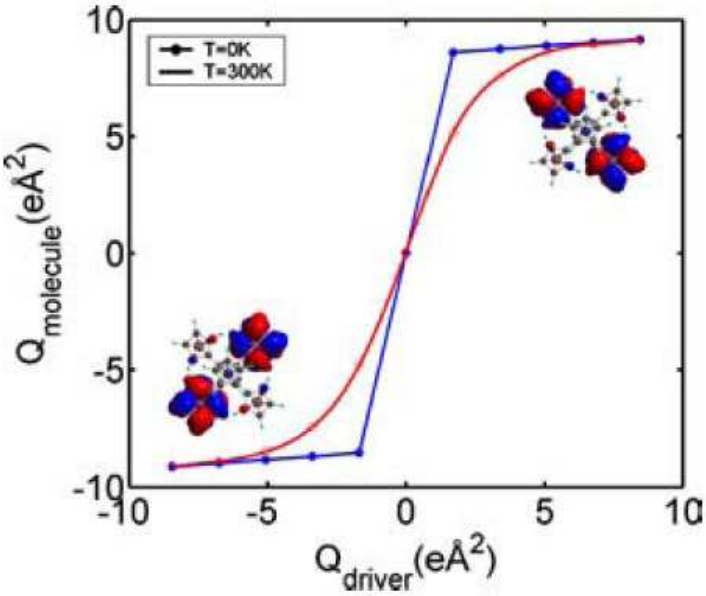
Two years later another di-mixed-valence complex[20] [{(η^5-C_5H_5)Fe(η^5-C_5H_4)}$_4$(η^5-C_4) Co(η^5-C_5H_5)]$^{2+}$, containing ferrocene fragments has been evaluated by Lent and coworkers as a molecular four-dot cell for the quantum cellular automata paradigm for electronic devices.[10] The X-ray structure determination revealed four ferrocene "dots" arranged in a square by C-C bonds to the corners of a cyclobutadiene linker as shown in Figure 8.

Figure 8 Self-assembly of four quantum dots

- a) Lent, *J. Comput. Electron. 4*, **2005**, 116



- b) Lent, *J. Comput. Electron. 4*, **2005**, 117.



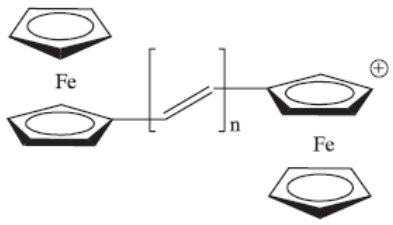
[20] J. Jiao, G. J. Long, F. G. Grandjean, A. M. Beatty, T. P. Fehlner, *J. Am. Chem. Soc.* **2003**, *125*, 7522.

The four ferrocene units project from alternating sides of the cyclobutadiene ring and are twisted to minimize interactions. Calculation proposed by Lent and Co-worker[21] shows that this molecule has two degenerate ground-state conformations, with two mobile electrons localized on either upperleft-lower-right or upper-right-lower-left dots. The two states can be distinguished by the opposite sign of their quadrupole moments (Figure 8b) shows the calculated electric quadrupole moment of the output molecule as a function of the quadrupole moment of the input molecule. Data represented by the blue curve are the induced quadrupole moment at 0K, and the red curve represents the response at 300K. The nonlinearity in the response curve shows that one molecule can be switched by its neighboring molecule even at room temperature. Nevertheless, at room temperature some vibrational distortions of the nuclear geometry are inevitable, fortunately it was proved (with computation count) that this molecule is error tolerant when the 4-fold symmetry is broken by a C C single-bond distortion. This illustrates the robustness of information encoding in the QCA scheme.

Mixed valece behaviour of diferrocenyl polyenes is a function of several parameters.

Remarkable for our research is a recent work[22] by C. S. Lent in which the mixed-valence diferrocenylpolyenes (Figure 9) were proposed as another class of molecules as QCA candidates and part of a mixed-valence diferrocenyl architecture.[23]

Figure 9 Diferrocenyl-polyenes molecules suitable as QCA cell.



[21] All calculations in this work were performed using the *Gaussian 98* software package, for major details see: M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery, R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Milliam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomberts, R.L. Martin, D.J. Fox, T.A. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B.G.Johnson, W. Chen, M.W. Wong, J.L. Andres, M. Head-Gordon, E.S. Replogle and J.A. Pople, *Gaussian 98*, *revision A.11* (Gaussian Inc. Pittsburgh, PA, **2001**).

[22] Y. Lu, C. S. Lent, *Nanotech*. **2008**, *19*, 11.

[23] A. C. Ribou, J.-P. Launay, M. L. Sachtleben, H. Li, C. W. Spangler, *Inorg. Chem*. **1996**, *35*, 3735.

The mixed-valence behavior between redox centers has been examinated as a function of several parameteres:

- *Distance*
- *Nature of the connecting bonds*
- *Relative orientations*

Lent established his own theoretical model to correlate the molecular QCA structure–property relationship. This structure–property relationship provides a simple yet reliable tool to examine the bistability of candidate molecules, which is a fundamental requirement for QCA cells. He appliied his model to mixed-valence diferrocenylpolyenes, exploring the switching behavior of these molecules. The mixed-valence diferrocenylpolyenes show well-defined localization of the charge and nonlinear bistable response only when they are driven by a fully polarized neighboring molecules at maximum polarization. In this condition molecules give two well-defined localized states enabling the encoding binary information. Lent and coworkers suggested that the approach developed in their article can provide a simple and relatively accurate way of determining the bistability of candidate molecules for use in QCA.

Approch to synthetic strategy

On the basis of Lent's works we have set some fundamental targets before starting to implement our synthetic strategy. Firstly we have established quantum dots by two ferrocene moieties to simplefy the synthesis so that each molecule acts as "half" *QCA* cell. Furthermore our approach to the construction of *QCA* cells consider the preparation of a new molecules with weak interaction among redox centers.[24] Generally every surface requires a specific functional group. We have taken into account the possibility to study different surfaces, where to link dinuclear complex. Indeed our strategy allows a quite flexibility to insert different linker from the popular thiol-gold surface attachment method[25] to a stronger covalent attachment one.[26] Althoungh for some analysis as AFM, STM ecc. we can used weak bond on surface for the final device we need to bind most strongly our substrate to the surface and the link must be resistant to rupture under oxidizing potentials.

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[24] for similar concept on diallyl radical cation see ref *7*.

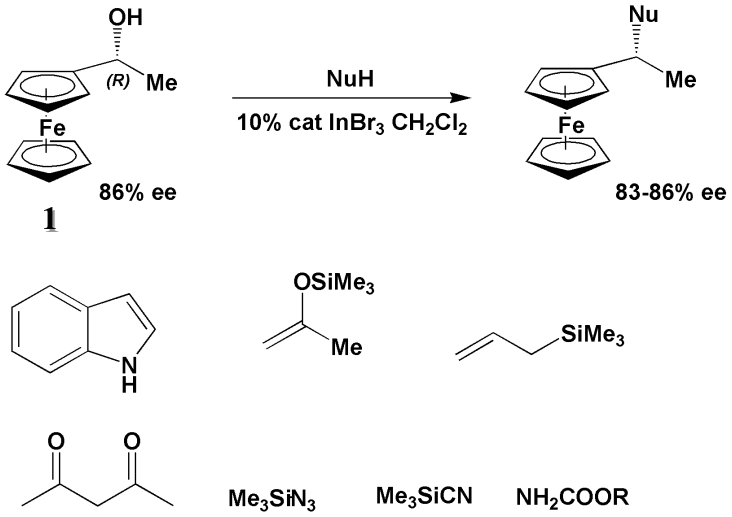
[25] a) R. G. Nuzzo, L. H. Dubois, D. L. Allara, *J. Am. Chem. Soc.* **1990**, *112*, 558; b) S. Maisch, F. Buckel, F. Effenberger, *J. Am. Chem. Soc.* **2005**, *127*, 17315; c) N. K. Devaraj, P. H. Dinolfo, C. E. D. Chidsey, J. P. Collman, *J. Am. Chem. Soc.* **2006**, *128*, 1794; d) M. Malicki, Z. Guan, S. D. Ha, G. Heimel, S. Barlow, M. Rumi, A. Kahn, S. R. Marder, *Langmuir* **2009**, *25*, 7967.

[26] a) Y. Yeon, Y. J. Park, J.-S. Lee, J.-W. Park, S.-G. Kang, C.-H. Jun, *Angew. Chem. Int. Ed.* **2008**, *47*, 109; b) T. Lummerstorfer, H. Hoffmann, *J. Phys. Chem. B* **2004**, *108*, 3963; c) S.-Y. Ku, K.-T. Wong, A. J. Bard, *J. Am. Chem. Soc.* **2008**, *130*, 2392.

Convenient rates under mild conditions and good coverage were also highly desirable properties.

Although other organic molecules were proposed for the preparation of QCA cells,[7] the chemistry in order to link them to a surface was adjusted case for case. In 2007 Paola Vicennati developed a facile Friedel-Crafts (FC) reaction of optycal active ferrocenyl derivatives that take place using optycal pure *(R)*-1-(hydroxyethyl)ferrocene **1** (obtained in optically pure form (99% ee) from Johnson Matthey and was prepared by the reduction of acetyl ferrocene with PPHOS ligand.[27]) by a direct reaction of the alcohols promoted by indium tribromide[28]. (Scheme 1)

Scheme 1 Stereoselective S_N1 type reaction.



We reasoned that FC reaction with suitable nucleophiles could be use in the presence of Lewis acids to access functionalized bis-ferrocene molecules with a feature to have a good control over redox centers gap (ferrocenyl moiety). For these reasons we have chosen electron-rich aromatics and heteroaromatics with two nucleophile positions as: 1,3-dimethoxybenzene **2**, dipyrromethane **3** and pyrrole **4** (Scheme 2).

[27] W.-S. Lam, S. H. L. Kok, T. T.-L. Au-Yeung, J. Wu, H.-Y. Cheung, F.-L. Lam, C.-H. Yeung, A. S. C. Chan, *Adv. Synt. Catal.* **2006**, *348*, 370.

[28] P. Vicennati and P. G. Cozzi, *Eur. J. Org. Chem.* **2007**, 2248. For further details about directly substituion of alcohol **1** with other nucleophiles see Chapter 2.

Preliminary results

Scheme 2 Prototype Scaffolds to molecular QCA Cells.

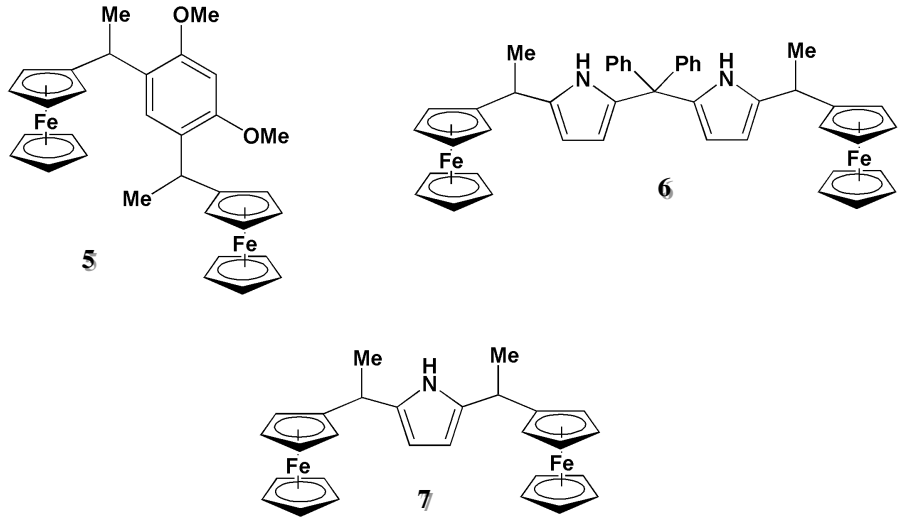
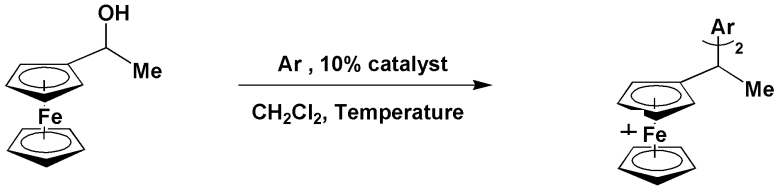


Table 2 Results of bifuntionalization.



Entry[a]	nucleophiles	Catalyst	Temperature (°C)	Yield (%)[b]
1	**2**	$InBr_3$	25	95
2	**3**	$Bi(OTf)_3$	-55	42
3	**4**	$InBr_3$	25	31

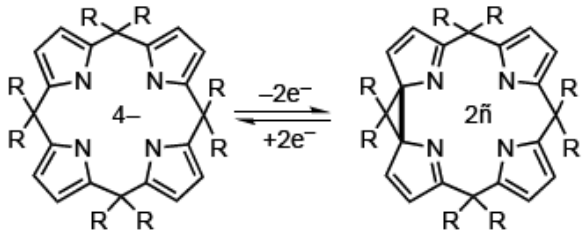
[a] All the reactions were carried out on a 0.1 mmol scale using the suitable equivalents of (*R*)-(1-hydroxyethyl)ferrocene **1**, 10% of the catalyst (respect to the alcohol **1**) under inert gas protection, until disappear of nulceophile, checked by TLC (0.5-1 hour), see experimental section for further details; [b] yields of purified products after chromatography.

1,3 dimethoxybenzene **2** and dipyrromethane **3** have given bis-ferrocenyl derivates in yields from good to excellent. Unfortunately bis-ferrocene products were readly discarded, **5** was found difficult to link on surface, while **6,** under electrochemical analysis, has shown an similar behaviuor to the calix[4]pyrrole reported by Floriani[29] (Figure 10).

[29] F. franceschi, E.Solari, R. Scopelliti, C. Floriani, *Angew. Chem. Int. Ed.* **2000**, *39*, 1685.

Figure 10 Reversible formation of C-C single bond via oxidative coupling.

- Floriani, *Angew. Chem. Int. Ed.* **2000**, *39*, 1685.



Althoungh pyrrole is normally hard starting material to manage, it has good features as: simply metodology to link on surface and quite acces to symmetrical bis ferrocenyl products **7**. To know its stability the compound **7** has been left 1 week in the air at room temperature. We have found it alterated (both oxidation and polymerization occur). Also this nucleophile failed to give interesting products for QCA cell building. Despite these preliminary results, we have looked for others heteroaromatic nucleophiles. In particular, carbazole **8** molecules attract our attention. It is a relatively stable, a well-known electron-donor and hole-transporting group[30]; substituted carbazole are used in OLED fabrication.[31] Is also quite easily functionalised through FC chemistry.[32] The nitrogen of carbazole can be used in attaching functionalized linkers[33]. For all these reason we have designed the molecules **9a-c** shown in Figure 11. Introduction of substituents suppresses the N–N and C–C coupling reaction between carbazole units, which are the chemical reactions that cause the irreversibility toward oxidation.[34] Carbazole monomers where the three, six, and nine positions are substituted are electrochemically reversible units.[35]

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[30] C. A. Walsh, D. M. Burland, *Phys. Lett.* **1992**, *195*, 309.

[31] a) A. van Dijken, J. J. A. M. Bastiaansen, N. M. M. Kiggen, B. M. W. Langeveld, C. Rothe, A. Monkman, I. Bach, P. Stoössel, K. Brunner, *J. Am. Chem. Soc.* **2004**, *126*, 7718; b) M. Guan, Z. Q. Chen, Z.Q. Bian, Z. Liu, Z. Gong, W. Baik, H. Lee, C. Huang, *Org. Electron. 7,* **2006**, 330; c) H.-Y. Fu, H.-R. Wu, X. Y. Hou, F. Xiao, B.-X. Shao, *Synth. Metals* **2006**, *156*, 809; d) J. Li, D. Liu, Y. Li, C.-S. Lee, H.-L. Kwong, S. Lee, *Chem. Mater.* **2005**, *17*, 1208; e) P.-I Shih, C.-L. Chiang, A. K. Dixit, C.-K. Chen, M.-C. Yuan, R.Y.Lee, C. T. Chen, E. W.-G. Diau, C.-F. Shu, *Org. Lett.* **2006**, *8*, 2799.

[32] a) M. Schaerlaekens, E. Hendrickxa, A. Hameurlaine, W. Dehaen, A. Persoons, *Chemical Physics* **2002**, *277*, 43. b) B.-M Zhao, N.-N. Fu, L.-H. Xie, L.-H. Wang, W. Huang, *Chem. Lett.* **2008**, *37*, 622; c) L.-H. Xie, X.-Y. Hou, Y.-R. Hua, C. Tang, F. Liu, Q.-L. Fan, W. Huang, *Org. Lett.* **2006**, *8*, 3701; d) P.-I. Shih, C.-L. Chiang, A. K. Dixit, C.-K. Chen, M.-C. Yuan, R.-Y. Lee, C.-T. Chen, E. W. G. Diau, C.-F. Shu, *Org. Lett.* **2006**, *8*, 2799; d) K.-T. Wong, Y.-M. Chen, Y.-T. Lin, H.-C. Su, C.-C. Wu, *Org. Lett.* **2005**, *7*, 5361.

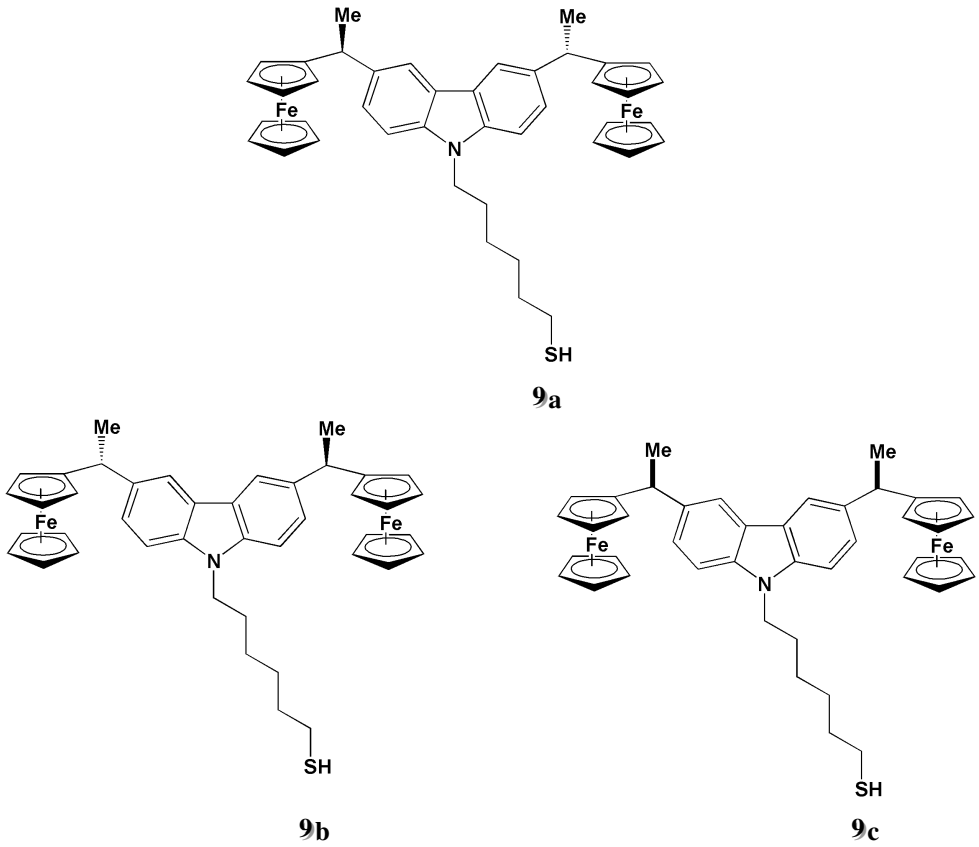
[33] a) A. Krasiński, Z.Radić, R. Manetsch, J. Raushel, P.r Taylor, K. B. Sharpless, H. C. Kolb *J. Am. Chem. Soc.* **2005**, *127*, 6686; b) C. Li, X. Liu, M. Yuan, J. Li, Y. Guo, J. Xu, M. Zhu, J. Lv, H. Liu, Y. Li, *Langmuir* **2007,** *23,* 6754; c) C. Xia and R. C. Advincula, *Chem. Mater.* **2001,** *13,* 1682; d) Z.-B. Zhang, M. Motonaga, M. Fujiki, C. E. McKenna, *Macromolecules* **2003**, *36,* 6956; for directly N arylation see: ref *32*.

[34] for detail over electropolymerization of Carbazole see: a) P. Maitland, S. H. Tucker, *J. Chem. Soc.* **1927**, 1388; b) T. Miyazaki, S.-K. Kim, K. Hoshino, *Chem. Mater.* **2006,** *18*, 5302. for details over electropolymerization of N-alkylcarbazoles a) S. Jegadesan, S.Sindhu, R. C. Advincula, S. Valiyaveettil, *Langmuir* **2006**, *22,* 780; b) see ref. *33c*.

[35] Z. Wei, Xu, N. Jingkun, D. Guangming, P. Yukou, S. J. Shouzhi, *Electroanal. Chem.* **2006**, 589, 112.

Final designof the bis-ferrocene unit.

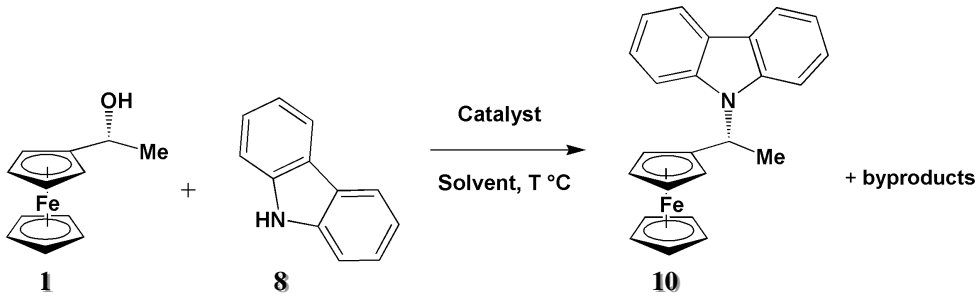
Figure 11 Molecular QCA candidates with linker for gold surfaces.



Preparation of **9** started with the direct reaction of (1-hydroxyethyl)ferrocene **1** in the presence of different Lewis acids and condition with carbazole **8**. Both racemic and optically active **1** gave the formation of the *N*-ferrocenyl compound[36] **10** in all condition tested, as shown in Table 3.

[36] For "tipe Mitsunobu" N-alkylation of carbazole with alcohols, see: A.Bombrun, G. Casi, *Tetrahedron Lett*. **2002**, 43, 2187.

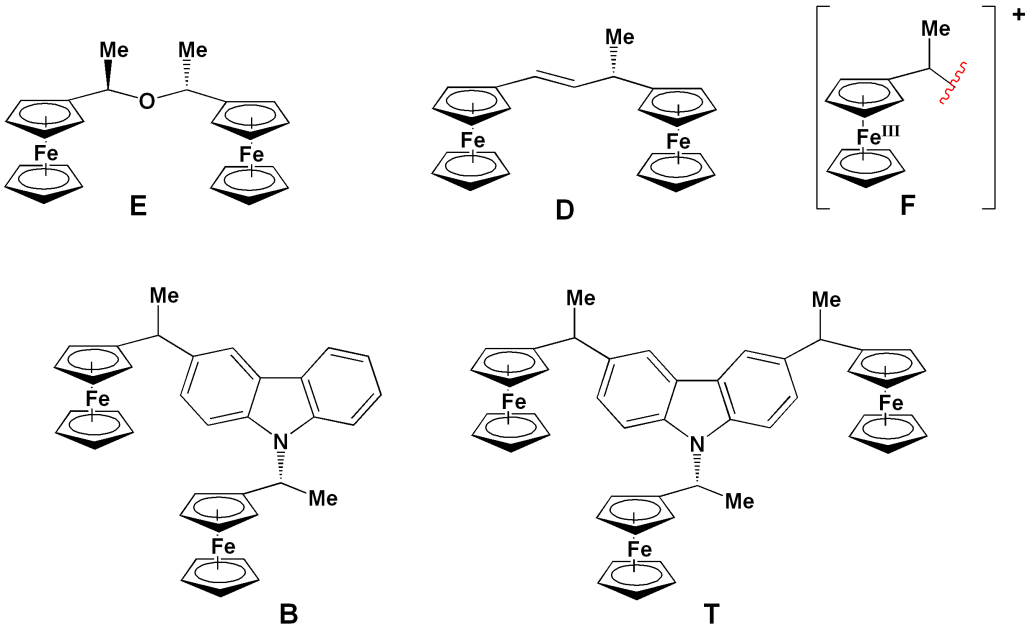
Table 3 Catalyst tested to change regioseletion in FC reactions on carbazole.



Entry[a]	catalyst (mol %)	By-products	Yield (%)[b]	Ee (%)
1	$InBr_3$[c]	E, B, T	62	-[d]
2	BF_3•Et_2O[e]	F[f]	-	-
3	PTSA	D	55	59
4	AuCl	-	77	95

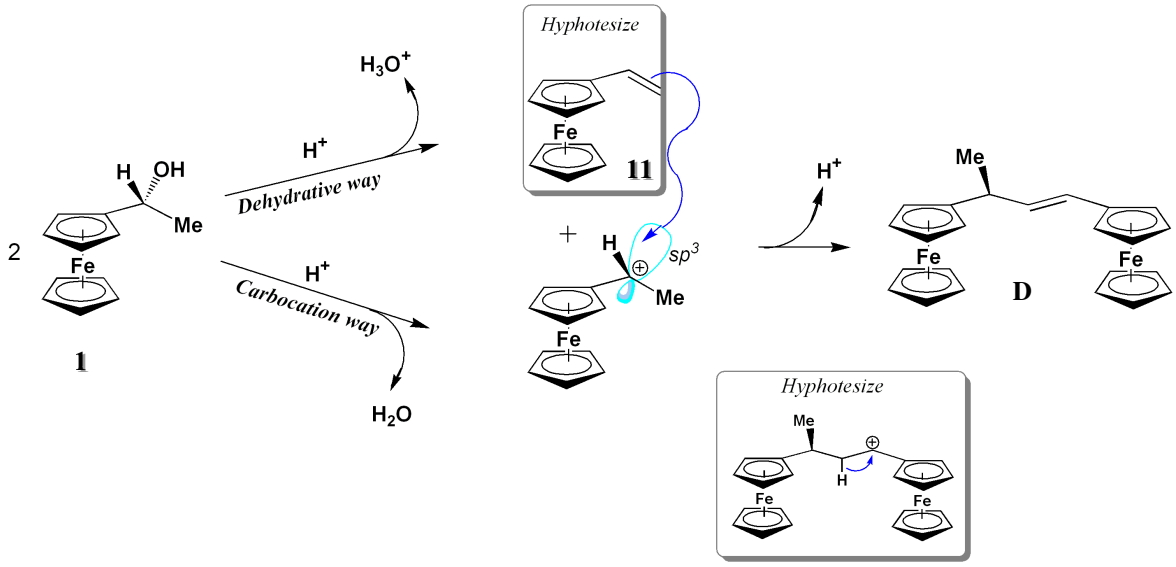
[a] All the reaction were carried out under inert atmosphere, with 0.1 mmol of (*R*)-**1**, 0.2 mmol of nucleophile and 10 mol% of catalyst in 1.0 mL of CH_2Cl_2 at room temperature for 2-5 hours; [b] Yields of purified products after chromatography; [c] $InBr_3$ is added as solution of AcCN 0.33M; [d] In this case racemic alcohol **1** was utilzed; [e] BF_3•Et_2O was addes stoichiometric; [f] We did not identify the nature of ferrocenium fragment **F** (oxidation of alcohol **1** or oxidation of byproducts **E**, **B**, **T**).

By-products:



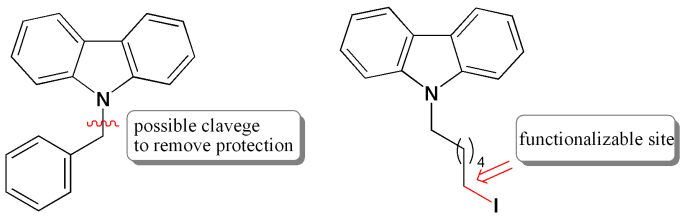
The formation of by-product **D** could be understood through dehydration of α-ethylferrocene cation, producing olefin **11**. Its addition to the α-ethylferrocene carbocation would afford the dimer carbocation. Subsequent elimination of a proton as shown in Scheme 3.[37]

Scheme 3 Hypothesis of mechanism for formation of by-product D.



Therefore, the FC reaction has been investigated on N-protected carbazole utilizing racemic alcohol **1**. In order to gain versatility, we have prepared the N-benzyl carbazole **12** and the *N*-6-iodohexyl-carbazole **13** shown in Figure 12. The first molecule was utilized to optimize FC reaction conditions, and furthermore could be de-protected after FC reaction; while the second molecule allowed immobilization on surfaces.

Figure 12 N-protected carbazoles

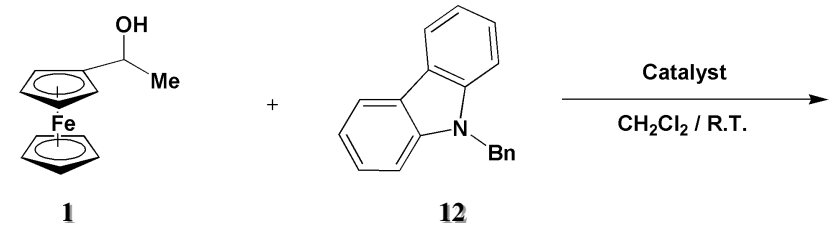


12 **13**

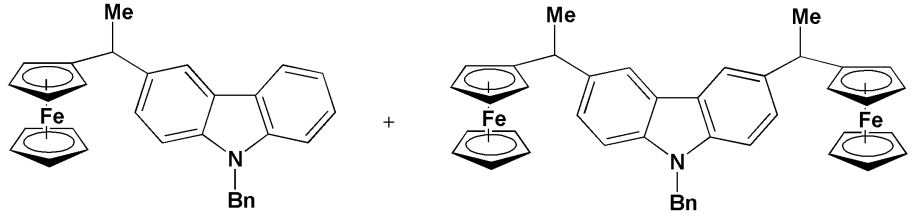
Our investigation has combinated several Lewis acids and conditions. We have taken into consideration the possibility to synthesize scaffolds within different redox center, so the

[37] Analog Mechanism was proposed by Sanz, see: R. Sanz, A. Martínez, V. Guilarte, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Eur. J. Org. Chem.* **2007**, 4642.

reaction conditions were optimized so that we could obtain mono[38] **14** or Bis **15** derivates. (Table 4)



1 **12**



14 **15**

Table 4 Optimizing of the reaction step: single substitution.

Entry[a]	Catalyst	Ratio **14**/**15**[b]	Yield **14** (%)[c]	Yield **15** (%)[c]
1	$InBr_3$[d]	1/1	23%	40
2	PTSA	1/-	15%	-
3	$Bi(OTf)_3$	9/2	36%	15
4	AuCl	-	-	-

[a] All the reaction were carried out under inert atmosphere, with 0.1 mmol of alcohol **1**, 0.25 mmol of nucleophile **12** and 10 mol% of catalyst in 1.0 mL of CH_2Cl_2 at room temperature for 2-5 hours; [b] The ratio was determinated by ^{1}HNMR signals of benzylic hydrogen of **14**, **15** in crude mixture; [c] Yields of purified products after chromatography; [d] $InBr_3$ is added as solution of AcCN 0.33M.

Table 5 Optimizing of the reaction step: double substitution.

Entry[a]	Catalyst	(equiv.)	Ratio **12**/**14**/**15**[b]	Yield **14** (%)[c]	Yield **15** (%)[c]
1	BF_3-OEt_2[d]	3	2/1/1	23	24
2	$InBr_3$[e]	0.15	4/4/3	35	24
3	$Bi(OTf)_3$	0.15	6/3/1	33	10
4	$Bi(OTf)_3$	0.5	1/2/2	40	40
5	$Bi(OTf)_3$	1	2/4/5	36	46
6	$Al(OTf)_3$	1	9/4/2	40	19
7	$Zn(OTf)_2$	1	3/4/3	39	32
8	PTSA[f]	1	-	-	-

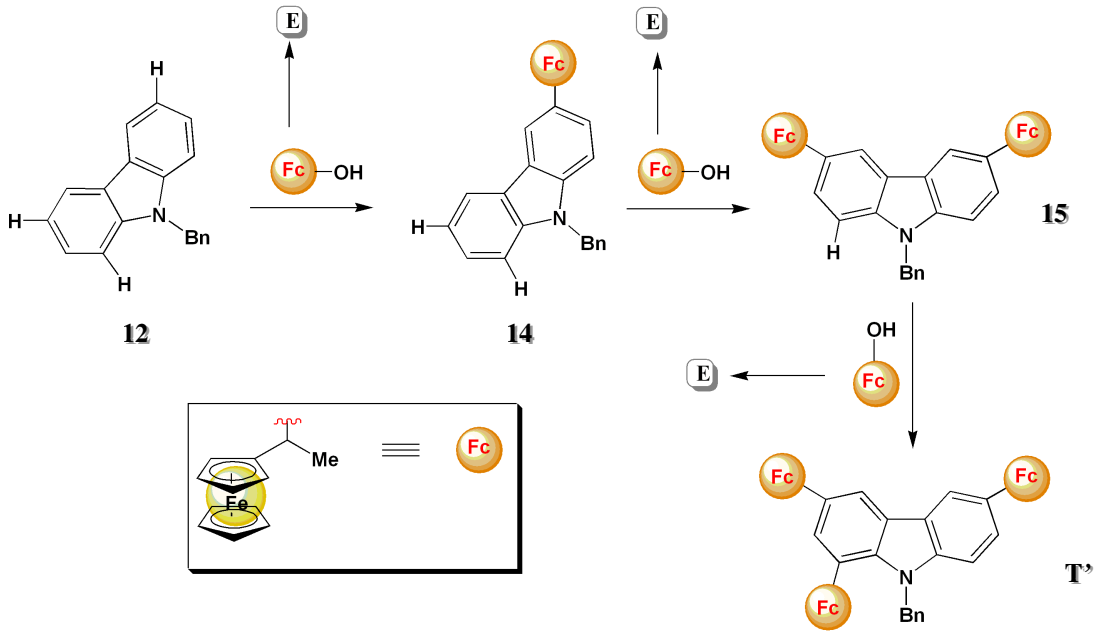
[a] All the reaction were carried out under inert atmosphere, with 0.22 mmol of alcohol **1**, 0.1 mmol of nucleophile **12** and the suitable of catalyst in 1.0 mL of CH_2Cl_2 at room temperature for 2-5 hours; [b] The ratio was determinated by ^{1}HNMR signals of benzylic hydrogen of **12**, **14**, **15** in crude mixture; [c] Yields of purified products after chromatography; [d] by-product **F** was observed in tracies; [e] $InBr_3$ is added as solution of AcCN 0.33M; [f] Only by-product **D** was recovered.

[38] Mono derivates **14** can be further funtionalized, with different metallocene, in a secons step reaction to diversify his formal potential from bis derivates **15**.

Mono-derivate **14** was obtained as unique product utilizing PTSA as catalyst, but in lower yield of 15%. Unfortunately we have never synthesized bis-derivates **15** as a single product but always in mixture with mono **14**. As shown in Table 4, a significant amount of N-benzyl-carbazole **12** and ferrocenyl ether **E** were recoverd; moreover we have observed by ^{1}HNMR analysis of the crude the presence of a carbazole side-product, in small amount, containing three ferrocenyl fragment. We have assumed that all nucleophilic species, **1**, **12**, **14**, **15**, compete with carbazole **8** by reacting with the α-ferrocenyl carbocation due to their comparable and low nucleophilicity.[39]

Figure 13 Contemporary presence of five species within reaction.

Hyphothesis

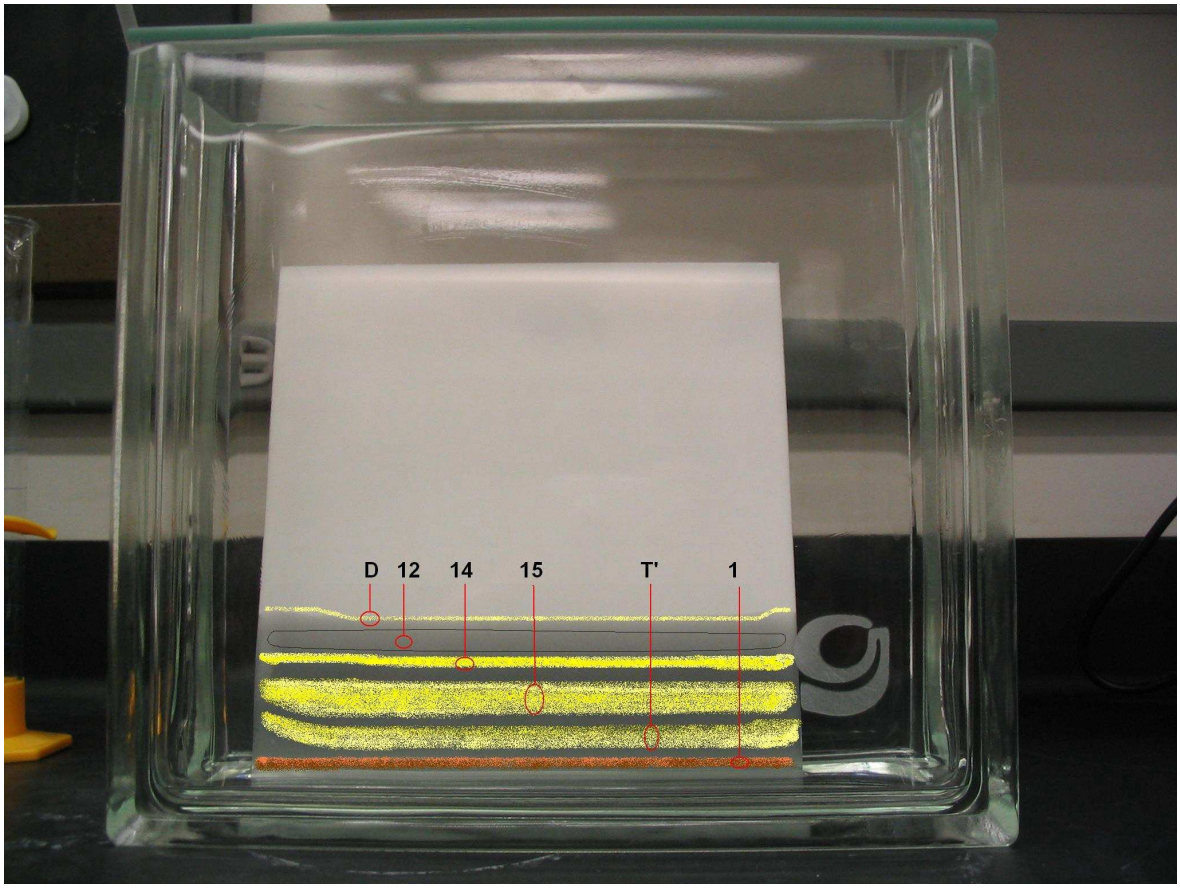


Chromatographic separation of carbazole ferrocenyl compound.

First of all we have separated apolar ferrocenyl-carbazole derivates: **12**, **14**, **15**, by tedious chromatography abd we nedeed several hours to recovere a mild amount of pure bis-derivates **15**. We have improved the separation of the desire product when we utilized for the first time the preparatory TLC (only amount lower than 50 mg can be loaded for a good separation).

[39] Unlinke indole, Carbazole is not a good nucleophile.

Figure 14 Simple separation of Crude and recovere by carefully scratchs.



Electrochemical characterization of mono and bis derivates

The dynamics of the electrochemical behavior of **15** were investigated using cyclic voltammetry (CV) at various scan rates (v) and temperatures.

The CV shown in Figure 15, furnish the sharpest evidence of the oxidation of two ferrocenyl groups ($E_{1/2}$ = 0.35 V) which have a very weak, although sizeable, electronic interactions between the two chemically-equivalent redox centers (97 mV separation between the two oxidations). In view of their relevance for the following investigation of the surface-confined species in their oxidized states, the standard potentials relative to the oxidation of the two Redox groups were determined by digital simulation of the curves, assuming Nernstian behavior for all redox processes. From simulation, the standard potentials for the oxidation of the two ferrocenyl moieties were 0.33 and 0.39 V respectively (60 mV separation between the two oxidations). In case of no interaction between the oxidable groups, the additional difficulty in removing the second electron would in fact only arise from statistical (entropic) factors and would amount at 35 mV.[40]

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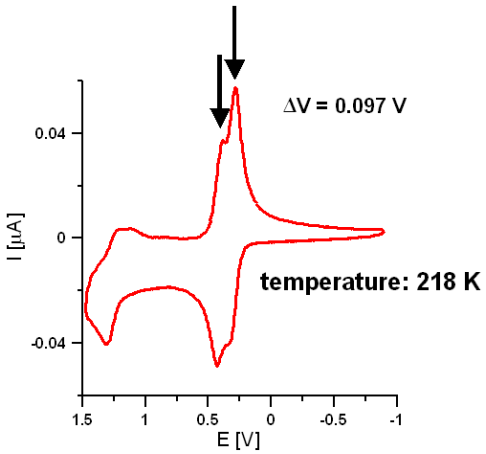
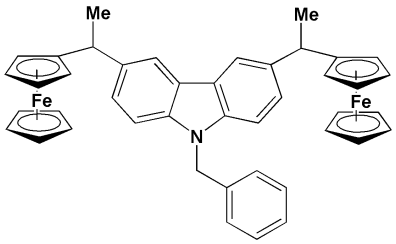
[40] A. J. Bard, L. R. Faulkner, Electrochemical Methods, *Wiley*: New York, **2001** *Chapter 6*.

Figure 15 Cyclic voltammetry of Bis ferrocenyl carbazole derivate 15.





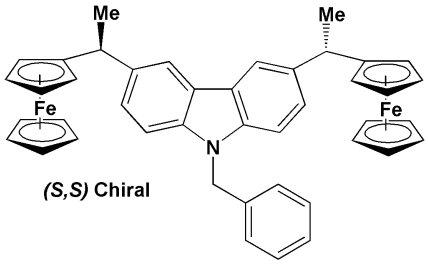
- working electrode: 125 µm Pt
- solvent: DCM
- supporting electrolite: TBAH
- scan rate: 1 Vs^{-1}
- temperature: 218°K (-55°C)

Therefore, these studies definitely confirmed the presence of very weak electronic interactions between the two redox centers, thus supporting the idea of little conjugation and charge localization, as required for QCA application.

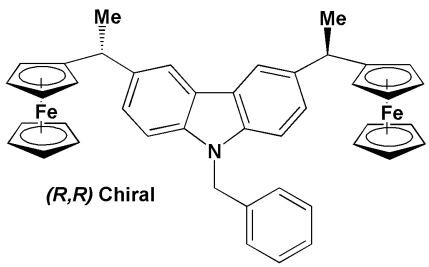
Stereoselective FC reaction furnish enantioenrich bis-ferrocenyl derivates

The reaction of two molecules of ferrocene with the *N*-protected carbazole **12** afforded two different diastereoisomers, the *(S,S)* and *(R,R)* chiral compounds and the *meso* diastereoisomer, as indicated in.

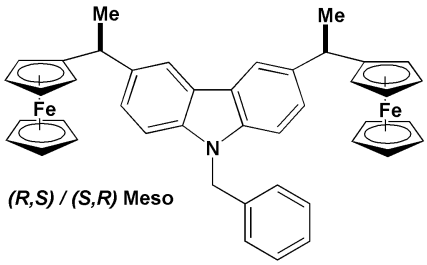
Figure 16 Molecular structure of (*S,S*), (*R,R*) and (*R, S)/(S, R),* configurations of compound 15



15a



15b

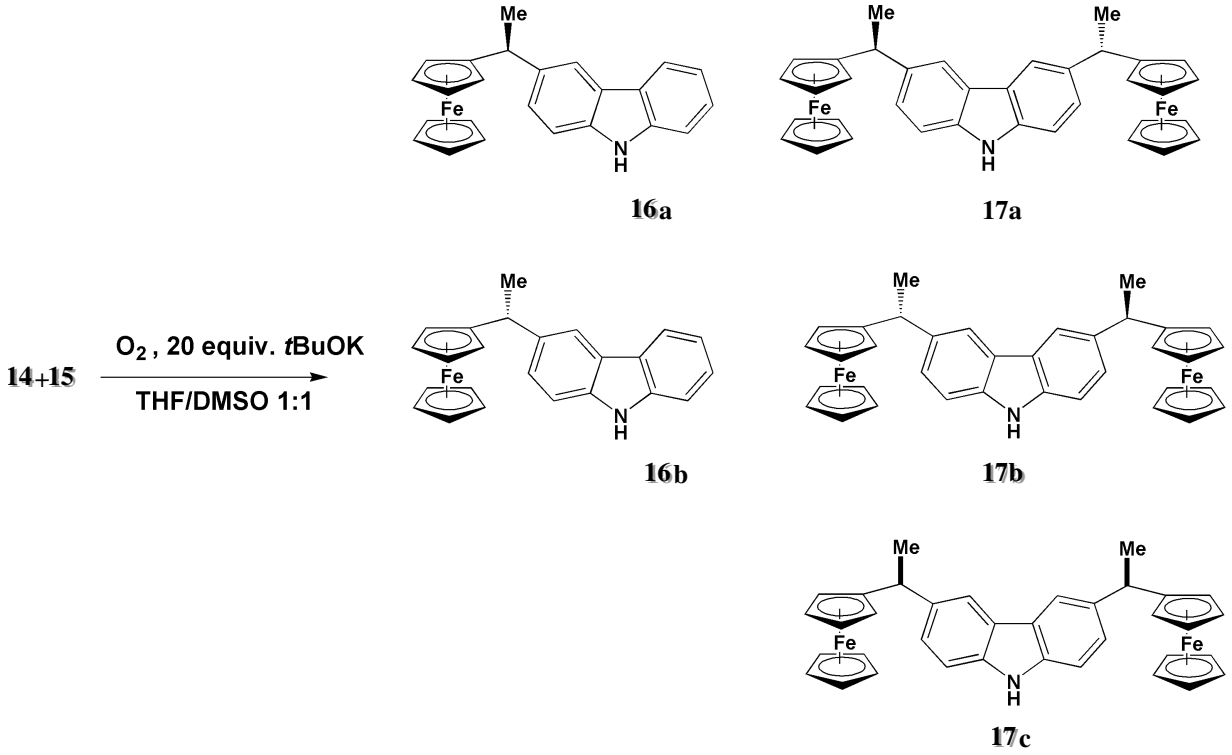


15c

As shown in Table 4, reaction with racemic ferrocenylethanol **1** in the presence of $Bi(OTf)_3$ used in stoichiometric amount gave the desired bis-ferrocene-*N* protected carbazole **15** in moderate yield; however, the NMR and HPLC analyses performed on the isolated products were not able to quantify the stereoselectivity of the reaction, due to the difficulties in the separation of the steroistereoisomers.

To our delight, we found that debenzylation[41] of the crude reaction mixture containing **14** and **15** (Scheme 4) gave the compounds **16a-b** and **17a-c**, easily separated by simple flash chromatografy (or preparative chromatography for a high pure product). The purified adduct **15a-c,** obtained as a statistical mixture of meso (*R*,*S* and *S*,*R*) and (*R*,*R*) and (*S*,*S*) stereoisomers, was also separated by chiral HPLC (see experimental section).

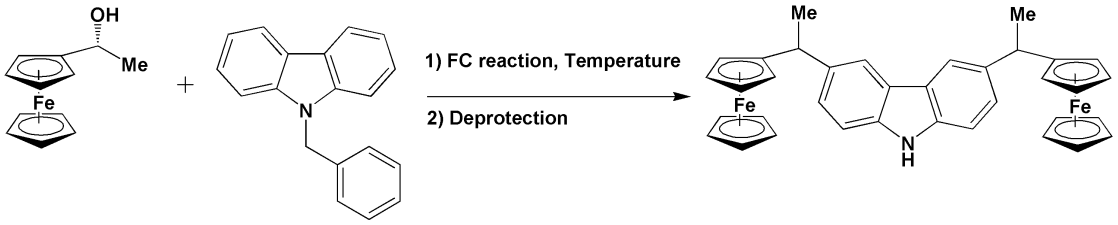
Scheme 4 Clavege of benzylic group directly on mixture of carbazole derivates.



With the conditions for HPLC separation in our hands, we then optimised the reaction in order to achieve the highest diastereoisomeric and enantiomeric ratio possible for Friedel-Crafts reaction (see Table 6). The reaction was performed using the (*R*) optically active 1-hydroxyethyl-ferrocene **1**, We have obtained the highest enantioselection and the best diasteromeric ratio of product **15a**, without lowering of the yield, by operating at –15 °C. (*R*)-**1** was slow added by syringe pump of the mixture of carbazole **12** and solid $Bi(OTf)_3$.

[41] A. A. Haddach, A. Kelleman, M. V. Deaton-Rewolinski, *Tetrahedron Lett*. **2002**, *43*, 399.

Table 6 Optimizing of the FC reaction conditions for increase ee% and dr.



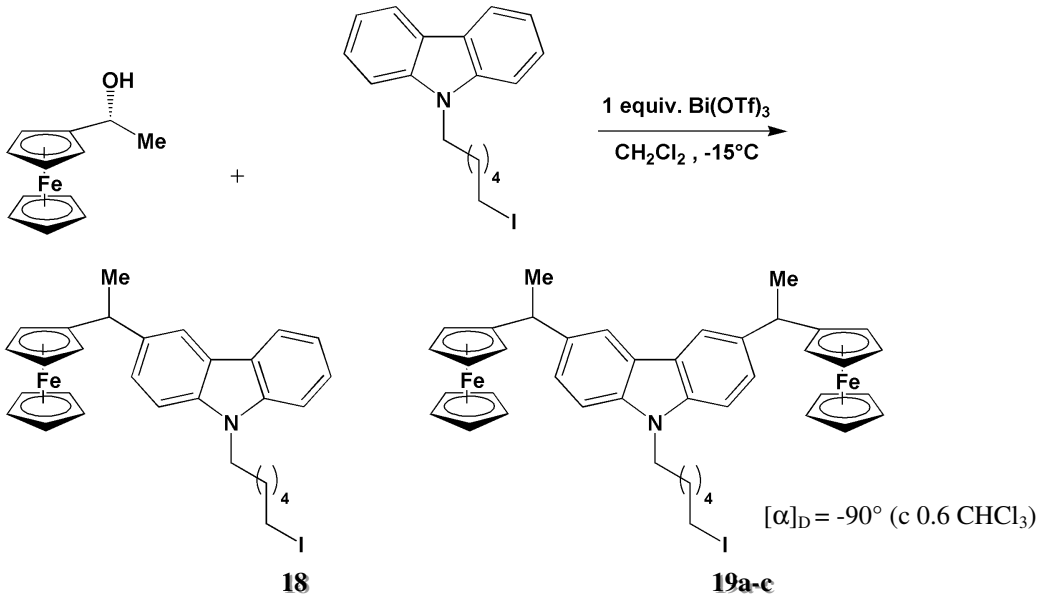
Entry[a]	Temperature (°C)	Time (h)	Yield (%)[b]	dr **16a,c : 16b**[c]	Ee (%)[d]
1	RT	5h	46	58:42	69
2	-15	20	33	85:15	99
3	-26	48	12	85:15	99
4	-40	72	6	91:9	99

[a] All the reaction were carried out under inert atmosphere, with 0.22 mmol of alcohol **1**, 0.1 mmol of nucleophile **12**; [b] Chromatography was done only at the second step reaction; [c] The ratio was determinated by HPLC ananlysis at 250 nm (**16a,c** and **16b** have the the same ε at this wavelenght); [d] Enantiomeric excess was determinated by HPLC analysis.

After two steps reactions (FC reaction and cleavage of benzyl group) the compound **16** was isolated in yield of 33%, as un-separable mixture of the enantiopure (99% ee) (*S*,*S*)-**15a** and *meso* (*RS*)/(*S*,*R*) **15c** diastereoisomer in 85:15 ratio. The presence of the inseparable meso compound **15c** in 15% derives from slight racemization of (*R*)-1-(hydroxyethyl)ferrocene **1** occurring during the Friedel-Crafts reaction[42].

Synthetic strategy to support bis-ferrocene 19 on gold surface

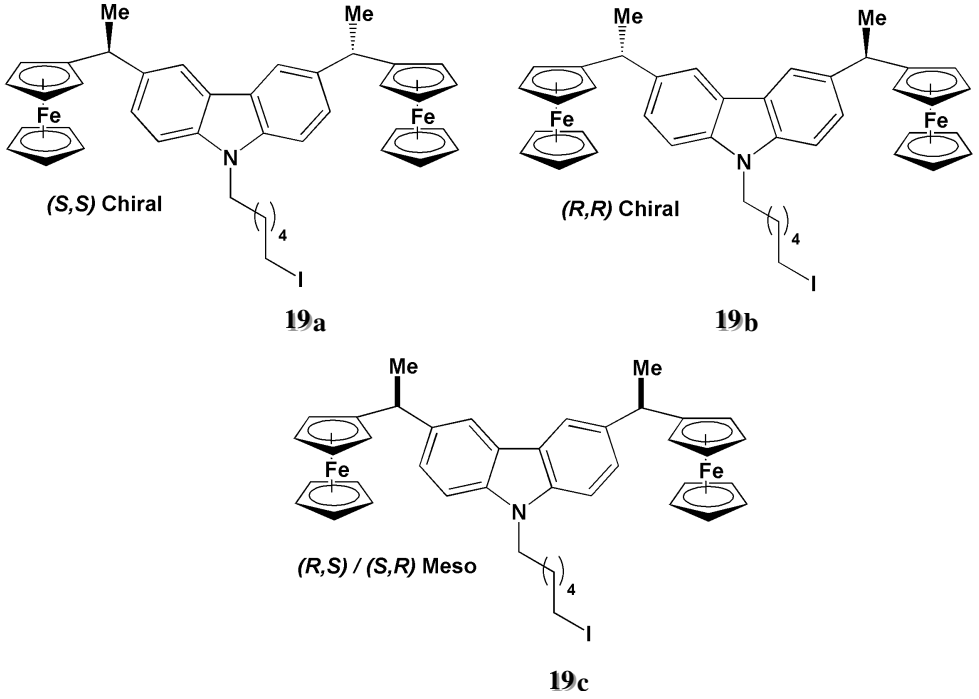
Scheme 5 Reaction of substituion for N-alkylated carbazole 13 to obtain 19.



18 **19a-c**

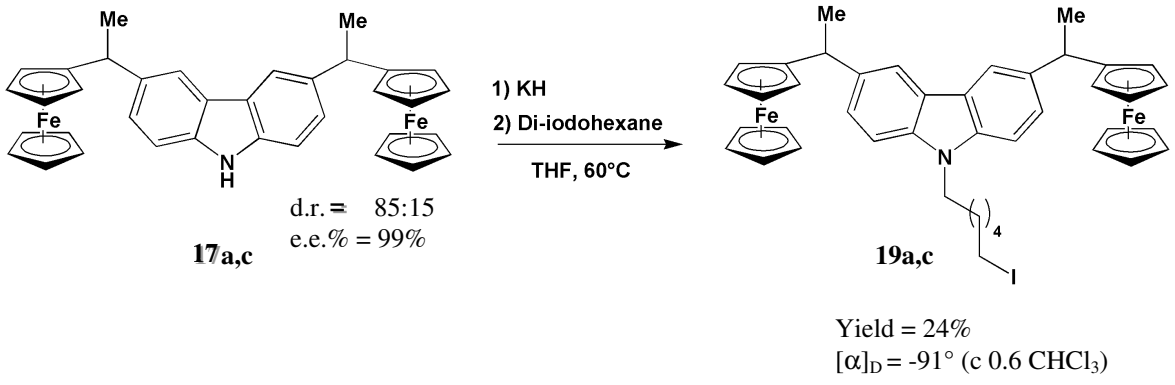
[42] Temperature played a similar role in the FC reaction with pyrrole, where an optically pure product were furnished only to -40°C, temperature at which the pyrrole is nevertheless reactive.

Figure 17 Structure of (*S,S*), (*R,R*) and (*R,S*)/(*S,R*), configurations of compound 19.



Similarly, a FC reaction promoted by $Bi(OTf)_3$ at –15 °C was performed on the carbazole derivative **13** by a syringe pump addition of **1**, to give a of mono-derivate **18a,b** and an un-separable mixture of bis-derivates **19a-c**. Unfortunately, as for the previouses compounds N-benzylated carbazole we were unable to quantify the stereoselectivity of the reaction by chiral HPLC analysis. However, we demonstrated that the FC reaction of optically pure (*R*)-**1** performed on benzyl and alkyl chain gave the same results in term of diastereoisomeric and enantiomeric excess. In fact, the inseparable mixture of de-benzylated derivatives **16a,c** (ratio 85:15) were alkylated with di-iodohexane to afford the mixture of products **19a** and **19c** in low yield[43] as shown in Scheme 6.

Scheme 6 Alkylation of 16a,c; a simple way to campare analytical data.



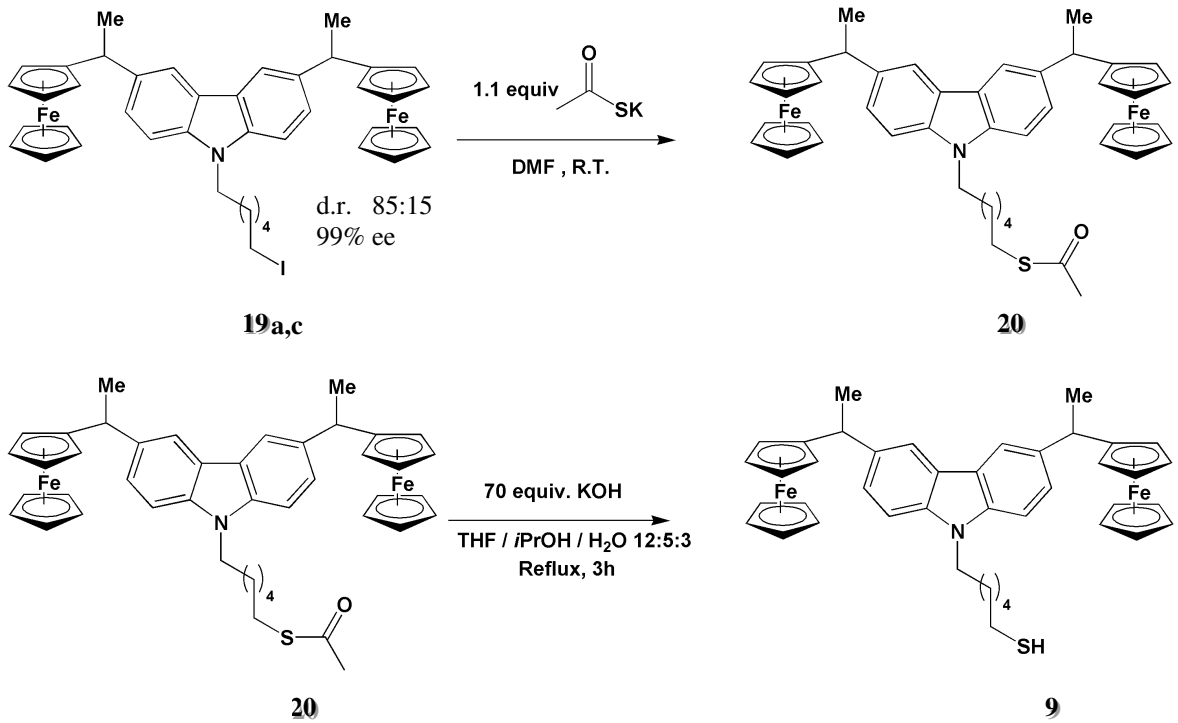
[43] Not optimized reaction condition.

Comparing the measured optical rotation of the mixtures of these compounds with those products provided through the FC reaction performed with *(R)*-**1** on the carbazole derivative **13,** we noticed a perfect matching values. Therefore, we can conclude that identical enantiomeric and diastereoisomeric ratios were obtained in the Friedel-Crafts reaction of *(R)*-**1** with the carbazoles **12** and **13.** In both cases, the di-substituted ferrocene compounds were obtained in 99% ee, and in a diastereoisomeric ratio of 85:15.

The synthesis of Bis-ferrocenes **9** reported suitable for immobilization on solid surfaces. The inseparable mixture of the iodo derivatives **19a,c** was transformed in the corresponding thiols **9a,c** by the simple sequence depicted in Scheme 7.

The transformation of the iododerivatives in the thioacetate **20** (was quite straightforward and was performed by reaction with the potassium thioacetate.

Scheme 7 Synthesis of thiol 9 by two reaction step



19a,c **20** **20** **9**

The hydrolysis of the thioacetate **20** was quite troublesome giving low yield, disulfyde dimer and desulfourated compounds. Finally, after many trials we were able to adjust the reaction conditions, using fresh distilled THF to avoid by-product formation. The thiol derivatives **9a,c** were then attached to gold surfaces (see experimental section for details about SAM preparation) as self-assembled monolayers and further investigated by scanning tunneling microscopy (STM).

Scanning Tunneling Microscopy and DFT analysis on immobilized Bis-ferrocenes 9.

Since electrostatic interaction among neighbor cells is geometry-dependent, control on the immobilization geometry and the spatial arrangement of the two ferrocenes is important. A disordered monolayer or non-fixed reciprocal dot positions – such as due to rotating moieties – are clearly not acceptable. For these reasons, we performed an Ultra High Vacuum Scanning Tunneling Microscopy (UHV-STM) study was performed and results compared with density functional theory (DFT) calculations. Moreover, for QCA, mobile charge for electrical bistability must be present, an aspect here investigated by electrochemical characterization. Both experimental results and theoretical simulations indicate our molecules as very interesting candidates for molecular-scale QCA implementations.[44]

Since in the case of thiol-derivatized ferrocenes redox-induced orientational changes were reported[45], a mixed SAM was prepared by including bis-ferrocenes **9** into a hexane-1,6-dithiol SAM that reduces the structural degree of freedom of the alkyl chain part (see Supp. information for details about preparation).

Firstly, a racemic mixture was studied. As well-known[46], the Au(111) surface consists of well defined terraces with a (22x√3) herringbone structure and 120° turns. As a result, thiols typically tend to auto-organize on the substrate following this superficial pattern[47, 48]. Typical images are shown in Figure 18. On the background, the self-assembly of hexane-1,6-dithiols into a striped phase can be recognized with bright features associated to sulfur-containing endgroup pairs, apparent heights of 0.06-0.08 nm and separation between adjacent stripes around 1.2±0.2 nm[47, 48]. Dipping the thiolated Au substrate in a solution containing the bis-ferrocenes leads to distinct additional features whose density can be controlled by acting on the bis-ferrocene concentration or on the incubation time. As a consequence, they were ascribed to **9** with brighter regions associated to areas containing the Fe atoms. Single and double lobe structures with approximately the same density were identified, randomly distributed and not arrayed. The lateral dimensions of bis-ferrocene in the racemic mixture range from 1.2 up to 1.7 nm for single lobe structures and from 2.4 up to 2.7 nm for double lobe features (see Figure 18a and b).

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[44] a) P. G. Cozzi, L. Zoli, A. Bramanti, "Composti carbazolici bistabili", Italian patent application n. **MI2008A 001613**; b) P. G. Cozzi, L. Zoli, A. Bramanti, "Bistable carbazolic compounds", International patent application **WO EP09006594**.

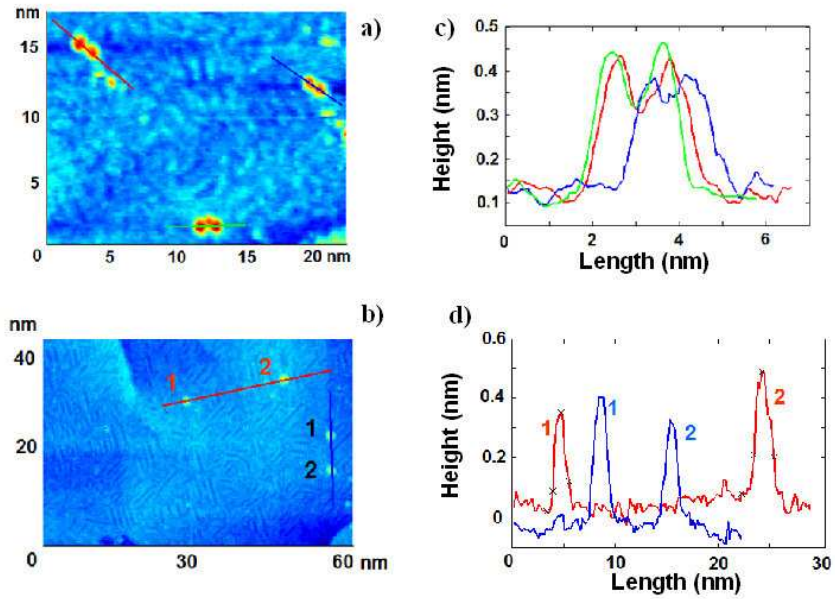
[45] J. S. Miller, A. J. Epstein, W. M. Reiff, *Chem. Rev*, **1996**, *88*, 201.

[46] J. V. Barth, H. Brune, G. Ertl, R. J. Behm, *Physical Review B* **1990**, *42*, 9307.

[47] T. Y. B. Leung, M. C. Gerstenberg, D. J. Lavrich, G. Scoles, F. Schreiber, G. E. Poirier, *Langmuir* **2000**, *16*, 549.

[48] G. Maruccio, C. Meyer, T. Matsui, D. V. Talapin, S. G. Hickey, H. Weller, R. Wiesendanger, *Small* **2009**, *5*, 808.

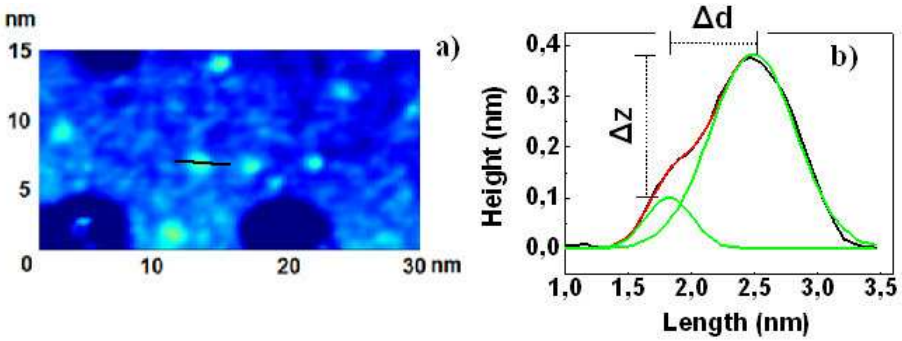
Figure 18 Topography (a, b) and line profiles (c, d) of the sample where double and single lobe structures have been seen



These values do not take into consideration possible tip convolution effects. In the last case, the distance between the two lobes is around 0.9±0.4 nm. On the other hand, the height of both features is very similar, around 0.25nm ±0.10 nm. Thus, these two types of structures can be tentatively associated to the "meso" compound *(R,S)* and the optically active compounds (*S,S* or *R,R*).

To confirm and detail this attribution, a SAM was prepared from a solution of inseparable *(S,S)*-enantiomerically-pure of the two diastereoisomer (ratio 85:15) **9**. As shown in Figure 19a, over the dithiol network, bright spots were again observed with typical lateral dimensions of 1.5±0.5 nm and heights of 0.3±0.2nm (see height profiles in Figure 19b). Apparently, the error values (calculated as standard deviations) seem very wide, but they are due to as we will detail in the following

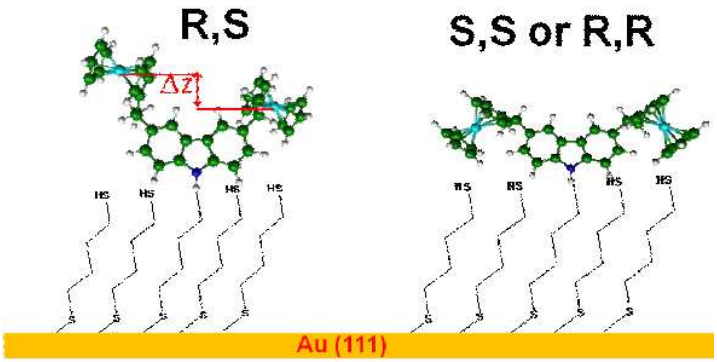
Figure 19 Bis-ferrocene SAM obtained after incubation of a hexane 1,6-dithiol SAM



As opposite to previous samples, however, single lobe structures were mostly observed in this case. Moreover, the few two lobes occasionally noticed within some small regions can be attributed to two close single lobe structures (as will be clarified later) since they appear very different from the previous double lobe structures, having variable and, anyway, far larger distances between the lobes (a minimum distance of about 2 nm was calculated versus the 0.9±0.4 nm of the previous case). Therefore, since single lobe structures were observed in both samples, they can be associated to optically active compounds, while the two lobe protrusions in the racemic mixture correspond to the "meso" compound (*R,S*)/(*S,R*). The surface being not chiral, one does not expect to discriminate among *R,R* and *S,S* distereoisomers. This attribution is supported by the fact that the same apparent height shows up at similar voltages in spite of different lateral dimensions. In addition, at a more detailed analysis (Figure 19b), the single lobe structures appear not very symmetric but rather as the convolution of two peaks of different intensities. Specifically, they can be ascribed to the presence of two ferrocenes at different height (Δz difference of 2.8 Å) whose distance Δd is 8 Å which appears rather similar to the value found for double lobe structures (9 Å).

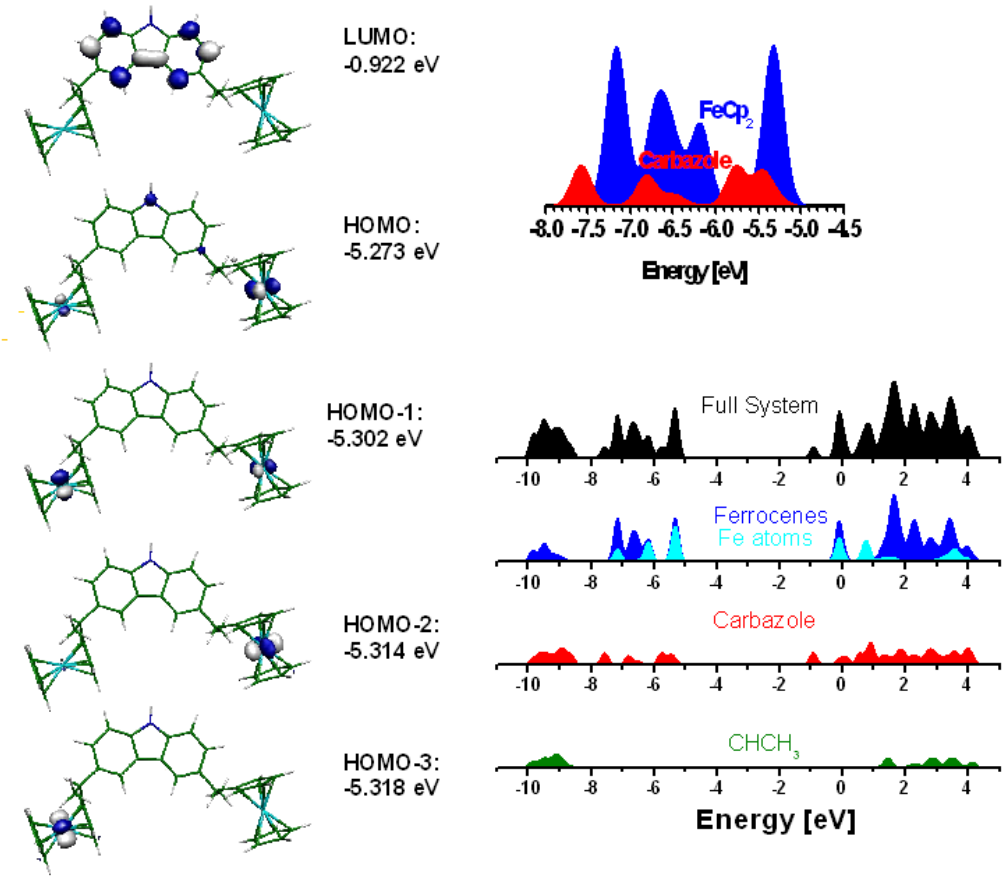
In order to gain a deeper insight into the electronic structure of the adsorbed molecules, first principle Density Functional Theory (DFT) calculations for the isolated systems were performed. For each diastereomer (*R,S* / *S,R* and *R,R*) three different conformers were found with respect to rotation around the bond connecting the carbazole and the asymmetric carbon atoms (Figure 20, see experimental section in Figure E3 and E4 for further details). An analysis of their relative energies on the B3-LYP/TZVP level of theory showed that the energetic differences for the two lowest rotamers of each stereoisomer are small (i.e. below 0.3 kcal/mol) and thus it can be concluded that, for the free structures, several molecular orientations can coexist at room temperature. Reference calculations with the SCS-MP2 approach came to the same result.

Figure 20 The possible orientation of the molecules 9a-c on the Au(111) surface.



The most important geometrical feature of these structures that will be mentioned in the discussion is the metal-metal distance between the two iron atoms, which was found in a range of 10 to 14 Å. A closer look at the molecular wavefunctions showed that also the electronic structure of the investigated isomers is rather similar, so the discussion can be restricted to the most stable rotamer of the (*R,S*) diastereomer.Figure 21a shows the frontier orbitals of the compound. The lowest unoccupied molecular orbital (LUMO) is localized on the carbazole bridge, whereas the highest occupied molecular orbital (HOMO) is localized at the iron atoms of the two ferrocene ligands, as well as the three next lower lying orbitals (HOMO-1 – HOMO-3) that are found in a range of only 0.05 eV below the HOMO. Figure 21b shows the total density of states (DOS) and projected density of states (pDOS) in a range of 14 eV. The pDOS distinguishes states localized on the ferrocenes from those on carbazole and the asymmetric ethylene-linker. From the inset it becomes clearly visible, that the highest occupied states are ferrocene states, that at about –5.5 eV start to overlap with states localized on the carbazole. The LUMO on the other hand is a pure carbazole state.

Figure 21 Frontier orbitals of the most stable *R,S* isomer and projected Density of States.



In previous reports[49], ferrocene molecules were observed in STM as bright spots with apparent dimensions around 0.5nm. Therefore, we could expect to image carbazole linked bis-ferrocene molecules as spaced double lobe structures with overall dimensions of 1.4 nm, a number that seems not to be in good agreement with the lateral size of the double lobe structures (ranging from 2.4 up to 2.7). However, this number is strongly affected by tip convolution effects, therefore the distance Δd between the two lobes is a better (less influenced) parameter. Specifically, from the experimental analysis, two average values can be extrapolated for Δd: 9 Å for double lobe and 8 Å for single lobe features to be compared with the distance between ferrocene units in the investigated molecules. Considering that the interatomic distance of the iron atoms ranges between 10 and 14 Å, the appearance of the double/single lobe structures in the STM experiments can be, with very high probability, assigned to an overlap of the STM tip with the two frontier orbitals

[49] a) R. F. Dou, D. Y. Zhong, W. C. Wang, K. Wedeking, G. Erker, L. Chi, H. Fuchs, *Journal of Physical Chemistry C* **2007**, *111*, 12139; b) K. Wedeking, Z. C. Mu, G. Kehr, J. C. Sierra, C. M. Lichtenfeld, S. Grimme, G. Erker, R. Frohlich, L. F. Chi, W. C. Wang, D. Y. Zhong, H. Fuchs, *Chemistry-A European Journal* **2006**, *12*, 1618; c) L. Müller-Meskamp, B. Lüssem, S. Karthäuser, M. Homberger, U. Simon, R. J. Waser, *Phys. Conference Series* **2007**, *61*, 855.

located on the ferrocene subunits. The Fe-Fe distances of the calculated structures vary as much as 4 Å over all possible rotamers. This variability could explain the wide error (0.4 nm) found for the experimental distance Δd between two double lobe structures.

Moreover, theoretical calculations evidenced for the "*meso*" compound (*R,S/S,R*), two rotational isomers with identical height of the ferrocenes and one with a height difference of 1.5 Å. On the other hand, three rotamers with respectively a height difference of 0.2 Å, 1.6 Å and 3.3 Å were found for the optical active compounds. Even though these values are valid for the isolated molecule, they support the idea, that for the *R,R* and *S,S* enantiomers at room temperature certain conformations are stable, where the two ferrocene subunits have a different overlap with the STM tip, leading to signals with different intensity. In the adsorbed state the conformational distribution will very likely be perturbed by interaction with the SAM, which might hinder free rotation of the ferrocene subunits. This intuition seems to be supported by experimental evidences and also to explain the wide standard deviation calculated for the height range of single and double lobe structures (respectively of 0.1 and 0.2nm).

As a matter of fact, the peak-to-peak Δd distances 9 and 8 Å experimentally found respectively for Δz=0 and 2.8 Å (double and single lobe structures respectively) indicate a distribution of the possible conformers for both the diastereoisomers (*R,S/S,R* and *S,S*) on the surface not far from the theoretical values of the rotamers *R,S3* and of the *R,R3* (see table E1 and Experimental section E3-E4). This is also in agreement with the RT (20°C) distribution of the conformers at room temperature that was found by theoretical calculations (table E1). In general, the Δz value seems to be larger for the optically active compounds and this means that the two ferrocenes could be located at different heights with respect to the gold surface. For (*R,S*/S,R) a conformation in which the two ferrocene rings are at the same height with respect to the surface should be preferred. Figure 20 shows a cartoon illustrating these possible configurations on the Au(111) surface.

As can be easily observed, the height range (0.28 - 0.24 nm) is rather broad for both structures, (0.18-0.10 nm variation). Such height variability can be attributed, as already widely discussed, to the presence of different rotamers with variable Δz as well as to fluctuation in the oxidation state between ferrocene (Fc) and ferrocenium cation (Fc^+). It has been shown that Fc^+ is observed as protrusions of 0.5 nm, while molecules in which the oxidation state fluctuate between Fc and Fc^+ show an apparent height of 0.2 nm. Furthermore, there is a clear variation in height and lateral distances of the double lobed structures (less evident for single lobe ones) with bias voltage ranging from 1 to 2V. It

seems that the height of the structures gradually increases with the voltage, sometimes achieving a 40% increment. Also the lateral dimension of these structures increases according to the voltage, reaching, in some cases, a 35% increment. We believe that the voltage dependence of the height and dimensions of the double lobe structures could be due to the presence of many rotamers as well as to the modulation of the electronic levels of the ferrocene moieties as already reported by Yokota et al.[50].

In conclusion, DFT simulations show that (I) the intramolecular distance of the two iron atoms is in the same range as the lateral distance of the peaks in the STM measurements, (II) the HOMO of the molecule is located on the ferrocene subunits and (III) the *R,S* and *R,R* isomers adopt different conformations with respect to rotations of the ferrocenes around the bond to the asymmetric carbon atom. Additional electrochemical investigations are required to prove their potential application for QCA.

Electrochemical investigation of Bis-ferrocenes 9 monolayers

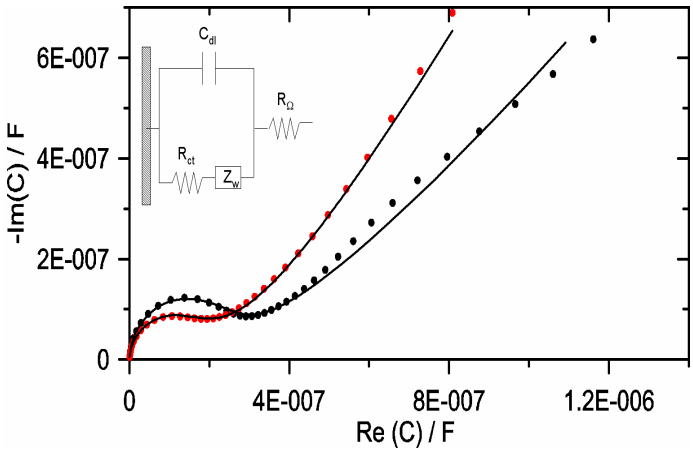
With the aim of demonstrating that the immobilization procedure does not influence the redox properties of the synthesized "two quantum dots" molecules, electrochemical investigations on bis-ferrocenes Monolayers were carried on. The bis-ferrocene **9a-c**, as a mixture of inseparable *(S,S)*-enantiomerically-pure of the two diastereoisomer (ratio 85:15) **9**, was grafted at the surface of a gold electrode, after mixing with 6-mercaptoexan-1-ol (MEO) according to the procedure described in Supp. information.

Electrochemical Impedance Spectroscopy (EIS) and double-potential step chronoamperometry (CA) were used to investigate the packing and redox addressability of **9**/MEO mixed SAMs on Au, prepared from mixtures having various molar ratio of the two species. Typically, rather low double-layer capacitance values were measured in the presence of SAM on the gold electrode, as shown in Figure 22 displaying the complex capacitance spectra (c-plot) obtained in particular for SAMs obtained from 50:50 and 25:50 1b/MEO ratios.

[50] Y. Yokota, K. Fukui, T. Enoki, M. Hara, *Journal Of The American Chemical Society* **2007**, *129*, 6571.

Figure 22 c-plot of thiol compound

- Complex capacitance plot (c-plot) recorded on **9a-c**/MEO mixed film (50:50, red dots; 25:75, black dots) on gold electrode in 0.1 M KCl aqueous solution, at 0.38 V. Full lines: fitting of EIS spectra assuming the Randles' equivalent circuit shown in the inset: R_Ω represents the solution resistance, C_{dl} the double-layer capacitance, R_{ct} the charge-transfer resistance. The Warburg element, associated with mass transport phenomena, was omitted in the present case since the redox species was assumed to remain confined during the experiment at the SAM surface.



The film capacitance was nearly independent on the applied potential, thus excluding any significant rearrangement of the SAM structure upon the application of potential. By contrast, the typical potential-dependent semicircle associated with relatively slow electron transfer (ET) processes was observed in the EIS spectra (Figure E5) that was attributed to the Fc moieties. Simulation and fitting of the EIS spectra obtained at various potentials allowed calculation of the relevant parameters associated with the electric response of the interface: C_{dl} was 5.8 and 11.0 μFcm^{-2} in the case of 50:50 and 25:75 SAMs respectively while the corresponding values for R_{ct} were 41 and 55 kΩ respectively. As expected, as **5** content increases in the SAM, R_{ct} decreases, which corresponds to faster electron transfer kinetics. This is in fact in line with the inverse dependence of R_{ct} on the surface coverage Γ: $R_{ct} = \left(RT/n^2F^2A\Gamma\right)\times\left(1/k^0\right)$. Rather unexpectedly, more blocking properties (i.e., lower capacitance) were also associated to higher **9** content, thus showing that the length of the C6 chain anchoring the bis-ferrocenyl carbazole moiety to the gold surface is adequate to accommodate the bulky head group over the mixed **9a-c**:MEO SAM.

Figure 23 Cyclic voltammetry curves on thiol compound

■ **a)** CV curves of a **9a-c/MEO** (50:50) SAM on gold in 0.1 M KCl aqueous solution. Scan rates: 0.05-5 V s^{-1}, T = 25 °C. Inset: oxidation peak current vs. scan rate plot.; **b)** Potential-dependent (relative) surface coverages of different redox states of **9a-c** calculated with the E° values obtained from the digital simulation of the voltammetric curves.

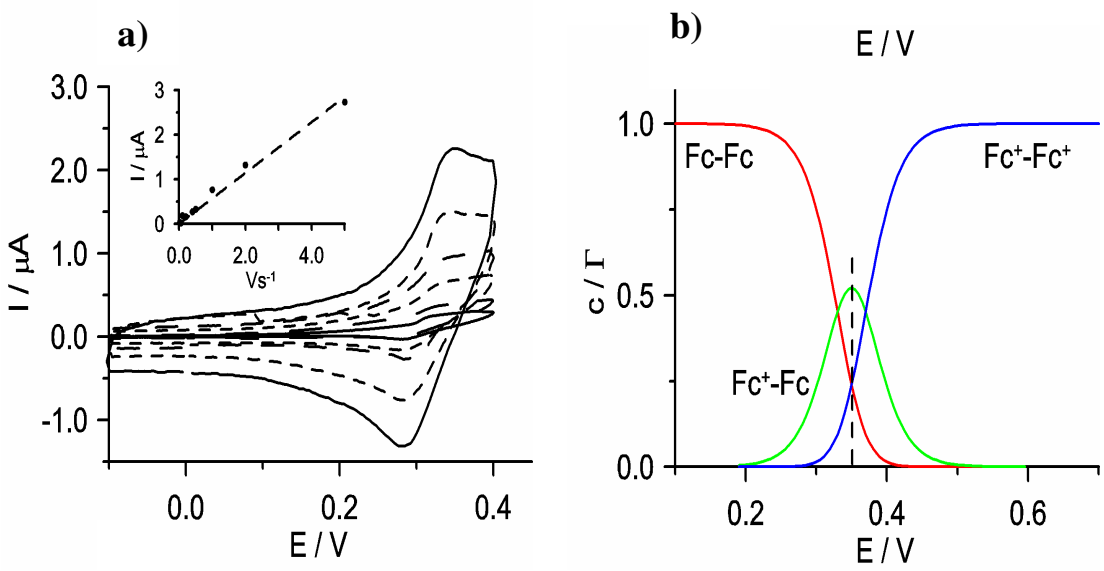


Figure 23 a shows the CV curves obtained for the 50:50 mixed **9**/MEO SAM on Au at various scan rates in the range 0.05-5 Vs^{-1}. The voltammetric current increased linearly with scan rate as typically observed for electron transfer from/to immobilized species. In particular, from the slope in the peak current vs. scan rate plot (inset in Figure 23a), we obtained a surface coverage of 1.2×10^{-12} mol cm^{-2}.

A value of $k^{\circ}\sim10^{2}$ s^{-1} was finally obtained for the heterogeneous ET rate constant by using the above relationship and the experimental values of R_{ct}. Such a low value, together with the rather small time constant of the electrode (~ 0.3 ms, also obtained by fitting of the EIS data), permitted an independent investigation of the heterogeneous ET kinetics to and from immobilized **9** by potential step chronoamperometry (CA)[51]. In such experiments (Figure 22), the electrode potential is stepped between two limiting values while the current is monitored continuously during the experiment over a timescale that fits in that of the relevant electrochemical process[52]. At very short times, double-layer charging dominates the current decay while, at relatively longer timescales, faradaic currents involving

[51] a) C. E. D. Chidsey, *Science* **1991**, *251*, 919; b) G. Fioravanti, N. Haraszkiewicz, E. R. Kay, S. M. Mendoza, C. Bruno, M. Marcaccio, P. G. Wiering, F. Paolucci, P. Rudolf, A. M. Brouwer, D. A. Leigh, *Journal Of The American Chemical Society* **2008**, *130*, 2593.

[52] A. J. Bard, L. R. Faulkner, Electrochemical Methods; *Wiley: New York*, **2001**.

oxidation of the redox centers on the surface are observed. By choosing initial and final potential levels that correspond to the ferrocenyls in their original reduced and fully oxidized states respectively, information concerning the dynamics of the ET processes is obtained from the exponential decay of the CA currents. The CA transients recorded for **9/MEO** on Au when the potential was stepped between 0 V and 0.4V (i.e., more positive than the oxidation potential of **9**) show symmetric backward and forward transients indicating that no structural change occurs under these conditions. All transients, recorded during either the forward or the backward steps, displayed a short-lived (~ 0.6 ms) component associated with double-layer charging in agreement with the very small time constant of the electrode as given by EIS. A relatively slower component (with τ ~ 6 ms) was finally observed in both transients, associated to the oxidation (in the forward step) and re-reduction (in the backward one) of the ferrocenyl moieities in **9**, in agreement with the EIS experimental findings.

In conclusion, the electrochemical investigation indicates that, both in solution and immobilized at the electrode surface, **9** undergoes fast (Nernstian) electron transfer processes generating, in the positive potential region, either the full oxidized Fc^+-Fc^+ or the partly oxidized Fc^+-Fc species. Calculations of the surface coverage of the various redox states of **9a,c** as a function of potential (Figure 23b) shows that, within a narrow potential range centered at 0.35 V, partly oxidized Fc^+-Fc represents the prevailing species, while fully oxidized Fc^+-Fc^+ prevails at E > ~ 0.4 V.

Conclusion

Looking for a new class of molecules to be useful for molecular computing applications, some bis-ferrocene derivatives were synthesized and basic studies on their electrochemical properties as well as on their self-organization capability on solid surfaces performed.

Electrochemical studies in liquid and in ordered self-assembled monolayers (SAMs) confirmed their attitude to undergo fast (Nernstian) electron transfer processes generating, in the positive potential region, either the full oxidized Fc^+-Fc^+ or the partly oxidized Fc^+-Fc species.

Scanning Tunneling Microscopy (STM) and density functional theory (DFT) calculations showed their molecular orientation, the existence of many rotamers as well as the location of the HOMO orbitals.

From the collected experimental observations and theoretical analysis we confidently indicate this class of molecules as very interesting candidates for QCA implementation.

Experimental section of Chapter 1

General information: All the reaction were carried out under nitrogen atmosphere.
^{1}H NMR spectra were recorded on Varian 200 MHz or Varian 300 MHz spectrometers. chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian 50 MHz or Varian 75 MHz spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were performed at an ionizing voltage of 70 eV. Analytical gas chromatography (GC) was performed on a Hewlett-Packard HP 6890 gas chromatograph with a flame ionization detector and split mode capillary injection system, using a Crosslinked 5% PH ME Siloxane (30 m) column or a Megadex5 chiral (25 m) column. Analytical high performance liquid chromatograph (HPLC) was performed on a HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190-600 nm), using Daicel Chiralcel^{TM} IC column (0.46 cm I.D. x 25 cm) (Daicel Inc.), HPLC grade isopropanol and *n*hexane were used as the eluting solvents. All the reactions were carried out under a nitrogen atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents. Anhydrous CH_2Cl_2 were purchased from the Fluka. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using gravity-fed chromatography, fash chromatography both with 240-400 mesh silica gel and preparatory TLC. Enantioenriched ferrocenyl alcohols **1** was obtained from Johnson Matthey, and was prepared by the reduction of acetyl ferrocene with PPHOS ligand.[27] Carbazole was purchased by Aldrich an purified before using by crystallization in boiling ethanol. $InBr_3$ 99,99% was purchased by Aldrich and introduced into the reaction flask as a solid, or using a 0.33M solution in anhydrous CH_3CN. PTSA was purified by crystallization in boiling AcCN.

Preparation of starting Materials

(1-hydroxyethyl)ferrocene 1.

Acetylferrocene (2.880 g, 12 mmol) was dissolved in MeOH (40 mL) and put to 0°C, then $NaBH_4$ (0.908 g, 24 mmol) was added as a solid in portion. The red solution was stirred for 20min at 0°C and warmed at romm temperature for 12h until judged complete by TLC (R_f

0.5, cyclohexane:diethylether 4:7), then the reaction was quenched with water-ice mixture. MeOH was evaporated under reduced pressure, and the resulting mixture was extracted with Et_2O (2 x 5mL). The combined organic phases were dried over Na_2SO_4, evaporated under reduced pressure to give a orange solid. The solid was triturated with a solution of hexane:diethylether (20:1, 10mL) and filtered. The resulting yellow solid was utilized without further purification for successive reactions. Yield 76%.
Yellow solid, mp = 80-82°C.

9-benzyl-Carbazole 12:

To a mixture of carbazole (0.87 g, 5 mmol) in dry THF (5mL), NaH (0.24 g, 10 mmol) was slowly added in portions. The mixture was stirred during 1 hour at room temperature, then benzylbromide (0.89 mL, 7.5 mmol) was added dropwise. The resulting mixture was stirred for 5 hours at room temperature until judged complete by TLC (R_f 0.44, cyclohexane:dichloromethane 4:1), then the reaction was quenched with water-ice mixture. THF was evaporated under reduced pressure, and the resulting mixture was extracted with Et_2O (2 x 5mL). The combined organic phases were dried over Na_2SO_4, evaporated under reduced pressure to give a white solid. The solid was triturated with hexane (10mL) and the mixture was filteredand utilizing without further purification for successive reactions. Yield 62%.
White solid; M. p. = 139°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.14 (d, 2H, J = 7.5Hz); 7.74-7.14 (m, 11H); 5.54 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 140.5 (2C), 137.0, 128.6 (2C), 127.2, 126.2 (2C), 125.7 (2C), 122.9 (2C), 120.3 (2C), 119.1 (2C), 108.8 (2C), 46.2. ESI-MS: rt: 12.34 min; no ionization.

9-(6-iodohexyl)-9H-carbazole 13.

To a mixture of carbazole (0.5 g, 2.99 mmol) in dry THF (6 mL), NaH (0.25 g, 6 mmol). was slowly added in portions. The mixture was stirred during 1 hour at room temperature, then the resulting suspension was transferred to a dropping funnel. The sodium carbazole suspension was added in 10 min to a solution in dry THF (3mL) of 1,6-diodohexane (3 ml, 18 mmoli). The mixture was stirred for further 2 hours at room temperature until judged complete by TLC (R_f = 0.55, cyclohexano:dichloromethane 3:1), then the reaction was quenched with water and ice. THF was evaporated under reduced pressure, and the resulting mixture was extracted with Et_2O (2 x 5mL). The combined organic phases were

dried over Na_2SO_4, evaporated under reduced pressure to give an oil purified by Flash chromatografy (hexane to hexane:dichoromethane 10:1). Yield 83%.

White solid; M. p. = 65-69°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.00 (d, 2H, J = 7.8 Hz); 7.35 (dt, 2H, J = 6.9, 1.2 Hz); 7.25 (d, 2H, J = 8,4 Hz); 7.12 (dt, 2H, J = 8.1, 1.2 Hz); 4.11 (t, 2H, J = 6.9 Hz); 3.02 (t, 2H, J = 6.9 Hz); 2.96 (t, 2H, J = 6.9 Hz);1.72-1.54 (m, 3H); 1.39-1.18 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 140.08 (2C), 125.4 (2C), 122.5 (2C), 120.1 (2C), 118.6 (2C), 108.4 (2C), 42.5, 33.0, 29.9, 28.5, 25.9, 7.0. ESI-MS: (M). rt: 16.03 min; m/z: 378; 132.2; 105.2.

***Preparation of Bis-fererrocene molecules via Friedel-Crafts reaction of bi-funtionalizate aromatics with (1-hydroxyethyl)ferrocene* 1.**

1,3-dimetoxy-4,6-bis-(1-ethylferrocene)benzene 5:

To a solution of 1,3-dimetoxy-benzene **2** (0.013 mL, 0.1 mmol) and $InBr_3$ (0.33M AcCN, 0.030 mL, 0.01 mmol) in CH_2Cl_2 (1 mL) 1-(hydroxyethyl)ferrocene **1** (0.051 g, 0.22 mmol) was introduced at room temperature. The resulting solution was stirred at room temperature for 2h then the reaction was quenched with water. The aqueous phase was exctracted with diethylether (3 x 5 mL). The organic phases were reunited, dried over Na_2SO_4, and evaporated at reduced pressure to give a crude product carfully purified by flash chromatography (cyclohexane:diethylethere 99:1). Yield 95% as a mixture of two diasteroisomers.

^{1}H-NMR (CDCl3, 200 MHz) δ: 6.68 (d, J = 6 Hz, 1H), 6.40 (s, 1H), 4.16-3.86 (m, 26H), 1,12 (d, J = 7.2 Hz, 6H). ESI-MS: rt: 24.60 min; m/z: 562.

1,9-bis-(1-ethylferrocene)-5,5-diphenyl-dipyrromethane 6:

To a solution of 5,5-diphenyl-dipyrromethane **3** (0.030 g, 0.1 mmol) and $Bi(OTf)_3$ (0.007 g, 0.01 mmol) in CH_2Cl_2 (1 mL) 1-(hydroxyethyl)ferrocene **1** (0.051 g, 0.22 mmol) was introduced at low temperature (-55°C). The resulting solution was stirred at low temperature (-45:-55 °C) for 2h until disappearance of **1** by TLC (R_f = 0.85 , cyclohexane:diethylether 4:1) then the reaction was quenched with water. The aqueous phase was exctracted with diethylether (3 x 5 mL). The organic phases were reunited, dried over Na_2SO_4, and evaporated at reduced pressure to give a crude product carfully purified by flash chromatography. Yield 42% as a mixture of two diasteroisomers.

^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.08 (bs, 2H), 7.32-7.17 (m, 10H), 5.85-5.79 (m, 2H), 4.25-4.00 (m, 18H), 3.91 (q, J = 7.2 Hz, 2H), 1.40 (d, J = 7.2 Hz, 6H); ^{13}C-NMR ($CDCl_3$,

75 MHz) δ: 146.2 (2C), 136.1 (2C), 133.6 (2C), 132.4, 130.0 (2C), 129.0 (2C), 128.2 (2C), 127.6 (2C), 126.5, 109.2 (2C), 103.6 (2C), 93.2 (2C), 55.8, 37.0 (2C), 21.9 (2C); ESI-MS: rt: 31.00 min; m/z: 722.

1,4-bis-(1-ethylferrocene)-pyrrole 7:

To a solution of distilled pyrrole **4** (0.050 mL, 0.5 mmol) and $InBr_3$ (0.33M AcCN, 0.150 mL, 0.05 mmol) in degassed CH_2Cl_2 (5 mL), 1-(hydroxyethyl)ferrocene **1** (0.115 g, 0.5 mmol) was introduced at room temperature. The resulting solution was stirred at room temperature for 1h until disappearance of **1** by TLC, then the reaction was quenched with water. The aqueous phase was exctracted with diethylether (3 x 5 mL). The organic phases were reunited, dried over Na_2SO_4, and evaporated at reduced pressure. The crude mixture was pumped under vacuum to eliminate the pyrrole in excess and carfully purified by flash chromatography. Yield 31% as a mixture of two diasteroisomers.

^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.81 (bs, 1H), 5.82 (d, 2H), 4.10 (m, 18H), 3.79 (q, J 0 7.2 Hz, 2H), 1.63 (d, J = 7.2 Hz, 6H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 134.9 (2C), 103.5 (2C), 93.5 (2C), 68.5 (10C), 67.5 (2C), 67.4 (2C), 67.3 (2C), 66.1 (2C), 32.2 (2C), 21.4 (2C).

(*R*)-9-(1-ethylferrocene)-carbazole 10 :

To a solution of carbazole **8** (0.042 g, 0.25 mmol) in CH_2Cl_2 (1 mL) (R)-1-(hydroxyfethyl)ferrocene (0.023 g, 0.1 mmol) was added, then AuCl (0.002 g, 0.01 mmol) was introduced in the solution at room temperature. The resulting solution was stirred at rt 3 h until judged complete by TLC (R_f = 0.75, cyclohexane:dichloromethane 3:1), then the reaction was quenched with water. Dichloromethane was added, then the organic phase was separated. The aqueous phase was exctracted with dichloromethane (3 x 5 mL). The organic phases were reunited, dried over Na_2SO_4, and evaporated at reduced pressure to give a crude product carfully purified by flash chromatography (cyclohexane:dichloro methane 6:1). Yield 77%, 95% ee.

Yellow solid; mp = 163-164°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.12 (s, 2H), 7.42 (s, 4H), 6.08 (q, J = 7.2, 1H), 4.44-4.03 (m, 9H), 1.92 (d, J = 7.2, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 139.3 (4C), 125.2 (2C), 120.1 (2C), 118.6 (2C), 110.0 (2C), 88.1, 69.0 (2C), 67.3, 67.1, 50.2, 17.7; ESI-MS: rt : 15.01 min; m/z: 379.

HPLC analysis AD: isocratic, 85:15 (hexane: *i*-PrOH) flow 0.8mL/min. TM: 6.01 min; tm: 9.69 min.

***Optimized procedure for the addition of N-alkylated carbazole molecules to (R)-(1-hydroxyethyl)ferrocene* 1.**

To a mixture of nucleophile (0.5 mmol) and $Bi(OTf)_3$ (0.328 g, 0.50 mmoli) in CH_2Cl_2 (3 mL) was introduced dropwise via syring pump a solution of (*R*)-1-(hydroxyethyl)ferrocene (0.253 g, 1.1 mmol) in CH_2Cl_2 (2 mL) at -15°C during of 2 hours. The resulting mixture was stirred at -15°C for 20h until judged complete by TLC, then the reaction was filtered and the solid was washed with CH_2Cl_2 one time. Organic solution was quenched with water. The aqueous phase was exctracted with CH_2Cl_2 (3 x 5 mL). The organic phases were reunited, dried over Na_2SO_4, and evaporated at reduced pressure to give a crude product purified by chromatography.

9-benzyl-3,6-bis(1-ethylferrocene)-9H-carbazole 15:

Prepared according to the optimized procedure from 9-benzyl-carbazole **12** (0.129 g, 0.50 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:dichloromethane 4:1) and purified by gravimetric chromatography (before cyclohexane, then from cyclohexane: dichloromethane 20:1 to cyclohexane:dichloromethane 9:2) or preparative TLC (3:1 hexane:dicholoromethane). Yield 30%, $[\alpha]_D$ = -73° (c 0.7, $CHCl_3$).

Yellow sticky solid. ^{1}H-NMR (CDCl3, 300 MHz) δ: 7.86 (s, 2H), 7.22-7.20 (m, 5H), 7.16-7.10 (m, 4H), 5.41 (s, 2H), 4.26-4.03 (m, 20H), 1.68 (d, 6H, J=7.4Hz). 13C NMR (CDCl3, 50 MHz) δ: 139.6 (2C), 138.5 (2C), 137.4, 128.7 (2C), 127.3, 126.5 (2C), 125.1 (2C), 122.8 (2C), 118.4 (2C), 108.5 (2C), 95.2 (2C), 68.6 (10C), 68.0 (2C), 67.5 (2C), 66.8 (2C), 66.4 (2C), 46.7, 39.8 (2C), 23.1 (2C). ESI-MS: rt: 58.02 min; m/z: 682, 681, 611, 591.

3,6-bis(1-ethylferrocen)-9-(6-iodohexyl)-9H-carbazole 19 :

Prepared according to the optimized procedure from 9-(6-iodohexyl)-9H-carbazole **13** (0.038 g, 0.1 mmol), until judged complete by TLC (R_f = 0.3 (cyclohexane:dichloro methane 3:1) and purified by gravimetric chromatography (before cyclohexane, then from cyclohexane:dichloromethane 20:1 to cyclohexane: dichloromethane 9:2) or Preparative TLC (3:1 hexane:dicholoromethane). $[\alpha]_D$ = -91° (c 0.6, $CHCl_3$).

Yellow solid. M. p. = 60-69°C. ^{1}H NMR($CDCl_3$, 300 MHz) δ: 7.83 (s, 2H); 7.27-7.23 (m, 4H); 4.25-4.02 (m, 20H); 3.13 (t, 2H, J=7Hz); 1.89-1.38 (m, 10H); 1.68 (d, 6H, J=7.4Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 139.3 (2C), 138.0 (2C), 124.9 (2C), 122.6 (2C), 118.3 (2C), 108.1 (2C), 95.3 (2C), 68.5 (10C), 68.9 (2C), 67.5 (2C), 66.8 (2C). 66.4 (2C), 42.9, 39.8

(2C), 33.2, 30.2, 28.9, 26.2, 23.1 (2C), 6.9. ESI-MS: rt: 88.87 min; m/z: 802.1, 801.2, 799.1, 400.5.

Cleavage of benzyl group

3,6-bis(1-ethylferrocen)-9H-carbazole 17.

Compounds 9-benzyl-3,6-bis(1-ethylferrocene)-9H-carbazole **15a-c** (0,068 g. 0.1 mmol) synbthesized by optimized procedure were dissolved in a mixture of DMSO (1.0 mL), THF (1.0 mL) and tBuOK solid (0.224 g, 2,0 mmoli) at room temperature. After the reaction mixture was bubbled dried O_2 (over P_2O_5) until judged complete by TLC (R_f = 0.2 , hexane:dichloromethane 2:1). The reaction was quenched with water and THF was removed at reduced pressure, then the resulting crude was extracted with Et_2O (3 x 5 mL) and the organic phases were collected: The resulting organic phase was washed with a water solution of HCl 0.1M (2 x 5 mL) to remove DMSO, then the organic phase was dried over Na_2SO_4, and evaporated under reduced pressure to give a crude product purified by flash chromatography (cyclohexane:dichloromethane 2:1) or preparative TLC (hexane:dichloromethane 3:1). Yield 83%, 99% ee (S,S), 85:15 d.r.

Yellow solid; M. p. =. 77-85°. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.86-7.18 (m, 7H); 4.26 (br, 2H); 4.16-4.02 (m, 20H); 1.67 (d, 6H, J=7.2Hz). ^{13}C NMR ($CDCl_3$, 50 MHz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 138.6 (2C), 138.3 (2C), 125,1 (2C), 123.1 (2C), 118.2 (2C), 110.2 (2C), 95.2 (2C), 68.5 (10C), 68.0 (2C), 67.5 (2C), 66.8 (2C), 66.4 (2C), 39.8 (2C), 23.1 (2C). ESI-MS: rt: 27.55 min; m/z: 593.0 592.1, 591.0. RF = 0.23 (hexano/dichloromethane 2/1).

HPLC analysis IC: gradient from 99:1 (hexane: *i*-PrOH) to 90:10, flow 0.5mL/min, 30°C. TM (*S,S*): 35.79 min; *meso* 42.55 min; tm (*R,R*): 48.71 min.

Synthetic strategy to funtionalize bis-ferrocene carbazole on gold surface:

S-6-[3,6-bis(1-ethyllferrocen)-9H-carbazol-9-yl]-6-hexylethanethioate 20.

Compound (3,6-bis(1-ethyilferrocene)-9-(6-iodohexyl)-9H-carbazole) **19** (0.42 g, 0.56 mmol) was dessolved in DMF (2 mL) and KSCOCH3 (0.072 g, 0.62 mmol) was added. The misture was stirred at room temperature overnight and checked by TLC (R_f = 0.3 cyclohexane:dichloromethane 3:1). The reaction was quenched by adding HCl 1M (10mL) then was diluted with CH_2Cl_2 (10mL). The mixture was extracted with HCl 0.1 M (2 x 5 mL) and the organic phase was separated, dried over Na_2SO_4 ed evaporate to a rieduced

pressure to give a crude product used without any further purification for successive reaction. Quantitative yield.

Yellow oil. ^{1}H-NMR (CDCl3, 300 MHz) δ: 7.85 (s, 2H); 7.27-7.22 (m, 4H); 4.27-3.94 (m, 20 H); 2.84 (t, 2H, J=6.9Hz); 2,32 (s, 3H); 1.82-1.38 (m, 8H); 1,70 (d, 6H, J=7.8Hz); 0.92 (t, 2H, J=7.2Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 197.7, 139.1 (2C), 137.8 (2C), 124.7 (2C), 122.4 (2C), 118.2 (2C), 108.0 (2C), 95.2 (2C), 68.4 (10C), 67.9 (2C), 67.3 (2C), 66.7 (2C), 66.3 (2C), 42.8, 39.6 (2C), 30.5 (2C), 29.2, 28.8, 28.3, 26.6, 23.0 (2C).

***(S,S)*-6-[3,6-bis(1-ethylferrocen)-9H-carbazol-9-yl]-6-hexan-1-thiol 9 :**

Compound (*S,S*)-S-6-[3,6-bis(1-ethyllferrocen)-9H-carbazol-9-yl]-6-hexylethanethioate **20**, (0.040 g, 0.053 mmol) was dissolved in a carefully degassed (freezing pump) mixture constituted by iPrOH:THF:H_2O (5:12:3). Solid KOH (0.218 g, 3.89 mmol) was added, and the misture was stirred a 60 °C for 3 h until judged complete by TLC (R_f = 0.3, cyclohexane:dichloro methane 3:2), then the reaction was quenched with HCl 1 M added until pH = 7. The mixture was extracted with Et_2O (3 x 5 mL), the organic phases were reunited, washed with water, dried over Na_2SO_4 and evaporated under reduced pressure to give a crude product oil purified by Flash Chromatography (cyclohexane:dichloromethane 3:1).

Yield 60%.

Yellow solid. M. p. = 65.5-87 °C. 1H-NMR (CDCl3, 200 MHz) δ: 7.83 (s, 2H); 7.27-7.22 (m, 4H); 4.25-3.98 (m, 20 H); 2.55 (t, 2H, J=7.2Hz); 2.32 (s, 2H); 1.89-0.8 (m, 10H); 1.68 (d, 6H, J=7Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 139.3 (2C), 137.9 (2C), 124.9 (2C), 122.6 (2C), 118.3 (2C), 108.2 (2C), 95.3 (2C), 68.5. (10C), 68.0 (2C), 67.5 (2C), 66.8 (2C), 66.4 (2C), 43.0, 39.7 (2C), 30.5, 28.9, 28.8, 28.6, 26.9, 23.1 (2C).

Chemicals

The novel ferrocene derivative *(S,S)*-6-[3,6-bis(1-ethylferrocen)-9H-carbazol-9-yl]-6-hexan-1-thiol **9** used for the study was synthesised. Commercially available Au(111) on mica substrates were purchased from ‘‘Molecular Imaging’’; ethanol and hexane-1,6-dithiol were purchased from Aldrich.

Electrochemistry

- Materials

All chemicals used were reagent grade. Tetrabutylammonium hexafluorophosphate (TBAH, Fluka) was used as supporting electrolyte as received. For the voltammetric experiments, the solvent was distilled into the electrochemical cell, prior to use, by a trap-to-trap procedure. Electrochemical impedance spectroscopy (EIS) and chronoamperometry (CA) experiments were carried out in aqueous (Millipore) solutions with 0.1 M KCl as supporting electrolyte.

- Instrumentation and Measurements

In the voltammetric experiments, a one-compartment electrochemical cell of airtight design was used, with high-vacuum glass stopcocks fitted with Viton (DuPont) O-rings to prevent contamination by grease. The connections to the high-vacuum line and to the Schlenck flask containing the solvent were made by spherical joints fitted with Viton O-rings. The pressure measured in the electrochemical cell prior to performing the trap-to-trap distillation of the solvent was typically $1.0–2.0 \times 10^{-5}$ mbar. The working electrode consisted of platinum disk ultramicroelectrodes (with radii from 5 to 62.5 μm) also sealed in glass. The counter electrode consisted of a platinum spiral, and the quasi-reference electrode was a silver spiral. The quasi-reference electrode drift was negligible for the time required by a single experiment. Both the counter and reference electrodes were separated from the working electrode by ~ 0.5 cm. Potentials were measured with the ferrocene or decamethylferrocene standards and are always referred to saturated calomel electrode (SCE). $E_{1/2}$ values correspond to $(E_{pc} + E_{pa})/2$ from CV. Ferrocene (or decamethylferrocene) was also used as an internal standard for checking the electrochemical reversibility of a redox couple. The temperature dependence of the

relevant internal standard redox couple potential was measured with respect to SCE by a nonisothermal arrangement. Voltammograms were recorded with an AMEL Model 552 potentiostat or a custom-made fast potentiostat controlled by either an AMEL Model 568 function generator or an ELCHEMA Model FG-206F. Data acquisition was performed by a Nicolet Model 3091 digital oscilloscope interfaced to a PC. Temperature control was accomplished within 0.1 °C with a Lauda thermostat. The minimization of ohmic drop was achieved through the positive feedback circuit implemented in the potentiostat.
ESI and CA experiments were performed using a two-compartment electrochemical cell also fitted with a saturated calomel electrode (SCE) and a platinum spiral as counter electrode with an Autolab Model PGSTAT 30 (ECO CHEMIE).

- Digital simulation of electrochemical experiments

The simulations of the electrochemical experiments were carried out by the DigiSim 3.0 software by Bioanalytical Systems Inc. All the fitting parameters were chosen so as to obtain a visual best fit over a 10^2–10^3-fold range of scan rates.

Scanning Probe Microscopy

VT UHV-STM. An Omicron Variable Temperature Ultra High Vacuum - Scanning Tunnelling Microscopy (VT UHV-STM) system was used to perform topographical and spectroscopic measurements (I/V). Experiments were carried out at room temperature and at UHV conditions (10^{-10} mbar). The STM tips used were commercially available Pt/Ir tips.

Sample Preparation

- Formation of a SAM of hexane-1,6-dithiol on the substrate

To immobilise the bisferrocene molecules on the Au(111) substrate, we initially prepared a self assembled monolayer (SAM) of hexane-1,6-dithiol on Au(111) surface by chemisorption process. Au(111) substrates were incubated for 20 hours into a 10^{-3} M hexane-1,6-dithiol in ethanol. The samples were washed by ethanol and dried using Nitrogen.

■ Preparation of Bisferrocene molecules on a SAM

Subsequently, the substrates were incubated in a 10^{-3} M bisferrocene solution in ethanol for a duration of 2 hours for the low coverage system (topographical details), and 10 hours for the high coverage system (spectroscopic details). Initially a racemic mixture was used, and later one of the diastereoisomer (*S,S*) of the optically active bisferrocene molecules was used. The dithiol SAM drives the chemisorption of single bisferrocene molecules and/or the formation of more ordered bisferrocene domains, by decreasing the rotational degree of freedom of the bisferrocene molecules that was observed in unmixed SAMs. After the incubation processes, the sample was dried using N_2, placed immediately into the UHV-STM and annealed in-situ at 120°C for 1 hour.

Photophysical properties

Figure E1 Absorption and emission spectra

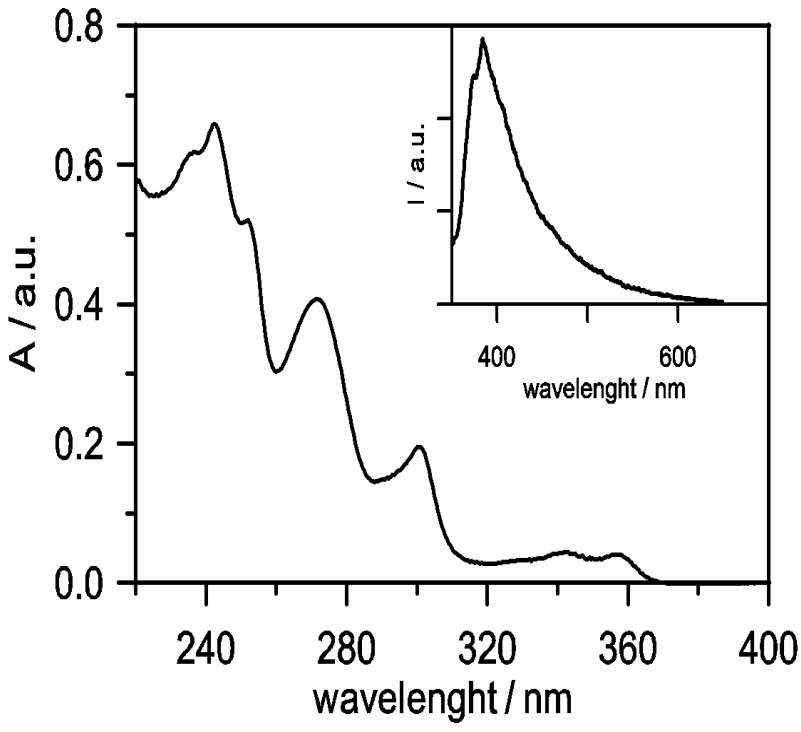


Figure E2 Cyclic Voltammetry curves to compare carbazole 9 and bis 14a-b

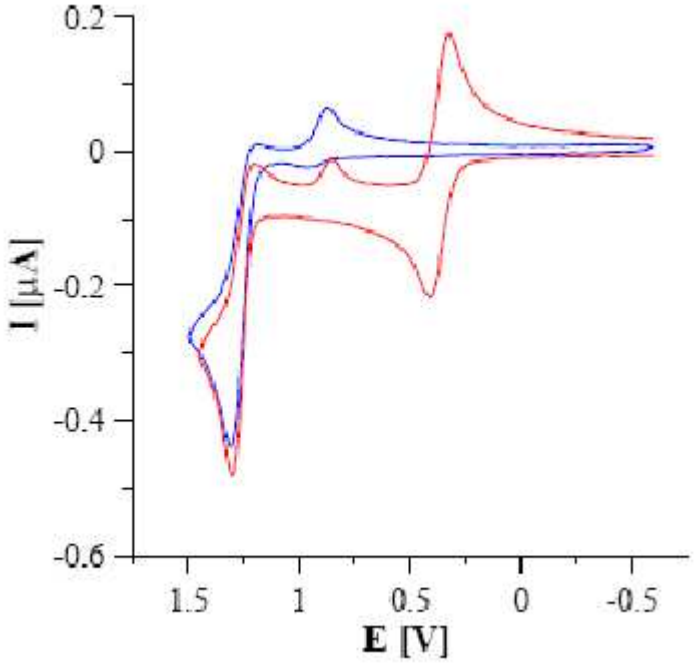


Figure E3 EIS spectra of Thiol derivate as iseparable mixture of two diasteroisomer.

- EIS spectra, at different potentials, of 9a-c/MEO·SAM on Au. Solution: aqueous 0.1 M KCl. *T* = 25 °C. The out-of-phase component of the impedance, –Z″, plotted vs. the in-phase one, Z′ – Z″ and Z′ being parametric functions of the frequency (Nyquist plot) – is shown.. The Warburg element, associated with mass transport phenomena, was omitted in the present case since the redox species was assumed to remain confined during the experiment at the SAM surface. The electrical parameters were evaluated by fitting procedures, using the CNLS method described by Boukamp.

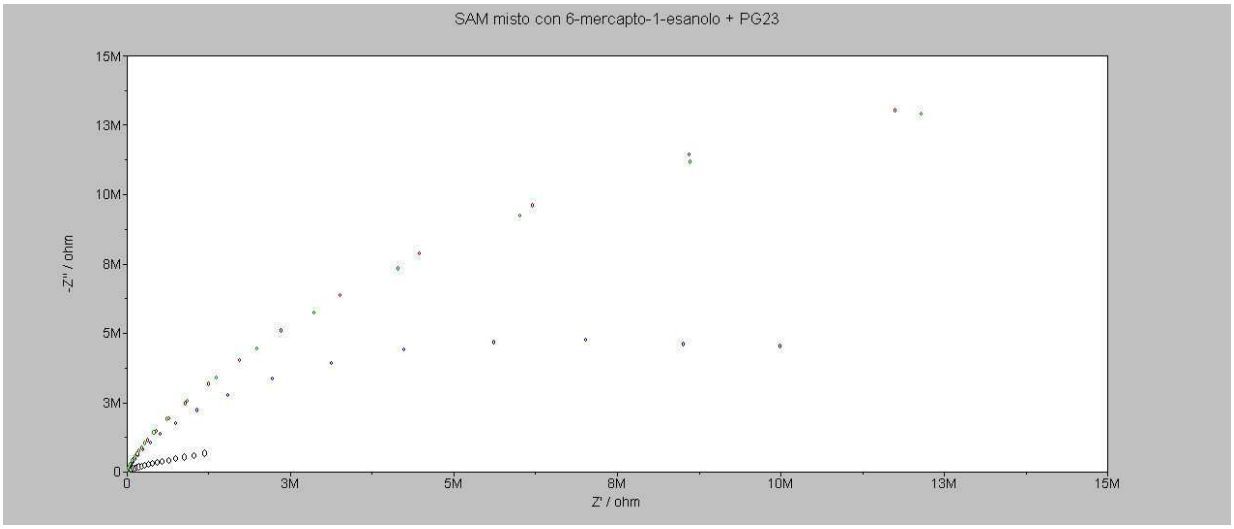


Figure E4 Randles equivalent circuit describing the electrical response of the electrochemical interface.

- In the circuit, R_Ω represents the solution resistance, C_{dl} the double layer capacitance, R_{ct} the charge transfer resistance (related to the exchange current i_0 and standard rate constant) and Z_W the Warburg element, describing the time (frequency) dependence of mass transport.

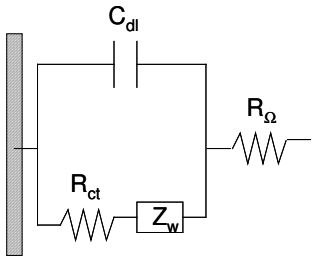


Figure E5. **CA**

- CA transient recorded for the mixed SAM 9a-c/MEO on gold. E = 0.38 V; step duration: 0.1 s. Solution: aqueous 0.1 M KCl, T = 25 °C.

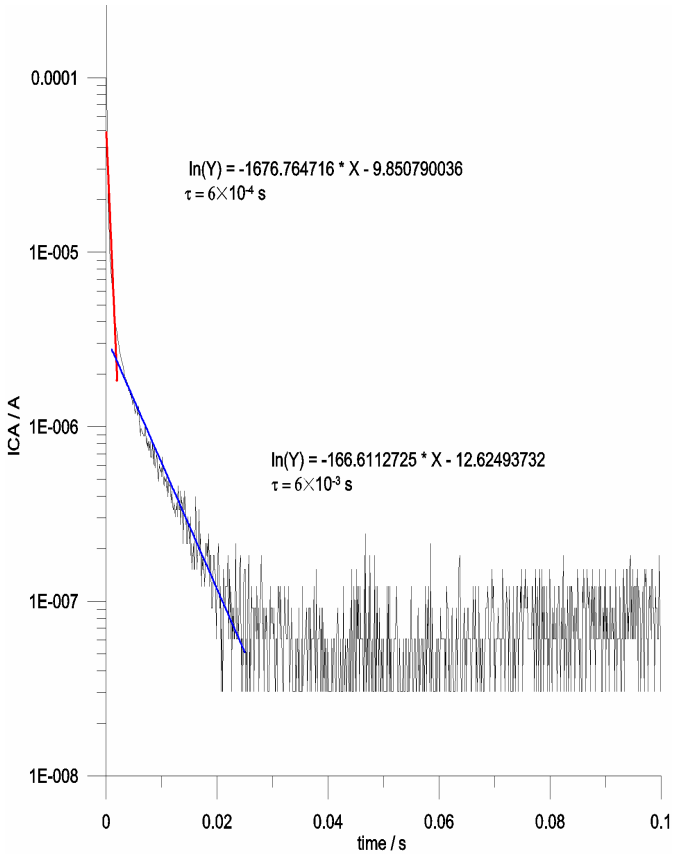
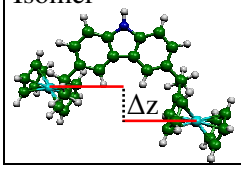


Table E1. Conformational analysis of the most stable rotamers of the *R,S* and *R,R* isomers. Syn and anti orientation refers to the relative position of the ferrocenes with respect to the carbazole plane. Iron-iron distances, as well as Δz values, which describe the difference in position of the iron atoms along the N-H direction are given in Angstrom. The product distribution at room temperature follows a Boltzmann analysis.

Isomer 	Orientation w.r.t Carbazole	Fe-Fe [Å]	Δz [Å]	ΔE (B3-LYP) [kcal/mol]	Distribution at RT [%]	ΔE (SCS-MP2) [kcal/mol]	Distribution at RT [%]
RS 1	Syn	13.2	0.1	3.68	<1	3.09	<1
RS 2	Anti	12.3	1.5	0.00	66	0.03	49
RS 3	Syn	10.2	0.0	0.25	34	0.00	51
RR 1	Anti	13.6	0.2	1.39	5	0.95	10
RR 2	Syn	11.8	3.3	0.00	46	0.00	50
RR 3	anti	11.4	1.6	0.20	39	0.13	40

Chapter 2

Facile access to optically active ferrocenyl derivatives with direct substitution of the hydroxy group catalyzed by indium tribromide

Introduction

In this chapter I present the chemistry of ferrocene in reactions involving ferrocenyl acohols and various nucleophiles. The chemistry described herein has been the basis of my work both on carbazole reported in the previous chapter so I considered relevant discuss these results obtained previously to my arrival in Cozzi's group.

The discovery of ferrocene and elucidation of its structure could be considered the starting point for the modern organometallic chemistry. The ferrocene framework is widely used in asymmetric catalysis[1] because it is able to incorporate a stereogenic plane with stereocenters as shown in Figure 1

Figure 1 Example of planar enantiomers

Planar stereogenicity and stereocenters often act cooperatively in a variety of stereoselective transformations.[2] The bio-organometallic chemistry of ferrocene has also been developed over recent years as a rapidly growing field.[3] Since the pioneering work of Ugi[4] it is generally accepted that ferrocenyl derivatives with a leaving group in the α position undergo nucleophilic substitution with the complete retention of the configuration (Scheme 1).[5] Typical S_N1 type reaction on ferrocene derivates.

---

[1] R. G. Arrayás, J. Adrio, J. C. Carretero, *Angew. Chem. Int. Ed.* **2006**, *45*, 7674 See also: a) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159; b) P. J. Guiry, C. P. Saunders, Adv. Synt. Catal. **2004**, *346*, 497; c) O. B. Sutcliffe, M. R. Bryce, *Tetrahedron: Asymmetry* **2003**, *14*, 2297; d) T. J. Colacot, *Chem. Rev.* **2003**, *103*, 3101; e) R. C. J. Atkinson, V. C. Gibson, N. J. Long, *Chem. Soc. Rev.* **2004**, *33*, 313; f) *Ferrocenes. Homogeneous Catalysis, Organic Synthesis, Material Science* (Eds. A. Togni, T. Hayashi), VCH, Weinheim, **1995.**

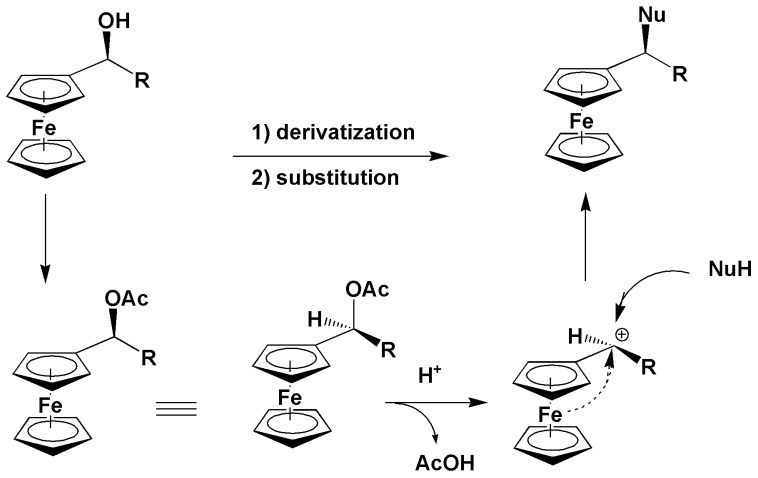
[2] T. Hayashi, K. Yamamoto, M. Kumada, *Tetrahedron Lett.* **1974**, *15*, 4405.

[3] D. R. van Staveren, N. Metzler-Nolte, *Chem. Rev.* **2004**, 104, 5931.

[4] a) D. Marquarding, H. Klusacek, G. W. Gokel, P. Hoffmann, I. Ugi, *J. Am. Chem. Soc.* **1970**, *92*, 5389; b) G. Gokel, D. Marquarding, I. Ugi, *J. Org. Chem.* **1972**, *37*, 3052.

[5] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Taijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062.

Scheme 1 Preparation of ferrocenyl products by indirect substitution.



This paradigm is extensively used in the preparation of chiral ferrocenyl derivatives.[6] Normally, the approach of nucleophiles to the reactive center of a prostereogenic ketone or aldehydes is the most studied and important reaction in organic chemistry. The reaction occurs through the presence of a partial positive charge on the attacked carbon atoms. Aldehydes and ketones are weak electrophiles, and normally they are activated toward the nucleophilic attack by the use of Lewis acid or organometallic complexes. Less studied and explored is the possibility to use stronger electrophiles, although iminium[7] and oxonium[8] ion are generated and employed in the presence of Lewis acids. From pioneering studies of Olah, the knowledge about carbocation has tremendously increased.[9] However, in the presence of a relatively poor leaving group, such as alcohol, racemization occurs in absence of good nucleophiles.[10] A variety of different nucleophiles, such as phosphines, and amines, can be used with ferrocenyl acetate.[4-6] Although Lewis acids were described as facilitating these reactions, even with carbon nucleophiles, stoichiometric amounts of Brønsted (AcOH) or Lewis acids (BF_3)[11] are normally used as shown in Scheme 1.

---

[6] Chiral phosphines ligands derived from Ugi's amine: a) BoPhoz: N. W. Boaz, S. D. Debenham, E. B. Mackenzie, S. E. Large, *Org. Lett.* **2002**, *4*, 2421, JosiPhos: see, ref. 5. TaniaPhos: b) T. Ireland, K. Tappe, G. Grossheimann, P. Knochel, *Chem Eur. J.* **2002**, *8*, 843; c) F. Spindler, C. Malan, M. Lotz, M. Kesselgruber, U. Pittelkow, A. Rivas-Nass, O. Briel, H.-U. Blaser, *Tetrahedron: Asymmetry* **2004**, *15*, 2299; d) WalPhos: T. Sturm, W. Weissensteiner, F. Spindler, *Adv. Synt. Catal.* **2003**, *345*, 160; e) Trap: M. Sawamura, H. Hamashima, M. Sugawara, R. Kuwano, Y. Ito, *Organometallics*, **1995**, *14*, 4549; f) PigiPhos: P. Barbaro, A. Togni, *Organometallics*, **1995**, *14*, 3570.

[7] J. T. Shaw, K. A. Woerpel, *Tetrahedron* **1999**, *55*, 8747.

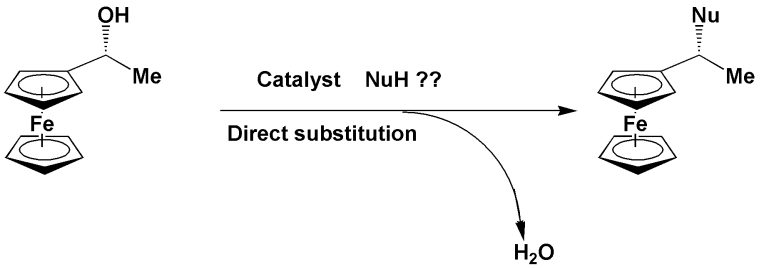
[8] B. E Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, A. C. Maryanoff,., *Chem. Rev.* **2004**, *104*, 1431.

[9] Carbocation Chemistry, Eds: G. Olah, G. K. Surya, Wiley Interscience **2004**.

[10] 1-(hydroxyethyl)ferrocene undergoes extensive racemization by heating in acetic acid solution; see rif 4b. See, also: H. Seo, B. Y. Kim, J. H. Lee, H. Park, S. U. Son, Y. K. Chung, *Organometallics* **2003**, *22*, 4783.

[11] C. F. Richards, A. J. Locke, *Tetrahedron: Asymmetry* **1998**, *9*, 2377.

Scheme 2 Hypothesize: catalytic substitution of (*R*)-1-(hydroxyethyl)ferrocene.



In order to expand the chemistry to sensitive nucleophiles and to avoid the acylation step, a direct substitution of the hydroxy group in a catalytic process under nearly neutral conditions would be an ideal procedure in ferrocene chemistry, expanding the use of this fascinating molecule in organic, organometallic, bioorganic chemistry, material chemistry and catalysis. (Scheme 2)

Catalytic activation of alcohols is generally rather difficult, because of the poor leaving group ability of the hydroxy group. Preliminary work was lead by Uemura using Ruthenium complex. Recently, Shibasaki, Baba and Beller, proposed Bismuth triflate, indium salt[12] or iron salt[13] as catalyst in the efficient replacement of benzylic, allylic or propargyl alcohol by nucleophiles and by various active methylene compounds, indoles acidic ketones, carbamates, carboxy amides and sulfonamides (Scheme 3).[14]

---

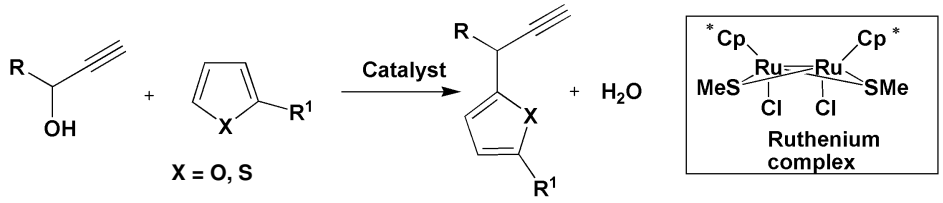
[12] a) M. Yasuda, T. Somyo, A. Baba, *Angew. Chem. Int. Ed.* **2006**, *45*, 793; b) M. Yasuda, S. Yamasaki, Y. Onishi, A. Baba, *J. Am. Chem. Soc.* **2004**, *126*, 7186; c) M. Yasuda, T. Saito, M. Ueba, A. Baba, *Angew. Chem. Int. Ed.* **2004**, *43*, 1414.

[13] I. Iovel, K. Mertins, J. Kishel, A. Zapf, M. Beller, *Angew. Chem. Int. Ed.* **2005**, *44*, 3913.

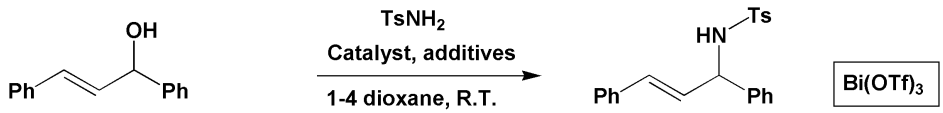
[14] For reports of catalyzed C-C, C-N and C-O bond formation through direct substitution of allylic or propargylic alcohols with nucleophiles, see: a) F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami, M. Yoshifuji, *J. Am. Chem. Soc.* **2002**, *124*, 10968; b) Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2002**, *124*, 11846; c) M. R. Luzung, D. F. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 15760; K. Manabe, S. Kobayashi, Org. Lett. **2003**, *5*, 3241; d) H. Kinoshita, H. Shinokubo, K. Oshima, *Org. Lett.* **2004**, 6, 4085; e) M. Kimura, R. Mukai, N. Tanigawa, S. Tanaka, Y. Tamaru, *Tetrahedron* **2003**, *59*, 7767; f) Y. Kayaki, T. Koda, T. Ikariya, *Eur. J. Org. Chem.* **2004**, 4989; g) M. Georgy, V. Boucard, J.-M. Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 14180; h) V. Terrasson, S. Marque, J.-M. Campagne, D. Prim, *Adv. Synt. Catal.* **2006**, *348*, 2063; i) Z. Zhan, W. Wang, R. Yang, J. Yu, J. Li, H. Liu, *Chem. Comm.* **2006**, 3352; j) Y. Nishibayashi, A. Shinoda, Y. Miyake, H. Matsuzawa, M. Sato, *Angew. Chem. Int. Ed.* **2006**, *45*, 4835; k) R. V. Ohri, A. T. Radosevich, K. J. Hrovat, C. Musich, D. Huang, T. R. Holman, F. D. Toste, *Org. Lett.* **2005**, *7*, 2501; l) K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem. Int. Ed.* **2006**, *45*, 2605; m) H. Qin, N. Yamaginawa, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2007,** 46, 409; n) R. Sanz, A. Martínez, D. Miguel, J. M. Álvarez-Guitiérrez, F. Rodríguez *Adv. Synt. Catal.* **2006**, *348*, 1841.

Scheme 3 Examples of direct alcohol substitution by transition metal catalyst

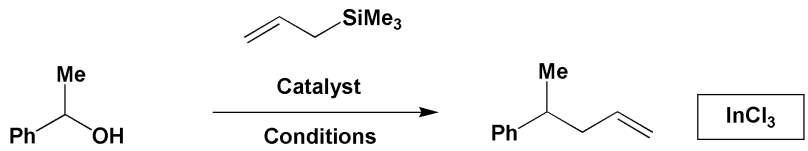
- Ruthenium-Catalyzed: Uemura, *J. Am. Chem. Soc.* **2002**, *124*, 11846.



- Bismuth-Catalyzed: Shibasaki, *Angew. Chem. Int. Ed.* **2007**, *46*, 410.



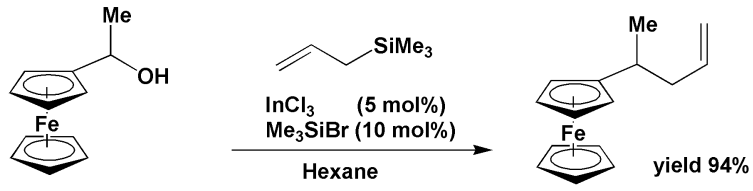
- Indium-Catalyzed: Baba, *J. Org. Chem.* **2006**, *71,* 8517.



Baba has also used a ferrocenyl carbinol as starting material in his investigations of the coupling reaction between alcohols and silyl compounds.[15]

Scheme 4 Indium-Silicon Combined Lewis Acid Catalyst

- Baba, *J. Org. Chem.* **2006**, *71*, 8519.



Combined Lewis acids
δ- δ+
$Cl_3In^{\cdots}Br$-$SiMe_3$

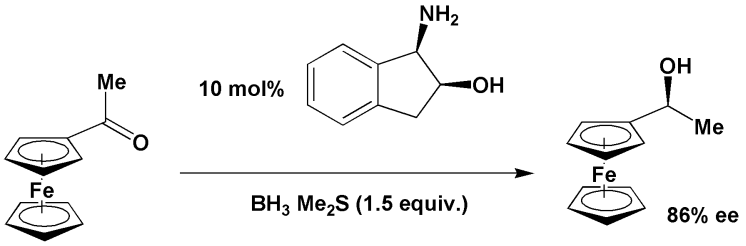
[15] a) T. Saito, Y. Nishimoto, M. Yasuda, A. Baba, *J. Org. Chem.* **2006**, *71*, 8516; b) T. Saito, M. Yasuda, A. Baba, *Synlett* **2005**, 1737.

Direct Substitution of the Hydroxy Group Catalyzed by Indium Tribromide

Although detailed mechanistic investigations have not yet been presented, and there is no clear evidence that a free carbocation is formed in these reactions, Cozzi's group proposed that the chiral cationic intermediate, formed by treatment of α-ferrocenyl alcohols with the catalytic amount of indium salt, could be used in substitution reactions with a variety of different nucleophiles.

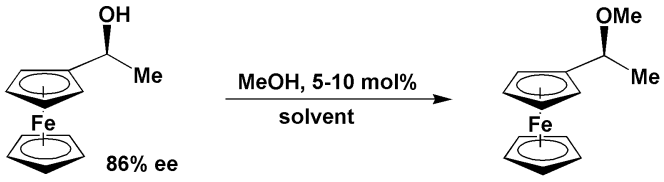
Table 1 Direct substitution of ferrocenyl alcohol 2 catalyzed by $InBr_3$.

- Synthesis of optically active (*S*)-1-(hydroxyethyl)ferrocene by acetylferrocene.



1 **2**

- Retention of the stereochemical information does not depend upon solvent nature.



2 **3**

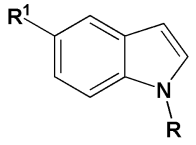
Entry[a]	Solvent	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	98	86
2	AcCN	72	86
3	THF	40	86
4	Et_2O	51	86
5	toluene	81	86
6[d]	CH_2Cl_2	86	86
7[e]	CH_2Cl_2	84	86

[a] All reaction were carried out under nitrogen atmospherere with alcohol (0.1 mmol) and nucleophile (0.2 mmol) in presence of 10 mol% of $InBr_3$. the reactions were quenched after 1h; [b] Yield of isolated product.[c] enantiomeric excess were determinated by HPLC (see experimental section); [d] 10mol% of $In(OTf)_3$ was used.

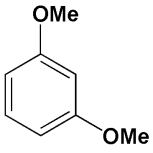
Optical active ferrocenyl alcohol **2** obtained in 86% *ee* by the aminoindanol/BH_3 reduction[16] of the ketone **1** was treated with MeOH[17] (2 equiv.) in the presence of different indium salts and reaction solvents (Table 1). Dichloromethane was the chosen solvent, and THF provide the lowest yield (40%). $InBr_3$ gave better results compared to the other indium salts tested. In all the reactions were observed retention of the stereochemical information. The selected reaction condition was tested with a variety of different nucleophiles as shown in Figure 2.

Figure 2 List of Nucleophiles used in S_N1 type reactions with 2, 8, 9.

- Indoles and 1,3 dimethoxybenzene for Friedel-Crafts reaction:

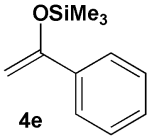


R = H R^1 = H **4a**
R = H R^1 = Br **4b**
R = Me R^1 = H **4c**

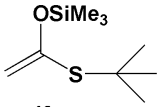


4d

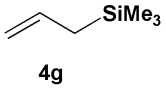
- Enol, Allyl, cyano and active methylene compound:



4e

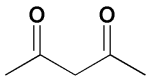


4f



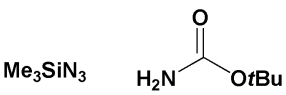
4g

4h



4i

Azido, Carbamates, small alcohol:



4j **4k** **4l** **4m**

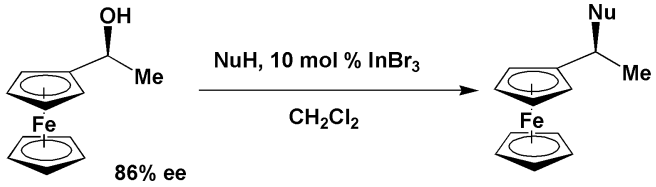
Indole **4a** and substituted indoles **4b,c** gave the 3-alkylated products in high yield and complete selectivity, and with complete retention of the stereochemical information.[12a]
No regioisomers deriving from *N*- or 2-alkylation were found. Different silyl nucleophiles (allylsilane, silyl enol ethers, silylazide, silylcyanide) were examined and afforded the corresponding products, once again with no loss of stereochemical information. Active methylene compound (entry 5) and carbamates[14m] (entries 11-13) provide the corresponding products in high yields. (Table 2)

---

[16] H. S. Wilkinson, G. Y. Tanoury, S. A. Wald, C. H. Senanayake, *Org. Proc. Res. Dev.* **2002**, *6*, 146, and ref. therein.

[17] For the catalytic addition of MeOH to ferrocenyl alcohol, see: T. Ireland, J. J. Almena Perea, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 1457. See also: R. Sanz, A. Martínez, D. Miguel, J. M. Álvarez-Guitiérrez, F. Rodríguez, *Eur. J. Org. Chem.* **2006**, 1683.

Table 2 Stereselective alkylation of alcohol 2 with different nucleophiles.



2 **5**

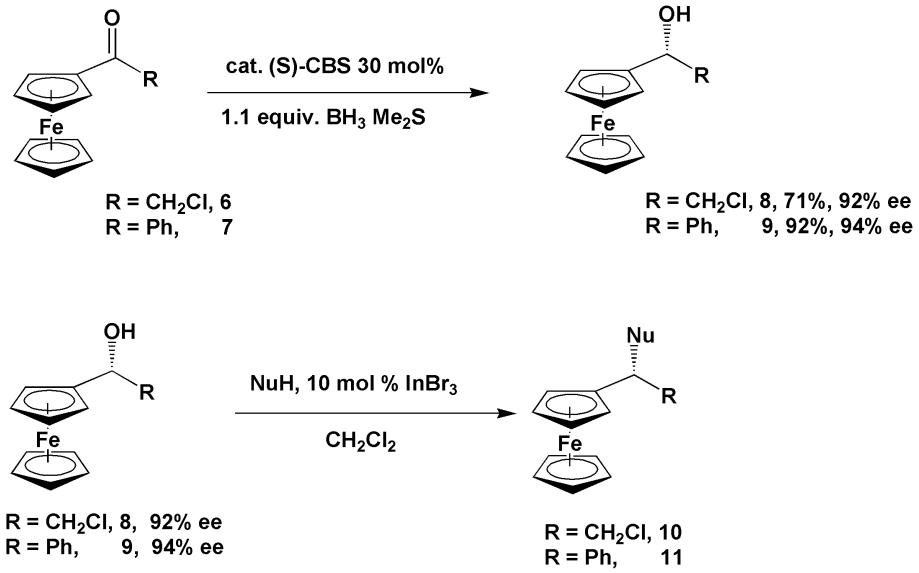
Entry[a]	Alcohol	Nucleophile	Yield (%)[b]	*ee* (%)[c]
1	**2**	**4a**	83	86
2[d]	**2**	**4a**	78	86
3	**2**	**4c**	83	86
4	**2**	**4b**	87	86
5	**2**	**4i**	82	86
6	**2**	**4h**	86	86
7	**2**	**4f**	84	85
8[e]	**2**	**4f**	80	85
9[f]	**2**	**4f**	70	85
10	**2**	**4e**	40	84
11	**2**	**4l**	85	85
12	**2**	**4k**	88	84
13[d]	**2**	**4k**	84	83
14	**2**	**4g**	80	86
15	**2**	**4j**	84	85
16[g]	**2**	**4d**	84	80

[a] All reaction were carried out under nitrogen atmospherere with alcohol (0.1 mmol) and nucleophile (0.2 mmol) in presence of 10 mol% of $InBr_3$. All the reactions were quenched by water after completion, checked by TLC (2-10 h). [b] Yields of isolated purified product; [c] Enantiomeric excesses were determined by HPLC (see experimental section for details); [d] A catalytic amount of 5 mol% of $InBr_3$ was used. The reaction was quenched after 24 h; [e] A catalytic amount of 10 mol% of $In(OTf)_3$ was utilzied; [f] A catalytic amount of 10 mol% of $InCl_3$ was used; [g] The ferrocenyl alcohol was slowly added to the mixture of 1,3 dimethoxybenzene and $InBr_3$ in CH_2Cl_2 (see experimental section for details)

To gain preliminary information about the scope of the reaction, in our laboratory were also examined ferrocenyl derivatives **8** and **9** (Table 3) with some selected nucleophiles. As is possible to see from the reported examples, ferrocenyl aryl alcohol **9** give the corresponding derivatives in high yield. However, in the reactions of **9** with the nucleophiles employed, racemization is observed, and it is more pronounced with methoxy derivative **11a**, which was obtained in only 60% *ee*.[18]

[18] Moyano has reported that the nucleophilic displacement with tertiary ferrocenyl carbon gives, in function of the reaction conditions, partial racemization, see: R. M. Moreno, A. Bueno, A. Moyano, *J. Org. Chem.* **2006,** *71*, 2528.

Table 3 Extended resuts over other ferrocenyl acohols



Entry[a]	Alcohol	Nucleophile	Yield (%)[b]	*ee* (%)[c]
1	**6**	**4m**	76	92
2	**6**	**4f**	82	93
3	**6**	**4l**	79	93
3	**6**	**4g**	63	92
5	**7**	**4m**	92	60
6	**7**	**4f**	67	89
7	**7**	**4k**	95	94
8	**7**	**4g**	98	80

[a] All reaction were carried out under nitrogen atmospherere with alcohol (0.1 mmol) and nucleophile (0.2 mmol) in presence of 10 mol% of $InBr_3$. All the reactions were quenched by water after completion, checked by TLC (2-10 h). [b] Yields of isolated purified product; [c] Enantiomeric excesses were determined by HPLC (see experimental section for details); [d] A catalytic amount of 5 mol% of $InBr_3$ was used. The reaction was quenched after 24 h; [e] A catalytic amount of 10 mol% of $In(OTf)_3$ was utilzied; [f] A catalytic amount of 10 mol% of $InCl_3$ was used; [g] The ferrocenyl alcohol was slowly added to the mixture of 1,3 dimethoxybenzene and $InBr_3$ in CH_2Cl_2 (see experimental section for details).

Conclusion

This chemistry allows a convenient and general direct substitution of the hydroxy group in ferrocenyl alcohols by nucleophiles such as allyl, enol, cyano, azido silane, indoles, an active methylene compound, and carbamates. This reaction is operationally simple as it occurs simply by mixing the substrates and the nucleophiles with $InBr_3$ in CH_2Cl_2 at room temperature or "0 °C" to give practical access to a variety of enantioenriched useful ferrocenyl intermediates. The preparation of enantiomerically enriched alcohols and the optimization of the reaction conditions for the substitution reaction were carried out in our laboratory before my arrival by Paola Vicennati. This preliminary work was the basis for my research developments on the ferrocene as the investigation of direct substitution of enantioenriched ferrocenyl alcohol without lewis or Brønsted acids reported in Chapter 3.

Experimental section of Chapter 2

Supporting Information for European Journal of Organic Chemistry, Paola Vicennati and Pier Giorgio Cozzi**,** *Eur. J. Org. Chem.* **2007**, 2248–2253. DOI 10.1002/ejoc.200700146

Chapter 3

Nucleophilic Substitution of Ferrocenyl Alcohols "on Water"

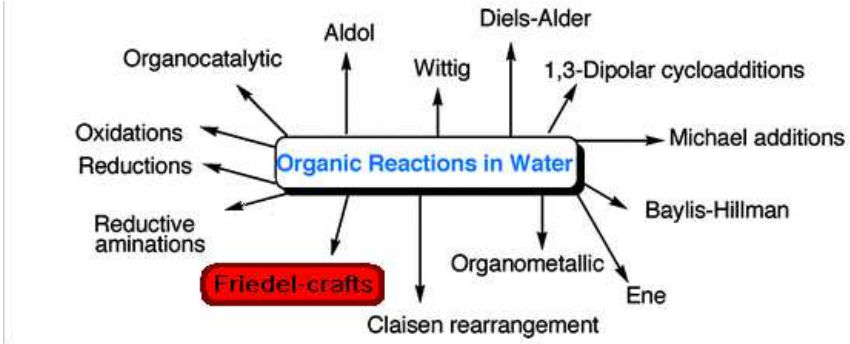
Introduction

The notion of the particular behaviour of water as reaction medium in organic synthesis began more than sixty years ago[1], but the use of water as reaction medium in organic synthesis has received considerably attention only many years later.[2]

Water as a reaction medium conveys many important advantages; it is considered cheap, safe and environmentally benign.[3]

Moreover, the application of water as a solvent in pericyclic reactions, Michael additions, and organometallic reactions has been reported and it has led to an observed difference in both reactivity, selectivity and reaction rate from what found in common organic solvents.[4]

Figure 1 Reaction classes enhancement in water



[1] R. B. Woodward, H. Baer, *J. Am. Chem. Soc.* **1948,** *70*, 1161.

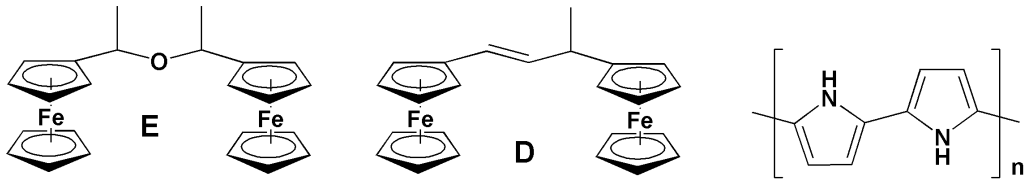
[2] a) D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980, 102**, 7816; b) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023 c) C.-J. Li, T.-H. Chan, *Organic Reaction in Aqueous Media;* WILEY; New York, **1997**; d) *Organic Synthesis in Water* (Ed: P.A. Grieco) Blackie Academic and Professional, London, **1998**; e) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095; f) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68; g) *Organic Reaction in Water* (Ed: U.M. Lindström) Blackwell Publishing, Oxford, **2007**.

[3] S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.

[4] a) U. M. Lindström, F. Andersson, *Angew. Chem. Int. Ed.* **2006**, *45*, 548; b) M. C. Pirrung, *Chem. Eur. J.* **2006,** *12*, 1312; c) S. Otto, J. B. F. N. Engberts, *Org. Biomol. Chem.* **2003**, *1*, 2809.

Many reactions have been promoted in acquose condition with a resulting improvement in yield and rate. We were especially interested in Friedel–Crafts alkylations, which are usually promoted by Lewis acids in inert solvents.[5] Indeed the reaction of substituion of (*R*)-(1-hydroxyethyl)ferrocene[6] **1** with nucleophiles, in the presence of catalytic amounts of indium salts[7] (see chapter 2) was generally found to be efficient, but there were some examples that proved to be more problematic (for example, in the addition of dimethyl and diethyl malonate, pyrrole and carbazole, under the reaction conditions applied. A significant amount of by-products is generated using these nucleophiles (Scheme 1, the formation mechanism of **D** has been thoroughly discussed in Chapter 1). It was our intetion to develop new milder reaction conditions to resolve these troubles.

Scheme 1 By-products observed with some nucleophiles.



In our opinion acquose media can prevent many of these problems, as avoid polimeritation of pyrrole[8] and increase of the yields of other ferrocenyl products. Synthetic strategy have to permite generation of the carbocation and involve it to react with nucleophiles, both in presence of acquose media. For example, in the prenylation of indole (that cover main role in the field of natural product synthesis) many progresses hve been made using water as solvent. The yield of the product was considerably improved at the same time the formation of byproducts has decreased. (Scheme 2)

[5] C. Friedel, J. M. Crafts, *J. Chem. Soc.* **1877**, *32*, 725.

[6] R. Gòmez Arrayás, J. Adrio , J. C. Carretero, *Angew. Chem. Int. Ed.* **2006**, *45*, 7674.

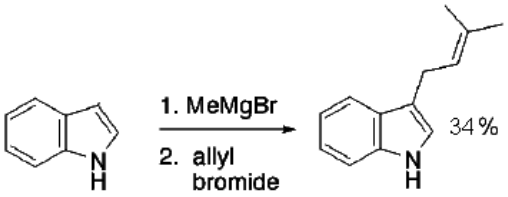
[7] P. Vicennati, P. G. Cozzi, *Eur. J. Org. Chem.* **2007**, 2248.

[8] J. K. Laha, S. Dhanalekshmi, M. Taniguchi, A. Ambroise, J. S. Lindsey, *Org. Process Res. Dev.* **2003**, *7*, 799.

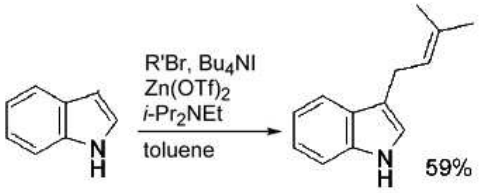
Some examples of reactions known reproposed under aqueous conditions

Scheme 2 Improvement on Friedel-Crafts reactions of indole to 3-alkylated derivates.

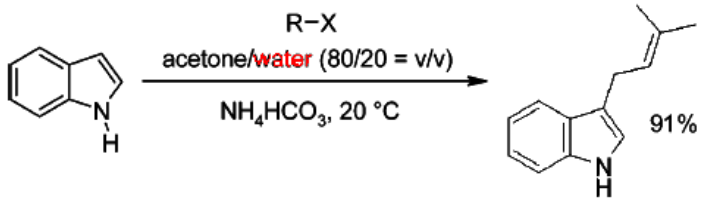
- Wenkert's strategy, (1986)[9]



- Ganesan' strategy (2002)[10]



- Mayr's strategy (2006)[12]



When such reactions are carried out in aqueous or alcoholic solutions, usually Brönsted or non-hydrolyzable Lewis acids are employed to generate small equilibrium concentrations of carbocations.[11]

Basic and even *neutral aqueous* or alcoholic solutions have been considered *prohibitive* for such reactions, since water and alcohols are intuitively considered as strong nucleophiles which instantaneously trap the intermediates of S_N1 reactions and do not give π–nucleophiles a chance to intercept the transient carbocations. (Scheme 3)

These assumptions have not prevented Mayr to develop the first prenylation reaction of indole in aqueous media without acid catalysis, to extend the discovery to more general benzylic halides. Clearly also other nucleophiles are suitable for S_N1 type reactions at the condition applied, despite the fact that carbocations may be generated in the process and π-nucleophile can successively compete with the acquose system in the trapping of the intermediate carbocation.[12] (Scheme 3)

---

[9] E. Wenkert, C. Angell, V. F. Ferreira, E. L. Michelotti, S. R. Piettre, J.-H. Sheu, C. S. Swindell, *J. Org. Chem.* **1986**, *51*, 2343.

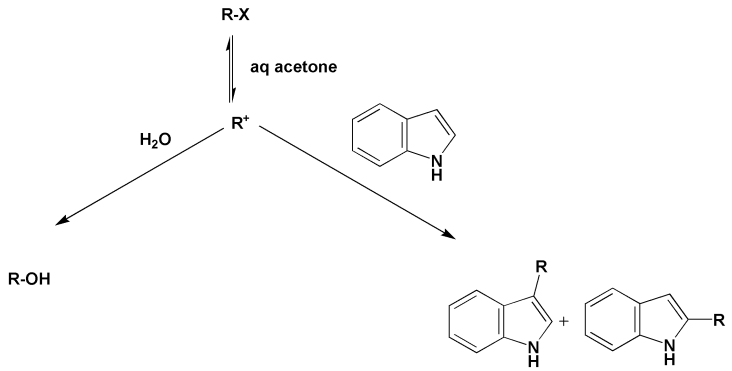
[10] A. Ganesan, *J. Org. Chem.* **2002**, *67*, 2705.

[11] a) S. Kobayashi, K. Manabe, *Chem. Eur. J.* **2002**, *8*, 4094; b) S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15; c) A. Corma, H. Garcia, *Chem. Rev.* **2003**, *103*, 4307; d) U. M. Lindstr, *Chem. Rev.* **2002**, 102, 2751; e) J. P. Richard, *Biochemistry* **1998**, *37*, 4305.

[12] a) M. Hofmann, N. Hampel, T. Kanzian, H. Mayr, *Angew. Chem. Int. Ed.* **2004**, *43*, 5402; b) M. Westermaier, H. Mayr, *Org. Lett.* **2006**, *8*, 4791.

Scheme 3 Indole, *Not Water*, intercepts the carbocation.

- Mayr, *Org. Lett.* **2006**, *8*, 4792.



These efficient protocols for carbon–carbon bond forming reactions can be further enhanced, when alcohols are used as substrates. In fact, in this case the by-product generated is water. The application of alcohols in nucleophilic substitution reaction is limited due to the poor leaving group ability of the hydroxy group,[13] nevertheless, there have been a number of catalytic methods for the promotion of direct nucleophilic substitution in organic solvents reported.[14] There have also been examples of efficient catalytic systems reported in literature to effect dehydrative nucleophilic substitution in water as solvent, however, this area still remains a challenging research topic.

Kobayashi during his studies of organic reaction in water[15] has disclosed that dodecylbenzenesulfonic acid (DBSA) efficiently catalyzes the dehydrative esterification of carboxylic acids in water[16] and he has reported that DBSA is also able to promote the catalytic nucleophilic substitution of benzylic alcohols with various carbon nucleophiles in water as shown in Scheme 4.[17]

---

[13] a) G. C. Gullickson, D. E. Lewis, *Aust. J. Chem.* **2003**, *56*, 385; b) F. Bisaro, G. Prestat, M. Vitale, G. Poli, *Synlett*, **2002**, 1823; c) S.J. Coote, S. G. Davies, D. Middlemiss, A. Naylor, *Tetrahedron Lett.* **1989**, 30, 3581.

[14] see chapter 2 , for more recent reports of catalyzed C-C, C-N and C-O bond formation through direct substitution of allylic or propargylic alcohols with nucleophiles, see: a) T. Saito, Y. Nishimoto, M. Yasuda, A. Baba, *J. Org. Chem.* **2006**, *71*, 8516; b) M. Yasuda, T. Somyo, A. Baba, *Angew. Chem. Int. Ed.* **2006**, *45*, 793; c) R. Sanz; D. Miguel; A. Martinez; J. M. Alvarez-Gutiérrez, F. Rodrìguez, *Org. Lett.* **2007**, *9*, 2027; j) R. Sanz; D. Miguel; A. Martinez, J. M. Alvarez-Gutiérrez, F. Rodrìguez, *Org. Lett.* **2007**, *9*, 727; k) M. Rueping, B. J. Nachtsheim, A. Kuenkel, *Org. Lett.* **2007**, *9*, 825; l) M. Noji, Y. Konno, Keitaro Ishii, *J. Org. Chem.* **2007**, *72*, 5161; o) J. Le Bras, J. Muzart, Tetrahedron, **2007**, *63*, 7942; p) J. Kischel, K. Mertins, D. Michalik, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2007**, *349*, 865.

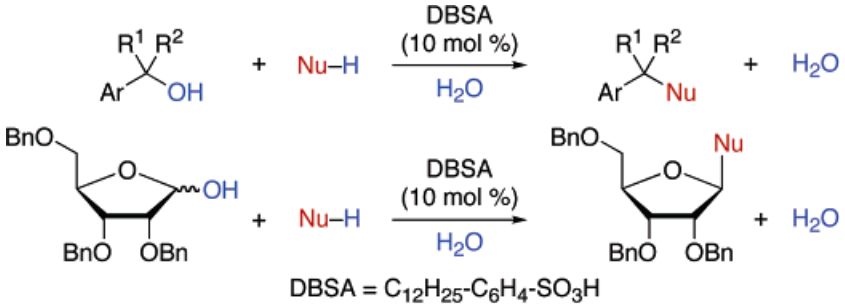
[15] S. Kobayashi, C. Ogawa, *Chem. Eur. J,* **2006**, *12*, 5945, and ref. therein.

[16] K. Manabe, S. Iimura, X.-M. Sun, S. Kobayashi, *J. Am. Chem. Soc.* **2002**, *124,* 11971.

[17] S. Shirakawa, S. Kobayashi, *Org. Lett*, **2007**, *9*, 311.

Scheme 4 Surfactants promote directly nucleophilic substitutions of alcohols in water.

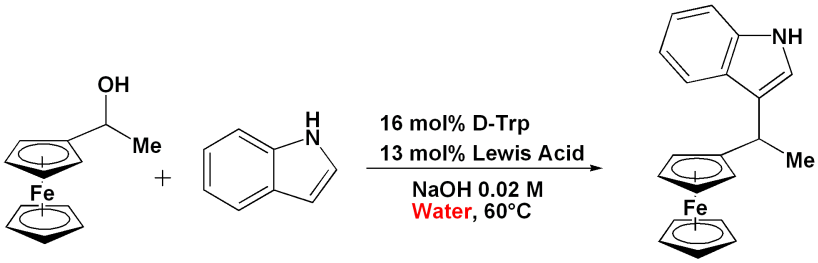
■ Kobayashi, *Org. Lett.* **2007**, *9*, 311.



Substitution of ferrocenyl alcohols via H-bond interactios

On the basis of these informations, we tested (*R*)-(1-hydroxyethyl)ferrocene **1** via Friedel-Crafts type substitution reaction with indole **2a**[18] in the presence of water and various lewis acids $Yb(OTf)_3$, $Al(OTf)_3$, $In(OTf)_3$, $Bi(OTf)_3$ with tryptophan[19] as ligand and we found excellent conversion at 60°C as shown in Table 1

Table 1 Optimizating substituion reaction catalized by lewis acids in acquose media.



1 **2a** **3a**

Entry[a]	Lewis acid (mol%)	Yield (%)[b]
1	$Yb(OTf)_3$	>99%
2	$Al(OTf)_3$	>99%
3	$In(OTf)_3$	>99%
4	$Bi(OTf)_3$	>99%
5	$Cu(OTf)_2$	50%

[a] All the reaction were carried out under inert atmosphere, with 0.1 mmol of alcohol **1**, 0.2 mmol of indole **2a** for 1 hour; [b] Yields of purified products after chromatography.

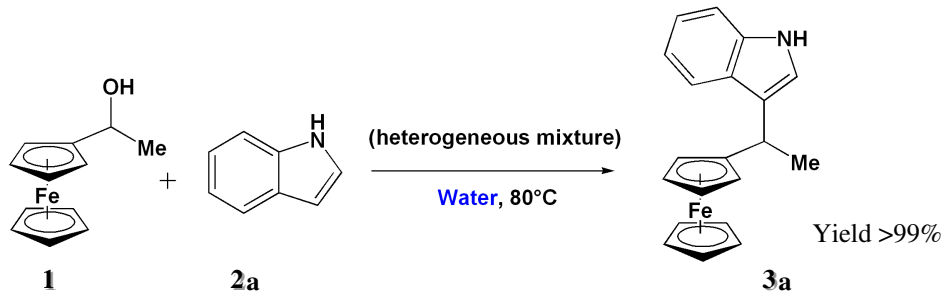
[18] For "on water" promoted direct coupling of indole with 1,4 benzoquinones, see: H.-B. Zhang, L. Liu, Y.-J. Chen, D. Wang, C.-J. Li, *Eur. J. Org. Chem.* **2006**, 869.

[19] K. Aplander, R. Ding, U. M. Lindström, J. Wennerberg, S. Schultz, *Angew. Chem. Int. Ed.* **2007**, *46*, 4543.

Encouraged by the early results, we have tested the 9*H*-Carbazole (problematic nucleophile described in Chapter 1), "on water" condition, hoping to carry out directly substitutions in position 3 and 6 of the 9*H*-carbazole, without the preventive insertion of benzyl group.[20] Unfortunately no reaction occured between carbazole and alcohol **1** and by-products of the ferrocenyl alcohol were recovered. These results corroborate our idea that there is a lower nucleophilecity value under which the water get to be a competitive nucleophile.[21]

The role of water in the formation of carbocation in substitution reactions of benzyl halides with nucleophiles, was largely explained by Mayr. Otherwise when benzyl alcohols are used as starting material the role of the water has not yet investigated. The formation of the carbocation is attributed entirely to catalysis acid. We propose as exception to this general rule, the substitution reaction between the alcohol **1** and indole in pure water without the aid of acid catalyst. The model reaction was performed at 80°C in pure water, giving complete conversion.

Scheme 5 Direct nucleophilic substitution of alcohol 1 with indole "on water".



To understand the role of water and temperature to promote reaction we tested other conditions without catalysts. Indole is milled at 25 °C with (1-hydroxy ethyl)ferrocene **1**, a reaction takes place immediately, but after 24h starting materials were recovered unchanged (plus a 10% of by-product **E**). If indole is mixed with racemic **1**, the two solids melt immediately. We put a sample to stir at 25 °C and another sample at 80°C, both for 24 hours. Tracies of by-product **E** and starting materials were recovered. Finally we could assert to have discovered the first direct substitution of optically active ferrocenyl alcohols "on water"[22] without the use of any type of Brønsted or Lewis acids.

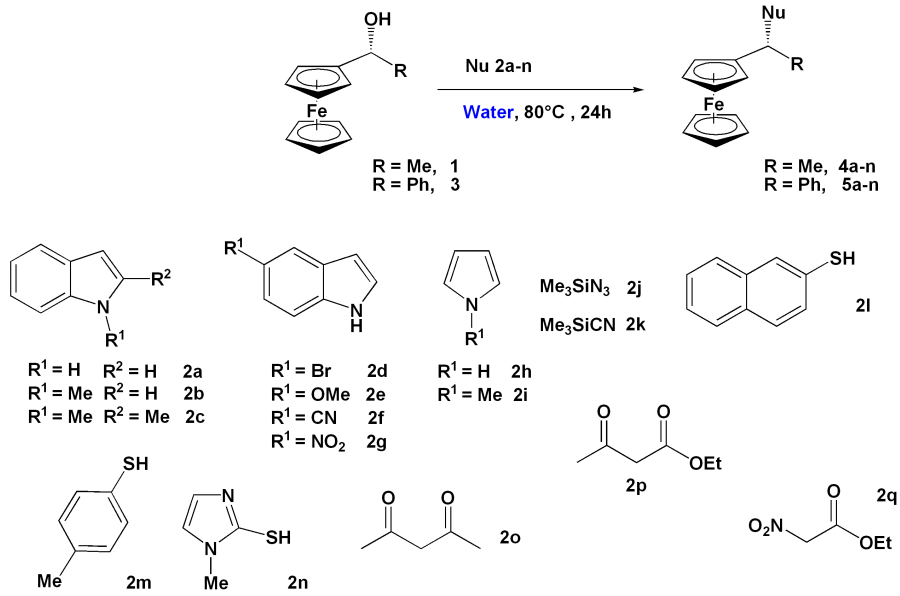
[20] For further details on the 9*H*-carbazole and (1-hydroxyethyl)ferrocene **1**, see Chapter 1.

[21] a) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003,** 36, 66; b) T. B. Phan, C. Nolte, S. Kobayashi, A. R. Ofial, H. Mayr, *J. Am. Chem. Soc.* **2009**, *131*, 13192; c) N. Streidl, A. Antipova, H. Mayr, *J. Org. Chem.* **2009**, *74*, 7328.

[22] Ferrocene alcohols **1** and **3** are insoluble in water. For a discussion of reactions performed in water, see: ref. *3*. See also: a) A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem. Int. Ed.* **2006**, *45*, 8100; b) Y. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 8103; c) J. E. Klijn, J. B. F. N. Engberts, *Nature* **2005**, *453*, 746.

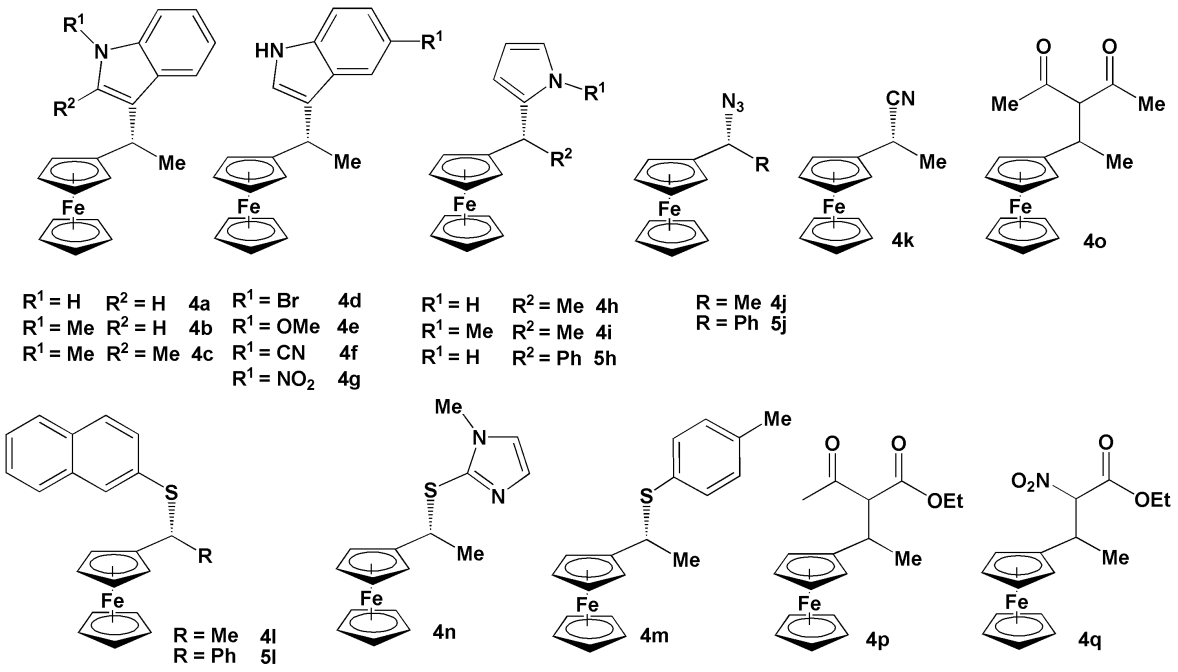
Substrate scope

Table 2 Substrate scope for the "on water" substitutions with 1 and 3



Entry[a]	Alcohol[b]	Nu	Product	Yield%[c]	Ee %[d]
1	**1**	**2a**	**4a**	95	99
2	**1**	**2b**	**4b**	68	99
3	**1**	**2c**	**4c**	82	99
4	**1**	**2d**	**4d**	45	99
5	**1**	**2e**	**4e**	81	99
6	**1**	**2f**	**4f**	43	99
7	**1**	**2g**	**4g**	0	-
8	**1**	**2h**	**4h**	58[e]	99
9[f]	**1**	**2h**	**4h**	68[e]	99
10	**1**	**2i**	**4i**	81	99
11	**1**	**2j**	**4j**	83	97
12	**1**	**2k**	**4k**	0[g]	-[g]
13	**1**	**2l**	**4l**	63	96
14	**1**	**2m**	**4m**	46	90
15	**1**	**2n**	**4n**	63	80
16	**1**	**2o**	**4o**	90[h]	-[i]
17	**1**	**2p**	**4p**	48[h]	-[i]
18	**1**	**2q**	**4q**	78[h]	-[i]
19[j]	**3**	**2h**	**5h**	60	94
20	**3**	**2j**	**5j**	95	72
21	**3**	**2l**	**5l**	47	94

[a] All the reaction were carried out on air with 0.1 mmol of (*R*)- **1** furnish by Jonson Matthey and 0.2 mmol of nucleophile suspended in 1.0mL of water at 80 °C for 24-36 hours; [b] Alcohol **1** 99% ee, alcohol **3** 94% ee; [c] Yield of purified product; [d] The enantiomeric excesses were evaluated by chiral HPLC (See experimetal section for details); [e] 2,5-di(1-ethylferrocene)pyrrole **6** was isolated in 10 mol.% (in the small-scale reaction), and in 15 mol. % (in the increased-scale reaction) as by-product of the reaction; [f] The reaction was performed with 1.5 mmol of (*R*)-(1-hydroxyethyl)ferrocene **1** with 10 equiv. of pyrrole **2h;** [g] by-product **E** was obtained as a mixture of two diastereoisomers in ratio 4:1, judged by 1H-NMR in yield of 71%. The absolute and relative stereochemistry was not assigned; [h] Racemic alcohol **1** was utilized; [i] Inseparable mixture of two diasteroisomers; [j] 2,5-di(phenylmethylferrocene) pyrrole was isolated in 30 mol% as by-product of the reaction.



For all the examined reactions the use of optically active ferrocene derivatives allows the straightforward preparation of the corresponding enantioenriched ferrocene derivates.[23] Other nucleophiles were tested[24] but failed to give ferrocenyl products. Remarkable as pyrrole, Me_3SiN_3 and thiophenols reacted with ferrocenyl alcohols in water without requirement for Lewis or Brønsted acids and in better yields than previous condition[7]. Electron rich and electron poor indoles could also be employed in the reaction although the conversions observed with indole substituted by electron withdrawing groups was inferior (Table 2, entry 4). 5-Nitroindole **2g** was not reactive in the reactions conditions, even with a prolonged reaction time of 36 hours.

Significant improvements are evident for some compounds

The reaction illustred in Table 3, entry 9 had the greatest improvement in "on water" condition whereas in our previous work[7] we were obliged to use neat pyrrole to operate the

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[23] A review about investigations of structural features of metallocene derivatives in which carbenium ion center is connected adjacent to a cyclopentadienyl ring η-bound to a transition metal was recently published; see: R. Gleiter, C. Bleiholder, F. Rominger, *Organometallics,* **2007**, *26*, 4850. Structure proposed and calculations suggested stereoselectivity for the nucleophile substitution of α-ferrocenylalkyl derivatives. This topic, well established in ferrocene chemistry, was dealt with Ugi see, a) G. W. Gokel, P. Hoffmann, H. Klusacek, D. Marquarding, E. Ruch, I. Ugi, *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 64; b) D. Marquarding, H. Klusacek, G. W. Gokel, P. Hoffmann, I. Ugi, *J. Am. Chem. Soc.* **1970**, *92*, 5389; c) G. W. Gokel, D. Marquarding, I. Ugi, *J. Org. Chem.* **1972**, *37*, 3052. For reaction of ferrocenyl acetates and other derivatives for the synthesis of optically active ferrocenyl phosphines, see ref. *6*.

[24] 2,5-Dimethylthiophene, 1,3-MeOC6H4, *t*BuOCONH$_2$, allyltin, allylsilane, 4-MeOC$_6$H$_4$NH$_2$, Bu$_3$SnCN, 4-butyn-1-ol, 3-acetylbutanol, 2,4-di*tert*butylphenol, p-toluensufonamide, and NaN_3 were tested as nucleophiles in the model reaction with water at 80°C for 24 h. In these cases only starting material was recovered. No decomposition of the alcohol, oxidation of ferrocene fragment, or formation of ferrocenyl ether **E** take place.

reaction at -30°C to preserve the enantiomeric excess at 99% ee in the product. Furthermore in this case the use of pyrrole was decrease to 4 equivalent.

Table 3 Notable results with pyrrole as nucleophile.

1 **2h** **4h**

Method	T (°C)	equiv. **2h**	Time (h)	Ee (%)	Yield (%)
A	-30	36	2h	95%	66[a]
B	80	4	24h	99%	58

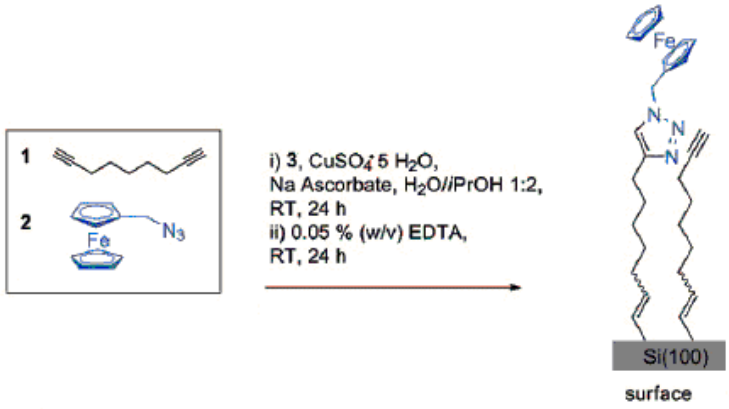
Method A: The reaction was performed in inert atmophere with **1** (0.023 g, 0.1 mmol) neat degassed pyrrole **2h** (0.250 mL, ≈36 equiv.) and 10 mol-% of $InBr_3$. The reactions were quenched after 1 h.[a] by-products: polipyrrole and β-confused derivate.
Method B: The reaction was carried out on air with **1** (0.023 g, 1 mmol) and pyrrole **2h** (0.277 mL, 4 mmol) suspended in 1.0 mL of water at 80 °C for 24 h.

As expected the absence of lewis acids avoid polymerization of pyrrole. This reaction could be readily scaled up (Table 2, entries 8,9). The reaction was easily performed with vigorous stirring in deionised water at 80 °C, and the work up was simply consisted of the separation of the products by the addition an organic solvent and a facile chromatography. The reaction "on water" with Me_3SiN_3 **2j** appear particularly remarkable since both ferrocene derivatives **1** and **3** provide the desired products **4j** and **5j** in high yields (Table 2, entries 11,20). These products are interesting optycal active building block for area of "Click Chemistry", (for example see Scheme 6).[25]

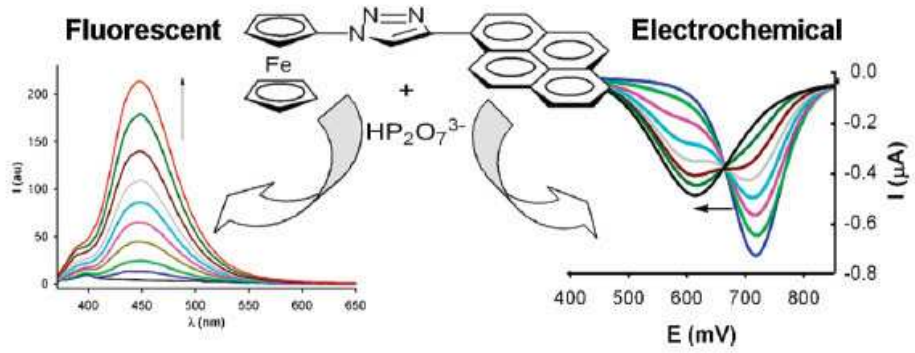
[25] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* 2001, **40,** 2004; b) S. Ciampi, P. K. Eggers, G. Le Saux, M. James, J. B. Harper, J. J. Gooding *Langmuir* **2009**, *25*, 2530; c) T. Romero, A. Caballero, A.Tárraga, P. Molina, *Org. Lett.* **2009**, *11*, 3466.

Scheme 6 "click chemistry" of triazole rings

- Campi , *Lagmuir* **2009**, *25*, 2532.



- Molina, *Org. Lett.* **2009**, *11*, 3466.



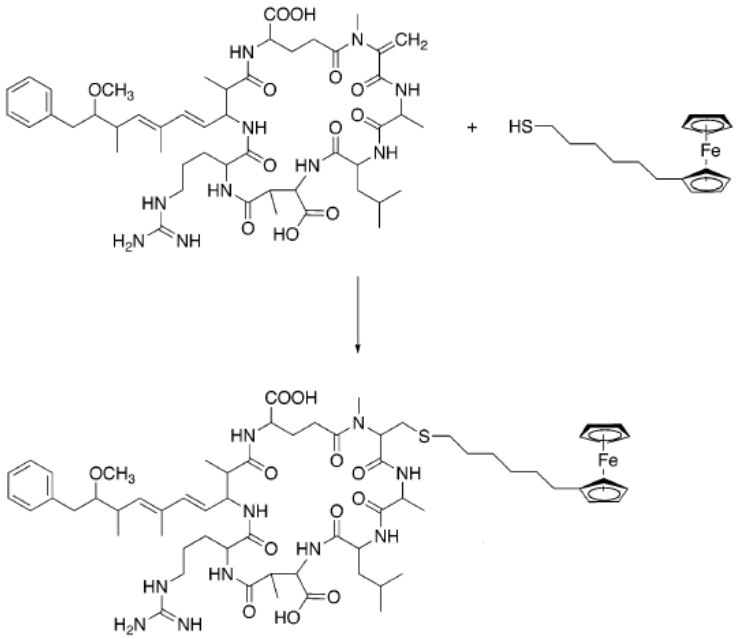
As the cycloaddition of alkynes catalyzed by copper(I) ascorbate is performed in water, a consecutive reaction between ferrocene azide derivatives obtained "on water", and alkynes, appears possible.[26] Thiophenols and 1-methyl-*H*-imidazol-2-thiol are also suitable nucleophiles for this reaction (Table 2 entries 13-15,18) and the corresponding thioethers **4l-n** and **5m** are produced in moderate yield. Thiol, functional group, is present in many natural compounds, as some polypeptides or macrocycles containig cysteines. In bioorganic chemistry this functional group can be tagged with a molecular probe.[27] Ferrocene and its derivates are usually employed to tag biological molecules thank to their optimal electrochemical properties. For example, a work of Lo Lam and co-workers, developed an elegant method that makes the detection of a particular macrocycle, microcystin, as shown in Scheme 7.

[26] For a recent reviews, see: a) V. Bock, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2006**, 51; b) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249; c) A. Dondoni, *Chem. Asian. J.* **2007**, *1*, 700. See also: P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2004**, 4095.

[27] D. R. van Staveren, N.s Metzler-Nolte *Chem. Rev.* **2004**, *104*, 5931.

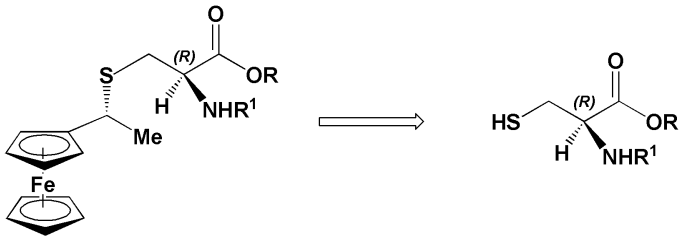
Scheme 7 Insertion of ferrocene fragment in polypeptide as probe.

- Addition at double bond: Metzler-Nolte *Chem. Rev*. **2004,** *104*, 5948.



This method is based on the specific derivatization of the exocyclic double bond of the R,α-unsaturated carbonyl moiety of microcystin with ferrocenylhexanethiol and the subsequent electrochemical detection of the (Fc/Fc^+) moiety in the ferrocene tagged conjugate. The electrochemical method, however, is quick, specific, and inexpensive.

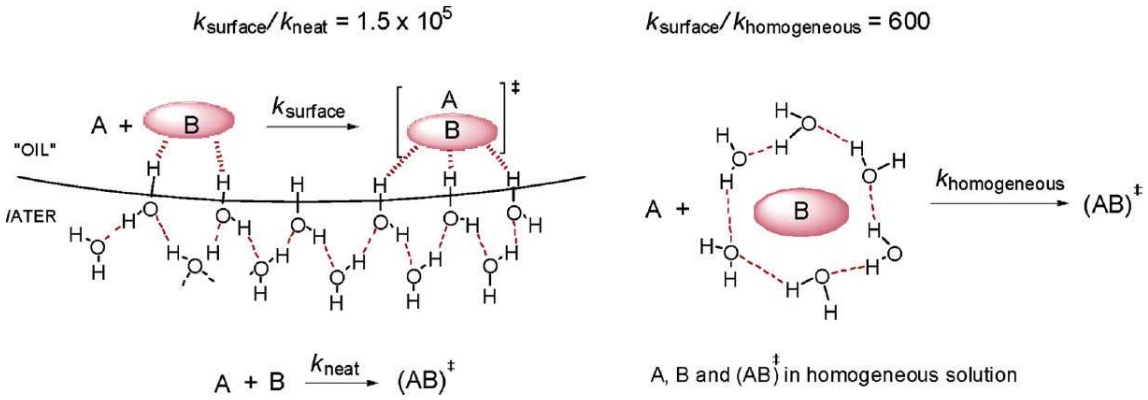
- Our idea: “on water”, acid free, condition to attach ferrocene in aminoacids.



We wanted to apply our chemistry to *t*-BOC-(L)-cysteine methylester. We tried to synthetize a mimetic of cystein conteining ferrocene moiety in biologycal conditions. This approch may extend molecolar tagging to “in vivo” test. Unfortunately *t*-BOC-(L)-cysteine methylester was found unreactive toward the alcohol **1** in any "on water" condition applied. To explain its unreactivity, we can assert that the nucleophiles **2*l*-n** have a less nucleophilic sulfhydryl group but a more stabylyzed conjugate anion. Furthermore the solubility of the *t*-BOC-(L)-cysteine methylester in water is greater then the one of **2*l*-n.**

Figure 2 Marcus's Water Theory.

- Marcus, *J. Am. Chem. Soc.* **2007**, *129*, 5494.



Our reaction could be classified, according to Sharpless,[3] as reaction "on water". Marcus has recently explained the origin of the rate increase of reactions carried out "on water". In particular, it is quite important the structure of water at the oil-water interface of an oil emulsion, in which free ("dangling") OH groups are protruding into the organic phase. These groups play a key role in catalyzing reactions via the formation of hydrogen bonds. The structural arrangement at the "oil-water" interface is quite different to the structure of water molecules around a small hydrophobic solute in homogeneous solution, where the water molecules are tangentially oriented.[28] The direct generation of ferrocenyl carbocation in water from alcoholic precursor is probably driven by the formation of hydrogen bonds between water and the hydroxy group of the alcohol. Acidic nucleophiles (i.e. 4-nitrophenol) or nucleophiles hydrolyzed in water to weak acids (Me_3SiCN to HCN) promoted the reaction of ferrocenyl alcohol with itself (Table 2, entry 12). We tested the benzylic, allylic alcohols[29] and benzydrols[17] "on water" condition to understand the limtis of our reaction. Unfortunately these alcohols did not react with indole in pure water.

It is possible that the stability of ferrocenyl cations generated and the easy formation of the stabilized cation play an important role in this reaction. Jørgensen has reported a Friedel-Crafts reaction of a reactive ethyl glyoxalate with indole and pyrrole in water, or in basic conditions.[30]

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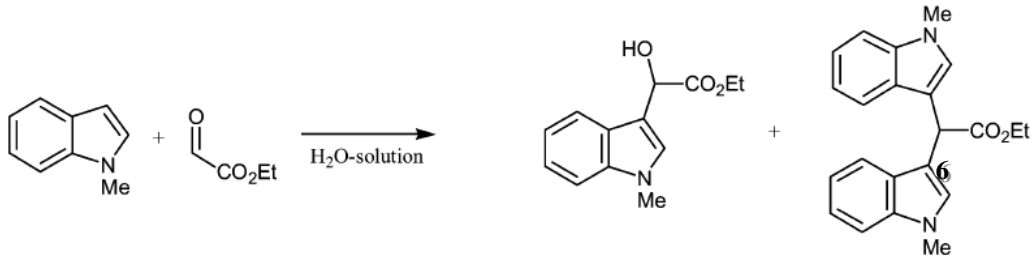
[28] Y. Jung, R. A. Marcus, *J. Am. Chem. Soc.* **2007**, *129*, 5492.

[29] We have tested in the standard reaction conditions benzylic alcohol, allylic alcohol and 2-(hydroxyethyl)naphtalene

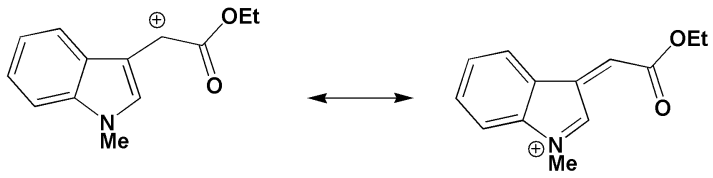
[30] W. Zhuang, K. A. Jørgensen, *Chem. Commun.* **2002**, 1336.

Scheme 8 Water interaction can promote formation of carbocation in this molecule

- Jørgensen, *Chem. Commun.* **2002**,1336.



- We invoce the formation of carbocation to explain formation of product **6**.



In neutral conditions the intermediates of S_N1 reaction could be trapped with electron rich π-systems. In the next chapter I will explain as our and Jørgensen results are based on the reactivity scale of carbocation as elcetrophile and some molecule as nucleophile revealed by Mayr.[31]

Conclusion

In summary, we have described a challenging dehydration reaction "on water" without the use of Lewis acids or surfactants, that allows the direct functionalyzation of ferrocene alcohols in pure water, which is an essential component for the reactions.

To the best of our knowledge this is the first example of a direct nucleophilic substitution of an alcohol "on water".[32] The mild reaction conditions and the use of water without the presence of co-solvents additive as Lewis or Brønsted acids has enhanced a Ferrocenyl pyrrole derivates **4h**, **5h** synthesis avoiding the formation of pyrrole polymers. In general the "on water " condition permit to introduce ferrocene moiety in biological molecules,[27] expanding the scope of ferrocene as sensitive electrochemical probe.

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[31] S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.* **2006**, *71*, 9088.

[32] For other interesting reaction "on water", see: a) M. C. Pirrung, K. D. Sarma, *J. Am. Chem. Soc.* **2004**, *126*, 444; b) B. K. Price, J. Tour, *J. Am. Chem. Soc.* **2006**, *128*, 12899; c) D. Gonzàles-Cruz, D. Tejedor, P. de Armas, F. Garcìa-Telaldo, *Chem. Eur. J.* **2007**, *13*, 4823.

Experimental section of chapter 3

General: ^{1}HNMR spectra were recorded on Varian 200 MHz or Varian 300 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian 50 MHz or Varian 75 MHz spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were performed at an ionizing voltage of 70 eV. Chromatographic purification was done with 240-400 mesh silica gel. Analytical gas chromatography (GC) was performed on a Hewlett-Packard HP 6890 gas chromatograph with a flame ionization detector and split mode capillary injection system, using a Crosslinked 5% PH ME Siloxane (30 m) column or a Megadex5 chiral (25 m) column. Elemental analyses were carried out by using a EACE 1110 CHNOS analyzer. Analytical high performance liquid chromatograph (HPLC) was performed on a HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190-600 nm), using Daicel Chiralcel™ OD column (0.46 cm I.D. x 25 cm) (Daicel Inc.), Daicel Chiralcel™ AD column (0.46 cm I.D. x 25 cm) (Daicel Inc.), Daicel Chiralcel™ OF column (0.46 cm I.D. x 25 cm) (Daicel Inc.), Daicel Chiralcel™ OJ column (0.46 cm I.D. x 25 cm) (Daicel Inc.); HPLC grade isopropanol and *n*hexane were used as the eluting solvents. All the reactions were carried out in deionised water under air, apart from the reactions in which pyrrole was used as nucleophile. Enantioenriched ferrocenyl alcohol **3** was prepared according to the procedures described by Knochel using the CBS (Corey-Bakshi-Shibata) protocol. The absolute configuration of the products was established by Supplementary Material (ESI) for Green Chemistry This journal is © The Royal Society of Chemistry 2007 comparison with the HPLC elution order and/or $[\alpha]_D$ values of products reported in literature, or assumed by analogy.

General procedure to addition of nucleophiles* 2a-n *to ferrocenyl alcohol* 1 *and* 3*:

Alcohol (0.1 mmol) and nucleophile (0.2 mmol) were introduced in a reaction flask under air, and deionised water (pH = 6.52, 1.0 mL) was added. The flask was sealed and stirred under air at 80°C for 24h, the allowed to cool to room temperature. Diethyl ether (5 mL) was added and the organic phase was separated, dried over anhydrous Na_2SO_4, and evaporated to reduced pressure to give a yellow oil purified by chromatography.

(*S*)-1-(3-indolethyl)ferrocene 4a.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and indole **2a** (0.023 g, 0.2 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:diethylether 4:1) and purified by flash chromatography (cyclohexane:diethyl ether 9:1). Yield 85%, 99% ee, $[\alpha]_D$ = -53° (c 0.6, $CHCl_3$).

Yellow solid; mp = 133 °C; IR: 3440, 3089, 1618 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.84 (bs, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.35 (dd, J = 1.4, 7.2 Hz, 1H), 7.16 (dq, J = 1.4, 7.2 Hz, 2H), 6.79 (s, 1H), 4.35-4.05 (m, 9+1 H), 1.73 (d, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 136.4, 126.6, 123.4, 121.9, 120.8, 119.4, 119.2, 111.3, 95.6, 69.3 (5C), 68.6, 67.8, 67.3, 67.0, 30.8, 21.8; ESI MS: 330 (M+1), 329 (M), 213.

HPLC analysis AD: isocratic, flux 0.8mL/m (hexane: *i*-PrOH) 85:15. TM: 10.41 min; tm: 11.47 min.

(*S*)-1-[3-(1-*N*-methylindole)ethyl]ferrocene 4b.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and 1-methylindole **2b** (0.026 g, 0.2 mmol), until judged complete by TLC (R_f = 0.4 , cyclohexane:diethylether 95:5) and purified by flash chromatography.

Yield 68%, 99% ee, $[\alpha]_D$ = -94° (c 0.4, $CHCl_3$).

Yellow solid; mp = 104-107 °C; IR: 3415, 3085, 1467 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.67 (d, J = 7.8 Hz, 1H), 7.30-7.10 (m, 3H), 6.60 (s, 1H), 4.45-4.05 (m, 9+1 H), 3.72 (s, 3H), 1.72 (d, J = 7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 137.3, 127.1, 125.8, 122.1, 121.7, 119.7, 118.8, 109.5, 95.3, 69.0 (5C), 68.6, 67.7, 67.1, 66.7, 32.9, 30.9, 22.2; ESI MS: 344 (M+1), 343 (M).

HPLC analysis AD: isocratic, flow 0.7mL/m (hexane: *i*-PrOH) 85:15. TM: 6.25 min; tm: 7.06 min.

(*S*)-1-[3-(1-*N*-methy-2-methylindole)ethyl]ferrocene 4c.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and 1,2-dimethylindole **4c** (0.029 g, 0.2 mmol), until judged complete by TLC (R_f = 0.5 , cyclohexane:diethylether 95:5) and purified by flash chromatography.

Yield 82%, 99% ee, $[\alpha]_D$ = -171° (c 1.0, $CHCl_3$).

Orange solid; mp = 105 °C; IR: 3415, 3085, 1467 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.35 (d, J = 6.8 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 7.00 (dd, J = 6.8 Hz, 8.1 Hz, 1H), 6.88 (dd, J = 8.1 Hz, 6.8 Hz, 1H), 4.35 (m, 1H), 4.20 (q, J = 7.2 Hz, 1H), 4.06 (m, 5H), 4.02 (m, 1H), 3.94 (m , 2H), 3.54 (s, 3H), 2.26 (s, 3H), 1.59 (d, J = 7.20 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 136.5, 131.3, 126.2, 120.1, 119.2, 118.3, 116.3, 108.4, 94.7, 68.6 (5C), 67.5 (2C), 66.9, 66.4, 31.1, 29.3, 20.9, 10.6; ESI MS: 357 (M+1), 356 (M).

HPLC analysis OD: ramp, flow 0.6mL/m (hexane: *i*-PrOH) from 99:1 to 90:10 in 20min. TM: 14.79 min; tm: 19.94 min.

(*S*)-1-[3-(5-bromoindole)ethyl]ferrocene 4d.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and 5-bromoindole **2d** (0.039 g, 0.2 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:diethylether 4:1) and purified by flash chromatography.

Yield 45%, 99% ee, $[\alpha]_D$ = -58° (c 0.5, $CHCl_3$).

Dark yellow solid; mp = 163 °C; IR: 3414, 3093, 1458 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.87 (bs, 1H), 7.78 (s, 1H), 7.31-7.15 (m, 2H), 6.74 (s, 1H), 4.37 (m, 9H), 4.06 (bs, 1H), 1.69 (d, J = 5.7 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 135.1, 128.5, 124.9, 123.3, 122.2, 112.9, 112.7, 102.6, 95.7, 69.7 (5C), 68.9, 68.4, 67.7, 67.2, 30.8, 21.9; ESI MS: 409 (M+1), 408 (M).

HPLC analysis AD: isocratic, flow 0.7mL/m (hexane: *i*-PrOH) 85:15. TM: 10.97 min; tm: 11.71 min.

(*S*)-1-[3-(5-Methoxyindole)ethyl]ferrocene 4e.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and 5-methoxyindole **2e** (0.072 g, 0.2 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:diethylether 4:1) and purified by flash chromatography. Yield 81%, 99% ee, $[\alpha]_D$ = -57° (c 0.4, $CHCl_3$).

Yellow oil; IR:3414, 3091, 1622, 1581, 1210, 1172 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.74 (bs, 1H), 7.22 (d, J = 8.9 Hz, 1H), 7.07 (d, J = 1.5 Hz, 1H), 6.83 (dd, J = 8.9, 1.5 Hz,

1H), 6.64 (s, 1H), 4.23 (m, 9H), 4.09 (q, 1H), 3.87 (s, 3H), 1.69 (d, J = 6.7 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 153.7, 131.5, 126.8, 123.0, 121.5, 111.9, 111.7, 101.4, 95.0, 68.8 (5C), 68.2, 67.5, 66.9, 66.6, 56.0, 30.6, 21.6; ESI MS: 360 (M+1), 359 (M).

HPLC analysis AD: isocratic, flow 0.8mL/m (hexane: *i*-PrOH) 85:15. TM: 15.47 min; tm: 18.52 min.

(*S*)-1-[3-(5-Cyanoindole)ethyl]ferrocene 4f.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and 5-cyanoindole **2f** (0.028 g, 0.2 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:diethylether 1:1) and purified by flash chromatography. Yield 43%, 99% ee, $[\alpha]_D$ = -27° (c 0.25, $CHCl_3$).

Yellow solid; mp = 76-78 °C; IR: 3387, 2913, 1094 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.13 (bs, 1H), 7.90 (s, 1H), 7.28 (s, 2H), 6.80 (s, 1H), 4.10-3.90 (m, 9H + 1H), 1.60 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 137.9, 126.1, 125.0, 124.6, 123.9, 122.8, 121.0, 112.0, 101.9, 94.5, 69.1 (5C), 68.3, 67.9, 67.4, 66.6, 30.5, 21.5; ESI MS: 355 (M+1), 354 (M). 344 (M+1), 343.

HPLC analysis AD: isocratic, flow 0.9mL/m (hexane: *i*-PrOH) 85:15. TM: 12.83 min; tm: 12.86 min.

(*S*)-1-(2-Pyrrolethyl)ferrocene 4h.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and pyrrole **2h** (0.069 mL, 1.0 mmol), until judged complete by TLC (R_f = 0.5 , cyclohexane:diethylether 4:1) and purified by flash chromatography.

Yield 68%, 99% ee, $[\alpha]_D$ = -46° (c 0.8, $CHCl_3$).

Orange solid; mp = 94 °C; IR: 3440, 3089, 1618 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.93 (bs, 1H), 6.58 (s, 1H) 6.08 (d, J = 2.8 Hz , 1H), 5.90 (s, 1H), 4.10-4.01 (m, 9H), 3.84 (q, J = 7.0 Hz, 1 H), 1.58 (d, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 136.7, 115.8, 107.9, 103.8, 93.1, 68.5 (5C), 67.6, 67.4, 67.3, 66.0, 32.1, 21.2; ESI MS: 280 (M+1), 279 (M).

HPLC analysis AD: ramp, flow 0.6mL/m (hexane: *i*-PrOH) from 99.5:0.5 to 80:20 in 20 min. TM: 15.07 min; tm: 19.55 min.

(*S*)-1-[3-(1-*N*-methylpyrrole)ethyl]ferrocene 4i.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and 1-methylpyrrole **2i** (0.089 mL, 1.0 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:dichloromethane 3:1) and purified by flash chromatography.

Yield 81%, 99% ee, $[\alpha]_D$ = +31° (c 0.8, $CHCl_3$).

Orange solid; mp = 51 °C; IR: 3096, 2925, 1488, cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 6.53 (d, J = 1.8 Hz, 1H), 6.08 (dd, J = 2.9 Hz, 1H), 5.85 (d, J = 1.8 Hz, 1H), 4.20-4.14 (m, 5H), 4.13-4.07 (s, 3H), 4.08-4.00 (s, 1H), 3.86 (q, J = 7.1 Hz, 1H), 3.61 (s, 3H), 1.68 (d = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 138.1, 120.9, 106.4, 105.0, 94.2, 68.4 (5C), 67.5, 67.2, 66.7 (2C),33.8, 30.6, 21.3; ESI MS: 294 (M+1), 293 (M), 213.

HPLC analysis OJ: ramp, flow 0.8mL/m (hexane: *i*-PrOH) from 99.5:0.5 to 80:20. TM: 12.41 min;tm: 16.05 min.

(*S*)-(2-pyrrolephenylmethyl)ferrocene 5h.

Prepared according to the general procedure from alcohol **3** (0.029g, 0.1mmol) and pyrrole **2h** (0.069 mL, 1.0 mmol), until judged complete by TLC (R_f = 0.4 , cyclohexane: diethylether 5:1) and purified by flash chromatography.

Yield 60%, 94% ee, $[\alpha]_D$ = +11° (c 1.1, $CHCl_3$).

Yellow solid; mp= 125 °C; IR: 3419, 3092, 2926, 1693, 1451 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.03 (bs, 1H), 7.38-7.21 (m, 5H), 6.68 (m, 1H) 6.15 (m, 1H), 5.89 (m, 1H), 5.15 (s, 1H), 4.28-4.00 (m, 9H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 143.9, 134.7, 128.7 (2C), 128.4 (2C), 126.7, 116.5, 108.2, 106.7, 91.1, 68.9, (5C), 68.7, 68.1, 68.0, 67.5, 45.2; ESI MS: 342 (M+1), 341 (M), 339.

HPLC analysis AD: gradient, flow 0.6mL/m (hexane: *i*-PrOH) from 99.5:0.5 to 80:20 in 20 min. TM: 15.72 min; tm: 19.45 min.

(*R*)-(1-azidoethyl)ferrocene 4j.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and trimethylsilyl azide **2j** (0.026 mL, 0.2 mmol), until judged complete by TLC (R_f = 0.6 , cyclohexane:diethylether 95:5) and purified by flash chromatography.

Yield 83%, 97% ee, $[\alpha]_D$ = -48° (c 3.2, $CHCl_3$). Orange oil; IR: 3092, 2097 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.38 (q, J = 6.6 Hz, 1H), 4.24 (m, 9H), 1.59 (d, J = 6.6 Hz, 3H); ^{13}C-

NMR ($CDCl_3$, 50 MHz) δ: 89.1, 69.2 (5C), 68.5 (2C), 67.7 (2C), 57.2, 20.1; ESI MS: 255.9 (M+1), 254.9 (M), 230.

HPLC analysis OJ: gradient, flow 0.7mL/m (hexane: *i*-PrOH) from 99:1 to 97:3 in 20min. TM: 9.65 min; tm: 10.32 min.

(*R*)-(3-azidophenylmethyl)ferrocene 5j.

Prepared according to the general procedure from alcohol **3** (0.029g, 0.1mmol) and trimethylsilyl azide **2j** (0.026 mL, 0.2 mmol), until judged complete by TLC (R_f = 0.6 , hexane and purified by flash chromatography. Yield 95, 72% ee, $[\alpha]_D$ = -44° (c 2.00 , $CHCl_3$).

Red oil; IR: 3089, 2929, 2082 1458 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.45-7.30 (m, 5H), 5.45 (s, 1H), 4.34-4.04 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 139.7, 128.5 (2C), 128.2, 127.4 (2C), 88.6, 69.0 (5C), 68.3, 68.1, 67.3, 67.2, 65.7; ESI MS: 565.8 (D-N_2), 317 (M), 292, 276 (M-N_3).

HPLC analysis OD: gradient, flow 0.6mL/m (hexane: *i*-PrOH) from 99.5:0.5 to 98:2 in 20min. TM: 17.88 min; tm: 28.53 min.

(*R*)-[1-(2-thionaphtyl)ethyl]ferrocene 4l.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and naphtalene-2-thiol **2l** (0.032 g, 0.2 mmol), until judged complete by TLC (R_f = 0.6 , hexane) and purified by flash chromatography. Yield 63%, 96% ee, $[\alpha]_D$ = -50° (c 2.3 , $CHCl_3$).

Orange solid; mp = 64-69°C; IR: 3056, 1454 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.806-7.75 (m, 4H), 7.52-7.44 (m, 3H), 4.29 (q, J = 6.9 Hz, 1H) 4.23-4.10 (m, 9H), 1.71 (d, J = 6.9 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 133.7, 132.9, 132.5, 131.8, 130.6, 128.3, 127.8, 127.6, 126.5, 126.2, 91.0, 68.9 (5C), 68.1, 67.9, 67.8, 66.3, 43.7, 21.4; ESI MS: not ionisable.

HPLC analysis OJ: gradient, flow 0.6mL/m (hexane: *i*-PrOH) from 99:1 to 80:20 in 20min. TM: 27.2 min; t: 33.7 min.

(*R*)-[(2-thionaphtyl)phenylmethyl]ferrocene 5l.

Prepared according to the general procedure from alcohol **3** (0.029g, 0.1mmol) and naphtalene-2-thiol **2l** (0.032 g, 0.2 mmol), until judged complete by TLC (R_f = 0.6 , hexane) and purified by flash chromatography. Yield 47%, 94%, $[\alpha]_D$ = -19° (c 1.8,

$CHCl_3$). Yellow solid; mp = 123 °C; IR: 1490, 11450 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.77-7.63 (m, 4H), 7.45-7.41 (m, 3H), 7.34-7.21 (m, 5H), 5.26 (s, 1H), 4.20-4.13 (m, 9H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 142.1, 133.6, 133.3, 132.3, 131.2, 130.0, 128.5 (2C), 128.3 (2C), 128.1, 127.7, 127.6, 127.3, 126.3, 126.1, 89.7, 69.2 (5C), 68.7, 68.3, 67.9, 67.8, 54.4; ESI MS: 434.9 (M+1), 434.0 (M), 275.

HPLC analysis OJ: gradient, flow 0.6mL/m (hexane: *i*-PrOH) from 99:1 to 80:20 in 20 min. TM: 19.34 min; tm: 23.54 min.

(*R*)-[1-(*N*-methyl-(3-thioimidazole)ethyl]ferrocene 4m.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and N-methyl-2-thioimidazole **2m** (0.024 g, 0.2 mmol), until judged complete by TLC (R_f = 0.6 , hexane) and purified by flash chromatography. Yield 63%, 80% ee, $[\alpha]_D$ = -66° (c 1.1, $CHCl_3$).

Yellow solid; mp = 139-142 °C; IR: 3117, 2929, 1560, 1523, cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 6.51 (d, J = 2.4 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 5.93 (q, J = 6.8 Hz, 1H), 4.30-4.15 (m, 9H) 3.59 (s, 3H), 1.69 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.0, 117.5, 113.9, 87.6, 69.0 (5C), 68.9, 68.7, 67.8, 65.9, 52.6, 34.8, 19.3; ESI MS: 327 (M+1), 326 (M), 213.

HPLC analysis OJ: isocratic, flow 0.6mL/m (hexane: *i*-PrOH) 80:20. TM: 24.8 min; t: 31.1 min.

(*R*)-[1-(4-methylthiophenol)ethyl]ferrocene 4n.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and 4-methylthiophenol **2n** (0.024 g, 0.2 mmol), until judged complete by TLC (R_f = 0.6 , hexane) and purified by flash chromatography. Yield 46%, 90%, $[\alpha]_D$ = -68° (c 1.0, $CHCl_3$).

Yellow oil; IR: 2916, 1499 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.28 (d, J = 7.8 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 4.25-3.99 (m, 10H), 2.36 (s, 3H), 1.63 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 137.4, 133.8 (2C), 131.4, 129.4 (2C), 91.0, 68.6 (5C), 67.9, 67.6, 67.5, 66.0 44.0, 21.1 (2C); ESI MS: 337 (M+1), 336 (M).

HPLC analysis OJ: isocratic, flow 0.8mL/m (hexane: *i*-PrOH) 98:2. TM: 14.7 min; t: 15.9 min.

[3-(Pentan-2,4-dione)ethyl]ferrocene 4o.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and pentan-2,4-dione **2o** (0.031 mL, 0.2 mmol), until judged complete by TLC (R_f = 0.4 , cyclohexane:diethylether 6:4) and purified by flash chromatography. Yield 90% as inseparable mixture of diasteroisomers.

Yellow solid; mp=53-71°C (with decomposition);IR: 3099, 2974, 1717, 1698 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.15-4.00 (m, 9H); 3.58 (d, J = 9.7 Hz, 1H); 3.33 (m, 1H); 2.15 (s, 3H); 1.87 (s, 3H); 1.32 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 204.5; 203.4; 91.5; 77.2; 68.6 (5C); 68.5; 67.6; 67.5; 65.2; 34.6; 31.9; 29.3; 18.3; ESI MS: 335. (M+23), 313. (M+1), 312 (M).

1-[2-(Ethyl-3-oxo-butyrate)ethyl]ferrocene 4p.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and ethyl-3-oxo-butyrate **2p** (0.025 mL, 0.2 mmol), until judged complete by TLC (R_f = 0.4 , cyclohexane:diethylether 9:1) and purified by flash chromatography. Yield 48%.

Red oil; IR: 3426, 2978, 1739, 1719, 1645, 1558 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz, mixture of two diastereoisomer 50:50) δ: 4.22-3.97 (m, 9H + 2H); 3.44-3.24 (m, 2H); 2.17 (s, 1.5H, diast.); 1.93 (s, 1.5H, diast.); 1.40 (d, J = 6.9 Hz, 3H); 1.25 (t, J = 7.1 Hz, 1.5H, diast.); 1.14 (t, J = 7.1 Hz, 1.5H, diast.); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 203.4; 202.6; 168.8; 168.5; 91.4; 91.3; 68.8 (2.5C); 68.7 (2.5C), 68.7, 68.6, 68.6; 68.4; 67.9; 67.5; 67.4; 67.4; 67.3; 65.6; 65.5; 61.2; 61.1; 33.9; 33.7; 31.2; 29.8; 29.7; 18.3; 17.9; 14.1; 14.0; ESI MS: 365 (M+23), 343 (M+1), 342 (M), 213.

1-[2-(Ethyl-2-nitroacetate)ethyl]ferrocene 4q.

Prepared according to the general procedure from alcohol **1** (0.023g, 0.1mmol) and ethyl-3-oxo-butyrate **2q** (0.022 mL, 0.2 mmol), until judged complete by TLC (R_f = 0.4 , cyclohexane:diethylether 4:1) and purified by flash chromatography. Yield 78% as inseparable mixture of diasteroisomers.

Red oil; IR: 3091, 2986, 1752, 1705, 1623, 1557 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz, mixture of two diastereoisomer 50:50) δ: 4.97 (d, J = 8.2 Hz, 1H), 4.53-4.15 (m, 9H + 2H); 3.60 (m, 1H); 1.50 (t, J = 7.1 Hz, 1.5H); 1.30 (t, J = 7.1 Hz, 1.5H); 1.19 (t, J = 7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 163.7; 163.3; 111.6; 93.9; 93.7; 87.9; 87.1; 70.4; 69.6; 68.8 (2.5C); 68.7 (2.5C); 68.4; 68.2; 68.1; 68.0; 67.9; 66.9; 66.1; 65.9; 62.7; 59.5; 35.6; 35.5; 16.7; 16.3; 13.9; 13.8; ESI MS: 345 (M), 299.

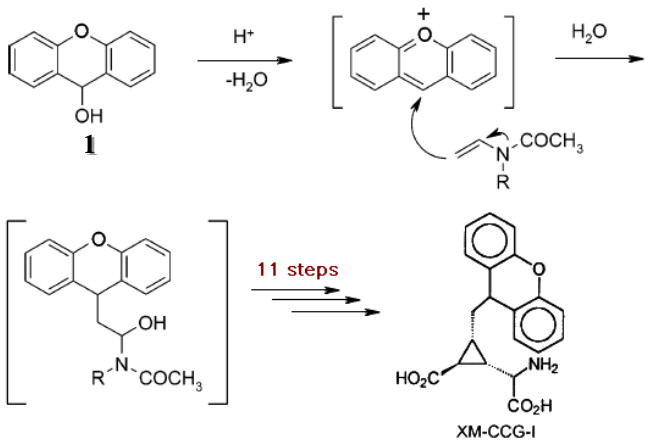
Chapter 4

A Rational Approach Towards the Nucleophilic Substitutions of Alcohols "on Water"[1]

Introduction

We sought to extend our "on water" ferrocenyl alcohols substitution concept, describe in chapter 3 toward a more general benzylic alcohols class. On the other hand access to substituted benzhydrols via free metal strategy is ongoing focus of organic synthetic strategy. Several drug synthesis count benzhydrols as key intermediates, for example in the synthesis of 2-(3'-xanthenylethyl-2'-carboxycyclopropyl)-glycine, (a potent group II antagonist with sub micromolar activity).[2]

Scheme 1 Several synthetic strategy have an carbocation intermedia.



[1] P.G. Cozzi, L. Zoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 4162.

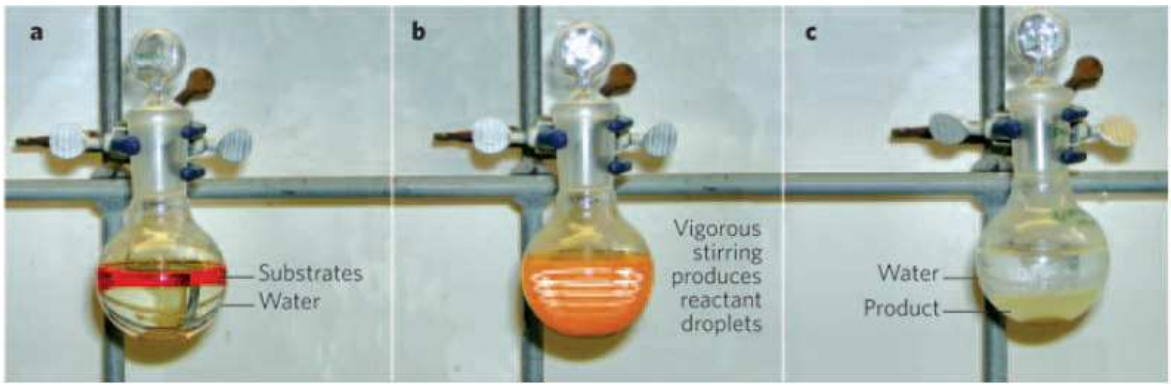
[2] a) R. Pellicciari, G. Costantino, M. Marinozzi, A. Macchiarulo, L. Amori, P. J. Flor, F. Gasparini, R. Kuhn, S. Urwyler, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3179; b) M. Prashad, Y. Lu, O. Repič, *J. Org. Chem.* **2004**, *69*, 584.

Over recent years great efforts have been made in the field of green chemistry to get synthetic processes that employ less toxic chemicals and does not produce pollutant by-products.[3] As part of this green concept, toxic solvents (for example: chlorinated solvents) and flammable organic solvents are replaced by alternative safe and health media. Furthermore solvents account for 75–80% of the waste related with the synthesis of APIs (Active Pharmaceutical Ingredient). Organic solvents are emploed as solvent media in reactions, in separations, and to clean reactor following a cycle.[4] For all these reasons, solvent-free conditions have attracted significant attention[5] for the advantages they offer in terms of green chemistry.[6] Unfortunately in many case, organic solvents are requested for example to keep controlled the temperature of the reaction or to mix reagents. Water is able to satisfactory both requirements.[7]

"On water"condition and the network of hydrogen bonds

Figure 1 Facile access to product by removal water by simple separation.

■ Klijn and Engbert, *Nature* **2005**, *435*, 746.



When water, which is unquestionably cheap, safe, and environmentally benign, is used as a solvent,[8] the reactivity and selectivity observed are different from those of the same reactions conducted in standard organic solvents:[9] Sharpless disclosed the concept of "on

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[3] A. Matlack, *Green Chem.* **2003**, *5*, 7.

[4] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey,dJ. L. Leazer, Jr. R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, 9, 411.

[5] J. Zhang, Z. Cui, F.Wang, Y.Wang, Z.Miao, R. Chen, *Green Chem.* **2007**, *9*, 1341.

[6] P. T. Anastas, J. C. Warner, *Green Chemistry-Theory and Practice*, Oxford University Press, New York, **1998**

[7] D. Almas¸ D. A. Alonso, A.-N. Balaguer, C. Nájera, *Adv. Synth. Catal.* **2009**, *351*, 1123.

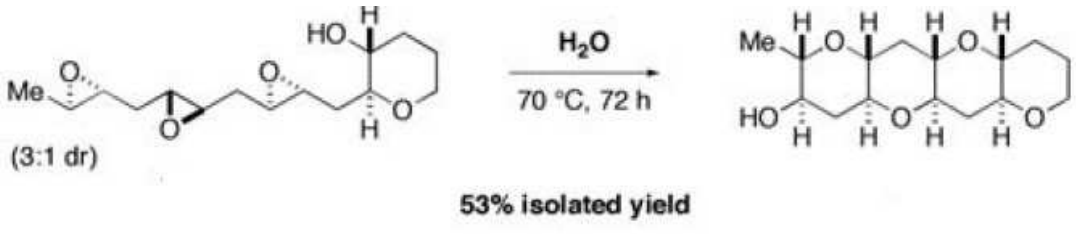
[8] a) C.-J. Li, T.-H. Chan, *Organic Reactions in Aqueous Media*,Wiley, New York, **1997**; b) *Organic Synthesis in Water* (Ed. : P. A.Grieco), Blackie Academic, Professional, London, **1998**; c) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095; C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68; d) *Organic Reactions in Water* (Ed. : U. M. Lindström), Blackwell Publishing, Oxford, **2007**.

[9] a) U. M. Lindström, F. Andersson, *Angew. Chem. Int. Ed.* **2006**, *45*, 548; b) M. C. Pirrung, *Chem. Eur. J.* **2006,** *12*, 1312; S. Otto, J. B. F. N. Engberts, *Org. Biomol. Chem.* **2003**, *1*, 2809; c) K. Aplander, R. Ding, U. M. Lindström, J. Wennerberg, S. Schultz, *Angew. Chem. Int. Ed.* **2007**, *46*, 4543.

water" applyied to Diels-Alder[10], (Figure 1) Mayr was successful in coupling reactions of benzylic halides with several nucleophiles via water media[11] (see previous chapter) and Vilotijevic reported a templated, water-promoted epoxide-opening cascade. It is interesting that the epoxide opening by the concomitant activation of the nucleophile (OH) and electrophile (epoxide) is mediated by a cooperative network of hydrogen bonds as shown in Scheme 2.[12]

Scheme 2 Water promoted epoxide-opening cascades via fused transition state.

- Cyclization to THP product: I. Vilotijevic, Science **2007**, *317*, 1191.



- Spiro or Fused transition state depend to combination of entropic and enthalpic effects.

The opening of epoxides "on water" is possible to due to the strain in cyclopropane ring. Alcohols generally have a stronger C-O bond, hard to break by "cooperative network of hydrogen bonds".[13] Another interpretation provides as in aqueouse solution such carbocations tend to have very short lifetimes as a result of their rapid reactions with water.[14] To carry out alcohol substitution without acid catalyse, both interpretations require stabilize carbocation intermedia to favor C-O cleavage and to increase carbocation lifetime.

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[10] S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.

[11] a) M. Hofmann, N. Hampel, T. Kanzian, H. Mayr, *Angew. Chem. Int. Ed.* **2004**, *43*, 5402; b) M. Westermaier, H. Mayr, *Org. Lett.* **2006**, *8*, 4791.

[12] I. Vilotijevic, T. F. Jamison, *Science* **2007**, *317*, 1189.

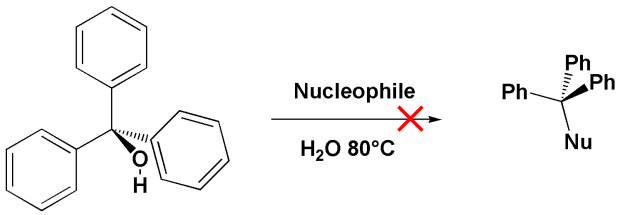
[13] a) G. C. Gullickson, D. E. Lewis, *Aust. J. Chem.* **2003**, *56*, 385; b) F. Bisaro, G. Prestat, M. Vitale, G. Poli, Synlett **2002**,1823; c) S. J. Coote, S. G. Davies, D. Middlemiss, A. Naylor,*Tetrahedron Lett* **1989**, *30*, 3581.

[14] J. P. Richard, T. L. Amyes, M. M. Toteva, *Acc. Chem. Res.* **2001**, *34*, 981.

Analysis of Carbocation stability

At the beginning of our work we tested alcohol triphenylmethanol **2**, which thanks to extra aromatic group should generate a more stable carbocation compare with alcohol diphenyl carbinol tested in chapter 3. Unfortunately starting materials **2** did not react with indole or trimethyl-silylazide (best nucleophiles used in chapter 3) and were recovered unchanged. (Scheme 3)

Scheme 3 Test reaction with alcohol 2 and nucleophiles "on water" condition.



2

Mayr clearly explained in his works how the carbocarbocation intercepts the nucleophile (indole) before quenching.[11] Alcohol **2** unreactivity is due to the absence of carbocation intermedia, or to the presence of the steric hindrance near the carbocation center.

Rationl approch to the problem

Mayr et al. introduced a table containing electrophilicity parameters of several benzydrol ions and nucleophilicity parameters of a sequence of generic nucleophiles. Mayr demonstrated that one parameter for the electrophile *(E)* and two parameters for the nucleophiles *(N , s)* into Logartimic equation $logk=s(N+E)$ are sufficient for a quantitative description of the rates of a large variety of electrophile–nucleophile combinations.[15] All Carbocations reported in Figure 2 were obtained by the treatment of corresponding halydes with stechiometric amount of lewis acids.[16]

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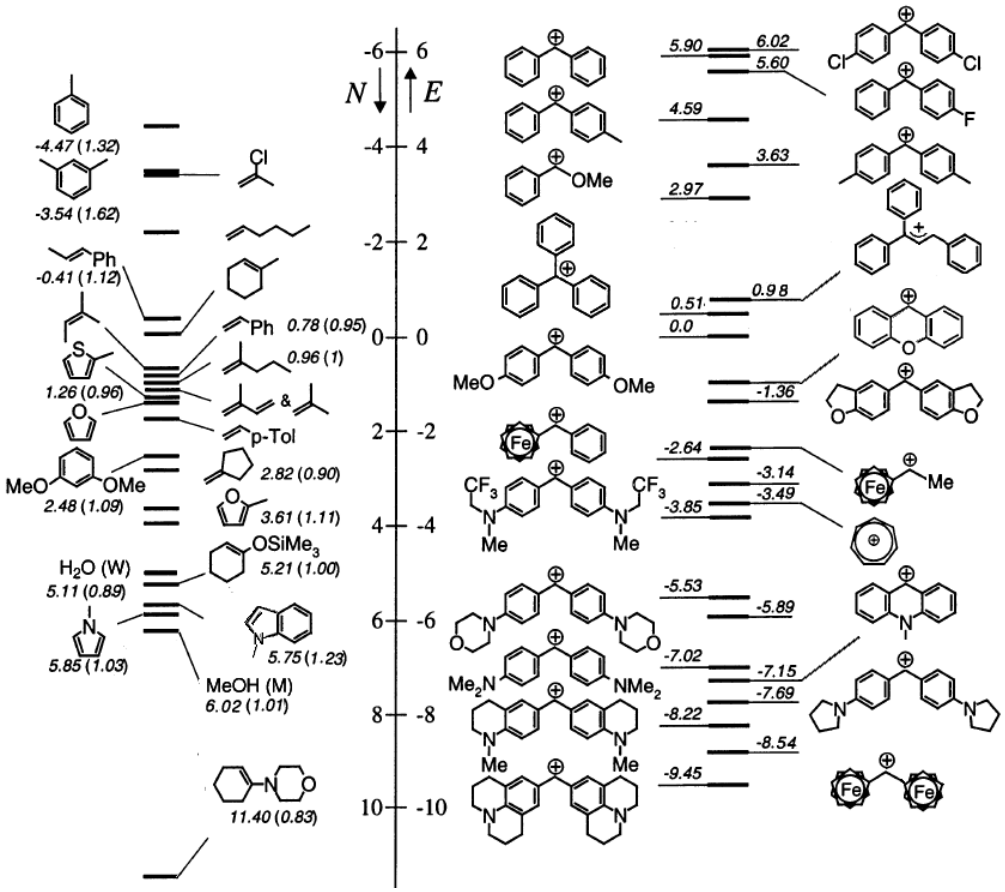
[15] a) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807; b) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66; c) S. T. A. Berger, F. H.Seeliger, F. Hofbauer, H. Mayr, *Org. Biomol. Chem.* **2007**, *5*, 3020; d) F. Seeliger, S. T. A. Berger,G. Y. Remennikov, K. Polborn, H. Mayr, *J. Org. Chem.* **2007**, *72*, 9170; e) S. Minegishi, H. Mayr *J. Am. Chem. Soc.* **2003**, *125*, 286.

[16] H. Mayr, T. Bug, M. Gotta, N. Hering, B. Irrgang, B. Janker, B Kempf, R. Loos, A. R. Ofial, G.Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *123*, 9500.

Figure 2 Scale achieved by combining more Mayr's scales.

■ Mayr: a) *Acc. Chem. Res.* **2003,** *36*, 67; b) *J. Am. Chem. Soc.* **2003**, *125*, 292; c) *J. Phy. Org. Chem.* **1998**, *11*, 647; d) *J. Am. Chem. Soc.* **1998,** *120*, 904.[15a,15e,17]



As depict in Figure 2 tritylium is characterized by an *(E)* value of 0.51[15e], while ferrocenylcarbenium ion (which has already reacted via "on water" condition) is characterized by an *(E)* value of -2.57 [15b]. Therefore we decided to start our exploration in the range of *(E)* parameters lower than -2.57. In order to do that lifetimes of carbocations have to be increased substantially by the introduction of electron-donating substituents on the aryl ring.[18]

Chase of desired alcohol

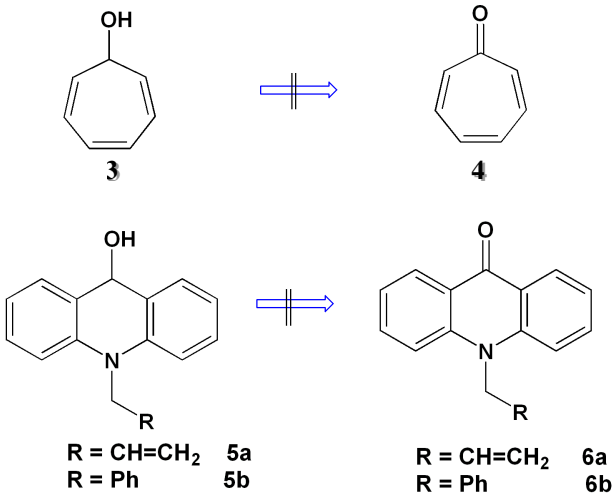
Unfortunately a lot of carbocation candidates instanced in Figure 2 presente a plodding synthesis of alcoholic parent compounds. It was not easy to find commercial aviable substrates or pratical synthesis to obtain starting materials. Consequently carbocations as

[17] a) H. Mayr, O. Kuhn, M. F. Gotta, M. Patzjou , *J. Phy. Org. Chem.* **1998**, *11*, 642; b) O. Kuhn, D. Rau, H. Mayr, *J. Am. Chem. Soc.* **1998,** *120,* 900.

[18] The 4,4'-bis(dimethylamino)diphenylmethane carbocation has a half-life of 10–20 s; see: R. A. McCLelland, V. M. Kanagasabapathy, N. S. Banait, S. J. Steenken, *J. Am. Chem. Soc.* **1989**, *111*, 3966.

tropylium and acridinium (teorically good candidates respectivaly with E = -3.49 the first, and -7.15 the second) were discard.

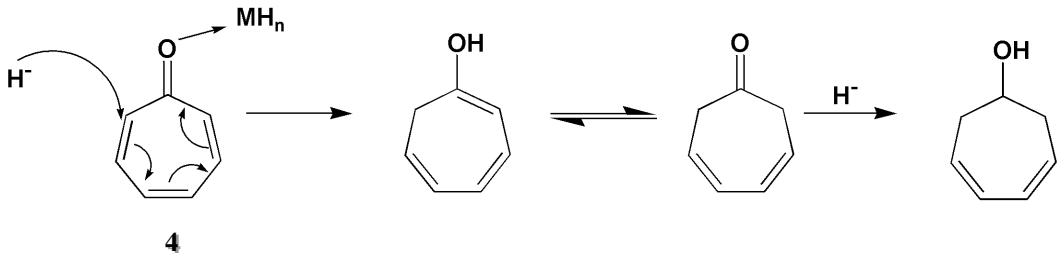
Figure 3 R etrosynthesis scheme about discarded alcohols.



Simple reduction of tropone to alcohol **3** leads to a non desired product as shown Scheme 4. Chapman[19] and Perkins[20] in their works describe similar results.

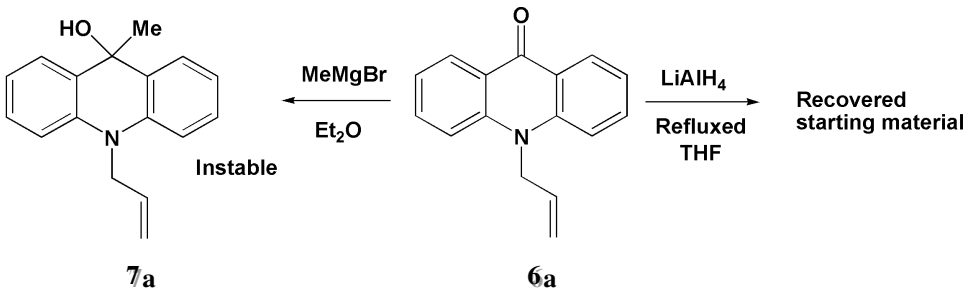
Scheme 4 Tropone reduction: unusual behavioure.

■ Mechanism reported for 1,8 cycloaddition proposed by chapman.



N-alkylated acridone **6a**,**b** treated at reflux condition with $LiAlH_4$ (as reductive agent) were found unchanged. Grignard reagent gives desired terziary alcohol as product but **7a** was found as instable compound. (Scheme 5).

Scheme 5 Typical reduction agents failed to give alcohol by acridone.



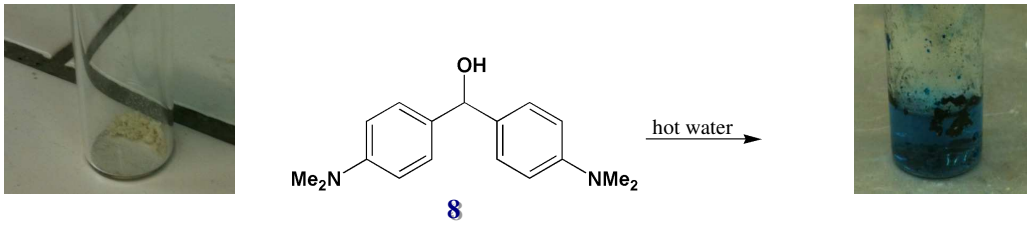
[19] a) O. L. Chapman, D. J. Pasto, A. A. Griswold, *J. Am. Chem. Soc.* **1962**, *84*, 1213; b) D. I. Schuster, J. M. Palmer, S. C. Dickerman J. Org. Chem. **1996**, *31*, 4281.

[20] W. C. Perkins, D. H. Wadsworth, *J. Org. Chem.* **1972**, *37*, 800.

Gratifyingly commercial aviable alcohol bis(4-Dimethylamino-phenyl)-benzhydrol **8** generates an stabilized carbocation (E = - 7.02). We tested this alcohol with "on water" optymizing condition seen in the chapter 3. Alcohol **8** reacted with indole to give quantitative yield of the desired product **11a**. We observed a stronger blue coloration when the two starting materials were put into hot water. At the end of the reaction the colouring desappeared. Mayr in his work[15a] described similar results, when the corresponding bromide **9** reacted with stochiometric amount of an lewis acid. This is a confirmation of the formation of the carbocation in our conditions.

Figure 4 Para-Electron donating substituents give major stability to benzhydryl ion.

- Carbocation by alcohol in "on water" reaction condition.



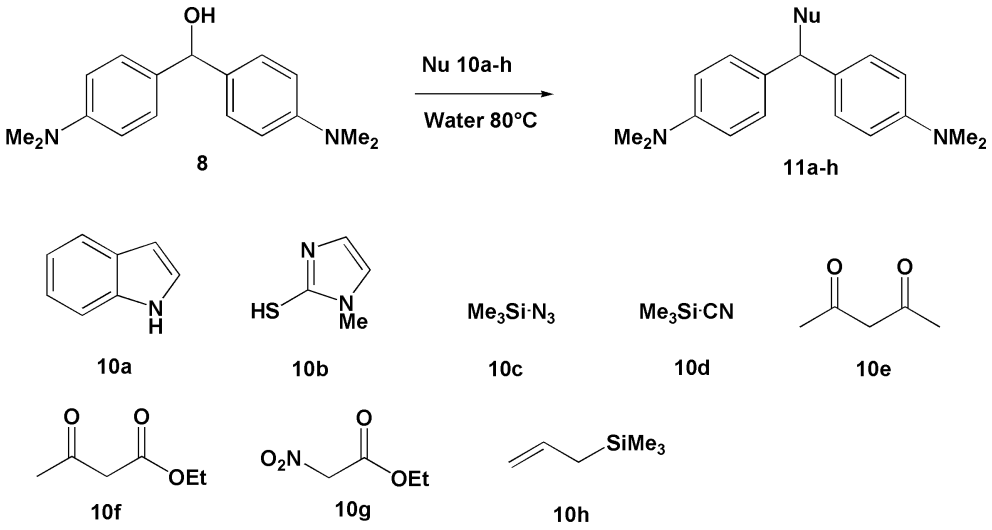
8

- Carbocation by halide Mayr reaction condition, *Acc. Chem. Res.* **2003**,*36*, 72.

9

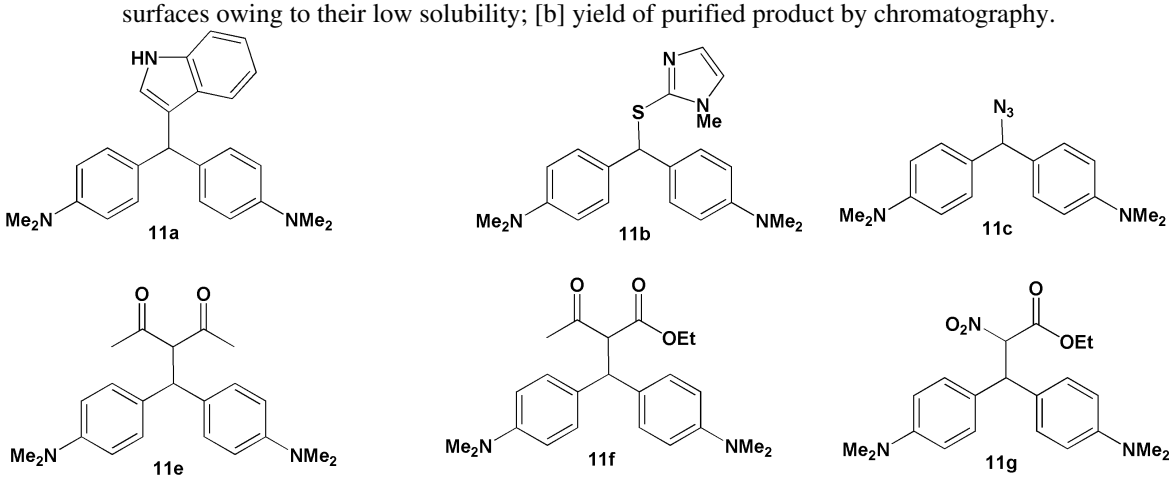
After the first encuraging result, we sought to improve the reaction scope. Several classes of nucleophile were tested (Table 1).

Table 1 "On water" condition tested over diaryl carbinol 8 with several mucleophiles.



Entry[a]	Nucleophiles	Time (h)	Yield (%)[b]
1	**10a**	14	98
2	**10b**	24	79
3	**10c**	24	85
4	**10d**	48	0
5	**10e**	24	92
6	**10f**	24	88
7	**10g**	24	91
8	**10h**	48	0

[a] All the reactions were carried out in deionized water (pH 6.52) at 80°C without inert gas protection and with vigorous stirring. Under these conditions the reactants alcohol **8** (0.2-0.4 mmol) and nucleophiles (0.4-0.8 mmol) float on the water emulsion surfaces owing to their low solubility; [b] yield of purified product by chromatography.



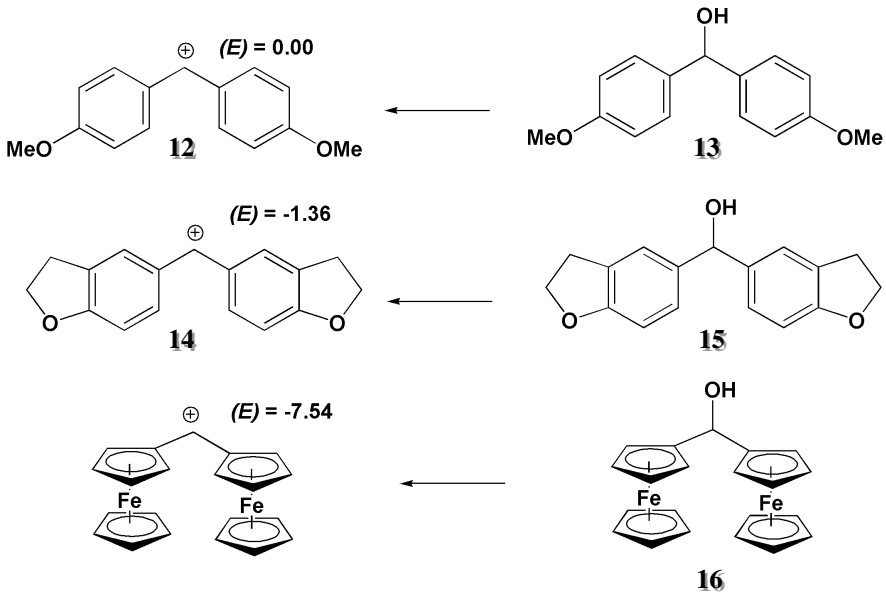
Remarkably, almost all tested nucleophiles reacted to give desired products in high levels yield. Various ketoesters, diketones, and nitroacetates were tested for the first time in "on water condtion" without the requirement for Lewis or Bronsted acids. As expected trimethyl allyl silane and trimethyl silyl cyanide did not react throungh “on water”

condition (similarly in the same conditions, they did not react with ferrocenyl alcohols).

Limits of reaction

To understand the range of electrophiles aviables for the direct substitution of their alcohol precursors "on water", further alcohols were tested as show in Figure 5.

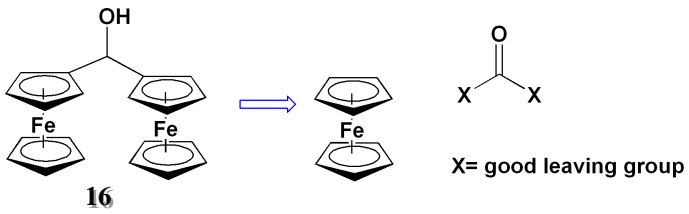
Figure 5 Further alcohols was synthesized to evalue their reacity



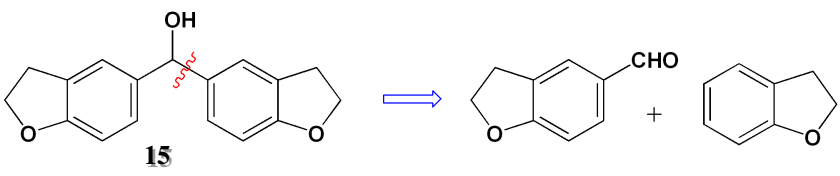
Their choice was determined on the basis of the parameters (*E*) of the carbocations generated. The electrophilicity (*E*) of **12** and **14** falls into the electrophilicity parameters of α-ferrocenyl carbocation (*E* = -2.57) and ion tritylium (E = 0.51). Instead bis-ferrocenyl alcohol **16** generates a carbocation ultrastabilized. Fortunately, **13** is commercially available, while the other two alcohols were synthesized in a simple way as described in Scheme 6.

Scheme 6 Synthesis of Alcohols 16 and 15.

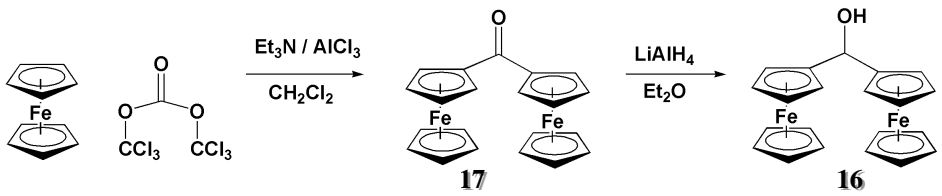
- Proposed retrosynthesis for diferrocenealcohol by double Friedel-Crafts reaction



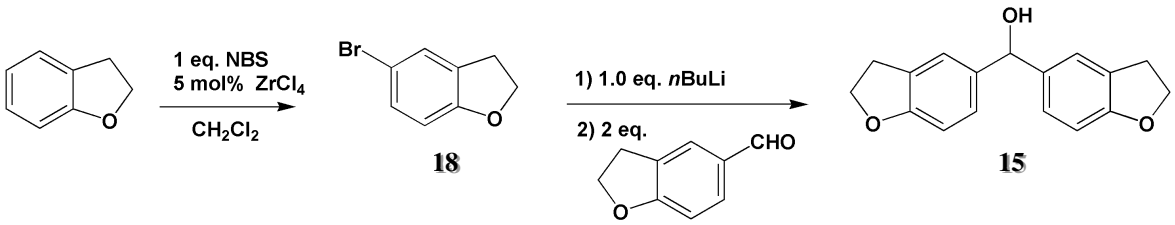
- Proposed retrosynthesis for dihydrobenzofurano-carbinol by metallation of aldehyde



- Reported synthesis for diferrocenealcohol [21,22]

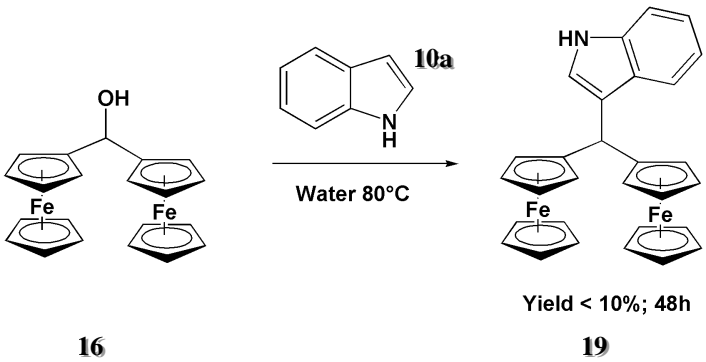


- Reported synthesis for dihydrobenzofurano-carbinol[23,24]



Electrophiles with *(E)* values close to "0" are simply too reactive. In fact, alcohols **13** and **15** were isolated unchanged after prolonged reaction time (3 days).

Scheme 7 Ultrastabilized carbocations are inert toward substitution.



The unsatisfactory results obtained with alcohol **16** could be explained by the higher stabilization of the generated carbocation in water. (Scheme 7).

Consequently, Alcohols, which reacts in "on water" condition keeping the *(E)* values for the corresponding carbocations in Mayr's scale range from -8.50 to -2.50 (Scheme 6).

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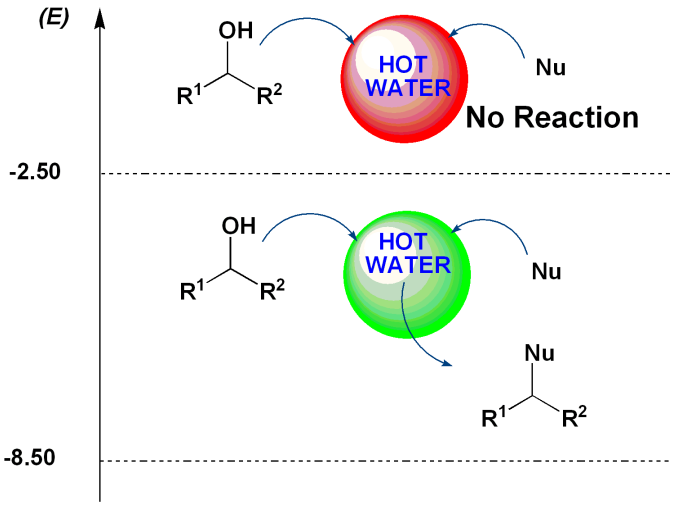
[21] Q. Wang, R. Huang, *J. Organomet. Chem.* **2000**, *604*, 287.

[22] Q. Wang, R. Huang, *J. Organomet. Chem.* **2000**, *604*, 287-289.

[23] A. Yahhua, H. Yamamoto, *PCT Int. Patent Appl.* **2007**, WO2007023920.

[24] J. P. Kelly, M. J. Jenkins, *J. Org. Chem.* **1983**, *49*, 409-413.

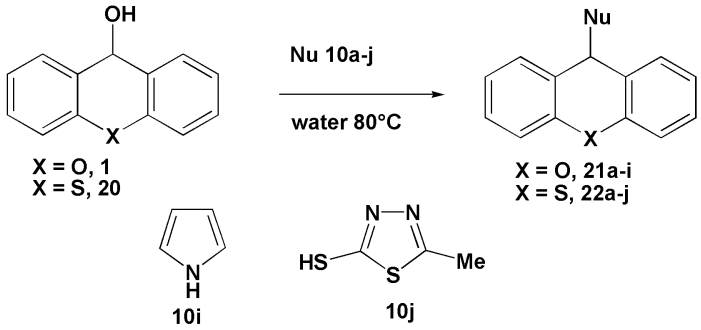
Figure 6 Hypothesis of reactivity range in S_N1 type reaction with alcohols.



Xanthene-9-ol **1** and Thioxanthen-9-ol **20** are an exception to the rule. These alcohols reacted through "on water" conditions with some nucleophiles.

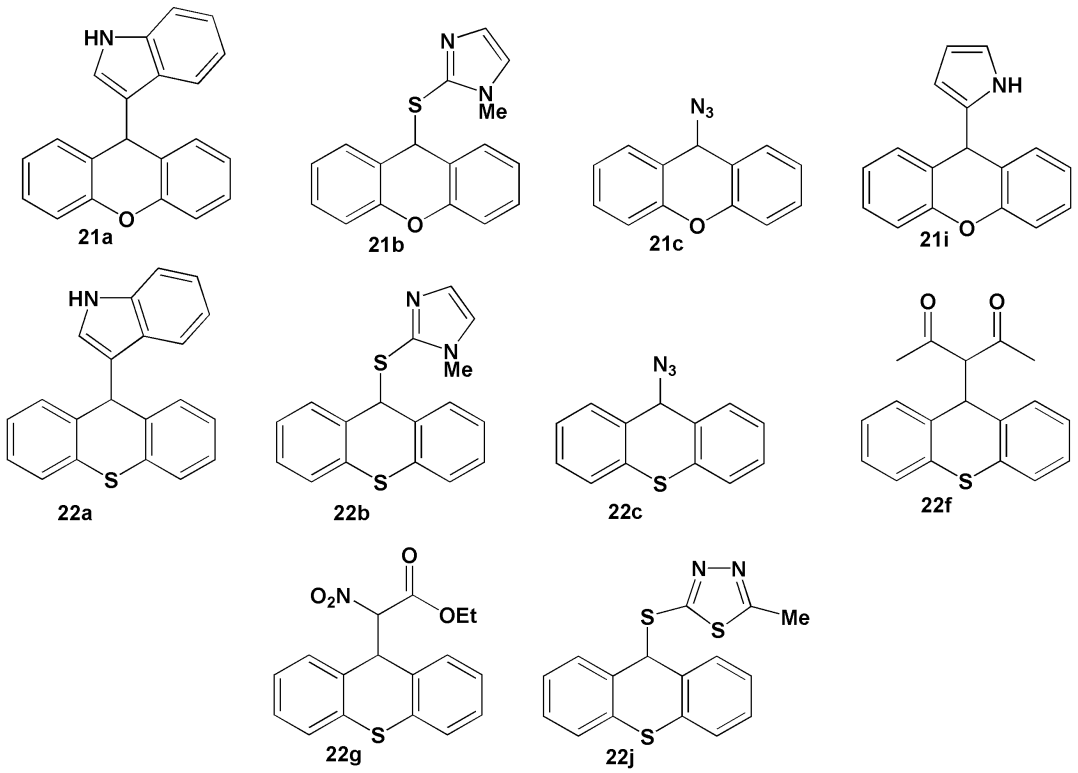
In Table 2 are disclosed the results obtained.

Table 2 Unespected reactivity via "on water" condition of alcohol 1 and 20.



Entry[a]	alcohol	nucleophile	time (h)	yield[b]
1	**1**	**10a**	16	82
2	**1**	**10b**	24	90
3	**1**	**10c**	16	95
4[c]	**1**	**10i**	72	65
5[d]	**1**	**10i**	72	80
6	**20**	**10a**	24	82
7	**20**	**10b**	24	90
8	**20**	**10c**	24	68
9	**20**	**10f**	24	83
10	**20**	**10g**	24	91
11	**20**	**10j**	24	85

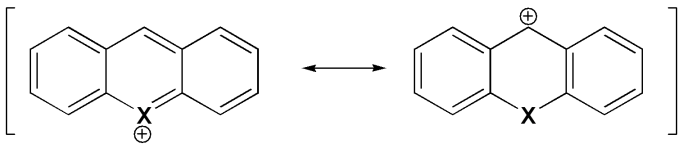
[a] All the reactions were carried out in deionized water (pH 6.52) at 80°C without inert gas protection and with vigorous stirring. Under these conditions the reactants, alcohols (0.2-0.4 mmol) and nucleophiles (0.4-0.8 mmol) float on the water emulsion surfaces owing to their low solubility; [b] yield of purified product by chromatography; [c] The reaction was performed with 4 equiv of pyrrole; [d] The reaction was performed with 8 equiv of pyrrole.



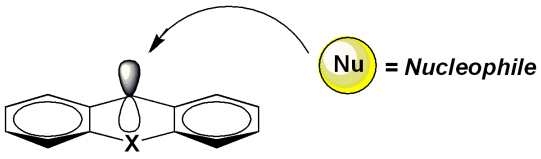
We hypothesized that the unexpected reactivity of the two alcohols is due to their lower steric hiderance compared to compound **15.** The carbocations generated by **1** and **20** are planar and aromatics compounds. On the contrary, the carbocation **14**'s aromatic ring rotates freely. Electrophilicity being equal, carbocations which are less selective towards the nucleophiles are those with greater steric hinderance, as shown in Scheme 8.

Scheme 8 Steric Hynderance can be lower selection of carbocation toward Nucleophile.

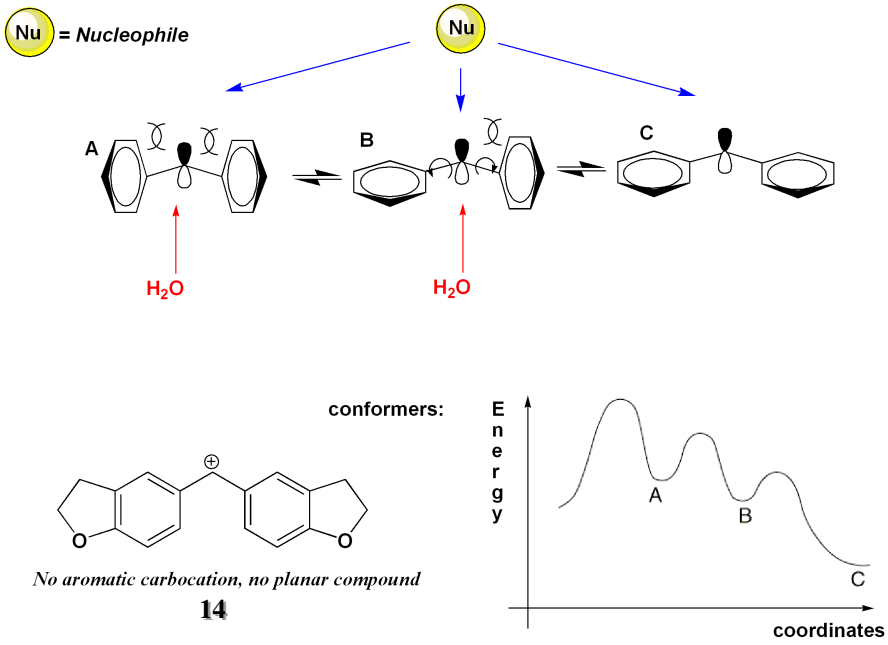
- Hypothesize on xanthen-9-ol and thioxanthen-9-ol reactivity.



xanthylium and thioxanthylium ions, planar rings within 14 electron (aromatics)



- hypothesize on benzyl alcohols **13**, **15** un-reactivity.



Carbocation **14** exist in many different conformers. Their energy levels vary depending on the aromatic ring's inclination when the carbocation interacts with the nucleophile. Subsequently, alcohols **15** and **13** in acquose media generate carbocation species, but small water molecules react faster than the nucleophile, producing alcohols. To compare the reactivity of alcohols "on water" with that under other conditions, we examined the reactions of alcohols (1-hydroxyethyl)ferrocene **23** and **8** with indole at room temperature and 80°C using a range of solvents as shown in Table 3

Table 3 **22** **and** **8** **with indole using different range conditions.**

Entry	Alcohol[a]	nucelophile	Solvent	Temperature[b]	hours	Yield[c]
1	**23**	**10a**	Toluene	25	24	0
2	**23**	**10a**	$C_2H_4Cl_2$	25	24	0
3	**23**	**10a**	Neat	25	24	0
4	**23**	**10a**	DMF	80	24	0
5	**23**	**10a**	DMSO	80	24	0
6	**23**	**10a**	Toluene	80	24	0
7	**23**	**10a**	CH_3CN	80	24	0
8	**23**	**10a**	Neat[d]	80	24	0
9	**23**	**10a**	D_2O	80	24	0
10	**23**	**10i**	Neat	80	24	0
11	**8**	**10a**	DMF	80	24	0
12	**8**	**10a**	DMSO	80	24	0
13	**8**	**10a**	$C_2H_4Cl_2$	80	28	88
14	**8**	**10a**	$C_2H_4Cl_2$[e]	80	28	0
15	**8**	**10a**	Toluene	80	24	91
16	**8**	**10a**	CH_3CN	80	48	0
17	**8**	**10a**	Neat[d]	80	12	66
18	**8**	**10a**	on H_2O	80	14	98
19	**8**	**10a**	Neat[d]	80	24	97
20	**8**	**10i**	Neat	80	24	0[f]
21	**8**	**10f**	Neat	80	24	76[g]
22	**8**	**10b**	Neat	80	24	76
23	**1**	**10b**	Neat	80	24	30

[a] All reactions were conduced in test tubes carefully monitoring the temperature; [b] The reaction was stopped after the indicated hours and it was not completed; [c] Yield of isolated product after chromatographic purification; [d] The reaction was conduced without a stirring bar. [e] solvent has been cleaned on basic alumina before use; [f] not identify by-products due to polymerization reaction; [g] obtain after chromatography as a inseparable mixture of desire product and by-products.

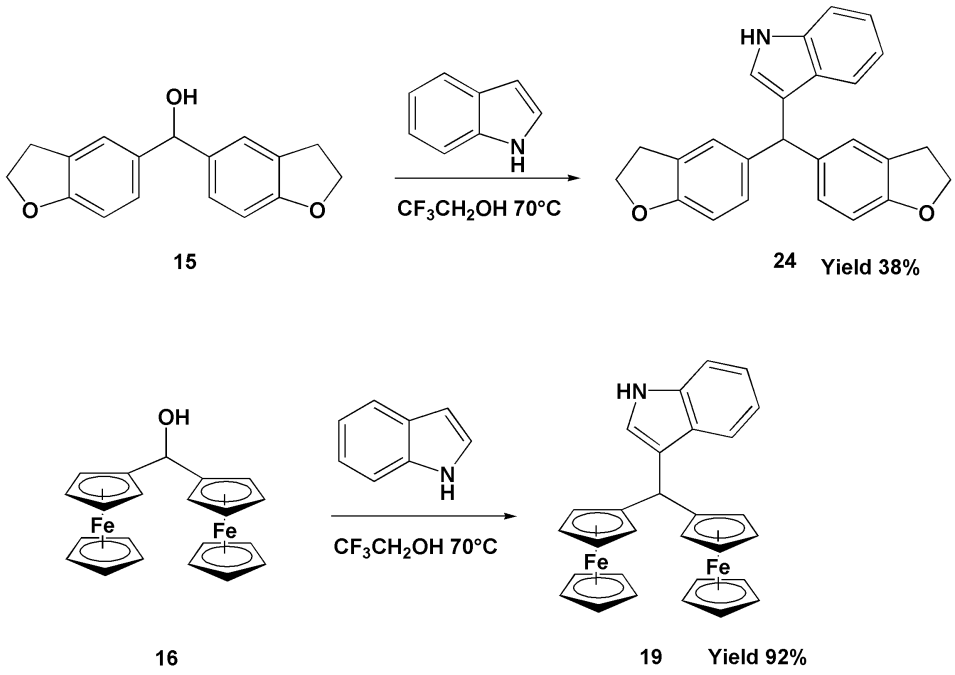
Alcohol **23** does not react in the absence of solvent or in a range of solvents without catalysts at room temperature or at 80°C. **8** and **1** gives aspected products reacting with nucleophiles in both the presence and absence of solvent, but the conversions dependes by nucleophiles and in many case the yields were lower than those of the corresponding reaction "on water".

Although benzylic alcohol **15** and diferrocenyl alcohol **16** are not reactive in water, we took into account the N parameter for solvents studied by Mayr et al.[25] and used the less nucleophilic 2,2,2-trifluoroethanol (Pka = 13) as the reaction solvent (Scheme 9).[26]

[25] M. Hofmann, N. Hampel, T. Kanzian, H. Mayr, *Angew. Chem. Int. Ed.* **2004**, *43*, 5402.

[26] For a recent report of 2,2,2-trifluoroethanol as a reaction solvent, see: a) I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis* **2007**, 2925; b) M. Westermaier, H. Mayr, *Chem. Eur. J.* **2008**, *14*, 1638.

Scheme 9 Direct substitution of alcohols 15 and 16 in 2,2,2-trifluoroethanol.



Remarkably, the reaction with indole provided the desired product, showing that other possible combinations of solvents able to form hydrogen bonds with alcohols are suitable for direct alcohol substitutions, without the need of Bronsted or Lewis acid.

Conclusion

In summary, to the best of our knowledge, this is the first report of general and direct substitution reactions of alcohols "on water", without the use of Lewis or Bronsted acids or surfactants. In the future, following the electrophilicity parameters established by Mayr we intend to obtain other products in these conditions. For example Nicholas-type reactions may also be possible[17b] highlights the applicability of this methodology.

Experimental section of Chapter 4

General: ^{1}H NMR spectra were recorded on Varian 200 MHz or Varian 300 MHz spectrometers. chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian 50 MHz or Varian 75 MHz spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were performed at an ionizing voltage of 70 eV. Chromatographic purification was done with 240-400 mesh silica gel. Analytical gas chromatography (GC) was performed on a Hewlett-Packard HP 6890 gas chromatograph with a flame ionization detector and split mode capillary injection system, using a Crosslinked 5% PH ME Siloxane (30 m) column or a Megadex5 chiral (25 m) column. IR analysis were performed with a NICOLET 380 FT-IR spectrophotometer. IR spectra are expressed by wavenumber (cm^{-1}). Elemental analyses were carried out by using a EACE 1110 CHNOS analyzer All the reactions were carried out in deionised water under air, apart from the reactions in which pyrrole was used as nucleophile. Alcohols **8** and **13** are commercially available, and were used as received.

Preparation of the starting materials:

9*H*-Xanthen-9-ol 1

Under a nitrogen atmosphere, to a solution of xanthone (0.196 g, 1 mmol) in Et_2O (5 mL) at 0°C was added $LiAlH_4$ (0.076 g , 2.0 mmol) in portions. The mixture was warmed to room temperature over 20 min and stirred for 1 h at this temperature until judged complete by TLC (R_f = 0.2 cyclohexane:ethylacetate 9:1). The reaction was quenched by addition of an amount of water (mL) egual to grams of $LiAlH_4$ used, resulting alluminium oxides salt were filter off. The Process was repeated two time utilizing for first so much mL of NaOH 15%, then a double amount of water. The organic phase was dried over Na_2SO_4 then concentrated *in vacuo*. The crude product was utilized without further purification.

Yield 99%.

White solid; mp= 123 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.38 (m, 1H); 7.76 (m, 1H); 7.52 (m, 1H); 7.41 (m, 1H); 7.19 (m, 2H); 7.05 (m, 2H); 4.07 (s, 1H); 2.06 (bs, 1H); GC MS: 181 (M-OH).

***9H*-Thioxanthen-9-ol 20.**

Under a nitrogen atmosphere, to a solution of thioxanthone (0.212 g, 1 mmol) in Et_2O (5 mL) at 0°C was added $LiAlH_4$ (0.050 g , 1.3 mmol) in portions. The mixture was warmed to room temperature over 20 min and stirred for 1 h at this temperature until judged complete by TLC (R_f = 0.3 (cyclohexane:dichloromethane 6:4). The reaction was quenched by addition of an amount of water (mL) egual to grams of $LiAlH_4$ used, resulting alluminium oxides salt were filter off. The Process was repeated two time utilizing for first so much mL of NaOH 15%, then a double amount of water. The organic phase was dried over Na_2SO_4 then concentrated *in vacuo*. The crude product was utilized without further purification. Yield 99%

Yellow solid; mp= 102 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.64 (d, J = 8.7 Hz, 2H); 7.51 (d, J = 8.7Hz, 2H); 7.37-7.29 (m, 4H); 5.59 (d, J = 6.6 Hz, 1H); 2.32 (d, J = 6.6 Hz, 1H).

GC MS: 197 (M-OH).

Diferrocenyl ketone 17.

Under a nitrogen atmosphere, to the magnetically stirred and cooled (-15°C) mixture of ferrocene (1.500 g, 8.0 mmol), anhydrous aluminium chloride (1.700 g, 8.0 mmol) and methylene dichloride (20 ml) were added dropwise a solution of triphosgene (0.4 g, 1.3

mmol) in CH_2Cl_2 (15 ml) and distilled triethylamine (0.67 mL, 4.8 mmol) simultaneously from separate addition funnels. Stirring was continued for 2 h at -15°C and 6 h at room temperature until judged by TLC (R_f = 0.3 , cyclohexane:diethylether 2:1). The reaction mixture was then poured into ice-water, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5mL). The combined organic phases were washed with water, and then dried over Na_2SO_4. The extract was concentrated and chromatographed on a silica gel column. then the solid was filtered and the filtrate was evaporated in vacuo to dryness. The residue was tritured with hot hexane and filtered. The filtrate was concentrated under reduced pressure and utilized without further purification. Yield 6% (110mg)

Red solid; mp= 204°C; IR: 3113.5, 1607.1, 1462.4, 1382.4, 1291.6, 1102.0, 1059.6, 804.6, 490.3 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 5.00 (m, 1H); 4.53 (m, 1H); 4.19 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 199.0; 80.38 (2C); 71.4 (4C); 70.6 (4C); 70.0 (10C); ESI MS: 399 (M+H).

(Hydroxyferrocenylmethyl)ferrocene 16.

Under a nitrogen atmosphere, to a solution of ketone **17** (0.080 g, 0.2 mmol) in Et_2O (10 mL) at room temperature was added $LiAlH_4$ (0.16 g , 0.4 mmol). The mixture was refluxed and stirred for 1 h at this temperature judged complete by TLC(R_f = 0.4 , cyclohexane:diethylether 2:1). The reaction was quenched by addition of an amount of water (mL) egual to grams of $LiAlH_4$ used, resulting alluminium oxides salt were filter off. The Process was repeated two time utilizing for first so much mL of NaOH 15%, then a double amount of water. The organic phase was dried over Na_2SO_4 then concentrated *in vacuo*. The crude product was utilized without further purification. Yield 99%

Yellow solid; mp=167-170°C; IR: 3441, 1656 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 5.22 (s, 1H); 4.20 (m, 18H); 2.39 (bs, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 92.9 (2C); 68.5 (10C); 68.1; 67.8 (2C); 67.6 (2C); 67.2 (2C); 66.1 (2C); ESI MS: 401 (M+H), 400 (M), 398.

5-Bromo-2,3-dihydrobenzofuran 18

Under a nitrogen atmosphere, to a solution of 2,3-dihydroxybenzo[b]furan (0.119 g, 1.0 mmol) in CH_2Cl_2 (2 mL) NBS (0.178 g, 1.0 mmol) and catalyst $ZrCl_4$ (0.011 g, 0.05 mmol) were added at 0°C and stirred until judged by TLC (R_f = 0.5 cyclohexane: dichloromethane 4:1), then the reaction was quenched by addition of water and extracted

with Et_2O (3 x 20 mL). The organic phases were collected and dried over Na_2SO_4 then concentrated *in vacuo*. The crude product was utilized without further purification.
White solid; mp= 54-56 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.26 (t, 0.8 Hz, 1H); 7.18 (dd, 2.1, 8.4 Hz, 1H); 6.64 (d, J = 8.4 Hz, 1 H,); 4.55 (t, J = 8.7 Hz, 2H); 3.18 (t, J = 8.7 Hz, 2H).

bis-(2,3-Dihydro benzofuran-5-yl)-methanol 15.

Under a nitrogen atmosphere, to a solution of 5-Bromo-2,3-dihydrobenzofuran **18** (0.039 g, 0.2 mmol) in Et_2O (4 mL) n-BuLi (1.0 M, 0.2 mL, 0.2 mmol) was added drop-wise at -20°C. The mixture was warmed to 0°C over 1h and stirred for 1 h at this temperature. Commercial aviable 5-carboxaldehyde-2,3-dihydrobenzofurano (0.050 mL, 0.4 mmol) until judged complete by TLC (R_f = 0.1 cyclohexane:dichloromethane 3:1), then the reaction was quenched by addition of water, the aqueous phase was extracted with Et_2O (3 x 5mL). The organic phases were collected and and dried over Na_2SO_4 then concentrated *in vacuo*. The crude product purified by flash chromatography.
White solid**;** mp= 97-100 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.18 (s, 2H); 7.04-7.13 (m, 2H); 6.71 (d, J = 8.3 Hz, 2H); 5.70 (s, 1H); 4.53 (t, J = 8.7 Hz, 4H); 3.15 (t, J = 8.7 Hz, 4H); 2.26 (s, 1H); ESI MS: 291 (M + Na), 251 (M – OH).

General procedure to addition of nucleophiles 10a-n to alcohols :

The alcohol (0.2 mmol) and nucleophile (0.4 mmol) were introduced in a reaction flask without inert gas protection, and deionised water (pH 6.52, 2.0 mL) was added. The flask was vigorously stirred at 80°C for 14-72 h, then allowed to cool to room temperature. Diethyl ether (5 mL) was added and the organic phase was separated, dried over anhydrous Na_2SO_4, and evaporated to reduced pressure to give a crude product purified by chromatography.

Alternative procedure to addition pyrrole to alcohols:

The alcohol (0.2 mmol) and distilled pyrrole (1,6 mmol) were introduced in a reaction flask under nitrogen, and degassed deionised water (pH 6.52, 2.0 mL) was added. The flask was vigorously stirred at 80°C for 72 h, then allowed to cool to room temperature. Diethyl ether (5 mL) was added and the organic phase was separated, dried over anhydrous Na_2SO_4, and evaporated to reduced pressure. The crude mixture was pumped under

vacuum to eliminate the pyrrole in excess. Finally, the crude product purified by chromatography.

3-[bis-(4-Dimethylamino-phenyl)-methyl]-indole 11a.

Prepared according to the general procedure from alcohol **8** (0.054 g, 0.2 mmol) and indole **10a** (0.047 g, 0.4 mmol), until judged complete by TLC (R_f = 0.44 , diethylether) and purified by flash chromatography. Yield 98%.

White solid; mp= 230-231°C (with decomposition); IR: 3412, 1659, 1633 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.90 (bs, 1H); 7.35-7.27 (m, 2H); 7.14-7.08 (m, 5H); 6.98 (m, 1H); 6.68-6.61 (m, 5H); 5.51 (s, 1H); 2.91 (s, 12H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 148.9 (2C); 136.7; 133.1 (2C); 129.5 (4C); 127.2; 123.8; 121.8; 121.3; 120.2; 119.1; 112.6 (4C); 110.8; 46.8; 40.8 (4C); ESI MS: 371 (M+H), 370 (M), 369.

1-Methyl-2-[bis-(4-dimethylamino-phenyl)-methyl]-sulfanyl-1*H*-imidazole 11b.

Prepared according to the general procedure from alcohol **8** (0.054 g, 0.2 mmol) and thiol **10b** (0.048 g, 0.4 mmol), until judged complete by TLC (R_f = 0.5, diethylether) and purified by flash chromatography. Yield 79%.

White solid; mp= 147-151°C; IR: 3423, 2886, 2793, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.19 (s, 1H); 7.07-7.04 (m, 4H); 6.71-6.69 (m, 5H); 6.60 (s, 1H); 3.66 (s, 3H); 2.96 (s, 12H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 162.5; 149.9 (2C); 129.2 (4C); 127.0 (2C); 117.2; 115.9; 112.3 (4C); 63.4; 40.4 (4C); 34.9; ESI MS: 367 (M+1), 253.

[bis-(4-Dimethylamino-phenyl)-methyl]-azide 11c.

Prepared according to the general procedure from alcohol **8** (0.054 g, 0.2 mmol) and trimethylsilylazide **10c** (0.052 mL, 0.4 mmol), until judged complete by TLC (R_f = 0.44 , diethylether) and evaporated to reduced pressure to give a clean product, which was no purified by chromatography (unstable over SiO_2). Yield 85%.

White solid; mp= 75°C; IR: 3419, 2090, 1649, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.23 (AA'BB', J = 8.8 Hz, 4H); 6.75 (AA'BB', J = 6.8 Hz, 4H); 5.63 (s, 1H); 2.99 (s, 12H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 150.0 (2C); 128.3 (4C); 127.9 (2C); 112.3 (4C); 68.2; 40.5 (4C); ESI MS: 253; GC MS: 281, 254.

3-[bis-(4-Dimethylamino-phenyl)-methyl]-pentane-2,4-dione 11e.

Prepared according to the general procedure from alcohol **8** (0.054 g, 0.2 mmol) and β-diketone **10e** (0.062 mL, 0.4 mmol), until judged complete by TLC (R_f = 0.4 , cyclohexane:diethylether 1:1) and purified by flash chromatography. Yield 92%

White solid; mp= 149-150°C; IR: 3420, 1642 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.10 (AA'BB', J = 8.8 Hz, 4H); 6.62 (AA'BB', J = 8.8 Hz, 4H); 4.62 (s, 2H); 2.88 (s, 12H); 2.00 (s, 6H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 203.9 (2C); 149.3 (2C); 129.9 (2C); 128.2 (4C); 112.9 (4C); 75.0; 49.8; 40.5 (4C); 29.7 (2C); ESI MS: 353 (M+H), 253.

Ethyl-2-[bis-(4-Dimethylamino-phenyl)-methyl]-3-oxo-butyrate 11f.

Prepared according to the general procedure from alcohol **8** (0.054 g, 0.2 mmol) and acetoacetate **10f** (0.050 mL, 0.4 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:diethylether 1:4) and purified by flash chromatography. Yield 88%

White solid; Mp= 119-124°C; IR: 3409, 1638 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.16-7.09 (m, 4H); 6.62 (d, J = 8.8 Hz, 4H); 4.59 (AB, J =12.1 Hz, 2H); 3.99 (q, J= 7.1 Hz, 2H); 2.87 (s, 12H); 1.56 (s, 3H); 1.05 (t, J = 7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 202.7; 168.1; 149.3; 149.2; 130.4; 129.7; 128.3 (2C); 128.1 (2C); 112.8 (2C); 112.8 (2C); 65.9; 61.1; 49.5; 40.6 (2C); 40.5 (2C); 29.6; 13.8; ESI MS: 383 (M+H), 308, 253.

Ethyl-3,3'-(4-dimethylamino-phenyl)-2-nitro propionate 11g.

Prepared according to the general procedure from alcohol **8** (0.054 g, 0.2 mmol) and nitroaceate **10e** (0.044 mL, 0.4 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:diethylether 6:4) and purified by flash chromatography. Yield 91%

White solid; mp= 80-86°C; IR: 3408, 2096, 1749, 1634 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.19-7.10 (m, 4H); 6.63 (AA'BB', J = 8.8Hz, 4H); 5.84 (d, J = 12.2 Hz, 1H); 4.84 (d, J = 12.2 Hz, 1H); 4.07-4.06 (m, 2H); 2.89 (s, 12H); 1.06 (t, J = 7.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 163.5; 149.8; 149.7; 128.7 (2C); 127.9 (2C); 126.6; 125.8; 112.7 (2C); 112.6 (2C); 91.8; 62.7; 50.8; 40.4 (4C); 13.6; ESI MS: 386 (M+H). 253.

3-(9*H*-Xanthen-9-yl)-1*H*-indole 21a.

Prepared according to the general procedure from alcohol **1** (0.038 g, 0.2 mmol) and indole **10a** (0.047 g, 0.4 mmol), until judged complete by TLC (R_f = 0.4 , cyclohexane:ethylacetate 9:1) and purified by flash chromatography. Yield 82%.

White solid; mp= 140-145°C; IR: 3436, 3048, 2925 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.03 (bs, 1H); 7.43-6.87 (m, 13H); 5.56 (s, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 151.3 (2C);

136.7; 129.4 (2C); 127.6 (2C); 125.9; 124.4 (2C); 123.0 (2C); 122.7; 122.1; 120.4; 119.7; 119.6; 116.3 (2C); 111.2; 35.5; GC MS: 297 (M), 296 (M-H), 181.

(9*H*-Xanthen-9-yl)-1*H*-pyrrole 21 i.

Prepared according to the alternative procedure from alcohol **1** (0.038 g, 0.2 mmol) and pyrrole **10i** (0.110 mL, 1.6 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:dichloromethane 3:2) and purified by flash chromatography. Yield 80%.

White solid; mp = 113-119°C; IR: 3452, 3403 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.69 (bs, 1H); 7.40-6.98 (m, 8H); 6.64 (m, 1H); 6.18 (m, 1H); 6.14 (m, 1H); 5.39 (s, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 151.2 (2C); 134.2; 129.4 (2C); 128.1 (2C); 123.3 (2C); 122.9 (2C); 118.1; 116.6 (2C); 107.9; 107.2; 37.2; ESI MS: no ionization; GC MS: 247 (M), 246 (M-H), 181.

1-Methyl-2-(9*H*-xanthen-9-ylsulfanyl)-1*H*-imidazole 21b.

Prepared according to the general procedure from alcohol **1** (0.038 g, 0.2 mmol) and thiol **10b** (0.048 g, 0.4 mmol), until judged complete by TLC (R_f = 0.2 , cyclohexane:ethylacetate 9:1) and purified by flash chromatography. Yield 90%

White solid; mp = 192°C (with decomposition); IR: 1602, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.64 (s, 1H); 7.49 (dd, J = 7.5, 1.2 Hz); 7.32 (dt, J = 8.7, 1.8 Hz, 2H); 7.19 (d, J = 7.8 Hz, 2H); 7.09 (t, J = 7.5 Hz, 2H); 6.54 (d, J = 2.5 Hz, 1H); 6.28 (d, J = 2.5 Hz, 1H); 3.07 (s, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 162.7; 151.1; 129.9 (2C); 129.7 (2C); 123.8 (2C); 119.3 (2C); 118.5 (2C), 116.8 (2C); 114.9; 51.5; 35.1; ESI MS: 317 (M+Na), 181.

9-Azido-9*H*-xanthene 21c.

Prepared according to the general procedure from alcohol **1** (0.038 g, 0.2 mmol) and trimethylsilylazide **10c** (0.052 mL, 0.4 mmol), until judged complete by TLC (R_f = 0.8 , cyclohexane:ethylacetate 9:1) and purified by flash chromatography. Yield 95%.

White Oil; IR: 2923, 2853, 2084 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.53-7.38 (m, 4H); 7.28- 7.20 (m , 4H); 5.61 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 133.3 (2C); 131.4 (2C); 129.1 (2C); 128.5 (2C); 127.0 (2C); 126.7 (2C); 65.2; ESI MS: 195.

3-(9*H*-Thioxanthen-9-yl)-1*H*-indole 22a.

Prepared according to the general procedure from alcohol **21** (0.042 g, 0.2 mmol) and indole **10a** (0.047 g, 0.4 mmol), until judged complete by TLC (R_f = 0.4 , cyclohexane:diethylether 4:1) and purified by flash chromatography. Yield 82%.

White solid; mp= 151°C; IR: 3392, 3053 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.97 (bs, 1H); 7.55-7.09 (m, 12H); 6.82 (s, 1H); 5.46 (s, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 164.1; 137.9 (2C); 136.6; 133.2 (2C); 128.7 (2C); 127.0 (2C); 126.5 (2C); 126.4 (2C); 123.5; 122.0; 120.1; 119.5; 114.3; 111.3; 45.7; ESI MS: 313 (M), 236, 197.

1-Methyl-2-(9*H*-thioxanthen-9-ylsulfanyl)-1*H*-imidazole 22b.

Prepared according to the general procedure from alcohol **21** (0.042 g, 0.2 mmol) and thiol **10b** (0.048 g, 0.4 mmol), until judged complete by TLC (R_f = 0.4 , cyclohexane:diethylether 7:3) and purified by flash chromatography. Yield 90%.

White solid; mp= 160°C (with decomposition); IR: 1588, 1562 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.77 (d, J = 7.5Hz, 2H); 7.68 (s, 1H); 7.42 (d, J = 7.8Hz, 2H); 7.32-7.22 (m, 4H); 6.73 (d, J = 2.1 Hz, 1H); 6.46 (d, J = 2.1 Hz, 1H); 3.57 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 161.7; 132.2 (2C); 131.5 (2C); 130.9 (2C); 128.6 (2C); 127.0 (2C); 126.4 (2C); 118.1; 115.6; 58.4; 35.2; ESI MS: 311 (M + H).

9-Azido 9*H*-thioxanthene 22c.

Prepared according to the general procedure from alcohol **21** (0.042 g, 0.2 mmol) and trimethylsilylazide **10c** (0.052 mL, 0.4 mmol), until judged complete by TLC (R_f = 0.4 , cyclohexane:diethylether 9:1) and purified by flash chromatography. Yield 68%.

White oil; IR: 2918, 2085 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.46 (m, 4H); 7.28 (m, 4H); 5.57 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 133.4 (2C); 131.4 (2C); 129.1 (2C); 128.4 (2C); 127.0 (2C); 126.7 (2C); 65.2; ESI MS: 197; GC MS: 211, 197.

2-Methyl-5-(9*H*-thioxanthen-9-ylsulfanyl)-[1,3,4]thiadiazole 22j.

Prepared according to the general procedure from alcohol **21** (0.042 g, 0.2 mmol) and thiol **10j** (0.053 g, 0.4 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:diethylether 7:3) and purified by flash chromatography. Yield 85%.

Yellow solid; mp = 161-170°C; IR: 1587, 1562, 1545 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.97 (s, 1H); 7.68 (dd, J = 7.5, 1.5 Hz, 2H); 7.40 (dt, J = 7.6, 1.6 Hz, 2H); 7.32-7.20 (m,

4H); 2.30 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75MHz) δ: 185.8; 155.9; 133.5 (2C); 130.3 (2C); 129.5 (2C); 128.6 (2C); 126.4 (2C); 126.1 (2C); 60.0; 16.4, ESI MS: 327, 326.

Ethyl -3-oxo-2-(9*H*-thioxanthen-9-yl)-butyrate 22f.

Prepared according to the general procedure from alcohol **21** (0.042 g, 0.2 mmol) and acetoacetate **10f** (0.050 mL, 0.4 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:diethylether 4:1) and purified by flash chromatography. Yield 83%.

White solid; 115-118°C; IR: 3416, 3053, 2950, 1730, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.53-7.36 (m, 4H); 7.26 (m, 4H); 4.98 (d, J = 11.0 Hz, 1H); 4.51 (d, J = 11.0 Hz, 1H); 3.99-3.98 (m, 2H); 1.88 (s, 3H); 1.09 (t, J = 7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 201.8; 167.3; 134.6; 134.4; 133.4; 133.3; 130.5; 130.2; 127.2 (2C); 127.2; 127.1; 126.8; 126.5; 61.3; 57.5; 48.3; 31.1, 13.8; ESI MS: 325.

Ethyl-2-nitro-(9*H*-thioxanthen-9-yl)-acetate 22g.

Prepared according to the general procedure from alcohol **21** (0.042 g, 0.2 mmol) and nitroacetate **10g** (0.044 mL, 0.4 mmol), until judged complete by TLC (R_f = 0.3 , cyclohexane:diethylether 4:1) and purified by flash chromatography. Yield 82%.

Yellow solid; mp = 115-116°C; IR: 3047, 2987, 2917, 1957, 1920, 1748 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.55-7.39 (m, 5H); 7.29 (m, 2H); 7.25 (m, 1H); 5.71 (d, J = 10.9 Hz, 1H); 5.19 (d, J = 10.9 Hz, 1H); 4.20-3.85 (m, 2H); 1.03 (t, J = 7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 163.0; 134.1; 133.1; 131.6; 130.9; 130.4; 130.2; 128.2; 128.1; 127.5 (2C); 127.2; 127.0; 85.2; 62.8; 49.8; 13.5; ESI MS: 328.

(3-indoleferrocenylmethyl)ferrocene 19.

The alcohol **16** (0.038 g, 0.1 mmol) and indole **10a** (0.034 g, 0.2 mmol) were introduced in a reaction flask without inert gas protection, and 2,2,2-trifluoroethanol was added (1mL). The flask was vigorously stirred at 70°C for 96h until judged complete by TLC (R_f = 0.2 , hexane:dichloromethane 3:2), then allowed to cool to room temperature. and evaporated to reduced pressure to give a crude product purified by chromatography. Yield 92%.

Yellow oil; IR: 3404, 3089, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.03 (bs, 1H); 7.50 (d, J = 8.1 Hz, 1H); 7.39 (dt, J = 8.1, 1.0 Hz, 1H); 7.19 (m, 2H); 7.14 (d, J = 1.2 Hz, 1H); 7.09 (d, J = 1.2 Hz, 1H); 7.05 (t, J = 1.0 Hz); 7.02 (d, J = 1.2 Hz, 1H); 5.20 (s, 1H); 4.23 (m, 2H); 4.09 (m, 2H); 4.03-3.99 (m, 14H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 136.0; 127.0;

121.7; 121.6; 120.9; 120.2; 119.1; 111.0; 93.9 (2C); 68.6 (12C); 68.0 (2C); 67.3 (2C); 66.5 (2C); 37.3; ESI MS 500 (M+1), 499 (M), 497.

3-[bis-(4-Dimethoxy-phenyl)-methyl]-indole 24.

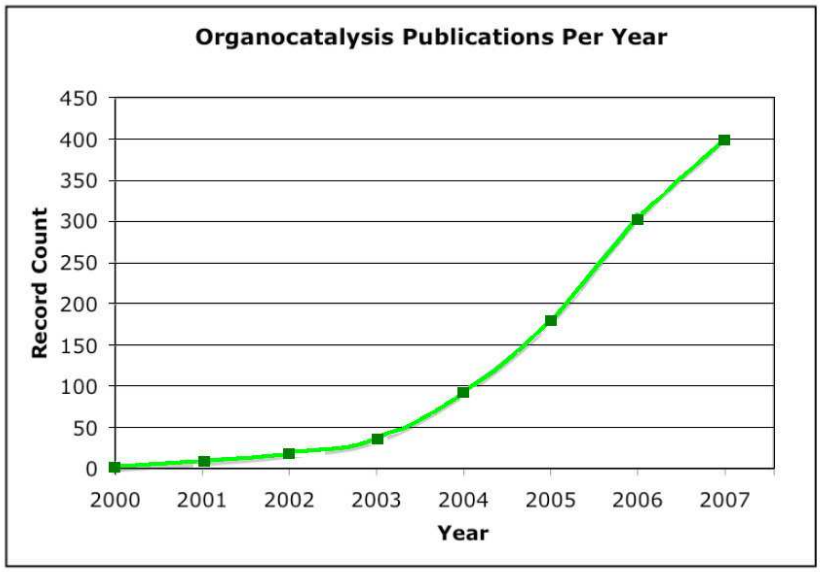
The alcohol **15** (0.024 g, 0.1 mmo) and indole **10a** (0.034 g, 0.2mmol) were introduced in a reaction flask without inert gas protection, and 2,2,2-trifluoroethanol was added (1mL). The flask was vigorously stirred at 70°C for 7 day until judged complete by TLC (R_f = 0.3 , hexane:diethylether 2:1), then allowed to cool to room temperature. and evaporated to reduced pressure to give a crude product purified by chromatography.

Yield 38%.

Yellow oil; IR: 3407, 2962, 2921, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.96 (bs, 1H); 7.36 (d, J =7.8 Hz, 1H); 7.25 (t, J = 6.3 Hz, 2H); 7.15 (d, J = 8.5 Hz, 4H); 7.00 (t, J = 7.5 Hz, 1H); 6.85 (m, 4H); 6.57 (s, 1H); 5.59 (s, 1H); 3.79 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 157.9 (2C); 136.7; 136.5 (2C); 129.8 (4C); 127.0; 123.8; 122.0; 120.6; 120.0; 119.3; 113.6 (4C); 111.0; 55.2 (2C); 47.2; ESI MS: (not ionisable)

Chapter 5

Organocatalytic Asymmetric Alkylation of Aldehydes by S_N1-Type reaction of alcohols



Introduction

During the last three decades, the field of organic chemistry has answered for the challenges of developing new strategy to access enantiomerically enriched products.[1] Fundamentaling this challenge marked the atom economical processes,[2] the opportunity for new chiral building blocks, and pharmaceutical industries to utilize enantiopure starting materials. The more transitions metals and new chiral-ligands are discovered, the more scientists tend to work in the field of asymmetric catalysis. These studies have culminated with pioneer works of Sharpless, Noyori, and Knowles that resolved in 2001 Nobel Prize in Chemistry.[3] Rarely these stereoselective processes involve radical, but more frequently is the nucleophile-electrophile pairs to be involved. Normally, the approach of nucleophiles to the reactive center of a prostereogenic ketone or aldehydes is the most studied and important reaction in asymmetric organic chemistry. The reaction occurs

[1] E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis*; Springer: Heidelberg, **1999**.

[2] a) B. M. Trost, *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 259; b) B. M. Trost, *Science* **1991**, *254*, 1471.

[3] a) K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2024; b) R. Noyori, *Adv. Synth. Cat.* **2003**, *345*, 15; c) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1999.

through the presence of a partial positive charge on the attacked carbon atoms. Electrophiles such as carbocations are more difficult to handle than carbonyls, especially in stereoselective reactions. From pioneering studies of Olah, the knowledge about carbocation has tremendously increased.[4] Although generally carbocation are believed "unstable" and fast reactive, there are indeed a seven or more order of magnitude in the stability and reactivity of carbocation. The precise and meticulous work of Mayr has help to shed light of the stability and reactivity of carbocation (see chapter 4). What is very important to design stereoselective reaction of carbocations is consider the *combination* of the electrophiles and the nucleophiles as reactants. In fact, Mayr has established a useful "rules of thumb[5] for such a reactions. Choosing a wrong combination of reactants will result in a reaction than can occur only in months! It can be expected that electrophiles will react with all nucleophiles located below themselves in the general Mayr's scales. As mentioned in Chapter 4 benzylic carbocations are positioned in the electrophilicity scale in function of the substituents. Strong electro-donating substituents are enhancing the stability of the carbocations. Benzylic carbocation are of moderate stability and high reactivity, (mesitylbenzylic carbocation is positioned at +6 of the Mayr scale) and are capable to react with a large variety of possible nucleophiles. Benzylic carbocation could be easily generated by stoichiometric[6] or catalytic[7] amount of Lewis or Brønsted acids. Chiral benzylic alcohols, which carry a functional group in the stereogenic position, react with various arenes (weak nucleophiles) in a highly selective fashion.[8] Diastereoselective Friedel-Crafts reactions are producing-diarylated *anti* and *syn* products (Scheme 1).

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[4] Carbocation Chemistry, Eds: G. Olah, G. K. Surya, Wiley Interscience **2004**.

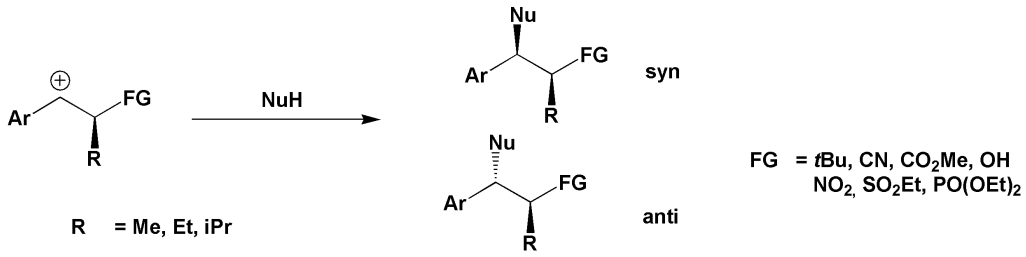
[5] Mayr reported that: "Considering the half-life of a bimolecular reaction with equal initial concentrations of the reactants, a mixture that is 1 M in both reactants requires a second-order rate constant of $k > 10^{-4}\ M^{-1}\ s^{-1}$ to give 50% conversion in less than 3 h. This condition is fulfilled when $E + N > -5.7$ to -3.3".

[6] F. Mhlthau and T. Bach, *Synthesis* **2005**, 3428.

[7] a) R. Sanz; D. Miguel; A. Martinez; J. M. Alvarez-Gutiérrez and F. Rodrìguez, *Org. Lett.* **2007**, *9*, 2027; b) T. Saito, Y. Nishimoto, M. Yasuda, A. Baba, *J. Org. Chem.* **2006**, *71*, 8516; c) M. Yasuda, T. Somyo, A. Baba, *Angew. Chem. Int. Ed.* **2006**, *45*, 793; d) M. Rueping, B. J. Nachtsheim, A. Kuenkel, *Org. Lett.* **2007**, *9*, 825; e) J. Kischel, K. Mertins, D. Michalik, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2007**, *349*, 865; f) V. Terrasson, S. Marque, J.-M. Campagne, D. Prim, *Adv. Synth. Catal.* **2006**, *348*, 2063; g) K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem. Int. Ed.* **2006**, *45*, 2605; h) H. Qin, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2007**, *46*, 409.

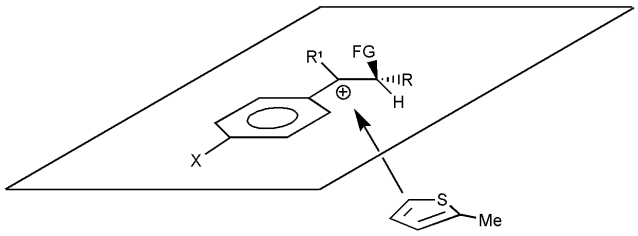
[8] a) F. Mühlthau, O. Schuster,T. Bach, *J. Am. Chem. Soc.* **2006**, *127*, 9348; b) F. Mühlthau, D. Stadler, A. Goeppert, G. A. Olah, G. K. S. Prakash, T. Bach, *J. Am. Chem. Soc.* **2006**, *128*, 9668; c) D. Stadler, F. Mühlthau, P. Rubenbauer, E. Herdtweck, T. Bach, *Synlett* **2006**, 2573; d) P. Rubenbauer, T. Bach, *Tetrahedron Lett.* **2008**, *49*, 1305; e) D. Stadler, T. Bach, *Chem. Asian J.* **2008**, *3*, 272; f) D. Stadler, A. Goeppert, G. Rasul, G. A. Olah, G. K. Surya Prakash, T. Bach, *J. Org. Chem.* **2009**, *74*, 312.

Scheme 1 Functionalyzation of benzylic carbocation to form diastereoisomeric products



Chiral benzylic cations are likely intermediates in these reactions, and in order to explain the high *anti* selectivity of these reactions, the energetic and geometric properties of the carbocationic intermediates were investigated more closely by DFT calculations. Evidence collected from DFT calculations and experiments[9e] suggested that cations exist in a preferred conformation that is determined by the 1,3-allylic strain. Substituents of the stereogenic center position are shielding in a preferentially manner one diastereotopic face (Figure 1)

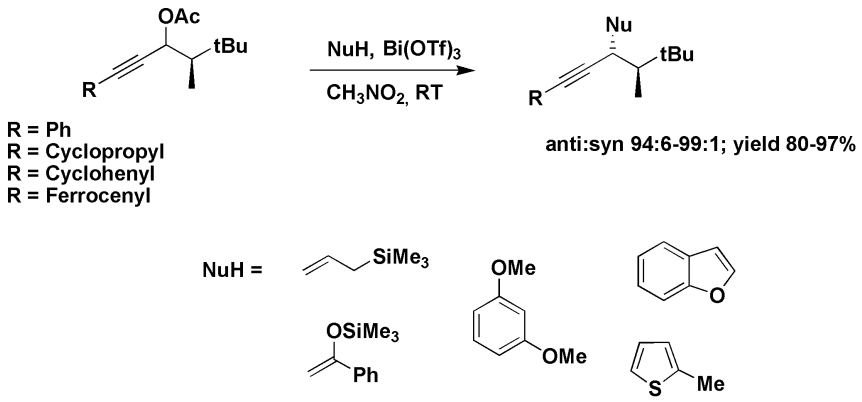
Figure 1 Diastereoselective attack of an arene (*N*=1.26) to a preferred conformation of a chiral benzyl cation.



The diastereoselectivity results from a preferred conformation, in which the two faces of the cationic center, are shielded differently by the methyl and FG substituents. The two substituents R and FG point toward different spatial directions relative to the plane containing the carbocation. An incoming nucleophile will, for steric reasons, approach the electrophilic center from the less shielded face. The A value of the individual substituents can be taken as an indication of their steric bulk. When FG are ethylsulfonyl (A=2.50), ethoxysulfonyl (A=2.50), and diethoxyphosphonyl (A=2.46) groups, they are larger than methyl and they shield the Si face. As a consequence, Re-face attack of is favored, which leads to the syn products. Bach was the leader in this chemistry, and he has investigated in details various nucleophiles and electrophiles as stabilization effect of the propargyl group

to a carbocation is well established, the investigation of propargylic cations was undertaken. In a quite interesting paper, Bach reported remarkable ideas for the further development of the area[9] The first interesting observation is the number of Lewis acid that is able to produce the desired transformation (Scheme 2) when they are employed in a catalytic amount. The list include $FeCl_3$, $InCl_3$, $AuCl_3$, $Cu(OTf)_2$, $[Au(PPh_3)]SbF_6$, and BF_3. $Bi(OTf)_3$ proved to be the most effective for the transformation but TMSOTf was nearly as effective. The generation of the carbocation could be coupled with various processes mediated by the same Lewis acid, and in this perspective, the recently rich chemistry displaced by gold salts could be certainly investigated further. More interestingly appears the high level of simple diastereoselection obtained irrespective by the Lewis acid employed.

Scheme 2 High facial diastereoselectivity reactions of chiral propargyl cations.



The fact that the transformation is not observed in the presence of the acetylenic alcohol could be related to the stability of the generated carbocation and its position in the Mayr scale[5] Again DFT calculation were able to shed light on the process. The *syn* vs *anti* ratio obtained in these reaction is again a function of the larger group that adopt the antiperiplanar orientation to a nucleophile approaching from the bottom side (Figure 1). Bach has reported examples of *syn* configurated products in the reaction of various chiral acetates with resorcine dimethyl ether as a reference electrophile by the use of $AuCl_3$ as catalyst.[10]As nucleophiles, electron rich aromatic compounds are showing good level of diastereoselectivity. Carbenium ion can be intercepted by nucleophiles with sufficient nucleophilicity. Although the exact electrophilicity of the chiral carbocation used by Bach was not determined, recent studies on studies about the reaction of methoxybenzyl cation

[9] P. Rubenbauer, E. Herdtweck, T. Strassner, T. Bach, *Angew. Chem. Int. Ed.* **2008**, *47*, 10106.
[10] P. Rubenbauer, T. Bach, *Adv. Synth. Catal.* **2008**, *350*, 1125.

with π-nucleophiles were reported by Mayr.[11] The choice of alcohol as electrophile is governed by a subtle balance between the Brønsted acidity of the acid and the Brønsted basicity of the alcohol. The acid must be sufficiently strong and its counter ion sufficiently non-coordinating to allow for cation formation. Optically pure starting material for the chemistry described by Bach is readily accessible via standard stereoselective aldol reactions or by lipase catalyzed kinetic resolution[9e]. Diastereoselective attack of nucleophiles to the generated carbocation occurs, in general, with no racemisation.[9e] this option was fully exploited in the preparation of drugs and in the synthesis of natural products. Using the concepts developed by Bach, a Merck group guided by Chung developed an high diastereoselective reaction to solve a synthetic problem connected to the development of a drug containing a 1,1,2-triarylalkane fragment, by the addition of indole to a benzylic carbocation[12] interestingly, the major diastereoisomer obtained in the reaction was the *anti*, in stringent contrast to those was reported by Bach in similar reactions. In fact, in these reactions, the phenyl ring played the role of the small group. However, as the nucleophile is indole, arene-arene interaction between the incoming indole and the phenyl ring could be responsible for the observed selectivity. This hypothesis was also correlated to the scope and limitation of this chemistry. Furthermore, Bach has recently completed the total synthesis of (-)-Podophyllotoxin by a diastereoselective addition of a chiral to the benzylic carbocation generated in situ with $FeCl_3$.[13, 8e]

Enantioselective reactions with carbocations.

In most of the reaction of direct substitution of alcohols, in which a carbocation is presumably generated, the stereochemical information of enantioenriched starting material is completely lost during the process.[8h] However, chiral carbocations of highly stability (The 1,13-dimethoxyquinacridinium cation) can be obtained in highly enantioenriched form.[14] Special case of stereochemical transfer of chiral information cans results when chiral ferrocenyl cation is formed.[15]

In general, the formation of a carbocation is posing a severe challenge for enantioselective transformations. The challenge can be addressed by the use of chiral nucleophilic environment, or by the use of chiral counter ion. Rueping observed the formation of a stabilized carbocation leading an interesting atropoisomeric compounds during his studies

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[11] L. Shi, M. Horn, S. Kobayashi, H. Mayr, *Chem. Eur. J.* **2009**, *15*, 8533; about metoxybenzylcation see Chapter 4.

[12] J. Y. L. Chung, D. Manchero, P. G. Dormer, N. Variankaval, R. G. Ball, N. N. Tsou, *Org. Lett.* **2008**, *10*, 3037

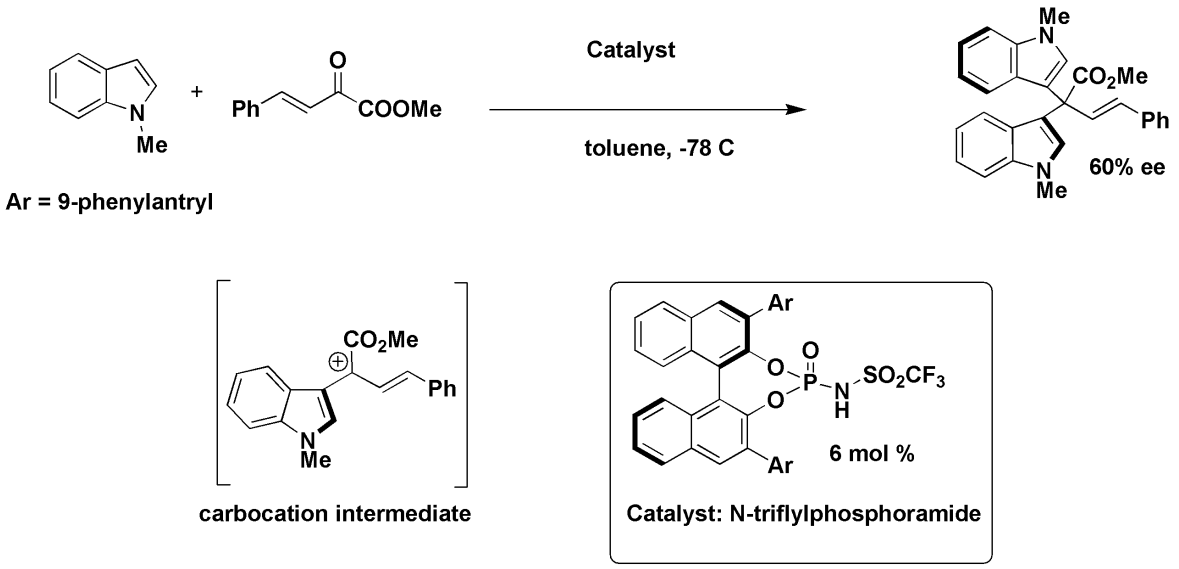
[13] D. Stadler, T. Bach, *Angew. Chem. Int. Ed.* **2008**, *47*, 7557.

[14] B. Laleu, P. Mobian, C. Herse, B. W. Lauersen, G. Hpfgarner, G. Berardinelli, J. Lacour, *Angew. Chem*; *Angew. Chem. Int. Ed.* **2005**, *44*, 1879.

[15] P. Vicennati, P. G. Cozzi, Eur. *J. Org. Chem.* **2007**, 2248.

of chiral counter ion in organocatalytic reactions[16] The addition of *N*-methylindole to the α-ketoester catalyzed by the strong Brønsted acid *N*-triflylphosphoramide resulted in an interesting adduct that exhibits atropoisomerism (Scheme 3). Similarly, Yun and coworkers have recently exploited the concept in the enantioselective synthesis of fluorene derivatives.[17] Underlined to these reactions, application of chiral counter ion is appealing in the chemistry of carbocation, as one diasteroisomeric face could be covered by a counter ion positioned near the carbocation, and more important and general contribution are expected for the future. In fact, chiral counter ion mediated reactions are quite useful in gold chemistry, as the incipient formation of a carbocations are presumably involved.[18]

Scheme 3 Studies of chiral counter ion to induce stereocontrol on carbocations.



When the nucleophilic compound is becoming in a transient state chiral, the carbocation can be approached only by one face of the attaching chiral nucleophiles. Indeed Jacobsen recently reported another important case of stereoselective reactions in which reactive cationic intermediates are generated.[19] Reactivity patterns in these additions were found to be consistent with an S_N1 pathway. In this reaction oxocarbenium ion as highly reactive cationic species can be engaged in exciting new possibilities for asymmetric catalysis. The oxocarbenium ion is generated by thiourea-assisted chloride dissociation from a transient

[16] M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem. Int. Ed.* **2008**, *47*, 593;

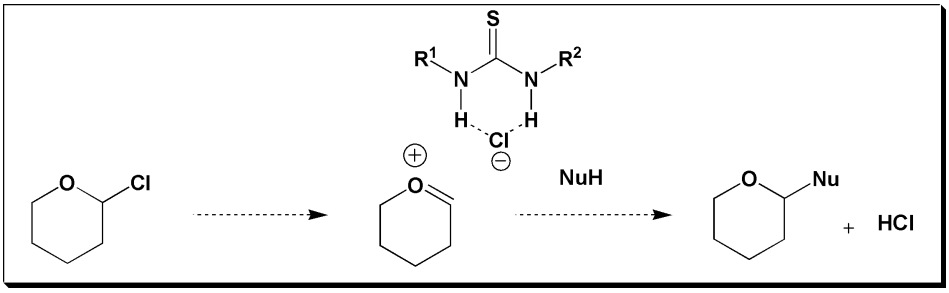
[17] F.-L. Sun, M. Zeng, Q. Gu, S.-H. You, *Chem Eur. J.* **2009**,*15*, 8709.

[18] G. L Hamilton, E. J.Kang, M. Mba, F. D. Toste, *Science*, **2007**, *317*, 5837.

[19] a) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558; b) M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 6700; c) I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 13404; d) I. T. Raheem, P. S. Thiara, E. N. Jacobsen, *Org. Lett.* **2008**, *10*, 1577; e) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198.

α-chloroamide.[20] The important concept discovered by Jacobsen is that chiral hydrogen-bond donors effectively promote highly enantioselective reactions of cationic intermediates[21].

Figure 2 Enantioselective Additions to oxocarbenium cation by Thiourea chiral counter ion interaction.



In these reactions stable and storable lactams or acetoxy lactams are used as precursors. The presence of controlled amounts of added water is important, as the chloramide is formed by action of HCl, obtained in the synergistic effect of TMSCl and catalytic H_2O. The generation of HCl by TMSCl is helping to driven the equilibrium by trapping water of acetic acid generated from the starting material. The intermediate proposed in the reaction, the chlorolactam was well characterized by spectroscopic data. The reactions discovered by Jacobsen t seem to proceed through an S_N1-type anion-binding mechanism analogous. The chiral thioureas developed by Jacobsen can be considered a chiral counter ion of the oxocarbenium ion, and the nucleophiles are able to attack the cationic intermediate from one side.

Organocatalysis history

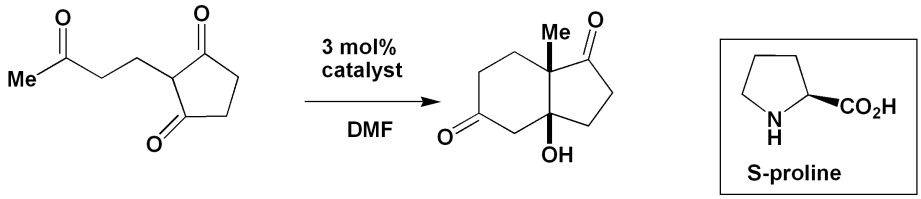
In these years this concept was exploited in organocatalysis as transient formation of chiral enamines acting as powerful nucleophiles[22] are formed. Recent advancements into the readily available chiral pool employ organic molecules, such as amino acids and sugars aviable as catalysts. Hajos-Parrish group reported a desymmetrizing intramolecular aldol cyclization catalyzed by aminoacid proline as shown in

[20] A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713.
[21] E. A. Peterson, E. N, Jacobsen, *Angew. Chem. Int. Ed.* **2009**, *48*, 6328.
[22] D.W. C. MacMillan, *Nature* **2008**, *455*, 304.

Figure 3.[23] This orienting work has driven the establishment of the burgeoning field of organocatalysis, by suggesting the development of new synthetic strategies and influencing the design of the future catalysts.[24]

Figure 3 Pioneer organocatalytic intramolecular aldol.

■ Hajos-Parrish, *J. Org. Chem.* **1974**, *39*, 1615.



98% ee

Nowadays, organocatalytic asymmetric strategy is acknowledged as an good and reliable alternative to traditional organometallic and biological approaches to asymmetric catalysis for the stereoselective preparation of relevance enantiopure molecules.[25] The use of simple and aviable organic molecules (for example aminoacids) as catalysts has exponatially enhanced asymmetric organocatalysis, which offers alternatives to the activation of substrates. In new synthetic strategy and in drug design expecially, metal-free organic catalysts, which are in many case safty, stable and readly aviable, are privileged. Dry conditions are not requested and air is tolerated. This guarantees operational simplicity. The ability of small organic molecules to promote transformations in a stereoselective fashion was known since 1971. Nevertheless, the term ″organocatalysis″ was coined by David MacMillan in 2000, when he suggested enantioselective Diels-Alder reaction via iminium way.[26] (Scheme 4)

At the same time List, Lerner, and Barbas,[27] found that chiral secondary amines are good catalysts in aldol reactions without auxylium of metal centers as show in Scheme 4.

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[23] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1612.

[24] P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138.

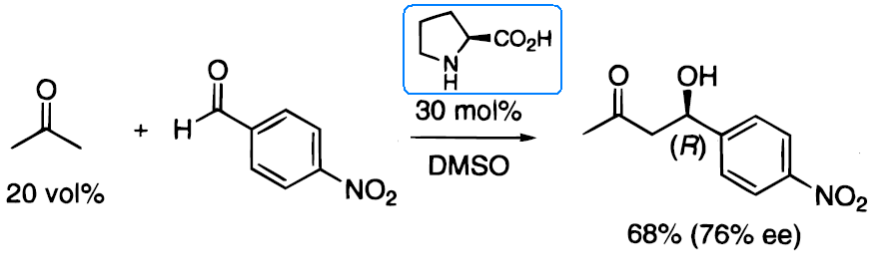
[25] For general reviews on asymmetric organocatalysis, see: a) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), *Wiley-VCH, Weinheim*, **2007**; b) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. C. Vo, *Drug Discovery Today* **2007**, 12, 8; c) B. List, J. W. Yang, *Science* **2006**, *313*, 1584; d) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719; e) Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis (Eds. : A. Berkessel, H. GröRger) *Wiley-VCH,*Weinheim, **2004**; f) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; for special issues on asymmetric organocatalysis, see: g) B. List, C. Bolm, *Adv. Synth. Catal.* **2004**, *346*, 1007; h) K. N. Houk, B. List, *Acc. Chem. Res.* **2004**, *37*, 487; for a recent review on the immobilization of organic catalysts, see: i) F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367; j) B. Alcaide, P. Almendros, *Angew. Chem. Int. Ed.* **2008**, *47*, 4632; k) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922.

[26] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.

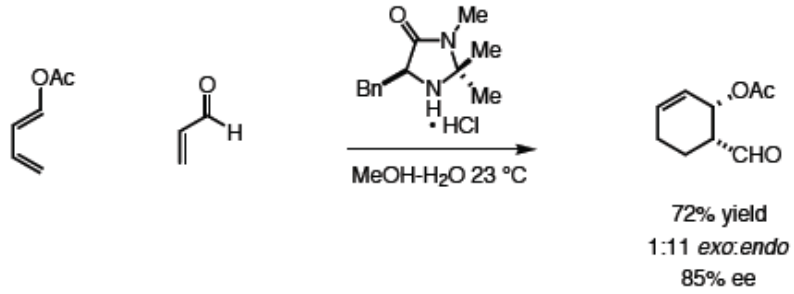
[27] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.

Scheme 4 The firsts metal-free catalysts: Proline and Imidazolidinone.

- Aldol reaction: List and Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.



- Diels-Alder Reaction, iminium way: MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.



Following these publications, numerous high quality studies on catalysis by chiral secondary amines (asymmetric aminocatalysis) were reported.[28]

While organocatalytic alkylation of carboxylic derivates[29] is readly aviable in several way, until now only few examples of direct asymmetric alkylation of the carbonyl group were developed.[30] Difficult to designing a catalytic asymmetric α-alkylation of aldehydes is generally complicated by the susceptibility of the nucleophilic Lewis- or Brønsted-base catalyst toward an unproductive alkylation reaction with the electrophile. In intermolecular R-alkylation reactiono catalyzed by proline unsurprisingly the only identified products is benzylated proline. Besides, racemization of the product could be a serious problem, so for

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[28] For recent reviews on asymmetric aminocatalysis, see: a) B. List, *Chem. Commun.* **2006**, 819; b) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001; c) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84; d) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580; e) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481; f) B. List, *Synlett* **2001**, 1675; for an excellent essay that provides historical context to the development of enamine/iminium ion based organocatalysis, see: g) C. F. Barbas III, *Angew. Chem. Int. Ed.* **2008**, *47*, 42; h) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471.

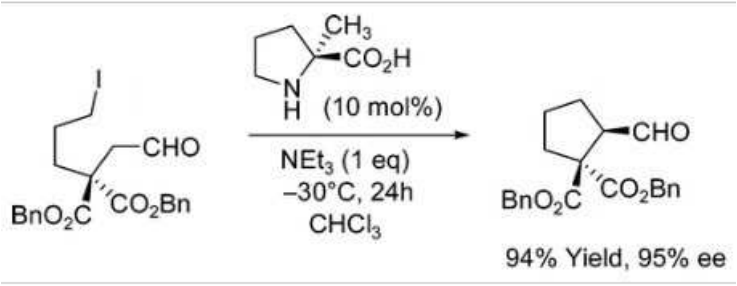
[29] For recent reviews of asymmetric phase-transpher catalysis, see: a) M. O'Donnel, In *Catalytic Asymmetric Synthesis*; Ed: I. Ojima, *Wiley-VCH*: New York, **2000**; b) T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222; c) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, 37, 506; d) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518; e) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013; f) K. Maruoka Org. P*rocess Res. Dev.* **2008**, *12*, 679;. also see: (g) U.-H. Dolling, P. Davis, E. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446; h) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414.

[30] a) N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *125*, 450; b) D. Enders, C. Wang, J. W. Bats, *Angew. Chem. Int. Ed.* **2008**, *47*, 7539; c) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77.

all these reasons in 2004, List[30a] and Vignola reported the first catalytic asymmetric **intramolecular** α-alkylation of aldehydes. (Scheme 5)

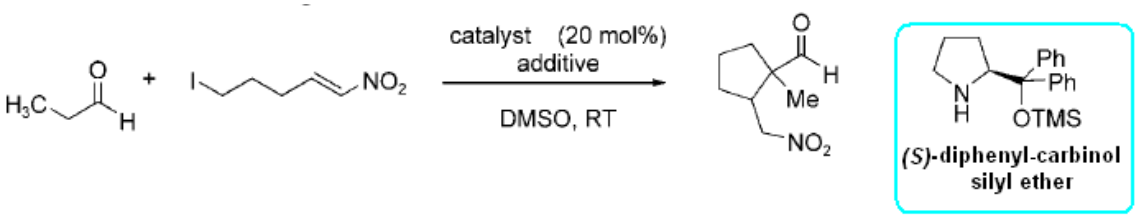
Scheme 5 α-alkylation of aldehyde via enamine catalysis.

■ Intramolecular α-alkylation: List, *J. Am. Chem. Soc.* **2004**, *125,* 450



Four years later, Enders[30b] focused on organocatalytic asymmetric domino reactions, which consisted of a Michael addition cascade to α-alkylation reaction between propanal aldehyde and *(E)*-5-iodo-1-nitropent-1-ene involving enamine–enamine-activation.[31]

■ Cascade Mannich and α-alkylation: Enders, *Angew. Chem. Int. Ed.* **2008**, *47*, 7540



In 2008 MacMillan[32] utilized SOMO[33] concept (one-electron oxidation of a transient enamine species reacts with an electron-deficient alkyl radical via reduction of an alkyl bromide, (Scheme 6).

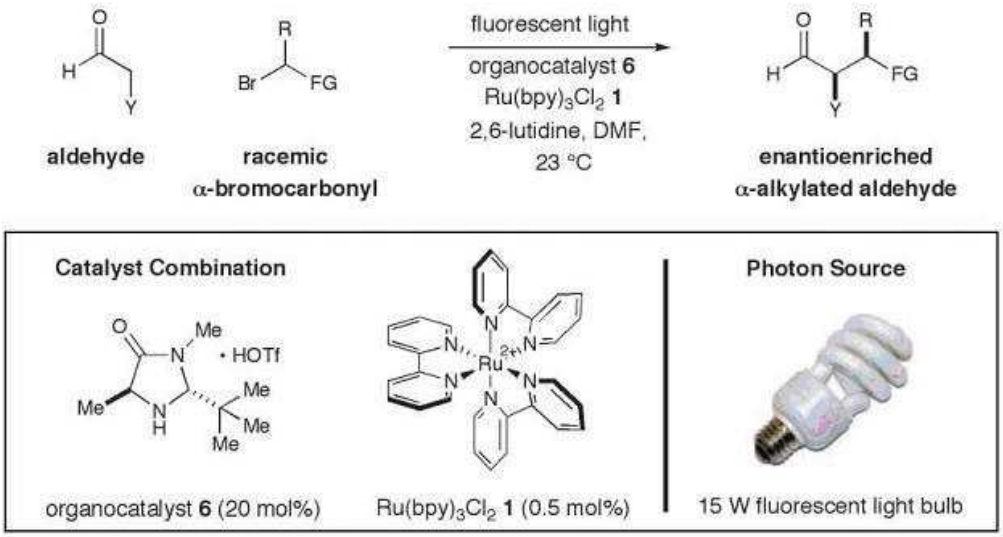
[31] For selected examples of organocatalytic domino reactions following enamine–enamine activation, see: a) A. Córdova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301; b) N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 9591; c) N. S. Chowdari, D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2003**, *5*, 1685.

[32] D.W. C. MacMillan, *Nature* **2008**, *455*, 304.

[33] T. D. Beeson, A. Mastracchio, J. B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582.

Scheme 6 Alternative meccanicistic way to α-alkylation of aldehyde

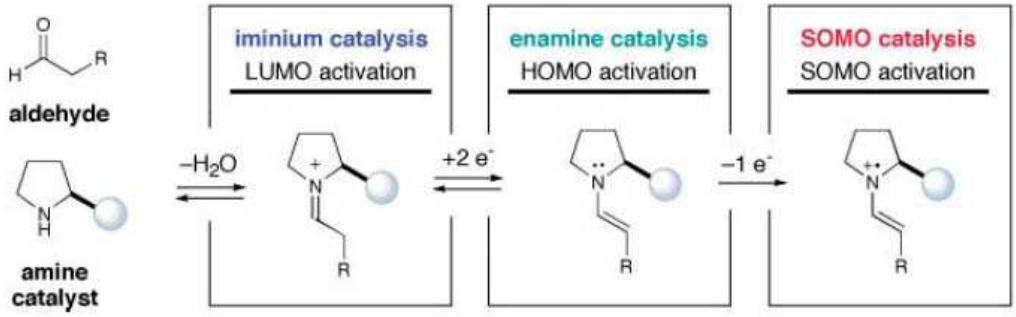
■ SOMO alkylation: MacMillan, *Science* **2008**, *322*, 77.



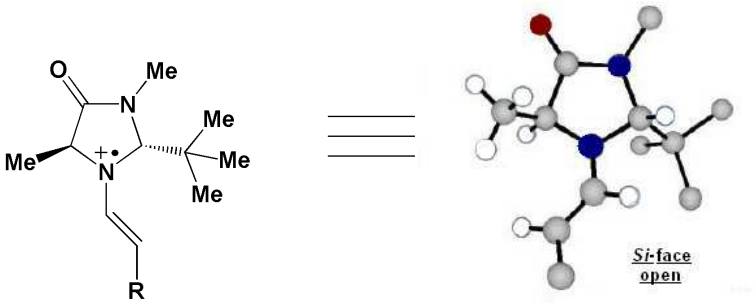
In other hand oxidate enamine should generate a three–pelectron radical cation with a singly occupied molecular orbital (SOMO) as show in Figure 4a. This approch disclosed a range of enantioselective catalytic transformations not currently possible with established catalysis concepts. MacMillan reported DFT structure of oxidate enamine (Figure 4b), the carbon radical-centered represented in Scheme 6 selectively populates an E configuration to minimize nonbonding interactions with the imidazolidinone ring. Furthermore enantiofacial discrimination is due to the methyl group on the catalyst system will effectively shield the Re face of the enamine, leaving the Si face exposed for enantioselective radical addition.

Figure 4 SOMO activation

■ a) MacMillan *Science* **2007**, *316*, 582.



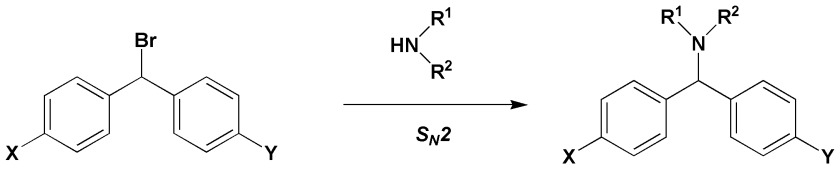
- b)



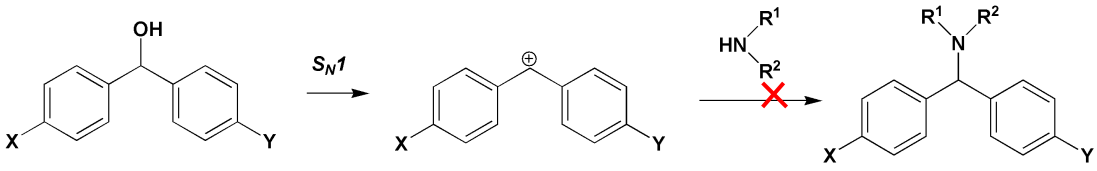
Several secondary and primary amines were introduced as catalysts in this field, but the reaction to carbocation was rarely explored. In fact, carbocations do not react with secondary amines used as catalysts[34], as shown in Scheme 7, this difference of reaction mechanism opens new possibilities in the alkylation of aldehydes by the enamine Way

Scheme 7 Different path way between bimolecular or monomolecolar substitution

- Halydes by bimolecular substitution inhibit catalyst.



- Alcohol by monomolecular substitution is unreactivity toward catalyst.



Enders,[35] Melchiorre and Petrini[36] have hypothesized the formation of highly stable carbocation fragment from indolic framework. The in situ formation of the hypothetical carbocation is occurring from stable precursors. Generation of chiral enamine from proline is establishing the chiral environment for the reaction of the carbocation (Scheme 8a). Despite the difficulties in a clear definition of this process, the process resembles an S_N1-type reaction involving the carbocation, leading to a "formal" α-alkylation.

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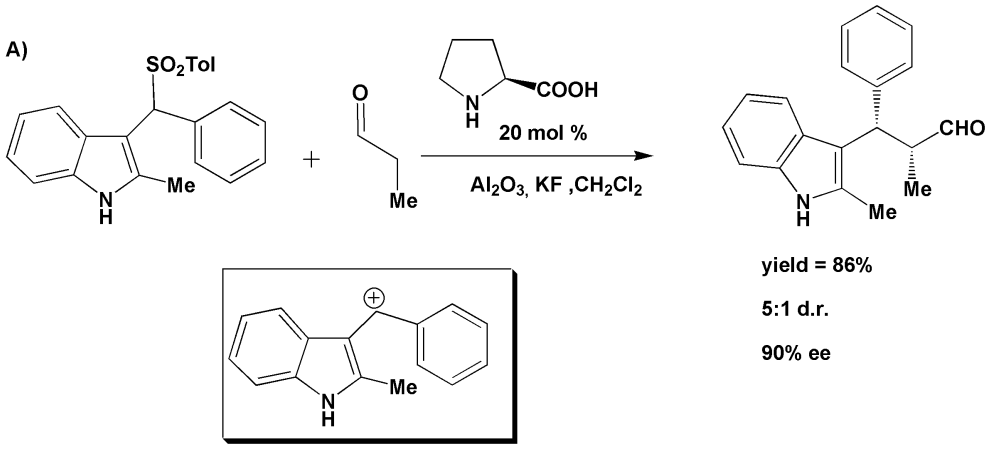
[34] T. B. Phan, C. Nolte, S. Kobayashi, A. R. Ofial H. Mayr *J. Am. Chem. Soc.* **2009**, *131*, 11392

[35] D. Enders, A. A. Narine, F. Toulgoat, T. Bisschops, *Angew. Chem. Int. Ed.* **2008**, *47*, 5661.

[36] R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2008**, *47*, 8707; 3-(1arylsulfonylalkyl)indoles are used as suitable electrophilic precursors, see: a) R. Ballini, A. Palmieri, M. Petrini, R. R. Shaikh, *Adv. Synth. Catal.* **2008**, *350*, 129; b) A. Palmieri, M. Petrini, *J. Org. Chem.* **2007**, *72*, 1863; c) R. Ballini, A. Palmieri, M. Petrini, E. Torregiani, *Org. Lett.* **2006**, *8*, 4093.

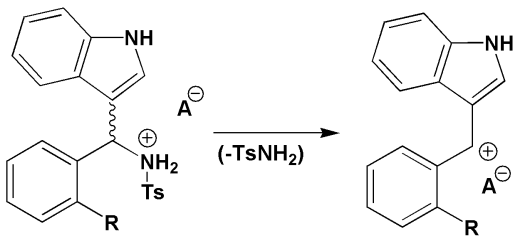
Scheme 8 α-alkylation of aldehydes through hypothetical indolic carbocation.

- Melchiorre, *Angew. Chem. Int. Ed.* **2008**, *47*, 8708.



- Enders, *Angew. Chem. Int. Ed.* **2008**, *47*, 5663.

B)



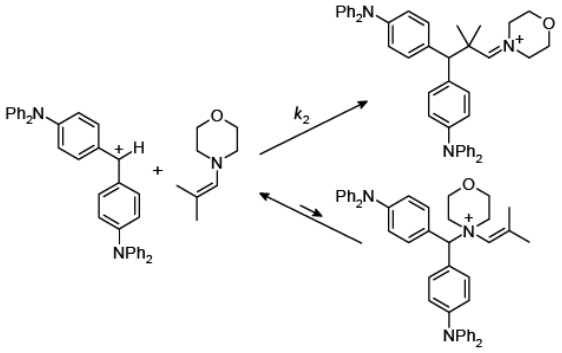
On the basis of preliminary works described in chapter 4, we know that some alcohols can give readly, stabilized, water tolerant carbocations placed between -2.5 and -7, of the Mayr list, can furnish relatively stable alkylating agents that are suitable for organocatalytic reactions, extending the preliminary work of Melchiorre. The carbocations can be generated by the Brønsted acids that is liberated from the MacMillan catalyst used as a salt. The formation of stabilized carbocation and the successive enantioselective reactions was exploited also in the presence of transition metals. [37]

The reaction between carbocations and enamines, which are better nucleophiles than indoles, is well-known[38] (Figure 5a). Mayr et al. have classified nucleophiles using a related nucleophilicity scale, in which the highly nucleophilic enamines are placed at the top of the list (Figure 5b)

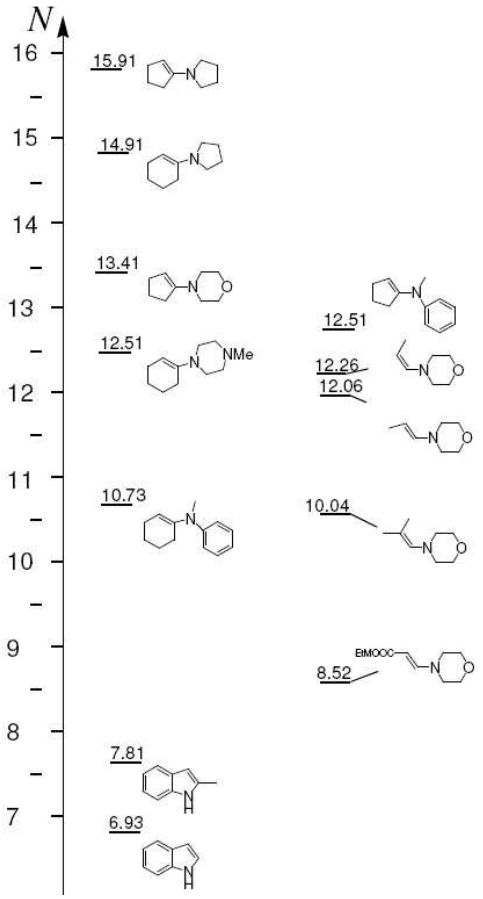
[37] a) P.G. Cozzi, M. G. Capdevila, L. Zoli, manuscript in preparation; b) Y. Nishibayashi, personal communication.
[38] B. Kempf, N. Hampel, A. R. Ofial, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 2209.

Figure 5 Mayr's scale: Nucleophilicity of enamines and indole by comparison.

- Mayr, *Chem. Eur. J.* **2003**, *9*, 2213.



- Mayr's Scale: *Chem. Eur. J.* **2003**, *9*, 2216.



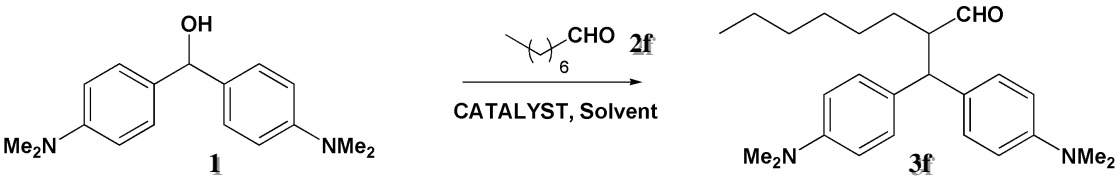
On this basis, we hypothesized that the elusive α-alkylation of an aldehyde might be realized in an effective and simple way by using enamine catalysis coupled with the benzylic alcohols. Bis(4-dimethylamino-phenyl)methanol **1**, which can form a stabilized carbocation,[39] was used in the model reaction with n-octanal.

[39] The 4,4'-bis(dimethylamino)diphenylmethane carbocation has a half-life of 10–20 seconds; see: R. A. McCLelland, V. M. Kanagasabapathy, N. S. Banait, S. J. Steenken, *J. Am. Chem. Soc.* **1989**, *111*, 3966.

Our investigation: dibenzyl alcohols to alkylate aldehyde

Table 1 Optimizating aldehyde α-alkylation

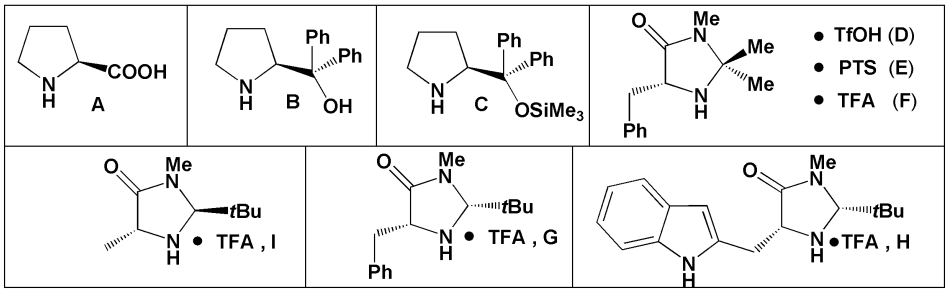
■ a) Model reaction with alcohol **1** and octanal, catalyzed by several amine



Entry[a]	Catalyst	Solvent	Ee[%][b]
1	**F**	Et_2O	70
2	**F**	CH_2Cl_2	55
3	**F**	DME	60
4	**F**	*t*BuOMe	66
5	**F**	AcOEt	55
6	**G**	CH_3CN	50
7	**G**	CH_3CN/H_2O (1:1)	53
8	**G**	THF/H_2O (1:1)	68
9	**F**	H_2O	70
7	**D**	Et_2O	38
8	**E**	Et_2O	18
9	**G**	Toluene	76
10	**G**	Et_2O	80
11[c]	**G**	Et_2O	80
12[d]	**G**	Et_2O	80
13[e]	**G**	Et_2O	80
14	**H**	Et_2O	54
15	**I**	Et_2O	50

[a] All the reaction were carried out on a 0.1 mmol scale using 3 equiv of *n*-octanal, 35% of the catalyst (respect to the alcohol **3f** until complete conversion, checked by TLC (4-24 hours). [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] The reaction was carried out with 15 mol% of catalyst added as salt. Isolated yield after 24 h was 90%. [d] The reaction was carried out with 10 mol% of catalyst added as salt. Isolated yield after 24 h was 66%. [e] The reaction was carried out with 5 mol% of catalyst added as salt. Isolated yield after 24 h was 40%.

■ b) CATALYSTS:

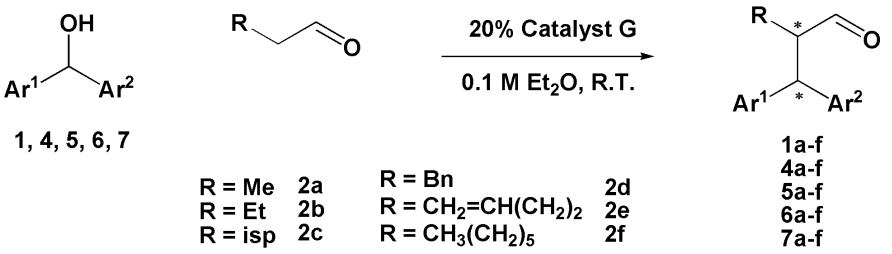


Different organocatalysts were tested in the model reaction and they were used as either the free amine or as a salt (Table1b). Among all the pyrrolidine derivatives tested, only l-proline (A) gave the desired product in MeOH, albeit in racemic form. After an extensive survey of various organocatalysts and conditions, we were delighted to find that the

MacMillan catalysts,[40] **F**, **G**, **H** and **I**, displayed unique and remarkable reactivities in the model reaction performed with n-octanal (Table 1).

By using the selected reaction conditions (catalyst **G**, Diethyl ethere as the reaction solvent), and on the basis of the correlation established between the stability of the carbocations and their reactivities "on water", we selected the alcohols reported below for demonstrating the scope of our alkylation.(Table 2)

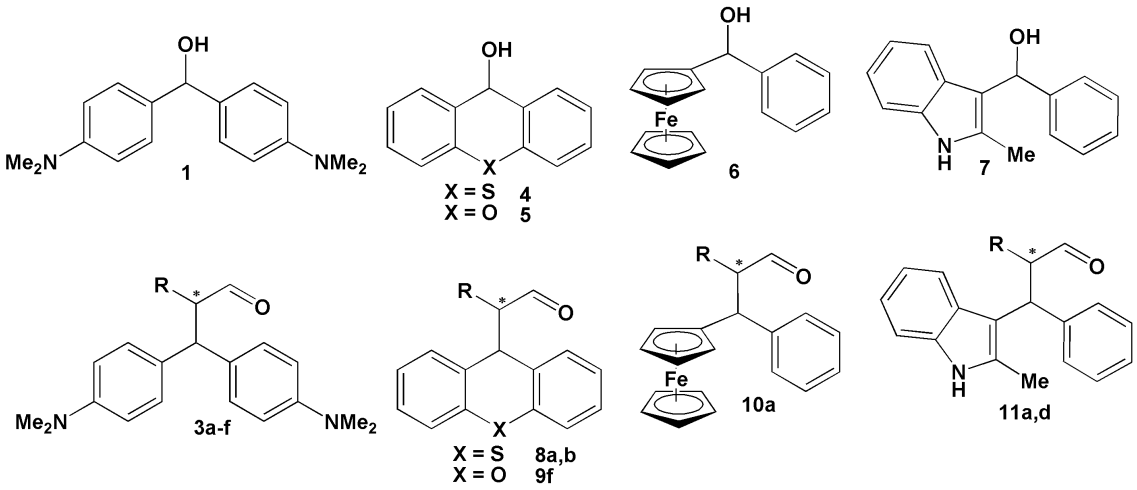
Table 2 Extension of substrate scope on several benzylic alcohols.



Entry[a]	time (h)	Alcohol	Aldehyde	Yield (%)[b]	d.r. [c]	Ee (%)[d]
1	24	**1**	**2a**	95	-	77 (*S*)
2	18	**1**	**2b**	79	-	69
3	20	**1**	**2c**	79	-	69
4	4	**1**	**2d**	77	-	77
5	9	**1**	**2e**	63	-	60
6	21	**1**	**2f**	92	-	78
7[e]	1	**1**	**2f**	85	-	78
8	24	**4**	**2a**	73	-	74
9	24	**4**	**2b**	56	-	77
10	24	**5**	**2f**	95	-	78
11[f]	90	**5**	**2f**	90	-	80
12[g]	24	**6**	**2a**	48	1:3	90 (2*S*,3*S*) syn
13	24	**6**	**2a**	30	1:1.3	70 (2*S*,3*S*) syn 77 (2*R*,3*S*) anti
14	2	**7**	**2a**	80	1.5:1	88 (2*S*,3*S*) anti 78 (2*S*,3*R*) syn
15[h]	42	**7**	**2a**	48	2.6:1	92 (2*S*,3*S*) anti 86 (2*S*,3*R*) syn
16[h]	96	**7**	**2d**	76	3:1	90 (2*S*,3*S*) anti 68 (2*S*,3*R*) syn

[a] All the reaction were carried out at room temperature on 0.1 mmol scale using 3 equivalent of aldehydes and 20 mol% of the catalyst **G**. [b] Isolated yield after chromatographic purification. [c] Determined by ^{1}H NMR or by chiral HPLC analysis on the crude reaction mixture. The ratio is indicated as anti *vs* syn. [d] Determined by chiral HPLC analysis (see experimental section for details). [e] The reaction was carried out without adding any solvent. [f] The reaction was carried out at 0°C. [g] The reaction was carried out using the enantioenriched alcohol (*R*)-**6** (94% ee), employing 90 mol% of the racemic catalyst **G**. [h] The reaction was carried out at – 25 °C.

[40] G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79; and references therein. For theoretical investigations, see: a) J. B. Brazier, G. Evans, T. J. K. Gibbs, S. J. Coles, M. B. Hursthouse, J. A. Platts, N. C. O. Tomkinson, *Org. Lett.* **2009**, *11*, 133; b) R. Gordillo, K. N. Houk, *J. Am. Chem. Soc.* **2006**, *128*, 3543.

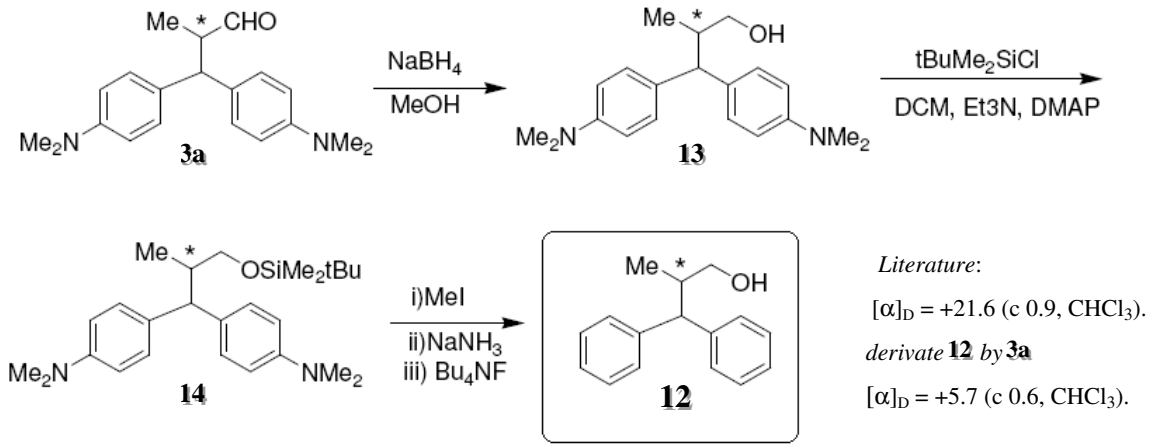


All the alcohols reported herein show smoothly reacted under our reaction conditions with different aldehydes, and the results obtained are reported in (. The products furnished by alcohol **1** present enantiomeric excesses in the range of 60 to 78% ee. The best results in terms of enantiomeric excess were obtained with the alcohols **5**, **6** and **7** ((entry 11-16). Notably, in all cases yields ranging from moderate to excellent were obtained.

Determination of absolute configuration

The absolute configuration of the products **3a-f** was established by chemical correlation with a known compound **12.**[41] We easly synthesized that compound by a pratical sequence for the direct deamination of *N*,*N*-dialkyl aniline rings reported by Paras and MacMillan[42] (Scheme 9).

Scheme 9 The absolute configuration of product 3a was established by correlation.

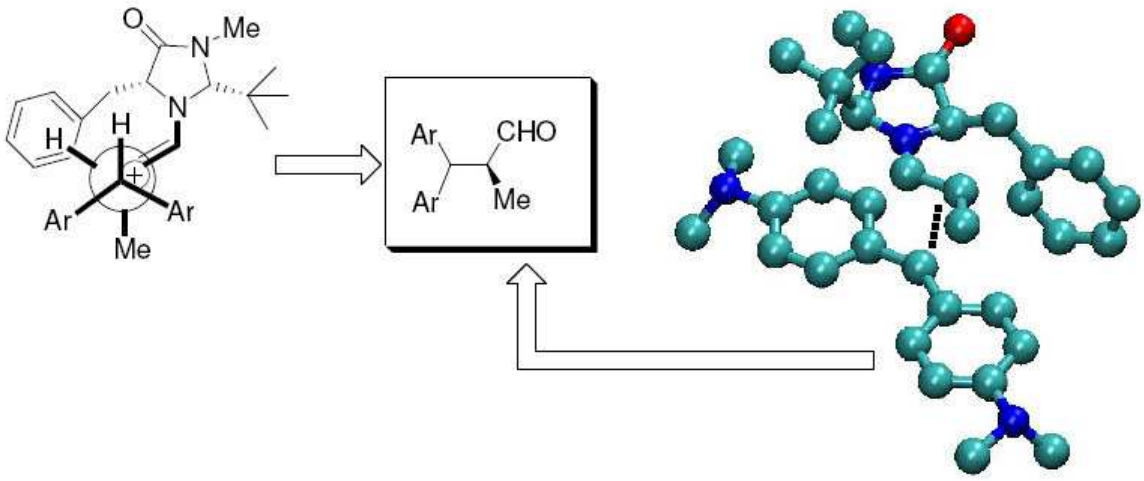


[41] H. M. Walborsky, C. G. Pitt, *J. Am. Chem. Soc.* **1962**, *84*, 4831.

[42] N. A. Paras, D.W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894.

Optycal rotation values of both **12** derivates was used to establish the *(S)*-absolute configuration of our product **3a**. On the basis of this result we have hypothesized a model of possible interaction carbocation enamine-catalyst.

Figure 6 Model and computationl modelling for the absolute configuration for 3a reaction.



Quite remarkable results were obtained with the ferrocenyl alcohol **6**, expecially when the reaction was performed with the optically active starting material (94% ee) and racemic organocatalyst **G.** Indeed the desired product in a diastereoisomeric ratio of 3:1 was obtained with a slight loss in stereochemical information (Table 2 entry 12). However, to accomplish the reaction it was necessary to increase the catalyst loading to 90 mol%. The same reaction performed with optically active organocatalyst **G** gave the product in low yield with an enantiomeric excess of 70%. To explain this behaviour of alcohol **6**, we need to invoke the not planarity of α-ferrocenyl carbocations described in chapters 2 and 3. In this context match and mismatch couples were involved between chiral ferrocenyl carbocation, and one of the two enantiomers of imidazolidinone. The major diastereoisomer and the absolute configuration obtained in the reaction using ferrocenyl alcohol **6** were assigned on the basis of the following consideration:

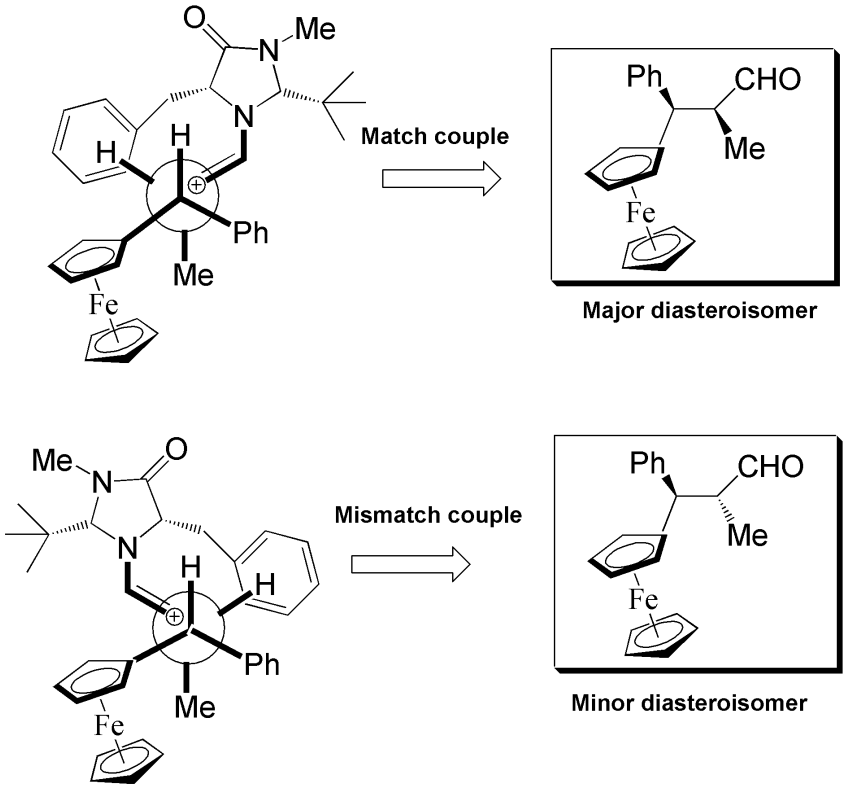
a) The reaction of alcohol (R)-**6** with racemic **G** occurrs with retention of configuration;

b) The same major diasteroisomer was obtained with racemic or optically active alcohol **6**;

c) The optically active catalyst *(2R,5R)***G** affords products having an *S* configuration at *C2*.

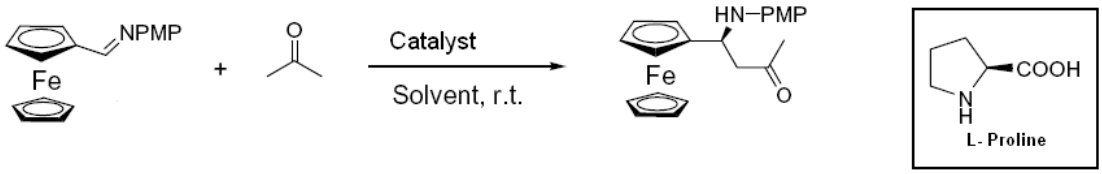
Consequently The model shown in Figure 7 was proposed.

Figure 7 Model for the absolute configuration obtained in the reaction (Alcohol 6).



The reaction of ferrocenyl racemic alcohols with aldehydes represents a new and effective way to prepare optically active ferrocene building blocks.[43] (Scheme 10)

Scheme 10 Via enamine aldol condesation give similar scaffolds.



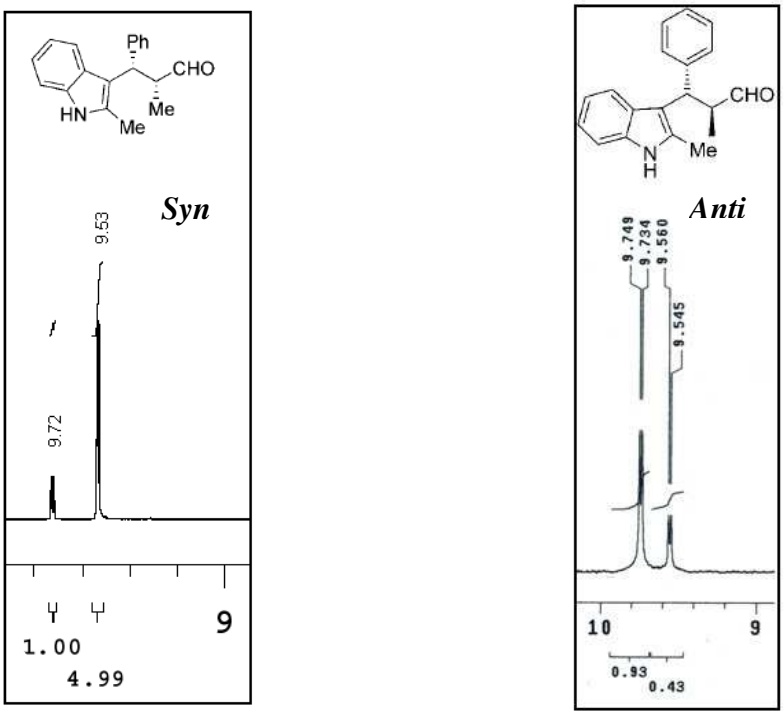
In addition, alcohol **7** is a representative of a class of useful starting materials for easy access to relevant indolyl derivatives.[36,24] Alcohol **7** smoothly reacted in a fast reaction at room temperature to afford the desired product ((, entry 14) in high enantiomeric excess, but with low control of the diastereoselection. Performing the reaction at low temperature (-25°C, Table 2, entry 15) provided better control of the stereoselection at the expense of the yield.

[43] G. Valero, A.-N. Balaguer, A. Moyano, R. Rios, *Tetrahedron Lett*. **2008**, *49*, 6559.

Fortunately we assigned the absolute configuration of the products **11a,d** only by a simple comparison between diagnostic ^{1}HNMR signals (Figure 8) of our derivates and those reported in the literature by Melchiorre in a reaction catalyzed by proline reported in Scheme 8.[36] Experimental evidences obtained supported the direct involvement of the carboxylic group of proline. The carboxylate of the proline can act by protonation of the vinylogous imino derivative by the carboxylic group, or the anionic enamine species might engage in electrostatic association through the pendant carboxylate, with the positively charged intermediate.[44] It is worthy to note the different selectivity for the two processes, although the intermediate carbocation could be the same. Probably, the chiral catalysts used in the reactions dictate this difference. As mentioned above, MacMillan catalyst and Proline are able to differentiate the face of incoming electrophiles in very different way. These reactions are proceeding in function of the stability of the carbocations generated by alcohols. Although benzylic carbocations are readily generated treating alcohols by Lewis or Brønsted acids, not all benzylic carbocations can be used in the presence of organocatalysts. Highly nucleophilic enamines are formed in situ with a liberation of water, and water can easily react with the carbocation, reforming the starting alcohol.

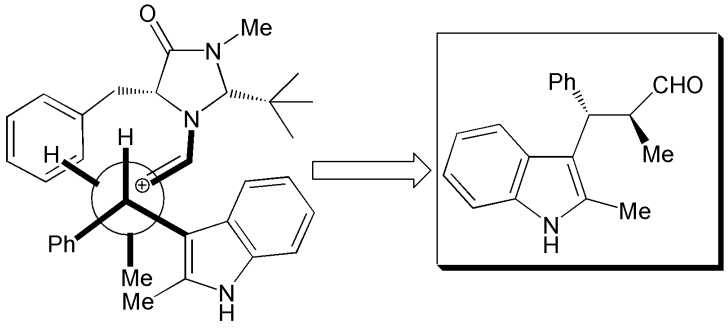
Figure 8 ^{1}H-NMR correlation between literature and our product 11a.

■ Melchiorre, proline catalyst[36] ■ Our work, MacMillan 2° catalyst[44]



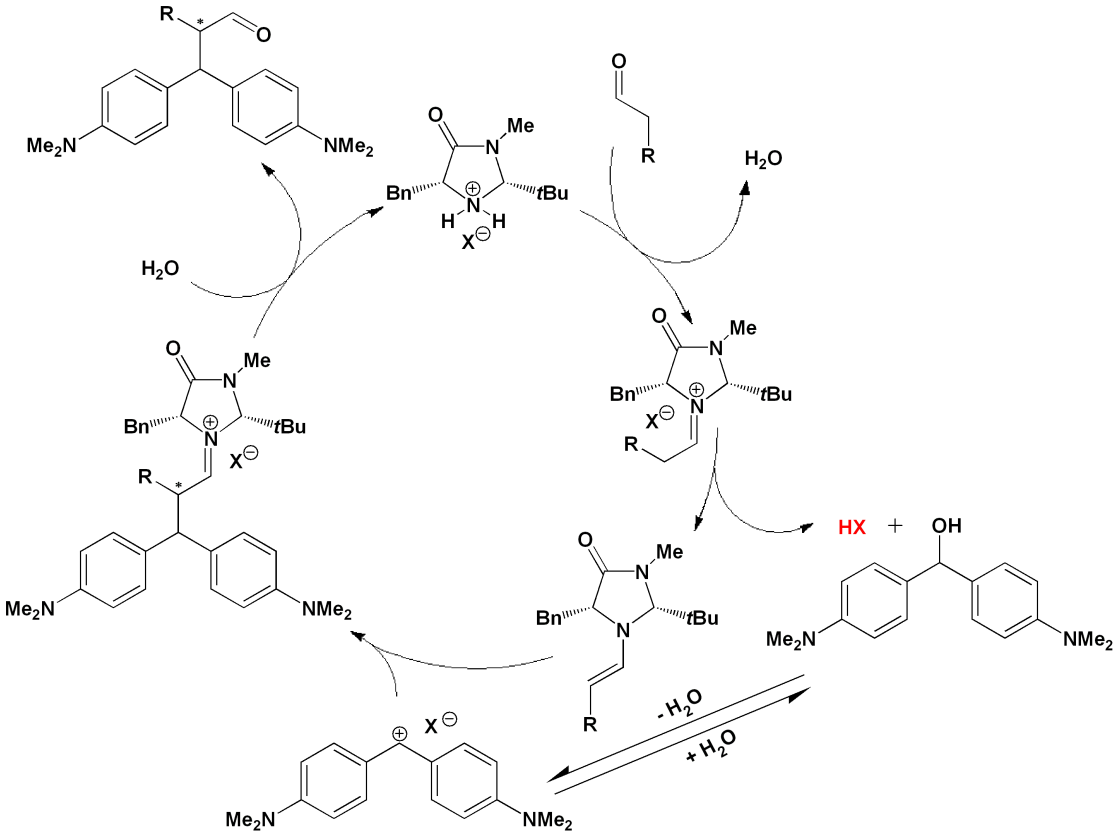
[44] P. G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem. Int. Ed.* **2009**, *48*, 1313.

Figure 9 Model for the absolute configuration hypothesized for alcohol 7.



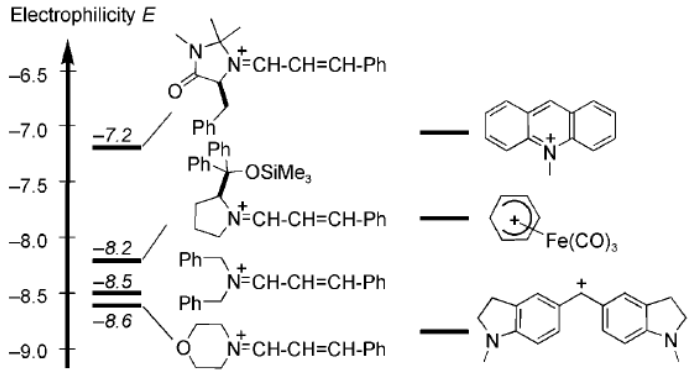
The absolute configuration of the products obtained can be explained by a model in which a carbocation attacks the less hindered face of the *E* enamine obtained in situ by the reaction of the aldehyde with the amine catalyst (Figure 9).

Figure 10 Proposed catalytic cycle for the organocatalytic transformation.



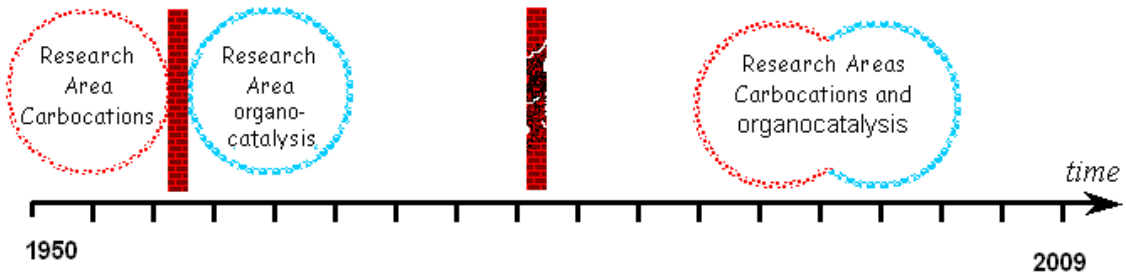
In the catalytic cycle illustrated in Figure 10 the formation of the free acid (HX) is probably responsible for the generation of the carbocation. Notably, the iminium ion formed in the first step of the catalytic cycle is placed at E= -7 on the Mayr scale.[45] The equilibrium established between the enamine and the carbocation might be possible with alcohols that are able to generate relatively stable carbocations of the same or slightly higher electrophilicity relative to enamine as shown in Figure 11.

Figure 11 Electrophile parameters for carbocation and imminium ions are correlated



Conclusion

In summary, we have reported an effective and very simple method to effect the enantioselective direct alkylation of aldehydes with unfunctionalized alcohols.[8b,10] This methodology opens several opportunities for realizing cascade, consecutive, and multicomponent organocatalytic reactions that include benzylic alcohols in their synthetic design. The scope of the present reaction, as well as the use of ketones[46] and other nucleophiles in the organocatalytic, enantioselective direct nucleophilic substitution of alcohols, is presently under active investigation in our laboratory.



[45] S. Lakhdar, T. Tokuyasu, H. Mayr, *Angew. Chem. Int. Ed.* **2008**, *47*, 8723.
[46]L. Zhang, L. Cui, X. Li, J. Li, S. Luo, J.-P. Cheng, *Chem. Eur. J.* **2010**, *16*, 2045.

Experimental section of Chapter 5

General: ^{1}H NMR spectra were recorded on Varian 200 MHz or Varian 300 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian 50 MHz or Varian 75 MHz spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were performed at an ionizing voltage of 70 eV. Chromatographic purification was done with 240-400 mesh silica gel. Analytical gas chromatography (GC) was performed on a Hewlett-Packard HP 6890 gas chromatograph with a flame ionization detector and split mode capillary injection system, using a Crosslinked 5% PH ME Siloxane (30 m) column or a Megadex5 chiral (25 m) column. Analytical high performance liquid chromatograph (HPLC) was performed on a HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190-600 nm), using Daicel Chiralcel^{TM} OD column (0.46 cm I.D. x 25 cm) (Daicel Inc.), Daicel Chiralcel^{TM} AD column (0.46 cm I.D. x 25 cm) (Daicel Inc.), Daicel Chiralcel^{TM} OF column (0.46 cm I.D. x 25 cm) (Daicel Inc.), Daicel Chiralcel^{TM} OJ column (0.46 cm I.D. x 25 cm) (Daicel Inc.), Daicel Chiralcel^{TM} IC column (0.46 cm I.D. x 25 cm) (Daicel Inc.); HPLC grade isopropanol and *n*hexane were used as the eluting solvents. Alcohol **7** was obtained from commercially available aldehyde by the addition of phenylmagnesium bromide (-40 °C, then RT 30 min, yield 66%). All the aldehydes were purified by distillation before their use.

General procedure for alkylation of aldehydes with alcohols:

In a vial organocatalyst **G** (20 mol %), the alcohol (0.1 mmol), and the aldehyde (0,3 mmol) were dissolved in Et_2O (1 mL) at the suitable temperature. The reaction mixture was stirred until judged complete by TLC. Organic solution was quenched with water. The aqueous phase was exctracted with diethylether (2 x 5 mL). The organic phases were reunited, dried over Na_2SO_4, and evaporated at reduced pressure to give a crude product purified by chromatography.

(*S*)-3,3-bis(4-(dimethylamino)phenyl)-2-methylpropanal 3a.

Prepared according to the general procedure from alcohol **1** (0.027 g, 0.1 mmol) and propionaldehyde **2a** (0.021 mL, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 95%, 77% ee, $[\alpha]_D$ = + 47.8 (c 0.5, $CHCl_3$).

White solid; Mp = 114°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.05 (3H, t, J = 6.8 Hz); 2.91 (6H, s); 2.92 (6H, s); 3.10-3.28 (1H, m); 3.92 (1H, d, J = 10.6 Hz); 6.63-6.71 (4H, m); 7.09-7.17 (4H, m); 9.59 (1H, d, J = 3.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.7, 40.6 (4C), 50.6, 56.9, 112.8 (2C), 112.9 (2C), 128.5 (2C), 128.6 (2C), 130.9 (2C), 151.0 (2C), 205.3; ESI-MS: rt: 11.0 min; *m/z*: 311 (M+1).

HPLC analysis AD: gradient from 99:1 (hexane: *i*-PrOH) to 8:2 in 20min, flow 0.7mL/min. TM: 19.0 min; tm: 21.6 min.

(S)-2-(bis(4-(dimethylamino)phenyl)methyl)butanal 3b

Prepared according to the general procedure from alcohol **1** (0.027 g, 0.1 mmol) and butyraldehyde **2b** (0.026 mL, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 79%, 69% ee, $[\alpha]_D$ = + 43.5 (c 0.6, $CHCl_3$).

White solid; Mp = 96°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.79 (3H, t, J = 7.2 Hz); 1.06-1.50 (2H, m); 2.84 (6H, s); 2.88 (6H, s); 2.93-3.12 (1H, m); 3.91 (1H, d, J = 11.0 Hz); 6.56-6.67 (4H, m); 7.08 (4H, d, J = 8.8 Hz); 9.42 (1H, d, J = 4.8 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz) δ: 14.0, 30.8, 40.6 (4C), 50.6, 56.1, 112.9 (4C), 128.5 (4C), 130.8 (2C), 151.0 (2C), 205.1; ESI-MS: rt: 11.6 min; *m/z*: 325 (M+1).

HPLC analysis AD: gradient from 99:1 (hexane: *i*-PrOH) to 8:2 in 20min, flow 0.7mL/min. TM: 25.4 min; tm: 29.1 min.

(S)-2-(bis(4-(dimethylamino)phenyl)methyl)-3-methylbutanal 3c

Prepared according to the general procedure from alcohol **1** (0.027 g, 0.1 mmol) and isovaleraldehyde **2c** (0.032 mL, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 79%, 69% ee, $[\alpha]_D$ = + 43.9 (c 0.7, $CHCl_3$).

White solid; Mp = 134°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.02 (3H, d, J = 6.8 Hz); 1.03 (3H, d, J = 6.9 Hz); 1.74-1.96 (1H, m); 2.88 (6H, s); 2.91 (6H, s); 2.98-3.09 (1H, m); 4.25 (1H, d, J = 11.8 Hz); 6.61-6.71 (4H, m); 7.11-7.18 (4H, m); 9.60 (1H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 16.6, 21.9, 28.6, 40.6 (4C), 48.2, 60.7, 112.9 (2C), 113.0 (2C), 128.3 (2C), 128.6 (2C), 131.2 (2C), 150.9 (2C), 206.4; ESI-MS: rt: 12.1 min; *m/z*: 339 (M+1).

HPLC analysis AD: gradient from 99:1 (hexane: *i*-PrOH) to 8:2 in 20min, flow 0.7mL/min. TM: 14.1 min; tm: 15.1 min.

(S)-2-benzyl-3,3-bis(4-(dimethylamino)phenyl)propanal 3d.

Prepared according to the general procedure from alcohol **1** (0.027 g, 0.1 mmol) and phenylpropyl aldehyde **3d** (0.039 mL, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 77%, 7% ee, $[\alpha]_D$ = + 7.3 (c 0.4, $CHCl_3$).

Yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.83-2.93 (2H, m); 2.88 (6H, s); 2.92 (6H, s); 3.42-3.56 (1H, m); 4.02 (1H, d, J = 11.2 Hz); 6.62 (2H, d, J = 8.8 Hz); 6.71 (2H, d, J = 8.8 Hz); 7.05-7.27 (9H, m); 9.53 (1H, d, J = 3.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 34.9, 40.5 (2C), 40.6 (2C), 50.7, 57.8, 112.9 (2C), 113.0 (2C), 126.2 (2C), 128.4, 128.6 (4C), 129.0 (2C), 130.8 (2C), 139.1, 149.3 (2C), 204.8; ESI-MS: rt: 12.8 min; *m/z*: 387 (M+1); 409 ($M+Na^+$).

HPLC analysis AD: gradient from 99:1 (hexane: *i*-PrOH) to 9:1 in 30min, flow 0.5 mL/min. TM: 31.8 min; tm: 33.5 min.

(S)-2-(bis(4-(dimethylamino)phenyl)methyl)hex-5-enal 3e.

Prepared according to the general procedure from alcohol **1** (0.027 g, 0.1 mmol) and 5-hexenal **2e** (0.029 g, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 63%, 60% ee, $[\alpha]_D$ = + 31.8 (c 0.8, $CHCl_3$).

Yellow oil; ^{1} NMR ($CDCl_3$, 200 MHz) δ: 1.51-1.73 (2H, m); 1.90-2.11 (2H, m); 2.89 (6H, s); 2.92 (6H, s); 3.06-3.25 (1H, m); 3.97 (1H, d, J = 11.0 Hz); 4.94-5.03 (2H, m); 5.60-5.80 (1H, m); 6.62-6.70 (4H, m); 7.12 (4H, d, J = 8.8 Hz); 9.50 (1H, d, J = 4.4 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz) δ: 27.7, 31.1, 40.5 (2C), 40.6 (2C), 50.7, 55.4, 112.9 (4C), 115.3, 128.5 (2C), 128.6 (2C), 130.6, 130.8, 137.8, 149.2, 149.3, 204.9; ESI-MS: rt: 12.5 min; *m/z*: 351 (M+1); 373 ($M+Na^+$).

HPLC analysis AD: gradient from 99:1 (hexane: *i*-PrOH) to 7:3 in 20min, flow 0.5 mL/min. TM: 18.8 min; tm: 20.0 min.

(S)-(bis(4-(dimethylamino)phenyl)methyl)octanal 3f

Prepared according to the general procedure from alcohol **1** (0.027 g, 0.1 mmol) and n-octanaldehyde **2f** (0.057 mL, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 92%, 78% ee, $[\alpha]_D$ = + 18.6 (c 1.0, $CHCl_3$).

White solid; Mp = 65°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.89 (3H, t, J = 6.6 Hz); 1.05-1.41 (8H, m); 1.43-1.61 (2H, m); 2.87 (6H, s); 2.89 (6H, s); 3.01-3.12 (1H, m); 3.95 (1H, d, J = 11.1 Hz); 6.62-6.69 (4H, m); 7.12 (4H, d, J = 8.4 Hz); 9.46 (1H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.9, 22.4, 26.9, 28.5, 29.1, 31.5, 40.5 (2C), 40.6 (2C), 50.5, 56.1, 112.8 (4C), 128.4 (2C), 128.5 (2C), 130.8, 131.0, 149.1 (2C), 205.0; ESI-MS: rt: 16.0 min; *m/z*: 381 (M+1); 403 ($M+Na^+$).

HPLC analysis AD: gradient from 9:1 (hexane: *i*-PrOH) to 7:3 in 20min, flow 0.5mL/min. TM: 13.7 min; tm: 15.3 min.

2-(*9H*-thioxanthen-9-yl)propanal 8a

Prepared according to the general procedure from alcohol **4** (0.021 g, 0.1 mmol) and propanaldehyde **2a** (0.021 mL, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 73%, 74% ee, $[\alpha]_D$ = + 14.7 (c 0.39, $CHCl_3$).

White sticky solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.91 (3H, t, J = 4.2 Hz); 3.15-3.25 (1H, m); 4.28 (1H, d, J = 9.8 Hz); 7.20-7.49 (8H, m); 9.56 (1H, d, J = 2.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 12.9, 45.7, 50.5, 126.4, 126.6, 127.0, 127.3 (2C), 127.5, 129.7, 130.0, 133.0 (2C), 135.5, 135.9, 203.8; ESI-MS: rt: 11.0 min; *m/z*: 197 ($M-C_3H_5O$).

HPLC analysis AD: gradient from 99:1 (hexane: *i*-PrOH) to 96:4 in 25min, flow 0.6mL/min. tm: 15.3 min; TM: 17.0 min.

2-(*9H*-thioxanthen-9-yl)butanal 8b

Prepared according to the general procedure from alcohol **4** (0.021 g, 0.1 mmol) and butyraldehyde **2b** (0.026 mL, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 56%, 77% ee, $[\alpha]_D$ = + 23.3 (c 0.3, $CHCl_3$).

White solid; Mp= 79°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.80 (3H, t, J = 7.2 Hz); 1.28-1.46 (1H, m); 1.49-1.65 (1H, m); 2.97-3.09 (1H, m); 4.33 (1H, d, J = 10.4 Hz); 7.19-7.49 (8H, m); 9.54 (1H, d, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.4, 21.4, 49.7, 52.5, 126.0, 126.3, 126.4, 127.0, 127.4, 127.5, 129.5, 129.9, 133.1, 133.2, 135.3, 135.7, 204.2; ESI-MS: rt: 11.5 min; *m/z*: 536 (2M).

HPLC analysis AD: gradient from 99:1 (hexane: *i*-PrOH) to 96:4 in 25min, flow 0.6mL/min. tm: 14.6 min; TM: 15.7 min.

2-(*9H*-xanthen-9-yl)octanal 9f

Prepared according to the general procedure from alcohol **5** (0.020 g, 0.1 mmol) and octanaldehyde **2f** (0.057 mL, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 95%, 78% ee, $[\alpha]_D$ = + 17.1 (c 0.35, $CHCl_3$).

Colourless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.83 (3H, t, J = 6.6 Hz); 0.98-1.60 (10H, m); 2.51-2.57 (1H, m); 4.49 (1H, d, J = 4.8 Hz); 7.04-7.32 (8H, m); 9.65 (1H, d, J = 2.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.9, 22.4, 25.4, 27.4, 29.1, 31.4, 40.1, 60.6, 116.7, 116.8, 123.4, 123.5, 128.2 (2C), 128.3 (2C), 128.7 (2C), 128.9 (2C), 204.0; ESI-MS: rt: 15.1 min; *m/z*: 331 ($M+Na^+$).

HPLC analysis (reduced to the corresponding alcohol) OF: gradient from 99:1 (hexane: *i*-PrOH) to 90:10 in 30min, flow 0.5mL/min. TM: 18.2 min; tm: 20.5 min.

3-ferrocenyl-3-phenyl-2-methyl-propanal 10a

Prepared according to the general procedure from alcohol R-**6** (0.029 g, 0.1 mmol) and proprionaldehyde **2a** (0.021 mL, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 48%, 90% ee of the *syn* diasteroisomer,

Orange sticky solid; ^{1}H NMR ($CDCl_3$, 200 MHz, mixture of two diasteroisomer) δ: 0.92 (3H, d, J = 7.0 Hz, diast.); 1.0 (3H, d, J = 7.0 Hz, diast.); 2.92 (2H, m); 4.19-3.79 (20H, m); 7.40-7.22 (10H, m); 9.52 (1H, d, J = 2.6 Hz, diast.); 9.73 (3 Hz, d, J = 1H, diast.); ^{13}C NMR ($CDCl_3$, MHz) δ: 13.3 8 (syn + anti), 47.4 (syn), 48.3 (anti), 52.5 (syn), 53.0 (anti), 67.0 (syn), 67.1 (2C anti), 67.4 (syn), 68.2 (anti), 68.3 (syn), 68.5 (syn), 68.6 (5C, anti), 68.7 (5C, syn), 69.3 (anti), 90.9 (syn + anti), 126.7 (syn), 126.9 (anti), 128.3 (2C syn), 128.4 (2C anti), 128.5 (2C syn), 128.6 (2C anti), 142.5, 204.6.; ESI MS: rt: 12.0 min; *m/z* 332(M).

HPLC analysis IC: gradient from 99:1 (hexane: *i*-PrOH) to 9:1 in 30min, flow 0.5 mL/min. TM (syn): 20.5 min; tm (syn): 22.7 min; TM (anti): 20.9 min; tm (anti): 21.9 min;

2-methyl-3-(2-methyl-1*H*-indol-3-yl)-3-phenylpropanal 11a

Prepared according to the general procedure from alcohol **7** (0.022 g, 0.1 mmol) and propionaldehyde **2a** (0.021 mL, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 80%, 88% ee of *anti* 78% ee of *syn*.

Colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.06 (3H, d, J= 6.8 Hz); 2.45 (3H, s); 3.58-3.80 (1H, m); 4.45 (1H, d, J = 11.0 Hz); 7.03-7.44 (8H, m); 7.59-7.63 (1H, m); 7.84 (1H, bs); 9.74 (1H, d, J = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 12.3, 13.7, 43.9, 48.9, 110.4, 112.1, 119.0, 119.5, 121.0, 126.3, 127.4, 127.9 (2C), 128.5 (2C), 131.7, 135.3, 142.6, 205.2; ESI MS: rt: 9.5 min; *m/z*: 278 (M+1); 300 ($M+Na^+$).

HPLC analysis IC: gradient from 99:1 (hexane: *i*-PrOH) to 8:2 in 30min, flow 1.0 mL/min. TM (anti): 12.0 min; tm (anti): 13.0 min; TM (syn): 17.3 min; tm (syn): 13.6 min;

2-benzyl-3-(2-methyl-1*H*-indol-3-yl)-3-phenylpropanal 11d

Prepared according to the general procedure from alcohol **1** (0.022 g, 0.1 mmol) and phenylpropyl aldehyde **2d** (0.039 mL, 0.3 mmol), until judged complete by TLC and purified by flash chromatography. Yield 76%, 90% ee of *anti* 68% ee of *syn*.

Colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (anti): 2.43 (3H, s); 2.80-3.05 (2H, m); 3.96-4.10 (1H, m); 4.53 (1H, d, J = 11.0 Hz); 7.00-7.43 (13 H, m); 7.75-7.79 (1H, m); 7.87 (1H,bs); 9.71 (1H, d, J = 3.4 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 12.3, 35.4, 43.4, 56.1, 110.6, 112.0, 119.0, 119.7, 121.1, 126.3, 126.4, 127.3, 127.9, 128.0, 128.4, 128.5, 128.6, 128.7, 129.0, 129.1, 131.9, 135.5, 138.6, 142.2, 205.3; ESI MS: rt: 11.0 min; *m/z*: 354 (M+1); 376 ($M+Na^+$).

HPLC analysis IC: gradient from 99:1 (hexane: *i*-PrOH) to 8:2 in 30min, flow 0.5 mL/min. TM (anti): 25.0 min; tm (anti): 30.2 min; TM (syn): 25.9 min; tm (syn): 21.7 min;

3,3-Bis-(4-dimethylamino-phenyl)-2-methyl-propanol 13.

In a vial aldehyde **2a** (0.031 g, 0.1 mmol) was dissolved with methanol (1mL) then $NaBH_4$ (0.007 g, 0.2 mmol) was slowly added to the solution at 0°C. The reaction was stirred until judged complete by TLC. Organic solution was quenched with water. The aqueous phase was exctracted with diethylether (2 x 5 mL). The organic phases were reunited, dried over Na_2SO_4, and evaporated at reduced pressure to give a crude product purified by chromatography.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.96 (3H, d, J = 6.8 Hz, d); 2.57-2.40 (1H, m); 2.90 (12H, s); 3.65-3.39 (2H, m); 6.67 (4H, J = 2.6, 9.2 Hz, dd); 7.17 (4H, J = 0.8, 8.0 Hz, dd).

***Tert*butyltrimethylsiloxy-3,3-bis-(4-dimethylamino-phenyl)-2-methyl-propane 14.**

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.04 (3H, s); 0.03 (3H, s); 0.91 (9H, s); 0.92 (3H, d, J = 6.6 Hz); 2.87 (12H, s); 2.25-2.42 (1H, m); 3.60-3.20 (3H, m); 6.50 (4H, d, J = 8.8 Hz); 7.13 (4H, d, J = 8.8 Hz).

***Diiodo tert*butyltrimethylsiloxy-3,3-bis-(4-trimethylamino-phenyl)-2-methyl-propane.**

^{1}H NMR (CH_3OD, 200 MHz) δ: 0.72 (3H, s); 0.68 (3H, s); 0.26 (9H, s); 0.28 (3H, d, J = J = 6.6 Hz); 2.05 (1H, m); 2.60-3.00 (2H, m); 2.91 (18H, s); 7.01 (4H, J = 8.8 Hz, d); 7.24 (4H, J = 8.8Hz, d).

***Tert*butyltrimethylsiloxy-3,3-diphenyl-2-methyl-propane.**

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.12 (6H, s); 0.91 (9H, s); 0.96 (3H, J = 6.6, d); 2.61-2.36 (m, 1H); 3.33 (1H, J = 5.6, 9.8 Hz, dd); 3.51 (1H, J = 3.4, 9.8 Hz, dd); 3.76 (1H, J = 11 Hz, d); 7.31-7.15 (m, 10 H).

2-Methyl-3,3-diphenyl-propan-1-ol 12.

$[\alpha]_D$ = + 5.7 (c 0.57, $CHCl_3$).

Lit: H. M. Walborsky, C. G. Pitt, *J. Am. Chem. Soc.* **1962**, *84*, 4831. (*S*)-2-Methyl-3,3-diphenyl-propan-1-ol ; $[\alpha]_D$ = + 21.6 (c 0.89, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.96 d (3H, J = 6.6 Hz); 1.25 (1H, br s); 2.64-2.50 (1H, m); 3.51 (1H, J = 5.8, 11 Hz, dd); 3.63 (1H, J = 4.0, 11 Hz, dd); 3.74 (1H, J = 11Hz, d); 7.42-7.21 (5H, m).