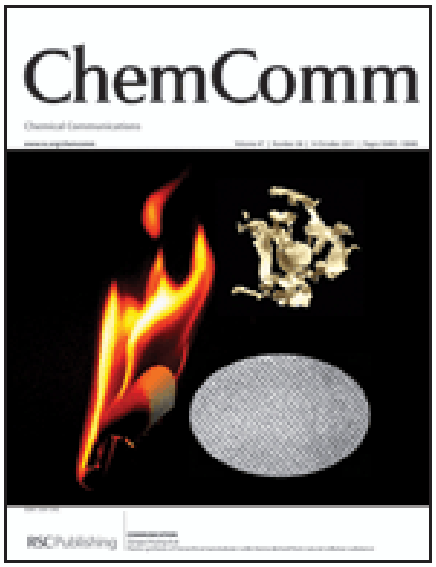

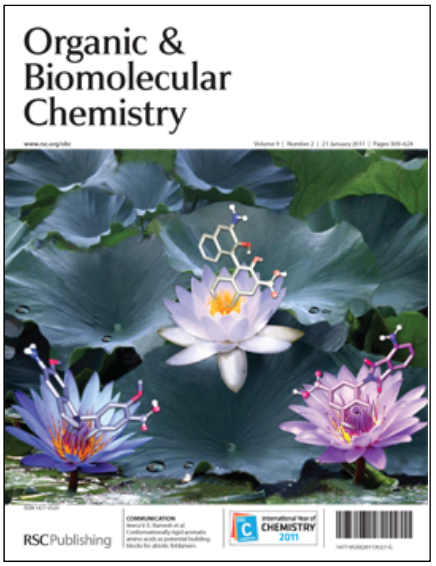

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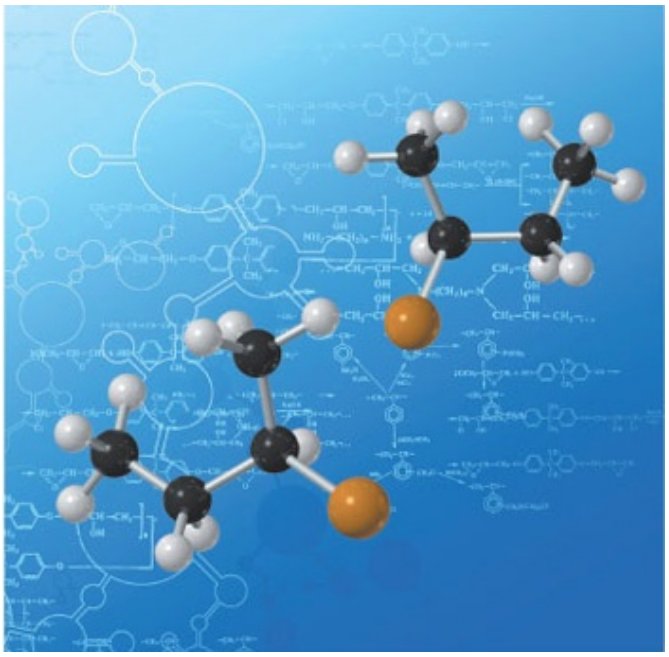

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COMMUNICATION

Hexafluorobenzene: a powerful solvent for a noncovalent stereoselective organocatalytic Michael addition reaction†‡

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Received 30th November 2011, Accepted 8th December 2011
DOI: 10.1039/c2cc17488j

A dramatic enhancement of the diastereo- and enantioselectivity in the nitro-Michael addition reaction organocatalysed by a commercially available α,α-L-diaryl prolinol was disclosed when performing the reaction in unconventional hexafluorobenzene as a medium. DFT calculations were performed to clarify the origin of stereoselectivity and the role of C_6F_6.

The development of highly enantioselective catalytic systems always requires stereoelectronic modifications of the chiral ligands or the organocatalysts used in metal-catalysed or metal-free promoted processes, respectively.[1] Consequently, different chiral sources have to be accessible and long or expensive syntheses are frequently necessary to obtain the best candidate. The enantioselectivity of a reaction can also greatly benefit from the employment of additives and co-catalysts,[2] and more recently, a remarkable advance has been disclosed in the context of chiral ion pairs mediated catalysis by combining chiral counteranions with chiral ligands/catalysts, in the so-called asymmetric counteranion-directed catalysis (ACDC) as coined by Mayer and List.[3] Concerning the experimental parameters, the choice of solvent is crucial during the optimization of an asymmetric process.[4] Although systematic solvent effects are clearly impossible to apply in the vast area of asymmetric catalysis as well as predictions on the effectiveness of a particular solvent, the discovery of novel media with unpredictable effects is of particular importance. Likewise, attempts to rationalize a dramatic solvent effect on the stereochemical outcome of a process may help to improve our tools to achieve better enantiocontrol by modification of the reaction conditions.

Some recent reports on Ru-catalysed olefin metathesis showed fluorinated aromatic solvents to have beneficial effects[5] in terms of reaction rate enhancement, regiocontrol and in one example also on the enantioselectivity.[6] It was speculated that π–π interaction between the catalyst and the solvent or direct fluorine–ruthenium interactions might be responsible for the observed amplifications. Aromatic non-polar solvents, such as toluene and xylenes, are well-recognised as the most suitable media to use in noncovalent organocatalysis. Indeed, they do not interfere with hydrogen bonding and more generally, polar interactions, established among the catalyst and the reagents responsible for catalytic activity and stereocontrol.[7] Taking into account that hexafluorobenzene is a non-polar solvent ($\varepsilon = 2.05$),[8] we were intrigued by the fact that it might positively influence the outcome of organocatalytic processes. The asymmetric Michael addition is a powerful and extensively applied reaction for the construction of C–C and C–heteroatom bonds.[9] Recently, we have been interested in the development of asymmetric organocatalytic reactions mediated by commercially or easily available α,α-L-diaryl prolinols.[10] These compounds proved to be effective in a variety of asymmetric Michael addition reactions providing noncovalent activation of the reagents. Hence, we choose to study the activity of α,α-L-diaryl prolinols in the conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes as a model reaction. Herein, we report the experimental and computational investigation of a remarkable solvent effect disclosed in the nitro-Michael addition reaction for the construction of vicinal tertiary and quaternary stereocenters catalysed by commercially available α,α-L-diaryl prolinols in C_6F_6 as solvent.[11]

The nitro-Michael addition of cyclic β-keto ester **2a** to *trans*-β-nitrostyrene **1a** was chosen for the optimization study (Table 1).

A first screening in toluene of catalysts **3a–f** (see ESI‡) and catalyst **3a** in different solvents showed similar behaviour and modest values of the diastereoselectivity and enantiomeric ratio (er) were achieved (entries 1–2). Fluorinated aromatic solvents such as trifluoromethyl benzene and C_6F_6 were checked using catalyst **3a** (entries 3 and 4). Significant improvement of diastereo- and enantioselectivity was observed in the reaction performed in C_6F_6 (entry 4). The performance of catalysts **3** in this medium (see ESI‡) enabled us to select the commercially available catalyst **3b** as the most effective compound (entry 5). Delightfully, in the presence of 15 mol% of catalyst **3b**, the product was obtained in excellent yield, almost as a single diastereoisomer and with a 95 : 5 er (entry 6). Reduction of catalyst **3b** loading to 10 mol% led only to slightly inferior results in terms of stereocontrol (entry 7).

With the optimal catalyst and reaction conditions in hand, the scope and limitations of the Michael addition of β-ketoesters **2** to nitroolefins **1** in C_6F_6 was studied (Table 2).

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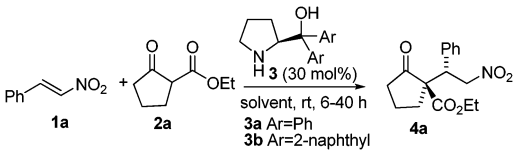
† This article is part of the joint ChemComm–Organic & Biomolecular Chemistry 'Organocatalysis' web themed issue.

‡ Electronic supplementary information (ESI) available: Experimental procedures and computational details. See DOI: 10.1039/c2cc17488j

Table 1 Catalyst and solvent optimization study for the Michael addition of β-ketoester **2a** to *trans*-β-nitrostyrene **1a**[a]

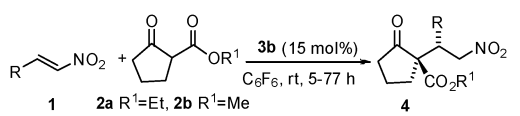


Entry	Catalyst	Solvent	Yield[b] (%)	dr[c]	er[d]
1	**3a**	Toluene	91	3 : 1	64 : 36
2	**3b**	Toluene	99	4 : 1	58 : 42
3	**3a**	$CF_3C_6H_5$	98	5 : 1	76 : 24
4	**3a**	C_6F_6	98	7 : 1	81 : 19
5	**3b**	C_6F_6	99	13 : 1	91 : 9
6[e]	**3b**	C_6F_6	98	24 : 1	95 : 5[f]
7[g]	**3b**	C_6F_6	94	19 : 1	93 : 7

[a] All reactions run at 0.5 M with 0.2 mmol of **1a** and **2a**. [b] Yield of isolated product. [c] The diastereoisomeric ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Determined for the major diastereoisomer by chiral HPLC. [e] Catalyst used at 15 mol% loading. [f] The absolute configuration (2*R*,3*S*) of product **4a** was assigned by comparing the optical rotation to the literature. [g] Catalyst used at 10 mol% loading.

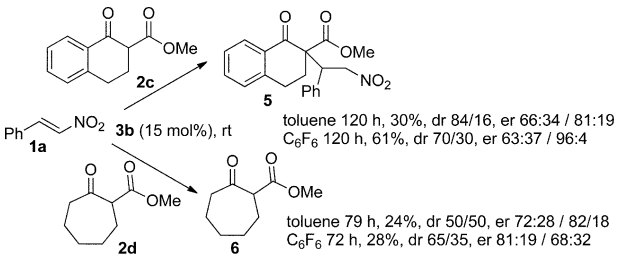
The adducts were generally obtained in excellent yield. The presence of electron-withdrawing groups is well tolerated also in the *ortho*-position of the benzene ring as well as 2-naphthyl and heteroaromatic residues, achieving high stereocontrol in the adducts **4** (entries 1–8). In the case of electron-donating groups, the product was obtained with somewhat lower diastereo- and enantioselectivity (entries 9 and 10). When employing the more challenging and less reactive aliphatic nitroalkene **1k**, the product was recovered in moderate yield and satisfactory level of stereocontrol (entry 11). Six- and seven-membered ring β-keto esters **2c** and **2d** were also reacted under optimized conditions with **1a** using toluene and C_6F_6 as solvents (Scheme 1). In the case of compound **2c**, higher conversion to the product was observed in C_6F_6 with respect to toluene. The diastereoisomeric ratio was slightly inferior in C_6F_6, whereas a notable improvement of the er ratio (er 96 : 4) was observed for the minor diastereoisomer. Conversion to the seven-membered ring derivative **6** proved to be modest in both solvents, although an improvement in the

Table 2 Catalytic asymmetric Michael addition of compounds **2** to nitroalkene[a]



Entry	**2**	R	Yield **4** (%)	dr	er
1	**2a**	Ph (**1a**)	98 (**4a**)	24 : 1	95 : 5
2	**2a**	2-Naphthyl (**1b**)	98 (**4b**)	19 : 1	94 : 6
3	**2a**	3-BrC_6H_4 (**1c**)	94 (**4c**)	19 : 1	95 : 5
4	**2a**	4-FC_6H_4 (**1d**)	98 (**4d**)	19 : 1	94 : 6
5	**2a**	2-ClC_6H_4 (**1e**)	92 (**4e**)	32 : 1	95 : 5
6	**2a**	2-Furyl (**1f**)	89 (**4f**)	10 : 1	86 : 14
7	**2b**	2-Thienyl (**1g**)	98 (**4g**)	16 : 1	92 : 8
8	**2b**	Ph (**1h**)	97 (**4h**)	16 : 1	94 : 6
9	**2b**	4-MeC_6H_4 (**1i**)	98 (**4i**)	13 : 1	83 : 17
10	**2b**	4-MeOC_6H_4 (**1j**)	95 (**4j**)	9 : 1	79 : 21
11	**2b**	Cyclohexyl (**1k**)	52 (**4k**)	24 : 1	81 : 19

[a] See footnote a in Table 1.



Scheme 1

diastereoselectivity and enantiomeric ratio for the major diastereoisomer was detected in C_6F_6. Unfortunately, the system proved to be poorly active with acyclic derivatives, as demonstrated by reacting α-methyl ethyl acetoacetate with **1a** under optimized conditions. The conversion to the product was inferior to 20% after 6 days in both solvents.

The feasibility of a more appealing use of C_6F_6 as additive rather than solvent was also investigated (Table 3). Compound **2a** was reacted with nitroalkene **1a** in diethyl ether and in mixtures of diethyl ether and hexafluorobenzene. *trans*-β-Nitrostyrene **1a** was firstly reacted in Et_2O affording compound **4a** in moderate yield, as 11 : 1 mixture of diastereoisomers and with an enantiomeric ratio of 80 : 20 for the major diastereoisomer (entry 1). Notably, the addition of 10 or 5 equivalents of C_6F_6 with respect to reagents (entries 2 and 3) was sufficient to achieve comparable results to that obtained in pure C_6F_6 (entry 1, Table 2). Reactions of representative nitroalkenes **1b**,**d** with compound **2a** using 5 equivalents of C_6F_6 gave satisfactory results, although it appears that the optimal amount of C_6F_6 to be added can be substrate-dependent (entries 4 and 5).

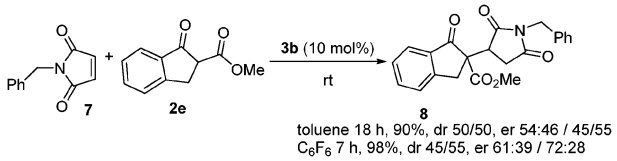
Motivated by these results, we also investigated the effect of C_6F_6 as a medium in another Michael-type reaction catalysed by diaryl prolinol **3b**, by reacting compound **2e** to maleimide **7** at room temperature (Scheme 2).

Product **8** was obtained in high yield, 1 to 1 diastereoisomeric ratio, although almost without enantiocontrol when the reaction was performed in toluene. Compound **8** was more rapidly and quantitatively formed with a similar diastereoisomeric ratio in C_6F_6 as a solvent. However, a significant improvement of the enantiomeric ratio (up to 72 : 28 er) was observed for both diastereoisomers. All these findings demonstrate that the use of C_6F_6 as solvent is beneficial to achieve higher conversion to the product and more interestingly to remarkably enhance the stereocontrol in different Michael addition reactions catalysed by α,α-L-diaryl prolinols. From a mechanistic point of view, the reactions are likely to proceed *via* noncovalent activation of the reacting partners by catalysts **3**. Indeed, Zhu *et al.*[12] did

Table 3 Catalytic asymmetric Michael addition in Et_2O with C_6F_6 as an additive[a]

Entry	R	C_6F_6 (equiv.)	Yield (%)	dr	er
1	Ph (**1a**)	—	64 (**4a**)	11 : 1	80 : 20
2	Ph (**1a**)	10	92 (**4a**)	19 : 1	95 : 5
3	Ph (**1a**)	5	90 (**4a**)	16 : 1	95 : 5
4[b]	2-Naphthyl (**1b**)	5	98 (**4b**)	24 : 1	87 : 13
5[c]	4-FC_6H_4 (**1d**)	5	98 (**4d**)	16 : 1	92 : 8

[a] Unless otherwise noted the reactions were run at 0.25 M in Et_2O with *x* equivalents of C_6F_6 and 0.2 mmol of **1** and **2a** at room temperature. [b] Reaction run at $C = 0.4$ M. [c] Reaction run at $C = 0.5$ M.



Scheme 2

not observe the formation of an enamine intermediate[13] when reacting compound **2a** with 100 mol% loading of catalyst **3a** in $CDCl_3$. NMR studies revealed the establishment of hydrogen bonding interactions between catalysts **3** and the enol form of compounds **2** in the α-sulfenylation of α-substituted β-ketoesters.

DFT calculations were performed to shed light on this unusual amplification of enantioselectivity.[14] For this reason, we focused on the stereoselectivity determining step corresponding to the formation of the C–C bond between **1a** and the enol form of **2a**, leading to the two major stereoisomers *R*,*S* and *S*,*R*. As a representative catalyst we considered **3a**. DFT calculations, consistent with the experiments, indicate that formation of **4a** through transition state (TS) pro-*R*,*S* is favored by 3.0 kcal mol^{-1} over TS pro-*S*,*R*.[15] Both transition states present the flat ester group of **2a** stacked over the phenyl group of **1a**, see Fig. 1.

However, TS pro-*R*,*S* is characterized by three H-bonds, indicated as HB1-3 in Fig. 1a, whereas TS pro-*S*,*R* is characterized by only 2 H-bonds, indicated as HB1and HB2 in Fig. 1b. This suggests that TS pro-*R*,*S* is favored by a higher number of H-bonds between reactants and catalyst. Moving to the beneficial impact of C_6F_6, we located TS pro-*R*,*S* and pro-*S*,*R* in the presence of a C_6F_6 molecule. We tried several orientations, the most stable are shown in Fig. 1c and d. In both geometries the C_6F_6 ring is stacked over the enolate group. This can be explained considering that C_6F_6 is characterized by a quadrupole moment with the positive lobes above the aromatic ring, which optimizes electrostatic interaction with electron density delocalized on the enolate π orbitals.[16] In the presence of a C_6F_6 molecule the energy difference between TS pro-*R*,*S* and pro-*S*,*R* increases from 3.0 to 4.3 kcal mol^{-1}, which is in agreement with the experiments. This increased preference is a consequence of steric interactions between the reacting system and C_6F_6 in TS pro-*S*,*R*, which prevent an optimal interaction of the reacting system with the C_6F_6 ring, see the longer distances in Fig. 1d, and Fig. S2 (ESI‡).

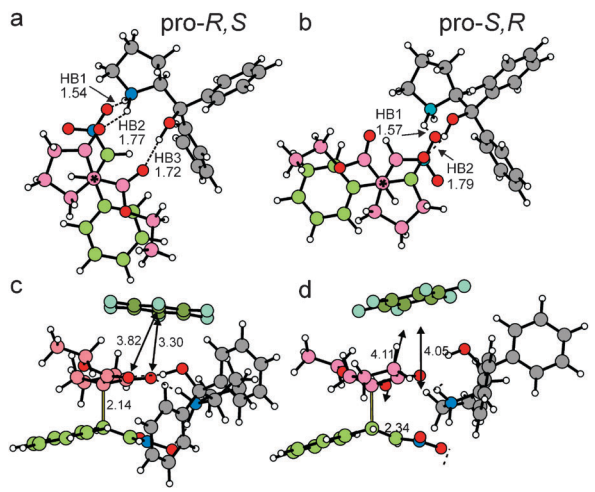


Fig. 1 Structure of TS pro-*R*,*S* and pro-*S*,*R*, (a) and (b), respectively, and of the same TS in the presence of C_6F_6, (c) and (d), respectively.

In conclusion, we have disclosed that, using C_6F_6 as solvent or additive, the nitro-Michael addition reaction for the construction of vicinal tertiary and quaternary stereocenters, conveniently catalysed by a commercially available α,α-diaryl-L-prolinol, can be turned from scarcely to highly stereoselective. The positive effect provided by C_6F_6 appears to be of wider applicability at least in asymmetric Michael type reactions catalysed by α,α-L-diaryl prolinols. DFT calculations clarified the origin of this unexpected amplification of selectivity, providing the conceptual tools for application of the same solvent strategy to other cases.

We thank MIUR for financial support and the Spanish MICINN for a Ramón y Cajal contract (RYC-2009-04170).

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