Organocatalysis

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Trends in Organocatalytic Conjugate Addition to Enones: An Efficient Approach to Optically Active Alkynyl, Alkenyl, and Ketone Products[**]

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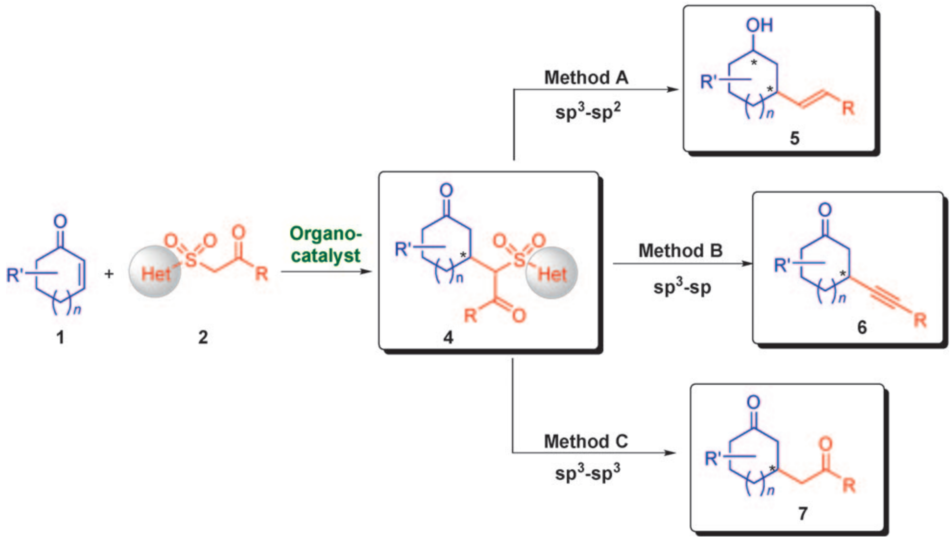
Asymmetric organocatalysis provides an elegant and easy procedure to introduce chiral information into a substrate.[1] Thus, the challenging problem of developing efficient organocatalytic methods for C–C bond formations has been attractive to many chemists, and within the past few years new reaction protocols have been disclosed by numerous research groups.[1,2]

Within this context, the organocatalytic asymmetric conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is a well-documented strategy, which provides a direct and simple route for the synthesis of versatile, enantiomerically enriched building blocks.[3] However, the majority of reports to date are limited to simple nucleophiles, which lead only to the bond formation between two sp^3-hybridized carbon atoms.[4] In contrast, asymmetric conjugate addition of sp^2- and sp-hybridized carbon-based nucleophiles remains a challenging task.[5,6]

Nowadays, new synthetic strategies offering high diversity and operational efficiency are becoming more evident.[7] In this respect, catalytic tandem reactions in an iterative manner are an especially robust model, which enables the efficient conversion of simple starting materials into a library of small molecules.[8] The general concept involves the formation of a chiral intermediate, which can be distinctly manipulated, through different transformations, to afford products containing divergent skeletal arrays.[9] Therefore, expanding the scope of the Michael reaction with respect to the nucleophilic species would represent an important advance. Herein we report the first highly enantioselective formal alkynylation, alkenylation, and homo-ketonylation using the concept of the conjugate addition of β-keto-heterocyclic sulfones **2** to cyclic α,β-unsaturated ketones **1**, catalyzed by the 9-*epi*-amino cinchona alkaloid salt **3**. We found that applying β-keto-sulfone **2** as a reaction partner leads to a privileged addition intermediate **4**,[10] which can be easily transformed into the corresponding *trans*-3-alkenyl cyclohexanols **5**, β-alkynylketones **6**, or the ketone products **7**, depending on the applied reaction conditions (Scheme 1).[11]



Scheme 1. Organocatalytic asymmetric alkynylation, alkenylation, and homo-ketonylation reactions of enones.

We began our investigations by examining the ability of the 9-amino-9-deoxyepiquinine TFA salt (**3**)[12] to promote the organocatalytic asymmetric conjugate addition of either β-keto-1-phenyl-1*H*-tetrazol-5-yl sulfone (**2a**) or β-keto-benzothiazol-2-yl sulfone (**2b**) to cyclohexenone (**1a**), and some representative results are presented in Table 1.

To our delight, by performing the reaction in toluene we were able to isolate the desired Michael adduct **4aa** in 80% yield and 91% *ee* (Table 1, entry 1). In attempts to improve the yield and enantioselectivity, we screened several solvents and different heterocyclic-substituted nucleophiles. Whereas

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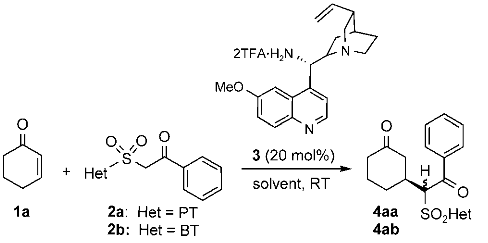
Table 1: Initial screening studies: Nucleophilic species and solvents.[a]



Entry	Het[b]	Solvent	*t* [h]	Product	Yield [%][d]	*ee* [%][e]
1	**2a**	toluene	24	**4aa**	80	91
2	**2a**	THF	48	**4aa**	67	94
3	**2a**	Et_2O	44	**4aa**	82	90
4	**2a**	dioxane	24	**4aa**	63	96
5	**2b**	dioxane	24	**4ab**	96	94
6[c]	**2b**	dioxane	24	*ent*-**4ab**	90	96

[a] Reactions conditions: **1** (0.4 mmol), **2** (0.2 mmol), and **3** (20 mol %). [b] PT = 1-phenyl-1*H*-tetrazol-5-yl; BT = benzothiazol-2-yl. [c] Quasi-enantiomer of **3** was used. [d] Yield of the isolated combined diastereomers. [e] Determined by chiral stationary phase HPLC analysis of the *trans*-3-alkenyl cyclohexanol **5ab**. THF = tetrahydrofuran.

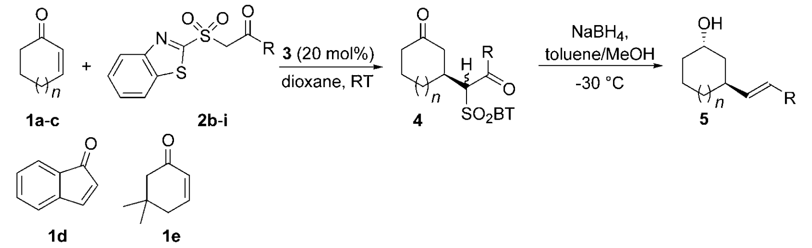
reactions carried out in THF or Et_2O were rather slow, we were pleased to find that reactions performed in dioxane proceeded with acceptable rates along with high enantioselectivities (Table 1, entries 2 and 3 versus 4). Next, the nucleophile **2** was modified to observe a possible effect on the yield and enantioselectivity. Using nucleophile **2b** led to the desired product in higher yield and maintained the excellent enantioselectivity, 96 % and 94 % *ee*, respectively (Table 1, entry 4 versus 5). As expected, the quasi-enantiomer of the catalyst furnished the desired product with virtually the same enantioselectivity and opposite configuration (Table 1, entry 6).

Having in hand a general and efficient protocol for the organocatalytic conjugate addition, we turned our attention to the scope and limitations of the envisaged transformations. The special value of the enantiomerically enriched compounds **5** obtained by the organocatalytic alkenylation protocol (Scheme 1, Method A) is partly because of their importance in the synthesis of numerous natural products which are of interest to the pharmaceutical industry.[13] In addition, the double-bond unit provides a convenient handle for several structural manipulations.[14] As shown in Table 2, when the reaction was performed with **1a**, a number of representative β-keto sulfones, **2b–i**, underwent conjugate addition with consistently high to excellent enantioselectivities, regardless of their steric or electronic nature (86–98 % *ee*). Both electron-withdrawing and electron-donating substituents, as well as *ortho*-, *meta*-, and *para*-substitution patterns were well tolerated, delivering the desired products with *E*/*Z* ratios in the range of 4:1 to 3:1 (Table 2, entries 1–5). The bulky β-keto-sulfone **2h**, derived from 2-naphthylketone, gave the *trans*-3-alkenyl cyclohexanol **5ah** in a slightly higher *E*/*Z* ratio (5:1) (Table 2, entry 6), whereupon the employment of the alkyl-substituted nucleophile **2i** resulted in a decrease of yield and enantioselectivity (Table 2, entry 7).

We next evaluated the effect of various enones in the asymmetric induction (Table 2, entry 8–11). It appears from these results that the enantioselectivity is very dependent on the ring size and substitution pattern of the ring. For **1b** and **1d**, the reaction proceeds well, however, the enantiomeric excess of the products were 60 % and 88 % *ee*, respectively. Furthermore a 1:1 and 4:1 mixture of *E*/*Z* isomers were obtained (Table 2, entry 8 and 10). Notably, increasing the ring size to a seven-membered ring led to an improvement in the enantioselectivity up to 98 % *ee* (Table 2, entry 9). We also investigated the alkenylation of **1e**, wherein the product was obtained in high enantiomeric excess (94 % *ee*) and a 4:1 *E*/*Z* ratio (Table 2, entry 11).

The absolute configuration of the stereogenic center formed in the Michael addition step was determined to be *S* by chemical comparison to the corresponding ketone of compound **5cb**.[5i] Additionally, in case of all employed six-membered cyclic enones the products **5** were obtained exclusively as the *anti*-configurated diastereoisomer, which

Table 2: Organocatalytic alkenylation of α,β-unsaturated ketones **1a-e** using β-keto-sulfones **2b-i**.[a]



Entry	Enone	Nu (R)	Product	Yield [%][b]	Product	Yield [%][b]	*E*/*Z*[c]	*ee* [%][d]
1	**1a** (*n* = 1)	**2c** (*o*-Me-C_6H_4)	**4ac**	98	**5ac**	64	4:1	98
2	**1a** (*n* = 1)	**2d** (*o*-BrC_6H_4)	**4ad**	90	**5ad**	59	4:1	96
3	**1a** (*n* = 1)	**2e** (*m*-ClC_6H_4)	**4ae**	92	**5ae**	67	3:1	94
4	**1a** (*n* = 1)	**2f** (*p*-MeC_6H_4)	**4af**	89	**5af**	57	3:1	93
5	**1a** (*n* = 1)	**2g** (*p*-FC_6H_4)	**4ag**	90	**5ag**	61	3:1	94
6	**1a** (*n* = 1)	**2h** (2-naphthyl)	**4ah**	91	**5ah**	62	5:1	96
7[f]	**1a** (*n* = 1)	**2i** [$(CH_2)_2Ph$]	**4ai**	90	**5ai**	48	4:1	86
8[g]	**1b** (*n* = 0)	**2b** (Ph)	**4bb**	96	**5bb**	56	1:1	60[e]
9[g,h]	**1c** (*n* = 2)	**2b** (Ph)	**4cb**	94	**5cb**	62	5:1	98[e]
10[h,i]	**1d**	**2b** (Ph)	**4db**	86	**5 db**	63	4:1	88[e]
11[h]	**1e**	**2b** (Ph)	**4eb**	93	**4eb**	68	4:1	94

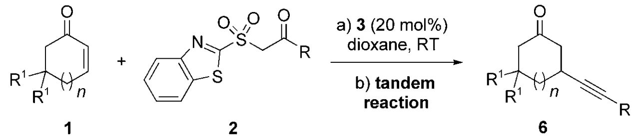
[a] Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), and **3** (20 mol %); then $NaBH_4$ (0.6 mmol) in a toluene/MeOH (4:1) solution. [b] Yield of isolated product. [c] Determined by ^1H NMR analysis of the crude reaction mixture of **5**. [d] Determined by chiral stationary phase HPLC analysis of **5**. [e] The *ee* values were determined by oxidation of the alcohol to the corresponding ketone derivatives. [f] $LiBH_4$ (0.4 mmol) in THF used for the reduction. [g] Observed *syn*/*anti* diastereomeric ratio was 1:1. [h] Reaction was performed at 45 °C. [i] Observed *syn*/*anti* diastereomeric ratio was 1:4.

was assigned by NOE analysis. Whereas the reduction of **4 db** still resulted in a 1:4 mixture of *syn*/*anti* isomer, the selectivity observed in cases of both **1b** and **1c** was 1:1.

Having been successful in our approach to the development of the tandem procedure, we decided to expand this organocatalytic diversity oriented synthesis to the asymmetric synthesis of β-alkynylated ketones **6** (Scheme 1, Method B). We judged this to be critical for our investigation, as the conjugate addition of alkynyl groups to cyclic α,β-unsaturated ketones has recently generated tremendous amount of interest, which originates from their synthetic utility.[15]

To our delight, under weak basic conditions the privileged intermediate **4** could be transformed into the corresponding chiral alkyne **6** and it was possible to develop a successful one-pot procedure for the enantioselective alkynylation of enones. A range of cyclic enones proceeded to react efficiently and cleanly with a wide variety of nucleophiles as presented in Table 3.

Table 3: Organocatalytic alkynylation of α,β-unsaturated ketones.[a]



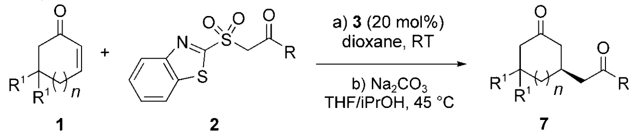
Entry	Enone	Nu (R)	Product	Yield [%][b]	*ee* [%][c]
1	**1a** ($n=1$, $R^1=H$)	**2b** (Ph)	**6ab**	58	95
2	**1a** ($n=1$, $R^1=H$)	**2c** (*o*-MeC$_6$H$_4$)	**6ac**	86	97
3	**1a** ($n=1$, $R^1=H$)	**2d** (*o*-BrC$_6$H$_4$)	**6ad**	59	97
4	**1a** ($n=1$, $R^1=H$)	**2g** (*p*-FC$_6$H$_4$)	**6ag**	46	95
5	**1a** ($n=1$, $R^1=H$)	**2h** (2-naphthyl)	**6ah**	57	96
6	**1b** ($n=0$, $R^1=H$)	**2b** (Ph)	**6bb**	40	55
7	**1c** ($n=2$, $R^1=H$)	**2b** (Ph)	**6cb**	51	99
8	**1e** ($n=1$, $R^1=Me$)	**2b** (Ph)	**6eb**	78	96

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), and **3** (20 mol%); then 2-ethyl-2-methyl-1,3-dioxolane (6.0 mmol), *p*TSA (0.06 mmol), toluene; sat. Na$_2$CO$_3$ solution, TBAI (0.24 mmol); 50% aq. TFA. [b] Yield of isolated product. [c] Determined by chiral stationary phase HPLC analysis.

As outlined in entries 1–5 of Table 3, both electron-rich and electron-poor aromatic nucleophiles **2** reacted successfully with cyclohexenone as the electrophile, providing the products **6** with excellent enantiomeric excesses and good yields. Interestingly, an electron-donating group attached at the *ortho* position was found to be beneficial to both the yield and selectivity (Table 3, entry 2, 86% yield and 97% *ee*). The efficiencies of the transformation vary significantly, probably as a result of the differing steric and electronic properties of the various intermediates. Thus, the alkynylation reaction **1e** gave a higher yield compared to the unsubstituted ketone derivative **1a** (Table 3, entry 8 versus entry 1). Furthermore, the transformation again proved to be dependent on the ring size of the enone used, as organocatalytic alkynylation of **1c** furnished the product in higher enantiomeric purity than that of **1b** (Table 3, entry 7 versus 6).

As a result of our success on the alkenyl- and alkynylation reactions with enones **1**, our attention was then directed toward the synthesis of chiral 1,5-dicarbonyl compounds **7** (Scheme 1, Method C)—the homo-ketone addition product which can be obtained by the same reaction concept. The reaction is an attractive alternative for the preparation of these synthetically useful compounds.[16] Consequently, considerable attention has been given to the development of a new and straightforward catalytic asymmetric method which can provide this useful synthon. We were pleased to find that the Michael adducts **4** can be easily converted into the corresponding enantioenriched 1,5-dicarbonyl compounds **7** by direct addition of solid Na$_2$CO$_3$ in a THF/*i*PrOH (1:1) solution. In an effort to realize our goal of generating synthetically useful products, a wide variety of nucleophiles and enones were examined and the results are given in Table 4.

Table 4: Organocatalytic synthesis of enantioenriched 1,5-dicarbonyl compounds.[a]



Entry	Enone	Nu (R)	Product	Yield [%][b]	*ee* [%][c]
1	**1a** ($n=1$, $R^1=H$)	**2b** (Ph)	**7ab**	61	94
2	**1a** ($n=1$, $R^1=H$)	**2c** (*o*-MeC$_6$H$_4$)	**7ac**	57[d]	98
3	**1a** ($n=1$, $R^1=H$)	**2d** (*o*-BrC$_6$H$_4$)	**7ad**	66	96
4	**1a** ($n=1$, $R^1=H$)	**2g** (*p*-FC$_6$H$_4$)	**7ag**	64	97
5	**1a** ($n=1$, $R^1=H$)	**2h** (2-naphthyl)	**7ah**	51	97
6	**1c** ($n=2$, $R^1=H$)	**2b** (Ph)	**7eb**	64	99
7	**1e** ($n=1$, $R^1=Me$)	**2b** (Ph)	**7cb**	76	94

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), and **3** (20 mol%); then Na$_2$CO$_3$ (0.6 mmol) in a 1:1 mixture of THF/*i*PrOH. [b] Yield of isolated product. [c] Determined by chiral stationary phase HPLC analysis. [d] 20% impurity of byproduct contained.

To our delight, different arylketo-sulfones **2** could be employed, generating the desired enantioenriched 1,5-dicarbonyl adducts **7** with moderate chemical efficiency and excellent enantioselectivity (up to 99% *ee*). The transformation proved again to be dependent on the steric and electronic requirements of either the nucleophilic or electrophilic species. Therefore, an improvement in the yield was observed when the employed ketone was bearing substituents (Table 4, entry 7 versus 1) or the nucleophile contained steric bulk, preferably in the *ortho* position (Table 4, entry 3 versus 1). Electron-withdrawing groups were shown to activate the substrate, furnishing **7ad** and **7ag** in good yields and in high enantiomeric excesses (Table 4, entries 3 and 4). This method was also applicable to enones having other ring sizes. For example, when **1c** was used the chiral 1,5-dicarbonyl compound was obtained in nearly enantiomerically pure form (Table 4, entry 6).

In conclusion, we have demonstrated that by application of an organocatalytic tandem strategy, a library of small important optically active organic molecules can rapidly and efficiently be achieved starting from a common set of starting materials. Importantly, the optical purities of the alkynyl-, alkenylation, and homo-ketone products were fully comparable and all were formed in high yields.

Experimental Section

Organocatalytic addition of β-keto heterocyclic sulfones to cyclic α,β-unsaturated ketones**:** A vial equipped with a magnetic stirring bar was charged with the nucleophile **2** (0.2 mmol, 1 equiv), the catalyst **3** (0.04 mmol, 0.2 equiv), and dioxane (2 mL). After addition of the ketone **1** (0.4 mmol, 2 equiv) the reaction mixture was stirred for 24 h. The volatiles were then removed under vacuum and the residue was purified by flash chromatography.

Alkenylation: A vial equipped with a magnetic stirring bar was charged with the addition product **4** (0.2 mmol, 1 equiv) and toluene (2 mL). After cooling the reaction mixture to −30 °C, NaBH$_4$ (0.6 mmol, 3 equiv) was added, and then MeOH was introduced (0.25 mL). The reaction temperature was maintained at this temperature and stirred for 3–12 h: The reaction mixture was then quenched by the addition of a sat. NH$_4$Cl solution, and then extracted with EtOAc. The collected organic solution was then dried over MgSO$_4$, concentrated in vacuum, and the resulting residue was purified by flash chromatography methods.

Alkynylation: A vial equipped with a magnetic stirring bar was charged with the addition product **4** (0.2 mmol, 1 equiv), 2-ethyl-2-methyl-1,3-dioxolane (6 mmol, 30 equiv), toluene (0.5 mL), and *p*-toluenesulfonic acid (0.06 mmol, 0.3 equiv). The reaction mixture was stirred for 12 h before it was washed sequentially with a sat. NaHCO$_3$ and sat. Na$_2$CO$_3$ solution. Without drying, the volatiles were removed under vacuum, the crude product was redissolved in toluene (2 mL), and then a sat. Na$_2$CO$_3$ solution (2 mL) and Bu$_4$NI (0.24 mmol, 1.2 equiv) were added. The reaction mixture was stirred at 45 °C for 48 h and then the phases were separated. The organic phase was washed with water, dried over MgSO$_4$, and evaporated. The obtained crude product mixture was filtered through a plug of silica gel before it was dissolved in toluene (2 mL). Then a 50 % aqueous solution of TFA (2 mL) was added to the reaction mixture. After stirring for 1 h, the reaction mixture was quenched by the addition of a sat. NaHCO$_3$ solution and then extracted with EtOAc. The collected organic solution was dried over MgSO$_4$, evaporated and the obtained alkynylated products **6** were pure as determined by NMR analysis.

1,5-Dicarbonyl compounds: A vial equipped with a magnetic stirring bar was charged with the addition product **4** (0.2 mmol, 1 equiv), THF (1 mL), *i*PrOH (1 mL), and Na$_2$CO$_3$ (0.6 mmol, 3 equiv). The reaction mixture was stirred at 45 °C for 96 h . The reaction mixture was then partitioned between EtOAc and water and the aqueous layer was additionally extracted with EtOAc. The collected organic solution was dried over MgSO$_4$, evaporated, and the resulting residue was purified by flash chromatography.

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[1] For recent reviews on organocatalysis, see: a) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. C. Vo, *Drug Discovery Today* **2007**, *12*, 8; b) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; c) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; d) *Chem. Rev.* **2007**, *107*(12), special issue on organocatalysis.

[2] a) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; b) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178.

[3] a) F. Lopez, A. J. Minnaard, B. L. Feringa, *Acc. Chem. Res.* **2007**, *40*, 179; b) C. A. Falciola, A. Alexakis, *Eur. J. Org. Chem.* **2008**, 3765; c) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796; d) T. Thaler, P. Knochel, *Angew. Chem.* **2009**, *121*, 655; *Angew. Chem. Int. Ed.* **2009**, *48*, 645.

[4] For selected examples using organocatalysis: a) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170; b) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204; c) A. Prieto, N. Halland, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 3897; d) C. Rabalakos, W. D. Wulff, *J. Am. Chem. Soc.* **2008**, *130*, 13524; e) J. Luo, L.-W. Xu, R. A. S. Hay, Y. Lu, *Org. Lett.* **2009**, *11*, 437; f) M. B. Cid, J. L-Cantarero, S. Duce, J. L. G. Ruano, *J. Org. Chem.* **2009**, *74*, 431; g) M. Bell, K. Frisch, K. A. Jørgensen, *J. Org. Chem.* **2006**, *71*, 5407; h) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331; i) B. Vakulya, S. Varga, T. Soós, *J. Org. Chem.* **2008**, *73*, 3475; j) Y.-Q. Yang, G. Zhao, *Chem. Eur. J.* **2008**, *14*, 10888; k) T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2008**, *120*, 8171; *Angew. Chem. Int. Ed.* **2008**, *47*, 8051; l) X. Han, J. Luo, C. Liu, Y. Lu, *Chem. Commun.* **2009**, 2044; m) H. li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906; n) J. Wang, H. Li, L. Zu, W. Jiang, H. Xie, W. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652; o) J. Pulkkinen, P. S. Aburel, N. Halland, K. A. Jørgensen, *Adv. Synth. Catal.* **2004**, *346*, 1077; p) G. K. S. Prakash, F. Wang, T. Steward, T. Mathew, G. A. Olah, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4090; q) C. Cassani, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem.* **2009**, *121*, 5804; *Angew. Chem. Int. Ed.* **2009**, *48*, 5694.

[5] For asymmetric sp^2-hybridized carbon nucleophile additions, see: a) T. L. May, M. K. Bown, A. H. Hoveyda, *Angew. Chem.* **2008**, *120*, 7468; *Angew. Chem. Int. Ed.* **2008**, *47*, 7358; b) M. A. Kacprzynski, T. L. May, S. A. Kazane, A. H. Hoveyda, *Angew. Chem.* **2007**, *119*, 4638; *Angew. Chem. Int. Ed.* **2007**, *46*, 4554; c) Y. Lee, K. Akiyama, S. G. Gillinghan, M. K. Brown, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 446; d) C. Hawner, K. Li, V. Cirriez, A. Alexakis, *Angew. Chem.* **2008**, *120*, 8334; *Angew. Chem. Int. Ed.* **2008**, *47*, 8211; e) J. J. Bürgi, R. Mariz, M. Gatti, E. Drinkel, X. Luan, S. Blumentritt, A. Linden, R. Dorta, *Angew. Chem.* **2009**, *121*, 2806; *Angew. Chem. Int. Ed.* **2009**, *48*, 2768; f) S. Oi, A. Taira, Y. Honma, Y. Inoue, *Org. Lett.* **2003**, *5*, 97; g) T. Hayashi, N. Tokunanga, K. Yoshida, J. W. Han, *J. Am. Chem. Soc.* **2002**, *124*, 12102; h) R. Shintani, Y. Ichikawa, T. Hayashi, J. Chen, Y. Nakao, T. Hiyama, *Org. Lett.* **2007**, *9*, 4643; i) Y. Otomaru, T. Hayashi, *Tetrahedron: Asymmetry* **2004**, *15*, 2647. For asymmetric sp-hybridized carbon nucleophile additions see: j) T. Nishimura, X.-X. Guo, N. Uchiyama, T. Katoh, T. Hayashi, *J. Am. Chem. Soc.* **2008**, *130*, 1576; k) T. Nishimura, T. Katoh, K. Takatsu, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 14158; l) Y.-S. Kwak, E. J. Corey, *Org. Lett.* **2004**, *6*, 3385; m) T. F. Knöpfel, P. Zarotti, T. Ichikawa, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 9682; n) T. Nishimura, S. Tokuji, T. Sawano, T. Hayashi, *Org. Lett.* **2009**, *11*, ASAP; o) R. B. C. Jagt, J. G. De Vries, B. L. Feringa, A. J. Minnaard, *Org. Lett.* **2005**, *7*, 2433; p) For an enantioselective conjugate addition of aryl alkynes to nitro olefins, see: M. Yamashita, K.-I. Yamada, K. Tomioka, *Org. Lett.* **2005**, *7*, 2369.

[6] a) T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.* **2007**, *129*, 4908; b) T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.* **2005**, *127*, 3244; c) T. Inokuma, K. Takasu, T. Sakaeda, Y. Takemoto, *Org. Lett.* **2009**, *11*, 2425.

[7] a) S. L. Schreiber, *Nature* **2009**, *457*, 153; b) R. A. Potyrailo, V. M. Mirshy, *Chem. Rev.* **2008**, *108*, 770; c) T. E. Nielsen, S. L. Schreiber, *Angew. Chem.* **2008**, *120*, 52; *Angew. Chem. Int. Ed.* **2008**, *47*, 48.

[8] K. S. Lam, M. Lebl, V. Krchnák, *Chem. Rev.* **1997**, *97*, 411.

[9] D. R. Spring, *Org. Biomol. Chem.* **2003**, *1*, 3867.

[10] M. Nielsen, C. B. Jacobsen, M. W. Paixão, N. Holub, K. A. Jørgensen, *J. Am. Chem. Soc.* **2009**, *131*, 10581.

[11] a) M. Julia, J. M. Paris, *Tetrahedron Lett.* **1973**, *14*, 4833; b) P. J. Kocienski, B. Lythgoe, S. Ruston, *J. Chem. Soc. Perkin Trans. 1* **1978**, 829; c) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Tetrahedron Lett.* **1991**, *32*, 1175; d) L. A. Warren, S. Smiles, *J. Chem. Soc.* **1930**, 1327. See also: e) A. El-Awa, M. N. Noshi, X. M. du Jourdin, P. L. Fuchs, *Chem. Rev.* **2009**, *109*, 2315; f) C. Nájera, M. Yus, *Tetrahedron* **1995**, *51*, 10659.

[12] For selected publications, see: a) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070; b) J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem.* **2008**, *120*, 7768; *Angew. Chem. Int. Ed.* **2008**, *47*, 7656; c) C. M. Reisinger, X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 8232; *Angew. Chem. Int. Ed.* **2008**, *47*, 8112; d) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Angew. Chem.* **2007**, *119*, 393; *Angew. Chem. Int. Ed.* **2007**, *46*, 389; e) X. Lu, Y. Liu, B. Sun, B. Cindric, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 8134; f) F. Pesciaioli, F. D. Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8831–8834; *Angew. Chem. Int. Ed.* **2008**, *47*, 8703–8706; g) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403; h) X. Lu, L. Deng, *Angew. Chem.* **2008**, *120*, 7824; *Angew. Chem. Int. Ed.* **2008**, *47*, 7710; i) B. Tan, X. Zhang, P. J. Chua, G. Zhong, *Chem. Commun.* **2009**, 779; j) B. Tan, P. J. Chua, X. Zeng, M. Lu, G. Zhong, *Org. Lett.* **2008**, *10*, 3489; k) B. Tan, Z. Shi, P. J. Chua, G. Zhong, *Org. Lett.* **2008**, *10*, 3425; l) B. Tan, P. J. Chua, Y. Li, G. Zhong, *Org. Lett.* **2008**, *10*, 2437; m) For a review see: G. Bartoli, P. Melchiorre, *Synlett* **2008**, 1759.

[13] J. K. F. Geirsson, L. Arnadottir, S. Jonsson, *Tetrahedron* **2004**, *60*, 9149.

[14] M. M. Hussain, P. J. Walsh, *Acc. Chem. Res.* **2008**, *41*, 883.

[15] a) S. Fujimori, T. F. Knöpfel, P. Zarotti, T. Ichikawa, D. Boyall, E. M. Carreira, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635; b) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963.

[16] a) S. P. Brown, N. C. Godwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192; b) A. Sartori, C. Curti, L. Battistini, P. Burreddu, G. Rassu, G. Pelosi, G. Casiraghi, F. Zanardi, *Tetrahedron* **2008**, *64*, 11697; c) W. Wang, H. Li, J. Wang, *Org. Lett.* **2005**, *7*, 1637.