Phase-Transfer Catalysis

DOI: 10.1002/ange.200906814

Reversal of Enantioselectivity by Tuning the Conformational Flexibility of Phase-Transfer Catalysts**

*Ming-Qing Hua, Han-Feng Cui, Lian Wang, Jing Nie, and Jun-An Ma**

Catalytic asymmetric synthesis provides one of the most powerful and economical approaches for the preparation of a variety of enantiomerically enriched compounds that are critical to developments in medicine, biology, and materials science.[1] In this scenario, the development of environmentally friendly, highly efficient, and selective chiral catalysts is important. Therefore, one crucial objective is the design and synthesis of new chiral catalysts, which enable challenging and/or previously unknown asymmetric transformations to occur in a highly efficient way. The requirement of maximum conformational rigidity is central to the design of a chiral catalyst. The rigid structure of the catalyst would enhance the enantiofacial differentiation by minimizing the possibilities of different conformers available to the coupling partners, and thus, deliver the maximum asymmetric induction from the chiral catalyst.[2] These semiempirical criteria have been applied to the creation of thousands of chiral catalysts in accord with the increasing need for enantiopure medicinal agents and the rapid advancement of the field of asymmetric synthesis.[3] Furthermore, most efficient catalysts with rigid structures, such as cinchona alkaloids, salen complexes, and binol (1,1′-bi-2-naphthol) derivatives, have demonstrated useful levels of enantioselectivity for a wide range of different asymmetric reactions.[4] On the other hand, the conformational flexibility is another fundamental characteristic of a chiral catalyst. Keeping the conformational flexibility at an optimal level is also essential to the catalyst reactivity and stereoselectivity. However, the effect of an appropriate balance between the conformational rigidity and flexibility in asymmetric catalysis has largely been ignored.[5] Herein we report the development of new chiral quaternary ammonium salts as phase-transfer catalysts (PTC) based on the concept of a linker-dictated structure that tunes rigidity and flexibility. This strategy led to the discovery of two catalysts that give access to both enantiomeric products of a catalyzed addition reaction from a common chirality source.

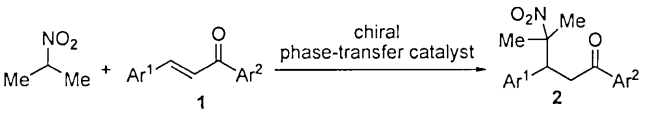
[*] M.-Q. Hua, H.-F. Cui, L. Wang, J. Nie, Prof. J.-A. Ma
Department of Chemistry, Tianjin University
Tianjin 300072 (China)
Fax: (+86) 22-2740-3475
E-mail: majun_an68@tju.edu.cn
Prof. J.-A. Ma
Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science
Shanghai 200032 (China)

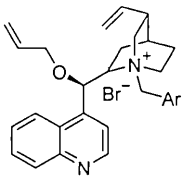
[**] This work was financially supported by the NSFC (no. 20772091 and 20972110). We thank Prof. Qingwei Yao, Northern Illinois University, for his helpful discussions and suggestions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200906814.

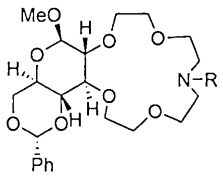
In recent years, chiral phase-transfer catalysis has emerged as an area of intense interest in asymmetric synthesis owing to its operational simplicity and mild reaction conditions.[6] Although impressive new advances have been made, there appears a growing number of challenging substrates and difficult transformations that cannot be promoted by existing phase-transfer catalysts. One such instance involves the conjugate addition of nitroalkanes to enones to give products that are useful and versatile precursors for a variety of structures such as aminocarbonyl compounds, aminoalkanes, and pyrrolidines.[7] Although the reactions can be successfully carried out with simple, unhindered linear nitroalkanes in high enantioselectivity,[8] utilization of sterically more demanding nitroalkanes for the reaction of bulky β-aryl-substituted enones such as the chalcones can be less rewarding.[9] Variable levels of asymmetric induction with unpredictable stereoselectivity were obtained when cinchona-alkaloid-derived quaternary ammonium salt **3**[9b] and the sugar-based azacrown ether **4**[9c,d] were used as chiral catalysts (Scheme 1). The structurally rigid and highly reactive chiral phase-transfer catalysts based on the binaphthyl scaffold, such as the *N*-spiroammonium salts **5** and **6**, which were recently developed by Maruoka et al.,[6e] and the analogous phosphonium salt **7**,[6s] gave poor performance for the addition of 2-nitropropane to chalcone. The reactions were plagued with extremely low yield and disappointing *ee* values ($<10\%$) as indicated by the results shown in Scheme 1.

We surmised that dual activation of both the nucleophile and the electrophile is necessary for this particularly challenging reaction. As depicted in Scheme 2, the modular dimeric structure **8** was anticipated to provide a potential entry into a chiral catalyst to fulfill such a goal. It is further expected that the key to creating a positive synergy between the two chiral fragments is the choice of a flexible linker. The linker we have chosen to explore can provide us with the following opportunities for the fine-tuning of the reactivity and stereoselectivity of the catalysts: 1) to regulate the distance between the quaternary ammonium centers by varying the chain length, so that the reactants can be synergistically stabilized and/or activated; 2) to maintain an optimal relative orientation of the two chiral binaphthyl moieties, by virtue of the flexibility of the -$(CH_2)_n$- chain through C–C bond rotation, to achieve a high level of enantioselectivity. The latter requires the nitronate nucleophile to be delivered to either the *Re* or the *Si* face of the enone. The use of the piperidine rings for the construction of the dimeric structure was based on the anticipation that the resulting *N*-spiroammonium centers, which bear the binaphthyl chiral elements, help preserve the rigidity of the

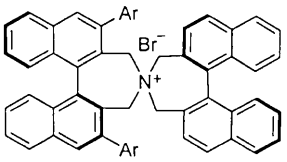




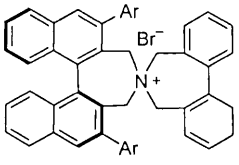
3a: Ar = 3,5-(*t*Bu)$_2$-4-MeOC$_6$H$_2$
61–94% yields, 31–71% *ee*
(Ar^1 = Ar^2 = Ph)
(7 mol%, room temperature)



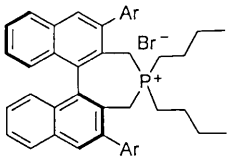
4: R = (CH$_2$)$_4$P(O)Ph$_2$
43% yield, 94% *ee* (Ar^1 = Ar^2 = Ph)
23–75% yields, 16–78% *ee*
(Ar^1 = Ar^2 = other aromatic groups)
(7 mol%, 22 °C)



5a: Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
5b: Ar = 3,4,5-F$_3$C$_6$H$_2$
<30% yield, <10% *ee*
(Ar^1 = Ar^2 = Ph)
(2 mol%, −20 °C, 60 h)



6a: Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
6b: Ar = 3,4,5-F$_3$C$_6$H$_2$
<30% yield, <10% *ee*
(Ar^1 = Ar^2 = Ph)
(2 mol%, −20 °C, 60 h)



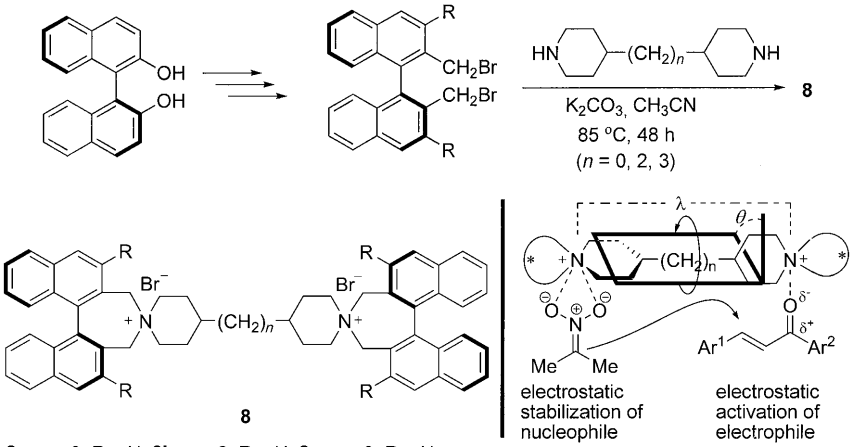
7a: Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
7b: Ar = 3,4,5-F$_3$C$_6$H$_2$
<5% yield (Ar^1 = Ar^2 = Ph)
(5 mol%, −20 °C, 60 h)

Scheme 1. Catalytic asymmetric conjugate addition of 2-nitropropane to chalcones **1** with the reported phase-transfer catalysts **3**–**7**.

chiral motifs. The dicationic nature of **8** could also be used to its advantage in catalyst recycling and reuse.

Starting from the commercially available (*S*)-binol, a series of (*S*)-3,3′-disubstituted 2,2′-bi(bromomethyl)-1,1′-binaphthyl derivatives were readily synthesized through an established protocol.[6j] The final quaternary ammonium bromides **8** were prepared by treatment with the corresponding appropriate bipiperidines in the presence of K_2CO_3 in CH_3CN and were purified by simple chromatography on silica gel or recrystallization, and gave the desired products (Scheme 2). Crystals suitable for X-ray crystallographic analysis were obtained for two of the bisquaternary ammonium salts, compounds **8j** and **8l** (see the Supporting Information).[10] As expected, the structural rigidity of the two chiral centers in both catalysts are well preserved and the two structures differ mainly in the size of the open cavity and the relative orientation of the chiral binaphthyl units, the latter could be a crucial element responsible for the sense of the stereoselectivity of each catalyst.

Preliminary screening on their reactivity as chiral phase-transfer catalysts was performed using the conjugate addition of 2-nitropropane with chalcone **1a** in the presence of K_2CO_3 in toluene (see the Supporting Information). Pleasingly, catalysts **8d**–**l** (Table 1, entries 4–17) with bulky substituents at the 3,3′-position of the binaphthyl scaffold significantly outperformed all of the monomeric catalysts listed in Scheme 1. Catalysts **8a**–**c**, which lack substituents at the 3,3′-position, were much less effective (Table 1, entries 1–3), thus clearly demonstrated the beneficial effect of the steric bulkiness at these positions as a necessary feature of the binaphthyl unit. Notably, a reversal of enantioselectivity that is directly related to the nature of the linker was achieved: the reaction gave adduct (*R*)-**2a** as the major enantiomer with catalysts **8a**, **8d**, **8g**, or **8j** ($n = 0$; Table 1, entries 1, 4, 7, and 10), whereas (*S*)-**2a** was the predominant enantiomer with catalysts **8h**, **8i**, **8k**, or **8l** ($n = 2$ or 3; Table 1, entries 8, 9, 11, and 12).[11] The linker-dependent enantioselectivity switching became most obvious with catalysts **8j** and **8l**, for which product **2a** was obtained in essentially quantitative yields and with completely reversed enantioselectivity (e.r. = 4:96 for **8j** and e.r. = 97:3 for **8l**). Therefore, catalysts **8j** and **8l**, which differ only in the length of the methylene chain of the linker, can be used as a surrogate of each other's enantiomer. This outcome represents a rare example of accessing both enantiomers of an asymmetric transformation by using catalysts possessing a common chiral element. Further improvement in the enantioselectivity was achieved using **8l** when the reaction was run at −20 °C (e.r. = 99.9:0.1; Table 1, entry 14). It was also found that the loading of **8l** could be as low as 0.25 mol% without sacrificing the enantioselectivity (Table 1, entries 15 and 16). Similarly, adduct (*R*)-**2a** was obtained in 98.5:1.5 e.r. using catalyst **8j** at −20 °C (Table 1, entry 17).

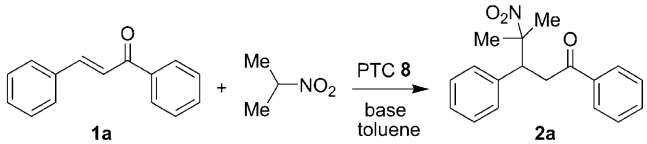


8a, *n* = 0, R = H; **8b**, *n* = 2, R = H; **8c**, *n* = 3, R = H;
8d, *n* = 0, R = C$_6$H$_5$; **8e**, *n* = 2, R = C$_6$H$_5$; **8f**, *n* = 3, R = C$_6$H$_5$;
8g, *n* = 0, R = 3,4,5-F$_3$C$_6$H$_2$; **8h**, *n* = 2, R = 3,4,5-F$_3$C$_6$H$_2$; **8i**, *n* = 3, R = 3,4,5-F$_3$C$_6$H$_2$;
8j, *n* = 0, R = 3,5-(CF$_3$)$_2$C$_6$H$_3$; **8k**, *n* = 2, R = 3,5-(CF$_3$)$_2$C$_6$H$_3$; **8l**, *n* = 3, R = 3,5-(CF$_3$)$_2$C$_6$H$_3$.

Scheme 2. Synthesis of a series of new phase-transfer catalysts **8**.

After **8l** and **8j** were identified as highly reactive and enantioselective catalysts for the conjugate addition of 2-nitropropane to **1a**, the scope of this reaction was further examined under the optimized conditions with a series of other chalcone derivatives or analogues as the electrophile (Table 2). The reaction proved to be exceptionally general and efficient. It tolerated the inclusion of a variety of sterically and electronically different substituent groups on both aryl rings (Table 2, entries 1–16). Catalysts **8l** and **8j** gave very comparable yields and e.r. while they delivered the product with a universal reversal of absolute configuration for all substrates tested. The scope of this reaction was not limited to chalcones, as substitution of the benzene rings with heterocycles, such as furan and thiophene, proved uneventful (Table 2, entries 17–22). When an enone derived from aliphatic ketone was employed, the reversal of enantioselectivity was also realized, albeit with modest yields and e.r. (Table 2, entries 23 and 24). To verify further the reversal of the enantioselectivity by using these catalysts, other nucleophilic donors with bulkier groups, such as nitrocyclopentane and nitrocyclohexane, which have rarely been used in conjugate addition owing to their intrinsic low reactivity, were also tested. Gratifyingly, successful reversal of the absolute configuration along with high e.r. was also observed (Table 2, entries 25–28).[12]

Table 1: Screening and optimization of new phase-transfer catalysts **8** for enantioselective conjugate addition of 2-nitropropane to chalcone **1a** to give **2a**.[a]



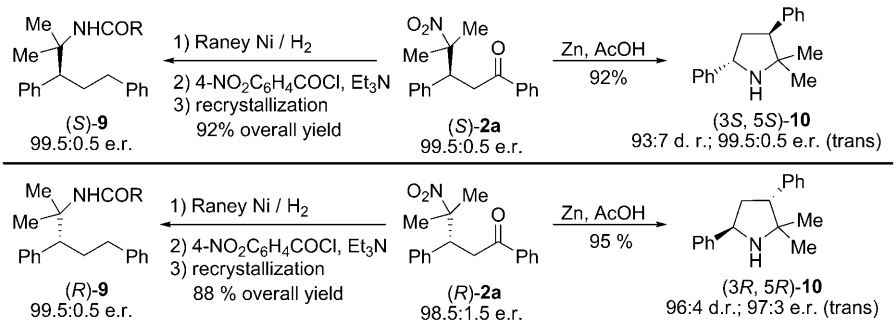
Entry	PTC (mol%)	T [°C]	t [h]	Yield [%][b]	e.r.[c]	Config.[d]
1	**8a** (2.5)	0	72	40	30:70	*R*
2	**8b** (2.5)	0	72	80	50:50	–
3	**8c** (2.5)	0	72	61	52.5:47.5	*S*
4	**8d** (2.5)	0	24	98	44.5:55.5	*R*
5	**8e** (2.5)	0	24	99	50:50	–
6	**8f** (2.5)	0	24	99	52.5:47.5	*S*
7	**8g** (2.5)	0	24	97	24.5:75.5	*R*
8	**8h** (2.5)	0	24	98	66.5:33.5	*S*
9	**8i** (2.5)	0	24	99	92.5:7.5	*S*
10	**8j** (2.5)	0	24	99	4:96	*R*
11	**8k** (2.5)	0	24	99	64:36	*S*
12	**8l** (2.5)	0	24	99	97:3	*S*
13	**8l** (2.5)	−20	48	99	99.5:0.5	*S*
14	**8l (1.0)**	**−20**	**60**	**99**	**99.9:0.1**	***S***
15	**8l** (0.5)	−20	72	85	99:1	*S*
16	**8l** (0.25)	−20	96	84	99:1	*S*
17	**8j (1.0)**	**−20**	**60**	**95**	**1.5:98.5**	***R***

[a] See the Supporting Information for details. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration was assigned according to references [9b–d].

These adducts **2** are versatile synthetic intermediates and can be readily transformed into functionalized amine derivatives that are otherwise difficult to access. For example, direct hydrogenation of both enantiomers of **2a** in the presence of Raney Ni provided (*S*)- and (*R*)-aminoalkanes **9** in high yields with excellent enantiomeric purities.[13] Reduction with Zn in AcOH delivered the highly functionalized substituted pyrrolidine **10** in both enantiomeric from (*S*)- and (*R*)-**2a** in a one-pot transformation with high diastereo- and enantioselectivity (Scheme 3).

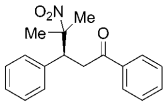
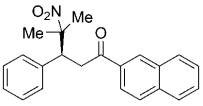
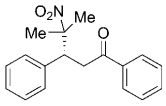
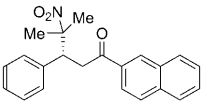
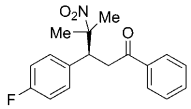
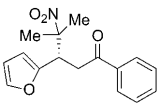
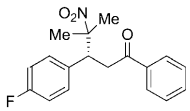
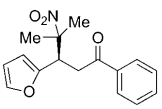
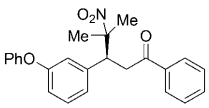
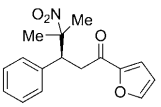
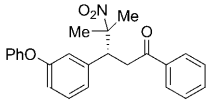
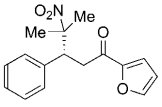
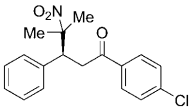
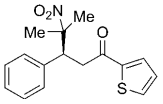
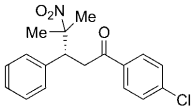
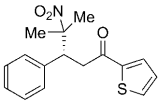
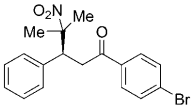
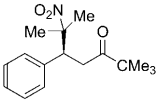
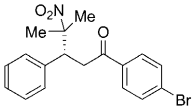
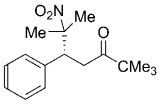
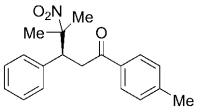
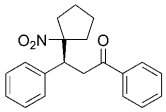
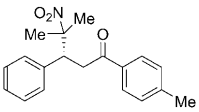
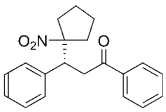
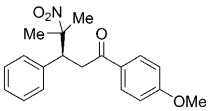
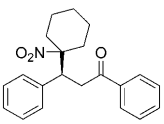
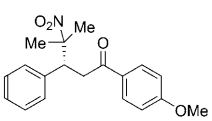
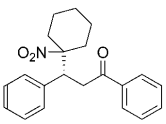
These results show that compounds **8j** and **8l** are very efficient phase-transfer catalysts for enantioselective synthesis. However, owing to the relatively high molecular weight of these quaternary ammonium salts, the mass of the catalyst—even at a loading of 0.25 mol%—is still high for their large-scale application. Fortunately, this drawback can be overlooked owing to the practical advantage that the chiral catalyst is easily recovered in excellent yield after one simple regenerating process. The recovered catalyst can be reused without any loss of reactivity and enantioselectivity.[14]

As a result of high activity and stereoselectivity, catalysts **8j** and **8l** and their variants represent a promising new generation of chiral phase-transfer catalysts for asymmetric synthesis. The conformational rigidity and flexibility are two indispensable features of a chiral catalyst. These studies indicate the broad potential for regulating the conformational rigidity and flexibility of chiral molecules in future catalyst design. Further investigation of the mechanism[15] and the application of these catalysts to other reactions are ongoing.



Scheme 3. Synthetic transformations of the chiral nitroketones **2a**.

Table 2: The scope of conjugate addition catalyzed with **8j** and **8l**.[a]

Entry		Product	PTC	Yield [%][b]	e.r.[c]	Entry	Product	PTC	Yield [%][b]	e.r.[c]
1	**2a**		**8l**	99	99.9:0.1	15[d]	**2h**		**8l**	90	98.9:1.1
2	**2a**		**8j**	95	1.5:98.5	16[d]	**2h**		**8j**	87	2.4:97.6
3	**2b**		**8l**	94	97.9:2.1	17[d]	**2i**		**8l**	98	96.3:3.7
4	**2b**		**8j**	92	2.9:97.1	18[d]	**2i**		**8j**	95	7.6:92.4
5	**2c**		**8l**	92	96.7:3.3	19	**2j**		**8l**	99	98.5:1.5
6	**2c**		**8j**	89	3.2:96.8	20	**2j**		**8j**	90	4.1:95.9
7	**2d**		**8l**	99	99.1:0.9	21[d]	**2k**		**8l**	97	96.7:3.3
8	**2d**		**8j**	92	2.3:97.7	22[d]	**2k**		**8j**	86	0.8:99.2
9	**2e**		**8l**	97	99.1:0.9	23	**2l**		**8l**	43	83.3:16.7
10	**2e**		**8j**	83	1.8:98.2	24	**2l**		**8j**	54	11.5:88.5
11	**2f**		**8l**	91	99.6:0.4	25[d]	**2m**		**8l**	98	98.3:1.7
12	**2f**		**8j**	88	1.9:98.1	26[d]	**2m**		**8j**	80	3.8:96.2
13[d]	**2g**		**8l**	99	99.1:0.9	27[d]	**2n**		**8l**	98	98.0:2.0
14[d]	**2g**		**8j**	84	6.6:93.4	28[d]	**2n**		**8j**	88	14.7:85.3

[a] Unless otherwise noted, all reactions were carried out with 1 mol% of catalyst **8l** or **8j** at −20°C for 48–96 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. The absolute configuration of adducts **2b**–**n** were assigned on the basis of analogy with studies of **2a**. [d] Reaction carried out at 0°C.

Received: December 3, 2009
Revised: February 9, 2010
Published online: March 12, 2010

Keywords: asymmetric synthesis · conformational flexibility · conjugate addition · enantioselectivity · phase-transfer catalysis

[1] a) R. Noyori, *Chem. Soc. Rev.* **1989**, *18*, 187; b) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; c) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**.

[2] T. P. Dang, H. B. Kagan, *J. Chem. Soc. Chem. Commun.* **1971**, 481.

[3] A. Thayer, *Chem. Eng. News* **2005**, *83*, 40.

[4] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691.

[5] S. J. Malcolmson, S. J. Meek, E. S. Sattely, R. R. Schrock, A. H. Hoveyda, *Nature* **2008**, *456*, 933.

[6] Selected reviews: a) E. V. Dehmlow, S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd ed., VCH, Weinheim, **1993**; b) A. Nelson, *Angew. Chem.* **1999**, *111*, 1685; *Angew. Chem. Int. Ed.* **1999**, *38*, 1583; c) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506; d) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518; e) T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300; *Angew. Chem. Int. Ed.* **2007**, *46*, 4222; f) S.-s. Jew, H.-g. Park, *Chem. Commun.* **2009**, 7090; selected examples: g) M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353; h) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595; i) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414; j) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519; k) S.-s. Jew, B.-S. Jeong, M.-S. Yoo, H. Huh, H.-g. Park, *Chem. Commun.* **2001**, 1244; l) H.-g. Park, B.-S. Jeong, M.-S. Yoo, J.-H. Lee, M.-k. Park, Y.-J. Lee, M.-J. Kim, S.-s. Jew, *Angew. Chem.* **2002**, *114*, 3162; *Angew. Chem. Int. Ed.* **2002**, *41*, 3036; m) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 5139; n) P. V. Ramachandran, S. Madhi, L. Bland-Berry, M. V. R. Reddy, M. J. O'Donnell, *J. Am. Chem. Soc.* **2005**, *127*, 13450; o) T. Ooi, K. Fukumoto, K. Maruoka, *Angew. Chem.* **2006**, *118*, 3923; *Angew. Chem. Int. Ed.* **2006**, *45*, 3839; p) L. Bernardi, J. López-Cantarero, B. Niess, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 5772; q) R. He, X. Wang, T. Hashimoto, K. Maruoka, *Angew. Chem.* **2008**, *120*, 9608; *Angew. Chem. Int. Ed.* **2008**, *47*, 9466; r) P. Elsner, L. Bernardi, G. D. Salla, J. Overgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2008**, *130*, 4897; s) R. He, X. Wang, T. Hashimoto, K. Maruoka, *Angew. Chem.* **2008**, *120*, 9608; *Angew. Chem. Int. Ed.* **2008**, *47*, 9466.

[7] a) R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, **1989**, p. 411; b) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**.

[8] Recent review: a) O. E. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1788; b) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933; c) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; catalysis by metal complexes: d) K. Funabashi, Y. Saida, M. Kanai, T. Arai, H. Sasai, M. Shibasaki, *Tetrahedron Lett.* **1998**, *39*, 7557; e) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313; organocatalysis: f) E. J. Corey, F.-Y. Zhang, *Org. Lett.* **2000**, *2*, 4257; g) T. Ooi, S. Fujioka, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 11790; h) B. Vakulya, S. Varga, A. Csampai, T. Soós, *Org. Lett.* **2005**, *7*, 1967; i) H. Gotoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2007**, *9*, 5307.

[9] a) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975; b) D. Y. Kim, S. C. Huh, *Tetrahedron* **2001**, *57*, 8933; c) T. Novák, J. Tatai, P. Bakó, M. Czugler, G. Keglevich, L. Töke, *Synlett* **2001**, 424; d) T. Bakó, P. Bakó, Á. Szöllõsy, M. Czugler, G. Keglevich, L. Töke, *Tetrahedron: Asymmetry* **2002**, *13*, 203; e) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331; f) S. B. Tsogoeva, S. Jagtap, *Synlett* **2004**, 2624; g) A. Prieto, N. Halland, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 3897; h) C. E. T. Mitchell, S. E. Brenner, S. V. Ley, *Chem. Commun.* **2005**, 5346; i) S. Hanessian, Z. Shao, J. S. Warrier, *Org. Lett.* **2006**, *8*, 4787; j) J. Wang, H. Li, L. Zuo, W. Wang, *Adv. Synth. Catal.* **2006**, *348*, 2047; k) B. Vakulya, S. Varga, T. Soós, *J. Org. Chem.* **2008**, *73*, 3475.

[10] CCDC 734390 (**8j**) and 734391 (**8l**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] Reviews: a) M. P. Sibi, M. Liu, *Curr. Org. Chem.* **2001**, *5*, 719; b) G. Zanoni, F. Castronovo, M. Franzini, G. Vidari, E. Giannini, *Chem. Soc. Rev.* **2003**, *32*, 115; c) T. Tanaka, M. Hayashi, *Synthesis* **2008**, 3361; d) M. Bartók, *Chem. Rev.* **2009**, DOI: 10.1021/cr9002352, and references therein; recent examples: e) D.-M. Du, S.-F. Lu, T. Fang, J. Xu, *J. Org. Chem.* **2005**, *70*, 3712; f) N. Kato, T. Mita, M. Kanai, B. Therrien, M. Kawano, K. Yamaguchi, H. Danjo, Y. Sei, A. Sato, S. Furusho, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6768; g) W. Zeng, G. Y. Chen, Y. G. Zhou, Y. X. Li, *J. Am. Chem. Soc.* **2007**, *129*, 750; h) W. Q. Wu, Q. Peng, D. X. Dong, X. L. Hou, Y. D. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 9717; i) M. I. Burguete, M. Collado, J. Escorihuela, S. V. Luis, *Angew. Chem.* **2007**, *119*, 9160; *Angew. Chem. Int. Ed.* **2007**, *46*, 9002; j) X.-X. Yan, Q. Peng, Q. Li, K. Zhang, J. Yao, X.-L. Hou, Y.-D. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 14362; k) K. Nakayama, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 17666.

[12] For the addition of nitroethane to chalcone: adduct isolated in 94% yield, d.r. = 33:67 (*syn*/*anti*), e.r. = 93:7 (*syn*), e.r. = 95.5:4.5 (*anti*) (by using catalyst **8l**).

[13] Interestingly, under these conditions the aryl ketone functionality underwent a complete deoxygenative reduction to form a methylene group.

[14] For example, catalyst **8l** (1 mol%) was used in the reaction of 2-nitropropane with **1a** on a 30 mmol scale, and delivered adduct (*S*)-**2a** in 99% yield with e.r. = 99.0:1.0; it was recovered in pure form in 97% yield. See the Supporting Information for experimental details for the recycling and reuse of the catalyst.

[15] Two monocationic analogues derived from piperidine and 4-methylpiperidine were prepared and used for the addition of 2-nitropropane to chalcone: yield < 40%, e.r. = < 52.5:47.5 (see the Supporting Information). These preliminary results suggest that both ammonium centers in **8j** and **8l** could be involved in the dual activation process of the reactants. In addition, the preparation of the corresponding chiral ammonium salts of carbanions (nitronate and/or malonate) is ongoing, and more data are being accumulated. For achiral ammonium salts of carbanions, see: a) M. T. Reetz, S. Hütte, R. Goddard, *J. Am. Chem. Soc.* **1993**, *115*, 9339; b) M. T. Reetz, S. Hütte, R. Goddard, *Z. Naturforsch. B* **1995**, *50*, 415; c) M. T. Reetz, H. M. Herzog, R. Goddard, *Eur. J. Org. Chem.* **2009**, 1687.

