Organocatalytic regioselective Michael additions of cyclic enones *via* asymmetric phase transfer catalysis†

Roberto Ceccarelli, Susanna Insogna and Marco Bella*

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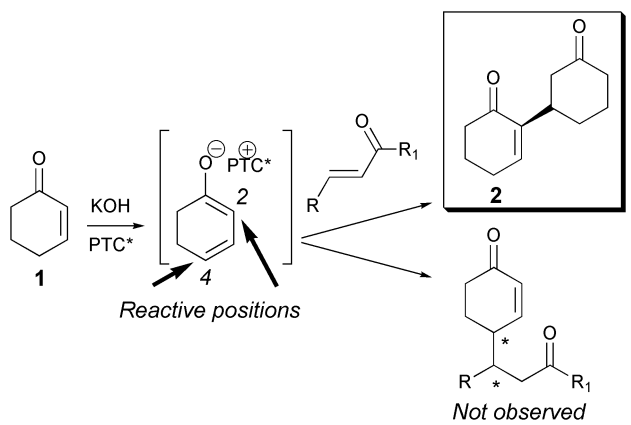
Cyclohexanone and cycloheptanone can be enantioselectively functionalized in the 3-position with up to 92% ee and 87% ee, respectively, by the base-promoted dimerization of the corresponding enones using 3,4,5-tribenzyloxybenzyl cinchoninium bromide, as a new effective catalyst.

The formation of ketone enolates, one of the most fundamental and thoroughly studied reactions in organic chemistry,[1] proceeds under PTC (phase transfer catalysis) conditions on activated compounds such as the systems related to 2-aryl-indanone,[2] β-ketoesters[3] and benzophenone imines of glycine.[4] Recent advances in the field of asymmetric PTC render this strategy very attractive.[5]

Here we show that 2-cyclohexenone **1**, which is activated towards deprotonation by a conjugate double bond, undergoes a regioselective Michael addition to itself as well as to other enones[6] under the PTC-conditions. If no other Michael acceptors were present, treatment of **1** under PTC conditions (KOH_{aq} 50%, toluene, 12.5% of catalysts **3a–q**, rt) afforded the dimerization product **2**, as a result of vinylogous enolate formation and electrophilic attack on the 2-position of a second molecule of 2-cyclohexenone **1** (Scheme 1)[7] and the reaction is greatly accelerated by the addition of a PTC.



Scheme 1 Vinylogous deprotonation–addition of 2-cyclohexenone.

Surprisingly, treatment of **1** with LDA (LDA, THF, −78 °C to rt) does not give an appreciable amount of dimerization product **2**.[8]

A simple filtration of the toluene phase of the reaction mixture through a plug of silica gel and evaporation of the solvent afforded nearly pure dimerization product. No byproducts or regioisomers were observed.

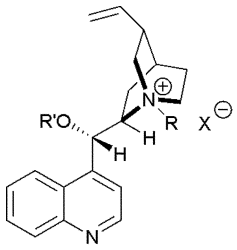
We focus our efforts initially on controlling the stereochemistry of the dimer **2**. The enantiomers of **2** readily separated on a GC-FID equipped with a chiral stationary phase column; we screened most of the known *Cinchona*-derived PTC catalysts, and results are summarized in Table 1. The asymmetric PTC dimerization of linear phenyl activated enones has been recently described by Corey and Zhang who employed the now commercially available catalyst **3d** developed in the Corey group.[9]

Simple *N*-benzyl cinchoninium chloride gave the dimerization product in 47% (entry 1, Table 1). The benzyl substituent on the nitrogen was necessary, methyl cinchoninium iodide **3b** gave nearly racemic products (entry 2) and any protection of the 9-OH of the *Cinchona* alkaloids led to a drop in asymmetric induction (entry 3). Employing Corey's catalyst **3d** (entry 4) we obtained a moderate 75% ee (er = 7 : 1), confirming the benefit of the bulky 9-methylanthracenyl substituent on the nitrogen with respect to the simple benzyl group of catalyst **3a**. The dimerization reaction of 2-cyclohexenone **1** is quite slow already at 0 °C therefore it was not possible to achieve synthetically useful levels of conversion if the transformation was run at lower temperatures. It is well known that the asymmetric induction increases in most cases with an electron-withdrawing group, such as fluorine, placed on the aryl moiety of benzyl cinchoninium salts, and we actually observed an increase in the ee, (entries 5 and 6) but more fluorine groups did not have the beneficial synergic effect as reported by Jew *et al.* in the alkylation of the benzophenone imine of glycine (entry 7).[10] Introduction of the bulky *t*-butyl group in the 4-position led to a modest decrease in the asymmetric induction (entry 8). A methoxy-group in the 3-positon of the aryl moiety slightly increased the ee (entry 9). The increase of the ee with the methoxy substituent on the aromatic ring is quite uncommon in *Cinchona* alkaloid PTC, and this prompted us to prepare a series of new catalysts based on this motif.[11] The effect of the alkoxy substituents is cooperative, and it seems to be due to both ion-pair stabilizing[12] electronic and steric effects. More sterically hindered 3,4-dibenzyloxybenzyl cinchoninium bromide **3l** turned out to be a better catalyst of 3,5-dimethoxybenzyl cinchonidinium bromide **3k** while less bulky 3,4-methylenedioxybenzyl cinchoninium bromide **3i** gave lower ee (entries 10, 11 and 12). The placement of a third methoxy group on the catalyst as in **3m** resulted in even higher ee (entry 13). Preparation of the 3,4,5-tribenzyloxybenzyl cinchoninium bromide **3n**, rewarded us with 88% ee (er = 15.5 : 1) at rt and 92% (er = 24 : 1) ee at 0 °C (entries 14,15). However, lower temperatures

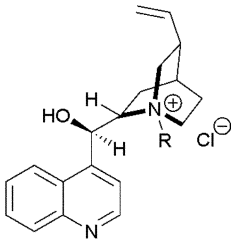
Dipartimento di Chimica and Istituto di Chimica Biomolecolare del CNR-Sezione di Roma, Università "La Sapienza", P.le Aldo Moro 5, 00185-Roma, Italy. E-mail: Marco.Bella@uniroma1.it

† Electronic supplementary information (ESI) available: Physical data, including copies of ^{1}H and ^{13}C NMR spectra, are given for new compounds. See DOI: 10.1039/b612606e

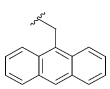
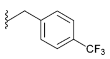
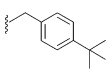
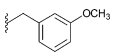
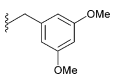
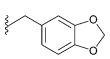
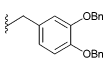
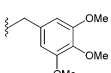
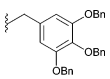
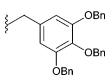
Table 1 Screening of the different catalysts for the dimerization reaction of 2-cyclohexenenone **2**[a]



3a-c, 3e-n

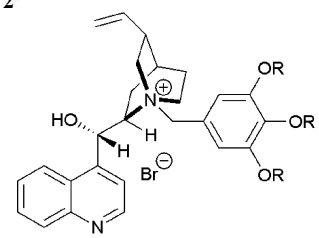


3d

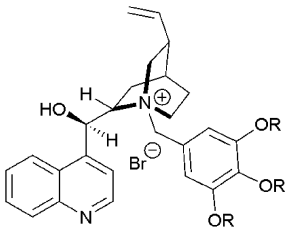
Entry	R	R′	X		Ee[b](%)	*Y* (%)
1		H	Cl	**3a**	47	96
2		H	I	**3b**	rac.	85
3		Allyl	Cl	**3c**	35	96
4		H	Cl	**3d**	−75[c,d]	95
5		H	Br	**3e**	59	82
6		H	Br	**3f**	71	95
7		H	Br	**3g**	65	95
8		H	Br	**3h**	42	92
9		H	Br	**3j**	58	80
10		H	Br	**3k**	64	82
11		H	Br	**3i**	38	86
12		H	Br	**3l**	70	80
13		H	Br	**3m**	70	70
14		H	Br	**3n**	88	90
15		H	Br	**3n**	92[e]	72

[a] Reactions were performed with 0.52 mmol of **1**, 4 mL of toluene, 0.4 mL of 50% KOH_{aq}, and 0.065 mmol of catalyst **3**. [b] Ees determined by CSP-GC. [c] *N*-Methylanthracenyl cinchonidinium bromide was used. [d] Negative ee refers to the formation of the opposite enantiomer. [e] Reaction performed at 0 °C. The absolute configuration was determined by comparison of optical rotation with a known compound, see ESI.†

Table 2 Effect of temperature, dilution, and alkaloid moiety on the ee of **2**[a]



3m, R=Me
3n, R=Bn



3o, R=Me
3p, R=Bn

Entry	Alkaloid	T/°C	Cat.	Ee[b] (%)	*Y* (%)
1	Cinchonine	rt	**3m**	80	91
2	Cinchonine	0	**3m**	87	70
3	Cinchonine	−20	**3m**	75	25
4	Cinchonidine	rt	**3o**	−78[c]	90
5	Cinchonidine	0	**3o**	−81[c]	61
6	Cinchonidine	−20	**3o**	−85[c]	24
7	Cinchonine	0	**3n**	92	26
8	Cinchonine	−20	**3n**	87	26
9	Cinchonidine	0	**3p**	−81[c]	23
10	Cinchonidine	−20	**3p**	−88[c]	23

[a] Reactions were performed with 0.52 mmol of **1**, 4 mL of toluene, 0.4 mL of 50% KOH_{aq}, and 0.065 mmol of catalyst **3**; reaction time 24 h or 4 d in entries 3 and 6–10. [b] Ees determined by CSP-GC. [c] Negative ee refers to the formation of the opposite enantiomer.

afford the reaction product in much longer reaction time and in low conversion.[13] Giving the numerous known applications of asymmetric phase transfer catalysis we hope that these new alkoxy-substituted catalysts **3a–n** can also be successfully employed in other new or known reactions. Next, we tested the effect of concentration and temperature on the level of asymmetric induction. As expected, the ee increased from 70% (er = 5.5 : 1) to 80% (er = 9 : 1) when performing the reaction at higher dilution (Table 2, entry 1). *Cinchona* alkaloid enantiomers are not commercially available, but it has been constantly observed that the "quasienantiomers" cinchonidine and cinchonine induce comparable levels of ee. Products of opposite absolute stereochemistry are formed in most reactions.[14] We expected the asymmetric induction to increase on decreasing the temperature, since a "tighter" ion pair is formed. However, the two "quasienantiomers" of the two *N*-3,4,5-trimethoxybenzyl catalysts **3m,3o** tested showed a singular behavior: the diastereoisomers derived from the *cinchonine* series *lowered* the level of asymmetric induction with the temperature (entries 2 and 3); the highest ee is observed at 0 °C (87%) and it drops to 75% at −20 °C. Further lowering of the temperature was not tested because at −20 °C conversion after 4 days was low. In contrast, the diastereoisomers derived from *cinchonidine* always *increased* the level of enantioselection on decreasing the temperature;[15] similar behaviour was observed using the *N*-3,4,5-tribenzyloxybenzyl pseudoenatiomeric catalysts **3n,3p** at −20 °C and 0 °C (entry 7–10).[16]

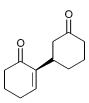
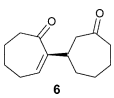
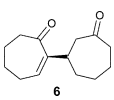
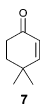
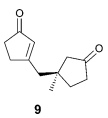
The reaction was tested on different cyclic enones and results are summarized in Table 3. 2-Cyclopentenone **4**, (entry 1, Table 3) does not give any product, because the double bond in the anion can isomerize easily; the anion is more stabilized with respect to the anion derived from 2-cyclohexenone **1** and consequently its reactivity is reduced.[17]

2-Cycloheptenone **5** (entry 3) instead affords the dimerization product showing a similar level of asymmetric induction as cyclohexenone **1**. If there are no α-hydrogens with respect to the double bond, no product is observed (entry 5). Dimerization of **8** does occur in comparable ees but the reaction is much slower, since a crowded quaternary stereocenter is formed (entry 6).

We were able also to isolate in nearly quantitative yields (94–95%) the adducts of 2-cyclohexenone **1** to conjugate ketone **10** that cannot dimerize (Scheme 2); while with the aryl trimethoxy catalyst **3m** the level of asymmetric induction was comparable to the cyclic enones (65% *vs.* 70% of the cyclic enones); our best performing catalyst **3n** gave only 47% ee.

We also tested esters as Michael acceptors, *e.g.* di-*t*-butyl fumarate, but in this case yields and ees were poor (catalyst **3m**: $Y = 20\%$, ee = 40%; catalyst **3n**: $Y = 32\%$, ee = 0%) but also here the best catalysts were the *N*-3,4,5-trimethoxybenzyl substituted ones, in contrast with what has been observed for the cyclic enones.

Table 3 Reaction of different enones catalyzed by **3n**[a]

Entry	Reactant	Product	Ee[b] (%)	*Y* (%)
1	 **4**	None	—	N. R.
2	 **1**	 **2**	88	90
3	 **5**	 **6**	−73	75[c,d]
4	 **5**	 **6**	87	80[d]
5	 **7**	None	—	N. R.
6	 **8**	 **9**	85	15[e]

[a] Reactions were performed with 0.52 mmol of reactant, 4 mL of toluene, 0.4 mL of 50% KOH_{aq}, and 0.065 mmol of catalyst **3n**, reaction time: 24 h. [b] Ees determined by CSP-GC. [c] Catalyst **3o** is used. [d] Reaction time: 2 d. [e] Reaction time: 4 d.

In summary, herein we present the development of a new class of *Cinchona* alkaloid-based catalysts used in the asymmetric Michael addition. Dimerization of 2-cyclohexenone **1** proceeds with up to 92% ee. Further work to define the scope of this reaction and to extend it to other electrophiles, is underway in our group.

Acknowledgements

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Notes and references

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2 U.-H. Dolling, P. Davis and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1984, **106**, 446.
3 (*a*) E. J. Park, M. H. Kim and D. Y. Kim, *J. Org. Chem.*, 2004, **69**, 6897; (*b*) T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2003, **42**, 3796.
4 Leading references: (*a*) M. J. O'Donnell, *Acc. Chem. Res.*, 2004, **37**, 506; (*b*) B. Lygo and B. I. Andrews, *Acc. Chem. Res.*, 2004, **37**, 518.
5 See also: (*a*) M. E. Halpern, *Phase-Transfer Catalysis. Mechanism and Synthesis*, American Chemical Society, Washington, DC, 1997; (*b*) Y. Sasson and R. Neumann, *Handbook of Phase-Transfer Catalysis*, Blackie A & M, London, 1997. Reviews: (*c*) K. Kacprzak and J. Gawronski, *Synthesis*, 2001, 961; (*d*) T. Ooi and K. Maruoka, *Chem. Rev.*, 2003, **103**, 3013; (*e*) A. Berkessel and H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, Germany, 2005, ch. 3 and 4.
6 Differently from **1**, chiral non-racemic 2-phenyl cyclohexananones, under solvent free liquid PTC conditions, are diastereoselectively deprotonated on the unexpected 6-position: E. Diez-Barra, A. de la Hoz, S. Merino and P. Sanchez-Verdu, *Tetrahedron Lett.*, 1997, **38**, 2359.
7 Product **2** has been previously isolated in low yield from the treatment of **1** with inorganic bases: see *e.g.* (*a*) N. J. Leonard and W. J. Musliner, *J. Org. Chem.*, 1966, **31**, 639 and ref. 16. Electrochemical synthesis: (*b*) M. Mubarak, M. Pagel, L. M. Marcus and D. G. Peters, *J. Org. Chem.*, 1998, **63**, 1319. Using Morita–Baylis–Hilman reaction: (*c*) G. Jenner, *Tetrahedron Lett.*, 2000, **41**, 3091, and; (*d*) J. R. Hwu, G. H. Hakimelani and C.-T. Chou, *Tetrahedron Lett.*, 1992, **33**, 6469. See also (formation of **2** mediated by *t*-buthoxide): (*e*) I. D. Reingold, A. M. Butterfield, B. C. Daglen, R. S. Walters, Jr., K. Allen, S. Scheuring, K. Kratz, M. Gembický and P. Baran, *Tetrahedron Lett.*, 2005, **46**, 3835.
8 For deprotonation in the 4-position of 3-alkoxy-2-cyclohexeneonones see *e.g.*: (*a*) E. R. Koft and A. B. Smith, *J. Am. Chem. Soc.*, 1982, **104**, 5568; (*b*) K. C. Nicolaou, T. Montagnon and G. Vassilikogiannakis, *Chem. Commun.*, 2002, 2478.
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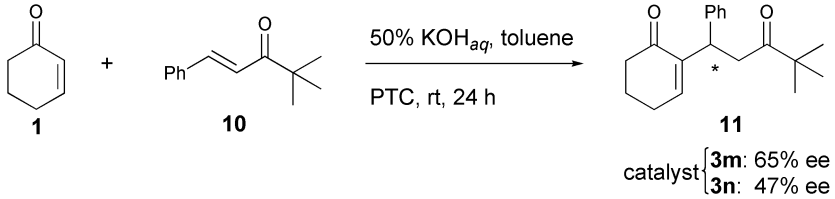
11 Recently, Malkov and Kočovský reported the benificial effect of a trimethoxy aryl moiety in the organocatalytic allylation of aldehydes; see: A. V. Malkov, M. Bell, F. Castelluzzo and P. Kočovský, *Org. Lett.*, 2005, **7**, 3219.



Scheme 2 Cross vinylogous deprotonation–addition of 2-cyclohexenone.

12 Asymmetric induction in *Cinchona* alkaloid-mediated PTC stems from weak interactions arising in a thight ion pair; for a useful discussion on the role of the 9-OH see ref. 5*c* and references cited therein.
13 Dendritic *Cinchona* alkaloids-derived PTC, in which benzyloxy groups substituted on the aromatic moiety in several patterns, have been prepared and employed in the alkylation of benzophenone imine glycine esters: G. Gulliena, R. Kreiter, R. van de Coervering, R. J. M. Klein Gebbink, G. van Koten, R. Chinchilla and C. Najera, *Tetrahedron: Asymmetry*, 2003, **14**, 3705; however the level of asymmetric induction achieved is moderate, 50% ee, if compared with Corey's catalyst, well above 90% ee.
14 For the use of the term quasienantiomers see: Q. Zhang and D. P. Curran, *Chem.–Eur. J.*, 2005, **11**, 4866.
15 A similar finding was observed by Jørgensen and co-workers: S. Brandes, M. Bella and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1147. Only relatively few papers dealing with *Cinchona* alkaloids mediated asymmetric PTC report high enantioselectivities with *both* quasienantiomeric catalysts.
16 Racemic **2** has a synergic herbicidal effect if used with atrazine: H. A. Kaufman and R. P. Napier, *German Patent*, DE 2016666, 1970, 1105.
17 (*a*) The charge delocalization of the 2-cyclopentenone anion can account for the facile isomerization in basic conditions of prostaglandin related systems: see *e.g.*: B. Y. Lee, J. W. Han, Y. K. Chung and S. W. Lee, *J. Organomet. Chem.*, 1999, **587**, 181; (*b*) Y. Fujita and T. Nakai, *Synthesis*, 1983, **12**, 997; no analogous isomerization is reported for 6-membered rings or larger cyclic enones.

