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SHORT COMMUNICATION

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Asymmetric Organocatalytic Protonation of Silyl Enolates Catalyzed by Simple and Original Betaines Derived from *Cinchona* Alkaloids

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The asymmetric protonation of silyl enolates derived from tetralone, benzosuberone, and cyclohexanone has been successfully achieved by using simple and original betaine catalysts derived from *Cinchona* alkaloids (quinine and quinidine series) to afford the desired α-substituted ketones in high yields and moderate enantioselectivities. The ease of implementation of this approach along with the easy accessibility of the betaine catalyst (four steps from cheap and commercially available quinine or quinidine) make this approach very appealing for the preparation of enantioenriched α-monosubstituted carbonyl compounds.

Introduction

The control of a tertiary stereogenic center at the α position with respect to a carbonyl moiety remains a challenging task despite the significant synthetic efforts already deployed. Of all the strategies reported to date for accessing α-monosubstituted carbonyl compounds, the catalytic enantioselective protonation of their corresponding lithium enolates or latent sources of enolates (silyl enolates or enol acetates) has proven to be very efficient leading to high enantioselectivities.[1] Silyl (or disilyl) enolates, due to their benign environmental impact with respect to metal enolates, have recently been investigated as the substrates of choice for the development of efficient organocatalytic approaches.[2] Thus, since the pioneering contribution by our group in 2007,[3] several research groups have reported efficient organocatalytic methodologies mainly based on the use of chiral Brønsted acid catalysts [i.e., *N*-triflylthiophosphoramides derived from BINOL,[4] *P*-spiro-diaminodioxaphosphonium barfates,[5] and chiral sulfinamide/achiral sulfonic acid combinations[6]]. Nevertheless, despite the high levels of enantioselectivity reached, these approaches remain limited to tetralone or cycloalkanone series. The recent report by Toste and co-workers based on a LBA (Lewis acid assisted Brønsted acid) approach involving a cationic gold(I) complex as catalyst, which proved to be very efficient for a wide range of substrates (i.e., tetralone, cycloalkanones, and aliphatic linear ketones) constitutes an important breakthrough in this field of research.[7] However, organocatalytic approaches still suffer from a lack of generality in terms of substrate scope and therefore there is still a need for the design of efficient and general methods for the organocatalytic enantioselective protonation of silyl enolates.

We have previously reported that tertiary ammonium aryloxides resulting from the reaction of a chiral tertiary amine and a phenol derivative could affect the asymmetric protonation of silyl enol ethers derived from 2-Me-tetralone in a modest 67% *ee*,[8] however, despite their greater stability with respect to the corresponding fluorides or hydrogenofluorides, quaternary ammonium aryloxides have been less studied. The main contributions have mainly emanated from the groups of Mukaiyama[9] and Ooi[10] and involved chiral quaternary ammonium phenoxides derived from *Cinchona* alkaloids and chiral ammonium betaines derived from BINOL, respectively. We recently reported on the use of chiral quaternary ammonium aryloxides as efficient catalysts for the organocatalytic direct vinylogous aldol reactions of (5*H*)-furanone derivatives with aldehydes with high enantioselectivities of up to 95%.[11] To further study the catalytic potential of quaternary ammonium aryloxides, we report herein an enantioselective protonation of silyl enolates catalyzed by simple and readily accessible quaternary ammonium aryloxides derived from *Cinchona* alkaloids including original betaine catalysts acting as cooperative ion pairs.[12]

Results and Discussion

Our basic idea was to protonate an intermediate chiral ammonium enolate ion pair[13] generated by the activation of silyl enolate **1** through the Lewis base properties of the aryloxide ion. The use of phenol derivatives as achiral stoichiometric proton sources would allow catalyst regenera-

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tion upon transfer of the proton to the chiral enolate to form the desired enantioenriched α-substituted carbonyl compound **2** (Figure 1).

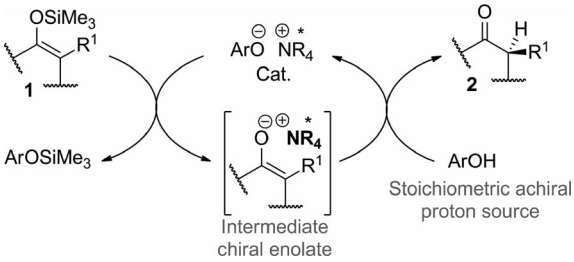


Figure 1. Working hypothesis.

For this purpose we undertook the synthesis of various quaternary ammonium aryloxides derived from the parent *Cinchona* alkaloids [i.e., quininium (QN^+), quinidinium (QD^+), cinchoninium (CN^+), and cinchonidinium (CD^+)] following known procedures (Figure 2).[9e,11]

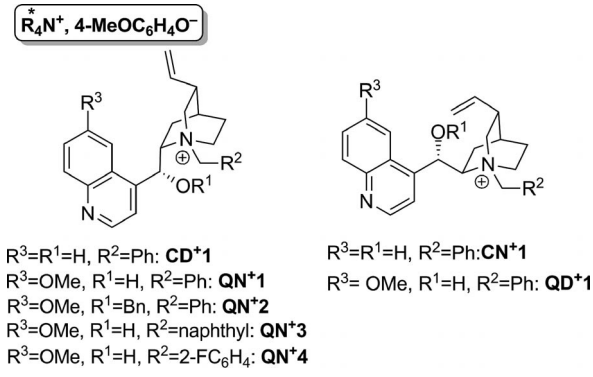
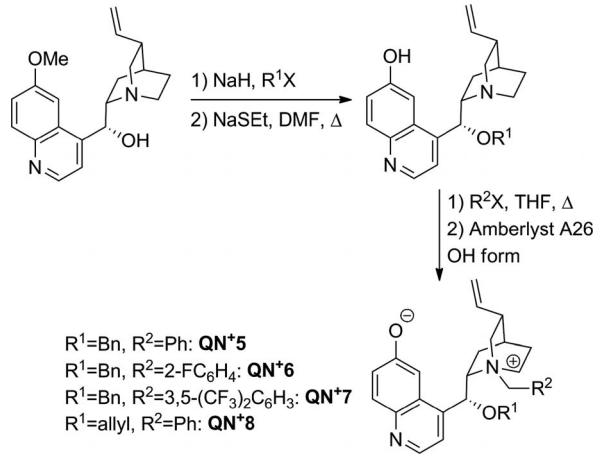


Figure 2. Structures of chiral ammonium aryloxides $R_4{*}N^+$, 4-$MeOC_6H_4O^-$.

We also turned our attention to the synthesis of betaine-type ammonium aryloxide catalysts derived from *Cinchona* alkaloids. Such catalysts are still very rare in the literature and, to the best of our knowledge, only one group has reported the synthesis of such catalysts in which the aryloxide moiety is located on the nitrogen of the quinuclidine part of *Cinchona* alkaloids.[14] We chose to take advantage of the methoxy group on the quinoline moiety of the quinine and quinidine to generate in a straightforward manner the oxoanion. Indeed, starting from commercial quinine or quinidine derivatives, the corresponding *O*-substituted cupreine was obtained by an *O*-alkylation/demethylation sequence.[15] After quaternization of the quinuclidine moiety, the betaine was obtained by treatment with ion-exchanged resin (Amberlyst A26 OH form; Scheme 1).[16]

With these catalysts in hand, we optimized the reaction conditions by using silyl enol ether **1a** derived from 2-Me-tetralone as the substrate (Table 1). First, we ensured that in the absence of catalyst no conversion could be detected (Table 1, entry 1). Then the reaction was performed at several temperatures by using **QN$^+$1** as the catalyst (Table 1, entries 2–4). The optimized temperature was set at –20 °C, which afforded the best balance between acceptable reac-

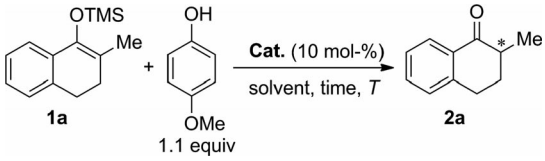


Scheme 1. General strategy for the synthesis of betaines.

tion time and enantiomeric excess. Several other chiral quaternary ammonium aryloxide salts were tested at this temperature (Table 1, entries 5–14). **QN$^+$1** gave higher enantioselectivity than the **QD$^+$1**, **CD$^+$1**, and **CN$^+$1** *Cinchona* alkaloids (Table 1, entry 3 vs. entries 5–7). We thus tried to examine the influence of the substituents on the ammonium moiety of the QN backbone (Table 1, entries 8–10), but, unfortunately, no improvement in enantioselectivity was observed. Chiral betaines **QN$^+$5**–**8** were also tested (Table 1, entries 11–14). The betaine **QN$^+$5** bearing two benzyl substituents on both the nitrogen and oxygen of the quinine led to a slightly improved enantiomeric excess (Table 1, entry 11). All other *N*,*O*-disubstituted betaines led to α-substituted ketones with similar or lower *ee*s (Table 1 entries 12–14 vs. 11). Having defined the best catalyst, the effect of solvent was investigated. Of the solvents assessed, apolar aprotic solvents were found to be superior to polar aprotic solvents (Table 1, entries 11, 17–19 vs. 15, 16). The best results were obtained with polytopic solvents such as diglyme or DME, DME being superior from a practical viewpoint. Moreover, in a last effort to improve the enantioselectivity, several other proton sources were screened, but unfortunately similar or lower *ee*s were obtained.[16]

The substrate scope was then investigated under the optimized reaction conditions with various silyl enol ethers **1a**–**m** (Table 2). From a general point of view, although enantioenriched ketones were obtained in high yields in the tetralone and benzosuberone series, the level of enantioselectivity reached was modest, ranging from 40 to 62% (Table 2, entries 1–11). The tetralone series provided the best *ee*s irrespective of the nature of the substituents at the α position (alkyl or benzyl; Table 2, entries 1–9). Substitution of the aromatic part of the tetralone by a methoxy group at the 5-, 6-, or 7-position did not significantly affect the enantioselectivity (Table 2, entries 6–9). The benzosuberone series and, above all, indanone furnished significantly lower *ee*s (Table 2, entries 10–12). Note that the general trend in the variation of *ee* between indanone and benzosuberone substrates is reversed to what was previously observed by making use of chiral tertiary amine cata-

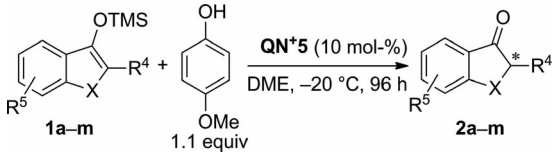
Table 1. Optimization of the reaction conditions.



Entry	Cat.	*T* [°C]	Solvent	Time [d][a]	*ee* [%][b]
1	–	RT	THF	1[c]	–
2	**QN$^+$1**	RT	THF	0.5	0
3	**QN$^+$1**	–20	THF	0.75	43
4	**QN$^+$1**	–45	THF	1[d]	nd
5	**QD$^+$1**	–20	THF	2	20
6	**CD$^+$1**	–20	THF	3	22
7	**CN$^+$1**	–20	THF	3	8
8	**QN$^+$2**	–20	THF	2	12
9	**QN$^+$3**	–20	THF	3	30
10	**QN$^+$4**	–20	THF	3	40
11	**QN$^+$5**	–20	THF	2	51
12	**QN$^+$6**	–20	THF	3	28
13	**QN$^+$7**	–20	THF	9	50
14	**QN$^+$8**	–20	THF	4	38
15	**QN$^+$5**	–20	DMF	2	13
16	**QN$^+$5**	–20	ACN	2	30
17	**QN$^+$5**	–20	2-MeTHF	3	30
18	**QN$^+$5**	–20	DME	4	58
19	**QN$^+$5**	–20	Diglyme	4	58

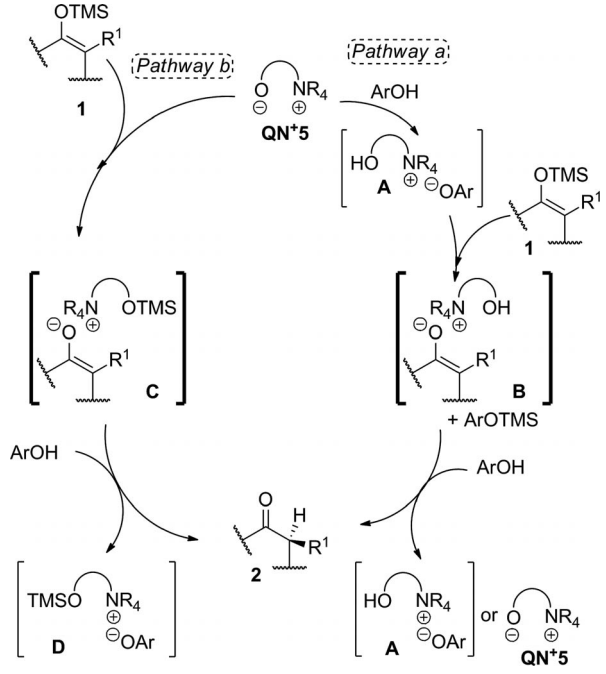
[a] Time to reach complete conversion. [b] Measured by HPLC analysis using a chiral column (see the Supporting Information). nd: not determined. [c] No conversion was observed. [d] 23% conversion was measured.

Table 2. Organocatalytic enantioselective protonation of silyl enolates **1a**–**m**.



Entry	X	R^4	R^5	**2**	Yield [%]	*ee* [%][a]	Abs. conf.[b]
1	$(CH_2)_2$	Me	H	**2a**	92	62	*S*
2		Et	H	**2b**	93	56	*S*
3		*i*Pr	H	**2c**	91	60	*R*
4		Bn	H	**2d**	97	50	*R*
5		4-MeOC$_6$H$_4$CH$_2$	H	**2e**	87	58	nd
6		Me	5-OMe	**2f**	80	54	nd
7		Bn	5-OMe	**2g**	91	57	nd
8		Bn	6-OMe	**2h**	95	54	nd
9		Bn	7-OMe	**2i**	86	51	nd
10	$(CH_2)_3$	Me	H	**2j**	84	44	nd
11		Et	H	**2k**	92	40	nd
12	CH_2	Et	H	**2l**	95	7	nd
13[c]	2,2,6-trimethylcyclohexanone			**2m**	85	34	*S*

[a] Measured by HPLC analysis using a chiral column (see the Supporting Information). [b] Determined by comparison with literature data. nd: not determined. [c] Reaction performed at room temperature.



Scheme 2. Mechanistic proposal.

lysts.[3,8,17] Indeed, in this study, higher enantioselectivities were obtained for the benzosuberone series (40% *ee* compared with 25% *ee*) whereas for the indanone, an almost racemic mixture of enantiomers was obtained (compared with 75% *ee*). Lastly, 2,2,6-trimethylcyclohexanone was obtained in 34% *ee*, which shows the superiority of cyclic aromatic ketones over their aliphatic analogues in terms of enantioselectivity (Table 2, entry 13). Nevertheless, the poor enantioselectivity observed could be partly explained by the need to perform the reaction at room temperature to reach completion.

To gain an insight into the mechanism of this organocatalytic enantioselective protonation reaction, several control experiments were conducted. To ascertain the first step of the reaction, two NMR experiments were performed at room temperature in [D$_8$]THF. The first one involving silyl enol ether **1a** and stoichiometric amounts of betaine catalyst **QN$^+$5** afforded the partial desilylation of **1a**. In the second, stoichiometric amounts of 4-MeOC$_6$H$_5$OH and betaine **QN$^+$5** were mixed resulting in a modification of the ^{1}H NMR signals of the two products. These two experiments indicate that two different pathways can be envisioned starting from the betaine **QN$^+$5** (Scheme 2).

Pathway a involves the deprotonation of the aryl alcohol by the betaine **QN$^+$5** to form an ammonium aryloxide bearing a free hydroxy group on the quinoline moiety (intermediate **A**). This latter species would then be able to generate the enolate (intermediate **B**) by desilylation of the silyl enol ether **1** to afford the desired product **2** after protonation with regeneration of either the betaine **QN$^+$5** or the intermediate **A** depending on the nature of the proton source (i.e., intermediate **A** or aryloxide, respectively). Pathway b first involves the desilylation of the silyl enol ether **1** by the betaine catalyst to provide a chiral ammonium enolate (intermediate **C**) bearing an OTMS group on the quinoline moiety of the catalyst. This chiral enolate would then be

subjected to protonation by the aryl alcohol to give the enantioenriched ketone **2** and a new catalytic species, namely an ammonium aryloxide bearing an OTMS group on the quinoline moiety (intermediate **D**).[18] Nevertheless, to date, we cannot rule out either of these two mechanisms and the modest level of enantioselectivity observed could be explained by competition between the two pathways.

Conclusions

We have reported an enantioselective organocatalytic protonation reaction of silyl enolates **1a**–**m** by using a new and simple betaine-type catalysts derived from readily accessible *Cinchona* alkaloid derivatives. By applying rather simple conditions (DME, –20 °C), moderate enantioselectivities have been attained for the tetralone series of substrates. Note that the benzosuberone series, which generally provides low *ee*s, furnished modest but unprecedented enantioselectivity of about 40%. These betaine catalysts are the subject of further study.

Experimental Section

A mixture of betaine **QN$^+$5** (12.2 mg, 0.025 mmol) and 4-methoxyphenol (34.1 mg, 0.275 mmol) in dry DME (0.25 mL) was stirred for a few minutes at room temperature until complete solubilization of the reagents. The reaction flask was placed at –20 °C and silyl enol ethers **1a**–**m** (0.25 mmol) were added as a solution in DME (0.25 mL). The reaction mixture was stirred at –20 °C until complete disappearance of the silyl enol ethers (monitored by GC-FID). The solvent was removed under vacuum and the residue purified by flash chromatography (petroleum ether/Et_2O = 95:5) to afford the pure ketones **2a**–**m**, which were analyzed by HPLC using chiral column to determine the enantiomeric excess.

Supporting Information (see footnote on the first page of this article): Experimental procedures, ^1H and ^{13}C NMR spectra of **QN$^+$5**–**QN$^+$8**, **1c**, **1k**, **2k**, HPLC traces for **2a**–**m**.

Acknowledgments

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[1] For general reviews on enantioselective protonation reactions, see: a) A. Claraz, S. Oudeyer, V. Levacher, *Curr. Org. Chem.* **2012**, *16*, 2192–2205; b) J. T. Mohr, A. Y. Hong, B. M. Stoltz, *Nat. Chem.* **2009**, *1*, 359–369; c) L. Duhamel, P. Duhamel, J.-C. Plaquevent, *Tetrahedron: Asymmetry* **2004**, *15*, 3653–3691.

[2] For a review on organocatalytic enantioselective protonation reactions, see: T. Poisson, S. Oudeyer, J.-F. Brière, V. Levacher in *Enantioselective Organocatalyzed Reactions I* (Ed.: R. Mahrwald), Springer, Dordrecht, Heidelberg, London, New York, **2011**, pp. 67–106.

[3] T. Poisson, V. Dalla, F. Marsais, G. Dupas, S. Oudeyer, V. Levacher, *Angew. Chem.* **2007**, *119*, 7220; *Angew. Chem. Int. Ed.* **2007**, *46*, 7090–7093.

[4] C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246–9247.

[5] D. Uraguchi, N. Kinoshita, T. Ooi, *J. Am. Chem. Soc.* **2010**, *132*, 12240–12242.

[6] E. M. Beck, A. M. Hyde, E. N. Jacobsen, *Org. Lett.* **2011**, *13*, 4260–4263.

[7] C. H. Cheon, O. Kanno, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 13248–13251.

[8] T. Poisson, V. Gembus, V. Dalla, S. Oudeyer, V. Levacher, *J. Org. Chem.* **2010**, *75*, 7704–7716.

[9] a) T. Mukaiyama, H. Nagao, Y. Yamane, *Chem. Lett.* **2006**, *35*, 916–917; b) H. Nagao, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2006**, *35*, 1398–1399; c) H. Nagao, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2007**, *36*, 666–667; d) H. Nagao, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2007**, *36*, 8–9; e) T. Tozawa, H. Nagao, Y. Yamane, T. Mukaiyama, *Chem. Asian J.* **2007**, *2*, 123–134.

[10] a) D. Uraguchi, K. Koshimoto, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 10878–10879; b) D. Uraguchi, K. Koshimoto, S. Miyake, T. Ooi, *Angew. Chem.* **2010**, *122*, 5699; *Angew. Chem. Int. Ed.* **2010**, *49*, 5567–5569; c) D. Uraguchi, K. Koshimoto, T. Ooi, *Chem. Commun.* **2010**, *46*, 300–302; d) D. Uraguchi, K. Koshimoto, C. Sanada, T. Ooi, *Tetrahedron: Asymmetry* **2010**, *21*, 1189–1190; e) D. Uraguchi, K. Koshimoto, T. Ooi, *J. Am. Chem. Soc.* **2012**, *134*, 6972–6975; f) D. Uraguchi, K. Oyaizu, T. Ooi, *Chem. Eur. J.* **2012**, *18*, 8306–8309.

[11] A. Claraz, S. Oudeyer, V. Levacher, *Adv. Synth. Catal.* **2013**, *355*, 841–846.

[12] For a recent review on cooperative ion-paring in asymmetric organocatalysis, see: J.-F. Briere, S. Oudeyer, V. Dalla, V. Levacher, *Chem. Soc. Rev.* **2012**, *41*, 1696–1707.

[13] For recent examples of the enantioselective protonation of chiral quaternary ammonium enolate intermediates derived from cycloalkanone and cycloalkenone enol chloroacetates, see: a) E. Yamamoto, A. Nagai, A. Hamasaki, M. Tokunaga, *Chem. Eur. J.* **2011**, *17*, 7178–7182; b) E. Yamamoto, D. Gokuden, A. Nagai, T. Kamachi, K. Yoshizawa, A. Hamasaki, T. Ishida, M. Tokunaga, *Org. Lett.* **2012**, *14*, 6178–6181.

[14] W.-Q. Zhang, L.-F. Cheng, J. Yu, L.-Z. Gong, *Angew. Chem.* **2012**, *124*, 4161; *Angew. Chem. Int. Ed.* **2012**, *51*, 4085–4088.

[15] H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907.

[16] See the Supporting Information for further details.

[17] T. Poisson, S. Oudeyer, V. Dalla, F. Marsais, V. Levacher, *Synlett* **2008**, 2447–2450.

[18] All our attempts to synthesize and isolate intermediate **D** failed.

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