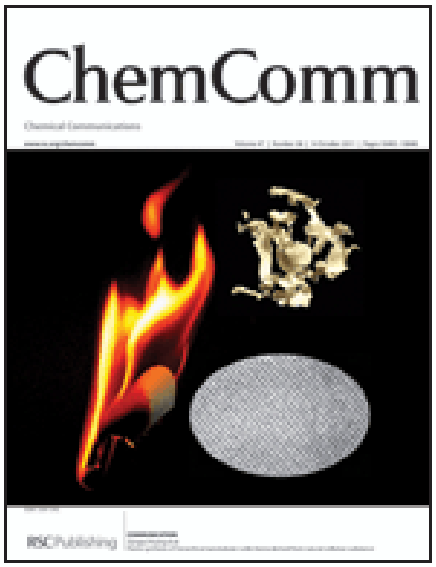

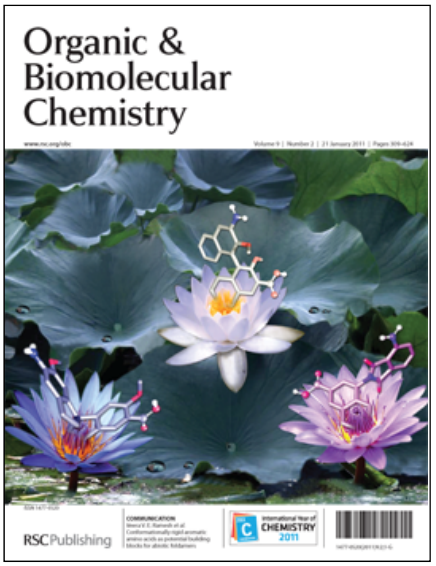

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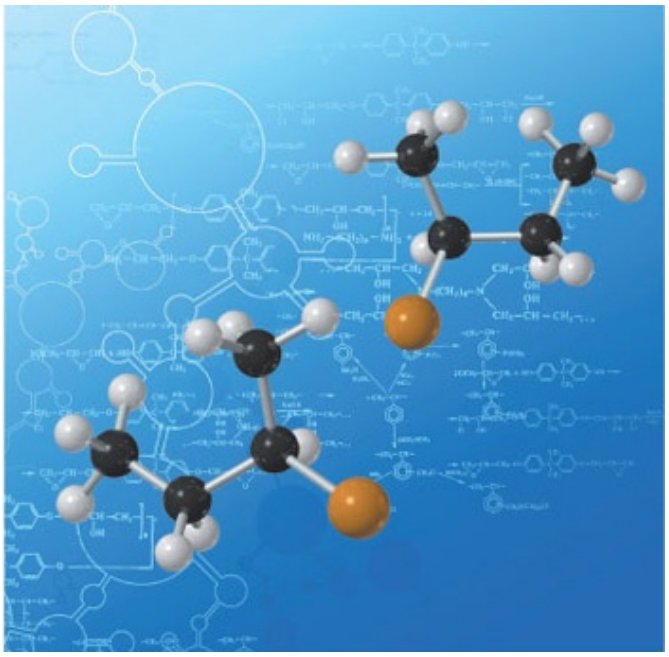

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COMMUNICATION

Biomimetic catalytic enantioselective decarboxylative aldol reaction of β-ketoacids with trifluoromethyl ketones†‡

Yan Zheng, Heng-Ying Xiong, Jing Nie, Ming-Qing Hua and Jun-An Ma*

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We disclose an organocatalyzed enantioselective decarboxylative ketone aldol reaction of β-ketoacids with trifluoromethyl ketones in the presence of biscinchona alkaloid $(DHQD)_2AQN$, affording chiral tertiary alcohols in up to 98% yield and 90% ee.

Nature uses enzymatic activation of malonic acid half thioesters (MAHTs) *via* decarboxylative transformation for the biosynthesis of polyketides and fatty acids.[1] Aspiring to imitate this biocatalytic process, organic chemists have succeeded in developing a host of asymmetric catalytic systems to demonstrate the synthetic usefulness of deployment of direct decarboxylative additions in enantioselective carbon–carbon bond-forming reactions.[2–5] Nearly all such studies have focused on the two-carbon extension asymmetric transformations of thioester enolates and their equivalents. In sharp contrast, the biomimicry of β-ketoacid decarboxylation for the asymmetric introduction of synthetically useful keto-carbonyl groups remains largely untapped. The lack of progress may be attributed to the unimolecular decomposition of β-ketoacids and the difficulty of stereochemical control as compared to thioester enolates and ester enolates. One example of asymmetric decarboxylative reaction of β-ketoacids came from Evans and co-workers, who reported a nickel-catalyzed addition of β-ketoacids to nitroalkenes to afford the enantiomerically enriched adducts.[6] Mahrwald and Rohr described an asymmetric decarboxylative aldol reaction of β-ketoacids, but the use of chiral aldehydes is a prerequisite for asymmetric induction.[7] Accordingly, the direct catalytic enantioselective decarboxylative ketone aldol reaction of β-ketoacids for the synthesis of chiral tertiary alcohols has not been reported so far, and thus remains an important challenge.

Asymmetric organocatalysis,[8] where small organic molecules catalyze the reactions without the presence of any metal, has become an attractive strategy in organic synthesis. Herein we report details of our discovery of the first enantioselective decarboxylative ketone aldol reaction of β-ketoacids catalyzed in the absence of metal ions. We found that the cinchona alkaloid-derived organocatalysts promote the decarboxylative aldol reactions of β-ketoacids with trifluoromethyl ketones under mild conditions. Furthermore, our preliminary investigation into the mechanism of this transformation suggests a stepwise process involving nucleophilic addition of β-ketoacid to the trifluoromethyl ketone followed by a subsequent decarboxylation reaction.

In an initial investigation, we conducted the decarboxylative aldol reaction of 3-oxo-3-phenylpropanoic acid **1a** with 2,2,2-trifluoroacetophenone **2a** by employing triethylamine as an organocatalyst to afford the desired product **3a** in 48% isolated yield.[9] In addition, a significant amount of acetophenone, generated through decarboxylative protonation of **1a**, was recovered in this case. Therefore, we tried slow addition of 2.0 equiv. of **1a** to a mixture of the catalyst and **2a**. As expected, the yield was improved to 98% even in the presence of catalytic triethylamine (20 mol%). Next, a series of natural chiral cinchona alkaloids and commercially available biscinchona alkaloids were tested (Fig. 1). It was found that $(DHQD)_2AQN$ was the most promising catalyst for the model reaction (Table 1, entry 7), whereas all the other chiral bases tested resulted in low enantioselectivities (entries 1–6 and 8). In addition, the solvent was found to have an important effect on the reactivity (entries 9–12). Among the solvents tested, THF was found to be the best with respect to catalytic activity and asymmetric induction. Substantial decrease in reaction temperature revealed that the enantioselectivity can be significantly improved from 63% ee (entry 7) to 85% and 90% ee

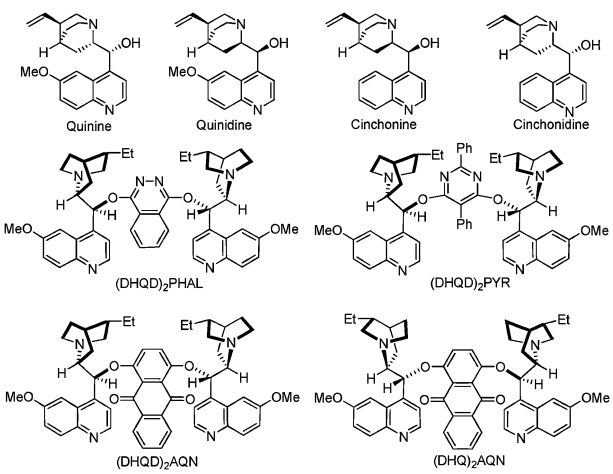

Fig. 1 Cinchona alkaloids tested in the decarboxylative aldol reaction of β-ketoacid **1a** with trifluoroacetophenone **2a**.

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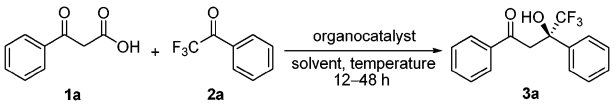
‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc30949a

Table 1 Optimization of conditions for the decarboxylative aldol reaction[a]



1a 2a 3a

Entry	Catalyst (mol%)	Solvent	Temp (°C)/ Time (h)	Yield (%)[b]	ee (%)[c]
1	Quinine (20)	THF	0/12	88	6 (+)
2	Quinidine (20)	THF	0/12	88	14 (−)
3	Cinchonine (20)	THF	0/12	87	0
4	Cinchonidine (20)	THF	0/12	86	6 (+)
5	$(DHQD)_2PYR$ (20)	THF	0/12	88	38 (−)
6	$(DHQD)_2PHAL$ (20)	THF	0/12	73	8 (−)
7	$(DHQD)_2AQN$ (20)	THF	0/12	95	63 (−)
8	$(DHQ)_2AQN$ (20)	THF	0/12	96	36 (+)
9	$(DHQD)_2AQN$ (20)	toluene	0/12	46	23 (−)
10	$(DHQD)_2AQN$ (20)	Et_2O	0/12	25	15 (−)
11	$(DHQD)_2AQN$ (20)	CH_2Cl_2	0/12	0	0
12	$(DHQD)_2AQN$ (20)	CH_3CN	0/12	0	0
13	$(DHQD)_2AQN$ (20)	THF	−20/24	97	85 (−)
14	$(DHQD)_2AQN$ (20)	THF	−40/28	96	90 (−)
15	$(DHQD)_2AQN$ (20)	THF	−60/48	53	90 (−)
16	$(DHQD)_2AQN$ (10)	THF	−20/48	88	87 (−)

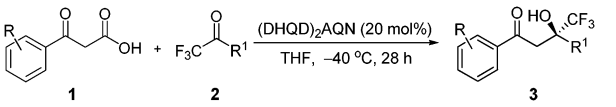
[a] The reaction was carried out with β-ketoacid **1a** (0.2 mmol) and trifluoromethyl ketone **2a** (0.1 mmol) in THF (0.6 mL). [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC analysis.

(entries 13 and 14). Further changes in reaction temperature and the amount of catalyst did not have any significant effect on the enantioselectivity; however, reduced yields were observed, even with prolonged reaction times (entries 15 and 16).

With the optimized reaction conditions in hand, the scope of this organocatalytic enantioselective decarboxylative aldol reaction was examined by varying both β-ketoacids and trifluoromethyl ketones. The results are summarized in Table 2. Most of the trifluoromethylated tertiary alcohols were obtained in high yields with the range of 64–90% ee (entries 1–5 and 10–14). However, by contrast, the substituent at the 2-position of the aryl rings has a little effect on the reactivity. These reactants gave the aldol products in moderate to good yields (entries 6–9, 15, and 16). When 1,1,1-trifluoroacetone was employed, the desired product was also obtained in 94% yield with 64% ee (entry 17).[10] It is noteworthy that the reaction worked well with 1,1,1-trifluoro-4-phenylbut-3-yn-2-one to give the 1,2-adduct in high yield and moderate enantioselectivity (entry 18). In addition, we investigated the decarboxylative aldol reaction of alkyl-substituted β-ketoacids including 3-oxobutanoic acid, 3-oxopentanoic acid, and 3-cyclopropyl-3-oxopropanoic acid with 2,2,2-trifluoroacetophenone **2a**. These substrates were found to be unsuitable for this asymmetric transformation and no desired products were observed.

An organocatalytic decarboxylative aldol experiment on a 2 mmol scale of **2a** was also carried out with **1a**, and the condensation product **3a** was obtained with excellent optical purity after single recrystallization from CH_2Cl_2/hexane (Scheme 1). Furthermore, the organocatalyst was recovered in almost quantitative yield and reused without any loss of reactivity and enantioselectivity.[11] In addition, the absolute configuration of **3a** was determined to be *R* by comparison with the sign of optical rotation of the deprotected compound

Table 2 Scope of the enantioselective decarboxylative aldol reaction[a]



1 2 3

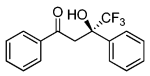
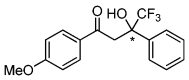
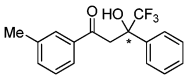
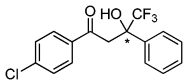
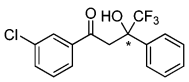
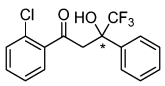
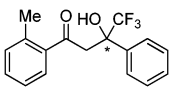
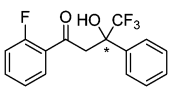
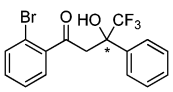
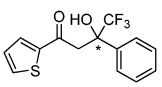
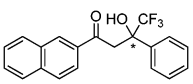
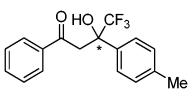
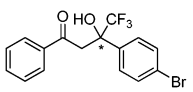
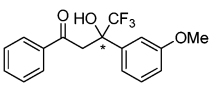
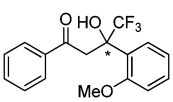
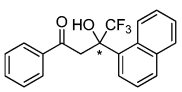
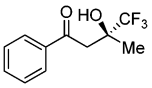
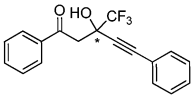
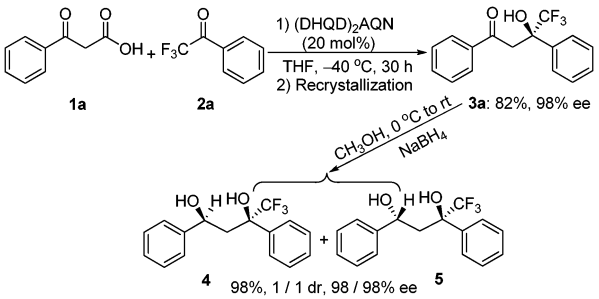
Entry	Product		Yield (%)[b]	ee (%)[c]
1		**3a**	96	90
2		**3b**	97	82
3		**3c**	93	80
4		**3d**	94	76
5		**3e**	86	80
6		**3f**	63	72
7		**3g**	80	74
8		**3h**	72	75
9		**3i**	60	85
10		**3j**	85	65
11		**3k**	98	65
12		**3l**	97	64
13		**3m**	95	78
14		**3n**	92	72
15		**3o**	60	60
16		**3p**	60	62

Table 2 (*continued*)

Entry	Product		Yield (%)[b]	ee (%)[c]
17		**3q**	94	64
18		**3r**	98	61

[a] The reaction was carried out with β-ketoacid **1a** (0.2 mmol) and trifluoromethyl ketone **2a** (0.1 mmol) in THF (0.6 mL), using 20% $(DHQD)_2AQN$ at −40 °C for 28 h. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC analysis.



Scheme 1 Scaled-up version of the decarboxylative aldol reaction, and further transformation.

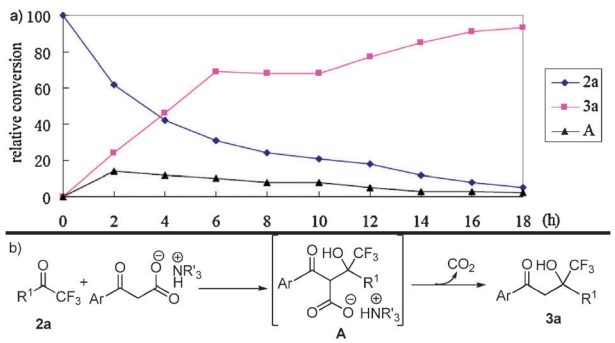


Fig. 2 (a) ^{19}F NMR monitoring of the reaction mixture of β-ketoacid **1a**, trifluoromethyl ketone **2a**, and NEt_3 in THF-d_8 as a function of time at 0 °C; (b) proposed mechanism for the organocatalytic decarboxylative aldol reaction of β-ketoacids with trifluoromethyl ketones.

reported in the literature.[10] Further reduction of enantio-enriched **3a** in the presence of $NaBH_4$ gave trifluoromethylated diols **4** and **5** (1 : 1 dr), which were easily isolated through silica gel column chromatography in 98% yield with excellent enantiomeric purities (98% ee).

It was noteworthy that ^{19}F NMR analysis of the reaction progress between **1a** and **2a** with triethylamine in THF-d_8 revealed the appearance of a new peak (at −85.05 ppm) that was tentatively assigned as the reaction intermediate (**A**).[12] With the disappearance of this intermediate **A** and the reactant **2a** (−72.35 ppm) from the catalytic system, the aldol product **3a** (at −80.95 ppm) was formed (Fig. 2a). Based on these preliminary results, a stepwise process could be involved in the catalytic cycle, in which nucleophilic addition of the ketoacid salt to trifluoromethyl ketones gave the addition intermediate, followed by the decarboxylation to afford the desired aldol product (Fig. 2b).

In conclusion, we have successfully developed the first organocatalyzed enantioselective decarboxylative ketone aldol reaction of β-ketoacids with trifluoromethyl ketones by employing chiral cinchona alkaloids as efficient catalysts. A series of chiral trifluoromethyl-substituted tertiary alcohols were obtained in good to high yields (60–98%) and enantioselectivities (60–90% ee). Further investigations to understand the mechanism and to improve the enantioselectivity are underway.

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Notes and references

1 J. Staunton and K. J. Weissman, *Nat. Prod. Rep.*, 2001, **18**, 380.
2 For a review, see: Y. Pan and C.-H. Tan, *Synthesis*, 2011, 2044.
3 For the catalytic enantioselective decarboxylative aldol reactions of MAHTs and their equivalents, see: (*a*) S. Orlandi, M. Benaglia and F. Cozzi, *Tetrahedron Lett.*, 2004, **45**, 1747; (*b*) D. Magdziak, G. Lalic, H. M. Lee, K. C. Fortner, A. D. Aloise and M. D. Shair, *J. Am. Chem. Soc.*, 2005, **127**, 7284; (*c*) K. C. Fortner and M. D. Shair, *J. Am. Chem. Soc.*, 2007, **129**, 1032; (*d*) D. J. Schipper, S. Rousseaux and K. Fagnou, *Angew. Chem., Int. Ed.*, 2009, **48**, 8343; (*e*) J. Baudoux, P. Lefebvre, R. Legay, M.-C. Lasne and J. Rouden, *Green Chem.*, 2010, **12**, 252; (*f*) N. Hara, S. Nakamura, Y. Funahashi and N. Shibata, *Adv. Synth. Catal.*, 2011, **353**, 2976; (*g*) X.-J. Li, H.-Y. Xiong, M.-Q. Hua, J. Nie, Y. Zheng and J.-A. Ma, *Tetrahedron Lett.*, 2012, **53**, 2117.
4 For the catalytic enantioselective decarboxylative Mannich reactions of MAHTs and their equivalents, see: (*a*) A. Ricci, D. Pettersen, L. Bernardi, F. Fini, M. Fochi, R. P. Herrera and V. Sgarzani, *Adv. Synth. Catal.*, 2007, **349**, 1037; (*b*) L. Yin, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 9610; (*c*) Y. Pan, C. W. Kee, Z. Jiang, T. Ma, Y. Zhao, Y. Yang, H. Xue and C.-H. Tan, *Chem.–Eur. J.*, 2011, **30**, 8363.
5 For the catalytic enantioselective decarboxylative Michael addition reactions of MAHTs and their equivalents, see: (*a*) J. Lubkoll and H. Wennemers, *Angew. Chem., Int. Ed.*, 2007, **46**, 6841; (*b*) M. Furutachi, S. Mouri, S. Matsunaga and M. Shibasaki, *Chem.–Asian J.*, 2010, **15**, 2351; (*c*) H. Y. Bae, S. Some, J. H. Lee, J.-Y. Kim, M. J. Song, S. Lee, Y. J. Zhang and C. E. Song, *Adv. Synth. Catal.*, 2011, **353**, 3196.
6 D. A. Evans, S. Mito and D. Seidel, *J. Am. Chem. Soc.*, 2007, **129**, 11583.
7 K. Rohr and R. Mahrwald, *Org. Lett.*, 2011, **13**, 1878.
8 For selected reviews, see: (*a*) B. List, *Tetrahedron*, 2002, **58**, 5573; (*b*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*c*) W. Notz, F. Tanaka and C. F. Barbas III., *Acc. Chem. Res.*, 2004, **37**, 580; (*d*) *Asymmetric Organocatalysis*, ed. A. Berkessel and H. Grcger, Wiley-VCH, New York, 2005; (*e*) *Enantioselective Organocatalysis*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2007; (*f*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471.
9 For the achiral decarboxylative aldol reactions with metal catalysts and organocatalysts, see: (*a*) M. Stiles, D. Wolf and G. V. Hudson, *J. Am. Chem. Soc.*, 1959, **81**, 628; (*b*) H. Brunner, J. Müller and J. Spitzer, *Monatsh. Chem.*, 1996, **127**, 845; (*c*) T. Kourouli, P. Kefalas, N. Ragoussis and V. Ragoussis, *J. Org. Chem.*, 2002, **67**, 4615; (*d*) G. Lalic, A. D. Aloise and M. D. Shair, *J. Am. Chem. Soc.*, 2003, **125**, 2852; (*e*) N. Blaquiere, D. G. Shore, S. Rousseaux and K. Fagnou, *J. Org. Chem.*, 2009, **74**, 6190.
10 Z.-J. Liu, Y.-Q. Mei and J.-T. Liu, *Tetrahedron*, 2007, **63**, 855.
11 The recycling and reuse of (DHQD)AQN in the model reaction: product **3a** was obtained in 97% yield with 89% ee.
12 All attempts to isolate this postulated intermediate failed.

