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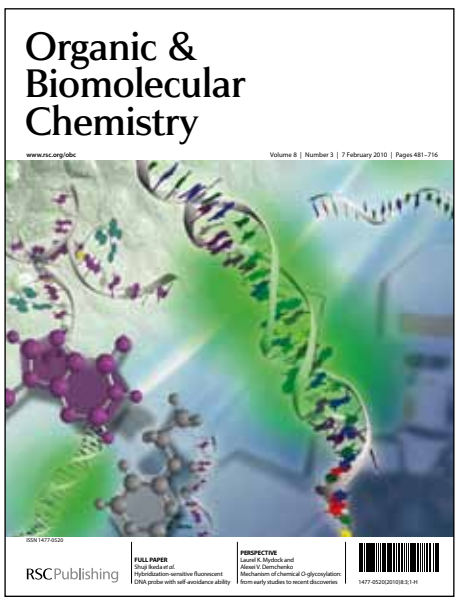

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Enantioselective α-hydroxylation of β-ketoamides

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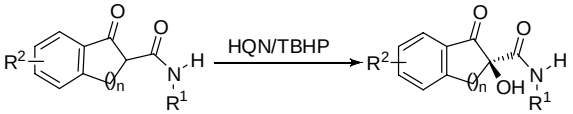
The first enantioselective α-hydroxylation reaction of α-substituted β-ketoamides has been developed by using the commercially available hydroquinine/TBHP system. The tertiary alcohols are obtained in good to high yield and up to 83% ee, which can be improved by a single crystallization.

The asymmetric α-hydroxylation of α-substituted-1,3-dicarbonyl compounds is an important transformation which allows to directly install a carbon-oxygen bond. These densely functionalised molecules bearing a quaternary stereocentre[1] are useful synthetic intermediates and the structural motif is found in a variety of natural products and insecticides as the Indoxacarb produced by Dupont.[2] A limited number of direct enantioselective α-hydroxylation reactions has been developed, predominantly focused on β-ketoesters, by using Ti-,[3] Ni-,[4] Pd-,[5] Cu-,[6] Zn-chiral ligand complexes[7] and different oxidants. In most cases, the hydroxylation reactions proceeded with good to excellent enantiocontrol. Cinchona alkaloids,[8] chiral β-amino alcohols[9] and phase transfer catalysts[10] have recently demonstrated to promote the α-hydroxylation of α-substituted β-ketoesters with alkyl hydroperoxides to afford the products in moderate to good level of enantioselectivity. Chiral phosphoric acids were also successfully employed to catalyze the enantioselective aminoxylation of β-ketoesters with nitroso compounds as the oxygen source.[11]

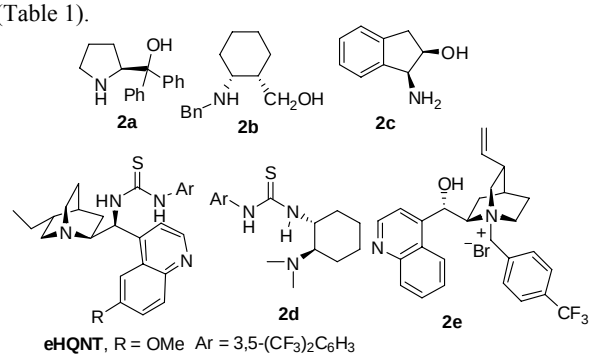
Surprisingly, investigations on the enantioselective α-hydroxylation of different 1,3-dicarbonyl compounds such as α-substituted β-ketoamides received poor attention,[12] although the amido group is amenable of further manipulations.[13] β-Ketoamides are challenging substrates for this process due to the lower acidity of the α-hydrogen and the requirement of more basic reaction conditions to generate the enolate. Very recently, Shibasaki developed the first asymmetric α-hydroxylation of *N*-unsubstituted α-alkoxycarbonyl amides with $Pr(OiPr)_3$ and chiral fluoro-substituted amide-based ligands using oxaziridines as the oxidant.[14] The corresponding synthetically useful tertiary alcohols were isolated in moderate to good yield and fairly good level of enantioselectivity.

Considering our long-standing interest in the development of enantioselective oxidation reactions,[15] we embarked in a study aimed to synthesize functionalised tertiary alcohols via asymmetric hydroxylation of α-substituted β-ketoamides. These substrates, in racemic form, have been recently demonstrated to be key-intermediates to access Brazilin-type compounds, showing promising antiproliferative activity against different human tumor cell lines.[16] In this study, we illustrate the first enantioselective α-hydroxylation reaction of β-ketoamides mediated by the commercially available hydroquinine/*tert*-butyl hydroperoxide (TBHP) system (Scheme 1). The products have been isolated in generally high yield and moderate to good enantioselectivity.



Scheme 1 Enantioselective organocatalytic α-hydroxylation of β-ketoamides.

Our initial screening focused on model β-ketoamide **1a**, using a variety of easily accessible bifunctional organocatalysts of different nature (Scheme 2), employed at 20 mol% loading with TBHP as the oxygen source in toluene at room temperature (Table 1).



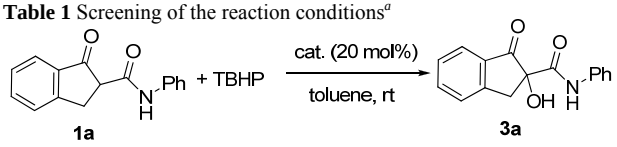
QN= quinine, **QD**= quinidine, **HQN**= hydroquinine, **HQD**= hydroquinidine

Scheme 2 Organocatalysts screened in the α-hydroxylation of β-ketoamide **1a**.

We were pleased to observe the formation of the expected product **3a** when using α,α-L-diphenyl prolinol **2a** bearing a secondary amine group, although it was obtained with 18% *ee* (entry 1). This result indicated the suitability of bifunctional organocatalysts, bearing a moderately basic site, as promoters for the oxidation. The employment of *cis*-1,2-amino alcohol derivative **2b** led to compound **3a** in low yield and enantioselectivity (entry 2). Interestingly, *cis*-(1*R*,2*S*)-amino indanol **2c**, bearing a primary amine moiety, enabled the formation of compound **3a** in 62% yield, although without enantiocontrol (entry 3).[17] Surprisingly, both Takemoto thiourea **2d** and *epi*-hydroquinine derived thiourea **eHQNT** proved to be less effective catalysts than amino alcohols **2a-c** (entries 4-5). We

also investigated the feasibility of the process under phase transfer catalysis by using *N*-[4-(trifluoromethyl)benzyl]cinchoninium bromide **2e**, cumyl hydroperoxide as the oxidant at 0°C under basic conditions (entry 6).

Table 1 Screening of the reaction conditions[a]



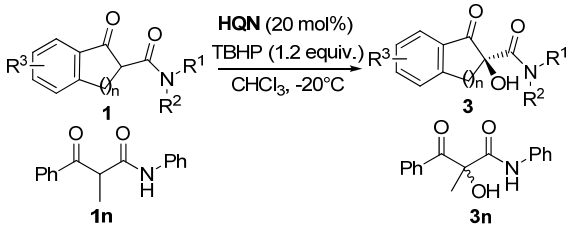
Entry	Catalyst	*t*/h	Yield (%)[b]	ee (%)[c]
1	**2a**	69	51	18
2	**2b**	51	38	2
3	**2c**	40	62	rac
4	**2d**	65	22	4
5[d]	**eHQNT**	70	13	4
6[e]	**2e**	42	90	-30
7	**QN**	43	79	50
8	**QD**	72	57	-44
9	**HQN**	65	99	54
10	**HQD**	70	92	-50
11[f]	**HQN**	48	81	45
12[g]	**HQN**	8	88	14
13[h]	**HQN**	12	90	52
14[i]	**HQN**	16	82	52
15[j]	**HQN**	16	94	49
16[k]	**HQN**	21	89	50
17[l]	**HQN**	18	97	56
18[l]	-	22	10[m]	-
19[l,n]	**HQN**	118	83	76

[a] Reaction conditions: **1a** (0.1 mmol), cat. (20 mol%), TBHP (1.2 equiv), solvent (0.5 mL). [b] Isolated yield after silica gel chromatography. [c] Determined by chiral HPLC analysis. Negative values indicate the preferential formation of the opposite enantiomer. [d] 10 mol% of catalyst was used. [e] Reaction conditions: **1a** (0.1 mmol), **2e** (5 mol%), CHP (1.5 equiv), K_2HPO_3 (50%) (0.5 mL), toluene (1 mL) at 0°C. [f] Cumyl hydroperoxide was used. [g] Reaction conditions: **1a** (0.1 mmol), HQN (20 mol%), H_2O_2 (50%) (1.2 equiv), $MgSO_4$ (45 mg), toluene (0.5 mL). [h] CH_2Cl_2 used as solvent. [i] CH_2Br_2 used as solvent. [j] $Cl(CH_2)_2Cl$ used as solvent. [k] C_6H_5Cl used as solvent. [l] $CHCl_3$ used as solvent. [m] Conversion to **3a** determined by ^1H NMR analysis. [n] $CHCl_3$ (2 mL) at -20°C.

Compound **3a** was obtained in high yield and 30% ee. Cinchona alkaloids were next tested and proved to be fairly active promoters (entries 7-10), affording the product in generally high yield and up to 54% *ee* when using HQN as the organocatalyst (entry 9). CHP and hydrogen peroxide, tested as alternative oxygen source in the presence of HQN as promoter, gave inferior results (entries 11 and 12). In halogenated solvents, the hydroquinine activity significantly increased (entries 13-17) and when the reaction was carried out in chloroform the product was isolated in 97% yield and 56% ee after 18 h (entry 17). A control experiment, performed in $CHCl_3$ without HQN, showed a poor conversion to the product after a comparable reaction time, which assured that the racemic oxidative pathway is a negligible process (entry 18). Performing the reaction at -20°C, under more diluted conditions, led to the isolation of compound **3a** in high yield and 76% ee (entry 19). The enantioselectivity did not improve when working at lower temperatures.

Having established the optimized reaction conditions, an investigation on the substrate scope was undertaken (Table 2).

Table 2 Enantioselective α-hydroxylation of β-ketoamides **1**[a]



Entry	R^1, R^2, R^3, n	*t*/h	Yield (%)[b]	ee (%)[c]
1	Ph, H, H, 1, **a**	118	83 (66)	76 (87)
2	Ph, H, 4-Br, 1, **b**	115	88 (66)	83 (96)
3	Ph, H, 5-Cl, 1, **c**	92	85	79
4	Ph, H, 5-Br, 1, **d**	117	87	78
5	Ph, H, 6-OMe, 1, **e**	117	84 (60)	81 (98)
6	1-Naphthyl, H, H, 1, **f**	64	82	74
7	2-ClC_6H_4, H, H, 1, **g**	111	76 (48)	67 (99)
8	3-$CF_3C_6H_4$, H, H, 1, **h**	93	88	56
9	4-O(*n*-pentyl)C_6H_4, H, H, 1, **i**	139	89	76
10[d]	Cyclohexyl, H, H, 1, **j**	144	37	40
11[d]	Bn, H, H, 1, **k**	142	50	29
12[d]	Bn, Me, H, 1, **l**	142	-	-
13[d]	Ph, H, H, 2, **m**	164	-	-
14[d]	**1n**	160	-	-

[a] Reaction conditions: **1a** (0.1 mmol), HQN (20 mol%), TBHP (1.2 equiv), $CHCl_3$ (2 mL). [b] Isolated yield after silica gel chromatography. In parenthesis yield after crystallization. [c] Determined by chiral HPLC analysis. In parenthesis ee after crystallization. [d] Reaction performed at rt.

Halogen atoms and electron-donating groups on the aromatic ring of the indane scaffold were tolerated and the products were obtained in high yield and up to 83% ee (entries 2-5). The 1-naphthyl substituted compound at the secondary amido moiety **1f**, was converted into the product likewise model compound **1a** (entry 6). The substitution pattern of the phenyl ring on the amide influenced the enantioselectivity with the electron-withdrawing groups bearing products being obtained with slightly lower ee values (compare entries 7 and 8 with entries 1 and 9). Compounds **1j-k**, with an aliphatic amido group, reacted sluggishly at room temperature affording the tertiary alcohol in modest yield and ee values (entries 10 and 11). The presence of the secondary amido group in the β-ketoamide was found to have an important role as exemplified by the lack of reactivity observed when reacting compound **1l**, bearing a tertiary amide portion (compare entry 12 with entry 11).

Similarly to data reported in organocatalytic α-hydroxylation reactions of less reactive tetralone based and acyclic β-ketoesters, the corresponding β-ketoamides **1m** and **1n** did not afford the product under usual conditions working at room temperature (entries 13 and 14). Pleasingly, products **3** could be recovered in high ee and good yield after a single crystallization (entries 1, 2, 5 and 7).

Single-crystal X-ray analysis on compound **3b** enabled to assign the absolute configuration of the quaternary stereocentre as

2*S* (Fig. 1).[18]

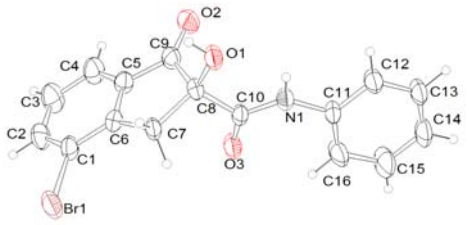


Fig. 1 Molecular structure of *S*-**3b** with ellipsoids set at 30% probability level.

The importance of the secondary amido group was firstly illustrated with the elegant work of Miller in the asymmetric epoxidation of functionalized alkenes catalyzed by small peptide organocatalysts and hydrogen peroxide.[19]

Hoping to get more insight into the nature of interactions established between HQN and the β-ketoamide, ^{1}H-NMR spectra of HQN were recordered in $CDCl_3$ at room temperature adding different amounts of compound **1a** (up to 3 equiv) (Fig. 2).

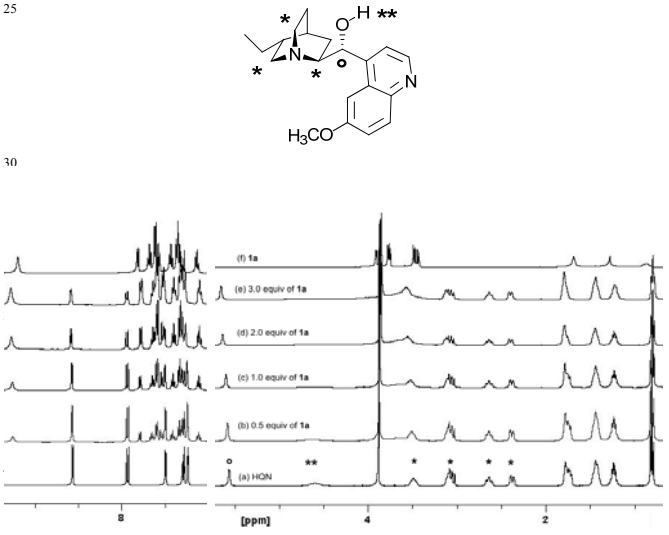


Fig. 2 ^{1}H-NMR spectra of HQN recordered with increasing amounts of compound **1a** in $CDCl_3$ (C 0.1 M) at room temperature. The HQN protons which were significantly shifted or broadened are marked with symbols.

Line broadening of the α-hydrogens to the quinuclidine nitrogen was observed increasing the amount of the **1a** which is consistent with the protonation of the nitrogen by the α-proton of compound **1a**.[20] This was also confirmed by significant line broadening of the β-ketoamide protons in the 3.4-4.0 ppm region. The carbinolic proton of the catalyst was slightly downshifted. The signal of the OH proton consistently decreased when adding **1a**. All these findings suggest that the catalyst OH group might be involved in hydrogen bonding interaction with the enolate of compound **1a**. Surprisingly, no significant shift of the CONH proton resonance at 9.3 ppm was observed. Results in Table 2 do not reveal any particular correlation of the ee values with the acidity of the amide proton as previously observed in asymmetric organocatalysed Michael addition reactions of β-ketoamides to β-unsubstituted α,β-unsaturated ketones and acrolein.[21a] In contrast to our findings (see Table 1, entry 4), in the conjugate addition reaction, Takemoto catalyst **2d** was found to be the most effective and the amidic acid form of the β-ketoamide was proposed to be involved favouring the deprotonation of the methine proton.[21a]

In conclusion, a simple methodology for the first enantioselective α-hydroxylation reaction of α-substituted β-ketoamides has been developed by using the commercially available HQN/TBHP system. The functionalized tertiary alcohols were isolated in good to high yield and up to 83% ee. From a practical point of view, products **3** can be eventually obtained in high ee after a single crystallization.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [NMR and HPLC spectra for all the new compounds]. See DOI: 10.1039/b000000x/

1 For reviews, see: *(a)* J. Christoffers, A. Baro and T. Werner, *Adv. Synth. Catal.*, 2004, **346**, 143; *(b)* A. M. R. Smith and K. K. Hii, *Chem. Rev.*, 2011, **111**, 1637; *(c)* A. Russo, C. De Fusco and A. Lattanzi, *RSC. Adv.*, 2012, **2**, 385.

2 *(a)* M. Nakayama, Y. Fukuoka, H. Nozaki, A. Matsuo and S. Hayashi, *Chem. Lett.*, 1980, 1243; *(b)* J. Zhu, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron Lett.*, 1994, **35**, 2787; *(c)* K. D. Wellington, R. C. Cambie, P.S. Rutledge and P. R. Bergquist, *J. Nat. Prod.*, 2000, **63**, 79; *(d)* G. Olack and H. Morrison, *J. Org. Chem.*, 1991, **56**, 4969; *(e)* G. Büchi, K. E. Matsumoto and H. Nishimura, *J. Am. Chem. Soc.*, 1971, **93**, 3299; *(f)* S. F. McCann, G. D. Annis, R. Shapiro, D. W. Piotrowski, G. P. Lahm, J. K. Long, K. C. Lee, M. M. Hughes, B. J. Myers, S. M. Griswold, B. M. Reeves, R. W. March, P. L. Sharpe, P. Lowder, W. E. Barnette and K. D. Wing, *Pest. Manag. Sci.*, 2001, **57**, 153.

3 P. Y. Toullec, C. Bonaccorsi, A. Mezzetti and A. Togni, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 5810.

4 T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru and S. Kanemasa, *J. Am. Chem. Soc.*, 2006, **128**, 16488.

5 *(a)* A. M. R. Smith, D. Billen and K. K. Hii, *Chem. Commun.* 2009, 3925; *(b)* A. M. Smith, H. S. Rzepa, A. J. White, D. Billen and K. K. Hii, *J. Org. Chem.*, 2010, **75**, 3085.

6 J.-J. Jiang, J. Huang, D. Wang, M.-X. Zhao, F.-J. Wang and M. Shi, *Tetrahedron: Asymmetry*, 2010, **21**, 794.

7 J. Li, G. Chen, Z. Wang, R. Zhang, X. Zhang and K. Ding, *Chem. Sci.*, 2011, **2**, 1141.

8 *(a)* E. G. Taylor, L. Birch, US Patent WO03/040083, PCT/US02/35615, 2003; *(b)* M. R. Acocella, O. G. Mancheño, M. Bella and K. A. Jørgensen, *J. Org. Chem.*, 2004, **69**, 8165.

9 *(a)* B. Gong, Q. Meng, T. Su, M. Lian, Q. Wang and Z. Gao, *Synlett*, **2009**, 2659; *(b)* Y. Cai, M. Lian, Z. Li and Q. Meng, *Tetrahedron*, 2012, **68**, 7973.

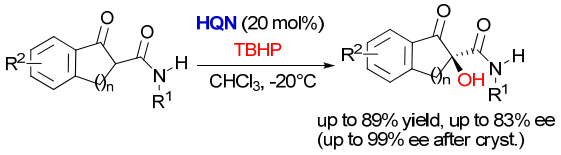
10 M. Lian, Z. Li, J. Du, Q. Meng and Z. Gao, *Eur. J. Org. Chem.*, 2010, 6525.

11 M. Lu, D. Zhu, Y. Lu, X. Zeng, B. Tan, Z. Xu and G. Zhong, *J. Am. Chem. Soc.*, 2009, **131**, 4562.

12 For some examples of enantioselective α-hydroxylation of acyl lactames, see ref. 3. For a racemic protocol, see: J. Yu, J. Cui and C. Zhang, *Eur. J. Org. Chem.*, 2010, 7020.

13 For selected examples, see: *(a)* A. W. Pilling, J. Böhmer and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2007, **46**, 5428; *(b)* A. W. Pilling, J. Böhmer and D. J. Dixon, *Chem Commun.*, 2008, 832; *(c)* J. Franzén and A. Fisher, *Angew. Chem., Int. Ed.*, 2009, **48**, 787; *(d)* Z. Jin, X. Wang, H. Huang, X. Liang and J. Ye, *Org. Lett.*, 2011, **13**, 564.
14 S. Takechi, N. Kumagai and M. Shibasaki, *Tetrahedron Lett.*, 2011, **52**, 2140.
15 *(a)* A. Lattanzi, P. Iannece, A. Vicinanza and A. Scettri, *Chem. Commun.*, 2003, 1440; *(b)* A. Lattanzi, *Org. Lett.*, 2005, **7**, 2579; *(c)* A. Lattanzi, S. Piccirillo and A. Scettri, *Adv. Synth. Catal.*, 2007, **349**, 357; *(d)* A. Russo, G. Galdi, G. Croce and A. Lattanzi, *Chem. Eur. J.*, 2012, **18**, 6152.
16 C. Pan, X. Zeng, Y. Guan, X. Jiang, L. Li and H. Zhang, *Synlett*, 2011, 425.
17 When using (1*R*,2*R*)-*trans*-amino indanol as catalyst under the same reaction conditions, racemic product **3a** was isolated in 56% yield.
18 CCDC-906681 contains the supplementary crystallographic data for compound **3b**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
19 *(a)* G. Peris, C. E. Jakobsche and S. J. Miller, *J. Am. Chem. Soc.*, 2007, **129**, 8710; *(b)* C. E. Jakobsche, G. Peris and S. J. Miller, *Angew. Chem., Int. Ed.*, 2008, **47**, 6707.
20 G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Marko and K. B. Sharpless, *J. Am. Chem. Soc.*, 1989, **111**, 8069.
21 *(a)* M. M. Sanchez Duque, O. Baslé, N. Isambert, A. Gaudel-Siri, Y. Génisson, J.-C. Plaquevent, J. Rodriguez and T. Constantieux, *Org. Lett.*, 2011, **13**, 3296. On the role of the amido group in organocatalysed asymmetric reactions, see also: *(b)* O. Baslé, W. Raimondi, M. M. Sanchez Duque, D. Bonne, T. Constantieux and J. Rodriguez, *Org. Lett.*, 2010, **12**, 5246.

Graphical Abstract



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