Organocatalytic peroxy-asymmetric allylic alkylation†

Xin Feng,[a] Yu-Qing Yuan,[b] Hai-Lei Cui,[a] Kun Jiang[a] and Ying-Chun Chen*[a]

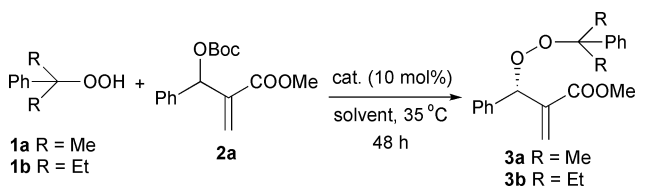
Received 19th June 2009, Accepted 17th July 2009
First published as an Advance Article on the web 31st July 2009
DOI: 10.1039/b912110b

The peroxy-asymmetric allylic alkylation of hydroperoxyalkanes with Morita–Baylis–Hillman carbonates was catalysed by modified cinchona alkaloids (up to 93% ee), from which chiral α-methylene-β-hydroxy esters could be efficiently derived.

The α-methylene-β-hydroxy esters, which contain both an α,β-unsaturated ester system and an allylic alcohol fragment, are useful compounds and are often employed for the synthesis of biologically important materials and natural products.[1] They are usually prepared *via* a Lewis base-catalysed aldol-type reaction of acrylates and aldehydes, the so-called Morita–Baylis–Hillman (MBH) reaction.[2] Much efforts have been devoted to the asymmetric MBH reaction over the past decades.[3] Nevertheless, the advancements for MBH reaction of acrylates are still far from satisfying.[4] A notable example was reported by Hatakeyama *et al.* who developed a highly enantioselective asymmetric MBH reaction of the activated 1,1,1,3,3,3-hexafluoroisopropyl acrylate and aldehydes catalysed by β-isocupreidine (β-ICD).[5] Chiral Lewis acid catalysts have also been employed for the asymmetric MBH reaction of acrylates, however, there were limitations for the enantioselectivity, chemical yields and generality of the substrates.[6] On the other hand, some indirect ways for the preparation of chiral α-methylene-β-hydroxy esters have been disclosed. Shimazaki *et al.* presented a tandem asymmetric aldol reaction and oxidative deselenisation to afford chiral α-methylene-β-hydroxy esters.[7] Connon *et al.* described the first nonenzymatic acylative kinetic resolution of MBH adducts.[8] Trost and co-workers have developed elegant deracemisation of MBH adducts catalysed by chiral Pd-complexes.[9] Therefore, the development of effective protocols to access enantiomerically pure α-methylene-β-hydroxy esters is still in demand.

Compounds that contain peroxide fragments are widely used in medical and chemical fields. Reliable approaches to peroxides, however, are extremely limited, especially for chiral peroxides.[10] Deng *et al.* have developed a highly enantioselective peroxidation of α,β-unsaturated ketones *via* iminium activation.[11] Very recently, we reported that commercially available cinchona alkaloids can act as excellent organocatalysts for asymmetric allylic alkylation (AAA) reactions with MBH carbonates.[12,13] It could be envisioned that an enantioselective peroxy-asymmetric allylic alkylation of hydroperoxyalkanes with MBH carbonates might be developed through the same strategy. Moreover, as outlined in Scheme 1, chiral α-methylene-β-hydroxy esters would be smoothly prepared from the corresponding chiral peroxides.

Table 1 Screening studies of organocatalytic peroxy-AAA reaction of hydroperoxyalkanes **1** and MBH carbonate **2a**[a]



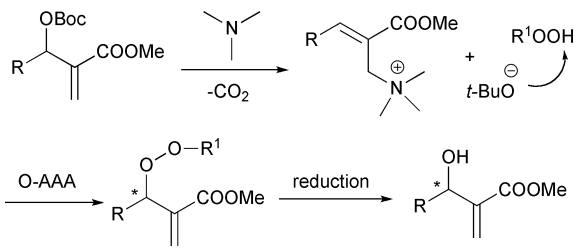
1a R = Me
1b R = Et

2a

3a R = Me
3b R = Et

Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1[d]	$(DHQD)_2AQN$	toluene	52	30
2	$(DHQD)_2AQN$	toluene	64	32
3	$(DHQD)_2PHAL$	toluene	60	82
4	$(DHQD)_2PYR$	toluene	63	79
5	$(DHQ)_2PHAL$	toluene	66	–80
6	$(DHQD)_2PHAL$	*m*-xylene	67	80
7	$(DHQD)_2PHAL$	mesitylene	67	82
8	$(DHQD)_2PHAL$	$PhCF_3$	74	82
9	$(DHQD)_2PHAL$	DCM	72	77
10	$(DHQD)_2PHAL$	DCE	65	77
11	$(DHQD)_2PHAL$	CCl_4	76	91
12[e]	$(DHQD)_2PHAL$	CCl_4	79	93
13[e]	$(DHQ)_2PHAL$	CCl_4	71	–90

[a] Unless noted otherwise, reactions were performed with 0.12 mmol of **1a**, 0.1 mmol of **2a**, 10 mol% of catalyst in 0.4 mL solvent for 48 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] At 50 °C. [e] **1b** was used.



Scheme 1 A tandem peroxy-AAA–reduction reaction to access chiral α-methylene-β-hydroxy esters.

The initial study was conducted with commercially available cumene hydroperoxide **1a** and MBH carbonate **2a** in toluene under the catalysis of $(DHQD)_2AQN$ at 50 °C. To our gratification, the desired peroxide **3a** was isolated in a moderate yield after 48 h, albeit in a poor ee value (Table 1, entry 1). A similar enantioselectivity was obtained at 35 °C but with a slightly better yield (entry 2). Subsequently, other modified cinchona alkaloids were screened at 35 °C. Good enantioselectivity (82% ee) was observed when $(DHQD)_2PHAL$ was used (entry 3), and $(DHQD)_2PYR$ showed similar enantiocontrol (entry 4). It

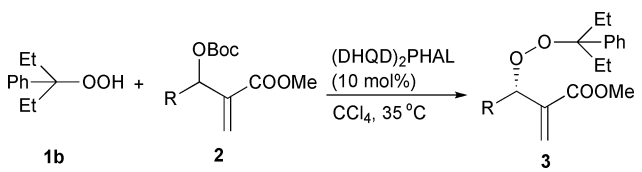
[a]*Key Laboratory of Drug-Targeting and Drug Delivery System of Education Ministry, Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu, 610041, China. E-mail: ycchenhuaxi@yahoo.com.cn; Fax: 86 28 85502609*
[b]*The Third Hospital of Chengdu, Chengdu, China*

† Electronic supplementary information (ESI) available: Experimental procedures, structural proofs, NMR spectra and HPLC chromatograms of the products. See DOI: 10.1039/b912110b

was pleasing that a good ee value was also obtained in the presence of $(DHQ)_2PHAL$, while the peroxide **3a** possesses the opposite configuration (entry 5). Encouraged by these results, we further investigated the effects of solvent by the catalysis of $(DHQD)_2PHAL$. Almost the same results were afforded in various arene solvents (entries 6–8). Although slightly decreased enantioselectivity was observed in DCM and DCE (entries 9 and 10), fortunately, a significantly improved enantioselectivity was gained when CCl_4 was utilised as the solvent (entry 11). Moreover, an excellent ee value (93% ee) was attained when a slightly more bulky hydroperoxyalkane **1b** was applied without affecting the reaction efficacy (entry 12). In addition, a satisfactory enantioselectivity could be obtained with $(DHQ)_2PHAL$ under the optimised conditions. Thus both enantiomers of the target peroxide could be available in a highly enantioenriched form.

Consequently, an array of MBH carbonates **2** were explored in the reactions with hydroperoxyalkane **1b** to establish the generality of this asymmetric transformation. The reactions were generally conducted in CCl_4 with 10 mol% of $(DHQD)_2PHAL$ at 35 °C. As summarised in Table 2, the electronic characteristics of MBH carbonates seemed to have limited effects on the enantioselectivity. Good to excellent ee values were obtained for a diversity of MBH carbonates bearing electron-withdrawing or -donating aryl groups, and moderate to good isolated yields were delivered (entries 1–9). In addition, heteroaryl-substituted MBH carbonates could be successfully applied, and excellent enantioselectivities were attained (entries 10 and 11).[14] On the other hand, we have tested more asymmetric reactions with $(DHQ)_2PHAL$, the peroxides **3d** and **3i** with the opposite configuration were also provided in high enantioselectivity (entries 12 and 13).

Table 2 Organocatalytic peroxy-AAA reaction of hydroperoxyalkane **1b** and MBH carbonates **2**[a]

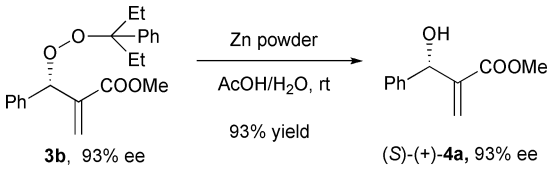


1b **2** **3**

Entry	R	3	t (h)	Yield[b] (%)	ee[c](%)
1	Ph	**3b**	48	79	93[d]
2	*p*-F-C_6H_4	**3c**	58	69	90[e]
3	*p*-Cl-C_6H_4	**3d**	58	71	89[e]
4	*m*-Cl-C_6H_4	**3e**	48	71	83[e]
5	3,4-Cl_2-C_6H_3	**3f**	46	73	88[e]
6	*p*-Me-C_6H_4	**3g**	50	65	86[e]
7	*m*-Me-C_6H_4	**3h**	47	67	92
8	*p*-MeO-C_6H_4	**3i**	47	73	93
9	3,4-methylene-dioxo-C_6H_3	**3j**	52	50	89
10	2-thienyl	**3k**	48	53	92[e]
11	2-furyl	**3l**	56	62	91
12[f]	*p*-Cl-C_6H_4	**3d**	58	72	–89
13[f]	*p*-MeO-C_6H_4	**3i**	56	65	–91[e]

[a] Unless noted otherwise, reactions were performed with 0.12 mmol of **1b**, 0.1 mmol of **2**, 10 mol % of $(DHQD)_2PHAL$ in 0.4 mL CCl_4 at 35 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configuration of **3b** was determined by comparison with literature optical rotation data after reduction with zinc powder (see Scheme 2). [e] Determined after conversion to the corresponding α-methylene-β-hydroxy ester. [f] $(DHQ)_2PHAL$ was used.

As illustrated in Scheme 2, the peroxo-allylic alkylation product **3b** could be efficiently converted to the corresponding α-methylene-β-hydroxy ester (*S*)-(+)-**4a** in high yield (93%) without any racemisation,[15] employing zinc powder as the reducing reagent in a mixture of acetic acid and water (1:1).



3b, 93% ee (*S*)-(+)-**4a**, 93% ee

Scheme 2 Synthesis of α-methylene-β-hydroxy ester.

In conclusion, we have developed the first peroxo-asymmetric allylic alkylation of bulky hydroperoxyalkanes with Morita–Baylis–Hillman (MBH) carbonates by the catalysis of commercially available modified cinchona alkaloids. The peroxides were generally obtained in high enantioselectivities (84–93% ee) in fair to good yields, from which the corresponding α-methylene-β-hydroxy esters could be smoothly derived without affecting the optical purity. Currently, the further application of modified cinchona alkaloids in other asymmetric allylic alkylations is under investigation in this laboratory.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (20772084).

Notes and references

1 (*a*) Y. Iwabuchi, T. Sugihara, T. Esumi and S. Hatakeyama, *Tetrahedron Lett.*, 2001, **42**, 7867; (*b*) Y. Iwabuchi, M. Furukawa, T. Esumi and S. Hatakeyama, *Chem. Commun.*, 2001, 2030; (*c*) V. Singh and S. Batra, *Tetrahedron*, 2008, **64**, 4511.

2 For reviews on the Morita–Baylis–Hillman reaction, see: (*a*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811; (*b*) P. Langer, *Angew. Chem., Int. Ed.*, 2000, **39**, 3049; (*c*) D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron*, 1996, **52**, 8001; (*d*) D. Basavaiah, K. V. Rao and R. J. Reddy, *Chem. Soc. Rev.*, 2007, **36**, 1581.

3 For reviews, see: (*a*) G. Masson, C. Housseman and J.-P. Zhu, *Angew. Chem., Int. Ed*, 2007, **46**, 4614; (*b*) T. Kataoka and H. Kinoshita, *Eur. J. Org. Chem.*, 2005, 45; for selected recent examples, see: (*c*) N. T. McDougal, W. L. Trevellini, S. A. Rodgen, L. T. Kliman and S. E. Schaus, *Adv. Synth. Catal.*, 2004, **346**, 1231; (*d*) N. T. McDougal and S. E. Schaus, *J. Am. Chem. Soc.*, 2003, **125**, 12094; (*e*) M. Shi and X.-G. Liu, *Org. Lett.*, 2008, **10**, 1043; (*f*) F. J. S. Duarte, E. J. Cabrita, G. Frenking and A. G. Santos, *Chem.–Eur. J.*, 2009, **15**, 1734; (*g*) A. Berkessel, K. Roland and J. M. Neudörfl, *Org. Lett.*, 2006, **8**, 4195; (*h*) J. Wang, H. Li, X. Yu, L. Zu and W. Wang, *Org. Lett.*, 2005, **7**, 4293; (*i*) J. E. Imbriglio, M. M. Vasbinder and S. J. Miller, *Org. Lett.*, 2003, **5**, 3471.

4 For selected examples of asymmetric MBH reactions of acrylates, see: (*a*) M. Shi and J.-K. Jiang, *Tetrahedron: Asymmetry*, 2002, **13**, 1941; (*b*) I. E. Markó, P. R. Giles and N. J. Hindley, *Tetrahedron*, 1997, **53**, 1015; (*c*) L. J. Brzezinski, S. Rafel and J. W. Leahy, *J. Am. Chem. Soc.*, 1997, **119**, 4317; (*d*) B. Pégot, G. Vo-Thanh, D. Gori and A. Loupy, *Tetrahedron Lett.*, 2004, **45**, 6425; (*e*) T. Oishi, H. Oguri and M. Hirama, *Tetrahedron: Asymmetry*, 1995, **6**, 1241; (*f*) T. Hayase, T. Shibata, K. Soai and Y. Wakatsuki, *Chem. Commun.*, 1998, 1271; (*g*) B. K. Senapati, G.-S. Hwang, S. Lee and D. H. Ryu, *Angew. Chem., Int. Ed*, 2009, **48**, 4398; (*h*) H. Tang, G. Zhao, Z. Zhou, P. Gao, L. He and C. Tang, *Eur. J. Org. Chem.*, 2008, 126; (*i*) S. I. Pereira, J. Adrio, A. M. S. Silva and J. C. Carretero, *J. Org. Chem.*, 2005, **70**, 10175; (*j*) S. Garre, E. Parker, B. Ni and A. D. Headley, *Org. Biomol. Chem.*, 2008, **6**, 3041.

5 (*a*) Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatakeyama, *J. Am. Chem. Soc.*, 1999, **121**, 10219; (*b*) A. Nakano, M. Ushiyama, Y. Iwabuchi and S. Hatakeyama, *Adv. Synth. Catal.*, 2005, **347**, 1790; (*c*) A. Nakano, S. Kawahara, S. Akamatsu, K. Morokuma, M. Nakatani, Y. Iwabuchi, K. Takahashi, J. Ishihara and S. Hatakeyama, *Tetrahedron*, 2006, **62**, 381; (*d*) A. Nakano, K. Takahashi, J. Ishihara and S. Hatakeyama, *Org. Lett.*, 2006, **8**, 5357.
6 K.-S. Yang, W.-D. Lee, J.-F. Pan and K. Chen, *J. Org. Chem.*, 2003, **68**, 915.
7 I. Shiina, Y.-S. Yamai and T. Shimazaki, *J. Org. Chem.*, 2005, **70**, 8103.
8 C. Ó. Dláigh and S. J. Connon, *J. Org. Chem.*, 2007, **72**, 7066.
9 (*a*) B. M. Trost, H.-C. Tsui and F. D. Toste, *J. Am. Chem. Soc.*, 2000, **122**, 3534; (*b*) B. M. Trost and M. K. Brennan, *Org. Lett.*, 2007, **9**, 3961.
10 (*a*) P. H. Dussault, T. K. Trullinger and F. Noor-e-Ain, *Org. Lett.*, 2002, **4**, 4591; (*b*) P. K. Dussault, C. T. Eary and K. R. Woller, *J. Org. Chem.*, 1999, **64**, 1789; (*c*) T. G. Driver, J. R. Harris and K. A. Woerpel, *J. Am. Chem. Soc.*, 2007, **129**, 3836; (*d*) M. Kawanishi, N. Kotoku, S. Itagaki, T. Horii and M. Kobayashi, *Bioorg. Med. Chem.*, 2004, **12**, 5297.
11 X.-J. Lu, Y. Liu, B.-F. Sun, B. Cindric and L. Deng, *J. Am. Chem. Soc.*, 2008, **130**, 8134.
12 (*a*) H.-L. Cui, J. Peng, X. Feng, W. Du, K. Jiang and Y.-C. Chen, *Chem.–Eur. J.*, 2009, **15**, 1574; (*b*) K. Jiang, J. Peng, H.-L. Cui and Y.-C. Chen, *Chem. Commun.*, 2009, 3955; (*c*) H.-L. Cui, X. Feng, J. Peng, J. Lei, K. Jiang and Y.-C. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, DOI: 10.1002/anie.200902093.
13 For other Lewis-base catalysed allylic alkylation of MBH adducts, see: (*a*) J. H. Gong, H. R. Kim, E. K. Ryu and J. N. Kim, *Bull. Korean Chem. Soc.*, 2002, **23**, 789; (*b*) C.-W. Cho and M. J. Krische, *Angew. Chem., Int. Ed*, 2004, **43**, 6689; (*c*) C.-W. Cho, J.-R. Kong and M. J. Krische, *Org. Lett.*, 2004, **6**, 1337; (*d*) Y. Du, X. Han and X. Lu, *Tetrahedron Lett.*, 2004, **45**, 4967; (*e*) D. J. V. C. van Steenis, T. Marcelli, M. Lutz, A. L. Spek, J. H. van Maarseveen and H. Hiemstra, *Adv. Synth. Catal.*, 2007, **349**, 281; (*f*) Y.-Q. Jiang, Y.-L. Shi and M. Shi, *J. Am. Chem. Soc.*, 2008, **130**, 7202; (*g*) G.-N. Ma, S.-H. Cao and M. Shi, *Tetrahedron: Asymmetry*, 2009, **20**, 1086.
14 MBH carbonates derived from aliphatic aldehydes exhibit much lower reactivity toward **1b** under the current catalytic system.
15 J. N. Kim, H. J. Lee and J. H. Gong, *Tetrahedron Lett.*, 2002, **43**, 9141.

