ORGANIC LETTERS

2013
Vol. 15, No. 13
3350–3353

Design of Chiral Bifunctional Quaternary Phosphonium Bromide Catalysts Possessing an Amide Moiety

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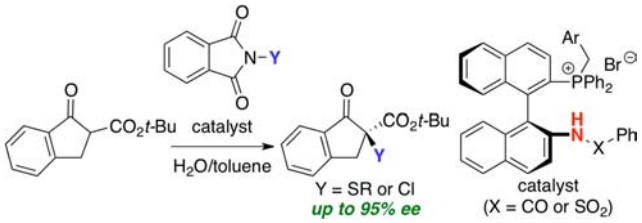
Received May 17, 2013

ABSTRACT



Novel bifunctional quaternary phosphonium bromides possessing an amide moiety were designed for the highly enantioselective sulfenylation and chlorination of β-ketoesters under base-free phase-transfer conditions. The tuning of an amide moiety of the catalyst was crucial to achieve high reactivity and enantioselectivity.

Asymmetric phase-transfer catalysis has been recognized as a powerful method for producing useful chiral compounds, and various types of chiral quaternary onium salts have been developed for this purpose in the past two decades.[1] In these areas, the design of bifunctional catalysts has obtained much attention in recent years,[2−5] and further advances in the design of structurally well-defined bifunctional chiral onium salts are highly desirable for achieving truly efficient asymmetric phase-transfer reactions. In the course of our design of effective chiral bifunctional phase-transfer catalysts, we recently reported a valuable set of chiral bifunctional quaternary phosphonium salts of type (*S*)-**1**, which possess a hydroxy group; these were easily synthesized from commercially available chiral phosphine compounds (Figure 1).[4e] In this study, we

(1) For recent reviews on asymmetric phase-transfer catalysis, see: (a) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3. (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (d) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (e) Vachon, J.; Lacour, J. *Chimia* **2006**, *60*, 266. (f) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222. (g) Ooi, T.; Maruoka, K. *Aldrichimica Acta* **2007**, *40*, 77. (h) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. (i) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679. (j) Jew, S.-s.; Park, H.-g. *Chem. Commun.* **2009**, 7090. (k) Maruoka, K. *Chem. Rec.* **2010**, *10*, 254. (l) Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4312.

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(4) For base-free phase-transfer reactions with chiral bifunctional phase-transfer catalysts, see: (a) He, R.; Shirakawa, S.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 16620. (b) Wang, L.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5327. (c) Shirakawa, S.; Terao, S. J.; He, R.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 10557. (d) Shirakawa, S.; Ota, K.; Terao, S. J.; Maruoka, K. *Org. Biomol. Chem.* **2012**, *10*, 5753. (e) Shirakawa, S.; Kasai, A.; Tokuda, T.; Maruoka, K. *Chem. Sci.* **2013**, *4*, 2248. See also: (f) Shirakawa, S.; Wang, L.; Kasai, A.; Maruoka, K. *Chem.—Eur. J.* **2012**, *18*, 8588.

(5) For examples of chiral bifunctional phase-transfer catalysts possessing amide groups, see: (a) Manabe, K. *Tetrahedron Lett.* **1998**, *39*, 5807. (b) Manabe, K. *Tetrahedron* **1998**, *54*, 14465. (c) Köhler, M. PhD Thesis, RWTH Aachen, Germany, 2003. (d) Ohmatsu, K.; Kiyokawa, M.; Ooi, T. *J. Am. Chem. Soc.* **2011**, *133*, 1307. (e) Johnson, K. M.; Rattley, M. S.; Sladojevich, F.; Barber, D. M.; Nuñez, M. G.; Goldys, A. M.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 2492. (f) Cao, D.; Chai, Z.; Zhang, J.; Ye, Z.; Xiao, H.; Wang, H.; Chen, J.; Wu, X.; Zhao, G. *Chem. Commun.* **2013**, *49*, 5972. See also: (g) Bernal, P.; Fernández, R.; Lassaletta, J. M. *Chem.—Eur. J.* **2010**, *16*, 7714. (h) Wang, H.-Y.; Chai, Z.; Zhao, G. *Tetrahedron* **2013**, *69*, 5104. (i) Li, M.; Woods, P. A.; Smith, M. D. *Chem. Sci.* **2013**, *4*, 2907.

10.1021/ol4013926
Published on Web 06/13/2013

reported that the hydroxy group of catalyst (*S*)-**1** was crucial for obtaining high enantioselectivity in the conjugate additions of 3-substituted oxindoles. Based on this observation, we became interested in the design of new bifunctional phosphonium salts[6,7] of type (*S*)-**2** and (*S*)-**3**, which possess an amide moiety instead of a hydroxy group.[5] The acidity of the amide (NH) in these catalysts can be easily tuned by introducing different substituents to the nitrogen (X−R). Additionally, the steric environment of the catalysts (*S*)-**2** and **3** can be controlled by tuning the steric size of the R group on the amide moiety as well as the aryl methyl group on the phosphorus (Figure 1). Here we report the design of new effective bifunctional phosphonium salts for the asymmetric sulfenylation[8] and chlorination[9] of β-ketoesters under base-free phase-transfer conditions.[4]

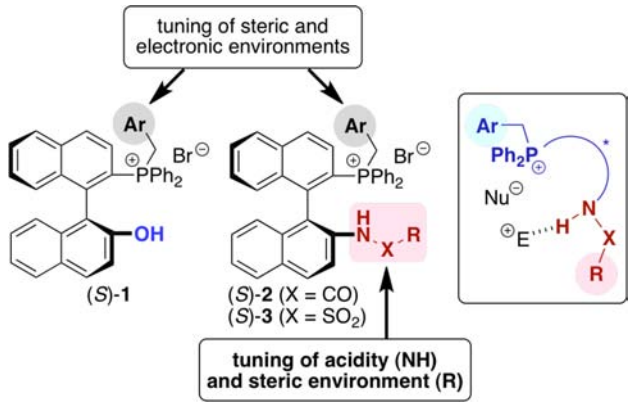

Figure 1. Bifunctional quaternary phophonium salts and a possible working model.

As a model reaction to examine the ability of bifunctional phosphonium salts **1**−**3**, the asymmetric sulfenylation of 1-oxo-2-indanecarboxylate with *N*-(phenylthio)phthalimide was selected (Table 1). In this reaction, the β-ketoester is activated by the phosphonium bromide to produce a phosphonium enolate intermediate, and the carbonyl groups of *N*-(phenylthio)phthalimide can potentially interact with the amide moiety (NH) of catalysts (*S*)-**2** and **3** via hydrogen-bonding.[2] Although several examples of asymmetric sulfenylation of β-ketoesters have been reported, none of them have succeeded in the sulfenylation of 1-oxo-2-indanecarboxylate in a highly enantioselective manner.[8]

The reaction between *tert*-butyl 1-oxo-2-indanecarboxylate and *N*-(phenylthio)phthalimide in H_2O/toluene (10:1) took place in the presence of hydroxylated (*S*)-**1a**[4e] (1 mol %) at room temperature (25 °C) over 24 h and afforded the sulfenylation product **4a** in good yield with moderate enantioselectivity (82% yield, 42% ee, entry 1 in Table 1). On the other hand, hydroxy-protected catalyst (*S*)-**1b** (R = Me) gave the product **4a** in low yield and enantioselectivity (29% yield, 17% ee, entry 2). These results suggested that the bifunctional design of the catalysts was benefiting the reaction. The screening of different aryl methyl groups on the phosphorus of (*S*)-**1** did not show significant improvement of the enantioselectivity (entries 3 and 4). These results prompted us to examine the chiral bifunctional phosphonium bromides possessing an amide moiety (*S*)-**2** and **3**, which were easily synthesized from known chiral phosphine compounds.[10] To our delight, benzamide substituted catalyst (*S*)-**2a** gave the product **4a** with high enantioselectivity (92% ee, entry 5), and further screening of the aryl methyl group of the catalyst (**2b** and **c**, entries 6 and 7) improved the yield and enantioselectivity further (98% yield, 94% ee, entry 7). A change of the benzamide group in the catalyst to acetamide (**2d**), pivalamide (**2e**), and sulfonamides (**3a** and **b**) reduced both the yields and enantioselectivities (entries 8−11). These results indicated that fine-tuning of the amide moiety of the catalyst was important to achieve high enantioselectivity. The absolute configuration of product **4a** was determined by X-ray diffraction analysis (Figure 2).[11]

With an effective chiral bifunctional quaternary phosphonium salt (*S*)-**2c** in hand, we studied the substrate generality of the asymmetric sulfenylation of various 1-oxo-2-indanecarboxylates under base-free phase-transfer

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(9) (a) Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425. (b) Ibrahim, H.; Kleinbeck, F.; Togni, A. *Helv. Chim. Acta* **2004**, *87*, 605. (c) Marigo, M.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem.—Eur. J.* **2004**, *10*, 2133. (d) Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4204. (e) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6219. (f) Shibatomi, K.; Tsuzuki, Y.; Iwasa, S. *Chem. Lett.* **2008**, *37*, 1098. (g) Kawatsura, M.; Hayashi, S.; Komatsu, Y.; Hayase, S.; Itoh, T. *Chem. Lett.* **2010**, *39*, 466. (h) Qi, M.-H.; Wang, F.-J.; Shi, M. *Tetrahedron: Asymmetry* **2010**, *21*, 247. (i) Etayo, P.; Badorrey, R.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Adv. Synth. Catal.* **2010**, *352*, 3329. (j) Cai, Y.; Wang, W.; Shen, K.; Wang, J.; Hu, X.; Lin, L.; Liu, X.; Feng, X. *Chem. Commun.* **2010**, *46*, 1250. (k) Hintermann, L.; Perseghini, M.; Togni, A. *Beilstein J. Org. Chem.* **2011**, *7*, 1421. (l) Jiang, J.-J.; Huang, J.; Wang, D.; Yuan, Z.-L.; Zhao, M.-X.; Wang, F.-J.; Shi, M. *Chirality* **2011**, *23*, 272. (m) Shibatomi, K.; Soga, Y.; Narayama, A.; Fujisawa, I.; Iwasa, S. *J. Am. Chem. Soc.* **2012**, *134*, 9836. (n) Luo, J.; Wu, W.; Xu, L.-W.; Meng, Y.; Lu, Y. *Tetrahedron Lett.* **2013**, *54*, 2623.

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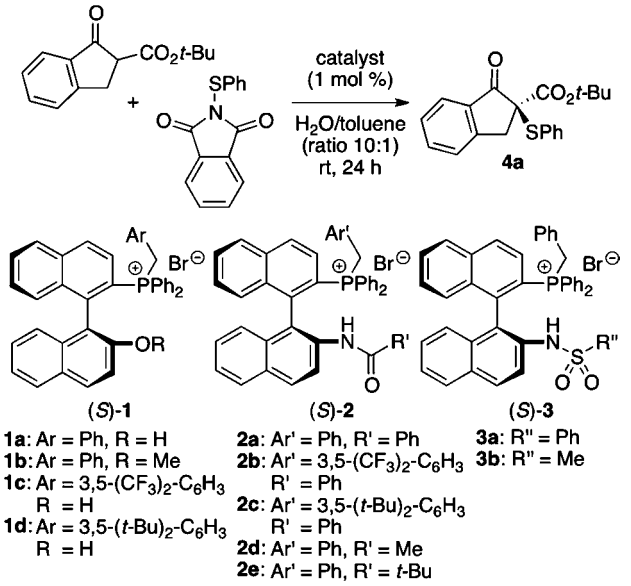
(11) The crystal structure of **4a** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 935041). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Effect of Catalysts[a]



entry	catalyst	yield (%)[b]	ee (%)[c]
1	(*S*)-**1a**	82	42
2	(*S*)-**1b**	29	17
3	(*S*)-**1c**	60	44
4	(*S*)-**1d**	98	48
5	(*S*)-**2a**	80	92
6	(*S*)-**2b**	80	94
7	(*S*)-**2c**	98	94
8	(*S*)-**2d**	38	84
9	(*S*)-**2e**	56	5
10	(*S*)-**3a**	5	60
11	(*S*)-**3b**	6	48

[a] Reaction conditions: *tert*-Butyl 1-oxo-2-indanecarboxylate (0.050 mmol), *N*-(phenylthio)phthalimide (0.060 mmol) in the presence of catalyst (1 mol %) in H_2O (2 mL)/toluene (0.2 mL) at room temperature (25 °C) for 24 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.

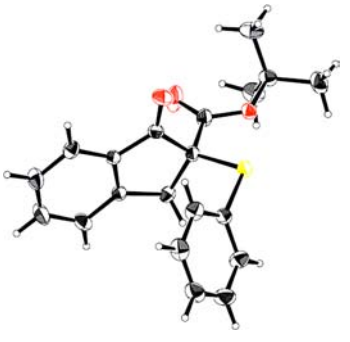
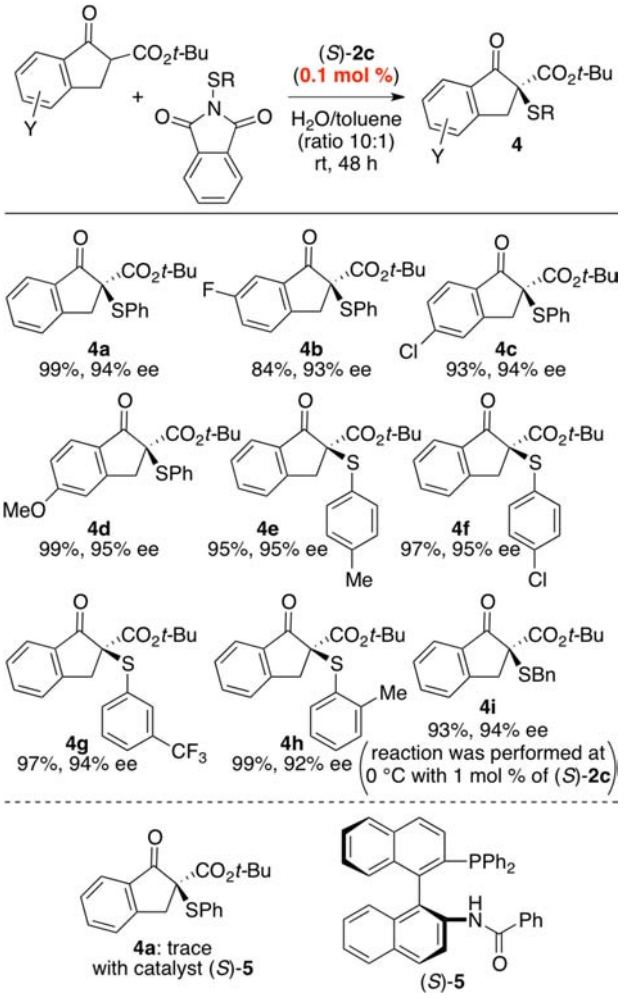


Figure 2. X-ray crystal structure of **4a**.

conditions (Scheme 1). To demonstrate the practicality of the present reaction, only 0.1 mol % of the chiral catalyst (*S*)-**2c** was used in these asymmetric sulfenylations. The introduction of electron-withdrawing and -donating substituents to the aromatic ring of 1-oxo-2-indanecarboxylate uniformly gave the products (**4a**–**d**) in excellent yields and enantioselectivities (93–95% ee) at low catalyst loadings. Furthermore, a variety of *N*-(arylthio)- and *N*-(benzylthio)-phthalimides were tolerated in the reaction, giving the products **4e**–**i** with high enantioselectivities (92–95% ee). It should be noted that triarylphosphine catalyst (*S*)-**5** did not show any catalytic activity in the present reaction; i.e., the quaternary phosphonium bromide moiety of catalyst (*S*)-**2c** was essential for the sulfenylation. Also, the reactions under homogeneous conditions in toluene without H_2O proceeded very sluggishly, indicating the importance of the coexistence of H_2O.[4]

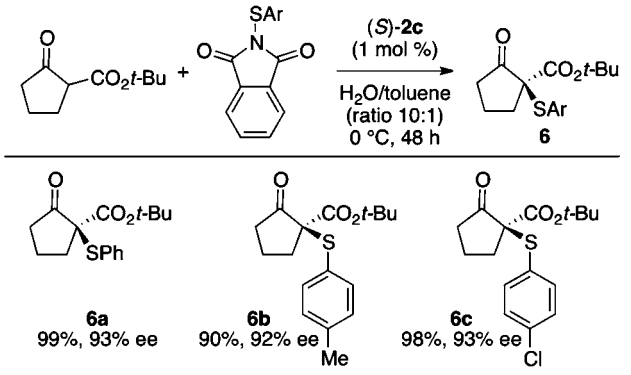
Scheme 1. Asymmetric Sulfenylation of 1-Oxo-2-indanecarboxylates



The asymmetric sulfenylations of *tert*-butyl 2-oxocyclopentanecarboxylate with *N*-(arylthio)phthalimides were also examined (Scheme 2), and sulfenylation products **6a**–**c** were obtained with high enantioselectivities (92–93% ee).[12] The absolute configuration of product **6a** was confirmed

(12) Unfortunately, 2-oxocyclohexanecarboxylates and acyclic β-ketoesters showed low reactivity under similar reaction conditions.

Scheme 2. Asymmetric Sulfenylation of 2-Oxocyclopentanecarboxylate

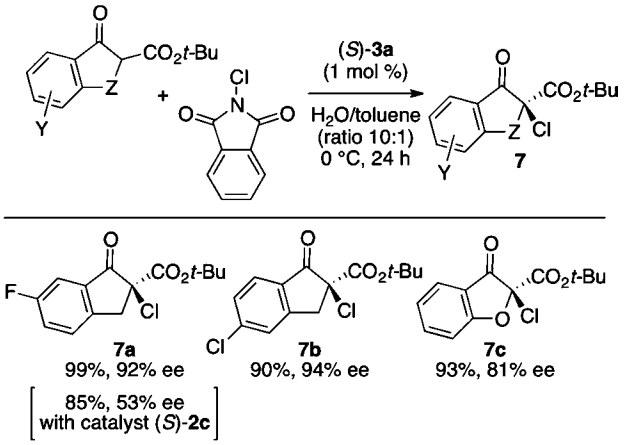


by comparison of the optical rotation with the literature value.[8b,e]

To further expand the synthetic utility of our bifunctional quaternary phosphonium bromides with an amide moiety, we also examined the asymmetric chlorination of β-ketoesters under base-free phase-transfer conditions (Scheme 3).[9] Although the reaction with benzamide substituted catalyst (*S*)-**2c** gave product **7a** with moderate enantioselectivity (53% ee), benzenesulfonamide substituted catalyst (*S*)-**3a** improved the enantioselectivity to give the chlorination product **7a** in high yield and enantioselectivity (92% ee).[13] These results suggest that the tunable acidity of an amide moiety of the catalyst could open up further possibilities for realizing other types of asymmetric transformation using these bifunctional catalysts. Various β-ketoesters could be employed for the chlorination with catalyst (*S*)-**3a**, and products **7b** and **7c** were obtained with good to high enantioselectivity (81−94% ee). The absolute configuration of product **7b** was confirmed by comparison of the optical rotation with the literature value.[9h,l,n]

(13) pK_a of amides in DMSO: $PhCONH_2$, 23.3; $PhSO_2NH_2$, 16.1. Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T.-Y.; Satish, A. V.; Whang, Y. E. *J. Org. Chem.* **1990**, *55*, 3330.

Scheme 3. Asymmetric Chlorination of β-Ketoesters



In summary, we have successfully designed novel bifunctional quaternary phosphonium salts that possess an amide moiety which function as effective chiral phase-transfer catalysts. These catalysts were applied in the highly enantioselective sulfenylation and chlorination of β-ketoesters under base-free phase-transfer conditions, and we found that fine-tuning of an amide moiety of the catalyst was important to achieve efficient asymmetric reactions. Further application of these bifunctional phosphonium bromides to other asymmetric reactions is currently underway in our group.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from JSPS and MEXT (Japan).

Supporting Information Available. Experimental details, characterization data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.