

Rh(I)-Catalyzed Asymmetric 1,2-Addition to α -Diketones with Chiral Sulfur–Alkene Hybrid Ligands

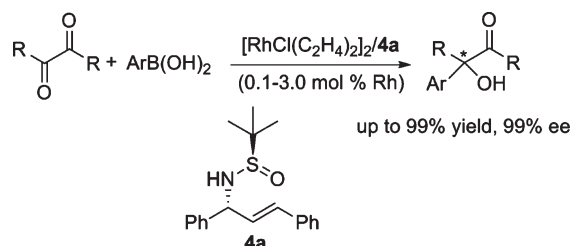
Xiangqing Feng,[†] Yanzhao Nie,[‡] Jing Yang,^{*,‡} and Haifeng Du^{*,†}

Beijing National Laboratory of Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China, and State Key Laboratory of Chemical Resource, College of Life Science and Technology, Beijing University of Chemical Technology, Beijing 100029, China

haifengdu@iccas.ac.cn; yangjingbuct@gmail.com

Received December 6, 2011

ABSTRACT



This paper describes a Rh(I)-catalyzed highly efficient and enantioselective 1,2-addition of arylboronic acids to α -diketones with the use of a simple sulfur–alkene hybrid ligand. With as low as a 0.1 mol % catalyst loading, a variety of optically active α -hydroxyketones can be furnished in high yields with excellent ee's.

The transition-metal-catalyzed nucleophilic addition of organometallic reagents to carbonyl compounds has become an extremely useful method for alcohol synthesis.¹ Especially, when using vicinal dicarbonyl compounds as substrates, such as α -ketoesters,² isatins,³ and α -diketones,⁴ nucleophilic addition will produce tertiary

α -hydroxy carbonyl compounds which are very important moieties contained in a number of biologically active compounds and which also have a wide application in synthetic chemistry.^{5,6} The catalytic asymmetric version of such a transformation will furnish highly desirable optically active tertiary α -hydroxy carbonyl compounds, and some important progress has already been achieved: for example, the Rh(I)-catalyzed asymmetric addition of organoboronic acids to α -ketoesters using spriophosphite

[†] Chinese Academy of Sciences.

[‡] Beijing University of Chemical Technology.

(1) For leading reviews, see: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774.

(2) (a) He, P.; Lu, Y.; Dong, C.-G.; Hu, Q.-S. *Org. Lett.* **2007**, *9*, 343. (b) He, P.; Lu, Y.; Hu, Q.-S. *Tetrahedron Lett.* **2007**, *48*, 5283. (c) Duan, H.-F.; Xie, J.-H.; Qiao, X.-C.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4351. (d) Hameury, T.; Guillemont, J.; Hifft, L. V.; Bellosta, V. *Org. Lett.* **2009**, *11*, 2397. (e) Cai, F.; Pu, X.; Qi, X.; Lynch, V.; Radha, A.; Ready, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 18066.

(3) (a) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353. (b) Toullec, P. Y.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2006**, *8*, 2715. (c) Lai, H.; Huang, Z.; Wu, Q.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 283. (d) Liu, Z.; Gu, P.; Shi, M.; McDowell, P.; Li, G. *Org. Lett.* **2011**, *13*, 2314.

(4) (a) Oi, S.; Moro, M.; Furuhashi, H.; Kawanishi, T.; Inoue, Y. *Tetrahedron* **2003**, *59*, 4351. (b) Miyamura, S.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 2255. (c) Ganci, G. R.; Chisholm, J. D. *Tetrahedron Lett.* **2007**, *48*, 8266.

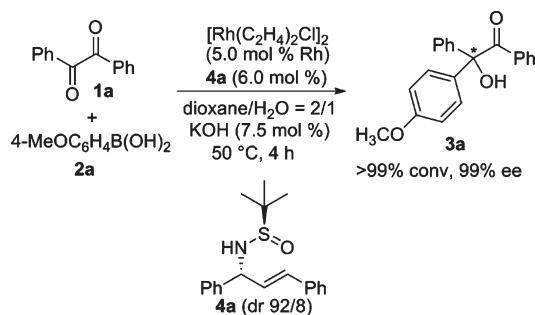
(5) For examples on Lewis acid catalyzed addition to vicinal dicarbonyl compounds, see: (a) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451. (b) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668. (c) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946. (d) Shintani, R.; Takastu, K.; Hayashi, T. *Chem. Commun.* **2010**, *46*, 6822. (e) Hanhan, N. V.; Sahin, A. H.; Chang, T. W.; Fetting, J. C.; Franz, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 744.

(6) For a leading review, see: (a) Coppola, G. M.; Schuster, H. F. *α -Hydroxy Acids in Enantioselective Synthesis*; Wiley-VCH: Weinheim, 1997. For selected examples, see: (b) Kiesewetter, D. O.; Silverton, J. V.; Eckelman, W. C. *J. Med. Chem.* **1995**, *38*, 1711. (c) Tokunaga, T.; Hume, W. E.; Umezono, T.; Okazaki, K.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H.; Nagata, R. *J. Med. Chem.* **2001**, *44*, 4641. (d) González, A.; Quirante, J.; Nieto, J.; Almeida, M. R.; Saraiva, M. J.; Planas, A.; Arsequell, G.; Valencia, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5270.

or allene-containing phosphine ligands by Zhou^{2c} (up to 93% ee) or Reddy^{2e} (up to 95% ee), and the Rh(I)-catalyzed addition to isatins using MeO-mop ligands by Hayashi^{3a} (up to 93% ee). However, to the best of our knowledge, no successful examples of transition-metal-catalyzed asymmetric addition of organometallic reagents to α -diketones are known,⁷ although the non-asymmetric version with arylstannanes or arylboronic acids has already been reported in 2003 and 2007, respectively.⁴ Searching for an effective chiral catalyst to overcome the challenge remaining in this asymmetric transformation is therefore of great importance.

To realize the challenging asymmetric 1,2-addition to α -diketones, a suitable chiral ligand is thus essential. As part of our ongoing project on the development of novel alkene ligands,^{8–11} recently, we found that simple sulfur–alkene hybrid ligands derived from chiral *tert*-butanesulfinamide¹² were effective for Rh(I)-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β -unsaturated carbonyl compounds.^{13–15} To our pleasure, we found that chiral sulfur–alkene hybrid ligands were also highly effective for Rh(I)-catalyzed 1,2-additions to α -diketones with as low as a 0.1 mol % catalyst loading to afford optically active tertiary α -hydroxyketones. Herein, we report our preliminary results on this subject.

Scheme 1. Initial Study on Rh(I)-Catalyzed Asymmetric Addition of 4-Methoxyphenylboronic Acid (**2a**) to Benzil (**1a**)



(7) During our preparation of the current manuscript, Xu and co-workers reported a similar work using 3.0 mol % catalyst; see: Zhu, T.-S.; Jin, S.-S.; Xu, M.-H. *Angew. Chem., Int. Ed.* DOI: 10.1002/anie.201106972.

(8) For leading reviews on chiral alkene ligands, see: (a) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364. (b) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840. (c) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482. (d) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31. (e) Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *Synlett* **2011**, 1345.

(9) For pioneering examples on chiral alkene ligands, see: (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.

(10) For leading references on chiral alkene ligands, see: (a) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (b) Gendrineau, T.; Chuzel, O.; Eijlsberg, H.; Genet, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669. (c) Luo, Y.; Carnell, A. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2750. (d) Pattison, G.; Piraux, G.; Lam, H. W. *J. Am. Chem. Soc.* **2010**, *132*, 14373. (e) Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhrer, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H. *Chem.—Eur. J.* **2004**, *10*, 4198. (f) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611. (g) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**,

Table 1. Optimization of Reaction Conditions for Rh(I)-Catalyzed Asymmetric Addition of 4-Methoxyphenylboronic Acid (**2a**) to Benzil (**1a**)^a

entry	cat. loading (mol %)	base	time (h)	temp (°C)	conv (%) ^b	ee (%) ^c
1	5.0	KOH	4	50	>99	99
2	1.0	KOH	2	25	>99	99
3	1.0	Et ₃ N	2	25	55	99
4	1.0	K ₃ PO ₄	2	25	>99	99
5	1.0	K ₂ CO ₃	2	25	86	99
6	1.0	KF	2	25	75	99
7	0.1	KOH	24	25	51	99
8	0.1	KOH	3	50	>99	98
9	0.05	KOH	17	50	59	98
10	0.01	KOH	16	80	12	95

^a All reactions were carried out with **1a** (0.20 mmol), **2a** (0.30 mmol), catalyst loading as indicated (Rh/**4a** = 1/1.2), and base (1.5 equiv of Rh) in dioxane/H₂O (v/v = 2/1) (1.5 mL) unless other noted; for entries 7–10, reactions were run with **1a** (2.0 mmol) and **2a** (3.0 mmol) in dioxane/H₂O (v/v = 2/1) (3.0 mL). ^b The conversion was determined by crude ¹H NMR. ^c The ee was determined by chiral HPLC.

Under previously reported reaction conditions,¹⁵ ligand **4a** was initially subjected to the Rh(I)-catalyzed asymmetric addition of 4-methoxyphenylboronic acid (**2a**) to benzil (**1a**). We were pleased to find that the reaction went smoothly to afford the desired product **3a** in quantitative conversion with 99% ee (Scheme 1). This promising result encouraged us toward further optimization of the reaction conditions. As shown in Table 1, bases were found to have some impact on reactivity but not on enantioselectivity (entries 2–6). The activity of the Rh/**4a** catalyst proved to

46, 3139. (h) Maire, P.; Breher, F.; Schönberg, H.; Grützmacher, H. *Organometallics* **2005**, *24*, 3207. (i) Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143.

(11) For examples of alkene ligands developed by our group, see: (a) Hu, X.; Zhuang, M.; Cao, Z.; Du, H. *Org. Lett.* **2009**, *11*, 4744. (b) Hu, X.; Cao, Z.; Liu, Z.; Wang, Y.; Du, H. *Adv. Synth. Catal.* **2010**, *352*, 651. (c) Cao, Z.; Du, H. *Org. Lett.* **2010**, *12*, 2602. (d) Wang, Y.; Hu, X.; Du, H. *Org. Lett.* **2010**, *12*, 5482. (e) Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054. (f) Cao, Z.; Liu, Y.; Liu, Z.; Feng, X.; Zhuang, M.; Du, H. *Org. Lett.* **2011**, *13*, 2164. (g) Cao, Z.; Liu, Z.; Liu, Y.; Du, H. *J. Org. Chem.* **2011**, *76*, 6401. (h) Liu, Z.; Cao, Z.; Du, H. *Org. Biomol. Chem.* **2011**, *9*, 5369.

(12) For leading reviews, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39. (c) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A.; Ellman, J. A. *Chem. Soc. Rev.* **2009**, *38*, 1162. (d) Robak, M. T.; Herbace, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(13) For leading reviews on Rh-catalyzed 1,4-additions, see: (a) Hayashi, T. *Synlett* **2001**, 879. (b) Reference 1a–b. (c) Gennari, C.; Monti, C.; Piarulli, U. *Pure Appl. Chem.* **2006**, *78*, 303. (d) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279. (e) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093.

(14) For examples on S/alkene hybrid ligands, see: (a) Thaler, T.; Guo, L.-N.; Steib, A. K.; Raducan, M.; Karaghiosoff, K.; Mayer, P.; Knochel, P. *Org. Lett.* **2011**, *13*, 3182. (b) Jin, S.-S.; Wang, H.; Xu, M.-H. *Chem. Commun.* **2011**, *47*, 7230. (c) Qi, W.-Y.; Zhu, T.-S.; Xu, M.-H. *Org. Lett.* **2011**, *13*, 3410. (d) Chen, G.; Gui, J.; Li, L.; Liao, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7681. (e) Xue, F.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 7256.

(15) For examples on sulfur–alkene ligands developed in our group, see: (a) Feng, X.; Wang, Y.; Wei, B.; Yang, J.; Du, H. *Org. Lett.* **2011**, *13*, 3300. (b) Feng, X.; Wei, B.; Yang, J.; Du, H. *Org. Biomol. Chem.* **2011**, *9*, 5927. (c) Wang, Y.; Feng, X.; Du, H. *Org. Lett.* **2011**, *13*, 4954.

be high, and the reaction can still proceed efficiently to give product **3a** in quantitative conversion and 98% ee when the catalyst loading was reduced to 0.1 mol % (Table 1, entry 8). Even though the amount of catalyst was further reduced to 0.05 mol %, α -hydroxyketone **3a** can be still obtained in a reasonable yield without the loss of ee (Table 1, entry 9).

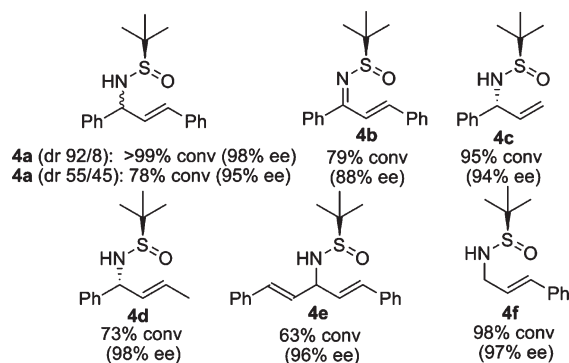


Figure 1. Evaluation of representative chiral sulfur–alkene hybrid ligands for Rh(I)-catalyzed asymmetric addition to benzil (**1a**).

A variety of representative chiral sulfur–alkene hybrid ligands were subsequently evaluated in the Rh(I)-catalyzed 1,2-additions to benzil (**1a**) under the optimal conditions (Table 1, entry 8). As shown in Figure 1, all these ligands proved to be effective for this enantioselective transformation. The chirality of carbon of **4a** affected the activity and selectivity slightly. Ligand **4b**^{15b} derived directly from the condensation of chiral *tert*-butanesulfinamide with chalcone showed reasonable activity and selectivity. Ligand **4c**^{15a} bearing a terminal alkene gave 95% conversion and 94% ee. Ligand **4f**^{15c} was found to be almost as effective as ligand **4a**.⁷

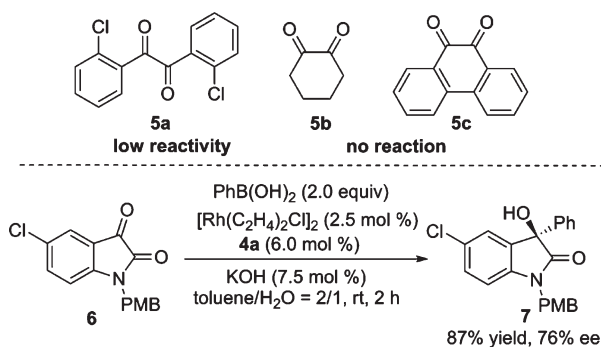
Encouraged by the aforementioned excellent results, the scope of arylboronic acids and α -diketones was subsequently investigated. As shown in Table 2, a variety of arylboronic acids were well tolerated for Rh(I)-catalyzed additions to benzil (**1a**) to give tertiary α -hydroxyketones in 56–99% yields with 96–99% ee's (entries 1–11). While only a 40% yield and 88% ee were obtained when using (*E*)-styrylboronic acid as a substrate (Table 2, entry 12), it was found that substituted diketones were also suitable substrates giving satisfactory results (Table 2, entries 13 and 14). 1,2-Di-(2-furyl or thienyl)-1,2-ethanedione exhibited excellent reactivity but gave poor ee's which might be partially due to the coordination of heteroatoms to rhodium (Table 2, entries 15 and 16). However, 2,2'-dichlorobenzil (**5a**) and cyclic α -diketones **5b** and **5c** were not suitable substrates for this addition (Scheme 2). To our delight, we found that the current catalytic system was also effective for the addition of phenylboronic acid to isatin **6** although the activity and selectivity still await further improvement (Scheme 2).

Table 2. Rh(I)-Catalyzed Asymmetric Addition of Arylboronic Acids to α -Diketones^a

entry	catalyst loading	time (h)	product	yield (%) ^b	ee (%) ^c
$\text{R}-\text{C}(=\text{O})-\text{C}(=\text{O})-\text{R} + \text{ArB}(\text{OH})_2 \xrightarrow[\text{dioxane/H}_2\text{O} (2/1), 50^\circ\text{C}]{[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2/\mathbf{4a}, \text{KOH} (1.5 \text{ equiv of Rh})} \text{R}-\text{C}(\text{OH})(\text{Ar})-\text{C}(=\text{O})-\text{R}$					
1	0.1 mol %	3		99	98
2	0.1 mol %	9		88	98
3	0.1 mol %	4		79	98
4	1.0 mol %	7		56	99
5	1.0 mol %	8		61	99
6	1.0 mol %	4		99	99
7	1.0 mol %	12		99	97
8	0.1 mol %	6		38	98
9	1.0 mol %	12		99	98
10	0.1 mol %	6		76	97
11	0.1 mol %	9		57	96
12	3.0 mol %	11		40	88
13	1.0 mol %	4		87	97
14	0.1 mol %	12		99	99
15	1.0 mol %	11		99	4
16	1.0 mol %	11		98	16

^a Reactions were carried out in 2.0 mmol scale and 3.0 mL of solvent for a 0.1 mol % catalyst loading and in 0.4 mmol scale and 1.5 mL of solvent for a 1.0 and 3.0 mol % catalyst loading at 50 °C. ^b Isolated yield. ^c The ee was determined by chiral HPLC.

Scheme 2. Rh(I)-Catalyzed Asymmetric Addition to Other α -Diketones or Isatins



In summary, using a simple chiral sulfur–alkene hybrid ligand, we have successfully developed a highly efficient

and enantioselective Rh(I)-catalyzed asymmetric addition of arylboronic acids to α -diketones with as low as a 0.1 mol % catalyst loading. Our study provides a useful method for the synthesis of important optically active tertiary α -hydroxyketones with high yields and ee's. Further application of the chiral sulfur–alkene ligand in other transition-metal-catalyzed enantioselective reactions is underway in our laboratory.

Acknowledgment. The authors are thankful for the financial support from the National Science Foundation of China (21072194, 21172222) and 973 program (2010CB833300).

Supporting Information Available. The procedure for rhodium-catalyzed additions, characterization of products, and data for the determination of enantiomeric excesses. This material is available free of charge via the Internet at <http://pubs.acs.org>.