Relay Catalysis by a Ruthenium Complex–Chiral Brønsted Acid Binary Sytem for Ternary Reaction Sequence Involving Enantioselective Pictet–Spengler-Type Cyclization as the Key Step

Yasunori Toda,[a] Masahiro Terada*[a,b]

[a] Department of Chemistry, Graduate School of Science, Tohoku University, Aoba-ku, Sendai 980-8578, Japan
Fax +81(22)7956602; E-mail: mterada@m.tohoku.ac.jp

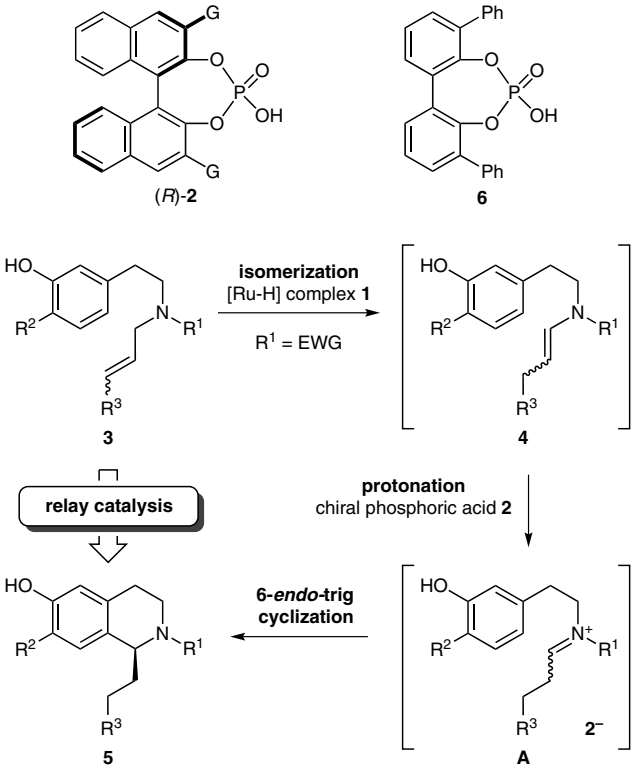
[b] Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Aoba-ku, Sendai 980-8578, Japan

Received: 04.01.2013; Accepted after revision: 01.02.2013

Abstract: Relay catalysis for a ternary reaction sequence composed of double-bond isomerization, protonation of the double bond, and enantioselective Pictet–Spengler-type cyclization was accomplished using a binary catalytic system consisting of a ruthenium hydride complex and a chiral phosphoric acid as the chiral Brønsted acid catalyst.

Key words: asymmetric catalysis, isomerization, protonation, cyclization, phenols

The combined use of a transition-metal catalyst and an organocatalyst has stimulated intensive interest in recent years[1] as it may potentially enable highly efficient and/or unprecedented transformations in a one-pot operation. Indeed, excellent approaches have been established by taking advantage of both of these catalytic approaches. Meanwhile, two types of combinations have been developed in the binary catalytic system. One is the simultaneous activation of two reactants by their respective catalysts; for instance, a metal catalyst is used to activate a nucleophile while an organocatalyst is used to activate an electrophile in a cooperative manner.[2] The other is the consecutive transformation using a binary catalytic system, that is, relay catalysis for a multistep sequence in which each catalyst promotes one type of reaction in a one-pot sequential manner.[3] Recently, we demonstrated relay catalysis by a ruthenium complex–Brønsted acid binary system in a tandem isomerization and carbon–carbon bond-forming sequence.[3a] The relay catalysis enables allylamides to generate imines in situ for further transformations. However, to the best of our knowledge, the enantioselective version of the analogous relay catalysis has never been reported. In this communication, we report a relay catalysis for a ternary reaction sequence composed of double-bond isomerization, protonation of the double bond, and enantioselective Pictet–Spengler-type cyclization using a binary catalytic system consisting of ruthenium hydride complex **1** and chiral phosphoric acid **2** as the chiral Brønsted acid catalyst[4,5] (Scheme 1). The ternary reaction sequence accomplished by the proposed relay catalysis involves: (i) isomerization of allylamide **3** by ruthenium hydride complex **1** to enamide **4**;[6] (ii) protonation of enamide **4** by chiral phosphoric acid **2** to generate reactive iminium ion intermediate **A**;[7] and (iii) subsequent 6-*endo*-trig cyclization under the influence of chiral conjugate base **2**$^-$ to afford tetrahydroisoquinoline derivative **5** in an optically active form.[8]



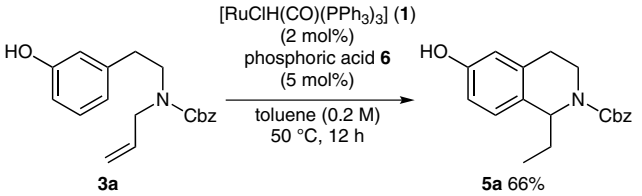
Scheme 1 Ternary reaction sequence mediated by ruthenium complex–chiral Brønsted acid binary catalytic system

The Pictet–Spengler reaction is a powerful and efficient methodology to synthesize tetrahydroisoquinoline or β-carboline derivatives and has been utilized as the key step for the synthesis of natural and unnatural alkaloids.[9] In the past decade, tremendous progress has been made in organocatalytic approaches to the Pictet–Spengler reaction. Indeed, excellent methods for the enantioselective version have been realized by either chiral thiourea catalysts or chiral phosphoric acid catalysts.[10,11] In most cases, however, indole subunits have been employed as the highly nucleophilic component.[10d,11f] To broaden the scope of this fascinating transformation, we envisioned the devel-

SYNLETT 2013, 24, 0752–0756
Advanced online publication: 27.02.2013
DOI: 10.1055/s-0032-1318302; Art ID: ST-2013-U0012-L

opment of the Pictet–Spengler-type cyclization of *m*-tyramine derivative **4** having a phenol subunit as the nucleophilic component, which has been scarcely employed in the catalytic enantioselective version of the Pictet–Spengler reaction. It seems that the combined use of chiral phosphoric acid **2** and ruthenium hydride complex **1** for the isomerization of **3** would enable us to generate iminium ion intermediate **A** as the highly electrophilic species via the isomerization–protonation sequence in a one-pot operation.

To ascertain the feasibility of the proposed relay catalysis, we initially attempted the reaction of *N*-Cbz-protected *m*-tyramine derivative **3a** using 2 mol% of [RuClH(CO)(PPh_3)$_3$] (**1**) and 5 mol% of racemic phosphoric acid **6** in toluene at 50 °C for 12 hours (Scheme 2). To our delight, the binary catalytic reaction proceeded smoothly to afford the desired tetrahydroisoquinoline derivative **5a** in fairly good yield, where the intermediary iminium ion underwent the cyclization at the *para* position of the phenol moiety. Indeed, the ruthenium complex–Brønsted acid binary catalytic system enabled us to establish the present ternary reaction sequence. This preliminary result prompted us to further develop the enantioselective version of the present relay catalysis.

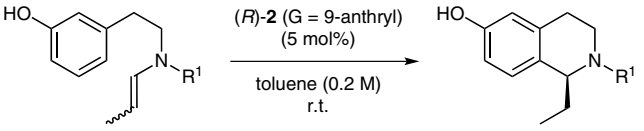


Scheme 2

Before demonstrating the enantioselective version of the relay catalysis, we attempted the transformation of enamides **4** into tetrahydroisoquinoline derivatives **5** via the protonation–Pictet–Spengler-type cyclization sequence using chiral phosphoric acid **2**. The reaction was conducted using 5 mol% of chiral phosphoric acid (*R*)-**2** (G = 9-anthryl) in toluene at room temperature. As expected, the reaction proceeded smoothly to afford product **5a** albeit with low enantioselectivity (Table 1, entry 1). To enhance the enantioselectivity, a range of N-protecting groups (R^1) were investigated. As shown in Table 1, *N*-Boc amide improved both chemical yield and enantioselectivity (entry 2).[12] Further screening for the N-protecting group, such as phosphoryl groups, resulted in a subtle change in the stereochemical outcome. Among the N-protecting groups tested, diphenylphosphinamide **4f** exhibited a slightly higher chemical yield and enantioselectivity (Table 1, entry 6). In terms of the removability of the N-protecting group, *N*-Boc amide and diphenylphosphinamide were employed for subsequent investigation of the enantioselective relay catalysis.

Having identified the last two steps of the ternary reaction sequence, namely protonation and enantioselective cyclization, in an effort to accomplish the enantioselective relay catalysis, we combined the established process with the first step of the ternary reaction sequence, that is, the isomerization of **3** in a one-pot sequential manner. Table 2 summarizes experiments carried out to probe the scope of the relay catalysis.[13,14] In all cases, products **5** were obtained in moderate to good yields. Investigation of the substituent effect on the aromatic ring (R^2) showed that high chemical yield and enhanced enantioselectivity were observed by the introduction of a methoxy group (Table 2, entry 2).[15]

Table 1 Optimization of Pictet–Spengler-Type Cyclization: Screening for N-Protecting Groups[a]

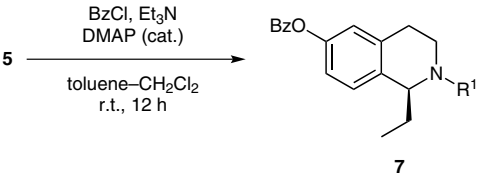


4 (*E*/*Z* mixture) **5**

a R^1 = Cbz **c** R^1 = P(O)(OEt)$_2$ **e** R^1 = P(O)(CH$_2$)$_5$
b R^1 = Boc **d** R^1 = P(O)(OPh)$_2$ **f** R^1 = P(O)Ph$_2$

Entry	4	Time (h)	5	Yield (%)[b]	ee (%)[c]
1	**4a**	12	**5a**	67	24
2	**4b**	12	**5b**	77	44
3	**4c**	24	**5c**	63	38
4	**4d**	24	**5d**	61	16
5[d]	**4e**	24	**5e**	58	14
6[d]	**4f**	24	**5f**	81	47

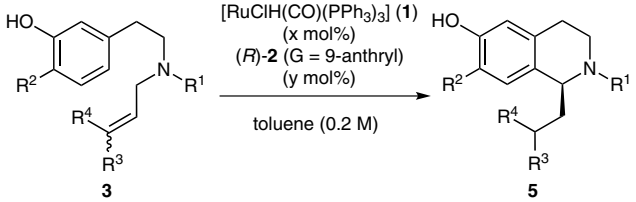
[a] Unless otherwise noted, all reactions were carried out using 0.0075 mmol of (*R*)-**2** (5 mol%) and 0.15 mmol of **4** in 0.75 mL of toluene.
[b] Isolated yield of **5**.
[c] Determined by chiral stationary phase HPLC analysis. The absolute configuration at the C1 position of **5** was determined to be *S* by comparing the optical rotation with the reported data after derivatization.
[d] Isolated yields and ee were determined after derivatization of product **5** to benzoate **7** (Scheme 3).



Scheme 3

Crotylamides **3h** and **3i** were also applicable to the present reaction, although the enantioselectivities were reduced presumably due to the high reaction temperature (Table 2, entries 3 and 4). The reaction of **3j** having dimethyl substituents at the terminal position of the double bond required harsh conditions for the isomerization, affording the product in a modest chemical yield with low enantioselectivity (Table 2, entry 5). The introduction of diphenylphosphinamide as the N-protective group resulted in the formation of products **5** in good yields albeit with low-

Table 2 Scope of the Relay Catalysis[a]

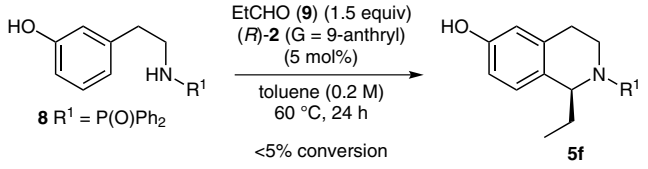


Entry	3	1 (mol%)	(*R*)-2 (mol%)	Temp (°C)	Time (h)	5	Yield (%)[b]	ee (%)[c]
1	**3b** R^1 = Boc, R^2 = R^3 = R^4 = H	2	5	50	12	**5b**	62	37
2	**3g** R^1 = Boc, R^2 = MeO, R^3 = R^4 = H	2	5	50	12	**5g**	80	53
3	**3h** R^1 = Boc, R^2 = H, R^3 = Me, R^4 = H	3	5	110	24	**5h**	78	27
4	**3i** R^1 = Boc, R^2 = MeO, R^3 = Me, R^4 = H	3	5	110	24	**5i**	79	33
5	**3j** R^1 = Boc, R^2 = H, R^3 = Me, R^4 = Me	7	8	160	24	**5j**	50	18
6[d]	**3f** R^1 = P(O)Ph_2, R^2 = R^3 = R^4 = H	3	5	60	24	**5f**	87	28
7[d]	**3k** R^1 = P(O)Ph_2, R^2 = H, R^3 = Me, R^4 = H	3	5	110	24	**5k**	72	20

[a] Unless otherwise noted, all reactions were carried out using 0.20 mmol of **3** in 1.0 mL of toluene.
[b] Isolated yield of **5**.
[c] Determined by chiral stationary phase HPLC analysis.
[d] Isolated yields and ee were determined after derivatization of product **5** to benzoate **7** (Scheme 3).

er enantioselectivities than that observed using the *N*-Boc group (Table 2, entries 6 and 7).

The distinct advantage of the present relay catalysis is highlighted by comparison with a control experiment using amide **8** (Table 2, entry 6 vs. Scheme 4).[16] The reaction of propionaldehyde (**9**) with **8** in the presence of acid **2** resulted in a considerable amount of **8** that remained unchanged. It can be considered that the condensation reaction of aldehyde **9** with amide **8** does not favor the generation of an iminium intermediate, because the nucleophilicity of the nitrogen atom of **8** is considerably reduced by the introduction of the electron-withdrawing and sterically demanding phosphinyl group.



Scheme 4

In conclusion, we have demonstrated a relay catalysis for a ternary reaction sequence composed of double-bond isomerization, protonation of the double bond, and enantioselective Pictet–Spengler-type cyclization using a binary catalytic system consisting of a ruthenium hydride complex and a chiral phosphoric acid as the chiral Brønsted acid catalyst. The present relay catalysis enables efficient access to tetrahydroisoquinoline derivatives in moderate to good yields albeit with insufficient enantioselectivities. Further studies on the improvement of the stereochemical outcome and the development of other types of enantioselective relay catalysis are in due course.

Acknowledgment

This work was partially supported by a Grant-in-Aid for Scientific Research on Innovative Areas 'Advanced Molecular Transformations by Organocatalysts' from MEXT, Japan and a Grant-in-Aid for Scientific Research (Grant No. 20245021) from the JSPS. We also thank the JSPS for a research fellowship for Young Scientists (Y.T.).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) For reviews on combined metal complex and organocatalyst systems, see: (a) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (b) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (c) Zhou, J. *Chem. Asian J.* **2010**, *5*, 422. (d) Hashmi, A. S. K.; Hubbert, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 1010. (e) de Armas, P.; Tejedor, D.; García-Tellado, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 1013. (f) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999. (g) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem. Eur. J.* **2010**, *16*, 9350. For a seminal study, see: (h) Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758.

(2) For selected examples of cooperative catalysis using metal complex–chiral phosphoric acid binary systems, see: (a) Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448. (b) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 6903. (c) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (d) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.;

Hu, J.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (e) Xu, X.; Zhou, J.; Yang, L.; Hu, W. *Chem. Commun.* **2008**, 6564. (f) Qian, Y.; Xu, X.; Jiang, L.; Prajapati, D.; Hu, W. *J. Org. Chem.* **2010**, *75*, 7483. (g) Xu, X.; Qian, Y.; Yang, L.; Hu, W. *Chem. Commun.* **2011**, *47*, 797. (h) Jiang, J.; Xu, H.-D.; Xi, J.-B.; Ren, B.-Y.; Lv, F.-P.; Guo, X.; Jiang, L.-Q.; Zhang, Z.-Y.; Hu, W. *J. Am. Chem. Soc.* **2011**, *133*, 8428. (i) Xu, B.; Zhu, S.-F.; Xie, X.-L.; Shen, J.-J.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2011**, *50*, 11483. (j) Chai, Z.; Rainey, T. J. *J. Am. Chem. Soc.* **2012**, *134*, 3615. (k) Qiu, H.; Li, M.; Jiang, L.-Q.; Lv, F.-P.; Zan, L.; Zhai, C.-W.; Doyle, M. P.; Hu, W. *Nat. Chem.* **2012**, *4*, 733.

(3) For selected examples of relay catalysis using metal complex–(chiral) phosphoric acid binary systems, see: (a) Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2008**, *130*, 14452. (b) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (c) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796. (d) Liu, X.-Y.; Che, C.-M. *Org. Lett.* **2009**, *11*, 4204. (e) Cai, Q.; Zhao, Z.-A.; You, S.-L. *Angew. Chem. Int. Ed.* **2009**, *48*, 7428. (f) Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 2266. (g) Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem. Int. Ed.* **2010**, *49*, 8666. (h) Chen, Q.-A.; Wang, D.-S.; Zhou, Y.-G.; Duan, Y.; Fan, H.-J.; Yang, Y.; Zhang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 6126. (i) Han, Z.-Y.; Guo, R.; Wang, P.-S.; Chen, D.-F.; Xiao, H.; Gong, L.-Z. *Tetrahedron Lett.* **2011**, *52*, 5963. (j) Chen, Q.-A.; Chen, M.-W.; Yu, C.-B.; Shi, L.; Wang, D.-S.; Yang, Y.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2011**, *133*, 16432. (k) Ren, L.; Lei, T.; Ye, J.-X.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 771. (l) Chen, Q.-A.; Gao, K.; Duan, Y.; Ye, Z.-S.; Shi, L.; Yang, Y.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2012**, *134*, 2442. (m) Terada, M.; Toda, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 2093. (n) Han, Z.-Y.; Chen, D.-F.; Wang, Y.-Y.; Guo, R.; Wang, P.-S.; Wang, C.; Gong, L.-Z. *J. Am. Chem. Soc.* **2012**, *134*, 6532. (o) Cai, Q.; Liang, X.-W.; Wang, S.-G.; Zhang, J.-W.; Zhang, X.; You, S.-L. *Org. Lett.* **2012**, *14*, 5022. (p) See also: Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796.

(4) For seminal studies of chiral phosphoric acid catalysts, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

(5) For recent reviews on chiral phosphoric acid catalysts, see: (a) Connon, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3909. (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31. (e) Terada, M. *Chem. Commun.* **2008**, 4097. (f) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101. (g) Terada, M. *Synthesis* **2010**, 1929. (h) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262. (i) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227. (j) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156.

(6) (a) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139. (b) Krompiec, S.; Pigulla, M.; Bieg, T.; Szczepankiewicz, W.; Kuźnik, N.; Krompiec, M.; Kubicki, M. *J. Mol. Catal. A: Chem.* **2002**, *189*, 169. (c) Greenwood, E. S.; Parsons, P. J.; Young, M. J. *Synth. Commun.* **2003**, *33*, 223. (d) Krompiec, S.; Pigulla, M.; Kuźnik, N.; Krompiec, M.; Baj, S.; Mrowiec-Białoń, J.; Kasperzyk, J. *Tetrahedron Lett.* **2004**, *45*, 5257. (e) Formentín, P.; Gimeno, N.; Steinke, J. H. G.; Vilar, R. *J. Org. Chem.* **2005**, *70*, 8235. (f) Krompiec, S.; Pigulla, M.; Kuźnik, N.; Krompiec, M.; Marciniec, B.; Chadyniak, D.; Kasperzyk, J. *J. Mol. Catal. A: Chem.* **2005**, *225*, 91.

(7) (a) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292. (b) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5565. (c) Baudequin, C.; Zamfir, A.; Tsogoeva, S. B. *Chem. Commun.* **2008**, 4637. (d) Terada, M.; Tanaka, H.; Sorimachi, K. *Synlett* **2008**, 1161. (e) Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 1075. (f) See also: Kobayashi, S.; Gustafsson, T.; Shimizu, Y.; Kiyohara, R. *Org. Lett.* **2006**, *8*, 4923.

(8) For selected examples of addition reactions to 3,4-dihydroisoquinoline derivatives, see: (a) Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc.* **2002**, *124*, 2888. (b) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700. (c) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 14010.

(9) (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (c) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

(10) (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (b) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (c) Mergott, D. J.; Zuend, S. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745. (d) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577. (e) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887.

(11) (a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (b) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 7485. (c) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405. (d) Wanner, M. J.; Boots, R. N. A.; Eradus, B.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2009**, *11*, 2579. (e) Holloway, C. A.; Muratore, M. E.; Storer, R. I.; Dixon, D. J. *Org. Lett.* **2010**, *12*, 4720. (f) Gómez-Sanjuan, A.; Sotomayor, N.; Lete, E. *Tetrahedron Lett.* **2012**, *53*, 2157. See also refs. 3c,o.

(12) For details regarding the screening of chiral phosphoric acid catalysts, see the Supporting Information.

(13) **Representative Procedure for the Relay Catalysis (Table 2, Entry 1)**

To a dried test tube were added (*R*)-**2** (G = 9-anthryl; 5 mol%, 7.01 mg) and **3b** (55.5 mg, 0.20 mmol). The mixture was dissolved in toluene (1.0 mL), and then the atmosphere was replaced with argon. [RuClH(CO)(PPh_3)$_3$] (**1**) (2 mol%, 3.81 mg) was added in portion at r.t., and the tube was flushed again with argon. After stirring at 50 °C for 12 h, the reaction mixture was diluted with sat. aq $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. After purification by flash column chromatography on silica gel (hexane–EtOAc = 10:1 to 2:1 as eluent), **5b** was obtained in 62% yield as a white solid. The ee of **5b** was determined by chiral stationary phase HPLC analysis.

Compound **5b**: white solid; R_f = 0.50 (hexane–EtOAc = 2:1). HPLC analysis Chiralpak IA (hexane–2-PrOH = 90:10, 0.8 mL/min, 254 nm, 30 °C): t_R (major) = 10.1 min; t_R (minor) = 12.5 min (37% ee); $[\alpha]_D^{26}$ +24.5 (*c* 1.1, $CHCl_3$); rotamer (major/minor = 60:40) was observed. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95–0.97 (3 H, m), 1.48 (9 H, s), 1.68–1.80 (2 H, m), 2.64–2.67 (1 H, m), 2.81–2.89 (1 H, m), 3.12–3.14 (0.60 H, m), 3.26–3.30 (0.40 H, m), 3.89–3.91 (0.40 H, m), 4.14–4.16 (0.60 H, m), 4.86–4.99 (2 H, m), 6.59 (1 H, s),

6.64–6.68 (1 H, m), 6.96–6.97 (1 H, m). ^{13}C NMR (125.65 MHz, $CDCl_3$): δ = 10.88, 11.18, 28.44, 28.66, 29.73, 30.09, 37.01, 38.48, 55.24, 56.08, 79.86, 80.19, 113.49, 114.98, 115.10, 128.00, 128.30, 129.29, 129.51, 135.21, 135.46, 154.73, 154.83, 155.38, 155.46. IR (ATR): 3330, 2971, 2932, 2875, 1687, 1656, 1613, 1427, 1232, 1160, 918, 863 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{16}H_{23}NO_3Na$ [M + Na]$^+$: 300.1570; found: 300.1569.

(14) The reaction of the product **5b** with ruthenium complex **1** and chiral phosphoric acid **2** under the same reaction conditions (50 °C, 12 h). **5b** was recovered quantitatively, and no racemization of **5b** was observed.

(15) (a) The absolute configuration was determined to be *S* by optical rotation after derivatization to (*S*)-1-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline: $[\alpha]_D^{24}$ –24.2 (*c* 2.2, CH_2Cl_2); literature value of *S*-isomer $[\alpha]_D^{20}$ –51.9 (*c* 2.1, CH_2Cl_2). See: Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 4859. (b) Compound **5g**: white solid; R_f = 0.45 (hexane–EtOAc = 2:1). HPLC analysis Chiralpak IA (hexane–EtOH = 96:4, 1.0 mL/min, 254 nm, 30 °C): t_R (minor) = 11.3 min; t_R (major) = 21.9 min (53% ee); $[\alpha]_D^{25}$ +49.7 (*c* 1.2, $CHCl_3$); rotamer (major/minor = 55:45) was observed. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98–0.99 (3 H, m), 1.48 (9 H, s), 1.71–1.80 (2 H, m), 2.57–2.61 (1 H, m), 2.74–2.86 (1 H, m), 3.09–3.13 (0.55 H, m), 3.23–3.27 (0.45 H, m), 3.85–3.92 (3.45 H, m), 4.16–4.18 (0.55 H, m), 4.84–4.86 (0.55 H, m), 4.96–4.98 (0.45 H, m), 5.53 (1 H, brs), 6.57 (1 H, s), 6.65–6.66 (1 H, m). ^{13}C NMR (125.65 MHz, $CDCl_3$): δ = 10.85, 11.09, 27.64, 27.78, 28.31, 29.57, 29.96, 36.62, 38.33, 55.06, 55.84, 79.22, 79.51, 109.29, 109.63, 114.21, 114.46, 126.52, 126.81, 129.15, 129.51, 144.06, 144.16, 144.95, 145.03, 154.92, 155.04; IR (ATR): 3369, 2969, 2932, 2842, 1683, 1515, 1420, 1364, 1271, 1241, 1111, 932, 863 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{17}H_{25}NO_4Na$ [M + Na]$^+$: 330.1676; found: 330.1675.

(16) Kobayashi and co-workers showed that the Pictet–Spengler reaction of benzaldehyde with *m*-tyramine using Brønsted acids, such as sulfonic acid and carboxylic acid, gave the corresponding product in low yield, see: Manabe, K.; Nobutou, D.; Kobayashi, S. *Bioorg. Med. Chem.* **2005**, *13*, 5154.

