Asymmetric Catalysis

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Catalytic Enantioselective Difluoroalkylation of Aldehydes**

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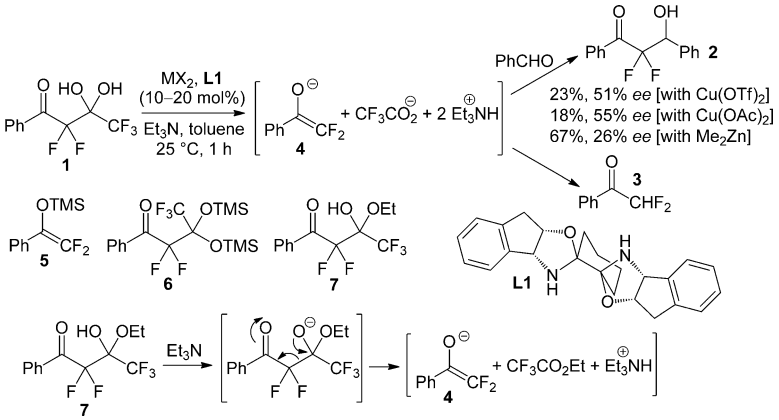
In recent years, chiral organofluorine compounds have become increasingly attractive synthetic targets because they often afford superior lipophilicity, bioavailability, and resistance to metabolic degradation compared to the non-fluorinated parent compounds.[1] The incorporation of a difluoromethylene group is particularly interesting because the high electronegativity of fluorine leads to increased dipole moments, conformational changes, hydration of adjacent carbonyl groups, and reduced pK_a values of acidic functionalities.[2] The stable hydrates of *gem*-difluoromethylene ketones have been shown to mimic tetrahedral intermediates of HIV1 protease and other important proteolytic enzymes, and therefore have significant therapeutic potential.[3]

In strong contrast to the general success of trifluoromethylations using $TMSCF_3$ (Ruppert–Prakash reagent),[4] the corresponding difluoromethylation with the significantly less reactive $TMSCHF_2$ has been unsuccessful.[5] While the synthesis of β-hydroxy esters with isolable difluoroketene silyl acetals has been accomplished by Iseki et al. with high asymmetric induction,[6] the formation of α,α-difluoro-β-hydroxy ketones from difluoroenolates and aldehydes has proven to be complicated. To date, several racemic methods typically involving $TMSCF_2SO_2Ph$ or $PhSO_2CF_2H$ as enolate precursors have been developed.[7] But the use of α,α-difluoroenolates in asymmetric reactions with aldehydes and ketones has remained a major challenge. The asymmetric nucleophilic addition of a zinc difluoroenolate complex to selected aldehydes and an Et_2Zn-mediated Reformatsky-type reaction with ethyl iodofluoroacetate and ketones have only been accomplished with stoichiometric amounts of chiral amino alcohols.[8] A catalytic procedure for the asymmetric synthesis of α,α-difluoro-β-hydroxy ketones from aromatic and aliphatic aldehydes has been elusive to date and few allylic alkylations restricted to cyclic monofluoroenolates[9] or aldol condensations using monofluoroacetone have been reported.[10]

We envisioned that the difficulties and limitations encountered with fluorinated carbanions could be addressed by mild in situ generation of the nucleophile. Few processes that couple the C–C bond scission of a prenucleophile with asymmetric catalysis have been reported.[11] Prager, Ogden, and Colby have shown that hexafluoroacetone and its pentafluorobutane-1,3-dione derivatives can afford carbanions suitable for achiral C–C bond formation when 3–4 equivalents of lithium salts or potassium *tert*-butoxide are used.[12] Our group recently prepared pentafluorinated β-hydroxy ketones in high yields by LHMDS-promoted generation of difluoroenolates from readily available 1-aryl and 1-alkyl 2,2,4,4,4-pentafluorobutane-1,3-dione hydrates.[13] However, all these methods are noncatalytic and yield racemic products.

We have now developed a catalytic enantioselective method that produces a series of α,α-difluoro-β-hydroxy ketones from aldehydes through direct difluoromethylation with α,α-difluoroenolates generated in situ from trifluoromethyl α,α-difluorinated β-keto *gem*-diol **1** and its derivatives (Scheme 1). An asymmetric aldol reaction between the monofluorinated analogue of **1** and nonenolizable *N*-benzyl isatins was recently reported by Fang, Wu, and co-workers.[14]



Scheme 1. Initial analysis of the catalytic difluoromethylation of aldehydes.

Importantly, this work is based on C–C bond formation followed by trifluoroacetate cleavage and therefore does not allow incorporation of a CF_2 unit. By contrast, our approach results in the incorporation of a difluoromethylene rather than a monofluoromethylene moiety next to the chiral center and the trifluoroacetate is cleaved prior to the C–C bond-forming step.

During initial NMR and ReactIR analysis of the effect of additives, base, solvent, and other parameters on this reaction we found that catalytic bond cleavage of **1** and subsequent C–C bond formation is indeed possible in the presence of 10–20 mol% of magnesium, copper, and zinc salts (see the Supporting Information). We then continued with the screen-

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ing of chiral metal complexes to determine whether this reaction sequence can also be accomplished with practical asymmetric induction. The reaction of prenucleophilic **1** and benzaldehyde in the presence of 10 mol% of copper(II) triflate or copper(II) acetate and bisoxazolidine **L1** gave the desired product **2** in up to 55% *ee* within 1 hour.[15] Although **1** was quantitatively consumed, the yields were generally below 30% due to a predominant side reaction leading to 2,2-difluoro-1-phenylethanone (**3**). We then employed enantioenriched **2** in our reaction procedure to determine whether the C–C bond-formation step is reversible. However, neither a sign of racemization nor formation of **3** was observed. The same analysis with **3** confirmed that the protonation of intermediate enolate **4** is irreversible under the conditions used. Apparently, the formation of **3** occurs by means of protonation of **4** by the Et_3NH^+ by-product (Scheme 1). We therefore attempted to avoid formation of triethylammonium by using silyl enolether **5** and the TMS analogue **6** in combination with TBAF and CsF, and explored typical Mukaiyama aldol conditions with $Ti(OiPr)_4$. But **2** was still obtained in low yields and *ee* values. These results underscore the general difficulty in producing chiral α,α-difluoro-β-hydroxy ketones such as **2** using **5** and other isolated difluoroenolates as discussed above.[5,7,8] However, the replacement of **1** with **7**, which reduces the amount of triethylammonium formed without changing the pathway of in situ enolate formation, did also not improve results. Screening of a wide range of organic and inorganic bases in various solvents then showed that **2** can be formed in 67% yield and 26% *ee* when Me_2Zn is used in toluene. At this point, we decided to apply several bisoxazoline ligands to our general reaction protocol. While the results obtained in the presence of catalytic amounts of copper(II) triflate and **L2**–**L9** varied considerably, **L10**–**l12** showed remarkable promise (Figure 1). We were very pleased to find that **2** is formed in almost quantitative yields and 61–68% *ee* within 1 h when these ligands are employed in THF.

Based on the wealth of crystal structures of Cu^{II}–bisoxazoline complexes available in the literature, one can assume that the transition state involves a distorted square-planar geometry although coordination of a counterion leading to a square pyramid is also possible.[16] Computational analysis of the Cu^{II}–**L11** complex loaded with benzaldehyde and enolate **4** correctly predicts the observed stereochemical outcome (verified by NMR analysis of Mosher ester derivatives) and is in agreement with a distorted square-planar Cu^{II} complex (Figure 1 and the Supporting Information). Our screening results also revealed that anionic ligands exhibiting a delocalized negative charge in the backbone, in particular semicorrin **L12**, allow completion of the reaction within 1 h. We assumed that Pfaltz's semicorrins should generally favor displacement of the aldol product from the copper center without compromising its Lewis acidity.[17] We then rationalized that this type of more active catalyst would enable us to perform the reaction at lower temperature to improve *ee* values while the competing protonation of the enolate to by-product **3** would remain relatively slow and thus not affect yields.

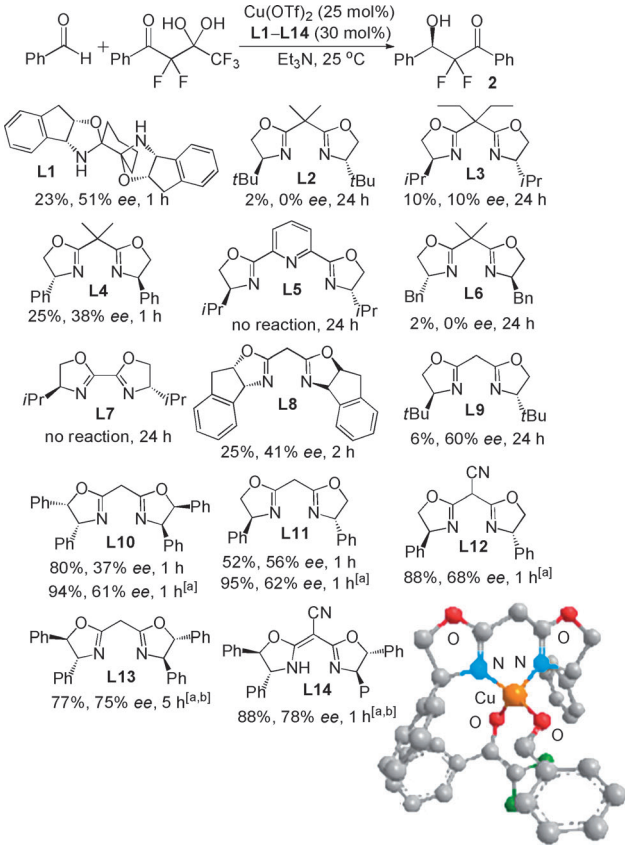
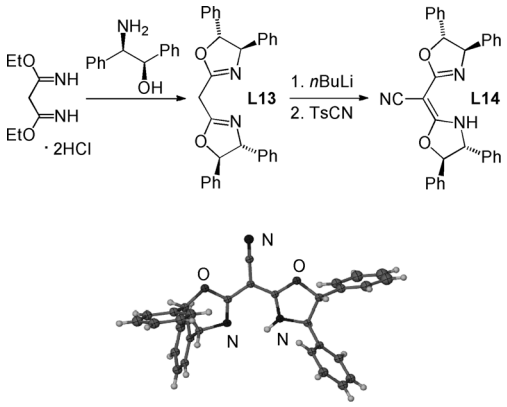


Figure 1. Result of screening chiral ligands and a MOPAC computation of the loaded catalyst (hydrogens are omitted for clarity). Reaction conditions: diol (0.2 mmol), $Cu(OTf)_2$ (25 mol%), ligand (30 mol%), PhCHO (2 equiv), Et_3N (2 equiv) in toluene, 25 °C. a) THF, b) $Cu(OTf)_2$ (10 mol%), ligand (12 mol%).

We therefore further modified the ligand structure and prepared **L13** and **L14** (Scheme 2).[18] A change of the relative configuration of the adjacent phenyl rings in **L10**, as in *anti* derivative **L13**, improved the enantioselectivity and introduction of a cyano group to the methylene bridge further increased catalytic activity and yield. With **L14** in hand, we were able to decrease the catalyst loading to 5 mol% and obtained **2** as well as analogues **8**–**10** in up to 98% yield and



Scheme 2. Synthesis and single-crystal X-ray structure of **L14**.

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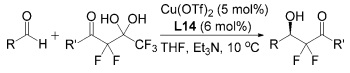
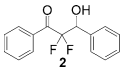
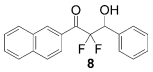
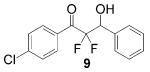
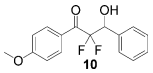
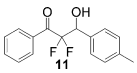
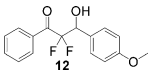
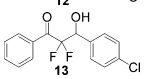
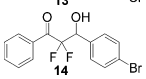
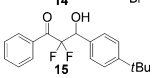
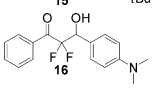
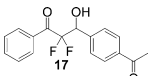
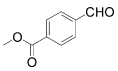
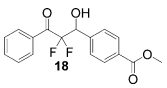
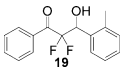
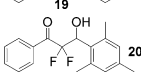
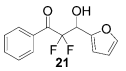
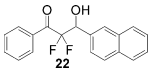
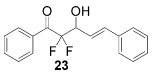
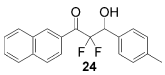
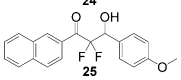
92% *ee* using 1.2 equivalents of benzaldehyde at 10°C (Table 1, entries 1–4).[19]

Table 1: Scope of the enantioselective aldol reaction.[a]



Entry	Aldehyde	Product	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1		 **2**	2.5	97	83
2		 **8**	5	96	91
3		 **9**	5	98	92
4		 **10**	1	88	77
5		 **11**	3	99	82
6		 **12**	2	90	79
7		 **13**	6	88	78
8		 **14**	6	92	81
9		 **15**	7	90	82
10		 **16**	2	93	80
11		 **17**	6	86	76
12		 **18**	23	90	76
13		 **19**	6	85	84
14		 **20**	11	79	87
15		 **21**	4	92	85
16		 **22**	5	91	80
17		 **23**	7	88	73
18		 **24**	8	94	88
19		 **25**	8	89	82
20		**26**	7	88	82
21		**27**	3	87[d]	79
22		**28**	3	90[d]	77

[a] Reaction conditions: diol (0.4 mmol), $Cu(OTf)_2$ (5 mol%), **L14** (6 mol%), aldehyde (1.2 equiv), Et_3N (2 equiv) in 2 mL of THF. [b] Yields of isolated products. [c] Determined by HPLC on a chiral stationary phase. [d] Diol (0.2 mmol), $Cu(OTf)_2$ (20 mol%), **L14** (24 mol%), Et_3N (2 equiv), aldehyde (2 equiv), 25°C.

We then applied a wide range of aldehydes to evaluate the reaction scope. In general, high yields and *ee* values were obtained with electron-rich and electron-deficient substrates (Table 1, entries 5–9). Importantly, this method tolerates the presence of amines, ketones, esters and other functional groups (Table 1, entries 10–12 and 15), and the reaction with sterically hindered aldehydes gave **19** and **20** with 79–85% yield and 84–87% *ee* (Table 1, entries 13 and 14). Finally, the copper-catalyzed aldol reaction between the 2-naphthyl-substituted geminal diol and various aldehydes, including enolizable substrates such as cyclohexanecarboxaldehyde and 3-phenylpropionaldehyde, gave **24**–**28** in up to 94% yield and 88% *ee* (Table 1, entries 18–22).

Our procedure provides unprecedented access to important chiral building blocks, including 2,2-difluoro-1,3-propanols.[20] For example, the reduction of **8** with DIBAL produces *anti*-**29** in high yields and with excellent diastereoselectivity (Scheme 3).[13] This establishes a convenient entry to C_1- and

Scheme 3. Formation of a representative *anti*-2,2-difluoro-1,3-diol and a 2,2-difluoro-3-hydroxy acid.

C_2-symmetric *anti*-1,3-diol motifs, which appear in many natural products and are of great pharmaceutical interest. Alternatively, we realized that the Baeyer–Villiger oxidation followed by mild hydrolysis affords the first asymmetric route to 2,2-difluoro-3-hydroxy carboxylic acids, which are crucial precursors of several enzyme inhibitors and other biologically active compounds.[21] Oxidation of **25** with *m*-CPBA to the

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corresponding 2-naphthoate **30** and basic hydrolysis gave 2,2-difluoro-3-hydroxy acid **31** in 85% yield and 86% *ee*.

In conclusion, we have introduced a practical method for the catalytic enantioselective addition of α,α-difluoroenolates to aldehydes using 5 mol% of copper(II) triflate and a new bisoxazoline ligand which can be easily prepared in two steps. High yields and *ee* values were obtained with a wide range of prenucleophiles and aldehydes, including aliphatic substrates, under mild conditions and in short reaction times. The value of this reaction is highlighted by the stereoselective reduction and Baeyer–Villiger oxidation of α,α-difluoro-β-hydroxy ketones to give an *anti*-2,2-difluoro-1,3-propanol and a 2,2-difluoro-3-hydroxy carboxylic acid, respectively. Further investigation of catalytic reactions between α,α-difluoroenolates and other electrophiles is currently underway in our laboratory.

Experimental Section

Ligand **L14** (11.6 mg, 0.024 mmol) and $Cu(OTf)_2$ (7.2 mg, 0.020 mmol) were dissolved in 1 mL of anhydrous THF under nitrogen at room temperature and stirred for 1 min. Then, 1-(2-naphthyl)-2,2,4,4,4-pentafluorobutane-1,3-dione hydrate (128.0 mg, 0.4 mmol) was added, and the solution was stirred for an additional minute followed by addition of 0.48 mmol of aldehyde (1.2 equivalents) dissolved in 0.5 mL of THF. The mixture was then transferred to a jacketed flask using another 0.5 mL of THF, cooled to 10 °C, and stirred for another 10 min. Finally, triethylamine (2 equivalents) was added. After completion of the reaction, solvents were removed and the crude residue was loaded directly onto a silica gel column. Chromatographic purification (EtOAc/hexanes 1:10) gave 120 mg (0.38 mmol, 96%, 92% *ee*) of **8** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 3.11$ (d, $J = 4.5$ Hz, 1H), 5.37 (ddd, $J = 4.5$ Hz, 4.5 Hz, 18.5 Hz, 1H), 7.36–7.45 (m, 3H), 7.51–7.57 (m, 3H), 7.63 (ddd, $J =$ 1.2 Hz, 1.2 Hz, 7.5 Hz, 1H), 7.87 (dd, $J = 8.8$ Hz, 8.8 Hz, 2H), 7.92 (d, $J = 8.2$ Hz, 1H), 8.03 (d, $J = 8.7$ Hz, 1H), 8.61 ppm (s 1H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 73.5$ (dd, $J_{C\text{-}F} = 22.7$ Hz, 28.1 Hz), 115.9 (dd, $J_{C\text{-}F} = 257.0$ Hz, 264.7 Hz), 124.7, 127.1, 127.8, 128.1, 128.3, 128.6, 129.0, 129.5, 130.2, 132.2, 133.3, 134.8, 136.1, 190.7 ppm (dd, $J_{C\text{-}F} = 29.4$ Hz, 31.6 Hz). The *ee* value was determined by HPLC on Chiralpak AS using IPA/hexanes (10:90) as the mobile phase. Anal. calcd. for $C_{19}H_{14}F_2O_2$: C 73.07, H 4.52; found: C 73.04, H 4.68.

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Keywords: aldol reaction · asymmetric catalysis · cleavage reactions · fluoroenolates · reactive intermediates

[1] a) J. Nie, H. C. Guo, D. Cahard, J. A. Ma, *Chem. Rev.* **2011**, *111*, 455–529; b) H. A. Schenck, P. W. Lenkowski, I. Choudhury-Mukherjee, S. H. Ko, J. P. Stables, M. K. Patel, M. L. Brown, *Bioorg. Med. Chem.* **2004**, *12*, 979–993; c) R. Betageri, Y. Zhang, R. M. Zindell, D. Kuzmich, T. M. Kirrane, J. Bentzien, M. Cardozo, A. J. Capolino, T. N. Fadra, R. M. Nelson, Z. Paw, D. T. Shih, C. K. Shih, L. Zuvela-Jelaska, G. Nabozny, D. S. Thomson, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4761–4769; d) S. Caron, N. M. Do, J. E. Sieser, P. Arpin, E. Vazquez, *Org. Process Res. Dev.* **2007**, *11*, 1015–1024; e) J. W. Corbett, S. S. Ko, J. D. Rodgers, L. A. Gearhart, N. A. Magnus, L. T. Bacheler, S. Diamond, S. Jeffrey, R. M. Klabe, B. C. Cordova, S. Garber, K. Logue, G. L. Trainor, P. S. Anderson, S. K. Erickson-Viitanen, *J. Med. Chem.* **2000**, *43*, 2019–2030.

[2] D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319.

[3] a) G. Lowe, D. Nurse, *J. Chem. Soc. Chem. Commun.* **1977**, 815b–817; b) R. Chen, D. G. Gorenstein, W. P. Kennedy, G. Lowe, D. Nurse, R. M. Schultz, *Biochemistry* **1979**, *18*, 921–926; c) D. O. Shah, K. Lai, D. G. Gorenstein, *J. Am. Chem. Soc.* **1984**, *106*, 4272–4273; d) B. Imperiali, R. H. Abeles, *Biochemistry* **1986**, *25*, 3760–3767; e) A. S. Balnaves, T. Gelbrich, M. B. Hursthouse, M. E. Light, M. J. Palmer, J. M. Percy, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2525–2535.

[4] a) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119–6146; b) S. Mizuta, N. Shibata, S. Akiti, H. Fujimoto, S. Nakamura, T. Toru, *Org. Lett.* **2007**, *9*, 3707–3710; c) L. Bernardi, E. Indrigo, S. Pollicino, A. Ricci, *Chem. Commun.* **2012**, *48*, 1428–1430.

[5] J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465–7478.

[6] K. Iseki, Y. Kuroki, D. Asada, Y. Kobayashi, *Tetrahedron Lett.* **1997**, *38*, 1447–1448.

[7] a) G. K. S. Prakash, A. J. Hu, *Acc. Chem. Res.* **2007**, *40*, 921–930; b) T. Hagiwara, T. Fuchikami, *Synlett* **1995**, 717–718; c) A. K. Yudin, G. K. S. Prakash, D. Deffieux, M. Bradley, R. Bau, G. A. Olah, *J. Am. Chem. Soc.* **1997**, *119*, 1572–1581; d) G. K. S. Prakash, J. Hu, T. Mathew, G. A. Olah, *Angew. Chem.* **2003**, *115*, 5374–5377; *Angew. Chem. Int. Ed.* **2003**, *42*, 5216–5219; e) G. K. S. Prakash, Y. Wang, J. Hu, G. A. Olah, *J. Fluorine Chem.* **2005**, *126*, 1361–1367; f) C. Ni, J. Hu, *Tetrahedron Lett.* **2005**, *46*, 8273–8277; g) J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465–7478; h) T. Poisson, M.-C. Belhomme, X. Pannecoucke, *J. Org. Chem.* **2012**, *77*, 9277–9285; i) Y. Zhao, B. Gao, J. Hu, *J. Am. Chem. Soc.* **2012**, *134*, 5790–5793. For racemic Diels–Alder reactions with silyl difluoroenolethers, see: j) H. Amii, T. Kobayashi, H. Terasawa, K. Uneyama, *Org. Lett.* **2001**, *3*, 3103–3105. Asymmetric additions to nonenolizable imines or oxindoles: k) W. Kashikura, K. Mori, T. Akiyama, *Org. Lett.* **2011**, *13*, 1860–1863; l) Y.-L. Liu, J. Zhou, *Chem. Commun.* **2012**, *48*, 1919–1921. The enantioselective aldol reaction between difluoromethyl phenyl sulfone and nonenolizable aldehydes has been achieved with only moderate *ee* values: m) C. Ni, F. Wang, J. Hu, *Beilstein J. Org. Chem.* **2008**, *4*, 21.

[8] a) R. J. Kloetzing, T. Thaler, P. Knochel, *Org. Lett.* **2006**, *8*, 1125–1128; b) M. Fornalczyk, K. Singh, A. M. Stuart, *Org. Biomol. Chem.* **2012**, *10*, 3332–3342.

[9] a) J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem.* **2005**, *117*, 7084–7087; *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927; b) M. Nakamura, A. Hajra, K. Endo, E. Nakamura, *Angew. Chem.* **2005**, *117*, 7414–7417; *Angew. Chem. Int. Ed.* **2005**, *44*, 7248–7251; c) E. Bélanger, K. Cantin, O. Messe, M. Tremblay, J.-F. Paquin, *J. Am. Chem. Soc.* **2007**, *129*, 1034–1035.

[10] a) T. Hoffmann, G. Zhong, B. List, D. Shabat, J. Anderson, S. Gramatikova, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **1998**, *120*, 2768–2779; b) X.-Y. Xu, Y.-Z. Wang, L.-Z. Gong, *Org. Lett.* **2007**, *9*, 4247–4249; c) G. Guillena, M. del Carmen Hita, C. Najera, S. F. Viozquez, *J. Org. Chem.* **2008**, *73*, 5933–5943.

[11] a) D. Magdziak, G. Lalic, H. M. Lee, K. C. Fortner, A. D. Aloise, M. D. Shair, *J. Am. Chem. Soc.* **2005**, *127*, 7284–7285; b) J. A. Keith, D. C. Behenna, J. T. Mohr, S. Ma, S. C. Marinescu, J. Oxgaard, B. M. Stoltz, W. A. Goddard, *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877; c) B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2008**, *130*, 11852–11853; d) L. Yin, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 9610–9611.

[12] a) J. H. Prager, P. H. Ogden, *J. Org. Chem.* **1968**, *33*, 2100–2102; b) C. Han, E. H. Kim, D. A. Colby, *J. Am. Chem. Soc.* **2011**, *133*, 5802–5805; c) M. V. Riofski, A. D. Hart, D. A. Colby, *Org. Lett.* **2013**, *15*, 208–211.

[13] P. Zhang, C. Wolf, *J. Org. Chem.* **2012**, *77*, 8840–8844.

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[14] I. Saidalimu, X. Fang, X.-P. He, J, Liang, X. Yang, F. Wu, *Angew. Chem.* **2013**, *125*, 5676 – 5680; *Angew. Chem. Int. Ed.* **2013**, *52*, 5566 – 5570.

[15] For the use of bisoxazolidine ligands in asymmetric catalysis, see: a) C. Wolf, S. Liu, *J. Am. Chem. Soc.* **2006**, *128*, 10996 – 10997; b) S. Liu, C. Wolf, *Org. Lett.* **2007**, *9*, 2965 – 2968; c) S. Liu, C. Wolf, *Org. Lett.* **2008**, *10*, 1831 – 1834; d) K. Y. Spangler, C. Wolf, *Org. Lett.* **2009**, *11*, 4724 – 4727; e) H. Xu, C. Wolf, *Chem. Commun.* **2010**, *46*, 8026 – 8028; f) H. Xu, C. Wolf, *Synlett* **2010**, 2765 – 2770; g) C. Wolf, P. Zhang, *Adv. Synth. Catal.* **2011**, *353*, 760 – 766; h) H. Xu, C. Wolf, *Chem. Commun.* **2011**, *47*, 3339 – 3350; i) C. Wolf, M. Moskowitz, *J. Org. Chem.* **2011**, *76*, 6372 – 6376; j) H. Xu, C. Wolf, *Angew. Chem.* **2011**, *123*, 12457 – 12460; *Angew. Chem. Int. Ed.* **2011**, *50*, 12249 – 12252.

[16] G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.* **2006**, *106*, 3561 – 3651.

[17] a) A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339 – 345; b) K. A. Nolin, R. W. Ahn, Y. Kobayashi, J. J. Kennedy-Smith, F. D. Toste, *Chem. Eur. J.* **2010**, *16*, 9555 – 9562.

[18] CCDC 918033 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] NMR analysis of Mosher ester derivatives revealed that the formation of the *R* enantiomer is favored when ligand **L14** is used (see the Supporting Information).

[20] G. K. S. Prakash, J. Hu, T. Mathew, G. A. Olah, *Angew. Chem.* **2003**, *115*, 5374 – 5377; *Angew. Chem. Int. Ed.* **2003**, *42*, 5216 – 5219.

[21] a) S. Kobayashi, H. Tanaka, H. Amii, K. Uneyama, *Tetrahedron* **2003**, *59*, 1547 – 1552; b) O. Jiménez, M. P. Bosch, A. Guerrero, *J. Org. Chem.* **2005**, *70*, 10883 – 10885.

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