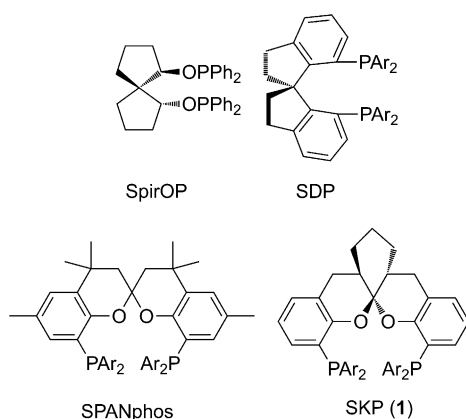


Aromatic Spiroketal Bisphosphine Ligands: Palladium-Catalyzed Asymmetric Allylic Amination of Racemic Morita–Baylis–Hillman Adducts**

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The design of chiral ligands plays a central role in the development of chiral catalysts for asymmetric reactions, in which the right combination of a sterically well-defined scaffold with a chelating moiety can lead to excellent enantioselective control in the catalysis.^[1] From this point of view, spirobackbones (Scheme 1) have been recognized as one of the privileged structures for the construction of chiral



Scheme 1. Spiro-backbone-based bisphosphine ligands.

ligands^[2] ever since the pioneering work by Chan et al. (SpirOP), Sasai and co-workers, and Zhou and co-workers (SDP).^[3] In contrast, van Leeuwen and co-workers reported the development of the bisphosphine ligands SPANphos

which have an interesting spiro-2,2'-bis(chroman) backbone and their transition-metal complexes have been studied in catalysis.^[4] Despite the success of their rhodium(I) complexes in the catalysis of methanol carbonylation,^[4c] the application of spiro-2,2'-bis(chroman)-based chiral ligands in asymmetric catalysis still remains relatively unexplored.^[4e,g,5]

Very recently, we developed a catalytic asymmetric synthesis of aromatic spiroketals by the tandem hydrogenation and spiroketalization of α,α' -bis(2-hydroxyarylidene)ketones^[6a] using Ir/SpinPHOX as the catalyst,^[6] and it provides a facile and practical synthesis of a new type of enantiopure analogue to SPANphos, namely SKP (**1**). In our ongoing endeavor towards seeking new spirochiral ligands for asymmetric catalysis, we communicate herein our preliminary results on the synthesis of one type of chiral bisphosphine ligand having an aromatic spiroketal motif (**1**; SKP) and their application in palladium-catalyzed enantioselective allylic amination of racemic Morita–Baylis–Hillman (MBH) adducts^[7] with aromatic amines. The developed methodology has provided a facile and efficient synthesis of optically active β -lactam derivatives,^[8] including the chiral drug Ezetimibe which is used to treat high cholesterol.^[9]

As shown in Scheme 2, synthesis of the enantiopure spiro-2,2'-bis(chroman)-based bisphosphine ligands (*R,R,R*)-**1** is quite simple and straightforward from readily available α,α' -bis(2-hydroxy-3-bromophenylidene)ketone (**2**) by using our previously published procedure.^[6a] The key intermediate, the 3-bromo-substituted aromatic spiroketal (*R,R,R*)-**3** was treated with *n*BuLi and the resulting lithium salt was reacted with $\text{Ar}_2\text{P-Cl}$ in THF to afford the corresponding enantiopure spiroketal-based bisphosphine ligands (*R,R,R*)-**1a–f** in moderate to good yields (40–80 %) on gram scale.

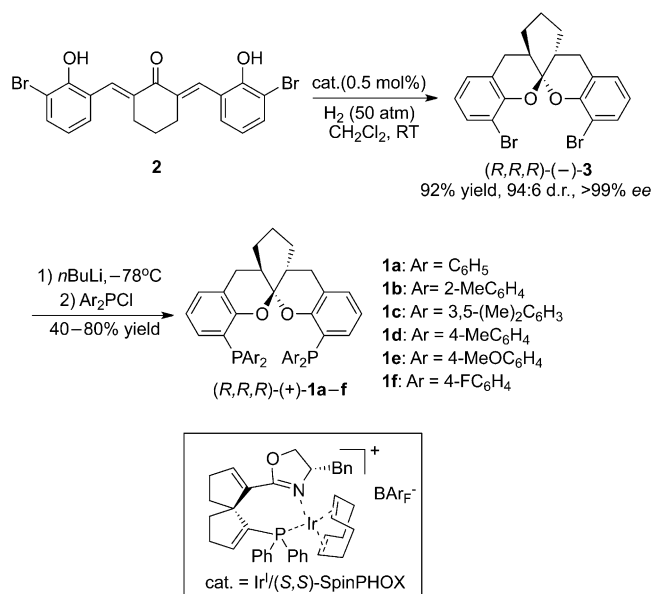
Optically active α -alkylidene- β -arylamino carbonyl compounds represent one type of valuable building blocks with wide applications in the synthesis of medicinally relevant molecules and natural products,^[10] but these building blocks are not readily accessible using direct asymmetric aza-MBH reactions because of the electron-rich nature of the corresponding N-aromatic imines.^[7,11] In contrast, the enantioselective, metal-catalyzed allylic amination is a useful method for the preparation of enantiomerically enriched allylic amines.^[12] Despite the success of palladium- or organocatalyzed asymmetric allylic aminations of esters of racemic MBH adducts using cyclic imides, aliphatic amines, or benzophenone imines as nucleophiles,^[10] the amination of racemic acyclic MBH adducts using less-nucleophilic aromatic amines to afford the corresponding optically active α -alkylidene- β -

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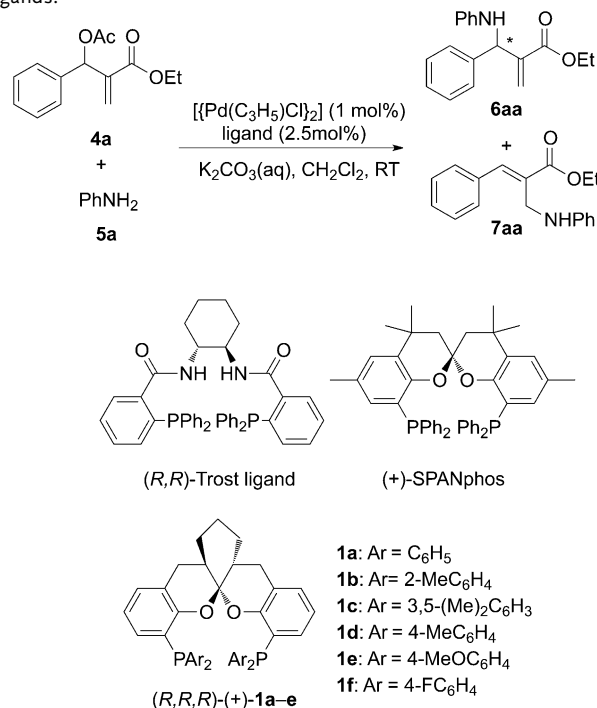
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Scheme 2. Synthesis of enantiopure the spiro-2,2'-bis(chroman)-based bisphosphine ligands (*R,R,R*)-1a–f.

arylamino carbonyl compounds still remains underdeveloped.^[13] With the spiro-bisphosphine ligands (*R,R,R*)-1a–f in hand, we then investigated their application in palladium-catalyzed asymmetric allylic amination of acyclic MBH adducts using aromatic amines as the nucleophiles.^[14] A preliminary survey of the reaction conditions was conducted for the amination of the methyl ester of a MBH adduct with aniline (**5a**) as the nucleophile using the complexes generated in situ from (*R,R,R*)-1a (2.5 mol%) and a variety of palladium precursors ([Pd] = 2 mol%) as the catalysts. Many reaction parameters were found to have impact on the reactivity as well as the regio- and enantioselectivities. As shown in Tables S1–S5 in the Supporting Information, the reaction performed in CH₂Cl₂ by using [Pd(η³-C₃H₅)Cl]₂ as the catalyst precursor at room temperature with aqueous K₂CO₃ as the base and the ethyl ester of the MBH adduct (**4a**) as the substrate turned out to be optimal, thus affording the corresponding amination product in 90% yield with a 94:6 regioselectivity for **6aa/7aa** and 93% enantioselectivity (Table 1; entry 1). Under the optimized reaction conditions, a variety of spiroketal-based bisphosphine ligands [(*R,R,R*)-1b–f] with different aryl substituents at the P atom were then evaluated to further improve the enantioselectivity of the catalysis. As shown in Table 1, the steric hindrance of the aryl groups on P has a significant impact on the asymmetric induction in the catalysis (entries 1–4). The ligand (*R,R,R*)-1b having 2-tolyl moieties on the P atoms obviously deteriorates the catalytic activity and enantioselectivity (entry 2) in comparison with the analogous variants (entry 2 versus entries 3–5 and 1). The introduction of the electron-withdrawing F group on the aryl rings appended to P slightly decreases the enantioselectivity of the reaction (entry 6). The ligand (*R,R,R*)-1c with 3,5-xylyl groups on P turned out to be the best in terms of both reactivity and enantioselectivity, thus affording the corresponding amination product (+)-**6aa** in 89% yield with a 92:8 regioselectivity and 96% ee (entry 3).

Table 1: Catalytic asymmetric allylic amination of **4a** with aniline **5a** catalyzed by palladium complexes of various enantiopure bisphosphine ligands.^[a]



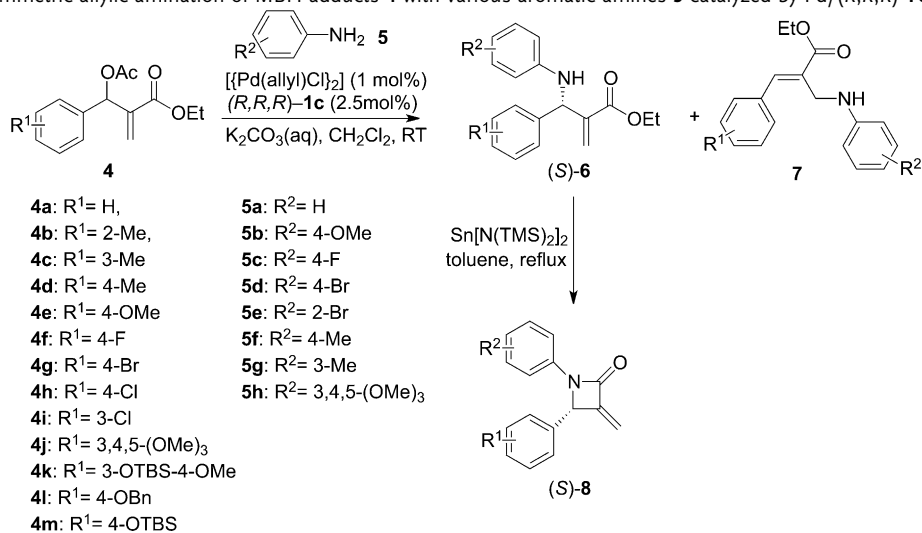
Entry	Ligand	6aa/7aa ^[c]	6aa Yield [%] ^[b]	ee [%] ^[d]
1	(<i>R,R,R</i>)-1a	94:6	90	93
2	(<i>R,R,R</i>)-1b	90:10	71	59
3	(<i>R,R,R</i>)-1c	92:8	89	96
4	(<i>R,R,R</i>)-1d	95:5	89	95
5	(<i>R,R,R</i>)-1e	92:8	90	93
6	(<i>R,R,R</i>)-1f	92:8	87	89
7	(+)-SPANphos	66:34	55	39
8	(<i>R</i>)-binap	13:87	6	10
9	(<i>R</i>)-SDP	20:80	10	11
10	(<i>R,R</i>)-Trostr ligand	31:69	25	–21

[a] Unless otherwise noted, the reactions were performed with **4a** (0.1 mmol) and **5a** (0.3 mmol) in CH₂Cl₂ (1 mL) for 3 h. [b] Yield of the isolated **6aa**. [c] Determined by ¹H NMR spectroscopy. [d] The ee value of **6aa** was determined by chiral HPLC with a chiral AD-H column.

The SPANphos developed by van Leeuwen was also resolved and examined in the model reaction, and afforded (+)-**6aa** in 55% yield with moderate regio- and enantioselectivities (entry 7). It is noteworthy that the application of some privileged ligands,^[1d] such as (*R*)-binap, (*R*)-SDP or (*R,R*)-Trostr ligand, in the catalysis only afforded poor catalytic performance (entries 8–10), thus indicating the unique feature of the present spiroketal skeleton of the bisphosphine ligand in this catalytic system. Although we are unable to clarify the underlying reason for the outstanding catalytic performance of the SKP-type ligands at the present stage, a relatively large bite angle of chelating P atoms and the unique geometry of the backbone in the ligand seems to be critically important for the regio- and stereocontrol of the catalysis.

With the optimized catalyst and reaction conditions in hand, we then investigated the substrate scope of the catalysis.

Table 2: Catalytic asymmetric allylic amination of MBH adducts **4** with various aromatic amines **5** catalyzed by Pd/(*R,R,R*)-**1c**.^[a]



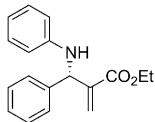
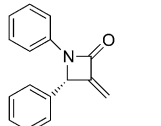
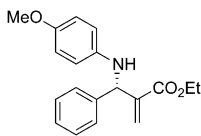
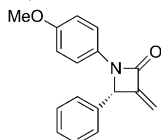
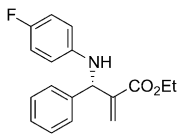
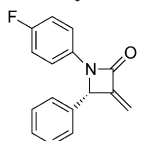
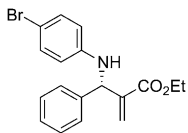
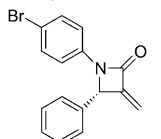
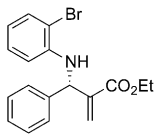
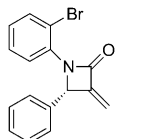
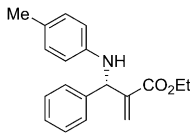
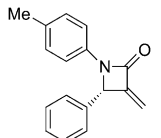
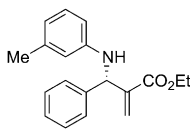
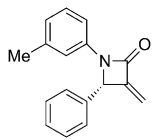
Entry	6	Yield [%] ^[b]	<i>ee</i> [%] ^[d]	6/7 ^[c]	8	Yield [%] ^[b]	<i>ee</i> [%] ^[d]		
1		6aa	89	96	92:8		8aa	85	96
2		6ab	88	95	91:9		8ab	94	95
3		6ac	89	95	92:8		8ac	79	95
4		6ad	83	95	90:10		8ad	73	95
5		6ae	67	95	75:25		8ae	72	95
6		6af	91	95	93:7		8af	81	97
7		6ag	86	96	95:5		8ag	74	97

Table 2: (Continued)

Entry	6	Yield [%] ^[b]	ee [%] ^[d]	6/7 ^[c]	8	Yield [%] ^[b]	ee [%] ^[d]
8		85	96	91:9		74	96
9		64	91	92:8		83	91
10		89	97	92:8		90	97
11		90	95	96:4		92	95
12		96	95	> 98:2		74	94
13		96	97	97:3		73	96
14		85	97	91:9		80	97
15		90	96	93:7		93	94
16		83	98	90:10		82	96
17 ^[e]		87	94	92:8		75	94

[a] Unless otherwise noted, the reactions were performed with **4** (0.5 mmol) and **5** (1.5 mmol) in CH₂Cl₂ (5 mL) for 3 h. [b] Yield of the isolated product. [c] Determined by ¹H NMR spectroscopy. [d] The ee value is determined by HPLC using a chiral column.

[e] 1.5 mol % [{Pd(η³-C₃H₅)Cl]₂}/(R,R,R)-**1c** was used. TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

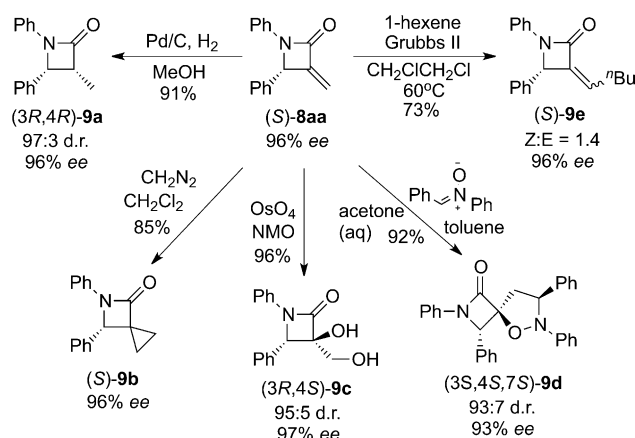
As shown in Table 2, the allylic amination of the racemic MBH adduct with various aromatic amines using the Pd/(R,R,R)-**1c** catalyst is quite general. The reaction proceeded

smoothly to afford the corresponding optically active amination products **6** in high yields (up to 96%) with excellent regioselectivities (up to > 98:2) and enantioselectivities (up to

98% *ee*). Neither the electronic property nor the steric hindrance of the aromatic amine (R^2) had an obvious influence on the enantioselectivity (Table 2, entries 1–8), but there was a slight negative effect, with regard to sterics, on the reactivity and regioselectivity (entry 5). Substituents on the aryl ring of the MBH adducts seem to have negligible effect on the catalytic performance (entries 9–17). The optically active allylic amination products **6** can be readily transformed into their corresponding β -lactam derivatives **8** in good yields without loss of enantioselectivity by reaction with $\text{Sn}[\text{N}(\text{TMS})_2]_2$ in refluxing toluene.^[15] It has been recognized that 1,4-diaryl-2-azetidinones (β -lactam) represents one type of potentially useful scaffolds for the development of antitumor agents that target tubulin.^[8f] In particular, the molecules containing a 4-methoxyphenyl, 3,4,5-trimethoxyphenyl, or 4-methoxy-3-hydroxyphenyl moiety displayed the most potent antiproliferative activity in inhibiting tubulin polymerization for human MCF-7 and MAD-MB-213 breast cancer cell lines without significant cytotoxicity in normal murine breast epithelial cells.^[8f] Therefore, we further investigated the reaction of the methoxy-substituted MBH adducts with methoxy-substituted anilines using this catalyst system. As shown in entries 18–21 of Table S6 in the Supporting Information, all the examined reactions proceeded very well to afford the corresponding allylic amination products **6** in excellent yields (84–92%), regio- (91:9–98:2) and enantioselectivities (93–98%). The resultant amination products were converted into the corresponding β -lactam derivatives **8** without loss of enantioselectivity (95–98% *ee*). The reaction of the substrates containing a fluorine atom (entries 22–23, Table S6) afforded the corresponding optically active fluorine-containing^[16] amination products and the β -lactam derivatives in good yields with excellent regio- and enantioselectivities. The absolute configuration of (+)-**8ad** was established by X-ray crystal diffraction analysis (Figure 1) to be *S* and the absolute configurations of the analogous β -lactam products were deduced by comparison of their Cotton effects with those of (*S*)-(+)-**8ad** as shown in the circular dichroism (CD) spectra (see the Supporting Information).

To demonstrate the utility of the present methodology, the optically active α -methylene β -lactam derivative (*S*)-**8aa** was subjected to chemical transformations into several types of

biologically interesting β -lactam derivatives. As shown in Scheme 3, the hydrogenation of (*S*)-**8aa** in the presence of 5 mol % of Pd/C gave (3*R*,4*R*)-**9a** as the major diastereomer (97:3 d.r.) in 91% yield.^[17a] The reaction of (*S*)-**8aa** with



Scheme 3. Transformation of (*S*)-**8aa** into a variety of biologically interesting β -lactam derivatives (**9a–e**). NMO = *N*-methylmorpholine *N*-oxide.

CH_2N_2 in CH_2Cl_2 afforded the corresponding cyclopropane derivative (*S*)-**9b** in 85% yield with the retention of stereochemistry at the β position. Dihydroxylation of (*S*)-**8aa** in the presence of OsO_4 and NMO gave (3*S*,4*R*)-**9c** with high diastereoselectivity (95:5 d.r.) in 96% yield. The [3+2] cycloaddition of (*S*)-**8aa** with diphenylnitron yielded the corresponding spiroisoxacolidine adduct (3*S*,4*S*,7*S*)-**9d** in 92% yield with a 93:7 d.r. and 93% *ee*.^[17b] Finally, the cross-metathesis of (*S*)-**8aa** with 1-hexene in the presence of the Grubbs II catalyst results in the formation of the butyl-substituted α -methylene β -lactam derivative (*S*)-**9e** with a *Z*/*E* ratio of 1.4:1. All these transformations clearly indicate the synthetic advantages of α -methylene moiety in the optically active β -lactam scaffold, thus providing a useful platform for the synthesis of various biologically interesting β -lactam derivatives.

Encouraged by the results mentioned above, we subsequently employed our methodology in the asymmetric synthesis of the drug Ezetimibe,^[9] a drug for treating high cholesterol, using (*R*)-**6lc** as the starting material (Scheme 4). (*R*)-**6lc** was obtained in 91% yield with 95% *ee* from the reaction of **4l** with **5c** in the presence 1.5 mol % of $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)_2\text{Cl}_2]/(\text{S,S,S})\text{-1c}$. The reaction of (*R*)-**6lc** with the nucleophile **10** under basic conditions afforded the corresponding Michael addition product, which was then treated with $[\text{Pd}(\text{PPh}_3)_4]$ (5 mol %) without purification to remove the allyloxycarbonyl group to give **11** in 71% total yield (2 steps). Treatment of **11** with LiHMDS in THF at -20°C yielded the β -lactam (3*R*,4*S*)-**12** as a single isomer in 77% yield with 95% *ee*. The β -lactam (3*R*,4*S*)-**12** can be readily transformed into Ezetimibe in two steps using reported methods.^[18] Thus the present methodology has provided an alternative process for the efficient synthesis of Ezetimibe by using the catalytic asymmetric allylic amination as the key step.

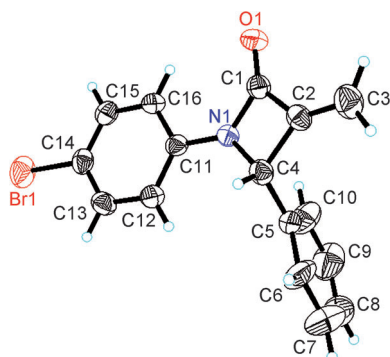
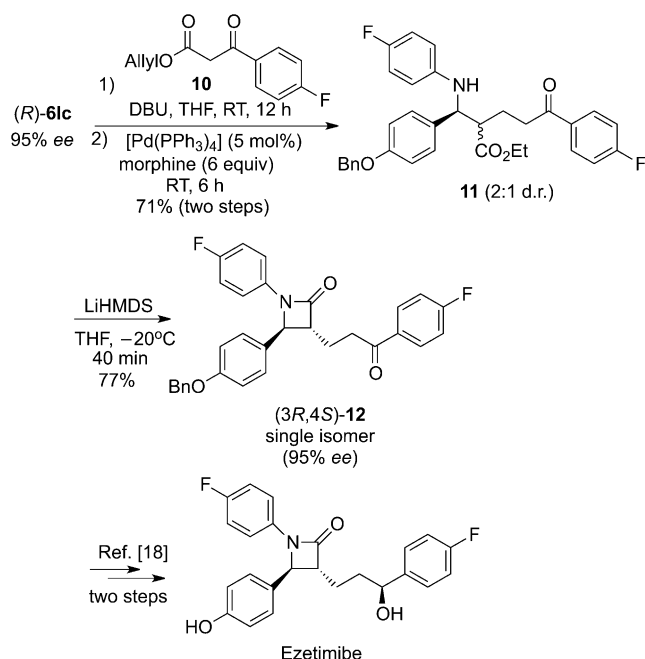


Figure 1. X-ray crystal structure (*S*)-**8ad** shown with thermal ellipsoids at 30% probability.^[19]



Scheme 4. Asymmetric synthesis of Ezetimibe using (R)-6lc as the key intermediate. Bn = benzyl, DBU = 1,8-diazabicyclo[5.4.0]undecene-7, HMDS = hexamethyldisilazide, THF = tetrahydrofuran.

In summary, a new class of aromatic spiroketal-based biphosphine ligands (SKPs) has been developed by simple transformation from readily available optically pure spiro-2,2'-bis(chroman) derivatives. Their palladium complexes were found to be highly efficient in the enantioselective allylic amination of the esters of racemic MBH adducts with aromatic amines, thus affording the corresponding optically active β -arylamino acid esters in good yields with high regio- and enantioselectivities. The resultant optically active β -arylamino acid esters can be readily transformed into their corresponding β -lactam derivatives without loss of enantioselectivity, thus providing a useful platform for the synthesis of various biologically important molecules. The utility of this method is demonstrated in the context of a facile synthesis of the drug Ezetimibe. The excellent performance of this type of ligand in the reaction will stimulate future explorations into their applications in transition metal catalyzed asymmetric reactions, and to further understand the underlying mechanistic aspects of the catalysis.

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- [1] For reviews, see: a) *Comprehensive Asymmetric Catalysis, Vol. I-III and Supplements 1 and 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, **2004**; b) *Catalytic Asymmetric Synthesis*, 3rd ed. (Ed.: I. Ojima), Wiley-Blackwell, Hoboken, **2010**; c) *Phosphorus Ligands in Asymmetric Catalysis* (Ed.: A. Börner), Wiley-VCH, Weinheim, **2008**; d) *Privileged*

- Chiral Ligands and Catalysts* (Ed. Q.-L. Zhou), Wiley-VCH, Weinheim, **2011**.
- [2] For reviews, see: a) J.-H. Xie, Q.-L. Zhou, *Acc. Chem. Res.* **2008**, *41*, 581; b) G. B. Bajracharya, M. A. Arai, P. S. Koranne, T. Suzuki, S. Takizawa, H. Sasai, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 285; c) K. Ding, Z. Han, Z. Wang, *Chem. Asian J.* **2009**, *4*, 32; d) P. W. N. M. van Leeuwen, Z. Freixa, E. Zuidema in *Phosphorus Ligands in Asymmetric Catalysis: Synthesis and Applications* (Ed.: A. Börner), Wiley-VCH, Weinheim, **2008**, pp. 1433–1454.
- [3] a) A. S. C. Chan, W.-H. Hu, C.-C. Pai, C.-P. Lau, *J. Am. Chem. Soc.* **1997**, *119*, 9570; b) M. A. Arai, M. Kuraishi, T. Arai, H. Sasai, *J. Am. Chem. Soc.* **2001**, *123*, 2907; c) Y. Fu, J.-H. Xie, A.-G. Hu, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Chem. Commun.* **2002**, 480; d) J.-H. Xie, L.-X. Wang, Y. Fu, S.-F. Zhu, B.-M. Fan, H.-F. Duan, Q.-L. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 4404.
- [4] a) Z. Freixa, M. S. Beentjes, G. D. Batema, C. B. Dieleman, G. P. F. van Strijdonck, J. N. H. Reek, P. C. J. Kamer, J. Fraanje, K. Goubitz, P. W. N. M. van Leeuwen, *Angew. Chem.* **2003**, *115*, 1322; *Angew. Chem. Int. Ed.* **2003**, *42*, 1284; b) P. W. N. M. van Leeuwen, M. A. Zuideveld, B. H. G. Swennenhuis, Z. Freixa, P. C. J. Kamer, K. Goubitz, J. Fraanje, M. Lutz, A. L. Spek, *J. Am. Chem. Soc.* **2003**, *125*, 5523; c) Z. Freixa, P. C. J. Kamer, M. Lutz, A. L. Spek, P. W. N. M. van Leeuwen, *Angew. Chem.* **2005**, *117*, 4459; *Angew. Chem. Int. Ed.* **2005**, *44*, 4385; d) C. Jiménez-Rodríguez, F. X. Roca, C. Bo, J. Benet-Buchholz, E. C. Escudero-Adán, Z. Freixa, P. W. N. M. van Leeuwen, *Dalton Trans.* **2006**, 268; e) X. Sala, E. J. G. Suárez, Z. Freixa, J. Benet-Buchholz, P. W. N. M. van Leeuwen, *Eur. J. Org. Chem.* **2008**, 6197; f) M. J.-L. Tschan, J.-M. López-Valbuena, Z. Freixa, H. Launay, H. Hagen, J. Benet-Buchholz, P. W. N. M. van Leeuwen, *Organometallics* **2011**, *30*, 792; g) O. Jacquet, N. D. Clément, Z. Freixa, A. Ruiz, C. Claver, P. W. N. M. van Leeuwen, *Tetrahedron: Asymmetry* **2011**, *22*, 1490.
- [5] a) J. Li, G. Chen, Z. Wang, R. Zhang, X. Zhang, K. Ding, *Chem. Sci.* **2011**, *2*, 1141; b) J. Li, W. Pan, Z. Wang, X. Zhang, K. Ding, *Adv. Synth. Catal.* **2012**, *354*, 1980.
- [6] a) X. Wang, Z. Han, Z. Wang, K. Ding, *Angew. Chem.* **2012**, *124*, 960; *Angew. Chem. Int. Ed.* **2012**, *51*, 936; b) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, *121*, 5449; *Angew. Chem. Int. Ed.* **2009**, *48*, 5345; c) Y. Zhang, Z. Han, F. Li, K. Ding, A. Zhang, *Chem. Commun.* **2010**, *46*, 156; d) Z. Han, Z. Wang, K. Ding, *Adv. Synth. Catal.* **2011**, *353*, 1584; e) J. Shang, Z. Han, Y. Li, Z. Wang, K. Ding, *Chem. Commun.* **2012**, *48*, 5172.
- [7] a) M. Shi, F.-J. Wang, M.-X. Zhao, *The Chemistry of the MBH Reaction*, RSC Publishing, London, **2011**; b) Y. Wei, M. Shi, *Acc. Chem. Res.* **2010**, *43*, 1005; c) D. Basavaiah, G. Veeraraghavaiah, *Chem. Soc. Rev.* **2012**, *41*, 68; d) D. Basavaiah, B. S. Reddy, S. S. Badsara, *Chem. Rev.* **2010**, *110*, 5447; e) Z. Qiao, Z. Shafiq, L. Liu, Z.-B. Yu, Q.-Y. Zheng, D. Wang, Y.-J. Chen, *Angew. Chem.* **2010**, *122*, 7452; *Angew. Chem. Int. Ed.* **2010**, *49*, 7294; f) Y. Wang, L. Liu, D. Wang, Y.-J. Chen, *Org. Biomol. Chem.* **2012**, *10*, 6908.
- [8] a) I. Ojima, *Acc. Chem. Res.* **1995**, *28*, 383; b) O. A. Mascaretti, G. O. Danelon, M. Laborde, E. G. Mata, E. L. Setti, *Curr. Pharm. Des.* **1999**, *5*, 939; c) G. S. Singh, *Mini-Rev. Med. Chem.* **2004**, *4*, 69; d) G. S. Singh, *Mini-Rev. Med. Chem.* **2004**, *4*, 93; e) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437; f) N. M. O'Boyle, M. Carr, L. M. Greene, O. Bergin, S. M. Nathwani, T. McCabe, D. G. Lloyd, D. M. Zisterer, M. J. Meegan, *J. Med. Chem.* **2010**, *53*, 8569; g) I. Banik, F. F. Becker, B. K. Banik, *J. Med. Chem.* **2003**, *46*, 12; h) S. Ruf, G. Neudert, S. Gürtler, R. Grünert, P. J. Bednarski, H.-H. Otto, *Monatsh. Chem.* **2008**, *139*, 847.
- [9] a) S. B. Rosenblum, T. Huynh, A. Afonso, H. R. Davis, Jr., N. Yumibe, J. W. Clader, D. A. Burnett, *J. Med. Chem.* **1998**, *41*, 973; b) J. W. Clader, *J. Med. Chem.* **2004**, *47*, 1.

- [10] a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, 103, 811; b) A. Lin, H. Mao, X. Zhu, H. Ge, R. Tan, C. Zhu, Y. Cheng, *Chem. Eur. J.* **2011**, 17, 13676, and references therein.
- [11] a) Y. Shi, M. Shi, *Eur. J. Org. Chem.* **2007**, 2905; b) G. Masson, C. Housseman, J.-P. Zhu, *Angew. Chem.* **2007**, 119, 4698; *Angew. Chem. Int. Ed.* **2007**, 46, 4614; c) V. Declerck, J. Martinez, F. Lamaty, *Chem. Rev.* **2009**, 109, 1.
- [12] a) B. M. Trost, *Acc. Chem. Res.* **1996**, 29, 355; b) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, 96, 395; c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, 103, 2921; d) L.-X. Dai, T. Tu, S.-L. You, W.-P. Deng, X.-L. Hou, *Acc. Chem. Res.* **2003**, 36, 659; e) L. A. Agrofoglio, I. Gillaizeau, Y. Saito, *Chem. Rev.* **2003**, 103, 1875; f) B. M. Trost, M. R. Machacek, A. Aponick, *Acc. Chem. Res.* **2006**, 39, 747; g) G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weinhofen, *Chem. Commun.* **2007**, 675; h) Z. Lu, S. Ma, *Angew. Chem.* **2008**, 120, 264; *Angew. Chem. Int. Ed.* **2008**, 47, 258.
- [13] a) S. Rajesh, B. Banerji, J. Iqbal, *J. Org. Chem.* **2002**, 67, 7852; b) T. Nemoto, T. Fukuyama, E. Yamamoto, S. Tamura, T. Fukuda, T. Matsumoto, Y. Akimoto, Y. Hamada, *Org. Lett.* **2007**, 9, 927.
- [14] For examples of the palladium-catalyzed asymmetric allylic substitution of MBH adducts using oxygen nucleophiles, see: a) B. M. Trost, H.-C. Tsui, F. D. Toste, *J. Am. Chem. Soc.* **2000**, 122, 3534; b) B. M. Trost, O. R. Thiel, H. C. Tsui, *J. Am. Chem. Soc.* **2002**, 124, 11616; c) B. M. Trost, M. R. Machacek, H. C. Tsui, *J. Am. Chem. Soc.* **2005**, 127, 7014; d) B. M. Trost, M. K. Brennan, *Org. Lett.* **2007**, 9, 3961.
- [15] a) W.-B. Wang, E. J. Roskamp, *J. Am. Chem. Soc.* **1993**, 115, 9417; b) H. Chen, L. N. Patkar, S.-H. Ueng, C.-C. Lin, A. S.-Y. Lee, *Synlett* **2005**, 2035.
- [16] a) B. K. Park, N. R. Kitteringham, P. O'Neill, *Annu. Rev. Pharmacol. Toxicol.* **2001**, 41, 443; b) S. Sun, A. Adejare, *Curr. Top. Med. Chem.* **2006**, 6, 1457; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, 317, 1881.
- [17] a) A. Basak, S. C. Ghosh, *Synlett* **2004**, 1637; b) A. Basak, H. M. M. Bdour, G. Bhattacharya, *Tetrahedron Lett.* **1997**, 38, 2535.
- [18] a) G. Wu, Y. Wong, X. Chen, Z. Ding, *J. Org. Chem.* **1999**, 64, 3714; b) C. H. V. A. Sasikala, P. R. Padi, V. Sunkara, P. Ramayya, P. K. Dubey, V. B. R. Uppala, C. Praveen, *Org. Process Res. Dev.* **2009**, 13, 907.
- [19] CCDC 880880 [(S)-**8ad**] 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.