Heterocycles

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# Access to Hexahydrocarbazoles: The Thorpe–Ingold Effects of the Ligand on Enantioselectivity

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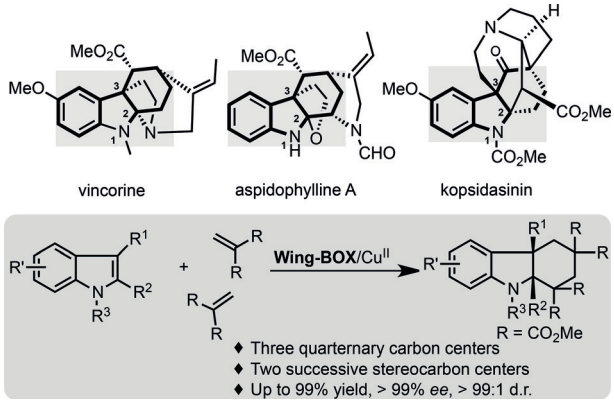
***Abstract:*** *A novel cyclization reaction of methylenemalonate with indoles is reported, and it provides efficient access to a variety of hexahydrocarbazoles. The enantioselective version was realized by a finely tuned ligand/$Cu^{II}$ catalyst. The optically active hexahydrocarbazoles contain three quaternary carbon centers and are obtained in up to 99% yield with greater than 99:1 d.r. and up to greater than 99% ee. This reaction can be carried out on gram scale and stereoselective transformation of the product led to the core structure of a series of alkaloids from Kopsia plants.*

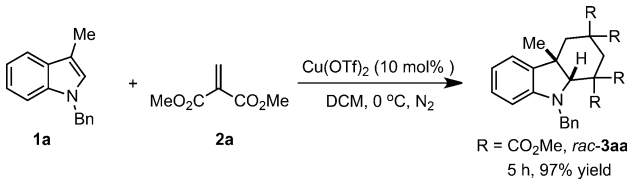
Hexahydrocarbazoles with a substituent in the 3-position, possessing a cyclohexyl-fused indoline scaffold with a quaternary carbon center, attract increasing interest from synthetic chemists because of their frequent occurrence in biologically active natural products such as vincorine, aspidophylline A, and kopsidasinin (Scheme 1).[1–3] Although several methods




***Scheme 1.*** Natural products and our approaches to hexahydrocarbazoles. For catalyst structure see Table 1.

have been developed for building optically active 3-substituted hexahydrocarbazoles,[3c,4] effective protocols are still limited compared to the rich diversity of useful molecules containing this chiral scaffold. Very recently we developed an unprecedented tandem cyclization reaction, which was unexpectedly achieved using indole and two molecules of methylenemalonate. This method provides a novel and efficient approach to hexahydrocarbazoles from simple starting materials. However, attempts to develop its asymmetric version proved challenging. Based on the observation that the Thorpe–Ingold effects of the ligand on the enantioselectivity, a new bis(oxazoline) (BOX) ligand was developed, thus providing easy access to optically active hexahydrocarbazoles bearing three quaternary carbon centers and two carbon stereocenters in up to 99% yield with up to greater than 99% *ee* in the presence of 1 mol% catalyst (Scheme 1). Herein, we report these preliminary results.

In our recent studies on tandem reactions with indole derivatives,[5] unexpectedly, an unprecedented [2+2+2] reaction of the indole **1a** with two molecules of methylenemalonate (**2a**) was observed, as shown in Scheme 2. Further study




***Scheme 2.*** Tandem [2+2+2] reaction of indole with methylenemalonate (**2a**). DCM = dichloromethane, Tf = trifluoromethanesulfonyl.

demonstrated that a broad range of indole derivatives were compatible with this reaction, including different functional groups at the 4-, 5-, 6, and 7- positions of the indole, as well as indole derivatives with C3-substituents other than a methyl group (20 examples; see Table S10 in the Supporting Information). Notably, this tandem cyclization reaction was capable of scale up to a 10 gram scale (30 mmol), thus giving 13.8 grams of the hexahydrocarbazole product (77% yield; see the Supporting information).

Inspired by the efficiency of constructing the hexahydrocarbazoles and its potential in organic synthesis, we explored the asymmetric version of this reaction. However, initial results were very frustrating. When either *i*Pr-BOX or *t*Bu-BOX ligands and $Cu(OTf)_2$ were used, only a trace amount of product was detected at 30 °C, while **2a** was almost completely consumed. Utilizing Py-BOX could barely promote the reaction, thus resulting in 6% yield based on $^1$H NMR analysis (see the Supporting Information). By changing to the Ph-BOX **L1** ligand, the desired product was obtained in 76% yield with 48% *ee* (Table 1, entry 1). With the insight gained from our previous work on asymmetric reactions with oxazo-

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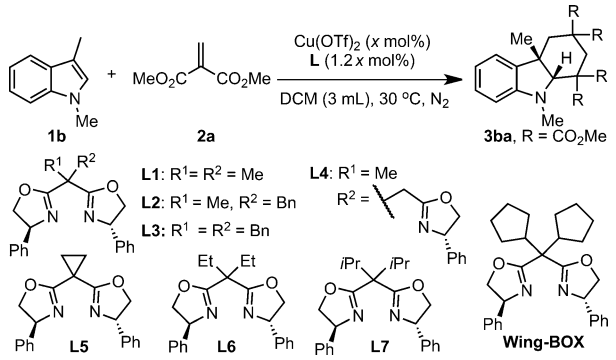
***Table 1:*** Optimization of the enantioselective reaction conditions.[a]



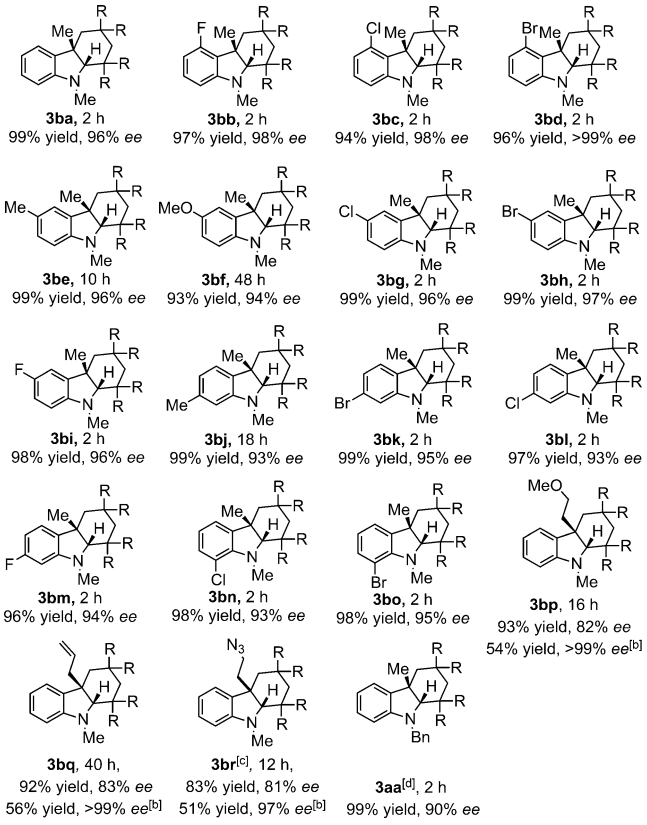

| Entry | L | x | T [°C] | t [h] | Yield [%][b] | ee [%][c] |
|---|---|---|---|---|---|---|
| 1 | **L1** | 10 | 30 | 24 | 76 | 48 |
| 2 | **L2** | 10 | 30 | 24 | 39 | 62 |
| 3 | **L3** | 10 | 30 | 24 | 16 | 57 |
| 4 | **L4** | 10 | 30 | 24 | 14 | 46 |
| 5 | **L5** | 10 | 30 | 48 | 56 | 45 |
| 6 | **L6** | 10 | 30 | 48 | 75 | 64 |
| 7 | **L7** | 10 | 30 | 72 | 71 | 70 |
| 8 | **Wing-BOX** | 10 | 30 | 72 | 56 | 75 |
| 9 | **Wing-BOX** | 10 | −78 | 2 | 99 | 92 |
| 10[d] | **Wing-BOX** | 1 | −78 | 2 | 99 | 96 |
| 11[e] | **Wing-BOX** | 0.5 | −78 | 12 | 99 | 95 |

[a] Reaction conditions: **1b** (0.2 mmol), **2a** (0.6 mmol), Lewis acid/**L** = 1:1.2, DCM (3 mL), $N_2$. [b] Yield of isolated product. [c] Determined by chiral-phase HPLC. [d] **1b** (1.0 mmol), **2a** (3.0 mmol), $Cu(OTf)_2$ (0.01 mmol), **L** (0.012 mmol). [e] **1b** (2.0 mmol), **2a** (6.0 mmol), $Cu(OTf)_2$ (0.01 mmol), **L** (0.012 mmol).

line ligands,[6,7] we expected the substituents on the bridging carbon center to have a profound effect on the configuration of the oxazoline group, thus affecting the acidity of the Lewis acid when coordinated. When the sidearm-modified BOX (SaBOX) ligand[7] **L2**, bearing a benzyl group was employed, the *ee* value increased to 62% (entry 2). However, no further improvement was achieved with the SaBOX ligands **L3** and **L4** (entries 3 and 4), so we turned to ligands with other substituents, such as alkyl groups. When the ligand **L5**, having a cyclopropane on the bridging carbon center was used, the *ee* value decreased to 45% (entry 5), while the ethyl-substituted ligand **L6** led to the desired product in 64% *ee* and 75% yield (entry 6), thus showing a strong influence of the Thorpe–Ingold effect of the ligand on the enantioselectivity. Thus, we changed the Et group to *i*Pr (**L7**) and it led to an increase of the *ee* value (entry 7). These results encouraged us to further alter *i*Pr into cyclopentyl (**Wing-BOX**), and 75% *ee* was obtained albeit with a slightly decreased yield (entry 8). To our delight, by lowering the temperature to −78 °C, the undesired polymerization[8] of **2a** was further suppressed, and 99% yield with 92% *ee* was achieved (entry 9). With 1 mol% catalyst and an increased substrate concentration ([**1b**] = 0.33 mol $L^{-1}$), the desired product could be obtained in 99% yield with 96% *ee* (entry 10). The reaction was further successfully scaled up (2.0 mmol of **1b**) and 99% yield with 95% *ee* was obtained, even when 0.5 mol% catalyst was employed (entry 11).

Under the optimal reaction conditions, we investigated the generality for different substrates (Table 2). Substrates

***Table 2:*** Substrate scope of the enantioselective tandem cyclization reaction.[a]

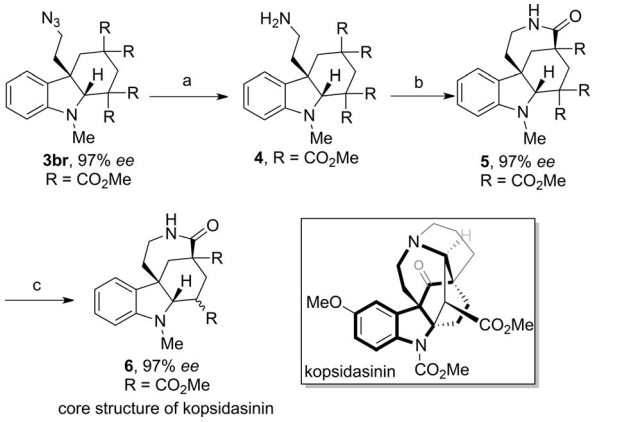

[a] **1** (1 mmol), **2a** (3 mmol), $Cu(OTf)_2$ (0.01 mmol), **Wing-BOX** (0.012 mmol) DCM (3.0 mL), −78 °C, $N_2$. Yield of isolated product. The d.r. values were determined by $^1H$ NMR analysis. The *ee* values were determined by chiral-phase HPLC. [b] The yield and *ee* value were obtained after recrystallization. [c] With 10 mol% catalyst, [**1**] = 0.014 mol $L^{-1}$. [d] With 10 mol% catalyst, [**1**] = 0.067 mol $L^{-1}$.

with electron-poor and electron-rich substituents at the 4-, 5-, 6-, and 7-positions all reacted smoothly to give excellent results (**3ba–bo**; up to 99% yield and >99% *ee*), thus demonstrating the outstanding ability for enantioinduction with 1 mol% catalyst. Substrates with electron-withdrawing groups at the 5-position of the indole showed higher reactivity compared to substrates with electron-donating groups, thus leading to a shorter reaction time, and suggesting that the ring-closing nucleophilic attack of the malonate carbanion on the iminium might be the rate-determining step in this reaction. In addition, this enantioselective cyclization reaction was carried out on gram scale with the substrate **1b**, thus giving the product **3ba** (1.27 g) in 98% yield with 96% *ee*. It was noteworthy that other substituents, such as alkoxy and allyl groups, at the 3-position of the indole, were also compatible in this transformation with good yields and greater than 99% *ee* after recrystallization (without recrys-

tallization: 82% *ee* for **3bp** and 83% *ee* for **3bq**). A 3-substituted indole bearing an azido group was also tolerated, thus giving the corresponding product **3br** in 83% yield with 81% *ee*. A 1-benzyl-substituted indole substrate was also explored, and furnished the corresponding product **3aa** in 99% yield with 90% *ee*. The absolute configuration of **3bh** was established by X-ray crystallography.[9]

As shown in Scheme 3, the product **3br**[10] could be easily transformed into **4**, with subsequent intramolecular lactamization in the presence of NaOMe/MeOH to afford the




***Scheme 3.*** Transformations of the tandem cyclization product. Reagent and conditions: a) 10 wt% Pd/C, $H_2$, MeOH, 30 °C. b) NaOMe, MeOH, reflux, 45% yield for two steps, >99:1 d.r. and 97% *ee*. c) LiCl/$H_2O$ (1:1), DMSO, 130 °C, 62% yield, 1.3:1 d.r., 97% *ee* for both diastereomers. DMSO = dimethylsulfoxide.

product **5** in 45% yield over two steps and with 97% *ee*. Mono-decarboxylation furnished the product **6** which represents a core structure of a series of alkaloids from *Kopsia* plants[2] in 62% yield.[9]

Among the screened ligands, **Wing-BOX** furnished the best results. To understand the impact of the Thorpe–Ingold effects of the ligand on the enantioselectivity, single crystals of **L1**/$CuBr_2$ and **Wing-BOX**/$CuBr_2$ were grown. According to the X-ray analysis[9] shown in Figure 1, copper(II) chelates with two nitrogen atoms in the oxazoline ring, along with two bromine atoms to form a highly twisted plane quadrangle. A comparison of the two crystal structures shows that although the bite angle of the two complexes are similar,[11] the coordination bond lengths of Cu1-N1 and Cu1-N1A in **Wing-BOX**/$CuBr_2$ are much shorter than the ones in **L1**/$CuBr_2$ (1.948 Å vs. 1.971 Å, 1.948 Å vs. 1.986 Å), and suggests the reaction center to be in closer proximity to the chiral environment. The dihedral angles of the chiral skeleton and the Cu–N bond have an obvious difference [Torsion (Cu1-N1-C1-C14)$_{\mathbf{L1}/CuBr_2}$ = 68.6°; Torsion (Cu1-N1-C1-C5)$_{\mathbf{Wing\text{-}BOX}/CuBr_2}$ = 47.6°]. These observations suggest that by installing the wings (cyclopentanyl groups), the chiral cavity of the **Wing-BOX**/$CuBr_2$ becomes more crowded compared to the cavity of the system based on the parent ligand **L1**. Both Eyring plots for the tandem cyclization reactions conducted with **L1** and **Wing-BOX** show a linear dependence of ln(major enantiomer%/minor enantiomer%) versus reciprocal temperature (Figure 1).[12] The slope of the line representing data for **Wing-BOX** is 0.78, while the slope for that representing **L1** is 0.16, thus indicating that the difference of activation energy of the transition state in the catalysis with **Wing-BOX** is much higher than that with **L1**, and leading to higher enantioselectivity when **Wing-BOX** is employed.

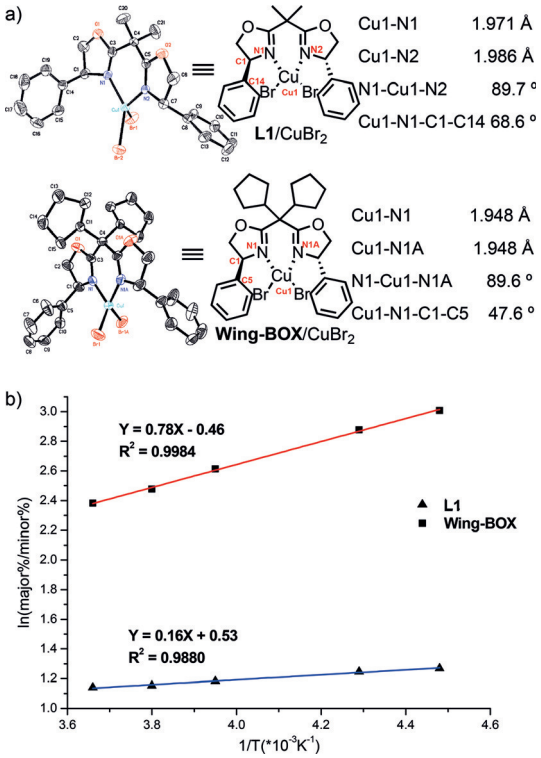



***Figure 1.*** Comparison of **L1** and **Wing-BOX**. a) X-ray crystal structures of **L1**/$CuBr_2$ and **Wing-BOX**/$CuBr_2$. b) Eyring plots for the tandem cyclization reaction of **1b** and **2a** catalyzed by **L1**/$Cu(OTf)_2$ and **Wing-BOX**/$Cu(OTf)_2$.

In conclusion, we have developed a novel tandem cyclization reaction with two molecules of methylenemalonate and an indole, thus enabling the preparation of a variety of hexahydrocarbazoles by a formal [2+2+2] process. The **Wing-BOX**/$Cu^{II}$ catalyst was designed for the asymmetric version based on Thorpe–Ingold effect considerations for the BOX ligands and their anticipated impact on the enantioselectivity. This method provides a facile way to construct optically active hexahydrocarbazoles with three quaternary carbon centers in up to 99% yield with greater than 99:1 d.r. and up to greater than 99% *ee*. The newly developed catalyst system has a number of advantages, including low catalyst loading, broad substrate scope, facile scale-up, and the possibility to generate readily transformable products. Our studies on the influence of Thorpe–Ingold effects showed that the lengths of the coordination bond and the steric hindrance at the catalytic center could be adjusted by the choice of the substituents on the bridge carbon of BOX. Understanding the influence of Thorpe–Ingold effects on the enantioselectivity paves a facile way in catalyst design. Further applications of **Wing-BOX** ligands in catalytic reactions are underway in our laboratory.

## Experimental Section

Typical procedure: A mixture of $Cu(OTf)_2$ (0.01 mmol) and **Wing-BOX** (0.012 mmol) in DCM (2.0 mL) was stirred at 30 °C for 2 h under $N_2$. The system was cooled to −78 °C before the indole **1** (1.0 mmol) was added. And then, 0.5 mL DCM was added to wash the tube-wall. A solution of **2a** (3.0 mmol) in DCM (0.5 mL) was then added dropwise to the system. When the reaction was completed (monitored by TLC), the reaction mixture was filtered through a thin layer of silica gel and eluted with DCM. The solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel (ethyl acetate/petroleum ether, 1:5–1:2) to afford the product.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** copper · cyclizations · enantioselectivity · heterocycles · ligand effects

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[1] a) M. M. Amer, W. E. Court, *Phytochemistry* **1980**, *19*, 1833–1836; b) D. Guillaume, A. M. Morfaux, B. Richard, G. Massiot, L. L. Men-Olivier, J. Pusset, T. Sévenet, *Phytochemistry* **1984**, *23*, 2407–2408; c) G. Subramaniam, O. Hiraku, M. Hayashi, T. Koyano, K. Komiyama, T.-S. Kam, *J. Nat. Prod.* **2007**, *70*, 1783–1789; d) G. Subramaniam, T.-S. Kam, *Helv. Chim. Acta* **2008**, *91*, 930–937; e) L. Liu, Y.-Y. Chen, X.-J. Qin, B. Wang, Q. Jin, Y.-P. Liu, X.-D. Luo, *Fitoterapia* **2015**, *105*, 160–164; f) M.-L. Yang, J. Chen, M. Sun, D.-B. Zhang, K. Gao, *Planta Med.* **2016**, *82*, 712–716.

[2] a) K. Homberger, M. Hesse, *Helv. Chim. Acta* **1982**, *65*, 2548–2557; b) M. O. Hamburger, G. A. Cordell, K. Likhitwitayawuid, N. Ruangrungsi, *Phytochemistry* **1988**, *27*, 2719–2724; c) T.-S. Kam, L. Arasu, Yoganathan, *Phytochemistry* **1996**, *43*, 1385–1387; d) T.-S. Kam, K.-M. Sim, *Phytochemistry* **1998**, *47*, 145–147.

[3] For selected examples of natural product total syntheses, see: a) M. Zhang, X. P. Huang, L. Q. Shen, Y. Qin, *J. Am. Chem. Soc.* **2009**, *131*, 6013–6020; b) L. S. Zu, B. W. Boal, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 8877–8879; c) W. W. Zi, W. Q. Xie, D. W. Ma, *J. Am. Chem. Soc.* **2012**, *134*, 9126–9129; d) B. D. Horning, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 6442–6445; e) W. W. Ren, Q. Wang, J. P. Zhu, *Angew. Chem. Int. Ed.* **2014**, *53*, 1818–1821; *Angew. Chem.* **2014**, *126*, 1849–1852; f) J. M. Smith, J. Moreno, B. W. Boal, N. K. Garg, *J. Am. Chem. Soc.* **2014**, *136*, 4504–4507; g) M. X. Teng, W. W. Zi, D. W. Ma, *Angew. Chem. Int. Ed.* **2014**, *53*, 1814–1817; *Angew. Chem.* **2014**, *126*, 1845–1848; h) J. Moreno, E. Picazo, L. A. Morrill, J. M. Smith, N. K. Garg, *J. Am. Chem. Soc.* **2016**, *138*, 1162–1165.

[4] a) Q. Cai, C. Zheng, J.-W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2011**, *50*, 8665–8669; *Angew. Chem.* **2011**, *123*, 8824–8828; b) Q. Cai, S.-L. You, *Org. Lett.* **2012**, *14*, 3040–3043; c) B. E. Daniels, J. Ni, S. E. Reisman, *Angew. Chem. Int. Ed.* **2016**, *55*, 3398–3402; *Angew. Chem.* **2016**, *128*, 3459–3463; d) S.-Z. Jiang, X.-Y. Zeng, X. Liang, T. Lei, K. Wei, Y.-R. Yang, *Angew. Chem. Int. Ed.* **2016**, *55*, 4044–4048; *Angew. Chem.* **2016**, *128*, 4112–4116.

[5] J. Zhu, Y.-J. Cheng, X.-K. Kuang, L. Wang, Z.-B. Zheng, Y. Tang, *Angew. Chem. Int. Ed.* **2016**, *55*, 9224–9228; *Angew. Chem.* **2016**, *128*, 9370–9374.

[6] For selected reviews on the chiral BOX ligands, see: a) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336–345; b) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325–335; c) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651; d) G. C. Hargaden, P. Guiry, *Chem. Rev.* **2009**, *109*, 2505–2550; e) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2011**, *111*, 284–437; f) J.-i. Ito, H. Nishiyama, *Synlett* **2012**, 509–523; g) S.-F. Zhu, Q.-L. Zhou, *Acc. Chem. Res.* **2012**, *45*, 1365–1377.

[7] For reviews on the sidearm strategy and related, see: a) J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2005**, *34*, 664–676; b) L. H. Gade, S. Bellemin-Laponnaz, *Chem. Eur. J.* **2008**, *14*, 4142–4152; c) S. Liao, X. L. Sun, Y. Tang, *Acc. Chem. Res.* **2014**, *47*, 2260–2272; for recent uses of SaBOX ligands, see: d) L. W. Feng, P. Wang, L. Wang, Y. Tang, *Sci. Bull.* **2015**, *60*, 210–215; e) Z. Xu, H. Ren, L. Wang, Y. Tang, *Org. Chem. Front.* **2015**, *2*, 811–814; f) Q.-J. Liu, L. Wang, Q.-K. Kang, X. P. Zhang, Y. Tang, *Angew. Chem. Int. Ed.* **2016**, *55*, 9220–9223; *Angew. Chem.* **2016**, *128*, 9366–9369; g) J.-L. Hu, L.-W. Feng, L. Wang, Z. Xie, Y. Tang, X. Li, *J. Am. Chem. Soc.* **2016**, *138*, 13151–13154.

[8] J. L. De Keyser, C. J. C. Decock, J. H. Poupaert, P. Dumont, *J. Org. Chem.* **1988**, *53*, 4859–4862.

[9] CCDC 1509447 (**6**), 1518089 (**3bh**), 1509455 ($CuBr_2$/**L1**), and 1509456 ($CuBr_2$/**Wing-BOX**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[10] The major enantiomer was obtained from the mother liquor.

[11] a) I. W. Davies, L. Gerena, L. Castonguay, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *Chem. Commun.* **1996**, 1753–1754; b) S. E. Denmark, C. M. Stiff, *J. Org. Chem.* **2000**, *65*, 5875–5878; c) S. E. Denmark, N. Nakajima, C. M. Stiff, O. J. C. Nicaise, M. Kranz, *Adv. Synth. Catal.* **2008**, *350*, 1023–045.

[12] D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.

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