Asymmetric Synthesis of Axially Chiral Isoquinolones: Nickel-Catalyzed Denitrogenative Transannulation**

Zhi-Jia Fang, Sheng-Cai Zheng, Zhen Guo, Jing-Yao Guo, Bin Tan,* and Xin-Yuan Liu*

Abstract: *The first Ni⁰/bis(oxazoline)-catalyzed asymmetric denitrogenative transannulation of 1,2,3-benzotriazin-4(3H)-ones with bulky internal alkynes to form novel axially chiral isoquinolones in an atroposelective manner has been developed. This method provides direct asymmetric access to axially chiral isoquinolones with excellent functional-group tolerance in excellent yields and stereoselectivities from readily available starting materials under mild reaction conditions. These axially chiral isoquinolones exhibit high cytotoxicity against a number of human cancer cell lines. DFT calculations reveal the nature of the transition state in the key annulation step.*

Axially chiral compounds are components which are omnipresent in naturally occurring and synthetic biologically active molecules,[1] and are important platforms for chiral catalyst/ligand development within the fields of asymmetric catalysis and synthesis.[2] Therefore, great synthetic efforts have been made to develop efficient asymmetric methodologies for constructing axially chiral biaryls,[1,3] including biaryl synthesis by [2+2+2] cycloaddition reactions,[3d,4a] dynamic kinetic resolution of biaryls,[4b–d] Suzuki–Miyaura couplings,[3c,4e] oxidative homocouplings,[4f–g] C−H bond functionalization,[4h] organocatalytic formations,[4i–o] and many others.[4p–r] Compared with the successful approaches toward biaryl atropisomers, only a few asymmetric routes to access atropisomeric aza-heterocycles have been reported.[3d,5] However, axially chiral aza-heterocycles bearing pyridone units have been recognized as core structures of pharmaceutically active molecules (Figure 1).[1,6] Thus, the development of a highly enantioselective strategy for accessing novel atropisomeric aza-heterocycles, bearing pyridone units, is still in great demand.
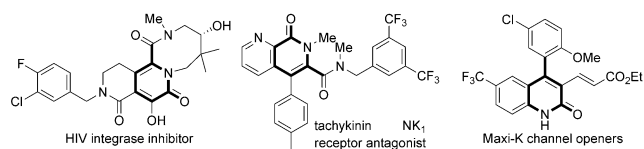

Figure 1. Axially chiral aza-heterocycles of medicinal interest.

Over the past decade, transition-metal-catalyzed denitrogenative transannulation of a triazole ring has attracted considerable attention as a powerful tool toward diverse aza-heterocyclic cores,[7] especially since the pioneering studies carried out by the research groups of Gevorgyan,[7b] Fokin,[7c] and Murakami.[7d] In this field, Murakami and co-workers reported seminal work on the use of nickel catalysts for such reactions of 1,2,3-benzotriazin-4(3H)-ones with various unsaturated compounds,[8] in which a five-membered aza-nickelacycle was formed. In particular, they demonstrated a non-enantioselective nickel-catalyzed synthesis of isoquinolones by annulation of either internal or terminal alkynes with good to moderate regioselectivity.[8a] Inspired by these seminal works, we hypothesized that a related catalytic asymmetric approach to an important class of axially chiral isoquinolones in an atroposelective manner could be realized with internal alkynes, bearing sterically encumbered substituents, by using the appropriate chiral ligands (Scheme 1). Indeed, the in situ
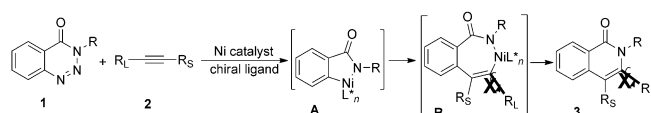
Scheme 1. Construction of axially chiral isoquinolones.

generated five-membered aza-nickelacycle **A** could undergo regioselective insertion of an alkyne, bearing a judiciously chosen sterically encumbered group, into the nickel–carbon bond to generate a configurationally fixed seven-membered nickelacycle (**B**) coordinated by a chiral ligand. Because of the significant hindrance around the R_L–alkenyl axis in **B**, the formation of the desired axially chiral isoquinolones in an atroposelective manner after reductive elimination might be expected. In this scenario, several challenges would be encountered: 1) the selection of appropriate alkynes to increase the reaction efficiency, control regioselectivity, and increase the rotational energy barrier through steric interactions so as to establish axial chirality; 2) the choice of a chiral ligand to efficiently induce axial stereocontrol; 3) the use of mild reaction conditions to obviate the axial rotation.

[*] Dr. Z.-J. Fang,[+] Dr. S.-C. Zheng,[+] J.-Y. Guo, Prof. Dr. B. Tan, Prof. Dr. X.-Y. Liu
Department of Chemistry
South University of Science and Technology of China
Shenzhen, 518055 (P.R. China)
E-mail: tanb@sustc.edu.cn
liuxy3@sustc.edu.cn

Prof. Dr. Z. Guo
College of Materials Science & Engineering, Taiyuan University of Technology, Shanxi (P.R. China)

[+] These authors contributed equally to this work.

As part of our continued interest in the construction of axially chiral compounds,[9] herein, we describe the first highly regio- and enantioselective chiral nickel(0)/bis(oxazoline)-catalyzed[10] denitrogenative transannulation of 1,2,3-benzotriazin-4(3H)-ones with bulky internal alkynes, thus providing a new synthetic route toward a novel class of axially chiral isoquinolones bearing multiple and diverse substitution patterns. Such structural motifs are important components of various biologically active natural products and medicinal compounds.[11]

The initial investigation to validate our hypothesis started with an annulation between N-tolyl-1,2,3-benzotriazin-4(3H)-one (**1a**) and the alkyne **2a**, which bears a bulky naphthalene ring (Scheme 2). Since the chiral P,N-type ligands have
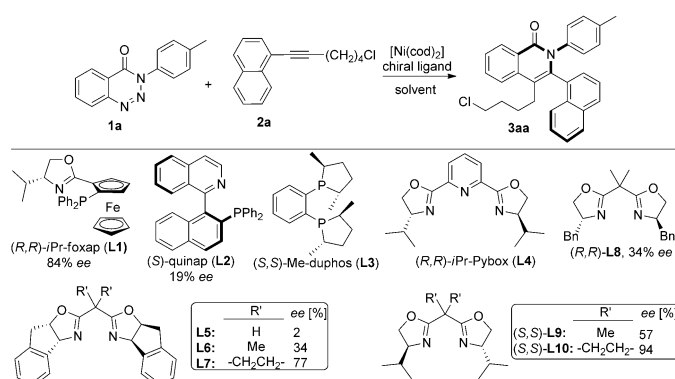
Scheme 2. Screening of the reaction conditions. cod = 1,5-cyclooctadiene.

proven to be excellent ligands in asymmetric nickel(0) catalysis,[8b,d] (R,R)-iPr-foxap (**L1**) was first examined as the ligand. To our delight, in the presence of [Ni(cod)₂] (20 mol%) and **L1** (22 mol%), the annulation of **1a** with **2a** gave the desired axially chiral product **3aa** with 84% ee and almost complete regioselectivities, albeit in only 20% yield (see Table S1 in the Supporting Information). Encouraged by this result, we then screened different chiral ligands and found that (S)-quinap, the bis(phosphine) ligand (S,S)-Me-duphos, and tridentate (R,R)-(iPr)-Pybox were considerably inferior to **L1** in terms of reactivity and enantioselectivity. We then examined the activity of chiral bis(oxazoline) ligands,[12] which were previously reported to be successfully applied in nickel-catalyzed asymmetric reactions.[10] Different indanyl-substituted ligands (**L5–L7**) with either a hydrogen-, bis(methyl)-, or cyclopropylidene-linker generated **3aa** in good yield but with only 2–77% ee, and the results revealed that tuning the bite angle of the ligand by changing the central linker significantly influenced the enantioselectivity of the catalyst. We are pleased to find that the cyclopropylidene-linked ligand (S,S)-**L10**, having an isopropyl substituent, exhibited excellent yield (87%) and good enantioselectivity (81% ee, see Table S1 in the Supporting Information). Among the reaction temperatures examined, the reaction at

room temperature gave the best results of 89% yield and 93% ee (see Table S1 in the Supporting Information). We then screened different organic solvents to find that 1,4-dioxane was optimal, thus suggesting a significant solvent impact on this reaction. It should be noted that the catalyst loading could be reduced from 20 to 10 mol% without significantly affecting the reaction efficiency and enantioselectivity (86% yield and 94% ee).

With the optimized reaction conditions in hand, we next investigated the scope of the internal alkyne partner. A wide range of alkynes with different substituents at different positions all reacted smoothly with **1a** to afford the corresponding axially chiral products as a single regioisomer with excellent efficiency and stereoselectivity (Table 1). Various groups, including alkyl halides (**2a**, **2b**), n-hexyl (**2c**), methyl (**2d**), ether (**2e**), and an allyl ether (**2f**) were well-tolerated. These results are significant since most groups are reactive and, thus, are difficult retain in many nickel-catalyzed organic transformations.[10] It is worth mentioning that the substrate **2g**, with an aryl substituent (R_s), also afforded the expected product **3ag** in 91% yield with 79% ee and 94:6 r.r. (regioisomeric ratio). This reaction is amenable to both electron-withdrawing and electron-donating groups at the 4-position of the naphthalene ring (**3ah–aj**) and these substitutions also exhibit a beneficial effect for the improvement of enantioselectivity. Most importantly, the more sterically hindered pyrene ring can also be incorporated into the product (**3ak**) in 93% yield with 94% ee, thus demonstrating that the substrate scope is not only limited to naphthyl acetylenes.
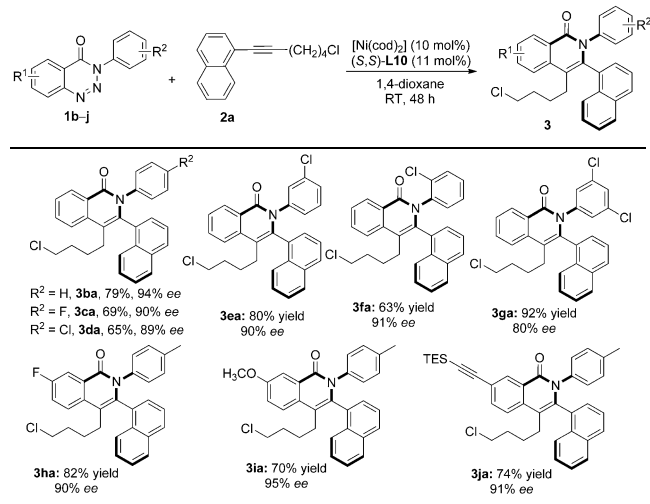
Next, the scope of the substituents on the nitrogen atom of **1** was explored in the reaction with **2a** under the standard reaction conditions (Table 2). In addition to **1a** (Table 1), which bears an electron-donating group, a variety of aryl substituents with electron-neutral or electron-deficient groups (R²) at different positions on the phenyl ring furnished the products **3ba–fa** in 63–80% yields with 89–94% ee. Meanwhile, the reaction also worked well for the substrate

Table 1: Reaction scope with respect to the internal alkynes.[a,b,c]
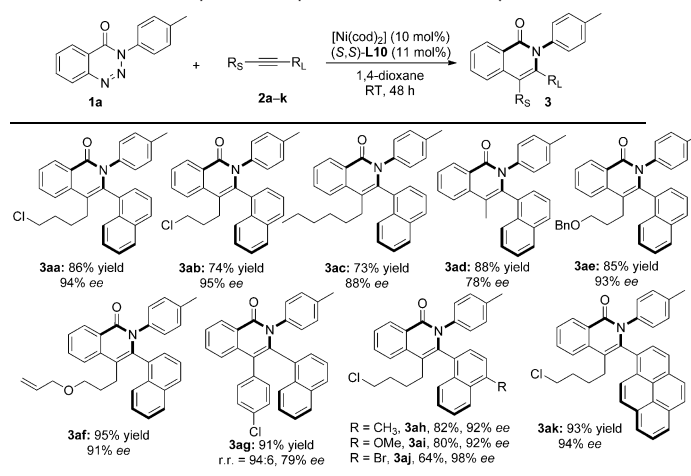
[a] All the reactions were conducted on a 0.1 mmol scale. [b] Yield of isolated product based on **1**. [c] Determined by HPLC analysis.
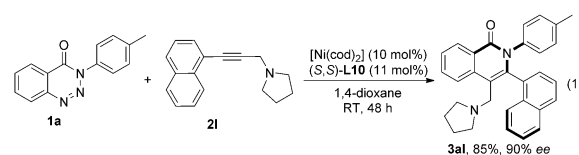
Table 2: Reaction scope with respect to the 1,2,3-benzotriazin-4(3H)-ones.[a,b,c]
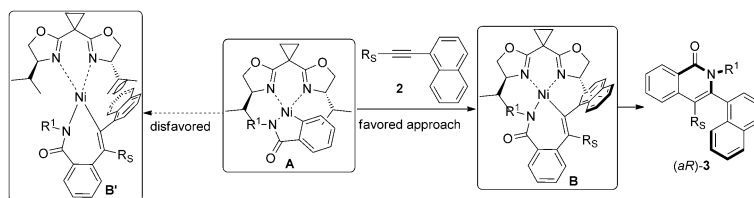

R² = H, **3ba**, 79%, 94% *ee*
R² = F, **3ca**, 69%, 90% *ee*
R² = Cl, **3da**, 65%, 89% *ee*

3ea: 80% yield
90% *ee*

3fa: 63% yield
91% *ee*

3ga: 92% yield
80% *ee*

3ha: 82% yield
90% *ee*

3ia: 70% yield
95% *ee*

3ja: 74% yield
91% *ee*

[a] All the reactions were conducted on 0.1 mmol scale. [b] Yield of the isolated product based on **1**. [c] Determined by HPLC analysis.


3al, 85%, 90% *ee* (1)

The structures of **3aa** and **3da** were confirmed by X-ray diffraction analysis of their single crystals and the absolute configuration was assigned to be *aR* (see Figure S1).[14] On this basis, together with the nickel-catalyzed annulation of 1,2,3-benzotriazin-4(3H)-ones with alkynes,[8] a working model was tentatively proposed to explain the regio- and enantioselectivity of the reaction (Scheme 3). The formation of the five-membered-ring aza-nickelacycle **A** through bidentate chelation of the isopropyl bis(oxazoline) (*S,S*)-**L10** to the cationic nickel(II) center[8b] should induce high reactivity and a rigid chiral environment. To avoid the repulsive steric interaction between the bulkier naphthyl substituent and the phenyl ring of the substrate, the regioselective insertion of alkyne into the nickel–carbon bond results in the formation of the seven-membered nickelacycle **B**. During this process, **B**,

1g, bearing two chloro groups, thus affording **3ga** in 92% yield with 80% *ee*. The substrates **1h** and **1i**, having an electron-donating and electron-withdrawing ring substituent, respectively, also underwent reaction to furnish the corresponding products **3ha** (82% and 90% *ee*) and **3ia** (70% and 95% *ee*). Moreover, even the reactive triethylsilyl (TES) alkynyl group remained intact throughout the reaction and the product **3ja** was obtained in 74% yield with 91% *ee*, and would offer opportunities for useful transformations.

Axially chiral isoquinolones have useful properties as either powerful organocatalysts or ligands, and as biologically active compounds.[13] To demonstrate the viability of our obtained products for such purposes, we examined the annulation of **1a** with the naphthyl acetylene **2l**, bearing a tertiary amine group, under the standard reaction conditions and were pleased to find that the desired axially chiral isoquinolone with a tertiary amine was obtained in 85% yield with 90% *ee* [Eq. (1)]. To further verify the stability of such axial compounds, we heated the obtained **3al** in toluene (1 mg mL⁻¹) at 100°C for 24 hours and no erosion of the *ee* value was observed, thus clearly demonstrating that such compounds display a remarkably high barrier to rotation about the naphthyl–alkenyl bond. Therefore, the obtained axially chiral compounds have been suggested to have potentially wide applications as effective asymmetric organocatalysts or ligands. The structure resemblance to a variety of biologically active compounds also encouraged us to evaluate the biological activity of our products. Our preliminary biological studies revealed that axially chiral isoquinolones **3aa**, **3ah**, and **3ha** exhibited good cytotoxicities against both HT-29 and K562 cancer cell lines with IC₅₀ values ranging from 18.5 to 22.3 and 10.5 to 14.3 μM, respectively (see Table S2), thus suggesting a potential application of this class of axially chiral isoquinolones in anticancer studies.

Scheme 3. Proposed working model for the regio- and enantioselectivity.

having an isopropyl group and the naphthyl substituent on opposite faces, is more favored than the intermediate **B′** owing to the absence of steric interactions between the isopropyl group of the ligand and the naphthyl substituent of the substrate, thus rendering hindrance about the naphthyl–alkenyl axis for the establishment of axial chirality to give (*aR*)-**3** in an atroposelective manner after reductive elimination.

To gain insight into the origin of the axial chirality observed in the annulation reaction, we investigated the reaction mechanism and characterized the transition states (TS) involved by performing hybrid density functional theory (DFT) calculations at the M06L/6-311G* level of theory. Starting from the generally assumed seven-membered intermediates **B** and **B′**, we have optimized two reaction pathways, I and II, which are responsible for generation of (*aR*)-**3** and (*aS*)-**3′**, respectively (Scheme 4). The calculated results revealed that the former pathway leading to (*aR*)-**3** is energetically more favorable than the latter by 3.6 kcal mol⁻¹ (12.6 versus 16.2 kcal mol⁻¹ for TSI versus TSII). This result is consistent with the experimental findings that nickel-catalyzed annulation with (*S,S*)-**L10** gave the (*aR*)-**3** with *ee* values of up to 94%. Inspection of the transition-state structures clearly demonstrate that the steric interaction between the naphthyl ring of the alkyne and the isopropyl group of the catalyst in TSI is not present as it is in TSII. This study
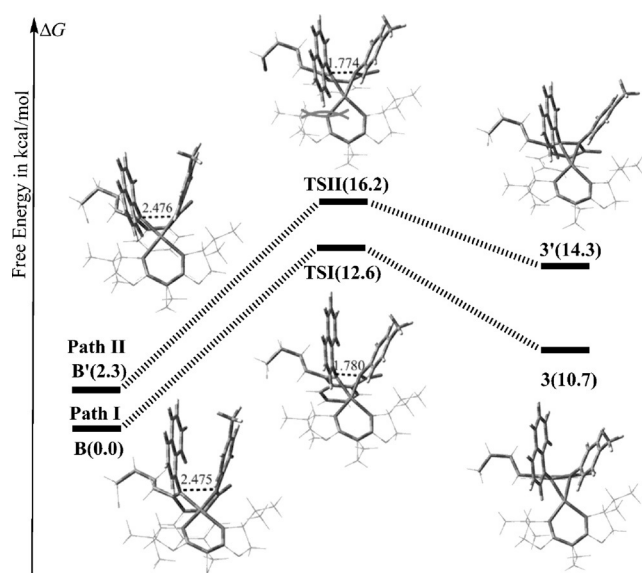
Scheme 4. Potential-energy surfaces for pathways I and II calculated at the M06L/6-311G* level of theory.

provides support for the preference of the *aR*-configured product when using (*S,S*)-**L10** as the chiral ligand, and it thus appears that axial chirality is determined by the reactant/chiral catalyst arrangement in the nickel(II) complex.

In conclusion, we have successfully developed the first nickel-catalyzed asymmetric denitrogenative transannulation of 1,2,3-benzotriazin-4(3*H*)-ones with bulky internal alkynes to give efficient access to a novel class of axially chiral isoquinolones in excellent yields with excellent enantioselectivities, and almost complete regioselectivity under mild reaction conditions. This new approach is highly convergent and functional-group tolerant, and allows the rapid construction of axially chiral complex isoquinolones from simple, readily available starting materials. Preliminary biological studies indicated that the axially chiral isoquinolones exhibit good cytotoxicity against a number of human cancer cell lines. DFT calculations were used to model the geometry of intermediates and characterize the transition states, thus providing a rationale for the observed atroposelectivity. Further applications of these axially chiral compounds in medicinal chemistry or as chiral ligands/organocatalysts in asymmetric synthesis, as well as a detailed study of the mechanism, are currently underway in our laboratory.

[1] For selected reviews on biaryl natural products, see: a) J. Chang, J. Reiner, J. Xie, *Chem. Rev.* **2005**, *105*, 4581; b) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193; c) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563.

[2] For the use of chiral biaryl ligands/catalysts in asymmetric catalysis, see: a) R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345; b) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; c) J.-H. Xie, Q.-L. Zhou, *Acc. Chem. Res.* **2008**, *41*, 581; d) Y. Canac, R. Chauvin, *Eur. J. Inorg. Chem.* **2010**, 2325; e) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047.

[3] For recent reviews on the synthesis of axially chiral biaryls, see: a) G. Bringmann, D. Menche, *Acc. Chem. Res.* **2001**, *34*, 615; b) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384; *Angew. Chem.* **2005**, *117*, 5518; c) O. Baudoin, *Eur. J. Org. Chem.* **2005**, 4223; d) K. Tanaka, *Chem. Asian J.* **2009**, *4*, 508.

[4] For selected recent examples, see: a) G. Nishida, K. Noguchi, M. Hirano, K. Tanaka, *Angew. Chem. Int. Ed.* **2007**, *46*, 3951; *Angew. Chem.* **2007**, *119*, 4025; b) J. L. Gustafson, D. Lim, S. J. Miller, *Science* **2010**, *328*, 1251; c) K. T. Barrett, S. J. Miller, *J. Am. Chem. Soc.* **2013**, *135*, 2963; d) K. T. Barrett, A. J. Metrano, P. R. Rablen, S. J. Miller, *Nature* **2014**, *509*, 71; e) X. Shen, G. O. Jones, D. A. Watson, B. Bhayana, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 11278; f) Z. Luo, Q. Liu, L. Gong, X. Cui, A. Mi, Y. Jiang, *Angew. Chem. Int. Ed.* **2002**, *41*, 4532; *Angew. Chem.* **2002**, *114*, 4714; g) Q.-X. Guo, Z.-J. Wu, Z.-B. Luo, Q.-Z. Liu, J.-L. Ye, S.-W. Luo, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* **2007**, *129*, 13927; h) J. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* **2014**, *53*, 13244; *Angew. Chem.* **2014**, *126*, 13460; i) K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 3964; j) G.-Q. Li, H. Gao, C. Keene, M. Devonas, D. H. Ess, L. Kürti, *J. Am. Chem. Soc.* **2013**, *135*, 7414; k) C. K. De, F. Pesciaioli, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 9293; *Angew. Chem.* **2013**, *125*, 9463; l) A. Link, C. Sparr, *Angew. Chem. Int. Ed.* **2014**, *53*, 5458; *Angew. Chem.* **2014**, *126*, 5562; m) G. Ma, J. Deng, M. P. Sibi, *Angew. Chem. Int. Ed.* **2014**, *53*, 11986; *Angew. Chem.* **2014**, *126*, 12180; n) R. J. Armstrong, M. D. Smith, *Angew. Chem. Int. Ed.* **2014**, *53*, 12822; *Angew. Chem.* **2014**, *126*, 13036; o) S. Lu, S. B. Poh, Y. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 11041; *Angew. Chem.* **2014**, *126*, 11221; p) V. Bhat, S. Wang, B. M. Stoltz, S. C. Virgil, *J. Am. Chem. Soc.* **2013**, *135*, 16829; q) A. Ros, B. Estepa, P. Ramírez-López, E. Álvarez, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2013**, *135*, 15730; r) C. K. Hazra, Q. Dherbassy, J. Wencel-Delord, F. Colobert, *Angew. Chem. Int. Ed.* **2014**, *53*, 13871; *Angew. Chem.* **2014**, *126*, 14091.

[5] For selected atropisomeric aza-heterocycle synthesis, see: a) K. Tanaka, A. Wada, K. Noguchi, *Org. Lett.* **2005**, *7*, 4737; b) K. Tanaka, Y. Takahashi, T. Suda, M. Hirano, *Synlett* **2008**, 1724; c) R. P. Hsung, R. Figueroa, W. L. Johnson, *Org. Lett.* **2007**, *9*, 3969; d) H. Imase, T. Suda, Y. Shibata, K. Noguchi, M. Hirano, K. Tanaka, *Org. Lett.* **2009**, *11*, 1805; e) T. Shibuya, Y. Shibata, K. Noguchi, K. Tanaka, *Angew. Chem. Int. Ed.* **2011**, *50*, 3963; *Angew. Chem.* **2011**, *123*, 4049; f) M. Augé, N. Barbazanges, A. T. Tran, A. Simonneau, P. Elley, H. Amouri, C. Aubert, L. Fensterbank, V. Gandon, M. Malacria, J. Moussa, C. Ollivier, *Chem. Commun.* **2013**, *49*, 7833.

[6] a) Y. Ikeura, Y. Ishichi, T. Tanaka, A. Fujishima, M. Murabayashi, M. Kawada, T. Ishimaru, I. Komo, T. Doi, H. Natsugari, *J. Med. Chem.* **1998**, *41*, 4232; b) P. Hewawasam, W. Fan, M. Ding, K. Flint, D. Cook, G. D. Goggins, R. A. Myers, V. K. Gribkoff, C. G. Boissard, S. I. Dworetzky, J. E. Starrett, N. J. Lodge, *J. Med. Chem.* **2003**, *46*, 2819; c) S. R. LaPlante, L. D. Fader, H. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller, P. J. Edwards, *J. Med. Chem.* **2011**, *54*, 7005.

[7] For a review, see: a) B. Chattopadhyay, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2012**, *51*, 862; *Angew. Chem.* **2012**, *124*, 886; for selected representative examples, see: b) S. Chuprakov, F. W. Hwang, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2007**, *46*, 4757; *Angew. Chem.* **2007**, *119*, 4841; c) T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 14972; d) T. Miura, M. Yamauchi, M. Murakami, *Chem.*

Commun. **2009**, 1470; e) N. Grimster, L. Zhang, V. V. Fokin, *J. Am. Chem. Soc.* **2010**, *132*, 2510; f) Y. Shi, A. V. Gulevich, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2014**, *53*, 14191; *Angew. Chem.* **2014**, *126*, 14415.

[8] a) T. Miura, M. Yamauchi, M. Murakami, *Org. Lett.* **2008**, *10*, 3085; b) M. Yamauchi, M. Morimoto, T. Miura, M. Murakami, *J. Am. Chem. Soc.* **2010**, *132*, 54; c) T. Miura, M. Morimoto, M. Yamauchi, M. Murakami, *J. Org. Chem.* **2010**, *75*, 5359; d) T. Miura, M. Yamauchi, A. Kosaka, M. Murakami, *Angew. Chem. Int. Ed.* **2010**, *49*, 4955; *Angew. Chem.* **2010**, *122*, 5075.

[9] D.-J. Cheng, L. Yan, S.-K. Tian, M.-Y. Wu, L.-X. Wang, Z.-L. Fan, S.-C. Zheng, X.-Y. Liu, B. Tan, *Angew. Chem. Int. Ed.* **2014**, *53*, 3684; *Angew. Chem.* **2014**, *126*, 3758.

[10] For selected reviews about homogeneous nickel catalysis, see: a) J. Montgomery, *Angew. Chem. Int. Ed.* **2004**, *43*, 3890; *Angew. Chem.* **2004**, *116*, 3980; b) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299; for selected examples of nickel/bis(oxazoline)-catalyzed asymmetric reactions, see: c) S. Lou, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 1264; d) Y. Liang, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 5520; e) J. Choi, P. Martín-Gago, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 12161; f) A. H.

Cherney, N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 7442; g) A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2014**, *136*, 14365.

[11] For selected examples, see: a) B. D. Krane, M. Shamma, *J. Nat. Prod.* **1982**, *45*, 377; b) J. Du, L. Xi, B. Lei, H. Liu, X. Yao, *Chem. Biol. Drug Des.* **2011**, *77*, 248.

[12] For reviews of bis(oxazoline) ligands in asymmetric catalysis, see: a) D. Rechavi, M. Lemaire, *Chem. Rev.* **2002**, *102*, 3467; b) G. C. Hargaden, P. J. Guiry, *Chem. Rev.* **2009**, *109*, 2505; c) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2011**, *111*, PR284.

[13] N. Arshad, J. Hashim, C. O. Kappe, *J. Org. Chem.* **2008**, *73*, 4755.

[14] CCDC 1057259 (**3aa**) and 1057260 (**3da**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.