Biaryl Atropisomers Hot Paper

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Enantioselective Synthesis of Atropisomeric Biaryls by Pd-Catalyzed Asymmetric Buchwald–Hartwig Amination

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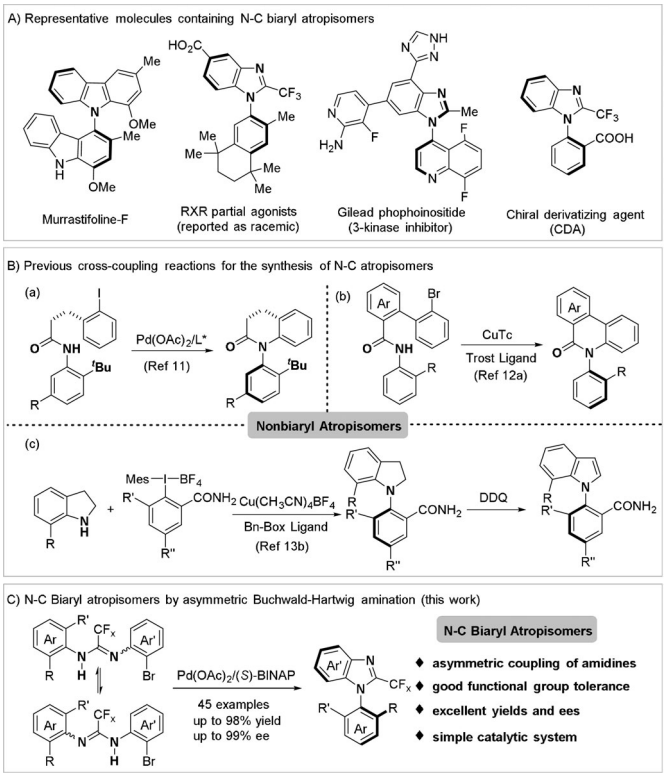
Abstract: *N–C Biaryl atropisomers are prevalent in natural products and bioactive drug molecules. However, the enantioselective synthesis of such molecules has not developed significantly. Particularly, the enantioselective synthesis of N–C biaryl atropisomers by stereoselective metal-catalyzed aryl amination remains unprecedented. Herein, a Pd-catalyzed cross-coupling strategy is presented for the synthesis of N–C axially chiral biaryl molecules. A broad spectrum of N–C axially chiral compounds was obtained with excellent enantioselectivities (up to 99 % ee) and good yields (up to 98 %). The practicality of this reaction was validated in the synthesis of useful biological molecules.*

Atropisomerism arises from the hindered free rotation of a molecule about an axis and exists widely in natural products, biologically active molecules, and chiral ligands.[1] The most representative examples are the axially chiral C–C biaryl compounds, which have been extensively investigated in recent years.[2] However, compared with the well-developed construction of chiral C–C biaryl skeletons, the enantioselective construction of N–C axially chiral molecules, especially N–C biaryl skeletons, is mostly unexplored and is a remarkably challenging task.[3] There are only a limited number of strategies for the atroposelective construction of N–C biaryl atropisomers, and these mainly comprise diastereoselective S_NAr reactions,[4] CPA-catalyzed enantioselective addition and cyclization,[5] asymmetric C–H bond functionalization of heteroarenes,[6] and metal-catalyzed annulation of alkynes.[7] Considering the prevalence of N–C biaryl atropisomers in natural products[8] and their remarkable applications in drug design[9] and synthesis of chiral derivatizing agents[10] (Scheme 1), methods for accessing the general enantioselective forms of biaryl N–C atropisomers are in high demand.

Although the atroposelective construction of N–C axially chiral molecules by transition-metal-catalyzed N-arylation is one of the most attractive routes, it remains largely unexplored. Kitagawa, Taguchi, and co-workers pioneered the construction of N–C non-biaryl atropisomers by the Pd-catalyzed asymmetric N-arylation of anilides, where the presence of an *ortho t*-butyl group in aniline was necessary to obtain high *ee* values (Scheme 1 B a).[11] Recently, Gu et al. reported an elegant Cu-catalyzed enantioselective intramolecular Ullmann-type amination reaction of anilides for the synthesis of N–C atropisomers (Scheme 1 B b).[12] Very recently, Wencel-Delord and co-workers reported the first case of a more challenging intermolecular atroposelective Ullmann-type N–C coupling reaction by utilizing C(sp^2)-hypervalent iodine reagents as carbon substrates and substituted indolines as nitrogen substrates (Scheme 1 B c).[13] Despite these contributions, the enantioselective synthesis of N–C biaryl atropisomers by metal-catalyzed aryl amination remains an unexplored field; however, the optically active biaryl products formed are highly valuable. We herein describe the Pd-catalyzed intramolecular N–C cross-coupling reactions of amidines[14] for the highly enantioselective synthesis of biaryl atropisomers to obtain N–C axially chiral biaryl atropisomers by Buchwald–Hartwig amination (Scheme 1 C).[15–17] It is worth noting that amidines are challenging



Scheme 1. Representative N–C biaryl molecules and asymmetric cross-coupling reactions for the construction of N–C atropisomers.

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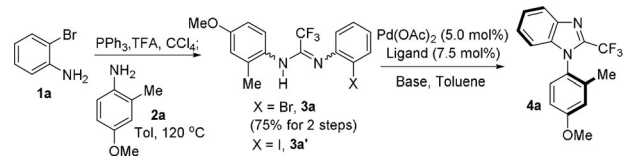
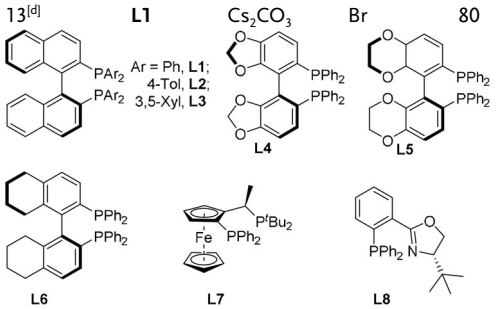
substrates for transition-metal-catalyzed N–C cross-coupling reactions not only because they coordinate strongly to the transition metal and cause catalyst deactivation but also because they undergo tautomerization and *E*/*Z* isomerization (6 possible isomers).[18] These issues make enantioselective control more complex and challenging.

We began optimizing the reaction conditions using amidine **3a**, which was easily prepared by a two-step reaction, as the model substrate (Table 1). Condensation of 2-bromoaniline (**1a**) with TFA in CCl_4 in the presence of triphenylphosphine afforded a trifluoroacetimidoyl chloride. Subsequent addition/elimination with substituted aniline **2a** produced amidine **3a** in a good yield. The reaction of **3a** in the presence of $Pd(OAc)_2$ (5 mol%), (*S*)-BINAP **L1** (7.5 mol%), and K_2CO_3 (1.2 equiv) in toluene at 60 °C afforded the desired product **4a** in 82% yield and 75% *ee* (entry 1). Slightly lower enantioselectivity was obtained when the Br substituent in the substrate was replaced by I (entry 2). To our delight, when KOH was used instead of K_2CO_3, **4a** was formed in 93% yield and 89% *ee* (entry 3). Further screening revealed that the best result was obtained when Cs_2CO_3 was used, with **4a** obtained in 98% yield and 92% *ee* (entry 4). A comparable *ee* was obtained when NaOH was used as the base, although the yield was slightly lower (entry 5). Next, the effect of different ligands was tested. Most of the biphosphine ligands resulted in good yields with moderate to good *ee* values (entries 6–10), except ligand **L7**, which resulted in the yield decreasing sharply (entry 11). Moreover, monophosphine **L8** was also effective, giving **4a** in 70% yield and 63% *ee* (entry 12). Furthermore, the catalyst loading could be lowered to 2.5 mol% to allow completion of the reaction with only a slight decrease in the yield and *ee* value (entry 13).

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

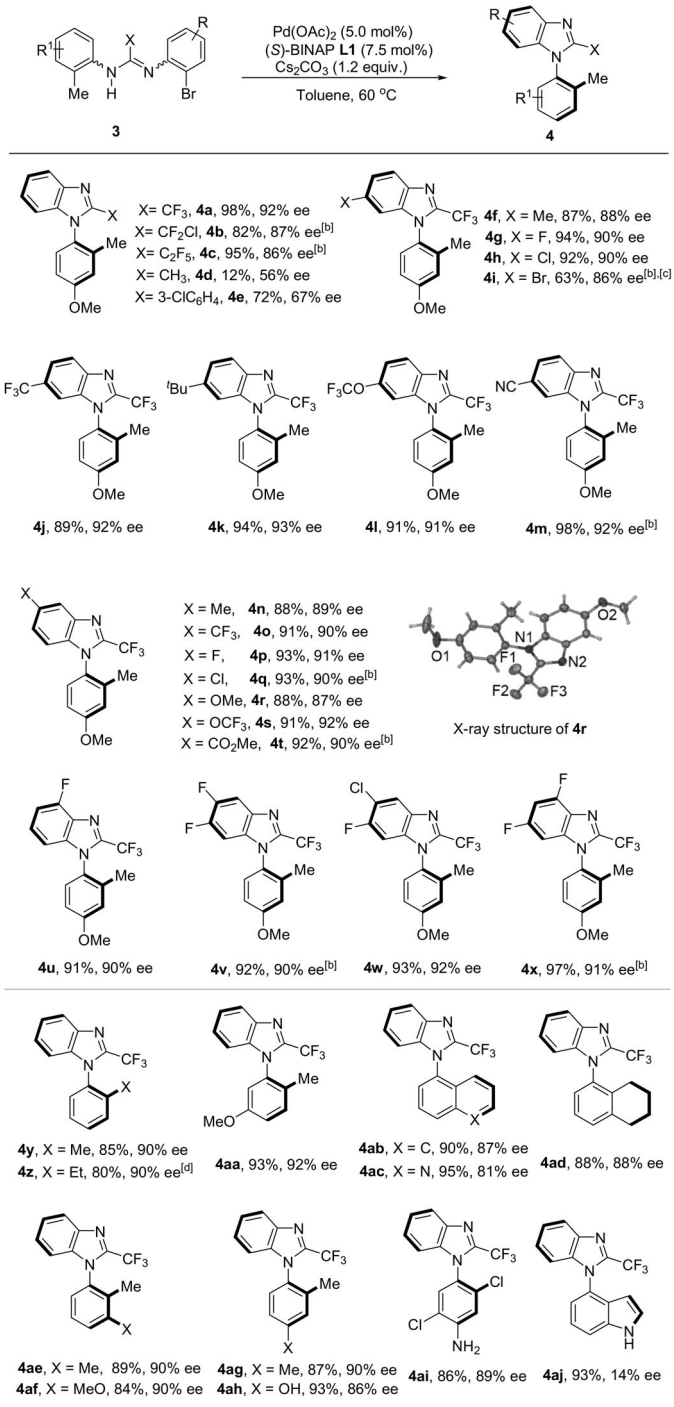


Entry	Ligand	Base	X	Yield [%][b]	*ee* [%][c]
1	**L1**	K_2CO_3	Br	82	75
2	**L1**	K_2CO_3	I	84	68
3	**L1**	KOH	Br	93	89
4	**L1**	Cs_2CO_3	Br	98	92
5	**L1**	NaOH	Br	92	92
6	**L2**	Cs_2CO_3	Br	90	89
7	**L3**	Cs_2CO_3	Br	85	88
8	**L4**	Cs_2CO_3	Br	82	84
9	**L5**	Cs_2CO_3	Br	80	70
10	**L6**	Cs_2CO_3	Br	78	62
11	**L7**	Cs_2CO_3	Br	10	–
12	**L8**	Cs_2CO_3	Br	70	63
13[d]	**L1**	Cs_2CO_3	Br	80	90

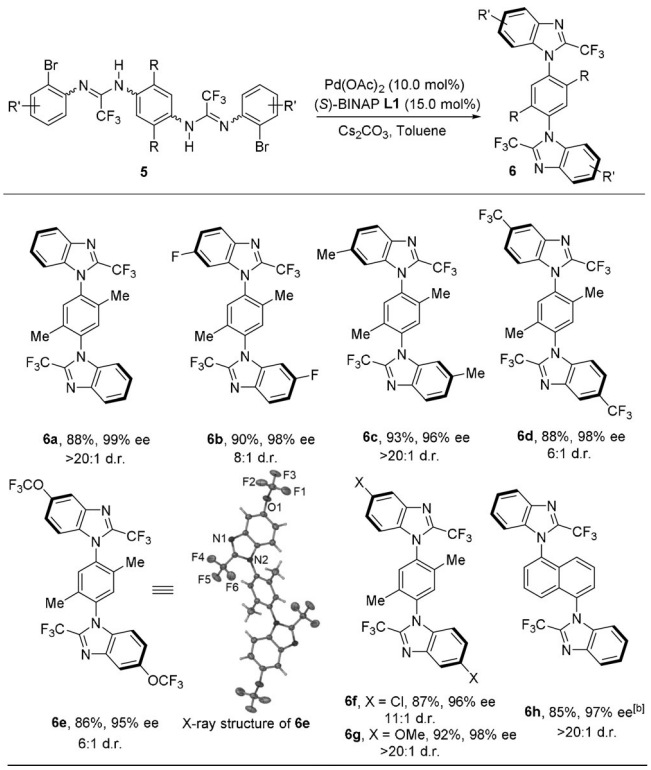


[a] Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (5.0 mol%), ligand (7.5 mol%), and base (1.2 equiv) in solvent (1.0 mL) at 60 °C for 18 h. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] $Pd(OAc)_2$ (2.5 mol%), ligand (3.75 mol%), reaction time: 36 h.

With the optimal conditions in hand, we next examined the substrate scope of the amidine (Scheme 2). A wide range of amidines were suitable, affording the desired biaryl atropisomers in good to excellent yields and enantioselectivities. First, the effect of substituents at the C1-position of the amidine moiety was examined. Slightly lower enantioselectivity was obtained when CF_3 was replaced by CF_2Cl (**4b**) or C_2F_5 (**4c**) on the substrate. However, when alkyl- and aryl-substituted amidines were used under identical reaction conditions, the enantioselectivities were reduced significantly (**4d**, **4e**), thus demonstrating the unique fluorine effect of the CF_3-bearing substrate. The racemization barriers ($\Delta G^{\ddagger}$) of **4a** and **4d** were measured to be 34.3 and 31.5 kcal mol^{-1}, respectively (see the Supporting Information for details), which may indicate that partial thermal racemization of the product can be excluded as the reason for the decrease in the *ee* value with **4d**. To investigate the effect of substituent R on the phenyl ring of the 2-bromophenyl moiety, we carried out the reaction of **3** with a series of amidines with *meta* and/or *para* substituents on the 2-bromophenyl moiety. The substituents included Me (**4f**, **4n**), *t*-Bu (**4k**), MeO (**4r**), halogen (**4g**-**4i**, **4p**, **4q**), CF_3 (**4j**, **4o**), OCF_3 (**4l**, **4s**), CN (**4m**), and CO_2Me (**4t**). The reactions smoothly furnished the coupling products with good to excellent yields (63–98%) and enantioselectivities (86–93%). The absolute configuration of **4r** (> 99% *ee* after recrystallization) was determined by X-ray crystallographic analysis.[19] In general, the *ee* values for substrates bearing electron-withdrawing substituents were higher than those for substrates bearing electron-donating substituents (**4f** vs. **4j** and **4o** vs. **4r**). Furthermore, *ortho*-F-2-bromophenylamidine also underwent transformation to form biaryl atropisomer **4u** in good yield and enantioselectivity. As expected, disubstituted substrates underwent the title reaction to give **4v**–**4x** with excellent *ee* values. The effect of substituents (R^1) on the aniline moiety was also examined. The *ortho*-alkyl group in the aniline moiety could be a simple methyl or ethyl group, although the yields slightly decreased when the MeO group was not introduced at the 4-position (**4y** and **4z**). Additional groups adjacent to the 2-methyl group affected neither the yield nor the enantioselectivity, with methyl (**4ae**, **4ag**) or methoxy groups (**4aa**, **4af**) at different positions affording the products in 90–92% ee. In addition, a substrate with a free hydroxy group was compatible in this reaction, with **4ah** obtained in 93% yield and 86% *ee*. The *ortho* groups in the aniline structure can be efficiently extended to a naphthyl (**4ab**) or (tetrahydro)naphthyl (**4ad**) scaffold to achieve good enantioselectivity. Furthermore, this reaction is also compatible with halogen-containing substrates and gives the corresponding product **4ai** containing a sensitive free NH_2 group in high yield and 89% *ee*. Moreover, the reaction is also compatible with quinoline and indole heterocyclic substrates. However, when indole



Scheme 2. Generality of the Pd-catalyzed asymmetric amination reaction. Reaction conditions: [a] **3** (0.2 mmol), $Pd(OAc)_2$ (5.0 mol%), **L1** (7.5 mol%), and Cs_2CO_3 (1.2 equiv) in toluene (2.0 mL) at 60°C for 18 h. [b] NaOH (1.2 equiv) was used as the base instead of Cs_2CO_3. [c] Reaction time: 72 h. [d] Reaction was performed at 50°C.

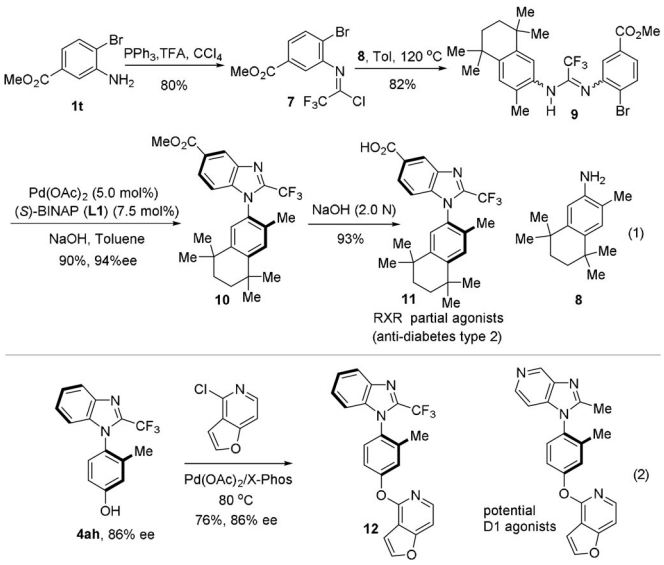


Scheme 3. Generality of the Pd-catalyzed double asymmetric amination reaction. [a] Reaction conditions: **5** (0.2 mmol), $Pd(OAc)_2$ (10.0 mol%), **L1** (15.0 mol%), and Cs_2CO_3 (2.4 equiv) in toluene (2.0 mL) at 60°C for 18 h. [b] NaOH (2.4 equiv) was used as the base instead of Cs_2CO_3.

substrate **3aj** was used, the target product **4aj** was obtained with very low enantioselectivity, presumably because of reduced steric hindrance.

Inspired by the above results, we further used the developed strategy to extend the construction to structural motifs possessing two chiral N-aryl axes (Scheme 3). Consequently, 2,4-diamidine **5a** was prepared and subjected to the standard reaction conditions. Gratifyingly, this double atroposelective amination reaction proceeded to give the desired 1,4-benzimidazole **6a** in excellent diastereoselectivity and enantioselectivity. To demonstrate the generality of this transformation, other 2,4-diamidines with various substituents on the phenyl ring of the 2-bromophenyl moiety were tested. All the desired products (**6b–6g**) were generated in good yields with *ee* values higher than 95%. Gratifyingly, besides the methyl group, 1,5-naphthyldiamidine reacted well, generating the corresponding 1,5-benzimidazole product **6h** in 85% yield and 97% *ee*.

The title reaction was applied in a relatively straightforward synthesis of an anti-diabetes type 2 drug candidate (shown in Scheme 1), starting from commercially available 2-bromoaniline derivative **1t** (Scheme 4 [Eq. (1)]). To implement this, **1t** underwent a condensation reaction with TFA in CCl_4 in the presence of triphenylphosphine to yield trifluoroacetimidoyl chloride **7**, which underwent an addition/elimination of substituted aniline **8** to yield amidine **9**. Amidine **9** was subsequently subjected to the Pd-catalyzed intramolecular C–N bond formation to afford the desired product **10** in 90% yield and 94% *ee*. Hydrolysis of the ester group afforded drug candidate **11**. Moreover, the present method can also be used for synthesizing a potential D1 agonist analogue (Scheme 4 [Eq. (2)]).[20] For example, phenol **4ah** successfully underwent the Pd-catalyzed C–O cross-coupling reaction

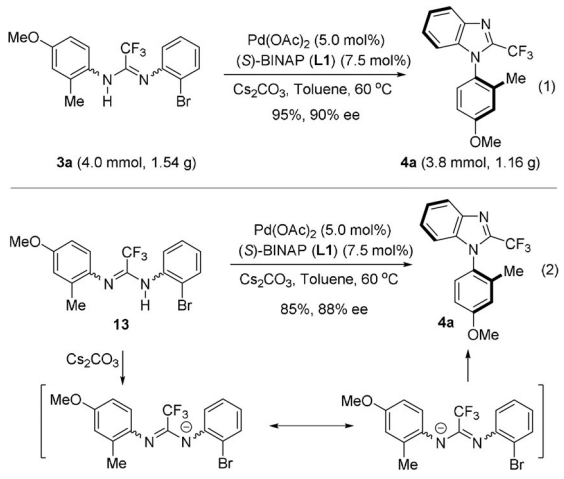


Scheme 4. Synthetic transformations.

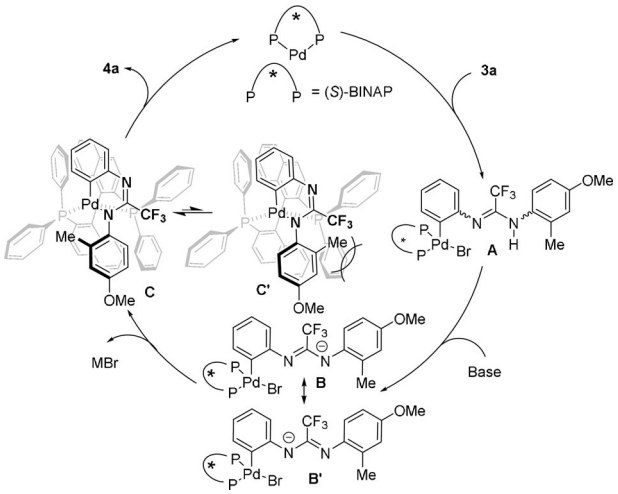
with halopyridine to give the products in good yield under mild conditions. Importantly, the *ee* value was unaffected by this transformation.

A gram-scale reaction of **3a** was conducted, with N−C atropisomer **4a** obtained in 95% yield and 90% *ee*, thus showing the reliability of the developed procedure (Scheme 5 [Eq. (1)]). Moreover, to demonstrate the tautomerization of amidines in the reaction, we synthesized substrate **13** from 2,2,2-trifluoro-*N*-(4-methoxy-2-methylphenyl)acetimidoyl chloride and 2-bromoaniline. Under the optimal conditions, **13** afforded the desired product **4a** in 85% yield and 88% *ee* (Scheme 5 [Eq. (2)]), thus confirming the tautomerization of amidines in this reaction.

Finally, a plausible catalytic cycle and a stereoinduction model were proposed (Scheme 6). Initially, amidine **3a** can undergo oxidative addition with the Pd^0 catalyst to give Pd^{II} complex **A**. Deprotonation generates amidine-Pd complex **B** or **B′** via tautomerization, which further gives **C** or **C′** by substitution of the bromide ligand with amidine. The *ortho*



Scheme 5. Gram-scale reaction and experiment to demonstrate amidine tautomerization.



Scheme 6. Plausible catalytic cycle.

group in the aniline moiety of **C′** experiences strong steric repulsion from the equatorial phenyl group on the phosphorus atom. Consequently, attack from the less sterically hindered site would be favored. Finally, reductive elimination of **C** affords **4a** and regenerates the Pd^0 catalyst.

In conclusion, we have developed a procedure for the Pd-catalyzed enantioselective amination of amidines to synthesize N−C biaryl atropisomers. A wide range of benzimidazoles with N−C axial chirality can be conveniently constructed with excellent enantioselectivity. Moreover, highly enantioenriched 1,4- and 1,5-dibenzimidazole possessing two chiral N−C axes could be accessed using this procedure. The gram-scale synthesis and the versatile transformations of the products may have broad applications in the synthesis of valuable pharmaceuticals containing N−C biaryl atropisomer skeletons.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: amidines · amination · asymmetric catalysis · atropisomerism · palladium

[1] a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3070; b) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563–639; c) J. E. Smyth, N. M. Butler, P. A. Keller, *Nat. Prod. Rep.* **2015**, *32*, 1562–1583; d) J. Wencel-Delord, F. Colobert, *SynOpen* **2020**, *4*, 107–115; e) Y.-D. Shao, D.-J. Cheng, *ChemCatChem* **2021**, *13*, 1271–1289.

[2] a) J. Wencel-Delord, A. Panossian, F. R. Leroux, F. Colobert, *Chem. Soc. Rev.* **2015**, *44*, 3418 – 3430; b) Y. B. Wang, B. Tan, *Acc. Chem. Res.* **2018**, *51*, 534 – 547; c) A. Link, C. Sparr, *Chem. Soc. Rev.* **2018**, *47*, 3804 – 3815; d) J. K. Cheng, S. H. Xiang, S. Li, L. Ye, B. Tan, *Chem. Rev.* **2021**, *121*, 4805 – 4902.

[3] a) T. Z. Li, S. J. Liu, W. Tan, F. Shi, *Chem. Eur. J.* **2020**, *26*, 15779 – 15792; b) V. Corti, G. Bertuzzi, *Synthesis* **2020**, *52*, 2450 – 2468; c) J. Frey, S. Choppin, F. Colobert, J. Wencel-Delord, *Chimia* **2020**, *74*, 883 – 889; d) V. Thönnißen, F. W. Patureau, *Chem. Eur. J.* **2021**, *27*, 7189 – 7192; e) O. Kitagawa, *Acc. Chem. Res.* **2021**, *54*, 719 – 730.

[4] a) K. Kamikawa, S. Kinoshita, H. Matsuzaka, M. Uemura, *Org. Lett.* **2006**, *8*, 1097 – 1100; b) K. Kamikawa, S. Kinoshita, M. Furusyo, S. Takemoto, H. Matsuzaka, M. Uemura, *J. Org. Chem.* **2007**, *72*, 3394 – 3402.

[5] a) Y. Wang, S. Zheng, Y. Hu, B. Tan, *Nat. Commun.* **2017**, *8*, 15489; b) L. Zhang, J. Zhang, J. Ma, D. J. Cheng, B. Tan, *J. Am. Chem. Soc.* **2017**, *139*, 1714 – 1717; c) Y. Kwon, J. Li, J. P. Reid, J. M. Crawford, R. Jacob, M. S. Sigman, F. D. Toste, S. J. Miller, *J. Am. Chem. Soc.* **2019**, *141*, 6698 – 6705; d) L. Wang, J. Zhong, X. Lin, *Angew. Chem. Int. Ed.* **2019**, *58*, 15824 – 15828; *Angew. Chem.* **2019**, *131*, 15971 – 15975; e) W. Xia, Q.-J. An, S.-H. Xiang, S. Li, Y.-B. Wang, B. Tan, *Angew. Chem. Int. Ed.* **2020**, *59*, 6775 – 6779; *Angew. Chem.* **2020**, *132*, 6841 – 6845; f) A. Kim, A. Kim, S. Park, S. Kim, H. Jo, K. M. Ok, S. K. Lee, J. Song, Y. Kwon, *Angew. Chem. Int. Ed.* **2021**, *60*, 12279 – 12283; *Angew. Chem.* **2021**, *133*, 12387 – 12391.

[6] a) C.-X. Ye, S. Chen, F. Han, X. Xie, S. Ivlev, K. N. Houk, E. Meggers, *Angew. Chem. Int. Ed.* **2020**, *59*, 13552 – 13556; *Angew. Chem.* **2020**, *132*, 13654 – 13658; b) S. Zhang, Q.-J. Yao, G. Liao, X. Li, H. Li, H.-M. Chen, X. Hong, B.-F. Shi, *ACS Catal.* **2019**, *9*, 1956 – 1961; c) Q. Ren, T. Cao, C. He, M. Yang, H. Liu, L. Wang, *ACS Catal.* **2021**, *11*, 6135 – 6140; d) U. Dhawa, C. Tian, T. Wdowik, J. C. A. Oliveira, J. Hao, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, *59*, 13451 – 13457; *Angew. Chem.* **2020**, *132*, 13553 – 13559.

[7] a) N. Ototake, Y. Morimoto, A. Mokuya, H. Fukaya, Y. Shida, O. Kitagawa, *Chem. Eur. J.* **2010**, *16*, 6752 – 6755; b) Y. Morimoto, S. Shimizu, A. Mokuya, N. Ototake, A. Saito, O. Kitagawa, *Tetrahedron* **2016**, *72*, 5221 – 5229; c) L. Sun, H. Chen, B. Liu, J. Chang, L. Kong, F. Wang, Y. Lan, X. Li, *Angew. Chem. Int. Ed.* **2021**, *60*, 8391 – 8395; *Angew. Chem.* **2021**, *133*, 8472 – 8476.

[8] a) G. Bringmann, S. Tasler, H. Endress, J. Kraus, K. Messer, M. Wohlfarth, W. Lobin, *J. Am. Chem. Soc.* **2001**, *123*, 2703 – 2711; b) C. C. Hughes, A. Prieto-Davo, P. R. Jensen, W. Fenical, *Org. Lett.* **2008**, *10*, 629 – 631.

[9] a) S. T. Toenjes, J. L. Gustafson, *Future Med. Chem.* **2018**, *10*, 409 – 422; b) S. R. LaPlante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller, P. J. Edwards, *J. Med. Chem.* **2011**, *54*, 7005 – 7022; c) F. Ohsawa, S. Yamada, N. Yakushiji, R. Shinozaki, M. Nakayama, K. Kawata, M. Hagaya, T. Kobayashi, K. Kohara, Y. Furusawa, C. Fujiwara, Y. Ohta, M. Makishima, H. Naitou, A. Tai, Y. Yoshikawa, H. Yasui, H. Kakuta, *J. Med. Chem.* **2013**, *56*, 1865 – 1877; d) J. Chandrasekhar, R. Dick, J. Van Veldhuizen, D. Koditek, E. I. Lepist, M. E. McGrath, L. Patel, G. Phillips, K. Sedillo, J. R. Somoza, J. Therrien, N. A. Till, J. Treiberg, A. G. Villaseñor, Y. Zherebina, S. Perreault, *J. Med. Chem.* **2018**, *61*, 6858 – 6868.

[10] M. Kriegelstein, D. Profous, A. Lyčka, Z. Travnícek, A. Přibylka, T. Volná, S. Benická, P. Cankař, *J. Org. Chem.* **2019**, *84*, 11911 – 11921.

[11] a) T. Hirata, I. Takahashi, Y. Suzuki, H. Yoshida, H. Hasegawa, O. Kitagawa, *J. Org. Chem.* **2016**, *81*, 318 – 323; b) O. Kitagawa, M. Takahashi, M. Yoshikawa, T. Taguchi, *J. Am. Chem. Soc.* **2005**, *127*, 3676 – 3677; c) O. Kitagawa, M. Yoshikawa, H. Tanabe, T. Morita, M. Takahashi, Y. Dobashi, T. Taguchi, *J. Am. Chem. Soc.* **2006**, *128*, 12923 – 12931.

[12] a) X. Fan, X. Zhang, C. Li, Z. Gu, *ACS Catal.* **2019**, *9*, 2286 – 2291; b) K. Zhao, L. Duan, S. Xu, J. Jiang, Y. Fu, Z. Gu, *Chem* **2018**, *4*, 599 – 612; c) K. Zhao, S. Yang, Q. Gong, L. Duan, Z. Gu, *Angew. Chem. Int. Ed.* **2021**, *60*, 5788 – 5793; *Angew. Chem.* **2021**, *133*, 5852 – 5857.

[13] a) J. Rae, J. Frey, S. Jerhaoui, S. Choppin, J. Wencel-Delord, F. Colobert, *ACS Catal.* **2018**, *8*, 2805 – 2809; b) J. Frey, A. Malekafzali, I. Delso, S. Choppin, F. Colobert, J. Wencel-Delord, *Angew. Chem. Int. Ed.* **2020**, *59*, 8844 – 8848; *Angew. Chem.* **2020**, *132*, 8929 – 8933.

[14] T. R. M. M. Rauws, B. U. W. Maes, *Chem. Soc. Rev.* **2012**, *41*, 2463 – 2497.

[15] For reviews, see a) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534 – 1544; b) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564 – 12649.

[16] For enantioselective Buchwald–Hartwig amination, see a) K. Rossen, P. J. Pye, A. Maliakal, R. P. Volante, *J. Org. Chem.* **1997**, *62*, 6462 – 6463; b) P. Ramírez-Lopez, A. Ros, A. Romero-Arenas, J. Iglesias-Sigüenza, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2016**, *138*, 12053 – 12056; c) H. Li, K. M. Belyk, J. Yin, Q. Chen, A. Hyde, Y. Ji, S. Oliver, M. T. Tudge, L. C. Campeau, K. R. Campos, *J. Am. Chem. Soc.* **2015**, *137*, 13728 – 13731.

[17] Atropisomeric benzimidazoles are widely used in drug and chiral phosphine ligand design: a) C. Grimmer, T. W. Moore, A. Padwa, A. Prussia, G. Wells, S. Wu, A. Sun, J. P. Snyder, *J. Chem. Inf. Model.* **2014**, *54*, 2214 – 2223; b) D. Bonne, J. Rodriguez, *Eur. J. Org. Chem.* **2018**, 2417 – 2431.

[18] a) G. Hafelinger, F. K. H. Kuske in *The Chemistry of Amidines and Imidates*, *Vol. 2* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1991**, p. 1; b) Y.-M. Wu, M. Zhang, Y.-Q. Li, *J. Fluorine Chem.* **2006**, *127*, 1168 – 1174.

[19] Deposition numbers 2092070 (**4r**), and 2092071 (**6e**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[20] J. E. Davoren, D. Nason, J. Coe, K. Dlugolenski, C. Helal, A. R. Harris, E. LaChapelle, S. Liang, Y. Liu, R. O'Connor, C. C. Orozco, B. K. Rai, M. Salafia, B. Samas, W. Xu, R. Kozak, D. Gray, *J. Med. Chem.* **2018**, *61*, 11384 – 11397.

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Communications

Biaryl Atropisomers

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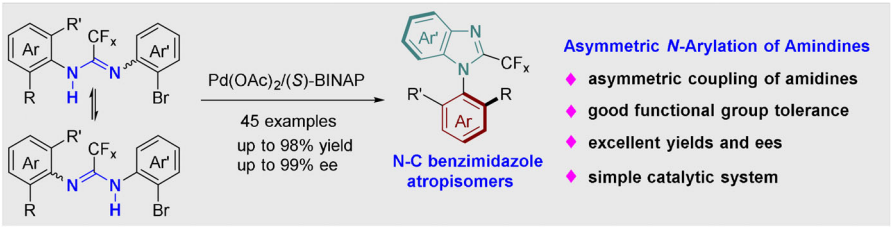
Enantioselective Synthesis of Atropisomeric Biaryls by Pd-Catalyzed Asymmetric Buchwald–Hartwig Amination



A Pd-catalyzed enantioselective amination of amidines has been developed for the synthesis of N–C biaryl atropisomers. A wide range of benzimidazole derivatives containing N–C axial chirality can be conveniently constructed in excellent yields and enantioselectivities by intramolecular amination.