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Copper-Catalyzed Enantioselective Intramolecular Aryl C−N Coupling: Synthesis of Enantioenriched 2-Oxo-1,2,3,4-tetrahydroquinoline-3-carboxamides via an Asymmetric Desymmetrization Strategy

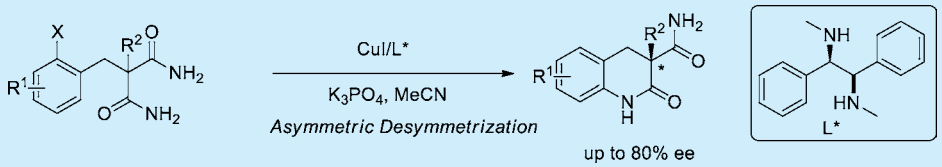
Nian He,[†,‡] Yanping Huo,*[,†] Jianguang Liu,[‡] Yusha Huang,[‡,§] Shasha Zhang,[‡] and Qian Cai*[,‡]

[†]School of Chemical Engineering and Light Industry, Guangdong University of Technology, No. 100 Waihuan Xi Road Guangzhou Higher Education Mega Center, Guangzhou, 510006, China

[‡]Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, No. 190 Kaiyuan Avenue, Guangzhou Science Park, Guangzhou, 510530, China

[§]Shenyang Pharmaceutical University, No. 103 Wenhua Road, Shenhe District, Shenyang, 110016, China

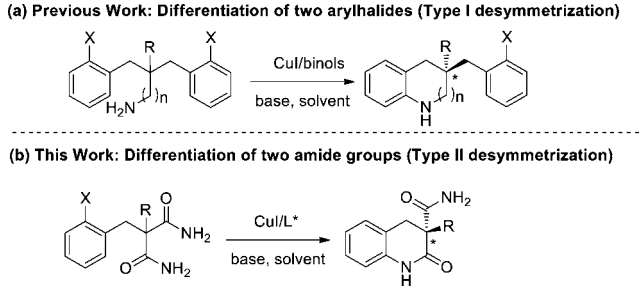
Supporting Information



ABSTRACT: The differentiation of two nucleophilic amide groups in malonamides through a copper-catalyzed enantioselective intramolecular aryl C−N coupling reaction is demonstrated based on an asymmetric desymmetrization strategy. Such a method afforded enantioenriched 2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamides in high yields and moderate to good enantioselectivity.

Enantioselective desymmetrization,[1] to differentiate two enantiotopic groups through simple transformations, is an efficient and powerful method in asymmetric synthesis. Such a strategy has been extensively applied in a broad range of organocatalytic[2] and transition-metal-catalyzed[3,4] reactions for the enantioselective synthesis of chiral compounds. Based on this strategy, our group has recently developed some Cu-catalyzed[5] intramolecular asymmetric aryl C−N coupling reactions for the enantioselective formation of chiral indolines, 1,2,3,4-tetrahydroquinolines and 2,3,4,5-tetrahydro-*1H*-benzo[*b*]azepines.[6] In these reactions, two aryl halide moieties were differentiated by intramolecularly reacting with an amine group (Scheme 1a). The enantioselectivity was well controlled by binol derived[6a,b] or amino acid derived[6c] chiral ligands.

Scheme 1. Design of Copper-Catalyzed Aryl C−N Coupling Reactions *via* Asymmetric Desymmetrization Strategy



To further explore copper-catalyzed asymmetric desymmetric aryl C−N coupling reactions, we turned our sights to another type of desymmetrization process, that is, to differentiate two symmetric nucleophilic amine-type groups by reacting with one aryl halide group. The enantiocontrol in this type of asymmetric desymmetric aryl C−N coupling reaction is more challenging in comparison to the first type of desymmetric reaction. The two *N*-nucleophilic groups in the substrates themselves are good chelating ligands for a copper catalyst, which may compete with the chiral ligands to bind with copper salts. Thus, the choice of chiral ligands and the design of substrates are very crucial for better enantioselectivity in such reactions. The Pd-catalyzed Buchwald−Hartwig reaction[7,8] has been used in such desymmetrization reactions, by using *N*-substituted malonamides to minimize the chelating effects of substrates with a metal catalyst as reported by Viirre[9] and Sasai.[10] However, only low to moderate enantioselectivity was obtained in most cases of these reactions. To the best of our knowledge, no copper catalyst has been investigated in such reactions. Herein, we would like to report the details of our research in a copper-catalyzed second type of aryl C−N coupling reactions through asymmetric desymmetrization of unprotected malonamides.

Considering that a strong background reaction may exist in 2-(2-iodobenzyl)propane-1,3-diamines due to the self-catalytic

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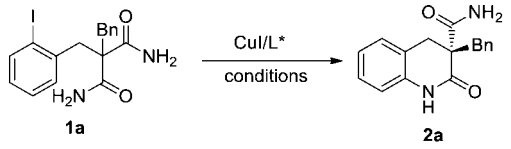
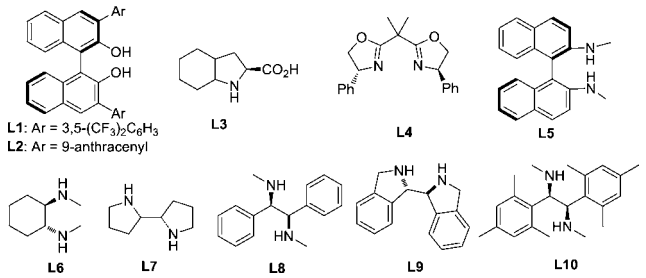
Table 1. Screening of Reaction Conditions[a]

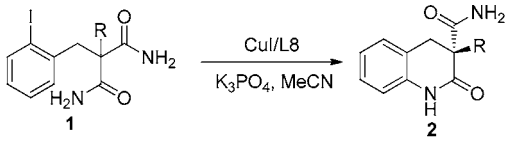


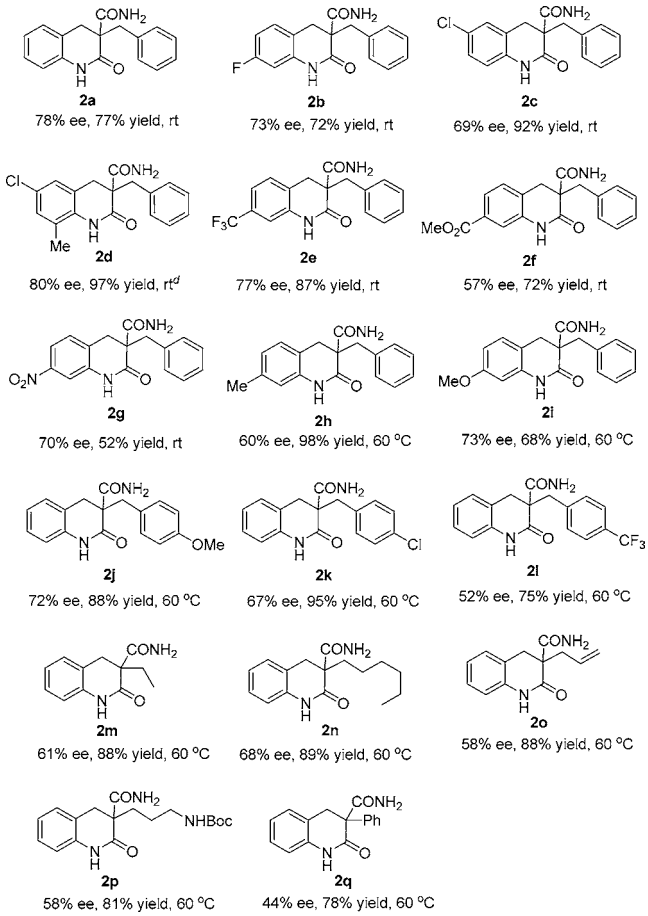


entry	L*	base	solvent	temp (°C)	yield (%)[b]	ee (%)[c]
1	–	K_3PO_4	MeCN	rt	50	–
2	L1	K_3PO_4	MeCN	rt	48	rac
3	L2	K_3PO_4	MeCN	rt	95	−10
4	L3	K_3PO_4	MeCN	rt	11	12
5	L4	K_3PO_4	MeCN	rt	70	rac
6	L5	K_3PO_4	MeCN	rt	89	rac
7	L6	K_3PO_4	MeCN	rt	64	70
8	L7	K_3PO_4	MeCN	rt	67	67
9	L8	K_3PO_4	MeCN	**rt**	77	**78**
10	L9	K_3PO_4	MeCN	rt	62	40
11	L10	K_3PO_4	MeCN	rt	45	60
12	L8	K_3PO_4	dioxane	rt	45	46
13	L8	K_3PO_4	DMF	rt	87	54
14	L8	K_3PO_4	THF	rt	38	67
15	L8	K_3PO_4	toluene	rt	12	14
16	L8	Cs_2CO_3	MeCN	rt	86	67
17	L8	K_2CO_3	MeCN	rt	13	70
18	L8	K_3PO_4	MeCN	60	86	72

[a]Reaction conditions: **1a** (0.25 mmol), CuI (0.025 mmol, 10 mol %), ligand (0.0375 mmol, 15 mol %), base (0.5 mmol, 2.0 equiv), 24 h. [b]Isolated yields. [c]Determined by HPLC analysis (Chiralpak AD-H column).

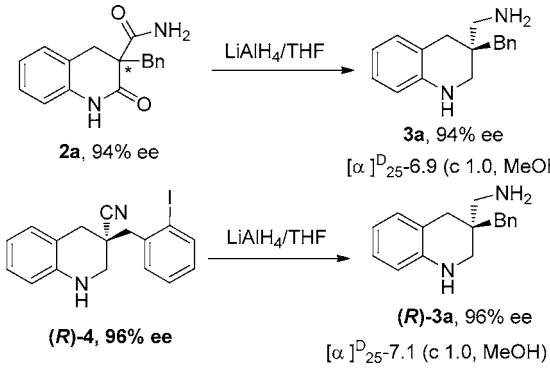
Table 2. Substrate Scope[a,b,c]





[a]Reaction conditions: **1a** (0.25 mmol), CuI (0.025 mmol, 10 mol %), ligand (0.0375 mmol, 15 mol %), base (0.5 mmol, 2.0 equiv), 24 h. [b]Isolated yields. [c]Determined by HPLC analysis. [d]Bromide substrate (**1a′**) was tested and afforded **2a** in 83% yield and 45% ee at 80 °C.

Scheme 2. Determination of the Absolute Configuration of Chiral Products through Simple Transformations



effect caused by the strong binding ability of two amine groups with copper salts,[11] we chose the reaction of 2-benzyl-2-(2-iodobenzyl)malonamide **1a** as a model case for the exploration of chiral ligands and reaction conditions. The binding ability of two nucleophilic amide groups in such substrates is relatively weaker by comparing with that of corresponding 1,3-diamines. Thus, it may be a more suitable model case for better enantiocontrol. As shown in Table 1, without adding any chiral ligands, the desired coupling product **2a** was obtained in 50% yield under the catalysis of CuI in acetonitrile, with K_3PO_4 as the base at room temperature. For a screening of chiral ligands, binol-derived ligands L1/L2, which showed excellent enantioselectivity in the first type of copper-catalyzed asymmetric desymmetric C−N coupling reactions in our previous studies,[6a,b] were first examined in this second type of desymmetric coupling reaction. However, both of them showed little effect on enantiocontrol (Table 1, entries 1 and 2). An amino acid derived ligand L3, which also showed moderate to good enantioselectivity in a previous study,[6c] has little effect on enantiocontrol in this model reaction as well (Table 1, entry 3). We speculated that the binding ability of binol or amino acid may not be strong enough to compete with the two amide groups in the substrate. Thus, chiral bisoxazoline and diamine-related ligands,[12] which were supposed to have a stronger chelating ability with CuI, were examined. Although chiral bisoxazole ligand (L4) and BINAM (L5) showed no effect

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on the enantiocontrol (Table 1, entries 5 and 6), we were pleased to find that chiral amine ligands L6−L8 worked well on the model reaction and afforded the desired product **2a** in good yields and higher enantiomeric ratios (Table 1, entries 5−9). Among them, 1,2-diphenylethane-1,2-diamine ligand L8 exhibited the best enantioselectivity (78% ee, Table 1, entry 9). Further modification of this ligand led to the cyclized diamine L9 and more sterically hindered diamine L10. However, when these two ligands were used in the model reaction, no improvement in either the yield or enantioselectivity was observed. With L8 as the ligand, other solvents and bases were also screened and all gave inferior results in enantioselectivity. The results revealed that the combination of K_3PO_4 and MeCN gives the best results. A higher yield was obtained by increasing the reaction temperature to 60 °C with slightly reduced enantioselectivity (72% ee, Table 1, entry 18).

With the optimized reaction conditions in hand, we further explored the reaction scope with a series of 2-substituted-(2-iodobenzyl)malonamides. As shown in Table 2, different substituents on the aryl ring were well tolerated in the reaction system. Substrates bearing halides such as F, Cl or electron-withdrawing groups such as CF_3, $-NO_2$, $-CO_2Me$ on the iodoaryl ring proceeded well at room temperature to deliver the products in high yields and moderate to good enantioselectivity. Substrates bearing electron-donating groups such as methyl, methoxyl showed poor reactivity at room temperature. Such substrates were reacted at 60 °C to afford the desired coupling products in high yields and moderate ee values (**2i** and **2h**). Different substituents such as ethyl, *n*-hexyl, allyl, phenyl on the prochiral carbon were also examined, and all afforded the desired products in moderate to good yields and moderate enantioselectivity at 60 °C. What is worth mentioning is that, for practical use, >90% enantioselectivity could be obtained through simple crystallization as in the examples of **2a** and **2c**. Bromide substrates were also examined and showed poor reactivity at room temperature or 60 °C. A good yield and moderate enantiomeric ratio were obtained at higher temperature (80 °C) as in the case of 2-benzyl-2-(2-bromobenzyl)malonamide (**1a′**).

To determine the absolute configuration of the coupling products, we chose **2a** as an example. Compound **2a** was reduced into amine **3a** by $LiAlH_4$, which was compared with (*R*)-**3a** obtained from the reduction of known compound **4** (Scheme 2).[13] Through this approach, the absolute configuration of **2a** was assigned as *R*. The absolute configurations of other coupling products were assigned analogously with that of **2a**.

In summary, the second type of copper-catalyzed asymmetric desymmetric aryl C−N coupling reaction through differentiation of two nucleophilic amide groups was developed by employing a CuI/chiral 1,2-diamine catalytic system. Such reactions afforded the desired six-membered quinolinone derivatives in good yields and moderate to high enantiomeric ratios. Further work for the modification of chiral ligands to improve enantioselectivity and broaden the substrate scope is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic details for substrates, procedures for coupling reactions, determination of absolute configuration of **2a**, and NMR and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yphuo@gdut.edu.cn.
*E-mail: cai_qian@gibh.ac.cn.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For general reviews about desymmetrization, see: (a) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313. (b) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (c) Studer, A.; Schleth, F. *Synlett* **2005**, 3033. (d) Rovis, T. In *New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; John Wiley & Sons, Inc.: 2007; pp 275−309. (e) Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683. (f) Díaz-de-Villegas, M. D.; Gálvaz, J. A.; Etayo, P.; Badorrey, R.; López-Ram-de-Víu, M. P. *Chem.—Eur. J.* **2012**, *18*, 13920−13935.

(2) For selected recent examples about organocatalytic desymmetrizations, see: (a) Mori, K.; Katoh, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 9652. (b) Li, L.; Siedel, D. *Org. Lett.* **2010**, *12*, 5064. (c) Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056. (d) Kanta De, C.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 14538. (e) Leon, R.; Jawalekar, A.; Redert, T.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 1487. (f) Sun, X.; Worthy, A. D.; Tan, K. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8167. (g) Müller, S.; Webber, M. J.; List, B. *J. Am. Chem. Soc.* **2011**, *133*, 18534. (h) Ikeuchi, K.; Ido, S.; Yoshimura, S.; Asakawa, T.; Inai, M.; Hamashima, Y.; Kan, T. *Org. Lett.* **2012**, *14*, 6016. (i) Wilking, M.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Hennecke, U. *J. Am. Chem. Soc.* **2013**, *135*, 8133. (j) Yao, L.; Liu, K.; Tao, H.-Y.; Qiu, G.-F.; Zhou, X.; Wang, C.-J. *Chem. Commun.* **2013**, *49*, 6078. (k) Rong, Z.-Q.; Pan, H.-J.; Yan, H.-L.; Zhao, Y. *Org. Lett.* **2014**, *16*, 208. (l) Di Iorio, N.; Righi, P.; Mazzanti, A.; Mancinelli, M.; Ciogli, A.; Bencivenni, G. *J. Am. Chem. Soc.* **2014**, *136*, 10250. (m) Meng, S.-S.; Liang, Y.; Gao, K.-S.; Zou, L.; Lin, X.-B.; Yang, H.; Houk, K. N.; Zheng, W.-H. *J. Am. Chem. Soc.* **2014**, *136*, 12249.

(3) For selected examples about Pd-catalyzed desymmetric reactions, see: (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738. (b) Ohshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1996**, *118*, 7108. (c) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101. (d) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184. (e) Oestreich, M.; Sempere-Culler, F.; Machotta, A. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 149. (f) Willis, M. C.; Powell, L. H. W.; Claverie, C. K.; Watson, S. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1249. (g) Albicker, M. R.; Cramer, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 9139. (h) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (i) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460. (j) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. (k) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438. (l) Rousseaux, S.; García-Fortanet, J.; Del Aguila Sanchez, M. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 9282. (m) Saget, T.; Lemouzy, S. J.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 2338.

(4) For selected recent examples about transition-metal-catalyzed desymmetrizations, see: [Rh]: (a) Cook, M. J.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 9302. [Rh]: (b) Phan, D. H. T.; Kou, K. G. M.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16354. [Ru]: (c) Takebayashi, S.; John, J. M.; Bergens, S. H. *J. Am. Chem. Soc.* **2010**, *132*, 12832. [Ru]: (d) Ito, M.; Kobayashi, C.; Himizu, A.; Ikariya, T. *J. Am. Chem. Soc.* **2010**, *132*, 11414. [Ru]: (e) Takebayashi, S.; John, J. M.; Bergens, S. H. *J. Am. Chem. Soc.* **2010**, *132*, 12832. [Zn]: (f) Trost, B. M.; Mino, T. *J. Am.*

DOI: 10.1021/ol5035386
Org. Lett. 2015, 17, 374−377

Chem. Soc. **2003**, *125*, 2410. [Mo]: (g) Teng, X.; Cefalo, D. R.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 10779. [Ag]: (h) Liu, K.; Teng, H.-L.; Yao, L.; Tao, H.-Y.; Wang, C.-J. *Org. Lett.* **2013**, *15*, 2250.

(5) For reviews about copper-catalyzed reactions, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (d) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (e) Ma, D.; Cai, Q. *Acc. Chem. Soc.* **2008**, *41*, 1450. (f) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chem. Soc. Rev.* **2014**, *43*, 3525.

(6) (a) Zhou, F.; Guo, J.; Liu, J.; Ding, K.; Yu, S.; Cai, Q. *J. Am. Chem. Soc.* **2012**, *134*, 14326. (b) Zhou, F.; Cheng, G.-J.; Yang, W.; Long, Y.; Zhang, S.; Wu, Y.-D.; Zhang, X.; Cai, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9555. (c) Liu, J.; Yan, J.; Qin, D.; Cai, Q. *Synthesis* **2014**, *46*, 1917.

(7) (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

(8) For a Pd-catalyzed enantioselective Buchwald−Hartwig reaction for the formation of a N−C chiral axis, see: (a) Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 3676. (b) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923. (c) Kitagawa, O.; Kurihara, D.; Tanabe, H.; Shibuya, T.; Taguchi, T. *Tetrahedron Lett.* **2008**, *49*, 471. (d) Takahashi, M.; Tanabe, H.; Nakamura, T.; Kuribara, D.; Yamazaki, T.; Kitagawa, O. *Tetrahedron* **2010**, *66*, 288. (e) Takahashi, I.; Morita, F.; Kusagaya, S.; Fukaya, H.; Kitagawa, O. *Tetrahedron: Asymmetry* **2012**, *23*, 1657.

(9) Porosa, L.; Viirre, R. D. *Tetrahedron Lett.* **2009**, *50*, 4170.

(10) Takenaka, K.; Itoh, N.; Sasai, H. *Org. Lett.* **2009**, *11*, 1483.

(11) A strong background reaction was observed when 2-(2-iodobenzyl)propane-1,3-diamine was used as a substrate, and no enantioselectivity was detected under the same conditions listed in Table 1.

(12) For diamine ligands in copper-catalyzed coupling reactions, see: Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13.

(13) The absolute configuration of compound **4** was determined in our previous reported work; see ref 6b.

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