ORGANIC LETTERS

2011
Vol. 13, No. 7
1666–1669

Synthesis of Chiral *N*-Heterocyclic Carbene Ligands with Rigid Backbones and Application to the Palladium-Catalyzed Enantioselective Intramolecular α-Arylation of Amides

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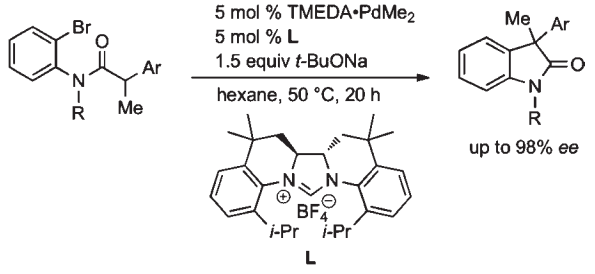
Received January 18, 2011

ABSTRACT



Chiral *N*-heterocyclic carbene (NHC) ligands having a 2,2′-bisquinoline-based C_2 symmetric skeleton were developed. The ligands exhibited good enantioselectivity in palladium-catalyzed intramolecular α-arylation of amides to give 3,3-disubsituted oxindoles.

N-Heterocyclic carbenes (NHCs) constitute an important class of ligands for transition-metal catalysis due to their unique properties such as strong σ-donating ability, robustness, and sterically demanding character.[1] Recent efforts have been directed to the development of chiral derivatives capable of promoting enantioselective transformations, which are difficult to control with conventional chiral phosphine ligands.[2,3] It has been shown with the help of DFT calculations that the rotational lability of the *N*-substituents leads to flexible behaviors of NHC-ligated metal complexes.[4] Therefore, chiral NHCs having fused rings that hamper rotation of the *N*-substituents have attracted much attention. Glorius developed C_2-symmetric oxazoline-fused NHCs **1**, which were

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(2) For reviews, see: (a) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951. (b) Cesar, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619. (c) Snead, D. R.; Seo, H.; Hong, S. *Curr. Org. Chem.* **2008**, *12*, 1370 and the references cited therein.

(3) For recent progress in asymmetric reactions catalyzed by transition metal-NHC complexes, see: (a) Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 8733. (b) Scarborough, C. C.; Bergant, A.; Sazamaa, G. T.; Guzeia, I. A.; Spencera, L. C.; Stahl, S. S. *Tetrahedron* **2009**, *65*, 5084. (c) Stenne, B.; Timperio, J.; Savoie, J.; Dudding, T.; Collins, S. K. *Org. Lett.* **2010**, *12*, 2032. (d) Tiede, S.; Berger, A.; Schlesiger, D.; Rost, D.; Lühl, A.; Blechert, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 3972. (e) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736 and references cited therein.

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(5) (a) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. W. *Chem. Commun.* **2002**, 2704. (b) Würtz, S.; Lohre, C.; Fröhlich, R.; Bergander, K.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 8344. (c) Bexrud, J.; Lautens, M. *Org. Lett.* **2010**, *12*, 3160.

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10.1021/ol200149s
Published on Web 03/08/2011

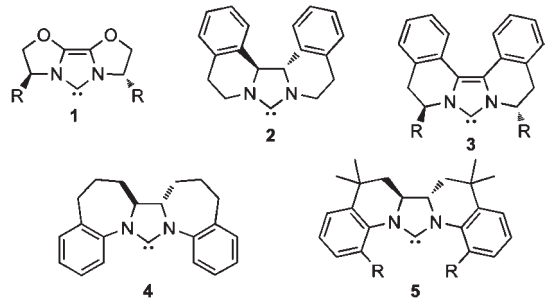
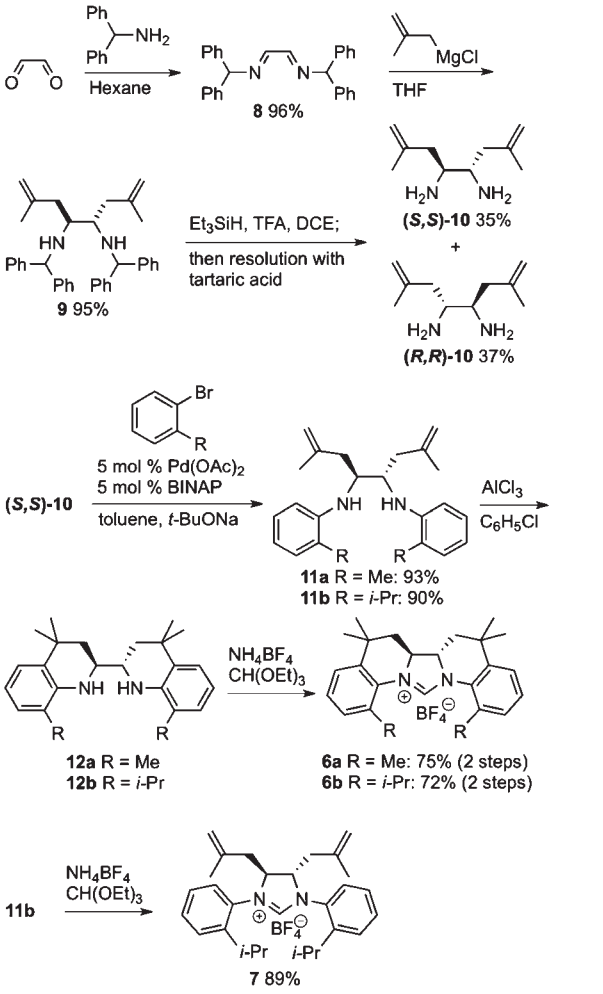


Figure 1. Chiral NHCs.

synthesized from aminoalcohols (Figure 1).[5] Herrmann and Cavell reported 1,1′-bisisoquinoline-derived saturated imidazolin-2-ylidenes **2**, in which the 4,5-positions of the imidazoline ring were chiral centers.[6] Hong developed 1,1′-bisisoquinoline-based unsaturated imidazol-2-ylidenes **3**, which possessed chiral centers at the α-positions of the *N*-substituents.[7] Grubbs synthesized chiral NHC **4** albeit in a racemic form.[8] We herein report the synthesis and application of new NHC **5**, which has a 2,2′-bisquinoline-based C_2 symmetric skeleton.[9] The *ortho* R groups on the *N*-aryl substituents point inward hanging over a metal center to create a chiral environment in proximity to the metal.

The synthesis of imidazolidinium tetrafluoroborate salts **6** and **7** is depicted in Scheme 1. Condensation of glyoxal with aminodiphenylmethane gave the diimine **8** in 96% yield. The diimine **8** reacted with 2-methallylmagnesium chloride in a stereoselective manner to furnish *trans*-diamine **9** as a racemic mixture. Deprotection of the diphenylmethyl groups of the diamine **9** with Et_3SiH in the presence of TFA afforded racemic diamine **10**, which was subjected to optical resolution using tartaric acid.[10] Both enantiomers of diamine **10** were obtained in an enantiomerically pure form by neutralization of the pure tartarate complexes of **10**. Next, enantiomerically pure **10** was coupled with 2-bromotoluene or 2-bromocumene by the catalysis of palladium to give arylated diamines **11a** and **11b**, respectively.[11,12] They underwent intramolecular Friedel−Crafts alkylation in the presence of $AlCl_3$ to afford the cyclic chiral diamines **12**. Finally, treatment of the diamines **12** with NH_4BF_4 and $HC(OEt)_3$ generated the pentacyclic chiral imidazolidinium tetrafluoroborate salts **6**. The nonfused imidazolidinium **7** was also synthesized from diamine **11b** in a similar manner.

Scheme 1. Synthesis of Chiral Imidazolidinium Tetrafluoroborate Salts **6** and **7**



To view their structural features as the chiral NHC ligand, the copper(I) complex **13** was prepared by treatment of **6b** with CuCl (1.0 equiv) in the presence of *t*-BuOK (1.0 equiv) in THF at room temperature (Scheme 2).[13] Single crystals suitable for an X-ray structural analysis were obtained by recrystallization from $CHCl_3$/hexane (Figure 2).[14] The crystal structure of **13** revealed that the dihedral angles between the *N*-aryl groups and the imidazole plane (61.7−66.0°) are much smaller than those of related nonfused NHC-copper complexes (almost perpendicular).[15] Thus, the isopropyl groups on the aryl moieties are located in close proximity to the metal center

(7) Seo, H.; Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *J. Org. Chem.* **2008**, *73*, 1983.

(8) Li, J.; Stewart, I. C.; Grubbs, R. H. *Organometallics* **2010**, *29*, 3765.

(9) For a meso-NHC ligand with a similar skeleton see: Vehlow, K.; Gessler, S.; Blechert, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 8082.

(10) See Supporting Information for experimental details.

(11) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

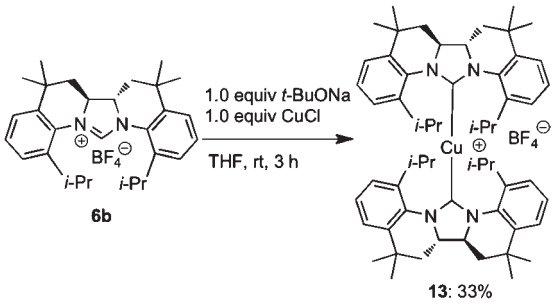
(12) The coupling reaction of diamine **10** with bulkier bromobenzenes such as 2-bromobiphenyl and 2-*tert*-butylbromobenzene failed to give the corresponding diarylated diamines.

(13) The palladium−NHC complexes were synthesized from various Pd(II) precursors with the chiral imidazolidinium salt **6**; however, recrystalization of the complexes failed to afford the single crystals suitable for X-ray crystallographic analysis.

(14) CCDC-802011 (**13**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(15) Díez-González, S.; Stevens, E. D.; Scott, N. M.; Petersen, J. L.; Nolan, S. P. *Chem.—Eur. J.* **2008**, *14*, 158.

Scheme 2. Synthesis of Chiral NHC-Copper Complex **13**



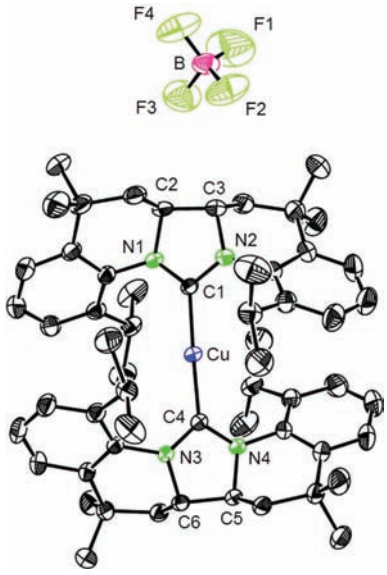
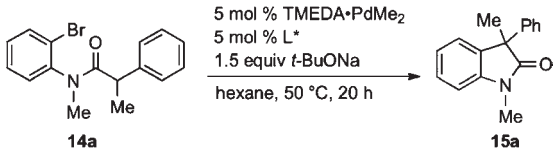


Figure 2. ORTEP drawing of **13** (ellipsoids at the 30% probability level). Hydrogen atoms and $CHCl_3$ are omitted for clarity.

hanging over them, and form a compact C_2 symmetric chiral environment around the metal.[16]

We then applied the chiral imidazolidinium tetrafluoroborates **6** and **7** to the palladium-catalyzed enantioselective intramolecular α-arylation of amides producing chiral 3,3-disubstituted oxindoles.[17,18] The intramolecular arylation reaction presents a standard reaction to estimate the efficiency of chiral induction, and various chiral NHCs have been applied to it. Hartwig demonstrated that pinene-derived NHC ligands gave better selectivity than conventional phosphine ligands.[19] Aoyama[20] and Dorta[21] respectively reported that the chiral imidazolidene ligands derived from 1,2-diamino-1,2-diphenylethane exhibited improved selectivity. Chiral phenethylamine-based NHCs developed by Kündig afforded excellent results (75−97% ee) and the ligands were applied to the enantioselective synthesis of 3-alkoxy- and 3-aminooxyindoles.[22] The most sterically demanding chiral NHC synthesized from (−)-menthone by Glorius gave oxindoles with high enantioselectivities ranging from 81 to 97% ee.[5b]

Table 1. Asymmetric Intramolecular Arylation of Amide **14a** to Form Enantioenriched Oxindole **15a**[a]



entry	L*	yield/%[b]	ee/%[c]	configuration
1	**6a**	99	71	R
2	**6b**	99	86	R
3	**7**	98	69	S

[a] Reaction conditions: amide **14a** (1.0 equiv), TMEDA·$PdMe_2$ (5 mol %), L* (5 mol %), *t*-BuONa (1.5 equiv), hexane, 50 °C, 20 h. [b] Isolated yield. [c] Determined by chiral HPLC. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylene-1,2-diamine

The results obtained with **6** and **7** are summarized in Table 1. When amide **14a** was treated with TMEDA·$PdMe_2$ (5 mol %), methyl-substituted imidazolidinium salt **6a** (5 mol %), and *t*-BuONa (1.5 equiv) in hexane at 50 °C for 20 h, oxindole **15a** was obtained in 99% yield with 71% ee (entry 1). Enantioselectivity was improved to 86% ee by replacing the methyl substituents with bulkier isopropyl substituents (entry 2). For comparison, we examined imidazolidinium **7** in which a fused rigid backbone was lacking. The reaction became slower, and in particular, the opposite configuration was favored (69% ee, entry 3). These results indicate that the rigid backbone of NHC plays an important role in terms of both the reactivity and the selectivity.

Thus, the isopropyl-substituted NHC ligand proved to be promising, and the arylation reaction of other substrates was examined using the ligand precursor **6b** (Table 2).[23] The substrate **14b**, which had a 4-tolyl group instead of a phenyl group on the α-carbon of the carbonyl

(16) The buried volume (% V_{bur}) of the NHC ligand in **13** was 42.5%, which was larger than that of SIPr in $[(SIPr)_2Cu]PF_6$ (39.9% V_{bur} for Cu-NHC length at 2.00 Å). The result indicates that the new NHC is sterically bulkier than SIPr. The % V_{bur} value of the new NHC was calculated by SambVca with the standard parameters: radius of sphere 3.5 Å, distance from sphere 2.1 Å, mesh step 0.05 Å. (a) Poater, A.; Cosenza, B.; Correa, A.; Giusdice, S.; Ragone, F.; Scarano, V.; Cavallo, L. *Eur. J. Inorg. Chem.* **2009**, 1559. (b) Clavier, H.; Nolan, S. P. *Chem. Commun.* **2010**, 841.

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(18) For a review of asymmetric synthesis of oxindoles bearing a tetrasubstituted stereocenter, see: Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381.

(19) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402.

(20) Arao, T.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 1743.

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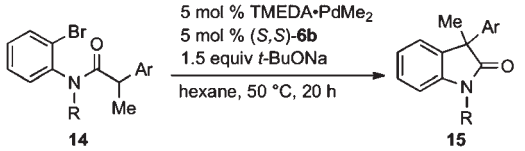
Table 2. Asymmetric Intramolecular Arylation of Amides.[a]



14 15

entry	14	R	Ar	15	yield/%[b]	ee/%[c]
1	**14b**	Me	4-tol	**15b**	99	84
2	**14c**	Me	2-tol	**15c**	99	96
3	**14d**	Bn	2-tol	**15d**	84	98
4[d]	**14e**	Me	2-$MeOC_6H_4$	**15e**	97	92
5	**14f**	Bn	2-$MeOC_6H_4$	**15f**	75	94
6	**14g**	Me	1-naphthyl	**15g**	98	97
7	**14h**	Me	2-ClC_6H_4	**15h**	80	97

[a] Reaction conditions: amide **14** (1.0 equiv), TMEDA·$PdMe_2$ (5 mol %), **6a** (5 mol %), *t*-BuONa (1.5 equiv), hexane, 50 °C, 20 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 70 °C.

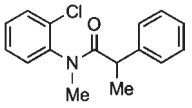
group, provided the oxindole **15b** in 99% yield with 84% ee (entry 1). When the substrates possessed sterically more demanding *ortho*-substituted aryl groups, the corresponding oxindoles were obtained with higher enantiolselectivities ranging from 92% to 98% ee. For example, **14c** (Ar = 2-tolyl) afforded **15c** in 99% yield with 96% ee (entry 2). *N*-Benzyl-substituted substrates which were easy to deprotect gave higher enantioselectivities than with the *N*-methyl-substituted substrates (entries 3 and 5). The substrate having an electron-rich 2-methoxyphenyl group worked well although higher reaction temperature was required (entry 4). 1-Naphthyl-substiuted amide **14g** gave oxindole **15g** in 98% yield with 97% ee (entry 6). The arylation reaction of the substrate possessing a 2-chlorophenyl group proceeded without decomposition of the chloro moiety to yield the chiral oxindole **15h** in 80% yield with 97% ee (entry 7).

In conclusion, we have synthesized chiral C_2 symmetric imidazolidiniums having a rigid backbone, and applied them to the palladium-catalyzed intramolecular α-arylation reaction of amides. The corresponding oxindoles were obtained in good yield and enantioselectivity. The two fused rings attached to the NHC core played an important role. Application of the NHC ligands to other challenging reactions is ongoing.

Acknowledgment. This work was supported by MEXT. L.L. and S.A. thank Research Fellowships of Japan Society for the Promotion of Science for Young Scientists. We thank Dr. Y. Nagata (Kyoto Univ.) for his help in X-ray single crystal analysis.

Supporting Information Available. Experimental procedures, spectroscopic data for new compounds, and details of X-ray crystallographic analysis for Cu-NHC complex **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

(23) No reaction was observed with aryl chloride **16** even at higher temperature and in other solvents such as dioxane and toluene.



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