ORGANIC LETTERS

2010
Vol. 12, No. 21
5008−5011

A Chiral 6-Membered *N*-Heterocyclic Carbene Copper(I) Complex That Induces High Stereoselectivity

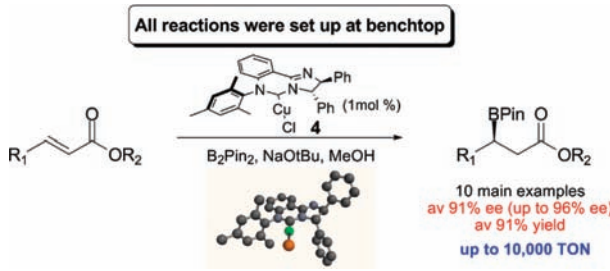
Jin Kyoon Park, Hershel H. Lackey, Matthew D. Rexford, Kirill Kovnir, Michael Shatruk, and D. Tyler McQuade*

Department of Chemistry & Biochemistry, Florida State University, Tallahassee, Florida 32306-4390, United States

mcquade@chem.fsu.edu

Received September 10, 2010

ABSTRACT



A chiral 6-membered annulated *N*-heterocyclic (6-NHC) copper complex that catalyzes *β*-borylations with high yield and enantioselectivity was developed. The chiral 6-NHC copper complex is easy to prepare on the gram scale and is very active, showing 10 000 turnovers at 0.01 mol % of catalyst without significant decrease of enantioselectivity and with useful reaction rates.

N-Heterocyclic carbenes (NHCs) are excellent organocatalysts and ligands.[1] 6-Membered *N*-heterocyclic carbene (6-NHC) metal complexes have unique electronic and steric properties[2] and show improved properties over 5-NHCs in some cases.[2b,c,i] In surprising contrast to organocatalytic carbenes,[3] however, no fused cyclic NHC-metal catalysts with rigid chiral groups have exhibited high enantioselectivity.[4] Recognizing the strengths of both 6-NHCs and annulated NHCs, we designed a 6-NHC with a rigid core (imidazoquinazoline) formed by segments **B** and **C**, steric blockade **D**, and chiral group **A** (Figure 1). Here, we present the synthesis of this new ligand and its rhodium and copper(I) complex. We also demonstrate that copper(I) complex can induce high enantioselectivity in a known reaction.

(1) (a) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (c) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 2988. (d) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619.

(2) (a) Kolychev, E. L.; Portnyagin, I. A.; Shuntikov, V. V.; Khrustalev, V. N.; Nechaev, M. S. *J. Organomet. Chem.* **2009**, *694*, 2454. (b) Binobaid, A.; Iglesias, M.; Beetstra, D. J.; Kariuki, B.; Dervisi, A.; Fallis, I. A.; Cavell, K. J. *Dalton Trans.* **2009**, 7099. (c) Tu, T.; Malineni, J.; Bao, X. L.; Dötz, K. H. *Adv. Synth. Catal.* **2009**, *351*, 1029. (d) Cesar, V.; Lugan, N.; Lavigne, G. *J. Am. Chem. Soc.* **2008**, *130*, 11286. (e) Bazinet, P.; Ong, T.-G.; O'Brien, J. S.; Lavoie, N.; Bell, E.; Yap, G. P. A.; Korobkov, I.; Richeson, D. S. *Organometallics* **2007**, *26*, 2885. (f) Lloyd-Jones, G. C.; Alder, R. W.; Owen-Smith, G. J. J. *Chem.—Eur. J.* **2006**, *12*, 5361. (g) Prasang, C.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2005**, *127*, 10182. (h) Lavallo, V.; Canac, Y.; Prasang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705. (i) Mayr, M.; Wurst, K.; Ongania, K.-H.; Buchmeiser, M. R. *Chem.—Eur. J.* **2004**, *10*, 1256. (j) Bazinet, P.; Yap, G. P. A.; Richeson, D. S. *J. Am. Chem. Soc.* **2003**, *125*, 13314.

(3) (a) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418. (b) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406.

(4) For biphenyl core, see: (a) Scarborough, C. C.; Bergant, A.; Sazama, G. T.; Guzei, I. A.; Spencer, L. C.; Stahl, S. S. *Tetrahedron* **2009**, *65*, 5084. (b) Scarborough, C. C.; Guzei, I. A.; Stahl, S. S. *Dalton Trans.* **2009**, 2284. For phenanthroline core, see: (c) Metallinos, C.; Du, X. *Organometallics* **2009**, *28*, 1233. For biisoquinoline core, see: (d) Seo, H.; Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *J. Org. Chem.* **2008**, *73*, 1983. (e) Baskakov, D.; Herrmann, W. A.; Herdtweck, E.; Hoffmann, S. D. *Organometallics* **2007**, *26*, 626. (f) Cavell, K. J.; Elliott, M. C.; Nielsen, D. J.; Paine, J. S. *Dalton Trans.* **2006**, 4922. For oxazoline core, see: (g) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704.

10.1021/ol1021756
Published on Web 10/04/2010

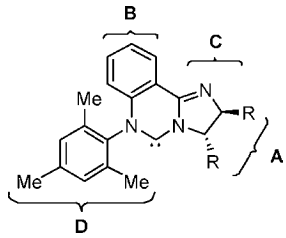
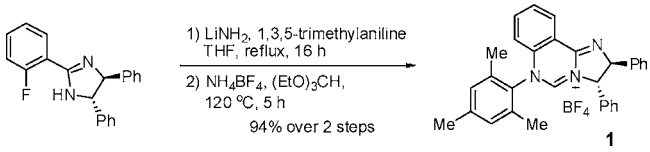


Figure 1. Design of the 6-NHC ligand.

Ligand precursor **1** was prepared as shown in Scheme 1. Fluoroimidazoline was synthesized via a known method[5a]

Scheme 1. Synthesis of the 6-NHC Precursor **1**



and the mesityl group was installed by using a nucleophilic aromatic substitution in 99% yield.[5b] Subsequent annulation with NH_4BF_4/triethyl orthoformate provided the carbene ligand precursor in 95% yield.

Salt **1** is a shelf-stable compound that is readily converted into metal complexes by two standard approaches. The first approach is to generate a carbene via addition of a suitable base such as lithium hexamethyldisilazide followed by addition of an appropriate metal salt.[2e,f,j] We used this method to synthesize a **1**-Rh complex that manifests itself as a mixture that includes a 1:1 rhodium:**1** and a 2:1 rhodium:**1** species. The ^{1}H NMR spectrum shown in Figure 2 exhibits two sets of peaks that we have assigned as the mono- and dirhodium species. The monorhodium species can be produced by treating the mixture with supported or free pyridine.

The stucture established by X-ray single-crystal diffraction confirms our assignment of the NMR data as both the dirhodium [(COD)Rh(μ2−1)Rh(COD)] species (**2**) species and monorhodium [(COD)Rh(1)] species (**3**) (COD = 1,5-cyclooctadiene) are cocrystallized in the unit cell of the complex (Figure 3). The structures also enable an analysis of the ligand geometry. It is evident from the data that the annulated ligand **1** is planar and that the central ring is aromatic as indicated by the near 120° bond angles and symmetric bond lengths. The crystal structure also demonstrates that the mesityl group provides a steric blockade on one side of the ligand and the diaminodiphenylethylene moiety provides a chiral pocket.

The second method used to make metal-**1** complexes combines **1** with a metal salt followed by addition of a base. The title copper(I) complex was made in this way[5c] and though a crystal structure of this species has alluded us thus

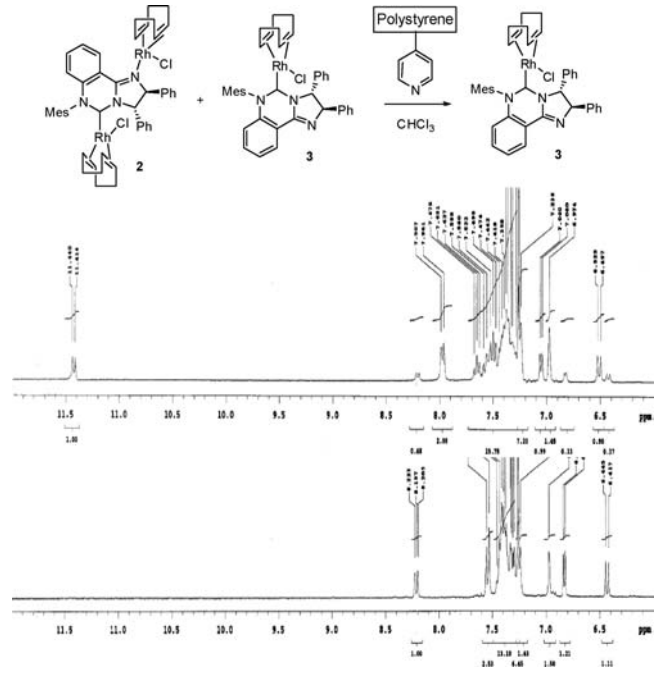


Figure 2. ^{1}H NMR data of a mixture of **2** and **3** (top) and only **3** (bottom).

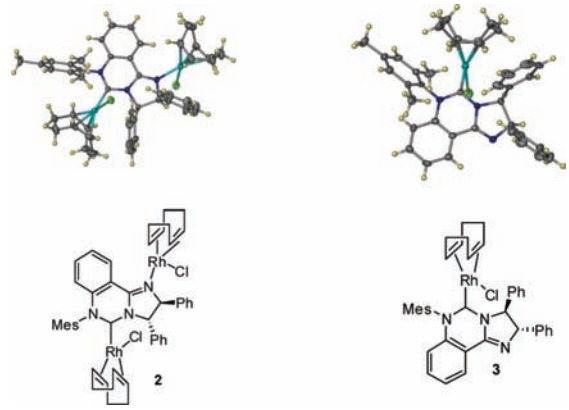
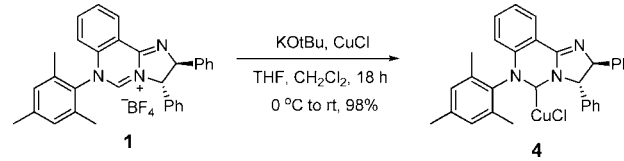


Figure 3. Dirhodium (**2**) and monorhodium (**3**) species cocrystallized in the structure of the **1**-Rh complex.

far, the resulting compound is an orange, shelf-stable solid that exhibits NMR and elemental analysis consistent with complex **4** (Scheme 2). This copper(I) species was explored

Scheme 2. Synthesis of the 6-NHC Copper Chloride **4**



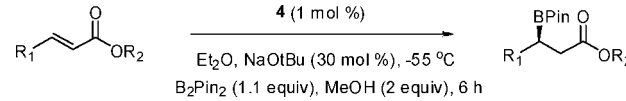
for catalytic activity and, as we discuss below, the catalyst shows excellent properties, suggesting that our 6-NHC ligand provides the necessary electronic and steric characteristics.

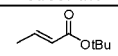
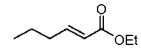
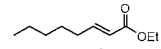
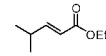
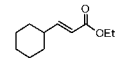
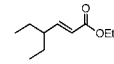
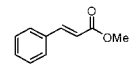
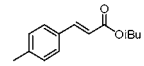
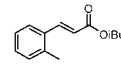
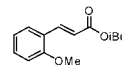
The conjugate addition of boron to electron-poor alkenes (β-borylation) provides access to intermediates useful in the construction of complex products. Prior studies reveal that copper(I) catalysts yield β-borylations with greater selectivity than other transition metals,[6,7] presumably via a Cu−B species.[8,9] Though both chiral phosphine and 5-NHCs are competent ligands for copper(I)-catalyzed β-borylations, phosphine catalysts generally have exhibited higher enantioselectivity.[7] Hoveyda's group, however, used a 5-NHC-copper complex to hydroborate trisubstituted electron-poor alkenes and styrenic alkenes with high yield and selectivity,[7a,10a] and also demonstrated an organocatalytic method requiring only a NHC to catalyze β-borylations.[10b] Thus far, no 6-NHC-copper complexes induce high enantioselectivity for β-borylation reactions. On the basis of the reported success of copper(I)-catalyzed β-borylations, we chose this reaction as a model for determining if our 6-NHC ligand could induce high enantioselection.

Exploratory studies[11] revealed that **4** is a highly active catalyst for β-borylations, providing complete consumption of starting materials within 1 min (1 mol % catalyst; 0 °C) in diethyl ether to give 78% ee of the desired product. Optimization revealed that higher selectivity could be realized at −55 °C and that *methanol was a necessary additive*.

Complex **4** was successful at transforming a variety of aliphatic and aromatic α,β-unsaturated esters to β-borylated products in high yield and enantioselectivity (Table 1). Linear aliphatic substrates such as ethyl hexenoate and ethyl octenoate had high enantioselectivities of 90% and 91%, respectively (entries 2 and 3). Increased γ-branching was also well tolerated (entries 4−6). Methyl cinnamate gave the highest ee (87% ee) among the methyl, ethyl, and isobutyl esters of cinnamic acid, which is opposite to the crotonate esters (90% ee) (entries 1 and 7).[11] Ortho-substituted cinnamate esters also showed high selectivity (entries 9 and 10). These data indicate that the 6-NHC ligand induces high enantioselectivity.

Table 1. Substrate Scope for β-Borylated Ester Synthesis[a]

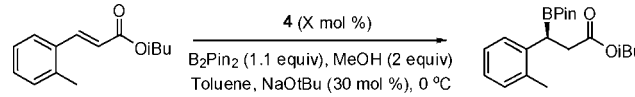


entry	substrate	yield (%)[b]	ee (%)[c]
1		93	90 (R)
2		92	90
3		90	91
4		91	96 (S)
5		95	90
6		92	91
7[d,e]		88	87
8[d,e]		91	82
9[d,f]		95	96
10[d,f]		90	92

[a] Reactions run under N_2 atm and repeated more than 2 times. [b] Isolated yields. [c] Determined by GC or HPLC after oxidizing the boronate to alcohol by the treatment with H_2O_2/NaOH. [d] Toluene as solvent. [e] 3 mol % catalyst was used. [f] Reactions run at −30 °C.

To quantify the activity of **4**, we reduced the catalyst loading (Table 2). At 0.01 mol % of **4**, the reaction proceeded within 100 min with high yield and enantioselectivity (entry 5). Though NHC-copper catalysts are known to provide very high turnover numbers (TONs),[12] we are unfamiliar with an asymmetric case with this activity.

Table 2. Catalyst Loading Experiment



entry	ester	mol %	time (min)	convn (%)[d]	ee (%)	TON
1[a]	44 mg	10	<1	>99	92	10
2[a]	44 mg	1	<1	>99	91	100
3[b]	0.44 g	0.1	3	>99	88	1 000
4[b]	0.44 g	0.05	80	>99	87	2 000
5[c]	2.0 g	0.01	100	>99 (93)[e]	88	10 000

[a] 0.2 M. [b] 0.4 M. [c] 0.8 M. [d] Determined by GC. [e] Isolated yield.

(5) (a) Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Lee, H.; Li, Z.; Liang, M.; Reeves, D.; Saha, A.; Varsolona., R.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 341. (b) Davis, E. M.; Nanninga, T. N.; Tjiong, H. I.; Winkle, D. D. *Org. Process Res. Dev.* **2005**, *9*, 843. (c) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417.

(6) (a) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821. (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47. (c) Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887. (d) Lee, J.-E.; Kwon, J.; Yun, J. *Chem. Commun.* **2008**, 733.

(7) (a) O'Brien, J. M.; Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630. (b) Schiffner, J. A.; Müther, K.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1194. (c) Feng, X.; Yun, J. *Chem. Commun.* **2009**, 6577. (d) Chen, I.-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664. (e) Sim, H.-S.; Feng, X.; Yun, J. *Chem.—Eur. J.* **2009**, *15*, 1939. (f) Lillo, V.; Prieto, A.; Bonet, A.; Díáz-Requejo, M. M.; Ramiéz, J.; Peŕez, P. J.; Fernández, E. *Organometallics* **2009**, *28*, 659. (g) Fleming, W. J.; Müller-Bunz, H.; Lillo, V.; Fernández, E.; Guiry, P. J. *Org. Biomol. Chem.* **2009**, *7*, 2520. (h) Lee, J.-E.; Yun, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 145.

(8) (a) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036. (b) Laitar, D. S.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 17196.

(9) (a) Zhao, H.; Dang, L.; Marder, T. B.; Lin, Z. *J. Am. Chem. Soc.* **2008**, *130*, 5586. (b) Dang, L.; Lin, Z.; Marder, T. B. *Chem. Commun.* **2009**, 3987. (c) Lillo, V.; Bonet, A.; Fernández, E. *Dalton Trans.* **2009**, 2899. (d) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 4443.

(10) (a) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160. (b) Lee, K.-s.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253.

(11) See the Supporting Information.

(12) Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8881.

In summary, we have synthesized a new annulated, chiral carbene precursor (**1**) and produced two new metal complexes using this ligand. The 6-NHC-rhodium complexes yield a crystal structure that reveals the 6-NHC to be planar about the carbene and the central ring to be aromatic. The 6-NHC-copper(I) complex (**4**) catalyzes β-borylations with high yield and enantioselectivity illustrating that the 6-NHC ligand provides an excellent chiral environment. The catalyst is also very active, showing 10 000 turnovers at 0.01 mol % of catalyst without significant decrease of enantioselectivity and with useful reaction rates indicating that the 6-NHC ligand provides an electronic environment about copper that enables high reactivity. Further studies concerning the mechanism and expansion of reaction scope are underway.

Acknowledgment. The authors thank NSF (CHE-0809261), and FSU support and FSU VP of Research and Dean of A&S for NMR upgrades. J.K.P. thanks the OLED group, LG Chem, Ltd.

Supporting Information Available: Experimental procedures and spectroscopic data of the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1021756