Synthesis of Chiral C_1-Symmetric N-Heterocyclic Carbene Ligands: Application toward Copper-Catalyzed Homocoupling of 2-Naphthols

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Received: 13.08.2013; Accepted after revision: 30.10.2013

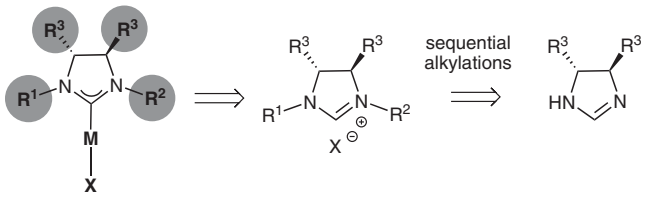
Abstract: Novel chiral C_1-symmetric NHC ligands can be prepared via dialkylation of chiral imidazoline scaffolds. Asymmetry in the ligand/metal complexes results from a chiral relay effect. The C_1-symmetric nature of the NHC ligand was proposed to allow for improved reactivity versus other achiral and chiral NHC complexes. The benefit of such ligands was demonstrated in copper-catalyzed oxidative coupling reactions.

Key words: oxidative coupling, binaphthols, N-heterocyclic carbenes, copper, catalysis

N-Heterocyclic carbenes (NHC) have had a tremendous impact in organic synthesis, both as organocatalysts and as ligands in transition-metal-based catalysis.[1] The impact of steric and electronic modifications of the carbene ligands upon their respective metal complexes continues to be an area of intense investigation. Recently, a number of asymmetric transformations catalyzed by chiral NHC complexes have appeared in the literature.[2] In general, NHC ligands having C_2 symmetry have garnered the most attention, most likely due to the ease of synthesis. However, recently greater attention has been given to NHC ligands which have a C_1-symmetric substitution pattern, despite the more laborious synthesis required. For example, copper complexes bearing C_1-symmetric NHC ligands have been found to afford ideal steric environments about the copper center,[3] allowing for a fine-tuning of both the reactivity and enantioselectivity of their respective processes.[4,5] In the majority of the studies reported, the optimization of the ligand structure could be tedious and time consuming. As such, new methods to rapidly afford NHC ligands for asymmetric catalysis are required.

Herein, we report a simple dialkylation protocol for the generation of C_1-symmetric NHC ligands. Our preliminary findings demonstrate the applicability of the NHC ligands in forming NHC–Cu complexes for use in the oxidative homocoupling of 2-naphthols.[6]

Our initial ligand design for the rapid generation of chiral C_1-symmetric NHC ligands consisted of exploiting the chiral imidazoline **1**, available on a gram scale via a four-step procedure (Table 1).[7] It was reasoned that control over the nature of the NHC structures could be achieved through sequential alkylations of the imidazoline core. One of the alkylations would have to install a relatively bulky substituent that would help define an eventual asymmetric environment around the metal through a chiral relay effect (Figure 1).[8] A second alkylation of the imidazoline motif would allow introduction of a substituent that could act to control the reactivity of the eventual metal complex. NHC ligands bearing combinations of bulky and small N-substituents have been previously exploited in asymmetric catalysis,[3,9] and served as inspiration for the development of a simple route to new ligands having similar steric properties.



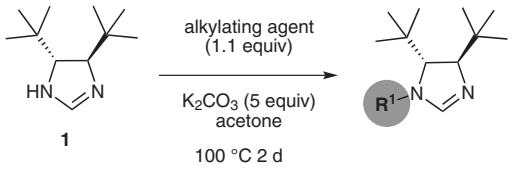
R^1 = bulky substituent to control asymmetry about the metal center
R^2 = small substituent to attenuate complex reactivity
R^3 = large groups to enforce a chiral relay towards the metal center

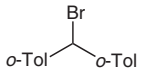
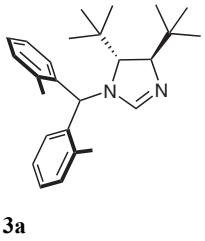
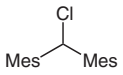
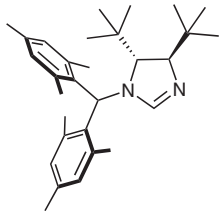
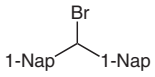
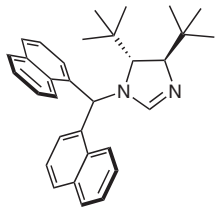
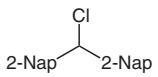
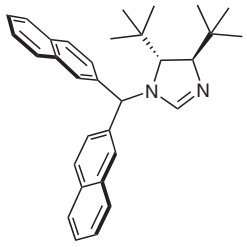
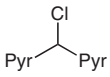
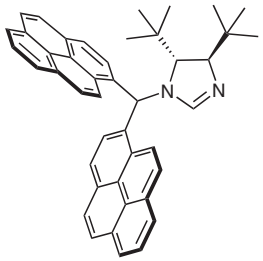
Figure 1 Rapid synthesis of chiral C_1-symmetric NHC ligands via dialkylation of a key imidazoline fragment

For introduction of a bulky substituent (R^1, Figure 1) that could be easily installed via alkylation, a series of diarylmethanes were investigated (Table 1). A bis(2-tolyl)methane group, previously utilized on a NHC–Cu complex to extend a chiral environment about a copper center,[10] was initially explored. Upon treatment of the imidazoline **1** with strong bases such as sodium hydride or butyllithium in tetrahydrofuran and subsequent treatment with diarylmethane **2a**, none of the desired product **3a** was isolated. However, refluxing the imidazoline **1** and the bromide **2a** together in acetone in the presence of potassium carbonate for one day afforded the N-substituted imidazoline **3a** in 30% isolated yield. Adding sodium iodide as an additive and extending the reaction time to two days afforded a slight increase in the yield of **3a** to 35%. Heating the mixture to 100 °C in a sealed tube over two days afforded the optimal yield of 45%. The addition of sodium iodide or other silver-based additives did not improve the yield. The challenging alkylation is thought to be due to the bulky *tert*-butyl groups found along the imidazoline skeleton. However, with optimized conditions in hand, it was found that other diarylmethanes could be used to alkylate **1** (Table 1, entries 2–5). The mesityl-derived alkyl chloride **2b**

SYNTHESIS 2014, 46, 0375–0380
Advanced online publication: 26.11.2013
DOI: 10.1055/s-0033-1338564; Art ID: SS-2013-M0565-OP

Table 1 Alkylation of Imidazoline **1**



Entry	Alkylating agent	Product	Yield[a] (%)
1	 **2a**	 **3a**	45
2	 **2b**	 **3b**	60
3	 **2c**	 **3c**	40
4	 **2d**	 **3d**	46
5	 **2e**	 **3e**	68

[a] Isolated yields after chromatography. *o*-Tol = 2-tolyl; Mes = mesityl; Pyr = pyren-1-yl; 1-Nap = 1-naphthyl; 2-Nap = 2-naphthyl.

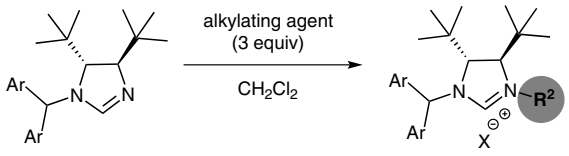
was found to participate in the alkylation and afforded the imidazoline **3b** in 60% isolated yield. Larger aromatics could also be installed on the ligand framework. For example, alkyl chlorides **2c** and **2d**, derived from 1-naphthyl and 2-naphthyl, respectively, each participated in the alkylation reaction of **1**. While the 1-naphthyl reagent **2c** provided a slightly lower yield of 40% for the corresponding imidazoline **3c**, the 2-naphthyl analogue **2d** provided the imidazoline **3d** in 46% yield. Diarylmethane **2e** bearing two pyren-1-yl substituents performed best, yielding monoalkylated imidazoline **3e** in 68% yield.

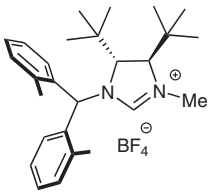
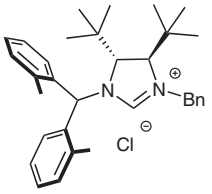
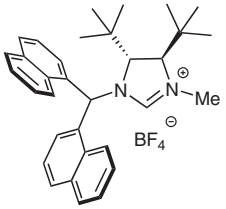
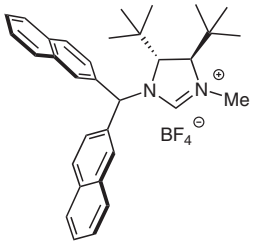
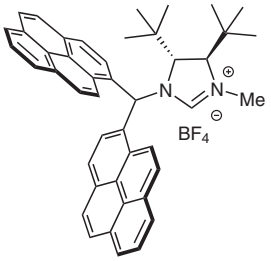
The goal of the second alkylation of the imidazolines (for example, **3a** → **4a**) was to introduce a smaller substituent that would act to modulate the reactivity of the resultant NHC–metal complexes. As such, simple alkyl groups such as a methyl and a benzyl were selected (Table 2). A one-pot alkylation of **3a** with iodomethane and counterion exchange with sodium tetrafluoroborate afforded the methyl-substituted imidazolinium salt **4a** in nearly quantitative yield (99%) over the two steps. The synthesis of the benzyl-substituted imidazolinium salt **4b** was more difficult, but could be accomplished via alkylation with benzyl chloride in dichloromethane, heated at 60 °C in a sealed tube, to afford **4b** in 60% yield. Methylation of other imidazolines was also investigated. The methylation and counterion exchange of the 1-naphthyl- and 2-naphthyl-substituted imidazolines afforded the corresponding imidazolinium salts **4c** and **4d** in 99% yield (entries 3 and 4). The larger imidazoline **3e** adorned with pyrene units also underwent alkylation and counterion exchange, albeit in lower isolated yield (72%) to afford **4e**.

Having demonstrated that various C_1-symmetric NHC ligands could be generated via the dialkylation protocol, the formation of metal complexes with the ligands was investigated. As a model, copper complexes of ligands **4a**, **4b**, and **4c** were prepared (Scheme 1). The methyl-substituted complex **5a** could be prepared on a gram scale using a published procedure involving treating the salt **4a** with sodium *tert*-butoxide in the presence of copper(I) chloride at room temperature.[12a] The resulting complex **5a** could be isolated by column chromatography in 60% yield. The procedure also successfully installed **4c** onto copper(I) chloride, although in diminished yield, giving 24% of **5c**. Unfortunately, the benzyl-substituted salt **4b** was unstable to the identical basic reaction conditions used for the methyl congeners **4a** and **4c**. In attempting to prepare **5b**, base, temperature, or solvent were modified, but did not afford **5b**. A possible explanation for the difficulties in obtaining complex **5b** could be competitive deprotonation of the benzylic proton. As such, an in situ transmetalation procedure was used employing silver(I) oxide and copper(I) chloride; complex **5b** could be isolated in 15–20% yield. X-ray crystallographic analysis of **5a** revealed that the conformation of the bis(2-tolyl)methane 'paddle' is effectively controlled by the *tert*-butyl groups on the NHC backbone, although some influence from allylic strain be-

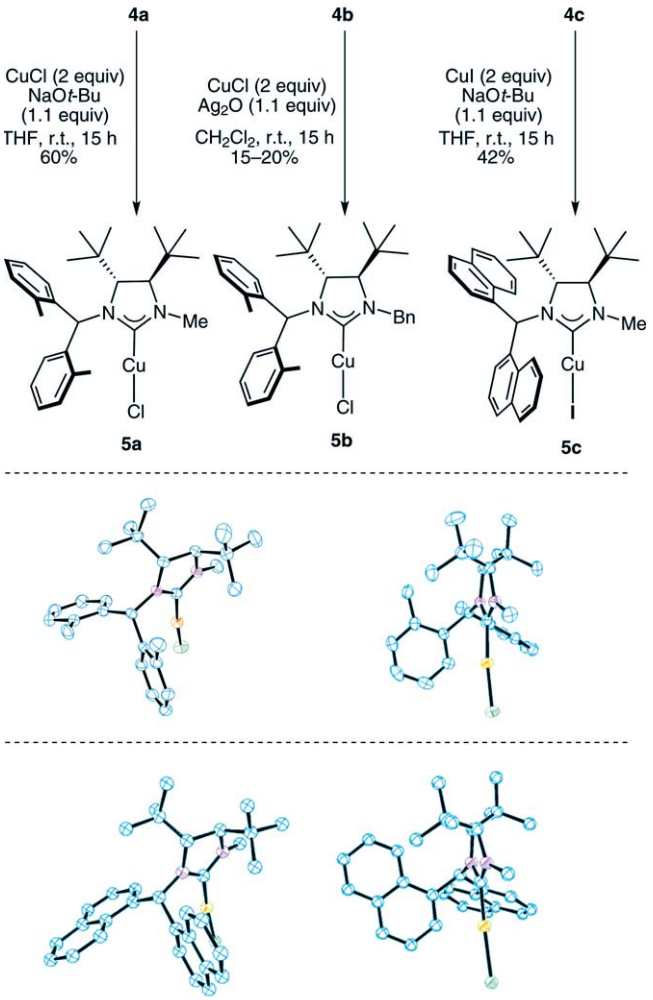
tween the bis(2-tolyl)methane 'paddle' and C–Cu bond might be responsible for the observed orientation.[11] One of the 2-tolyl groups shields one side of the copper atom. The Cu–Cl bond is slightly bent (Cu–Cl: 2.107 Å, C–Cu–Cl: 171.5°) and the complex has a buried volume similar to the (IPr)CuCl complex (for **5a**: C–Cu: 1.893 Å, $\%V_{bur}$: 44.5%).[12b,c]

Table 2 Second Alkylation To Form Imidazolinium Salts



Entry	Conditions	Product	Yield[a] (%)
1	**3a**, MeI, $NaBF_4$ (5 equiv), 21 °C, 2 d	 **4a**	99
2	**3a**, BnCl, 60 °C, 15 h	 **4b**	60
3	**3c**, MeI, $NaBF_4$ (10 equiv), 21 °C, 3 d	 **4c**	99
4	**3d**, MeI, $NaBF_4$ (10 equiv), 21 °C, 3 d	 **4d**	99
5	**3e**, MeI, $NaBF_4$ (10 equiv), 21 °C, 3 d	 **4e**	72

[a] Isolated yields after chromatography.

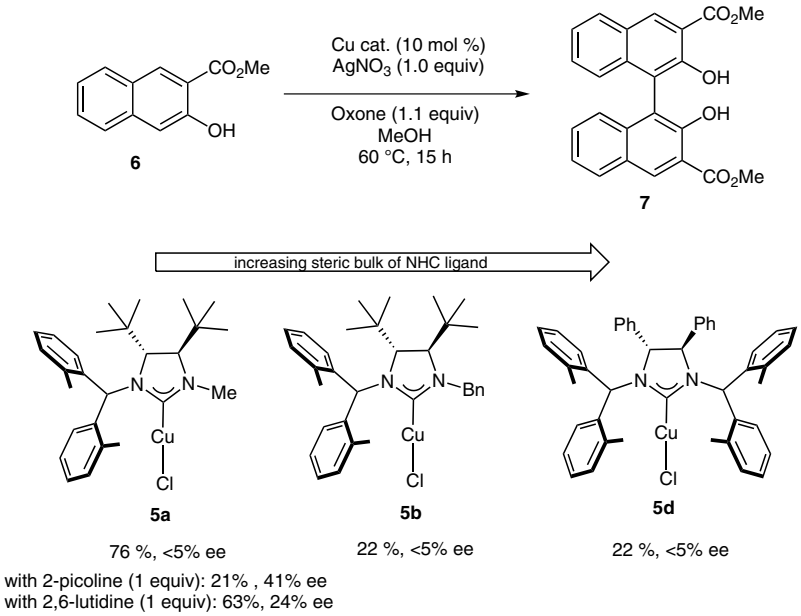


Scheme 1 Synthesis of Cu-NHC complexes (top), X-ray crystallographic analysis of methyl-substituted complex **5a** (middle: front view, left; side view, right), X-ray crystallographic analysis of methyl-substituted complex **5c** (bottom: front view, left; side view, right)

The methyl-substituted complex **5c** could also be prepared from the carbene formed from salt **4c** and sodium *tert*-butoxide. While low yields of the resulting complex from copper(I) chloride were obtained (24%), good yields of the complex **5c** were obtained by treating the carbene formed from **4c** with copper(I) iodide (42%). X-ray crystallographic analysis of **5c** revealed a conformation very similar to that of copper complex **5a** (Scheme 1). The bis(1-naphthyl)methane 'paddle' is again controlled by the *tert*-butyl groups on the NHC backbone and shields one side of the copper atom. The Cu–I bond is slightly bent (Cu–I: 2.397 Å, C–Cu–I: 173.2°) and the complex has a buried volume similar to **5a** (for **5c**: C–Cu: 1.894 Å, $\%V_{bur}$: 43.9%).

Following synthesis of the copper complexes **5a**–**c**, complexes **5a** and **5b** bearing similar counterions were evaluated in oxidative couplings of 2-naphthols (Scheme 2). These oxidative couplings represent a green and biomimetic chemical route towards the preparation of biaryls.[13] Some of the current challenges associated with the coupling of 2-naphthols involve improving asymmetric routes and application towards the synthesis of complex natural products.[14] Utilizing metal complexes based on metals other than copper has also been an area of intense interest,[15] and some complexes have been explored in the challenging oxidative coupling of electronically dissimilar 2-naphthols.[16,17]

Recently, we reported that N-heterocyclic carbene (NHC) copper complexes[6,18] could catalyze an oxidative heterocoupling of electron-poor and electron-rich 2-naphthols. Preliminary investigations into the oxidative homocoupling of 2-naphthols began with NHC–Cu complexes **5a** and **5b** using previously established conditions (Scheme 2).[6] The reactivity of the catalysts **5a** and **5b** was purposely compared to copper-based catalyst **5d** having a bulky C_2-symmetric NHC ligand in an effort to validate whether



Scheme 2 Influence of NHC structure on the oxidative homocoupling of methyl ester **6a**

the C_1-symmetric NHC would allow some control over reactivity. When methyl ester **6** was treated with copper catalyst **5a**, silver nitrate as a silver salt in methanol using Oxone as the oxidant, the desired BINOL product **7** was isolated in 76% yield. No decomposition of the catalyst or NHC ligand was observed. Although disappointed by the lack of enantioinduction observed, we were encouraged by the reactivity displayed by complex **5a**. Both copper complex **5b** bearing a benzyl group on the NHC ligand, and the copper complex **5d** having a bulky C_2-symmetric NHC ligand afforded only a 22% yield of BINOL **7** under identical reaction conditions. The above results suggest that the C_1-symmetric nature of the NHC ligand having one large and one small N-substituent was helping to afford increased reactivity.

In summary, a sequential alkylation protocol was developed to rapidly generate C_1-symmetric imidazolinium salts from a readily available chiral imidazoline. The salts can act as precursors for novel NHC ligands. Two representative copper-based complexes were prepared and characterized. X-ray crystallographic analysis of complex **5a** and **5c** highlights the effective shielding of one face of the copper atom by an aryl group on the ligand. The copper-based complexes were evaluated in oxidative coupling reactions to demonstrate the increased reactivity possible through fine-tuning of the steric properties of the NHC ligand. Complex **5a** afforded higher reactivity towards oxidative coupling than both achiral and chiral copper complexes bearing C_2-symmetric NHC ligands. Preliminary studies have shown that the addition of Lewis basic additives such as 2-picoline and 2,6-lutidine influence both the yield of the oxidative coupling reaction and the enantiomeric excess of the product **7** (Scheme 2). Steric hindrance about the nitrogen-containing heterocyclic additive could influence the binding of the additive to the copper center and the yield and enantioselectivity of the process. Future work is aimed at fine tuning of the catalysts and additive structure to improve the enantiomeric excesses in the oxidative homocoupling.

Representative procedures are given below, for full experimental details see the Supporting Information.

Alkylation Procedures

(4*R*,5*R*)-4,5-Di-*tert*-butyl-1-[bis(2-methylphenyl)methyl]-4,5-dihydro-1*H*-imidazole (3a); Typical Procedure 1

In a sealed tube was placed imidazoline precursor **1** (1.0 g, 5.5 mmol), alkyl halide **2a** (1.66 g, 6 mmol), and K_2CO_3 (3.75 g, 27.1 mmol). To the mixture was added acetone (100 mL) and the tube was sealed and placed in a 100 °C oil bath for 2 d. The tube was removed from the oil bath and cooled to r.t. The solution was then diluted with EtOAc and filtered on Celite. The solvent was removed in vacuo to yield a crude oil. The crude product was purified by column chromatography (silica gel, Et_3N–Et_2O, 2:98) yielding **3a** (0.93 g, 45%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 7.5 Hz, 1 H), 7.31 (s, 1 H), 7.25–7.18 (m, 2 H), 7.18–7.03 (m, 4 H), 6.96 (d, *J* = 6.4 Hz, 1 H), 5.91 (s, 1 H), 3.49 (dd, *J* = 4.4, 1.4 Hz, 1 H), 3.33 (d, *J* = 4.5 Hz, 1 H), 2.53 (s, 3 H), 2.04 (s, 3 H), 0.84 (s, 9 H), 0.75 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.7, 135.8, 130.4, 127.5, 126.4, 126.0, 70.2, 19.0.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{37}N_2$: 377.2951; found: 377.2954.

(4*R*,5*R*)-4,5-Di-*tert*-butyl-3-methyl-1-[bis(2-methylphenyl)methyl]-4,5-dihydro-1*H*-imidazolium Tetrafluoroborate (4a); Typical Procedure 2

To a solution of **3a** (430 mg, 1.14 mmol) in CH_2Cl_2 (10 mL) was added MeI (0.21 mL, 3.42 mmol) and $NaBF_4$ (625 mg, 5.7 mmol). The resulting suspension was stirred at r.t. for 2 d. The mixture was filtered. Solvent and excess MeI were removed in vacuo giving **4a** (543 mg, >95%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 1 H), 8.09 (d, *J* = 7.8 Hz, 1 H), 7.64–7.54 (m, 2 H), 7.34 (t, *J* = 6.7 Hz, 2 H), 7.26–7.18 (m, 3 H), 6.13 (s, 1 H), 3.91 (d, *J* = 3.2 Hz, 1 H), 3.79 (s, 3 H), 3.66 (d, *J* = 3.9 Hz, 1 H), 2.65 (s, 3 H), 2.15 (s, 3 H), 0.99 (s, 9 H), 0.97 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.8, 136.7, 134.8, 134.2, 133.8, 131.3, 130.8, 129.3, 128.9, 128.5, 128.4, 127.7, 127.1, 75.7, 73.5, 61.6, 38.8, 35.8, 35.2, 26.3, 25.4, 20.3, 19.6.

HRMS (ESI+): *m*/*z* $[M]^+$ calcd for $C_{27}H_{39}N_2$: 391.3108; found: 391.3112.

Acknowledgment

The authors acknowledge the Natural Sciences and Engineering Research Council of Canada (NSERC), Université de Montréal and the Centre for Green Chemistry and Catalysis (CGCC) for generous funding. The Canadian Foundation for Innovation (CFI) is acknowledged for generous funding of infrastructure. Francine Bélanger and Benoît Deschênes Simard are acknowledged for X-ray crystallography.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are experimental procedures and characterization data for all new compounds.

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