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Communication

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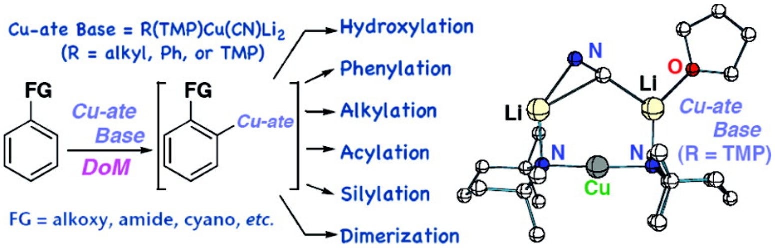

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COMMUNICATIONS

Direct *ortho* Cupration: A New Route to Regioselectively Functionalized Aromatics

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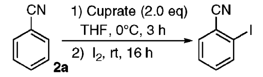
The use of organocuprate compounds has opened up new avenues in organic and organometallic chemistry.[1] Recently, increasing attention has been devoted to heteroleptic cuprates ($[R-Cu-R']^-$), as well as the large body of homoleptic cuprates ($[R-Cu-R]^-$). Organoamidocuprates are an important class of heteroleptic cuprate by virtue of their structural features[2] and unique reactivities: they have many applications in organic transformations, especially in stereoselective syntheses[3,4] because the amido ligand can act not only as a dummy (nontransferable) group but also as a chiral auxiliary. The nontransferability of amido (heteroatom) ligands on Cu-ates in carbon−carbon bond-forming reactions has also been theoretically clarified by DFT calculations.[5] We present here new uses of amidocuprates, wherein the amido ligand transfers (reacts) first as a base for chemoselective directed *ortho* cupration (DoC) and may also function as a switch in the successive C−C bond-formation process.

To develop new applications of amidocuprates, we focused on the deprotonative metalation of functionalized benzenes.[6] Initial studies used benzonitrile (**2a**) as a model aromatic compound with an electron-withdrawing group to identify favorable reaction conditions and indicated that a 2,2,6,6-tetramethylpiperidino (TMP) group as the amido moiety and THF as solvent were suitable starting points for the optimization of DoM reaction conditions (Table 1). Attempts to use Gilman-type amidocuprates prepared from CuI proved unsuccessful in terms of the reactivity (yields) and (DoC) selectivity. On the other hand, Lipshutz-type[7] amidocuprates prepared from CuCN turned out to promote the DoC reaction of **2a**, without any catalyst, in good yields at 0 °C. We found that although in the latter case at least one TMP ligand, one of the bulkiest available amido ligands, is crucial for good yield and chemoselectivity, the scope for the other ligand on the Cu atom is rather wide (various alkyl, phenyl, or even another TMP can be utilized). This is in sharp contrast to the strict structural requirements of recently reported zincate[8] and aluminate bases[9] in the DoM reactions of functionalized aromatic compounds.

The structures of the amidocuprates were examined by X-ray and DFT studies (Figure 1). After several attempts, we obtained X-ray-grade crystals from a toluene solution of the complex generated from CuCN and LTMP in a ratio of 1:2. The crystal structure of $(TMP)_2Cu(CN)Li_2$ (notwithstanding THF) (**1f**) is that of a prototype Lipshutz-type cuprate (not a Gilman-type dimeric structure) having a linear −Cu− geometry, and with the CN moiety coordinated to two lithium atoms but not directly to copper. The bond lengths and angles noted in the solid-state structure of **1f** are in good agreement with DFT calculation of the model cuprate $(Me_2N)_2Cu(CN)Li_2{\bullet}OMe_2$.

Table 1. Screening of Cuprates for Directed *ortho* Cupration



Entry	Cuprates[a]		Yield (%)[b]	Entry	Cuprates[a]		Yield (%)[b]
1	TMPCu(CN)Li	**1a**	0	6	$(TMP)_2Cu(CN)Li_2$	**1f**	74
2	$(TMP)_2CuLi{\bullet}LiI$	**1b**	0	7	$MeCu(CN)(TMP)Li_2$	**1g**	91
3	$MeCu(TMP)Li{\bullet}LiI$	**1c**	51	8	$^nBuCu(CN)(TMP)Li_2$	**1h**	83
4	$MeCu(CN)(NMe_2)Li_2$	**1d**	0	9	$^tBuCu(CN)(TMP)Li_2$	**1i**	70
5	$MeCu(CN)(N^iPr_2)Li_2$	**1e**	53	10	$PhCu(CN)(TMP)Li_2$	**1j**	93

[a] TMP = 2,2,6,6-tetramethylpiperidino. [b] Isolated yield.

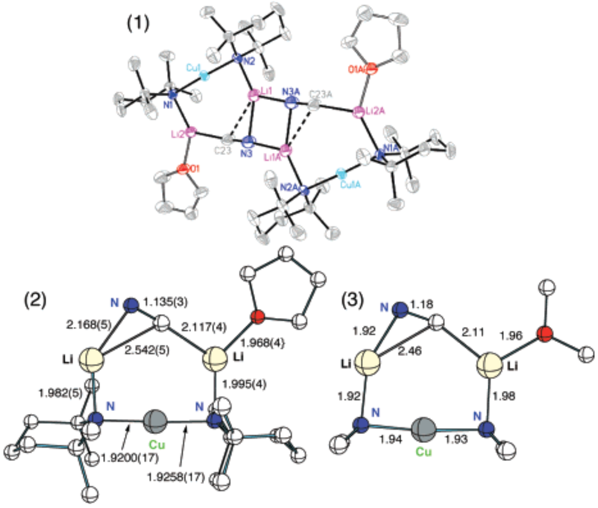


Figure 1. (1) The crystal structure of **1f** shown at 40% probability; (2) the asymmetric unit (monomer) in (1); and (3) the B3LYP/631SVP calculated structure of $(Me_2N)_2Cu(CN)Li_2{\bullet}OMe_2$. Hydrogen atoms and minor THF disorder in the crystal structure are omitted for clarity. Figures represent distances in Å.

Representative results from the DoM reactions of various functionalized aromatic compounds with a model cuprate base **1g** are summarized in Table 2. Not only methoxy groups but also a variety of polar functional groups including cyano, amide, and halogen, as well as heteroaromatics, such as benzothiazole, pyridine, and indole, are tolerated in the reaction. Functionalized aromatic iodides, which are good substrates for iodine−copper exchange reactions,[10] also worked smoothly. The regioselectivity of deprotonation is very high; while deprotonative metalation of *meta*-substituted benzenes (**2b**−**d** and **2h**), *para*-substituted benzenes (**2f** and **2g**), and functionalized heteroaromatics (**2i**−**k**) can take place in several positions, deprotonative cuprations proved to occur with complete regioselectivity. In the reaction of *meta*-functionalized bromobenzene (**2h**) with **1g**, the generation of benzyne was suppressed and only cupration occurred, again regio- and chemoselectively.[8b]

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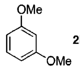
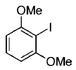
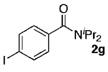
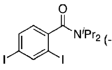
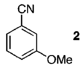
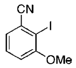
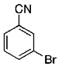
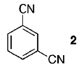
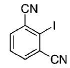
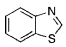
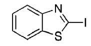
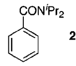
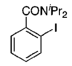
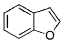
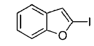
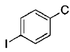
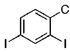
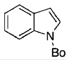
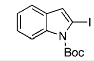
Table 2. Deprotonative Cupration of Functionalized Aromatics[a]

Entry	Substrate	Product	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]
1	 **2b**		95 (0°C, 3 h)	6	 **2g**		100 (-78°C, 3 h)
2	 **2c**		90 (0°C, 3 h)	7	 **2h**		82 (-78°C, 3 h)
3	 **2d**		90 (0°C, 3 h)	8	 **2i**		90 (0°C, 3 h)
4	 **2e**		92 (0°C, 3 h)	9	 **2j**		70 (0°C, 3 h)
5	 **2f**		96 (-78°C, 3 h)	10	 **2k**		88 (-40°C, 3 h)

[a] Deprotonative cupration was carried out using $MeCu(TMP)(CN)Li_2$ (2.0 equiv) and substrate (1.0 equiv) in THF. [b] Isolated yield.

Chart 1. A Survey of the Electrophilic Trapping of Functionalized Arylcuprate **3e**

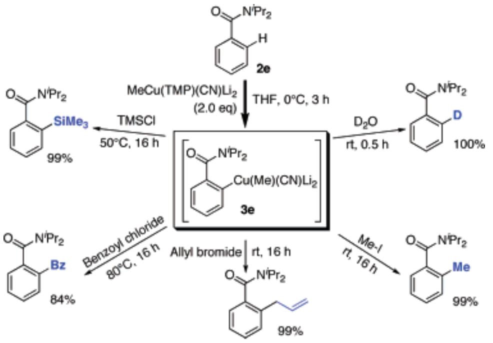
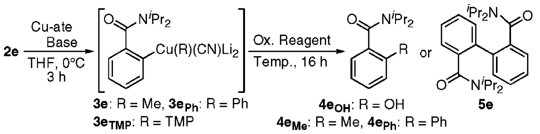


Table 3. Oxidation of Functionalized Phenyl Cuprate Intermediates



Cu-ate Base	Intermediate	Ox. Reagent	Temp.	Product	Yield (%)
1g	**3e**	O_2/CuCN (1eq)	rt	**4e$_{OH}$**	56
1g	**3e**	$PhNO_2$	0°C	**4e$_{Me}$**	93
1j	**3e$_{Ph}$**	$PhNO_2$	rt	**4e$_{Ph}$**	91
1f	**3e$_{TMP}$**	$PhNO_2$	0°C	**5e**	100

Having established a general preparative method for functionalized aromatic copper compounds, we next demonstrated that the (typical) functionalized arylcopper intermediate **3e** can be utilized as an aryl anion equivalent (Chart 1). Intermediate **3e**, generated from **2e** using **1g**, was treated with D_2O to give the corresponding *ortho*-deuterated product in a quantitative yield. Intermediate **3e** also undergoes C−C and C−Si bond-forming reactions, such as methylation, allylation, benzoylation, and trimethylsilylation, in high yields and with high chemo- and regioselectivities, without the requirement for any cocatalyst. This contrasts with the documented need for a copper or palladium catalyst to achieve comparable chemistry using arylzinc[8] or arylaluminum[9] intermediates.

Finally, we examined the oxidation of intermediary aryl-Cu(I)-ates with various oxidants (Table 3).[11] When intermediate **3e** was exposed to molecular oxygen in the presence of 1.0 equiv of CuCN, the corresponding phenol was obtained in 56% yield, realizing the regioselective introduction of an OH group.[12] On the other hand, when $PhNO_2$ was used in place of O_2, the oxidative ligand coupling reaction of **3e** proceeded smoothly and selectively to give *ortho*-methylated product **4e$_{Me}$**. The use of $PhCu(TMP)(CN)Li_2$ **1j** instead of **1g** for the deprotonative cupration of **2e** gave the desired cross-coupling biphenyl product **4e$_{Ph}$** in 91% yield. Interestingly, the deprotonation of **2e** by homoleptic amidocuprate $(TMP)_2Cu(CN)Li_2$ **1f** followed by oxidation with $PhNO_2$ gave the homocoupling product **5e** in quantitative yield.

In summary, highly chemo- and regioselective deprotonative cupration of functionalized aromatic and heteroaromatic compounds was realized using newly developed Lipshutz-type TMP-Cu-ate bases. In all cases, an amido ligand on the Cu-ates reacts first to deprotonate the aromatic ring. This contrasts with the C−C bond-forming reactions noted in the case of organoamidocuprates. Such a result clearly indicates that the transfer aptitude of ligands on the Cu-ates changes according to the reaction pattern. Functionalized phenyl cuprate intermediates react with various electrophiles as aryl anions with no additional catalyst. Furthermore, in the oxidation of the $[Ar-Cu(I)-R]^-$ intermediates, three types of reaction could be made to occur selectively on the aromatic ring by appropriately changing the oxidants and cuprate bases, that is, the introduction of an OH group, cross-coupling, and homocoupling. Further studies to establish the scope and limitations of this directed *ortho* cupration (DoC) reaction are underway, together with a mechanistic and structural investigation of this novel metalation and the successive oxidation.

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

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