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Letter

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Copper-Catalyzed Umpolung of Imines through Carbon-to-Nitrogen Boryl Migration

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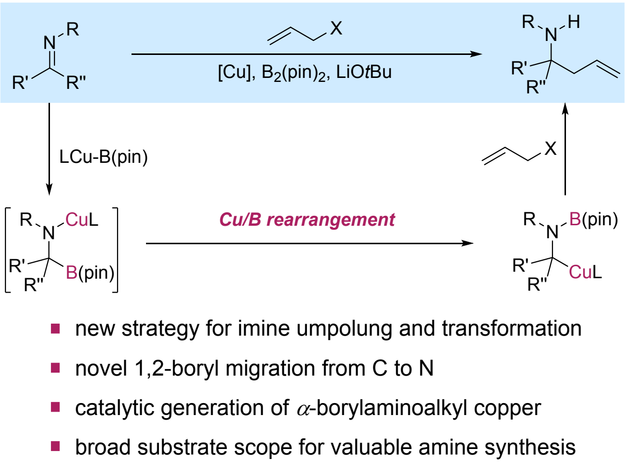
ABSTRACT: We report a general strategy for the catalytic umpolung of imines which was enabled by an unprecedented 1,2-boryl carbon-to-nitrogen migration. Based on the discovery of a rearrangement of an *α*-borylalkylamido copper intermediate to an *α*-borylaminoalkyl copper species through 1,2-migration of a boryl group from carbon to nitrogen and copper migration from nitrogen to carbon, we have developed a copper-catalyzed selective allylation of a wide range of aldimines and ketimines with allyl electrophiles in the presence of $B_2(pin)_2$ and LiO*t*Bu. We expect this catalytic imine-umpolung strategy may derive useful methodologies for the synthesis of various functionalized amines.

KEYWORDS: allylation, amine synthesis, imine umpolung, boryl migration, copper catalysis

The polarity-reversed (umpolung) reactions open up new vistas for the development of synthetic methodologies.[1] Compared with carbonyl umpolung chemistry, which has made tremendous success in organic synthesis, the umpolung reactions of imines are still largely underdeveloped.[2] Inverting the inherent polarity of imines may enable novel reaction patterns and provide access to useful synthetic protocols that are complementary to the reactions using imines as electrophilic precursors for the preparation of valuable amines.[3] Previously, limited types of imine umpolung have been reported. A benzoin-type aromatic aldimine coupling afforded diamines in the presence of NaCN.[4] The umpolung reactions of *N*-benzyl imines have been achieved via 2-azaally anion intermediates in the presence of a base.[5,6] *N*-heterocyclic carbenes (NHC) have been reported to facilitate the addition of aromatic aldimines to Michael acceptors through the aza-Breslow intermediates.[7] Under photoredox catalysis conditions, the generation of either nucleophilic radicals[8] or carbanionic intermediates[9] have been observed, some of which have been trapped with electrophiles in several catalytic reactions. Despite these recent advances, the development of a general strategy for the umpolung of simple imines remains an attractive and important research subject.

During our previous studies on the reactions of borylcopper species with alkynes and aldehydes,[10] we became interested in the transformation of imines by borylcopper complexes.[11] Herein, we report an unprecedented intramolecular rearrangement of an *α*-borylalkylamido copper intermediate to an α-borylaminoalkyl copper species via 1,2-boryl migration from carbon to nitrogen and copper migration from nitrogen to carbon (Scheme 1). Previously, the migration of a silyl group from a carbon atom to a nitrogen atom in aza-Brook rearrangement and a boryl migration from a carbon atom to an oxygen atom in bora-Brook rearrangement have been reported.[12] The current discovery represents a novel carbon-to-nitrogen boryl migration.

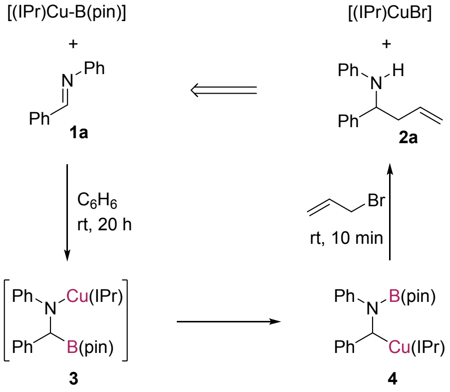
Scheme 1. Cu-Catalyzed Imine Umpolung via 1,2-Boryl Migration



Envisaging that the resulting *α*-aminoalkyl anion could be trapped by an electrophile, we have developed an efficient catalytic umpolung of simple imines, which has led to the selective allylation of a wide range of aldimines and ketimines with allyl electrophiles in the presence of a copper catalyst, bis(pinacolato)diboron ($B_2(pin)_2$), and LiO*t*Bu. This work features several advantages, including: a) providing a novel strategy for umpolung of simple imines; b) revealing a novel boryl migration from carbon to nitrogen; c) catalytically generating a nucleophilic *α*-borylaminoalkyl copper species; d) proving a model reaction design for amine synthesis from imines and potential electrophiles.

At first, we examined the reaction of *N*-benzylideneaniline **1a** with a borylcopper complex [(IPr)CuB(pin)] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), which was prepared from [(IPr)CuO*t*Bu] and B$_2$(pin)$_2$,[13,14] at room temperature in benzene. To our surprise, an *α*-borylaminoalkyl copper complex **4** (rather than a straightforward, nucleophilic addition product such as **3**) was isolated in 78% yield (Scheme 2). The molecular structure of **4** was unambiguously confirmed by the X-ray crystallographic analysis (Figure 1). When allyl bromide was added to a benzene solution of **4** at room temperature, [(IPr)CuBr] was isolated in 99% yield along with the homoallylic amine **2a** in 95% yield after treatment with silica gel.

Scheme 2. Sequential Reactions of a Boryl Copper Complex with an Imine and Allyl Bromide



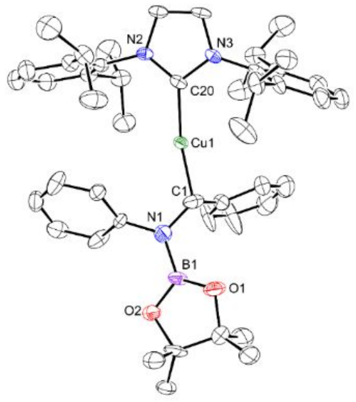


Figure 1. ORTEP drawing of **4** with thermal ellipsoids set at 30% probability. H atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Cu1–C1, 1.897(6); Cu1–C20, 1.898(5); N1–C1, 1.392(8); N1–B1, 1.483(9); C1–Cu1–C20, 169.9(3); N1–C1–Cu1, 124.4(5).

We then monitored the reaction of **1a** with [(IPr)CuB(pin)] in C$_6$D$_6$ by ^{1}H and ^{13}C NMR analyses. In the ^{1}H NMR monitoring, the instant formation of an *α*-carbon-borylated species assignable to **3** was identified as shown by the typical *α* C−H signal at 4.26 ppm (Figure 2). The transformation of **3** to **4** occurred almost spontaneously as identified by the *α* C−H signal at 5.02 ppm. DFT calculations revealed that **4** is thermodynamically favorable over **3** by about 8.6 kcal/mol. To the best of our knowledge, this is the first example of direct observation of 1,2-boryl migration from carbon to nitrogen.[12]

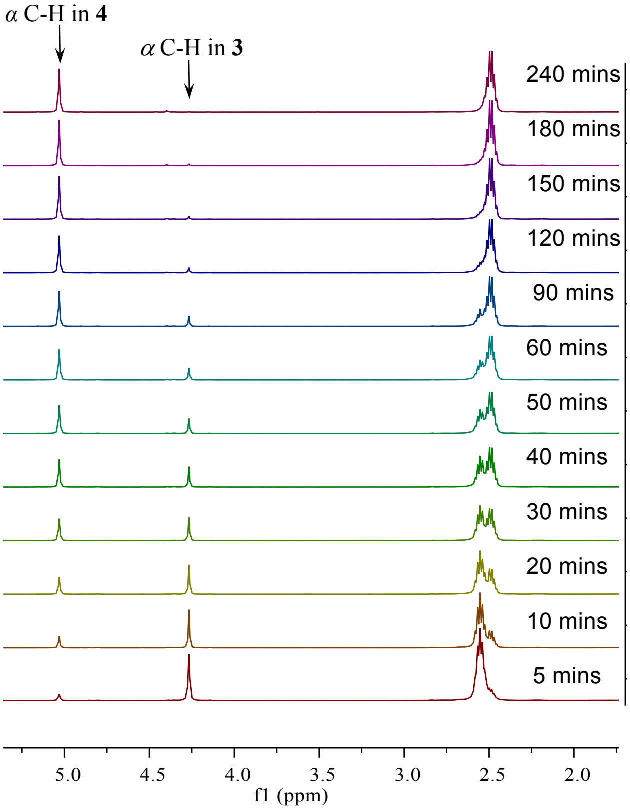
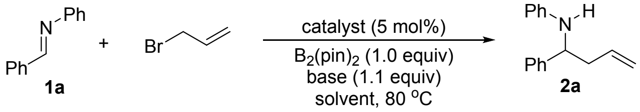


Figure 2. ^{1}H NMR monitoring of transformation of **3** to **4** (see Supporting Information for details).

Based on the stoichiometric reactions described above, we envisioned that a catalytic allylation of imines with allyl electrophiles may be achieved through the copper-catalyzed imine umpolung. Table 1 summarizes the results of our examination of the reaction of *N*-benzylideneaniline **1a** with allyl bromide in the presence of a catalytic amount of a copper compound, B$_2$(pin)$_2$, and LiO*t*Bu. It was found that [(SIMes)CuCl] (SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene) showed higher catalytic activity than [(IPr)CuCl] (entry 1) and [(IMes)CuCl] (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) (entry 2), affording the desired homoallylic amine **2a** almost quantitatively at 80 °C in 18 h (entry 3). The NHC-free CuCl also served as an excellent catalyst (entry 4). However, the CuCl/PCy$_3$ combination or CuCl/bipy combination gave lower yields (entry 5, 6). The formation of **2a** was not observed in the absence of a copper catalyst (entry 7). A systematic screening of base and solvent showed that LiO*t*Bu and dioxane were the best combination for this catalytic transformation (Table 1).

With the optimized reaction conditions in hand, we first investigated the umpolung allylation of various aldimines with allyl bromide by using [(SIMes)CuCl] as the catalyst (Table 2).[15] Aldimines derived from aniline and benzaldehydes bearing electron-donating groups such as Me and MeO performed well in the current reaction, affording the desired products such as **2b** and **2c**, respectively, in good yields. Thioanisole-containing aldimine was compatible with the reaction conditions to give the corresponding homoallylic amine product **2d** efficiently. Halides such as Br and F were also tolerated and the corresponding products **2e-g** were isolated in high yields. Aldimines bearing trifluoromethyl, biphenyl or naphthyl group worked efficiently to deliver the desired amines **2h-j** in very high yields. Remarkably, aldimine bearing an alkyne unit, which is generally sensitive towards a borylcopper species, functioned well in this reaction and afforded **2k** selectively. Oxygen and nitrogen-containing heteroaromatic cycles also survived the reaction conditions, leading to the isolation of functionalized amines **2l** and **2m** in high yields. It is noteworthy that cyclic imine **1n** which was originated from aliphatic aldehyde is also a suitable substrate, affording the corresponding product **2n** in good yield. Besides, aldimines derived from benzaldehyde and electron-rich or electron-poor anilines could also be used in this reaction, affording **2o-q** in high yields. Furthermore, the reaction of relatively less reactive *N*-alkyl aldimine **1r** also worked well to yield the *N*-hexyl substituted homoallylic amine **2r**.

Table 1. Cu-Catalyzed Allylation of *N*-Benzylideneaniline with Allyl Bromide[a]

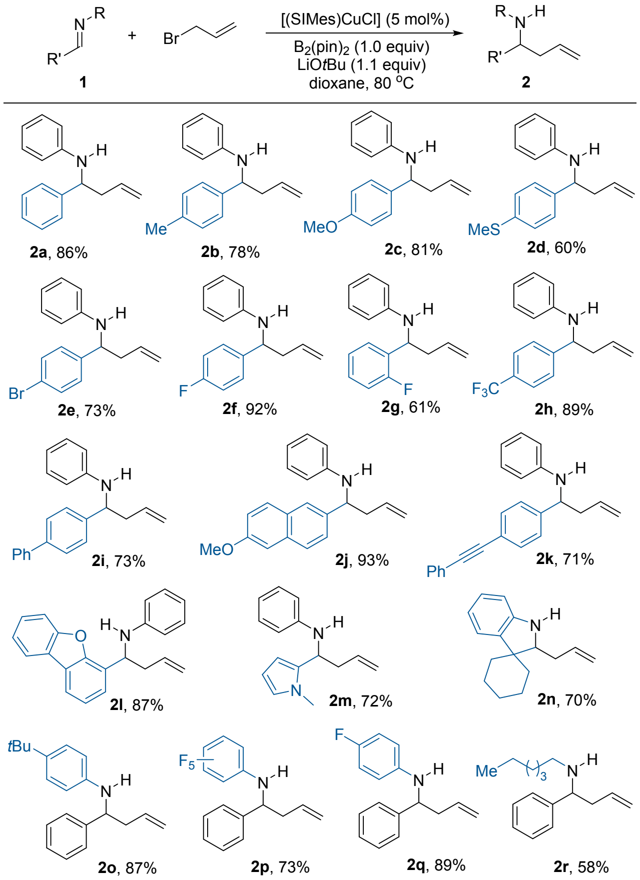


entry	catalyst	base	solvent	yield (%)[b]
1	[(IPr)CuCl]	LiO*t*Bu	dioxane	25
2	[(IMes)CuCl]	LiO*t*Bu	dioxane	85
3	[(SIMes)CuCl]	LiO*t*Bu	dioxane	97 (86)
4	CuCl	LiO*t*Bu	dioxane	99 (88)
5	CuCl/PCy$_3$ (1:3)	LiO*t*Bu	dioxane	56
6	CuCl/bipy (1:2)	LiO*t*Bu	dioxane	79
7	-	LiO*t*Bu	dioxane	0
8	CuCl	LiO*t*Bu	THF	68
9	CuCl	LiO*t*Bu	DME	53
10	CuCl	LiO*t*Bu	toluene	10
11	CuCl	LiO*t*Bu	hexane	12
12	CuCl	NaO*t*Bu	dioxane	15
13	CuCl	KO*t*Bu	dioxane	18
14	CuCl	LiOMe	dioxane	4

[a]Reaction conditions: catalyst (5 mol%), **1a** (0.5 mmol), allyl bromide (1.0 equiv), B$_2$(pin)$_2$ (1.0 equiv), base (1.1 equiv), solvent (3 mL), 80 °C, 18 h. [b]NMR yield with CH$_2$Br$_2$ as an internal standard. Isolated yields are shown in parentheses.

Considering the importance of generation of quaternary carbon centers from the allylation of ketimines, we then investigated the umpolung allylation of a series of ketimines (Table 3). Despite the increased steric hindrance vs. its aldimine counterparts, the ketimine substrate **5a** derived from acetophenone worked well in this reaction at 100 °C, affording the desired homoallylic amine **6a** in 81% isolated yield. Electron-rich ketimines containing isopropyl, methoxyl, or thioether groups are also good substrates, yielding the corresponding products **6b-d** efficiently. Chloride could tolerate the current conditions to give **6e** selectively. The reactions of ketimine substrates bearing biphenyl or naphthyl group also occurred smoothly to generate products **6f** or **6g** in good yields, respectively. The reaction of ketimine **5h** which is derived from electron-rich aniline afforded **6h** in 88% yield. Less reactive *N*-butyl ketimine **5i** also worked well to yield the *N*-alkyl substituted homoallylic amine **6i**. Besides the methyl phenyl ketone-originated ketimines, ethyl, *iso*-propyl, and benzyl substituted ketimine substrate **5j-l** could also be used in our reaction. Despite increased steric hindrance, products **6j-l** could be obtained efficiently. Particularly, the reaction of more sterically demanding benzophenone imine **5m** yielded the desired product **6m** selectively, albeit in moderate yield. It's worth noting that a primary amine **6n** could be obtained selectively from benzophenone imine. Remarkably, ketimine prepared

Table 2. Catalytic Umpolung Allylation of Aldimines[a]

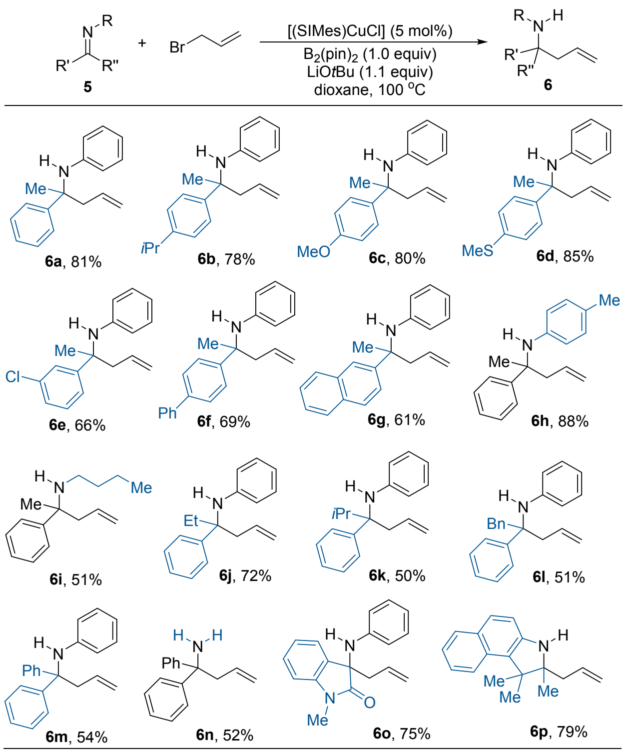


2a, 86%
2b, 78%
2c, 81%
2d, 60%
2e, 73%
2f, 92%
2g, 61%
2h, 89%
2i, 73%
2j, 93%
2k, 71%
2l, 87%
2m, 72%
2n, 70%
2o, 87%
2p, 73%
2q, 89%
2r, 58%

[a]Reaction conditions: [(SIMes)CuCl] (5 mol%), **1** (0.5 mmol), allyl bromide (1.0 equiv), B$_2$(pin)$_2$ (1.0 equiv), LiO*t*Bu (1.1 equiv), dioxane (3 mL), 80 °C, 18 h. Isolated yields are shown.

from 1-methylisatin also worked well to deliver the heterocycle containing homoallylic amine **6o** in good yield. Furthermore, a cyclic ketimine **5p** which was derived from aliphatic ketone could also afford the corresponding product **6p** in good yield. To the best of our knowledge, this protocol represents a rare example of umpolung allylation of simple ketimines.[6,8a]

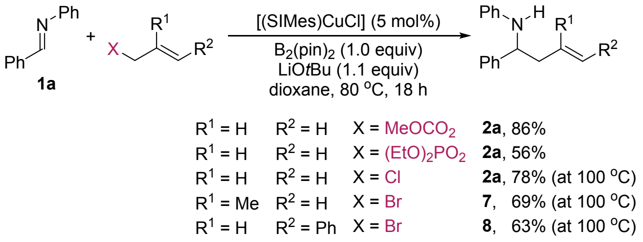
Table 3. Catalytic Umpolung Allylation of Ketimines[a]



[a]Reaction conditions: [(SIMes)CuCl] (5 mol%), **5** (0.5 mmol), allyl bromide (1.0 equiv), $B_2(pin)_2$ (1.0 equiv), LiO*t*Bu (1.1 equiv), dioxane (3 mL), 100 °C, 18 h. Isolated yields are shown.

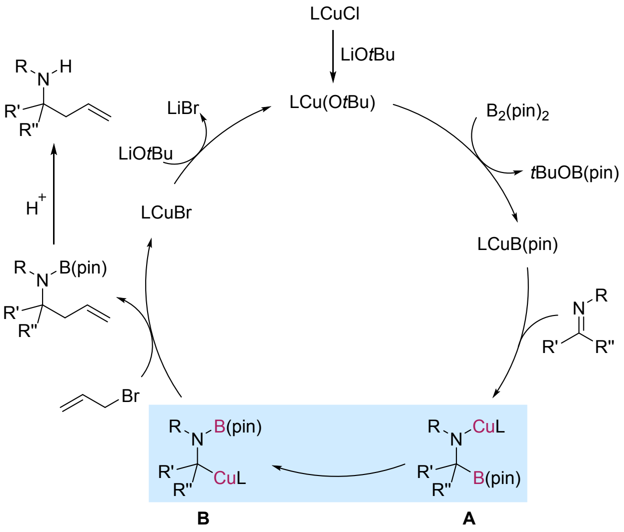
Under the current reaction conditions, we further investigated the reactions of **1a** with other allyl electrophiles (Scheme 3).[16] The reaction employing allyl methyl carbonate efficiently afforded product **2a** in 86% isolated yield. Allyl diethylphosphate could also be used as an allylation reagent for **1a**, although the yield of **2a** was lower under the same conditions. Besides, the reaction of allyl chloride afforded **2a** in 78% yield at 100 °C. Furthermore, both 3-bromo-2-methylpropene and cinnamyl bromide worked well in the current reaction to afford the corresponding allylation product **7** and **8**, respectively.

Scheme 3. Cu-Catalyzed Umpolung Allylation of *N*-Benzylideneaniline with Other Allyl Electrophiles



A possible reaction mechanism of the catalytic allylation of imines with allyl bromide is shown in Scheme 4. The nucleophilic addition of a borylcopper species LCuB(pin) to the C=N double bond of an imine substrate should give a carbon-borylated amidocopper species like **A**. The subsequent copper/boron rearrangement through the migration of the boryl group from carbon to nitrogen and migration of the copper unit from nitrogen to carbon would afford an *α*-borylaminoalkyl copper species **B**. This rearrangement may be driven by the formation of a strong B–N bond. The cross-coupling reaction between the nucleophilic *α*-aminoalkyl copper species and the electrophilic allyl bromide gives the *N*-borylated homoallylamine products, which are converted to the corresponding amines after protonolysis.

Scheme 4. Proposed Mechanism of Cu-Catalyzed Umpolung Reaction of Imines



In summary, we have discovered that the intramolecular 1,2-migration of the boryl group from carbon to nitrogen in an *α*-borylalkylamido copper species can take place to generate a carbon-nucleophilic *α*-borylaminoalkyl copper complex. Based on this discovery, we have developed a novel strategy for the catalytic umpolung of simple imines, which has enabled the selective formation of homoallylic amines in the reaction of a wide range of imines with allyl electrophiles such as allyl bromide, chloride, carbonate and phosphate in the presence of a copper catalyst, $B_2(pin)_2$, and LiO*t*Bu. Both aldimines and ketimines are suitable for this transformation. Good functional tolerance has been observed. This strategy may open the door to a wide range of umpolung reactions of imines with various electrophiles for the synthesis of diversified functional amines.

ASSOCIATED CONTENT

Supporting Information

Experimental details, spectroscopic and analytical data for new compounds, and crystallographic data of complex **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(16) Under the current conditions (80 °C), only trace amount of the desired products were detected in the reactions of **1a** with benzyl bromide, ethyl bromoacetate, prenyl bromide, or crotyl bromide. No significant improvement was observed when the reactions were carried out at 100 °C.

Table of Contents