Copper Catalysis

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Allyl-, Allenyl-, and Propargyl-Transfer Reactions through Cleavage of C–C Bonds Catalyzed by an N-Heterocyclic Carbene/Copper Complex: Synthesis of Multisubstituted Pyrroles**

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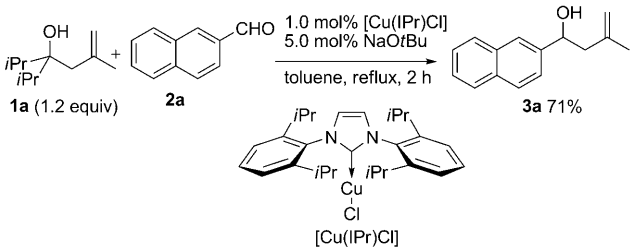
Development of efficient methods for transition-metal-catalyzed selective cleavage of C–C bonds and their application has been a challenging subject of modern organic synthesis.[1] Recently, our research group[1g,2] and others[3] have developed transition-metal-catalyzed retro-allylation of homoallyl alcohols as a C–C bond-cleavage strategy and thus have succeeded in the generation and use of allylmetals under mild conditions. However, expensive transition metals such as palladium, rhodium, and ruthenium were required in these reactions.[4] Thus, it is more cost-efficient to replace such expensive transition-metal catalysts with cheaper ones. With this in mind, we have focused on the possibility of copper-catalyzed selective cleavage of C–C bonds by retro-allylation of homoallyl alcohols. While copper can often replace palladium and rhodium in many catalytic bond-forming processes,[5] use of this cheaper and ubiquitous alternative in catalytic C–C bond cleavage reactions has remained unexplored.[6,7]

Initially, we examined the reaction of homoallyl alcohol **1a** with aldehyde **2a** using phosphine-ligated copper complexes, however, these reactions failed to proceed. To our delight, the use of the NHC (N-heterocyclic carbene)-ligated copper complex[8,9] [Cu(IPr)Cl] led to the desired methallylated product **3a** in 71% yield (Scheme 1). Naturally, copper-catalyzed retro-allylation should generate allylcopper species, which represents the first copper-catalyzed $C(sp^3)$–$C(sp^3)$ bond cleavage.

The scope of the allyl transfer was then examined (Table 1). Electron-rich aldehydes successfully underwent the allylation (Table 1, entries 1 and 2). The reaction of electron-poor 4-fluorobenzaldehyde gave a moderate yield of **3d** (Table 1, entry 3). Steric hindrance around the carbonyl functionality did not significantly retard the allylation (Table 1, entries 4 and 5). Heteroaromatic aldehydes were also suitable substrates (Table 1, entries 6 and 7). Selective 1,2-addition occurred in the reaction of cinnamaldehyde with alcohol **1a** (Table 1, entry 8).



Scheme 1. Methallylation of aldehyde **2a** catalyzed by [Cu(IPr)Cl].

This allyl transfer is applicable to the allylation of an imine (Table 1, entry 9). Remarkably, the present catalytic system has proved to be effective for allyl transfer from secondary homoallyl alcohols (Table 1, entries 10–12). Metal-mediated retro-allylation of secondary homoallyl alcohols is difficult because the process always suffers from overwhelmingly smooth oxidation through β-hydrogen elimination from the corresponding metal alkoxides. To the best of our knowledge, this represents the first example of catalytic allyl transfer reaction by retro-allylation using secondary homoallyl alcohols as allyl donors.[10]

Encouraged by the success of the allylation reaction catalyzed by [Cu(IPr)Cl], we next applied this catalytic system to allenylation and propargylation of imines. Pleasingly, the reaction of allenic alcohol **6a** with imine **4a** proceeded to afford allenylated product **7aa** in excellent yield (Scheme 2). Intriguingly, the reaction exhibited high selectivity in favor of the formation of **7aa** (**7aa**/**8aa** = 96:4). Allenylmetal species are generally in equilibrium with the corresponding propargylmetal.[11] Therefore, controlling the regioselectivity in the reactions using allenyl- and propargylmetals remains an important challenge in organic synthesis.[12]

When the crude product containing **7aa** was heated in aqueous ethanol before chromatographic purification, **7aa** was converted into 3-pyrroline **9aa** (Table 2, entry 1).[13] Notably, purified **7aa** did not isomerize into **9aa** under the same reaction conditions. We eventually found that [Cu(IPr)Cl] was also highly effective for the cyclization to **9aa** (Scheme 3) as well as the allenyl transfer reaction. Although

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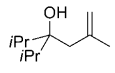
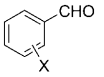
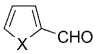
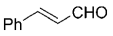
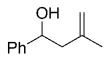
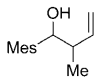
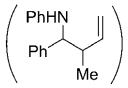
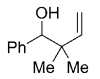
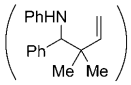
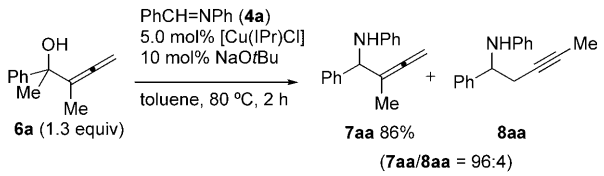
Table 1: Allylation of aldehydes and imine **4a** with homoallyl alcohols catalyzed by [Cu(IPr)Cl].[a]

Entry	Alcohol	Electrophile	Cu/Base [mol%]	Yield [%]
				
1	**1a**	X = 4-OMe	1.0:5.0	**3b**, 93
2	**1a**	X = 4-NMe_2	1.0:5.0	**3c**, 79[b]
3	**1a**	X = 4-F	2.0:6.0	**3d**, 63
4	**1a**	X = 2-Me	2.0:6.0	**3e**, 97[c]
5	**1a**	X = 2,4,6-Me_3	2.0:6.0	**3f**, 92[c]
				
6	**1a**	X = O	1.0:5.0	**3g**, 71
7	**1a**	X = S	2.0:6.0	**3h**, 65
8	**1a**		1.0:5.0	**3i**, 88
				
9	**1a**	**4a**	1.0:5.0	**5a**, 99
				
10	**1b**	**4a**	10:20	**5a**, 77[d]
				
11[e]	**1c**	**4a**	5.0:10	**5b**, 90
				
12	**1d**	**4a**	7.5:15	**5c**, 80[f]

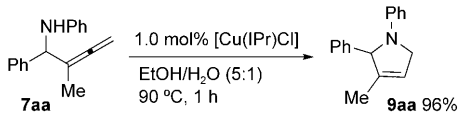
[a] Reaction conditions: homoallyl alcohol (0.60 mmol), electrophile (0.50 mmol), [Cu(IPr)Cl], NaO*t*Bu, toluene (3.0 mL), reflux, 2 h. Yields are of the isolated products. [b] For 1 h with **1a** (1.5 equiv). [c] For 12 h. [d] For 9 h with **1b** (2.0 equiv). [e] For 3 h. **1c**: *syn*/*anti* = 1.2:1. **5b**: *syn*/*anti* = 1.9:1. [f] For 6 h. Mes = 2,4,6-trimethylphenyl.



Scheme 2. Selective allenylation of aldimine **4a** catalyzed by [Cu(IPr)Cl].

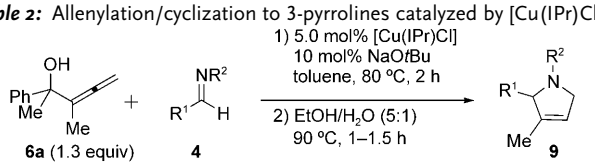
Au, Ag, and Pd are known to catalyze similar cyclization of 2,3-alkadienylamines,[14] its copper-catalyzed variant has not been reported so far.

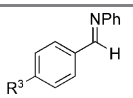
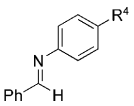
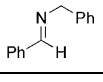
3-Pyrroline units are prominent structural motifs in natural products, and straightforward methods for their preparation should to be explored.[14,15] We therefore investigated the utility of the copper-catalyzed allenylation/cyclization for synthesizing 3-pyrrolines **9** (Table 2). The electronic nature of benzimine substrates does not significantly affect



Scheme 3. Cyclization of **7aa** catalyzed by [Cu(IPr)Cl].

Table 2: Allenylation/cyclization to 3-pyrrolines catalyzed by [Cu(IPr)Cl].



Entry	Imine		Yield [%][a]
			
1	**4a**	R^3 = H	**9aa**, 80
2[b]	**4b**	R^3 = OMe	**9ab**, 76
3	**4c**	R^3 = CF_3	**9ac**, 88
4	**4d**	R^3 = CO*t*Bu	**9ad**, 87
5	**4e**	R^3 = CO_2Me	**9ae**, 72
6	**4f**	R^3 = CN	**9af**, 97[c]
			
7	**4g**	R^4 = Cl	**9ag**, 90
8	**4h**	R^4 = Br	**9ah**, 88
9	**4i**	R^4 = I	**9ai**, 91
10[d]	**4j**		**9aj**, 68

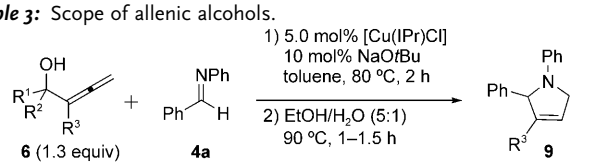
[a] Yield is of isolated product. [b] At 90 °C with **6a** (2.0 equiv). [c] Determined by ^{1}H NMR spectroscopy. [d] At reflux with **6a** (2.0 equiv).

the reaction efficiency (Table 2, entries 1–6). The reaction tolerates a variety of functional groups such as keto, ester, and cyano (Table 2, entries 4–6). Carbon–halogen bonds could also survive, and are useful for further elaboration of the products (Table 2, entries 7–9). In addition, *N*-alkyl imine **4j** was also a suitable substrate to yield **9aj** in good yield (Table 2, entry 10).

Next, the scope of allenic alcohols was explored (Table 3). Allenic alcohols bearing an alkyl-, aryl-, or silyl-substituted allene moiety all worked well, and provided **9** in good yields. In the case of **6d**, 3-pyrroline **9da** containing a versatile vinylsilane moiety was obtained (Table 3, entry 3). Secondary allenic alcohol also reacted efficiently (Table 3, entry 4).

To gain insight into the mechanism and the high allenyl selectivity, homopropargyl alcohol **10** was subjected to the standard reaction conditions (Scheme 4). Interestingly, the predominant product was again **7aa**, which was the same product derived from **6a** (Scheme 2). This result can be explained as follows: allenylcopper **D**, generated by retropropargylation[16] of intermediate **B**, is less stable owing to steric repulsion between the methyl group and the bulky NHC. Accordingly, isomerization of **D** occurs to afford more

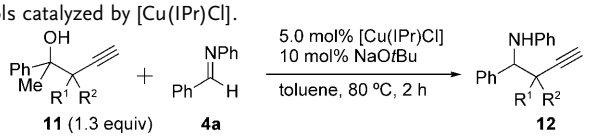
Table 3: Scope of allenic alcohols.



Entry		Allenic alcohol			Yield [%][a]
		R^1	R^2	R^3	
1	**6b**	Ph	Me	Bu	**9ba**, 81
2	**6c**	Ph	Me	Ph	**9ca**, 79
3[b]	**6d**	Ph	Me	$SiMe_3$	**9da**, 66
4[c]	**6e**	Mes	H	Me	**9aa**, 72

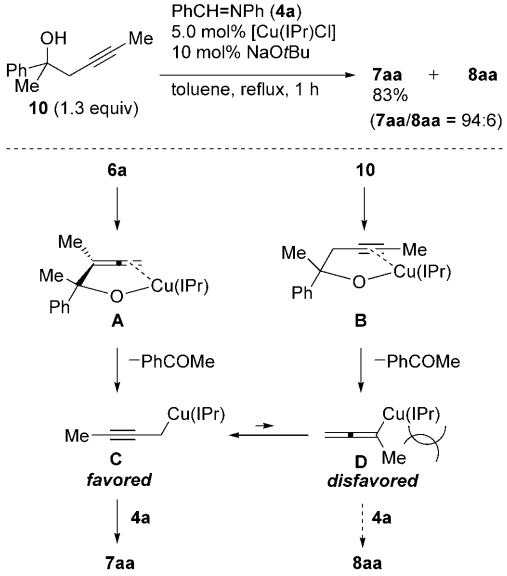
[a] Yield is of isolated product. [b] [Cu(IPr)Cl] (10 mol%), NaO*t*Bu (20 mol%), and **6d** (2.0 equiv) were used in the allenylation step, while [Ag(phen)OTf] (10 mol%) was used in the cyclization step. [c] At reflux for allenylation.

Table 4: Propargylation of imine **4a** with various homopropargyl alcohols catalyzed by [Cu(IPr)Cl].

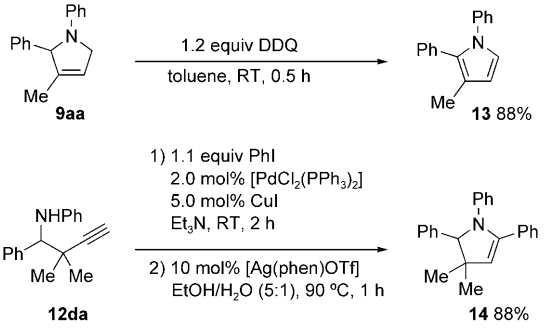


Entry		Alcohol		*T* [°C]	Yield [%][a]	d.r.[b]
		R^1	R^2			
1	**11a**[c]	Me	H	80	**12aa**, 96	3.3:1
2	**11b**[c]	C_5H_{11}	H	80	**12ba**, 100	4.6:1
3	**11b**[c]			50	**12ba**, 90	4.6:1
4	**11c**[d]	Ph	H	25	**12ca**, 94[a,d]	1.2:1
5	**11d**	Me	Me	80	**12da**, 98	–

[a] Yield is of isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] *Syn* isomer. [d] d.r. = 1.1:1. [d] With **11c** (1.5 equiv).



Scheme 4. Mechanistic investigations.



Scheme 5. Transformations of **9aa** and **12da**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, phen = 1,10-phenanthroline, Tf = trifluoromethanesulfonyl.

stable propargyl copper **C**, which then reacts with imine **4a** to furnish **7aa**.

Homopropargyl alcohol **11a** bearing a methyl group at the propargyl position led to complete reversal of regioselectivity, and homopropargylamine **12aa** was exclusively formed (Table 4, entry 1). The effect of the substituent at the propargyl position is general (Table 4, entries 2–5). The bulky NHC would shift the allenyl–propargyl equilibrium toward allenylcopper, thus resulting in the propargylation of imines. In some cases, the reaction proceeded under milder reaction conditions (25 to 50 °C).

In addition to 3-pyrrolines, other important azacycles could be easily prepared (Scheme 5). Oxidation of 3-pyrroline **9aa** mediated by DDQ cleanly provided pyrrole **13**. Homopropargylamine **12da** also underwent the Sonogashira cross-coupling reaction[17] and subsequent silver-catalyzed cyclization[18] to yield 2-pyrroline[19] **14** in 88% yield.

In conclusion, we have developed a retro-allylation of homoallyl alcohols and allylation reaction of carbonyl compounds catalyzed by a NHC–Cu complex, namely [Cu(IPr)Cl]. Cleavage of $C(sp^3)$–$C(sp^3)$ bond through retro-allylation by the copper catalyst is the key step. We have also applied this method to selective allenylation and propargylation of imines—a process that provides synthetically useful allenic amines or homopropargyl amines with excellent selectivity. These products can also be transformed into valuable five-membered azacycles such as 2-pyrroline, 3-pyrroline, and pyrrole derivatives.

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