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Letter

Copper-Catalyzed Hydroalumination of Allenes with Diisobutylaluminum Hydride: Synthesis of Allylic Ketones with α-Quaternary Centers via Tandem Allylation/Oppenauer Oxidation

Sangback Lee, Sanghyun Lee, and Yunmi Lee*

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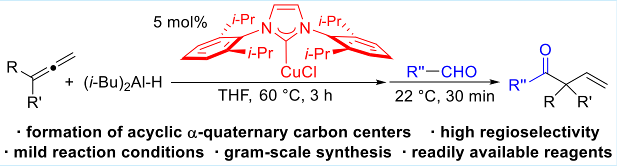
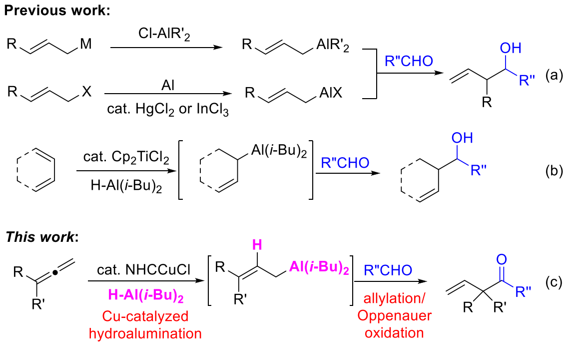
ABSTRACT: An efficient and straightforward approach to allylaluminum reagent synthesis through Cu-catalyzed hydroalumination of readily accessible allenes with diisobutylaluminum hydride is described. The N-heterocyclic carbene-based copper complex promotes hydride addition to various functionalized allenes under mild reaction conditions. The catalytic reaction is applied to a highly selective one-pot synthesis of allylic ketones with α-tertiary and α-quaternary centers through tandem nucleophilic addition of in situ-generated allylaluminums to aldehydes/Oppenauer oxidation.



· formation of acyclic α-quaternary carbon centers · high regioselectivity
· mild reaction conditions · gram-scale synthesis · readily available reagents

The addition of allylic organometallic reagents to carbonyl compounds is a powerful and widely used method for the preparation of homoallylic alcohols and allylic ketones, which are valuable intermediates in the synthesis of complex molecules, natural products, and biologically active molecules.[1] While numerous examples of allylation using allylstannanes, allylsilanes, allylboranes, and allylzincs have been reported, allylmetal reagents based on aluminum, which is the most abundant metal and has low toxicity, have received relatively little attention, presumably because of the absence of convenient and efficient access. Typical strategies for the synthesis of allylaluminum reagents include the direct insertion of aluminum metal into allylic halides in the presence of a catalytic amount of $HgCl_2$ or $InCl_3$[2] and transmetalation with Grignard or lithium reagents (Scheme 1a).[3] A complementary approach reported by Vasse, Szymoniak, and co-workers involves titanium-catalyzed hydroalumination of conjugated dienes with diisobutylaluminum hydride (DIBAL-H) (Scheme 1b).[4] Despite the invention of several methods, some compelling issues to be addressed for their practical utility remain: access to certain allylic halides is problematic, and the substrate scope in the catalytic process is limited to cyclic dienes.

Scheme 1. Generation of Allylaluminum Reagents and Their Reactions with Aldehydes



Copper-catalyzed hydrometalation of allenes with a hydride source could be a promising route for synthesizing allylic metal reagents because it is a simple and atom-economical process, uses a relatively low-cost and easy-to-handle copper catalyst, and employs readily accessible allene substrates. To date, a few examples of copper hydride-catalyzed reactions with allenes have been reported.[5] In all of those studies, only silane was used as a hydride source, leading to the formation of a copper hydride complex that undergoes hydrocupration with allenes to generate a catalytic amount of allylcopper intermediates. Therefore, the allylcopper reagents served as allylic nucleophiles for allylation with electrophiles, including aldehydes, imines, alkyl triflates, and CO_2. Unlike the previous CuH-catalyzed reactions involving silanes, we proposed that Cu-catalyzed hydride addition of DIBAL-H[6] to allenes would produce allylaluminum reagents via allylcopper intermediates, which could be further utilized to develop unexplored allylation reactions by applying the intrinsic reactivity and Lewis acidity of aluminum (Scheme 1c).

Tandem nucleophilic addition/Oppenauer oxidation with an aldehyde has emerged as a mild and efficient method for the synthesis of ketones.[7] This form of oxidation was proposed to

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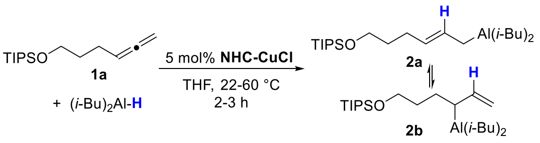
proceed by transfer of the hydride to the aldehyde from in situ-generated metal alkoxide intermediates obtained from nucleophilic attack of the aldehyde. Various types of organometallic reagents, such as nucleophiles based on organomagnesium,[8] -zinc,[9] -aluminum,[10] -tin,[11] -boron,[12] -indium,[13] and -zirconium,[14] are involved in this transformation. Among them, allylmetal reagents are particularly attractive because they can be used to prepare synthetically useful allylic ketones bearing α-tertiary and even difficult-to-access α-quaternary stereogenic centers under simple and mild reaction conditions.[15] Although one example of tandem allylation/Oppenauer oxidation with an aldehyde engaging allylic chromiums, which afforded α-substituted allylic ketones, was reported by Wessjohann and co-workers,[16] the reaction was carried out with allylic bromide in the presence of excess chromium chloride, and the substrate scope was limited to three kinds of allylic bromides: crotyl, prenyl, and geranyl bromide. Considering the significance and challenges of the construction of acyclic all-carbon quaternary centers in the α-carbon position of allylic ketones, we pursued the exploration of an efficient and simple method on a synthetically useful level.[17] To the best of our knowledge, access to α-substituted allylic ketones through Oppenauer oxidation of aldehydes with allylaluminum reagents has not been reported.[18] Furthermore, most reactions of aldehydes with allylic organometallic reagents have been used primarily to produce homoallylic alcohols, not allylic ketones.

In this study, we developed a new and promising strategy to access synthetically useful allylaluminum reagents through Cu-catalyzed hydroalumination of DIBAL-H with easily accessible allenes in the presence of CuCl based on an N-heterocyclic carbene (NHC) ligand. In addition, we describe a one-pot synthesis of versatile α-substituted-β,γ-unsaturated ketones containing α-quaternary centers, which are difficult and challenging to synthesize, through regioselective allylation of in situ-generated allylaluminum reagents with an aldehyde and sequential Oppenauer oxidation (Scheme 1c).

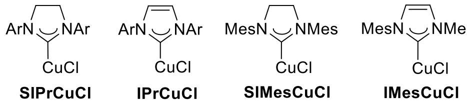
We began our investigations by examining the Cu-catalyzed hydroalumination of model allene **1a** with DIBAL-H, as shown in Table 1. Treatment of allene **1a** with 5 mol % **SIPrCuCl** and 1.5 equiv of DIBAL-H at room temperature for 2 h provided the desired allylaluminum **2** in 47% yield (entry 1). After considerable efforts, the use of 5 mol % **IPrCuCl** and 1.2 equiv of DIBAL-H at 60 °C for 3 h was found to be optimal, affording the corresponding allylaluminum reagents **2** in >98% yield (entries 2−4). **SIMesCuCl** and **IMesCuCl** catalysts were not effective in promoting the hydroalumination of allene **1a** (8−16% yield; entries 5 and 6). It was noted that Cu-catalyzed hydroalumination of allene **1a** selectively generated allylaluminum reagents rather than vinylaluminum reagents.[19] As illustrated in entries 7 and 8, the reaction did not proceed in the presence of CuCl itself or without a catalyst (<2% conversion), indicating that an NHC ligand was required to promote the addition of DIBAL-H to allene **1a**. On the basis of previous studies involving CuH catalysis by Tsuji, Lalic, Bai, and co-workers,[20] we assumed that the reaction of NHC−CuCl with DIBAL-H would generate a copper hydride species complexed with the NHC ligand, which might play an important role in stabilizing the CuH species and enhancing the activity of hydride addition to allenes.

Table 1. Optimization of the Cu-Catalyzed Hydroalumination of Allene 1a[a]



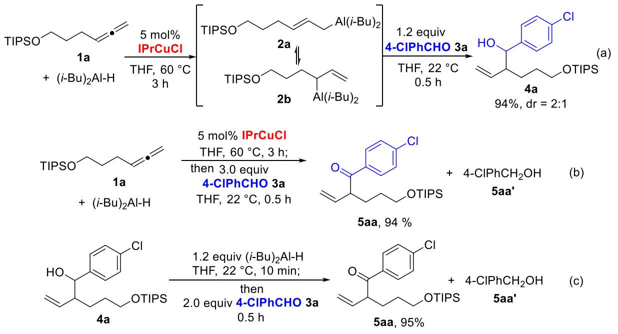
entry	NHC−CuCl	equiv of DIBAL-H	temp. (°C)	time (h)	conv. (%)[b]	yield of 2 (%)[b]
1	**SIPrCuCl**	1.5	22	2	47	47
2	**SIPrCuCl**	1.2	60	2	87	87
3	**IPrCuCl**	1.2	60	2	90	90
4	**IPrCuCl**	1.2	60	3	>98	>98
5	**SIMesCuCl**	1.2	60	3	16	16
6	**IMesCuCl**	1.2	60	3	8	8
7	CuCl	1.2	60	3	<2	<2
8	none	1.2	60	3	<2	<2

[a] Reaction conditions: allene **1a** (0.200 mmol), $(i\text{-Bu})_2AlH$ (0.240−0.300 mmol), **NHC-CuCl** (5 mol %), THF (0.2 M), under N_2. [b] Determined by analysis of ^1H NMR spectra of unpurified mixtures after quenching with H_2O using 1,3,5-trimethoxybenzene as an internal standard; see the Supporting Information for details.



(Ar = 2,6-$i\text{Pr}_2C_6H_3$)

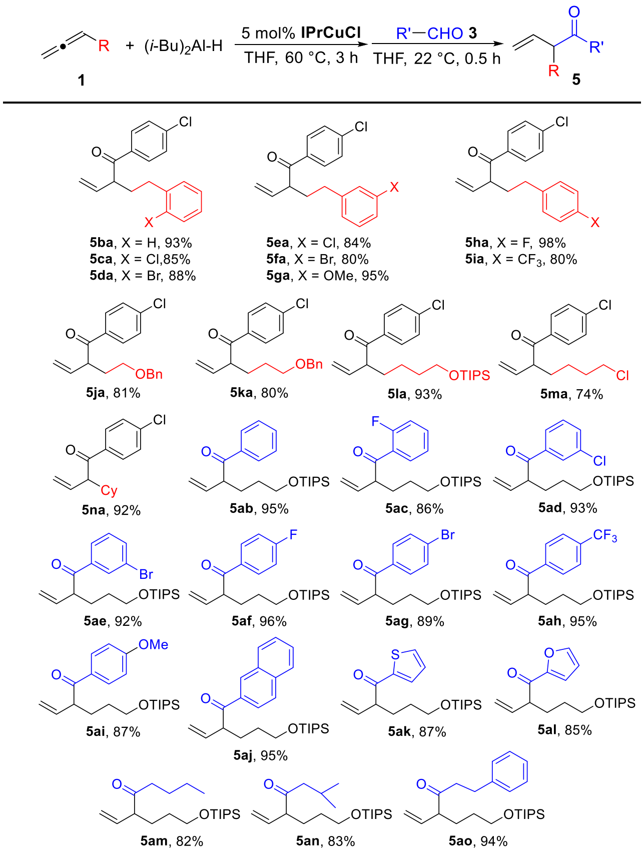
Scheme 2. Allylation of Allene 1a with Aldehyde 3a



After the optimized reaction conditions were established, we investigated tandem allylation/Oppenauer oxidation using allylaluminum reagents, as shown in Scheme 2. The addition of 1.2 equiv of aldehyde **3a** to allylaluminum reagent **2** derived directly from the catalytic hydroalumination of allene **1a** with DIBAL-H provided homoallylic alcohol product **4a** in 94% yield (Scheme 2a).[21] On the other hand, when 3.0 equiv of aldehyde **3a** was introduced, allylic ketone **5aa** was predominantly and markedly obtained in 94% yield at room temperature within 30 min, along with the formation of benzyl alcohol **5aa′**, indicating that hydride transfer to the aldehyde from the aluminum alkoxide intermediate occurred through Oppenauer oxidation (Scheme 2b). The allylation with aldehyde **3a** took place with exclusive regioselectivity, affording **5aa** as a single regioisomer.[1,22] It was found that an excess amount of benzyl alcohol **5aa′** was observed in 200% yield. This might have occurred because hydride transfer to aldehyde **3a** proceeded competitively not only from the aluminum alkoxide but also probably from the two isobutyl groups on the aluminum center during the oxidation. Therefore, the use of 3.0 equiv of the aldehyde was required to obtain a high yield of the ketone product. To gain some insight into the reaction intermediate, the direct oxidation of homoallylic alcohol **4a** was carried out (Scheme 2c). When **4a** was treated with DIBAL-H to generate an aluminum alkoxide intermediate and then aldehyde **3a** was added as a hydride acceptor, alcohol **4a** was readily oxidized, furnishing allylic ketone **5aa** in 95% yield. This result explained that the copper catalyst used in the hydroalumination reaction did not play a main role in facilitating oxidation in the one-pot synthesis and that the Oppenauer oxidation proceeded via the aluminum alkoxide intermediate.

Under the established reaction conditions, the Cu-catalyzed hydroalumination/allylation/Oppenauer oxidation could be successfully carried out with a wide range of monosubstituted allenes and aldehydes (Scheme 3). All of the transformations were promoted by 5 mol % **IPrCuCl** catalyst and showed high efficiency and excellent regioselectivity (>99:<1), affording versatile *α*-substituted *β*,*γ*-unsaturated ketones. The Cu-catalyzed hydroaluminations of DIBAL-H with phenethyl-substituted allenes **1b–i**, including chloro, bromo, fluoro, trifluoromethyl, or methoxy moieties on the phenyl group, proceeded smoothly to generate the corresponding allylaluminum reagents, which directly reacted with aldehyde **3a** to provide the desired ketone products **5ba–ia** in 80–98% yield. Synthetic functional groups such as a benzyl ether, silyl ether, or chloro substituent on allenes **1j–m** were well-tolerated in the Cu-catalyzed process. The corresponding functionalized allylic ketones **5ja–ma** were obtained in high yields (74–93%). The reaction with the sterically demanding cyclohexyl-substituted allene **1n** also showed good reactivity, giving the desired allylic ketone **5na** in 92% yield. Next, when various aromatic aldehydes **3b–i** containing fluoro, chloro, bromo, trifluoromethyl, or methoxy groups at the *ortho*, *meta*, or *para* position were utilized for tandem Oppenauer oxidation with allene **1a**, the corresponding allylic ketones **5ab–ai** were efficiently obtained in 86–95% yield. However, reaction with benzaldehydes bearing chloro or bromo substituents at the *ortho* position of the phenyl group gave homoallylic alcohol products in 94–95% yield; the Oppenauer oxidation did not proceed, presumably as a result of steric hindrance. Naphthaldehyde (**3j**) and heteroaromatic aldehydes **3k** and **3l** bearing a thienyl or furyl group reacted with high efficiency and regioselectivity (85–95% yield of **5aj–al**). Aliphatic aldehydes, such as valeraldehyde (**3m**), isovaleraldehyde (**3n**), and 3-phenylpropanal (**3o**), were also suitable for this transformation, affording allylic ketones **5am–ao** in high yields (82–94%).

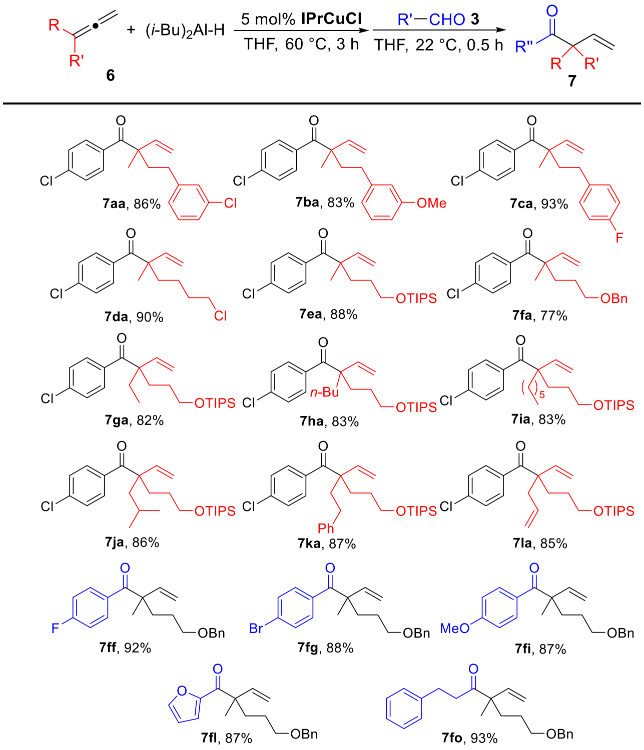
Scheme 3. Reaction of Monosubstituted Allenes with Various Aldehydes[a]



[a]Reaction conditions: allene **1** (0.300 mmol), $(i\text{-Bu})_2$Al–H (0.360 mmol), **IPrCuCl** (5 mol %), aldehyde **3** (0.900 mmol), THF (0.15 M), under N_2. Yields of the isolated products are shown.

Our new copper-catalyzed hydroalumination with 1,1-disubstituted allenes significantly contributes to the efficient construction of congested *α*-quaternary carbon centers on acyclic *β*,*γ*-unsaturated ketones, which are synthetically challenging moieties. As summarized in Scheme 4, a variety of 1,1-disubstituted allenes exhibited excellent reactivity and regioselectivity. Under mild reaction conditions, allenes substituted with methyl and various alkyl functionalities, such as chloro-, methoxy-, or fluoro-substituted phenethyl groups (**6a–c**), a chloro-substituted alkyl group (**6d**), a silyl ether (**6e**), or a benzyl ether (**6f**), were successfully converted to the corresponding *α*-quaternary-substituted allylic ketones **7aa–fa** in high yields (77–93%). The reactions of silyl ether-substituted allenes **6g–l**, including ethyl, *n*-butyl, *n*-hexyl,

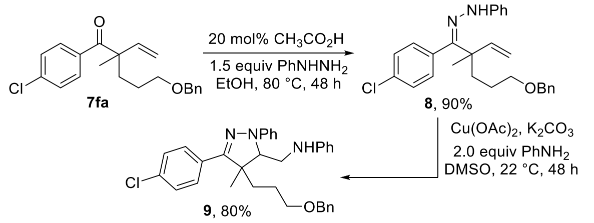
Scheme 4. Reaction with Various 1,1-Disubstituted Allenes



isobutyl, phenethyl, and allyl units, all proceeded well and provided the desired products **7ga–la** in 82–87% yield. In addition, when a variety of aromatic, heteroaromatic, and aliphatic aldehydes were applied to the process with allene **6f**, high yields of the new functionalized allylic ketones **7ff–fo** were observed with high efficiency.

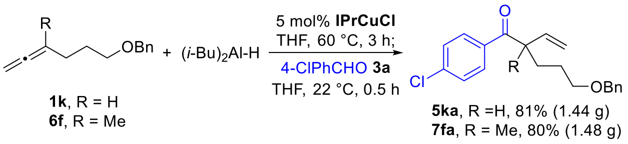
To illustrate the synthetic potential of the newly developed one-pot Oppenauer oxidation, we applied the α-quaternary-substituted ketone product **7fa** to the synthesis of a pyrazoline derivative, which can serve as a valuable building block for biologically active molecules (Scheme 5).[23] Allylic ketone **7fa** was converted to hydrazone **8** in a reaction with phenylhydrazine in the presence of acetic acid. When hydrazone **8** was treated with aniline and $Cu(OAc)_2$, copper-mediated diamination smoothly proceeded to give pyrazoline **9** in 80% yield.

Scheme 5. Transformation of Ketone 7fa



This method was also capable of the one-pot gram-scale synthesis of α-substituted allylic ketones (Scheme 6). The reactions of more than 1 g of allenes **1k** and **6f** with aldehyde **3a** were efficiently carried out, affording the corresponding allylic ketones **5ka** and **7fa** in 81 and 80% yield, respectively. These results highlight the potential of this mild and simple one-pot process in significant practical applications.

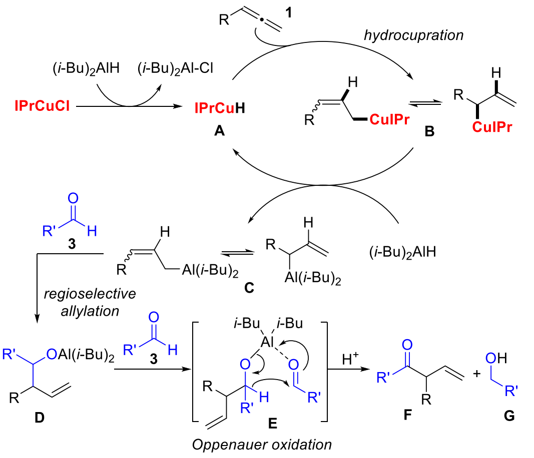
Scheme 6. Gram-Scale Reactions



On the basis of our observations, we propose a plausible mechanism in Scheme 7. The reaction of **IPrCuCl** with DIBAL-H would generate copper hydride species **A**,[20] which would insert into allene **1** to form allylcopper complex **B** via hydrocupration. The allylcopper intermediate **B** would react with DIBAL-H to regenerate IPrCuH species **A** with concomitant release of the allylaluminum intermediate **C**. Subsequently, allylaluminum reagent **C** would regioselectively attack aldehyde **3** to give the corresponding aluminum alkoxide **D**. Then another aldehyde **3** would coordinate to alkoxide **D**, leading to the six-membered-ring transition state **E**, which would then undergo hydride transfer to give the final ketone product **F** and alcohol **G** after protonation.

In conclusion, we have developed an efficient method for the preparation of functionalized allylaluminum reagents from commercially available and readily accessible DIBAL-H and allenes through copper-catalyzed hydride addition. The use of the NHC ligand was key for achieving this catalytic transformation. The catalytic process allowed for the development of a new strategy for synthesizing α-quaternary-substituted allylic ketones with high efficiency and regioselectivity through one-pot Cu-catalyzed hydroalumination/allylation/Oppenauer oxidation under mild reaction conditions. Further research on the scope of this new copper-catalyzed hydride addition and mechanistic insights is ongoing in our laboratory.

Scheme 7. Proposed Mechanism



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01876.

Experimental details, characterization data, and NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

Yunmi Lee – *Department of Chemistry, Kwangwoon University, Seoul 01897, Republic of Korea*; orcid.org/0000-0003-1315-4001; Email: ymlee@kw.ac.kr

Authors

Sangback Lee – *Department of Chemistry, Kwangwoon University, Seoul 01897, Republic of Korea*

Sanghyun Lee – *Department of Chemistry, Kwangwoon University, Seoul 01897, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01876

Notes

The authors declare no competing financial interest.

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