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Enantioselective Allylation Using Allene, a Petroleum Cracking Byproduct

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Supporting Information Placeholder

ABSTRACT: Allene (C_3H_4) gas is produced and separated on million-metric-ton scale per year during petroleum refining but is rarely employed in organic synthesis. Meanwhile, the addition of an allyl group (C_3H_5) to ketones is among the most common and prototypical reactions in synthetic chemistry. Herein, we report that the combination of allene gas with inexpensive and environmentally benign hydrosilanes, such as PMHS, can serve as a replacement for stoichiometric quantities of allylmetal reagents, which are required in most enantioselective ketone allylation reactions. This process is catalyzed by copper catalyst and commercially available ligands, operates without specialized equipment or pressurization, and tolerates a broad range of functional groups. Furthermore, the exceptional chemoselectivity of this catalyst system enables industrially relevant C3 hydrocarbon mixtures of allene with methylacetylene and propylene to be applied directly. Based on our strategy, we anticipate the rapid development of methods that leverage this unexploited feedstock as an allyl anion surrogate.

The production of valuable compounds from simple and widely available building blocks constitutes a core mission of synthetic chemistry. To date, considerable resources have been dedicated to the development of new organic transformations, intended to augment the space of products that chemists can access.[1] Meanwhile, as our community enters the age of sustainability, improving the ideality of starting materials and reagents has become an increasingly important focus of synthetic research.[2] Particularly in the context of the most widely practiced reactions, the elimination of costly, inefficient, or dangerous reactants in favor of alternative precursors carries the potential for broad, long-term impact. In the past decade, a number of methods that employ widely available chemicals such as methane,[3,4] ethane,[4] ethylene,[5,6] 2-butene,[7] and butadiene[8] in organic synthesis have been developed. Inspired by these collective efforts, we wondered whether we could take advantage of other underutilized feedstock chemicals that, despite their availability and advantageous properties, currently lack avenues for productive utilization.

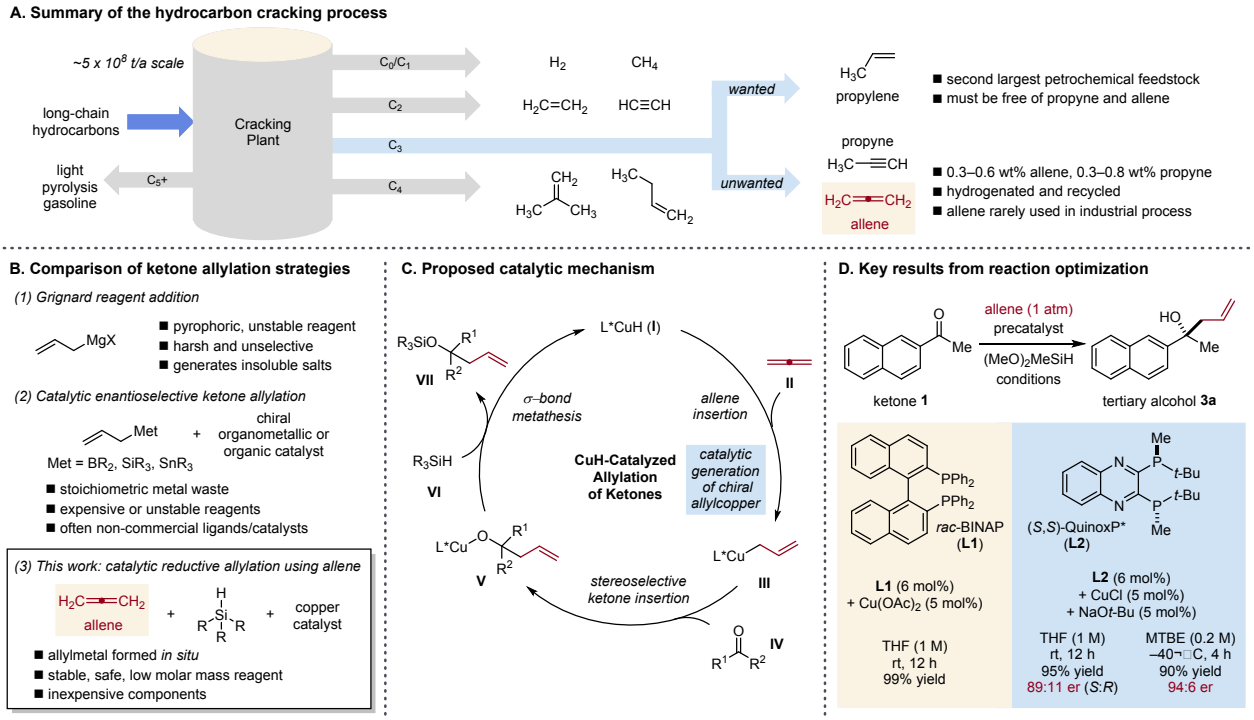


Figure 1. Overview of Allene-Based Ketone Allylation. For experimental details, see the Supporting Information.

Hydrocarbon cracking is among the largest-scale chemical processes in operation worldwide, converting over 500 million metric tons of material per year to products such as valuable α-olefins (Fig. 1A).[9a] Allene, or 1,2-propadiene, is a cumulene byproduct that constitutes 0.3–0.6 mass percent (wt%) of this total output, or roughly 6 mole percent (mol%) of the crude C3 fraction.[9b] The development of synthetic methods that employ *substituted* allenes has been very successful, as evidenced by the large number of catalytic reactions that use these compounds.[10a-g] In contrast, useful transformations of the parent compound allene are significantly more challenging to discover for several reasons: it is a gas at room temperature, it is highly reactive, and it is often available as a mixture with other reactive compounds such as propylene or methylacetylene, which are difficult to separate completely (*vide infra*). Accordingly, synthetically useful transformations of parent allene are exceedingly rare.[10h-k] Without pathways for productive use, allene is currently considered to be an undesired contaminant in the supply of propylene. Therefore, allene-containing mixtures are generally processed via catalytic hydrogenation to propane and recycled back into the cracking plant in an energy-intensive operation. In the context of our ongoing research on hydrofunctionalization of olefins, we considered whether this largely unexploited hydrocarbon feedstock might be productively engaged as an economical low-molecular-weight C3 source in chemical synthesis.

We selected allylation of ketones as the model reaction due to the prevalence and versatility of the homoallylic alcohol products in organic synthesis, as well as the unique chemical challenges presented.[11] Despite the ubiquity of this transformation in chemical research and manufacturing, many existing methods for the parent allylation of ketones are far from ideal (Fig. 1B). First, the high reactivity and basicity of organometallic allylation reagents can lead to poor chemoselectivity and incompatibility with functionalized substrates. For instance, Woerpel has shown that allylmagnesium chloride reacts at the diffusion limit, indiscriminately attacking esters, ketones, and aldehydes.[12b,c] In addition, the generation of insoluble metal salts and large quantities of heat limit the utility of these reactions on scale.[13] Finally, asymmetric reactions of ketones in general are difficult to achieve due to the reduced steric differentiation between carbonyl substituents and attenuated reactivity in relation to aldehydes. Many stereoselective ketone allylation reactions exist, either using stoichiometric chiral controllers[14] or asymmetric catalysis.[15-17] However, highly enantioselective installation of the parent allyl group is particularly challenging due to the existence of multiple potential pathways leading to the minor enantiomer (see the Supporting Information for additional discussion). Most crucially, even these "catalytic" reactions almost always require the prior generation, in a separate operation, of superstochiometric quantities of allylmetal reagents, which is intrinsically wasteful in terms of energy, time, and material. In comparison, an alternative allylation method that relies directly on feedstock chemicals as reagents, eliminating the necessity of organometallic intermediates, would be highly desirable.

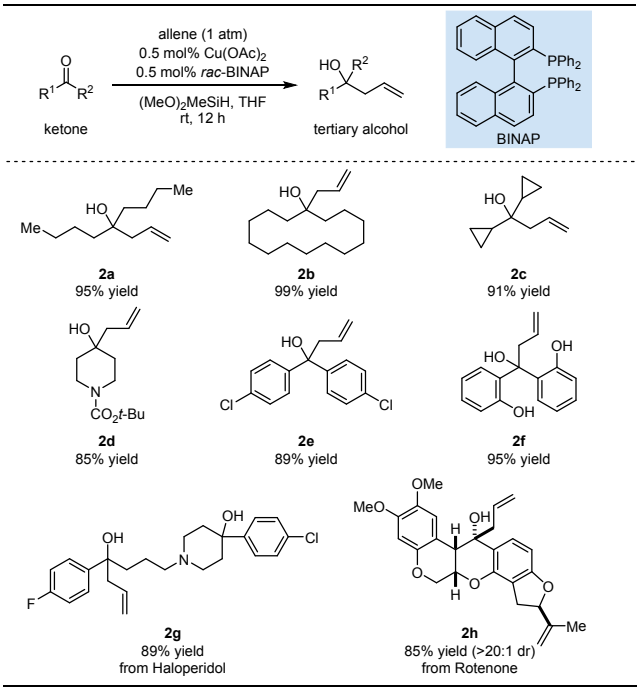
Groundbreaking research on reductive C–C bond formation by Krische,[8,18] Montgomery,[19] and Jamison,[20] and elegant examples of copper-catalyzed borylative[21] couplings have been described the past few years. Among these impressive precedents, however, the use of allene gas remains largely unexplored: in the only report of such a process, Krische was able to effect the racemic coupling reaction with a single, activated aldehyde electrophile, albeit in low yield.[18b] Our laboratory has recently developed several classes of copper-catalyzed stereoselective reactions of in situ generated olefin-derived nucleophiles with carbon-[22] and nitrogen-centered electrophiles.[7,23] We thought that the mildness and chemoselectivity of CuH catalysis might allow for more efficient coupling reactions using parent allene. As an additional advantage, while Ir- and Ru-catalyzed procedures work well for addition of many nucleophiles to aldehydes and imines, the Cu-catalyzed methods developed in our laboratory are among the few that can engage ketones.[24] Thus, we saw the opportunity to develop an important complement to the existing olefin-carbonyl reductive coupling toolbox: a practical, asymmetric parent allylation of ketones using allene gas.

Our proposed transformation might proceed through the following catalytic mechanism, postulated on the basis of previous mechanistic and computational studies (Fig. 1C).[22a,b] Initially, insertion of allene (**II**) into a hydride complex **I**, formed in situ from a phosphine ligand, copper source, and silane reductant, could generate an allylcopper(I) species **III**. This nucleophilic species could react with a ketone **IV** through a six-membered, cyclic transition state to form alkoxide **V**. Subsequent metathesis with the hydrosilane **VI** would regenerate **I**, while releasing the desired product **VII** in a silyl-protected form, which would be deprotected during work-up.

Using copper(II) acetate as the precatalyst, a variety of commercially available ligands were evaluated for the proposed allylation process, using 2-acetonaphthone as a model substrate (Figure 1D, see the Supporting Information for details). An atmospheric pressure of allene gas was applied over the reaction mixture with the aid of aballoon. At ambient temperature, reactions using the inexpensive racemic BINAP ligand provided the desired product with high efficiency. Meanwhile, when *P*-stereogenic ligand QuinoxP*, which is also commercially available, was employed, the same product was produced with high enantiomeric excess, which was further enhanced upon lowering the temperature to –40 °C and changing the solvent to MTBE. At cryogenic temperatures, we found that using copper(I) *tert*-butoxide, generated *in situ* from copper(I) chloride and sodium *tert*-butoxide, the active catalyst is formed more efficiently than when using common copper(II) salts. It is notable that direct reduction of the ketone, often an extremely rapid and competing reaction in the presence of copper–hydride complexes,[22c] is not observed in these experiments.

Using 0.5 mol% each of BINAP and copper(II) acetate, a range of symmetrical and unsymmetrical ketones were effectively allylated on a 1 mmol scale (Table 1). Simple linear and cyclic ketones reacted cleanly and in near-quantitative isolated yield (**2a**, **2b**). A cyclopropyl ketone was converted efficiently without any observable ring opening byproducts (**2c**). A carbamate protecting group (**2d**), an aryl chloride (**2e**), and free hydroxyl groups (**2f**), which are rapidly silyl-protected under our reaction conditions, were tolerated by the mild conditions of this procedure. Furthermore, haloperidol, a common anti-psychotic ketone drug bearing a tertiary alcohol, a tertiary amine, an aryl fluoride, and an aryl chloride, reacted in high yield (**2g**). In addition, Rotenone, a broad-spectrum insecticide, underwent allylation with high substrate-controlled diastereoselectivity (**2h**, >20:1 dr).

Table 1. Scope of copper-catalyzed allylation of ketones using allene gas.[a]

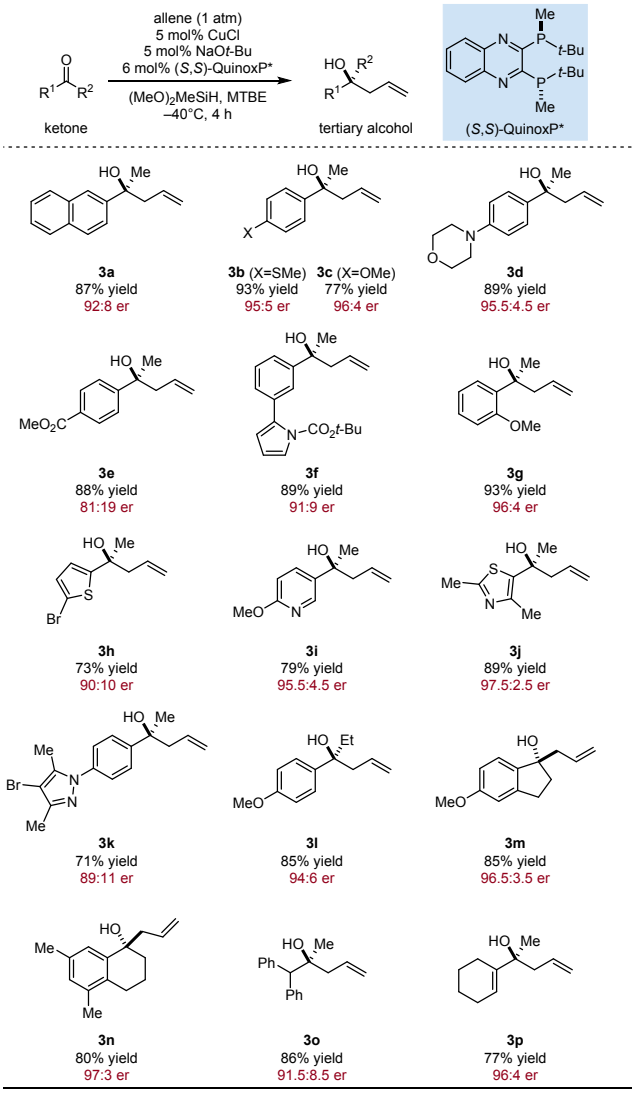


[a] Average results from two identical runs on 1 mmol scale of ketone. For experimental details, see the Supporting Information.

Next, we examined the scope of the enantioselective allylation procedure. Aryl methyl ketones bearing sulfur- (**3b**), oxygen- (**3c**), and nitrogen-based (**3d**) substituents performed the desired reaction in high yield and with good enantioselectivity. Substitution at the meta (**3f**) and ortho (**3g**) positions were well tolerated. Highlighting the chemoselectivity of this reaction, a methyl ester (**3e**) and a heteroaryl bromide (**3h**) reacted cleanly, with useful enantioselectivity, and without undesired reaction at these non-participating functional groups. Both five- (**3f**, **3h**, **3j**, **3k**) and six-membered (**3i**) heterocyclic ketones were employed successfully. In addition, ketones with substituents other than methyl were suitable substrates for this reaction. For instance, an ethyl ketone (**3l**) and cyclic ketones (**3m**, **3n**) provided the corresponding homoallylic ketone products with good-to-excellent enantioselectivity. A hindered dialkyl ketone also reacted stereoselectively (**3o**) and in high yield, despite bearing a very acidic α-proton. Finally, a vinyl ketone was found to be an effective substrate, providing **3p** in high optical purity and without generating undesired 1,4-allylation or conjugate reduction byproducts.

While reagent-grade purified allene gas is affordable on scale (<$20/mol), direct utilization of industrially produced methylacetylene–propadiene (MAPD) mixtures or ternary mixtures involving propane or propylene would render the process more practical yet. Although previous attempts to use allene gas as a reagent have found even trace (ppm) methylacetylene to be detrimental,[18b] our calculations indicated that insertion of allene into hydride complex **I** should be greatly favored over alkynes or terminal alkenes (Fig. 2A). Indeed, when a roughly equimolar mixture of propylene, methylacetylene, and allene was employed, allylation product **3a** was obtained with nearly identical yield and stereoselectivity as when purified allene was used (84% yield, 93:7 er). Furthermore, this reaction was conducted using the very inexpensive polymer PMHS (<$1/mol), a waste product of the silicone industry, with identical results. The allylation process can be scaled easily to produce multigram quantities of product without specialized equipment (Fig. 2B). Using a reduced catalyst loading of 2 mol%, 3.7 g (19 mmol) of **3g** was obtained with high stereoselectivity (95:5 er).

Table 2. Scope of enantioselective copper-catalyzed allylation of ketones using allene gas.[a]



[a] Average results from two identical runs on 1 mmol scale of ketone.For experimental details, see the Supporting Information.

We further demonstrated the utility of the reaction in the synthesis of anti-psychotic drug Clopenthixol (Sordinol, **4d**), first introduced by Lundbeck in 1961, and one of several structurally related thioxanthene antagonists of dopamine receptor D2, commercially available as either a mixture of *E*/*Z*-isomers or as the pure *Z*-isomer, obtained by selective crystallization[25] (Fig. 2C). The traditional synthesis of this substance relies on cyclopropyl or allyl Grignard reagents, presenting challenges for scale-up or implementation in continuous flow processes[14] due to large exotherm and formation of insoluble magnesium salts. In our synthesis, the unpurified reaction mixture resulting from the allene–ketone coupling reaction was directly subjected to copper-catalyzed hydroamination conditions previously reported by our group.[26] Acidic work-up efficiently removed the Boc

protecting group and eliminated an equivalent of silanol to yield intermediate **4c**, observed by high performance liquid chromatography (HPLC) but not purified before proceeding. Direct S_N2 alkylation of this mixture with 2-bromoethanol yielded Clopenthixol (**4d**) in 54% overall yield with only one chromatographic separation. Finally, the allylation procedure was also employed to synthesize alcohol **5**, a core building block in elegant synthetic efforts toward the Veratrum alkaloid family, which previously required a three-step iodination/allylation/Kumada coupling sequence starting from 2-cyclohexene-1-one (Fig. 2D).[27]

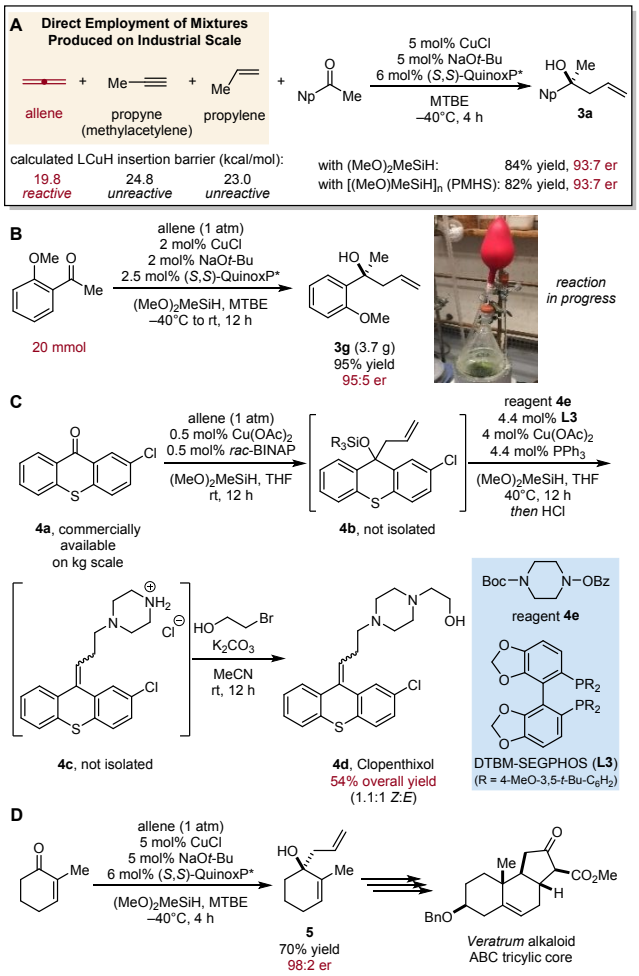


Figure 2. Extensions and applications of the allylation process. Np = 2-naphthyl, for experimental details, see the Supplementary Information.

Density functional theory (DFT) calculations suggested an intuitive model for rationalizing the stereoselectivity of the allylation process. The steric profile of the C_2-symmetric (*S*,*S*)-QuinoxP* ligand is illustrated by a quadrant diagram (Fig. 3, top right). In the preferred transition state (Favored $\mathbf{TS_{III\rightarrow V}}$), the smaller ketone substituent (Me) occupies the pseudoaxial position of the chair-like cyclic construction, positioned in less sterically hindered quadrant I, thus forming the observed (*S*)-product. Due to the unsubstituted nature of the allyl nucleophile, the catalyst must destabilize two minor pathways, both of which lead to the undesired (*R*)-product. Relative to the favored transition state, rotation of the ketone to place the large group (Ph) pseudo-axial (Disfavored $\mathbf{TS1_{III\rightarrow V}}$, +1.3 kcal/mol) incurs an energetic penalty due to increased steric interaction with the ligand Me group in quadrant I. Alternatively, inversion of the entire chair-like structure (Disfavored $\mathbf{TS2_{III\rightarrow V}}$, +2.5 kcal/mol) is also disfavored since a ketone substituent is now directed toward the ligand *t*-Bu group in quadrant II.

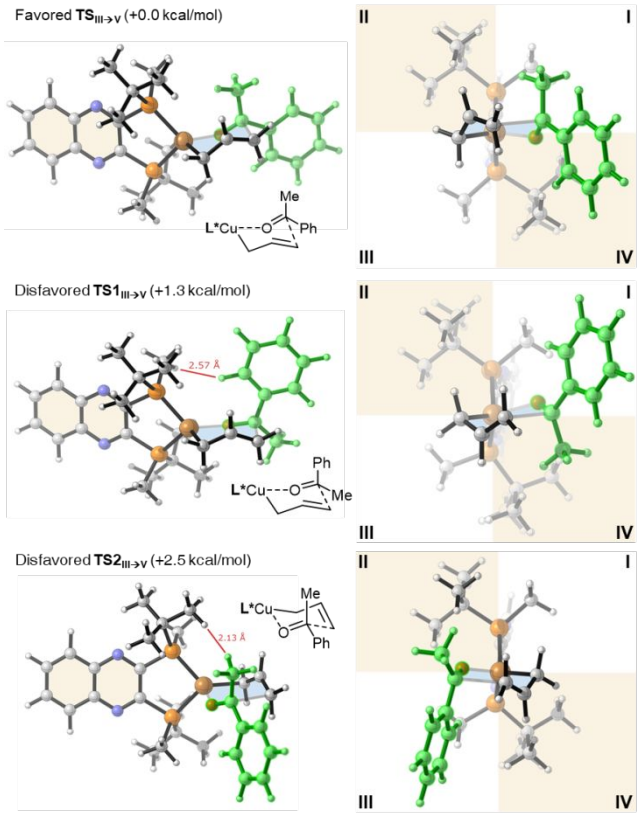


Figure 3. Model for the enantioselectivity of the ketone allylation process. Energy values represent relative Gibbs free energies for transition states calculated using the M06/6-311+G(d,p)-SDD(Cu)/SMD(PhMe)//B3LYP/6-31G(d)-SDD(Cu).

In summary, we describe the application of allene, an underutilized hydrocarbon feedstock, as a surrogate for traditional allylmetal reagents in copper-catalyzed enantioselective ketone addition reactions. We anticipate that allene gas will serve as a versatile and economical reagent in a variety of additional carbon–carbon and carbon–heteroatom coupling reactions soon to be discovered.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data for new compounds, computational details, additional discussion, NMR spectra, chromatography traces (PDF)

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Notes

The authors declare no competing financial interests.

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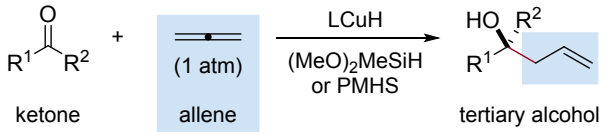

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- no pressurization required
- all materials commercially available