Title: Enantioselective Allylation from Allene, a Petroleum Cracking Byproduct

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Abstract: Allene (C$_3$H$_4$) gas is produced and separated on million-metric-ton scale per year during petroleum refining but is only rarely employed in chemical manufacturing. Meanwhile, the addition of an allyl group (C$_3$H$_5$) to ketone-containing molecules is among the most common and prototypical reactions in organic synthesis. Herein, we report that the combination of allene with environmentally benign hydrosilanes can replace harsher, more wasteful, and more expensive allylmetal reagents in enantioselective ketone allylation reactions. This process is catalyzed by an earth-abundant metal and commercially available ligands, operates without specialized equipment or pressurization, and tolerates a broad range of functional groups. Furthermore, the exceptional chemoselectivity of our 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 a surrogate for existing nucleophilic allylation reagents.

One Sentence Summary: Allene, an abundant but underutilized petrochemical, can replace sensitive metal reagents in a classic chemical reaction.

Main Text: The production of valuable and functional compounds from simple and widely available building blocks constitutes a core mission of synthetic organic 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, 2). 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 (3, 4). Particularly in the context of the most widely practiced reactions, the elimination of costly, harsh, inefficient, or dangerous reactants in favor of alternative precursors carries the potential for broad, long-term impact. As an archetypal example, the recent discovery of general, highly stereoselective, and
exceedingly mild methods for H$_2$-mediated C–C coupling from the Krische group has disrupted the traditional carbonyl addition paradigm by replacing stoichiometric organometallic reagents with inexpensive, stable, and safe olefins (5). In the same vein, a multitude of other methods for the employment of widely available chemicals such as methane (6, 7), ethane (7), ethylene (8, 9), 2-butene (10), and butadiene (11) in organic synthesis have been developed in the past decade. Inspired by these collective efforts, we wondered whether we could take advantage of other unexploited or underutilized feedstock chemicals that, despite their availability and advantageous properties, currently lack avenues for productive utilization.

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 (12) (Figure 1A). 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 C$_3$ fraction (13). Although a miniscule proportion of this resource is productively employed, allene is predominantly considered to be an undesirable contaminant in the supply of propylene, a more valuable and important product. Therefore, allene-containing mixtures are generally processed via catalytic hydrogenation to propane, and recycling 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 C$_3$ source in chemical synthesis. Specifically, we report below that in combination with hydrosilanes, which are inexpensive and environmentally benign byproducts derived from the silicone industry, allene gas or allene-containing gas mixtures can serve as an allyl nucleophile surrogate in an efficient and enantioselective nucleophilic addition reaction.
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 (14). According to comprehensive chemical databases (see the Supplementary Materials for details), the allyl group is the most common three-carbon nucleophile, typically introduced using stoichiometric organomagnesium (Grignard) reagents (15). Moreover, among all reactions employing allylic Grignard reagents, the majority involve specifically the parent allyl, rather than substituted allyl groups, and the majority of electrophilic partners are carbonyl derivatives such as ketones. Despite the ubiquity of this transformation in chemical research and manufacturing, many existing methods for the parent allylation of ketones are far from ideal (Figure 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 (16). In addition, the use of stoichiometric metal reagents is intrinsically wasteful, and the generation of insoluble metal salts and large quantities of heat limit the utility of these reactions on a large scale (17). 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. While several catalytic, stereoselective ketone allylation reactions exist (18), 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 Supplementary Materials for stereochemical model and further analysis). Further, many of the leading methods employing stoichiometric organometallic reagents require non-commercially-available catalysts (19, 20), and relatively expensive or water-sensitive allylmetal compounds (21, 22).
Inspired by pioneering research in reductive C–C bond formation by Krische (10, 11, 23), Montgomery (24), and Jamison (25), and by elegant examples of copper-catalyzed borylative (26, 27) couplings, our laboratory recently developed several classes of copper-catalyzed stereoselective reactions of in situ generated olefin-derived nucleophiles with carbon- (28–30) and nitrogen-centered electrophiles (9, 31). In the current study (Figure 1C), we proposed a reaction involving allene, a ketone, and a hydrosilane, which might proceed through the following catalytic mechanism, postulated on the basis of previous mechanistic and computational studies (29, 30). 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 easily deprotected during the reaction 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 Supplementary Materials for details). An atmospheric pressure of allene gas was applied over the reaction mixture with the aid of a standard balloon. 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 and changing the solvent to methyl tert-butyl ether (MTBE). It is notable that direct reduction of the ketone, often an
extremely rapid and competing reaction in the presence of copper–hydride complexes (28), 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 (Figure 2A). 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) 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).

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 (\(<$20/\text{mol}\) ), 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 (23), our calculations indicated that insertion of allene into hydride complex 1 should be greatly favored over alkynes or terminal alkenes (Figure 3A). 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 (\(<$1/\text{mol}\) ), 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 (Figure 3B). Using a reduced catalyst loading of 2 mol\%, 3.7 g (19 mmol) of 3g was obtained with high stereoselectivity (95:5 er).

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 (32), commercially sold as either a mixture of \(E/Z\)-isomers or as the pure \(Z\)-isomer, obtained by selective crystallization (Figure 3C). The traditional synthesis of this substance relies on cyclopropyl or allyl Grignard reagents, presenting challenges for scale-up or implementation in continuous flow processes (17) 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 (33). Acidic work-up efficiently removes the Boc protecting group and eliminates 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 yields 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 (34) (Figure 3D).

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 will serve as a versatile and economical reagent in a variety of additional carbon–carbon and carbon–heteroatom coupling reactions soon to be discovered.

References and Notes:


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**Supplementary Materials:**

Materials and Methods

Figs. S1 to S7

Table S1

NMR Spectra

SFC Traces
Figure 1. Overview of Allene-Based Ketone Allylation. A: Summary of the hydrocarbon cracking process. B: Comparison of ketone allylation strategies. C: Proposed catalytic mechanism for the Cu-catalyzed allene-based process. D: Key results from reaction optimization. wt% = weight percentage, L* = a chiral ligand, Me = methyl, Ph = phenyl, t-Bu = tert-butyl, Ac = acetyl, THF = tetrahydrofuran, MTBE = methyl tert-butyl ether, er = enantiomeric ratio. The yields were determined by $^1$H nuclear magnetic resonance (NMR) spectroscopy, using 1,1,2,2-tetrachloroethane as an internal standard. The er of the non-racemic compounds was determined by supercritical fluid chromatography (SFC) using commercial chiral stationary phases. For experimental details, see the Supplementary Materials.
**Figure 2. Scope of copper-catalyzed allylation of ketones using allene gas.** A: Scope of the process using racemic catalyst derived from BINAP. B: Scope of the process using non-racemic catalyst derived from QuinoxP*. Ac = acetyl, THF = tetrahydrofuran, Me = methyl, t-Bu = tert-butyl, rt = room temperature, dr = diastereomeric ratio, MTBE = methyl tert-butyl ether, er = enantiomeric ratio. The yield and er data represent the average values from isolated and purified products of two identical runs on 1 mmol scale of ketone. The er of the non-racemic compounds was determined by supercritical fluid chromatography (SFC) using commercial chiral stationary phases. For experimental details, see the Supplementary Materials.
Figure 3. Extensions and applications of the allylation process. A: Allylation of ketones using a mixture of three-carbon gases. B: Multi-gram-scale enantioselective allylation with reduced catalyst loading. C: Concise synthesis of a drug substance using an allylation–hydroamination–alkylation sequence. D: Synthesis of a chiral building block for natural product synthesis. Me = methyl, t-Bu = tert-butyl, MTBE = methyl tert-butyl ether, rt = room temperature, THF = tetrahydrofuran, Ac = acetyl, er = enantiomeric ratio. The er of the non-
racemic compounds was determined by supercritical fluid chromatography (SFC) using commercial chiral stationary phases. For experimental details, see the Supplementary Materials.