Synthetic Methods

International Edition: DOI: 10.1002/anie.201601545
German Edition: DOI: 10.1002/ange.201601545

Asymmetric Catalysis with CO_2: The Direct α-Allylation of Ketones

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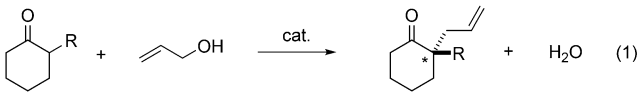
Abstract: *Quaternary stereocenters are found in numerous bioactive molecules. The Tsuji–Trost reaction has proven to be a powerful C–C bond forming process, and, at least in principle, should be well suited to access quaternary stereocenters via the α-allylation of ketones. However, while indirect approaches are known, the direct, catalytic asymmetric α-allylation of branched ketones has been elusive until today. By combining "enol catalysis" with the use of CO_2 as a formal catalyst for asymmetric catalysis, we have now developed a solution to this problem: we report a direct, highly enantioselective and highly atom-economic Tsuji–Trost allylation of branched ketones with allylic alcohol. Our reaction delivers products bearing quaternary stereocenters with high enantioselectivity and water as the sole by-product. We expect our methodology to be of utility in asymmetric catalysis and inspire the design of other highly atom-economic transformations.*

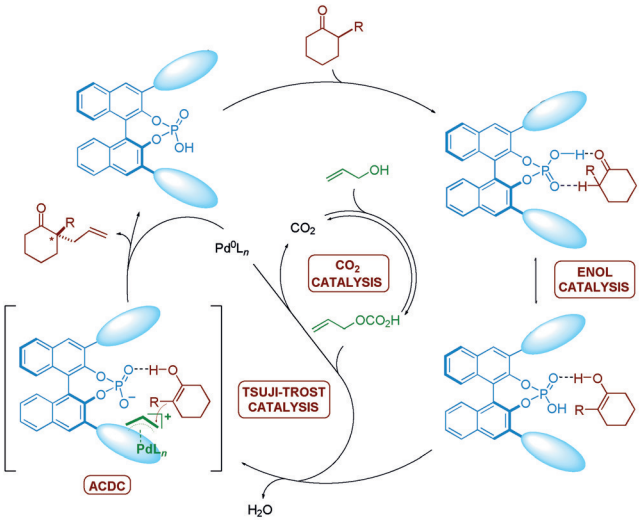
Quaternary stereocenters are common motifs in natural products and they can be found in more than ten percent of the top 200 prescription drugs.[1] In the last decade, progress has been made towards the stereoselective construction of quaternary stereocenters[2] and among other methods, the asymmetric Tsuji–Trost[3] α-allylation has proven to be of use in this context.[4–6] However, when unsymmetrical α-branched ketones (e.g. 2-phenyl or 2-methylcyclohexanone) are employed as substrates, an additional problem arises from the difficult control of isomeric enolates (tetra- vs. trisubstituted). Since the pioneering work by the Trost group,[7] alternative indirect approaches to this challenge have been developed. Phase transfer catalysis conditions (PTC) with activated substrates have also been disclosed.[8] Most of the reported approaches employ Pd^0 and chiral ligands and have until now involved specific classes of substrates (e.g. β-ketoesters, 1,3-diketones, tetralones),[7,9] preformed enolates (e.g. enol ethers or metal enolates),[10] and/or decarboxylative allylic alkylation conditions.[5,11] These indirect approaches are less atom-economic, require additional, sometimes low yielding synthetic steps for the substrate preparation, and often suffer from a lack of generality. Hence, despite major advances in the field, a general and direct catalytic enantioselective α-allylation of unsymmetrical ketones has never been achieved.

We have recently developed a direct α-allylation of branched aldehydes with allylic alcohols using an achiral amine/chiral Brønsted acid/Pd^0 catalytic system,[12] in which the enantioselectivity was controlled solely by the enantiopure counteranion.[13] Furthermore, the Carreira group developed an enantio- and diastereodivergent α-allylation of branched aldehydes, catalyzed by a chiral amine in combination with a chiral iridium π-complex.[14]

The use of unsymmetrical cyclic ketones presents a challenging regioselectivity problem, as the more hindered enol needs to selectively react. We recently proposed the concept of enol catalysis,[15] in which a nucleophilic enol is formed from the interaction between a branched ketone and a chiral phosphoric acid catalyst,[16] mimicking an enzymatic enolization.[17] This activation mode appeared ideally suited for the targeted direct α-allylation reaction as it preferentially proceeds via the more substituted enol. Furthermore, towards maximizing atom economy, we aimed at using simple allylic alcohols as electrophiles, an unprecedented feature in combination with ketones [Eq. (1)].



Allylic alcohols have proven to be suitable for the α-allylation of aldehydes,[12b] but failed in initial attempts with ketones. To solve this problem, we envisioned an activation mode for allylic alcohols, in which CO_2 would be utilized as a catalytic reagent, potentially generating a more reactive π-



Scheme 1. Design of a direct asymmetric α-allylation of branched ketones with allylic alcohols. ACDC = asymmetric counteranion-directed catalysis.

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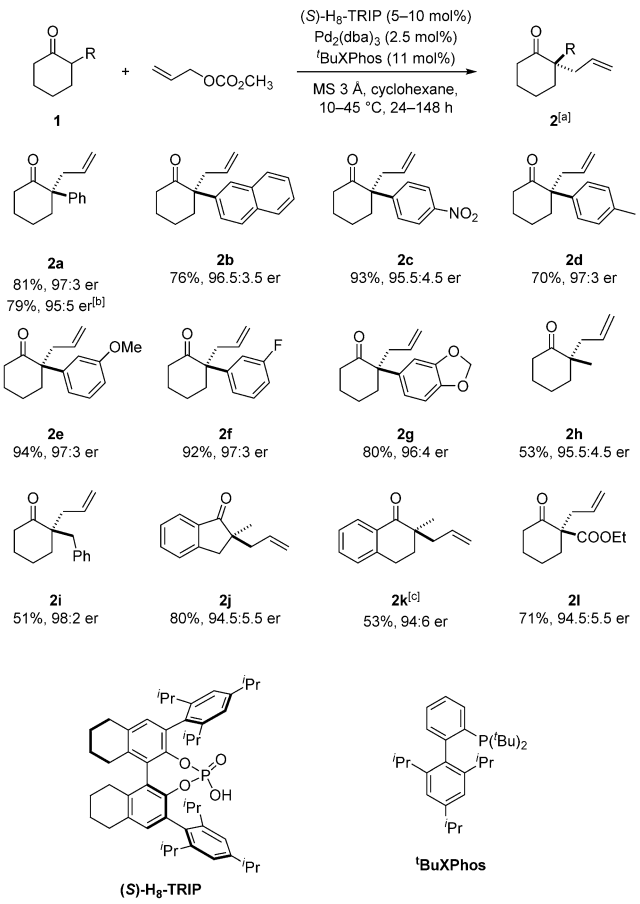
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201601545.

allyl precursor species, such as a carbonic acid ester.[18] Accordingly, we designed the following triple catalytic cycle (Scheme 1). The chiral phosphoric acid (HA*) initially interacts with the ketone, preferentially enabling reactivity from the thermodynamically more stable enol. In turn, the allylic alcohol is activated by CO_2 to form the corresponding carbonic acid ester, potentially via acid or Pd catalysis. In a parallel Tsuji–Trost catalytic cycle, the π-allyl-Pd electrophile is generated in an oxidative addition into the carbonic acid ester. Upon release of water and regeneration of CO_2, a $[Pd\text{-}allyl]^+A^{*-}$ complex would be formed in this step. The successive nucleophilic attack of the enol onto the π-allyl cation, reductive elimination, and release of the chiral acid would afford the desired product bearing a quaternary stereocenter, and simultaneously regenerate the catalysts.

To investigate if the overall ketone α-allylation was feasible, we first proceeded to develop the methodology with allyl methyl carbonate as electrophile, by reacting 2-phenylcyclohexanone in the presence of 10 mol% of commercially available (*S*)-TRIP phosphoric acid, an excess of allylating agent, and 2.5 mol% of different Pd^0 sources (Supporting Information (SI), Table S1). In the absence of a phosphine ligand, only traces of the desired allylated product were obtained, probably due to the instability of the Pd complex and the rapid formation of Pd black. However, promising enantioselectivities could be observed (up to 89:11 er). We hypothesized that the Pd ligand should influence both the yield and enantioselectivity as it would modify the sterics and stability of the electrophile. Indeed, when different phosphines were tested, a strong effect, both on reactivity and enantioselectivity, was found (SI, Table S2). Bulky and electron-rich biphenyl-based phosphine ligands almost exclusively afforded the desired regioisomer and, when highly hindered ^{t}BuXPhos[19] was employed in combination with the chiral acid, good enantioselectivities could also be achieved (88:12 er). To our delight, upon fine tuning of the catalyst and optimization of the reaction conditions (SI, Tables S3–S6), product **2a** could be isolated in 81% yield and an er of 97:3 using (*S*)-H_8-TRIP as catalyst at 35 °C.

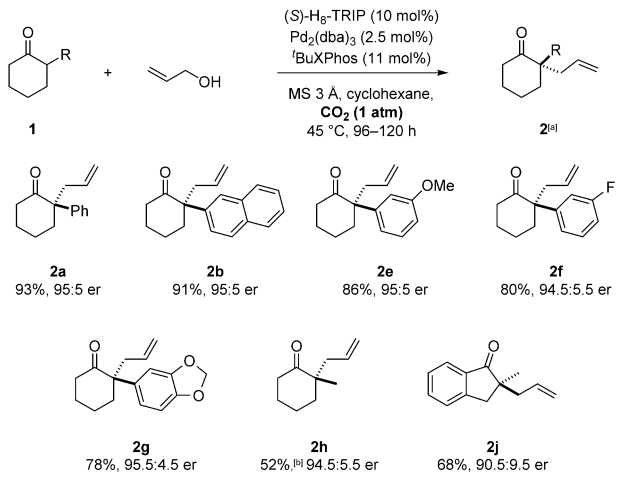
Gratifyingly, our reaction design indeed enabled the first general, highly enantioselective and regioselective direct α-allylation of branched ketones (Scheme 2). Low pK_a ketones (e.g. α-aryl substituted ones), represent a challenging substrate class that has previously been shown to be unsuitable under decarboxylative asymmetric allylic alkylation conditions, and only rare examples with preformed metal enolates have been reported.[10e] By employing our method, both electron-rich and electron-poor α-aryl substituted ketones reacted smoothly and afforded the desired products **2a**–**2g** in excellent yields and unprecedented enantioselectivities (up to 97:3 er). Higher pK_a substrates such as α-alkyl substituted ketones also afforded the desired products **2h**–**2i** in excellent enantioselectivities (up to 98:2 er), and in this case moderate to good yields were obtained, along with small amounts of the corresponding regioisomer. Other classes of substrates such as β-ketoester, indanone, and tetralone derivatives all proved to be compatible with our general protocol and afforded products **2j**–**2l** in good yields and enantioselectivities (up to 94.5:5.5 er).



Scheme 2. Direct catalytic asymmetric α-allylation of branched ketones with allyl methyl carbonate. [a] Isolated yields of reactions run on 0.1 or 0.2 mmol scale with 3 equiv of carbonate. Absolute configurations were determined by comparison of optical rotations with literature data. [b] Reaction run at 70 °C (10 mol%, 5 h). [c] 20 mol% acid. All enantiomeric ratios were determined by HPLC analysis using a chiral stationary phase.

Having established a general asymmetric protocol, we turned our attention towards our final goal: the use of allylic alcohols as ideal atom-economic alternative to carbonates. As expected, under our optimized conditions, either under argon or air, the conversion dropped to less than 15%, yet the enantioselectivity was only slightly diminished. However, when the reaction was run under an atmosphere of CO_2, reactivity, good conversion, and enantioselectivity were restored, and product **2a** could be isolated in 93% yield and with an er of 95:5 (see SI).

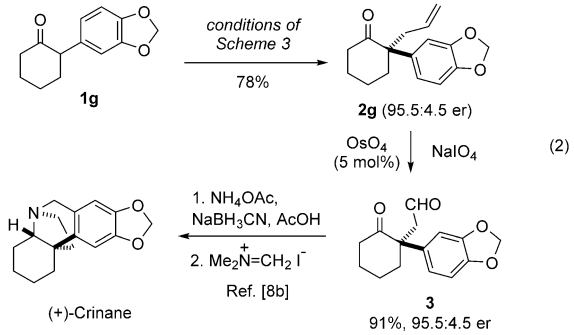
The generality of this CO_2-based protocol and the suitability of our design were confirmed by the successful reaction of other representative α-substituted ketones (Scheme 3). These results suggest the in situ generation of a π-allyl precursor which resembles allyl carbonates. The exact mechanism by which CO_2 activates allylic alcohol is unclear at this point, but we envision the establishment of an equilibrium between CO_2/allylic alcohol and the corresponding allyl carbonic acid ester.[18] This would then be followed by oxidative addition of Pd, regeneration of CO_2 and release of a molecule of H_2O. Interestingly, only catalytic amounts of



Scheme 3. Direct asymmetric α-allylation of branched ketones with CO_2 and allylic alcohol. [a] Isolated yields of reactions run on 0.1 mmol scale with 3 equiv of allylic alcohol. [b] NMR yield determined by using triphenylmethane as internal standard.

carbon dioxide are formally required for this type of activation.

To highlight the synthetic potential of our method for the synthesis of natural products, we have developed a short enantioselective formal total synthesis of the Amaryllidaceae alkaloid, (+)-crinane [Eq. (2)] from commercially available ketone **1g**. By employing our novel CO_2-promoted α-allylation reaction, product **2g** was obtained in 78% isolated yield and 95.5:4.5 er. The successive oxidation afforded compound **3**, which can be readily converted into (+)-crinane in 2 steps.[8b] Our four step approach represents the shortest synthesis of (+)-crinane.



(2)

Key features for the design of new methodologies for chemical synthesis are generality, selectivity, efficiency, and atom-economy. Guided by these principles, we designed and successfully realized the first solution to the long-standing problem of the direct α-allylation of branched ketones. The successful combination of palladium catalysis, enol catalysis, asymmetric counteranion directed catalysis, and an unprecedented CO_2-catalyzed substrate activation, led to a method to access challenging quaternary stereocenters, a key motif in numerous bioactive molecules. We believe that our operationally simple protocol will be widely applicable in natural product and drug synthesis, and the concepts described herein may inspire other highly selective and atom-economic reactions.

Experimental Section

Catalytic asymmetric synthesis of (*S*)-**2a** with CO_2-activated allylic alcohol: in a Schlenk equipped with a condenser/cold finger, 2-phenylcyclohexanone (0.1 mmol, 1 equiv), MS 3 Å (100 mg), (*S*)-H_8-TRIP (10 mol%), ^{t}BuXPhos (11 mol%), $Pd_2(dba)_3$ (2.5 mol%) were dissolved in 1 mL of cyclohexane (0.1M). After three freeze/vacuum/thaw/CO_2 backfill cycles, the reaction mixture was stirred at 45 °C for 96 h under a CO_2 atmosphere (1 atm, balloon). The crude mixture was then cooled to room temperature and directly purified by flash column chromatography. For complete experimental details and compound characterization, see Supporting Information.

Acknowledgements

We are grateful for the generous support from the Max-Planck-Society, the Fonds der Chemischen Industrie (fellowship to G.P.) as well as the GC department of the MPI für Kohlenforschung for analytics and Hendrik van Thienen for the synthesis of (*S*)-TRIP.

Keywords: allylic alcohol · atom economy · enol catalysis · quaternary stereocenters · α-allylation

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 6099–6102
Angew. Chem. **2016**, *128*, 6204–6207

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Received: February 12, 2016
Published online: April 13, 2016

