Direct and enantioselective α-allylation of ketones via singly occupied molecular orbital (SOMO) catalysis

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The first enantioselective organocatalytic α-allylation of cyclic ketones has been accomplished via singly occupied molecular orbital catalysis. Geometrically constrained radical cations, forged from the one-electron oxidation of transiently generated enamines, readily undergo allylic alkylation with a variety of commercially available allyl silanes. A reasonable latitude in both the ketone and allyl silane components is readily accommodated in this new transformation. Moreover, three new oxidatively stable imidazolidinone catalysts have been developed that allow cyclic ketones to successfully participate in this transformation. The new catalyst platform has also been exploited in the first catalytic enantioselective α-enolation and α-carbooxidation of ketones.

asymmetric synthesis | organocatalysis

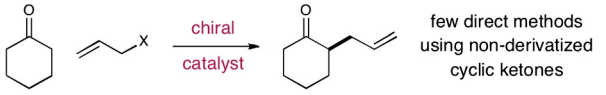
The enantioselective catalytic α-alkylation of simple ketones remains a fundamental goal in chemical synthesis (1–4). Seminal work from Doyle and Jacobsen (5), Trost and co-workers (6–8), Stoltz and co-workers (9, 10), Braun and co-workers (11, 12), and Hartwig and co-workers (13, 14) has introduced valuable previously undescribed technologies for (*i*) the enantioselective alkylation of preformed or in situ generated metal enolates (5, 6, 11–17) and (*ii*) the asymmetric and decarboxylative conversion of allyl keto carbonates to α-allylated ketones (7–10). With these key advances in place, a goal now for asymmetric catalysis has become the direct α-allylation of simple ketone substrates (18, 19), an elusive yet potentially powerful bond construction (Scheme 1).

Recently, we questioned whether the catalytic principles of singly occupied molecular orbital (SOMO) activation (20) might be translated to ketonic systems, thereby providing an unreported mechanism for direct and enantioselective α-carbonyl alkylation. Despite the superficial similarities between aldehydes and ketones, these carbonyl families exhibit largely different steric and electronic properties with respect to catalyst interactions. As a consequence, the translation of enantioselective activation modes between these carbonyl subclasses is often difficult (if not unattainable in many cases) (21, 22). Herein, we describe the invention of a previously undisclosed family of organocatalysts that enable cyclic ketones to successfully function within the SOMO-activation platform while being chemically robust to oxidative reagents. Moreover, we document the introduction of a previously undescribed catalytic α-ketone alkylation reaction that is immediately amenable to asymmetric induction.

Enantioselective SOMO Catalysis

Over the last decade, the field of enantioselective synthesis has witnessed tremendous progress in the successful implementation of small organic molecules as asymmetric catalysts. In particular, two modes of carbonyl activation by chiral secondary amines have led to the discovery of a large number of previously undescribed reactions (Scheme 2): (*i*) Iminium catalysis (23), wherein lowest unoccupied molecular orbital (LUMO) lowering activation is accomplished via the transient condensation of an α,β-unsaturated aldehyde and an amine catalyst, has enabled the enantioselective conjugate addition or cycloaddition of enals with a wide range of external π-nucleophiles or cycloaddition partners and (*ii*) enamine catalysis (24), a reaction mode wherein a catalytic amount of a chiral enamine exhibits increased propensity to react with a broad selection of electrophiles by raising the highest occupied molecular orbital (HOMO).

Elusive Transform: Direct Enantioselective α-Allylation of Ketones



Scheme 1.

In view of the established utility of these activation modes for the development of a variety of previously undisclosed, valuable transformations, we recently wondered if the existing two-electron interconversion between iminium and enamine species could be redirected to utilize a 3π electron species and thereby establish a previously undescribed reaction platform that relies on SOMO intermediates (20). In pursuit of this goal, three design elements proved to be extremely important: First, selective oxidation of an equilibrium concentration of enamine in lieu of the aldehyde substrate and amine catalyst was imperative. Known ionization potentials of analogous substrates indicated that such a selective oxidation was indeed feasible (Scheme 3) (20). The second design element required the identification of an amine catalyst that could generically provide high levels of enantiodiscrimination in the subsequent bond-forming processes with π-rich SOMOphiles. Density functional theory (DFT) calculations indicated that the radical cation derived from imidazolidinone catalyst **1** is partitioned away from the bulky *tert*-butyl group and that the carbon-centered radical populates an (*E*)-geometry in order to minimize allylic nonbonding interactions with the imidazolidinone framework (Scheme 3) (20). The enantiodetermining event would then be governed by C-5 benzyl shielding of the *Re* face, leaving the *Si* face exposed. Finally, the propensity of the SOMO intermediate to engage in stereodefined C–C bond formation with a large variety of π-rich nucleophiles was anticipated.

Importantly, the successful realization of this previously unreported catalytic activation mode has enabled our laboratory to introduce a variety of previously unprecedented enantioselective transformations. Examples include the direct allylic alkylation (20), the α-arylation (20, 25), α-enolation (26), α-vinylation (27), α-carbooxidation of alkenes (28), α-nitro alkylation en route to corresponding amino acids (29), as well as α-chlorination (30) (Scheme 4). Given the high synthetic utility of these enantioenriched aldehyde synthons, we recently recognized the importance (as well as the potential difficulties) in extending this SOMO catalysis concept to ketonic motifs.

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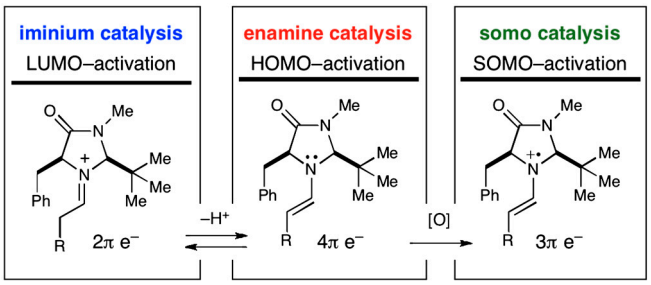
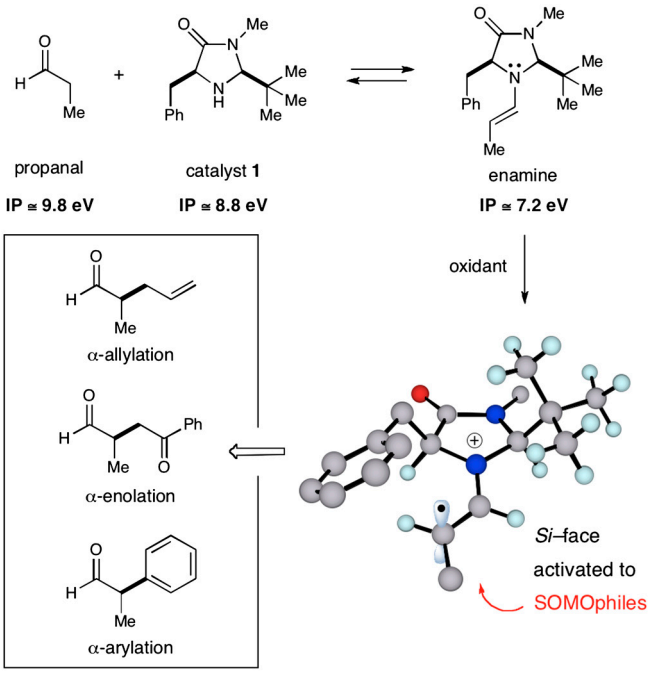


Scheme 2. An evolution of activation modes in organocatalysis.

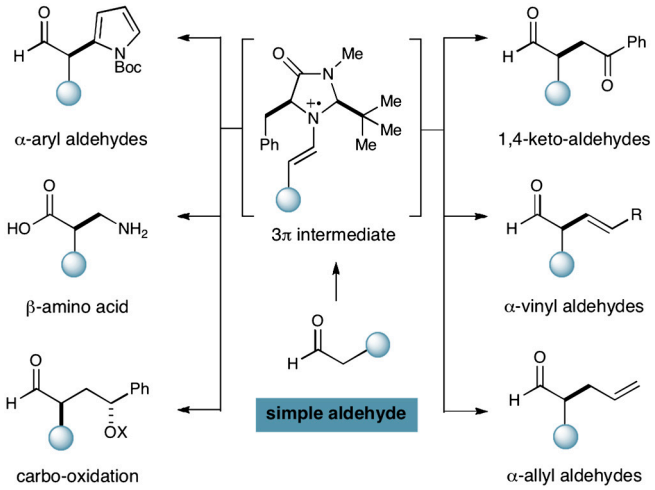
Results and Discussion

The application of our SOMO-activation platform to enantioselective ketone allylation was first evaluated with cyclohexanone, allyltrimethylsilane, ceric ammonium nitrate, and 20 mol% of imidazolidinone **2**, an amine catalyst that has previously enabled Diels–Alder reactions with cyclic enones via iminium activation (21, 22). As revealed in Scheme 5, we were happy to find that the critical alkylation step could be achieved in both a direct and enantioselective fashion using imidazolidinone **2**; however, competitive catalyst degradation (via methyl furan oxidation) consistently led to poor levels of reaction efficiency (Scheme 5, 42% yield, 93% ee).

Heartened by these initial results, we sought to design a second generation catalyst that would be less prone to oxidation while retaining the critical architectural features that confer enantiocontrol. In this context, we hypothesized that either (a) derivatization of the furan methyl group of catalyst **2** to a trifluoromethyl moiety (**4**), or (b) direct replacement of the furyl ring with heteroaryl systems that are less electron-rich (e.g., benzofuran **5**, benzothiophene **6**) might render a more robust system. Indeed, imidazolidinones **4**, **5** and **6** were all found to catalyze the direct α-allylation of cyclohexanone in good yield while maintaining excellent levels of enantioselectivity (75–85% yield, 88–94% ee). The broad-spectrum utility of this unreported imidazolidinone family **4–6** prompted us to initiate our investigation into substrate scope using all three catalysts.

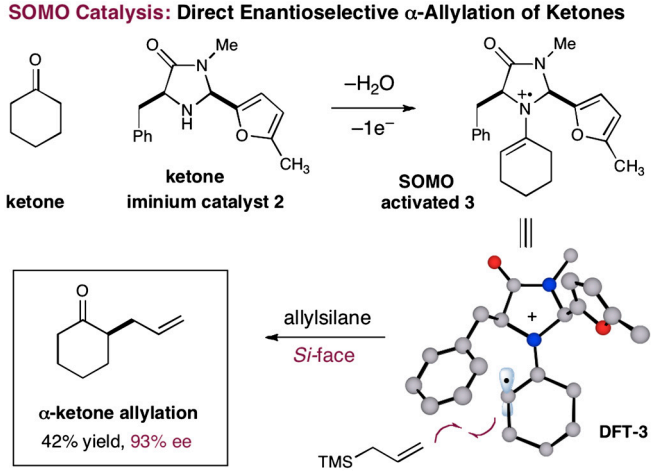


Scheme 3. Relevant ionization potentials of reactive species; DFT minimized radical cation; representative transformations.



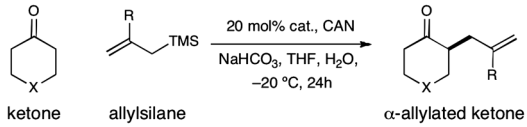
Scheme 4. Selected transformations using SOMO catalysis.

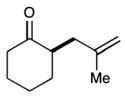
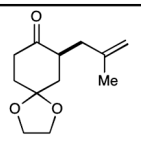
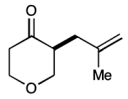
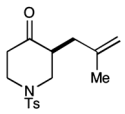
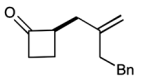
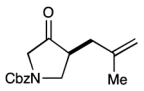
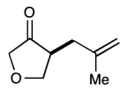
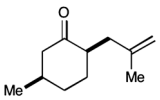
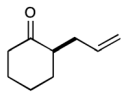
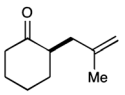
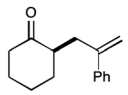
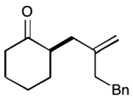
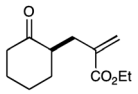
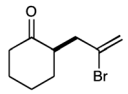
Experiments that probe the scope of the ketone component have revealed that a variety of four-, five-, and six-membered carbocycles and heterocycles can be readily employed in this asymmetric alkylation reaction (Table 1, entries 1–9, 84–99% ee). Moreover, this protocol is successful with ketones that incorporate alkyl and heteroatom substituents at the β and γ ring positions, an important consideration with respect to natural product synthesis (entries 2, 4, 6, and 8, 85–99% ee). Furthermore, this protocol is generally successful with only two equivalents of ketone, although 20 equivalents are required for the cyclobutane example. Perhaps most notable, we have found that nonsymmetrical cyclic ketones such as 3-pyrrolidinones (entry 6) and 3-furanones (entry 7) afford exclusively the C(4)-alkylation product as determined by GLC (>200:1) or HPLC (>100:1) analysis. These results are striking given that the 2-enamine isomer should be formed competitively [based on kinetic acidities (31)] and more readily oxidized (based on ionization potentials) (32). With respect to 3-methylcyclohexanone, we assume that the observed sense of regiocontrol can be explained on the basis of steric constraints (entry 8, 99% ee). Curiously, cyclopentanone undergoes exclusive formation of the C_2-symmetric 2,5-bis-allylation product (entry 9, 99% ee) (33). Given that 2-allylcyclopentanone (12) is not converted to this C_2-bis-allylation adduct when exposed to the same reaction conditions, we presume that the first cyclopentanone alkylation step leads to an iminium/enamine species that undergoes a second oxidation-allylation sequence faster than iminium hydrolysis. It is important to note that the



Scheme 5. Initial result of direct ketone allylation.

Table 1. Scope of direct ketone allylation.*,†



1		2		3	
	4, 82%, 91% ee		**4**, 85%, 90% ee		**4**, 78%, 90% ee
4		5‡		6	
	4, 76%, 90% ee		**5**, 66%, 91% ee		**6**, 77%, 85% ee
7§		8§		9§	
	5, 79%, 84% ee		**5**, 70%, 5:1 dr, 99% ee		**5**, 71%, 99% ee
10§		11		12	
	5, 85%, 91% ee		**4**, 82%, 91% ee		**4**, 83%, 81% ee
13		14		15§	
	6, 86%, 96% ee		**6**, 80%, 83% ee		**5**, 74%, 87% ee

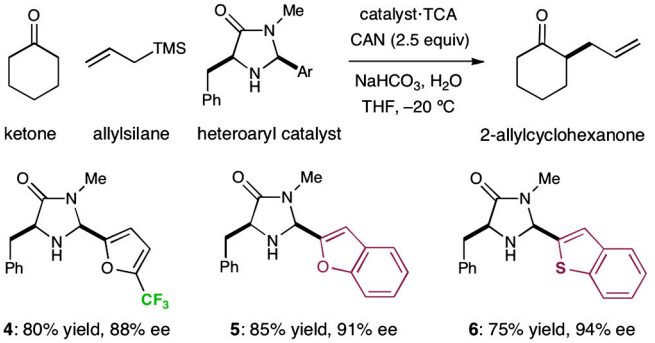
*For each entry: catalyst #, % yield, % ee.
†Enantiomeric excess determined by chiral HPLC, supercritical fluid chromatography, or GLC analysis.
‡Performed with 20 eq of ketone.
§Performed in the absence of $NaHCO_3$.

sense of asymmetric induction observed in all cases (Table 1 and Schemes 5–7) is consistent with selective engagement of the SOMOphile with the *Si* face of the radical cation, in accord with the calculated structure (**DFT-3**) (34).

The nature of the allyl silane component in this ketone alkylation reaction has also been evaluated. As revealed in Table 1, this catalytic protocol can accommodate π-rich olefinic silanes (entries 10–13, 82–86% yield, 81–96% ee) as well as electron-deficient silanes (entries 14–15, 74–80% yield, 83–87% ee), including a vinyl bromide (entry 15, 74% yield, 87% ee). Such halogenated olefin adducts should prove to be valuable synthons for use in conjunction with established cross-coupling methodologies (e.g., Buchwald–Hartwig or Stille couplings).

In an effort to further demonstrate synthetic utility, we have sought to apply our ketone-SOMO-activation platform to a series of bond constructions that have only previously been possible with aldehydic substrates. For example, catalyst **6** has successfully enabled the enantioselective α-enolation of cyclohexanone under oxidative conditions (chemical formula 1, Scheme 7, 84% ee). Moreover, the asymmetric α-homobenzylation of cyclohexanone can also be accomplished via a two-step α-carbo-oxidation-hydrogenation sequence using the same imidazolidinone catalyst (chemical formula 2, Scheme 7, 80% ee) (26, 28).

Design of Robust Amine Catalysts for Oxidative Ketone α-Allylation



Scheme 6. Catalyst design and reaction efficiency.

In summary, we have developed a family of oxidatively stable imidazolidinone catalysts **4–6** that are readily employed for the SOMO activation of cyclic ketones. These catalysts allow the direct α-allylation, α-enolation, and α-carbooxidation of carbocyclic ketones with excellent levels of enantiocontrol. Further application of these organocatalytic methodologies will be reported shortly.

Methods

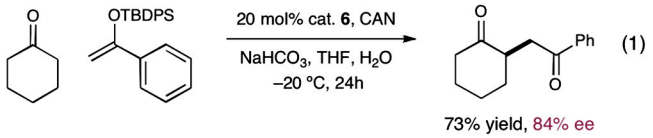
Full experimental details and spectral data are included in *SI Text*.

General Procedure for the α-Allylation of Ketones. To a 10-mL oven-dried round-bottom flask equipped with a magnetic stir bar was added cocatalyst trichloroacetic acid or HCl (0.15 mmol, 0.20 eq), imidazolidinone catalyst **4**·TFA, **5**, or **6** (0.15 mmol, 0.20 eq) (as indicated below), $NaHCO_3$ (94.9 mg, 1.13 mmol, 1.50 eq), and ceric ammonium nitrate (1.03 g, 1.88 mmol, 2.50 eq). The reaction vessel was evacuated by high vacuum (0.3 torr) at −78 °C for 1 min. After backfilling with argon, tetrahydrofuran (3.0 mL, 0.25 m) and water (10–20 eq, as indicated below) were added to the reaction vessel, and the reaction mixture was subsequently degassed by repeated evacuation and backfilling with argon (three cycles of 2 min each) at −78 °C. The allyl silane (0.75 mmol, 1.00 eq) was then added via syringe followed by the respective ketone (1.50 mmol, 2.00 eq). The reaction vessel was moved from the −78 °C bath into a −20 °C cooling bath and stirred with a high rate of vortex for 24 h under argon atmosphere. At the end of the indicated reaction time, diethyl ether (5.0 mL) was added to the crude mixture and stirring was continued at −78 °C for 20 min to precipitate the cerium salts. Filtration through a plug of silica gel using diethyl ether as a solvent concentration under reduced pressure furnished the crude product as a yellowish liquid, which was purified by flash chromatography to afford the analytically pure α-allylated ketone.

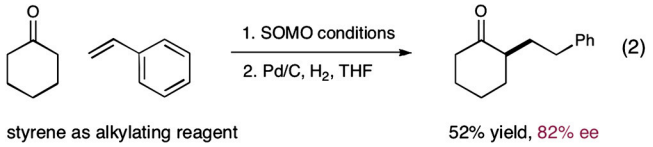
Method A. The general procedure was followed using (2*R*,5*R*)-5-benzyl-3-methyl-2-(benzofuran-2-yl)imidazolidin-4-one (**5**) (46 mg, 0.15 mmol, 0.20 eq) and trichloroacetic acid (24 mg, 0.15 mmol, 0.20 eq) in the presence of water (0.27 mL, 15 mmol, 20 eq) without the addition of $NaHCO_3$.

Method B. The general procedure was followed using (2*R*,5*R*)-5-benzyl-3-methyl-2-(benzothiophen-2-yl)imidazolidin-4-one (**6**) (48 mg, 0.15 mmol,

Enantioselective α-Enolation



Enantioselective α-Homobenzylation



Scheme 7. General utility of ketone α-functionalization.

0.20 eq) and conc. HCl (6.0 μL, 0.20 eq, 0.15 mmol) in the presence of water (0.27 mL, 15 mmol, 20 eq) and $NaHCO_3$ (94.5 mg, 1.12 mmol, 1.50 eq).

Method C. The general procedure was followed using the trifluoroacetic acid salt of (2*R*,5*R*)-5-benzyl-3-methyl-2-(5-trifluoromethylfuran-2-yl)imidazolidin-4-one (**4**·TFA) (63 mg, 0.15 mmol, 0.20 eq) in the presence of water (0.14 mL, 7.5 mmol, 10 eq) and $NaHCO_3$ (94.5 mg, 1.5 eq, 1.12 mmol).

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