

Oxy-Allyl Cation Catalysis: An Enantioselective Electrophilic Activation Mode

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S Supporting Information

ABSTRACT: A generic activation mode for asymmetric LUMO-lowering catalysis has been developed using the long-established principles of oxy-allyl cation chemistry. Here, the enantioselective conversion of racemic α -tosyloxy ketones to optically enriched α -indolic carbonyls has been accomplished using a new amino alcohol catalyst in the presence of electron-rich indole nucleophiles. Kinetic studies reveal that the rate-determining step in this S_N1 pathway is the catalyst-mediated α -tosyloxy ketone deprotonation step to form an enantiodiscriminant oxy-allyl cation prior to the stereodefining nucleophilic addition event.

Over the past two decades, the field of asymmetric organocatalysis has grown at a rapid pace, fueled largely by the development of generic modes of substrate activation. Indeed, electrophile activation via hydrogen bonding¹ or iminium catalysis² has provided more than 60 novel transformations that allow for the enantioselective construction of C–C, C–X, and C–H bonds. In more recent years, urea or thiourea-mediated anion binding has found widespread utility for the generation of enantiodifferentiated ion pairs, another LUMO-lowering platform that offers a vast array of unique applications.³ HOMO-raising asymmetric induction has been widely accomplished with enamine catalysis, an activation mode that enables aldehydes and ketones to readily undergo α -carbonyl functionalization with a variety of electrophilic coupling partners.⁴ The utility of enamine catalysis is readily appreciated given the prevalence of α -aromatic, α -aminated, and α -oxygenated carbonyls within the fields of pharmaceutical, fine chemical, and natural product synthesis. With this consideration in mind, we recently questioned whether enantioselective α -carbonyl functionalization might be accomplished using LUMO-lowering catalysis, specifically founded upon a new oxy-allyl cation activation mode. As a critical design element, we recognized that the use of a LUMO-lowering pathway would allow for the implementation of nucleophile coupling partners in lieu of electrophiles, a strategy that should enable a dramatic increase in the structure and scope of α -carbonyl products that would be accessible using asymmetric organocatalysis.

Oxy-allyl cations have been long known as transient electrophilic species since they were first employed as intermediates in the Favorskii rearrangement in 1894.⁵ Since that time, they have also been used as an activation mode for [4 + 3] cycloadditions⁶ and Nazarov cyclizations⁷ in a variety of natural

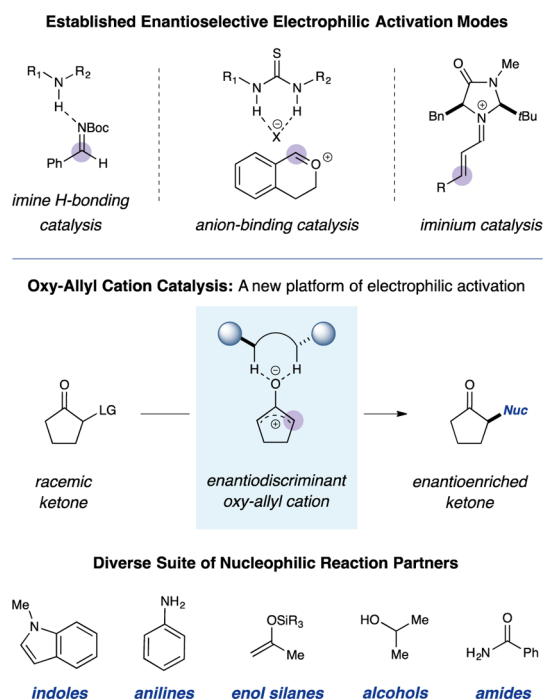


Figure 1. Accessing novel organocatalytic platforms of catalysis.

product syntheses. In 2013, our laboratory found that oxy-allyl cations generated under mild conditions from α -tosyloxy ketones (using weak base) do not readily undergo Favorskii contraction and, more importantly, can be trapped by a large array of σ - or π -nucleophiles to directly furnish α -heteroaromatic, α -aromatic, α -aminated, and α -oxygenated carbonyl products.^{8,9} Anticipating that this generic mode of α -carbonyl activation might be rendered enantioselective, we subsequently sought to find chiral organocatalysts to (a) enable α -tosyloxy ketones to readily undergo soft enolization/fragmentation and (b) subsequently form enantiodiscriminant oxy-allyl cations. Herein we report the successful execution of these ideals and describe a new amino alcohol catalyst that allows the enantioselective coupling of indoles with racemic α -tosyloxy ketones.

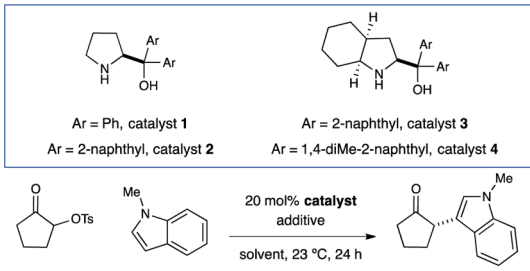
Results. As shown in Figure 1, we hypothesized that chiral hydrogen bond-donating catalysts should reversibly bind with α -tosyloxy ketones and thereby enable them to undergo soft-

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enolization/fragmentation to form enantiodiscriminant oxy-allyl cations. In this vein, we elected to evaluate a variety of amino alcohols given their capacity to function as carbonyl LUMO-lowering catalysts while at the same time being compatible with mildly basic conditions. Preliminary studies from our lab demonstrated that commercially available phenyl prolinol-derived amino alcohol **1** can induce enantiocontrol in the coupling of α -tosyloxy cyclopentanone and *N*-methylindole in the presence of the mild base K_2HPO_4 and benzene, albeit with poor levels of selectivity (Table 1, entry 1).¹⁰ The effect of

Table 1. Initial Studies and Reaction Optimization



entry	catalyst	solvent	additive	yield ^a	ee ^b
1	1	C ₆ H ₆	K ₂ HPO ₄	58%	37%
2	2	C ₆ H ₆	K ₂ HPO ₄	50%	55%
3	3	C ₆ H ₆	K ₂ HPO ₄	54%	73%
4	3	1:1 C ₆ H ₆ /C ₆ F ₆	K ₂ HPO ₄	55%	79%
5	3	C ₆ F ₆	K ₂ HPO ₄	33%	81%
6 ^c	4	C ₆ F ₆	K ₂ HPO ₄ , H ₂ O ^d	91%	92%
7	none	C ₆ F ₆	K ₂ HPO ₄ , H ₂ O ^d	0%	—
8	4	C ₆ F ₆	H ₂ O	4%	—

^aYield determined by ¹H NMR. ^bEnantioselectivities determined by chiral HPLC. ^cReaction time of 48 h. ^d1 equiv of H₂O.

changing to the bis-naphthyl-substituted catalyst **2** and extending the prolinol core to an octahydroindolinol framework (catalyst **3**)¹¹ further improved the enantioselectivity to 55% and 73% ee, respectively (entries 2 and 3). We propose that this net increase in enantiocontrol is due to enhanced cation- π stabilization between the oxy-allyl cation and the aryl substituents on the catalyst framework. On this basis we next examined the use of perfluorobenzene instead of benzene as the reaction medium, a change that should disfavor any competing cation- π interactions between the solvent and the critical oxy-allyl cation intermediate.¹² Indeed, the perfluorobenzene system exhibited a marked increase in asymmetric induction (entries 3–5). Finally, incorporation of methyl groups at the 1- and 4-positions of the naphthalene rings (catalyst **4**) increased the selectivity to 92% ee, while the presence of water further augmented the yield (entry 6, 91% yield). Control experiments revealed that the presence of the amino alcohol catalyst is critical for the reaction to proceed (entry 7), while the absence of K_2HPO_4 severely inhibits the overall efficiency (entry 8, 4% yield), indicating the soft enolization step requires both a catalyst and mild base.

With optimal conditions in hand, we next examined the scope of this new and enantioselective oxy-allyl cation addition protocol with respect to the indole component. As revealed in Figure 2, this transformation is amenable to changes in both sterics and electronics of the nucleophilic partner.¹⁰ Notably, we were able to extend this oxy-allyl cation activation mode to an iminium cascade sequence that allows the rapid construction of a

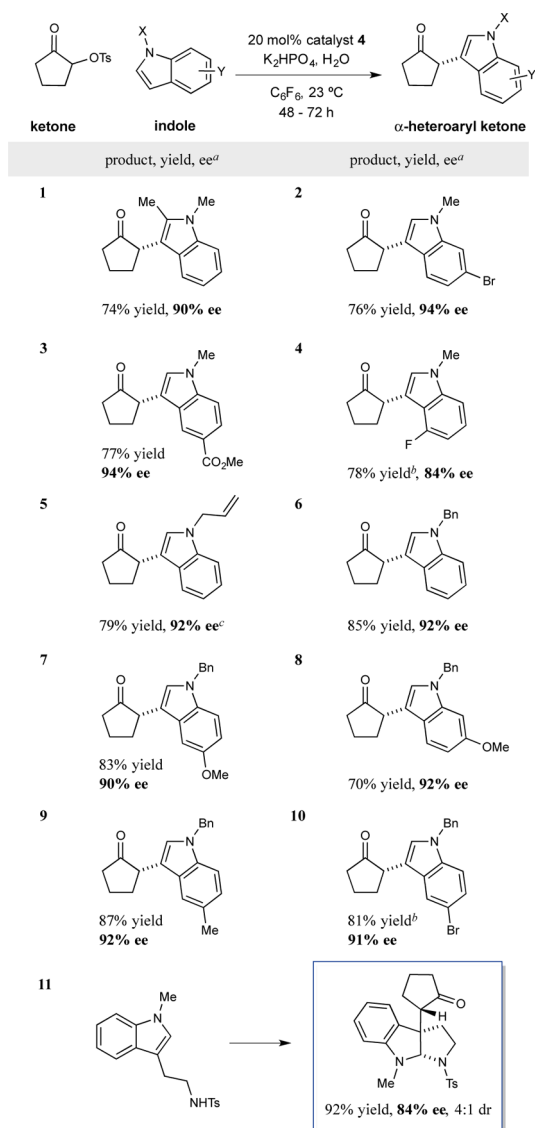


Figure 2. Scope of the indole nucleophile. ^a Isolated yields; see Supporting Information (SI) for experimental details. ^b Reaction time of 96 h. ^c Using 1,4-diOMe-2-naphthyl-octahydroindolinol catalyst.

complex pyrroloindoline architecture, a motif commonly found among a variety of natural product classes.¹³ As revealed in entry 11, the use of a tryptamine nucleophile with α -tosyloxy cyclopentanone in the presence of catalyst **4** leads to facile formation of the corresponding pyrroloindoline in 92% yield, 84% ee, and 4:1 dr.

We next evaluated the scope of α -tosyloxy ketones (Figure 3). Interestingly, the use of enantioenriched methyl-substituted α -tosyloxy cyclopentanones provided an indolic adduct as a single regioisomer with excellent diastereoselectivity (>20:1 dr) using the matched (*S*)-prolinol catalyst (entries 5 and 6, 70% and 62% respectively). As a useful mechanistic probe, the formation of the identical indole addition adduct is observed from the 3-methyl as well as the 4-methyl-substituted α -tosyloxy cyclopentanone system, reaffirming that the transformation proceeds through a common oxy-allyl cation intermediate.¹⁰

Mechanistic Studies. To gain a better understanding of the mechanistic details of this new oxy-allyl cation activation mode, initial rate kinetics experiments were performed to elucidate the reaction order for both the ketone and indole coupling partners

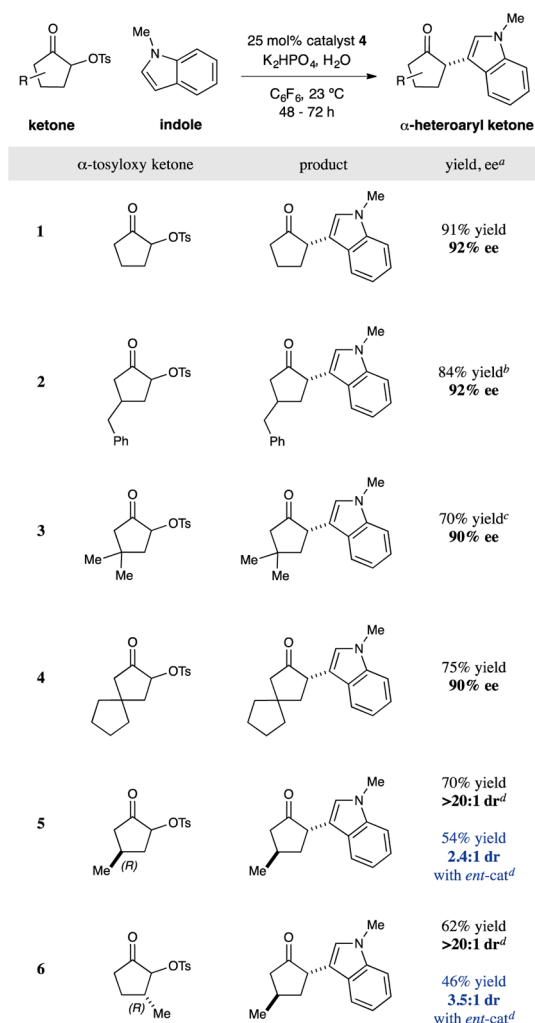


Figure 3. Scope of the ketone electrophile. ^a Isolated yields; see SI for experimental details. ^b 1:1 dr of product. ^c Reaction time of 96 h. ^d Using 1,4-diOMe-2-naphthyloctahydroindolinol catalyst.

and for the prolinol catalyst.¹⁰ As revealed in Figures 4, 5, and 6, respectively, a first-order dependence in both ketone and organocatalyst and a zero-order dependence in *N*-methylindole was observed. These experiments are consistent with a pathway wherein the rate-determining step occurs prior to indole addition to the oxy-allyl cation. Moreover, as demonstrated in Scheme 1, a primary KIE of 3.5 was found for α -tosyloxy ketones with proton vs deuterium labels at the α -carbonyl positions. These studies provide insight that the deprotonation in the initial enolization step is rate-determining. At this stage we cannot state whether the fragmentation/ionization step happens in concert with the deprotonation event.

Having found that the soft enolization step is rate-determining, we reasoned that there might be an opportunity to demonstrate chemoselectivity for functionalization of α -tosyloxy cyclopentanones in the presence of an almost identical aliphatic cyclohexanone derivative. More specifically, we were aware that five-membered cyclic ketones undergo rapid α -deprotonation in comparison to their cyclohexanone counterparts due to the unfavorable strain energy that arises from introducing unsaturation into six-membered over five-membered rings. Indeed, when both ketones were subjected to this asymmetric catalytic protocol in the same vessel, complete selectivity for α -tosyloxy cyclopentanone functionalization was observed, yielding 91% of

the smaller ring adduct and near-quantitative recovery of the α -tosyloxy cyclohexanone (Scheme 2).¹⁴

Finally, a series of experiments were conducted using α -Br and α -OMs cyclopentanones to discriminate between two possible pathways for asymmetric induction, namely (a) catalyst bound enantiodiscriminant oxy-allyl cation formation and (b) an ionic catalyst–substrate anion-binding activation mode. While the use of different anion leaving groups on the cyclopentyl moiety should have no effect on the enantioselectivity conferred via a common oxy-allyl cation intermediate, we were aware that anion-binding catalysis typically exhibits large variations in enantiocontrol as a function of the halide or tosylate leaving group employed.^{3e} In the event, the observed selectivities were 92% and 90% ee, respectively for the bromo and mesylate groups, strongly suggesting that the catalyst is hydrogen bonded to the oxy-allyl cation in the enantiodetermining step.

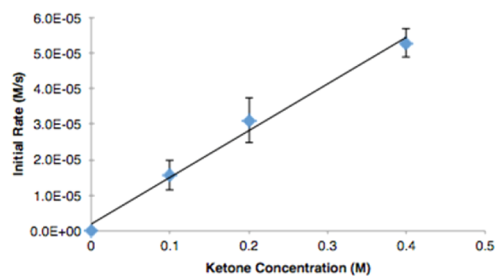


Figure 4. Plot of initial rate (M/s) versus [ketone] (M).

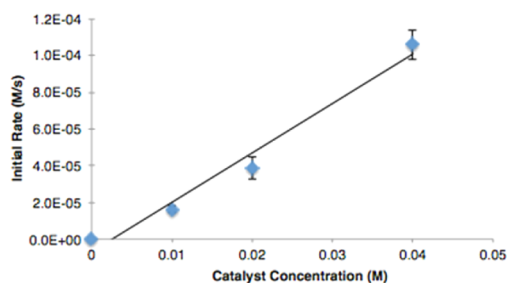


Figure 5. Plot of initial rate (M/s) versus [organocatalyst] (M).

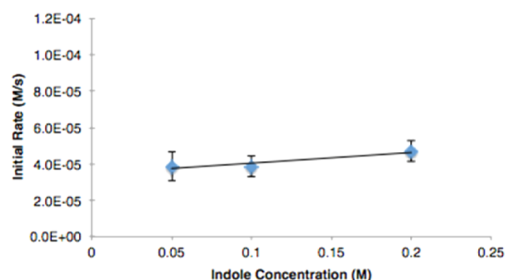
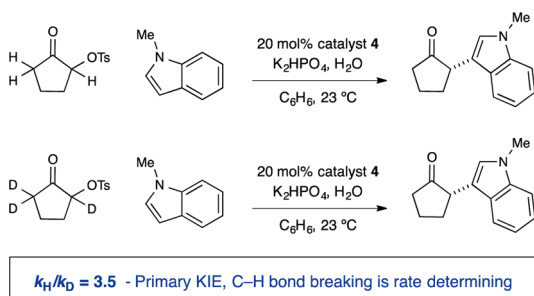


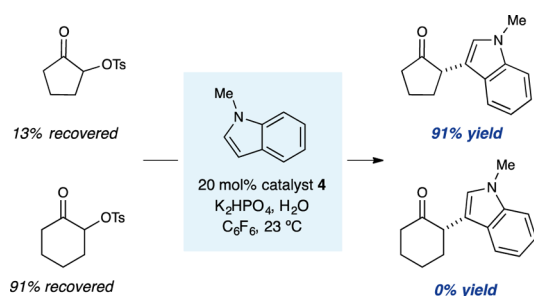
Figure 6. Plot of initial rate (M/s) versus [indole] (M).

Taking into account the combined results of our mechanistic studies, we believe the following catalytic pathway is operative. Hydrogen bonding of amino alcohol 4 to α -tosyloxy ketone 1 induces a rate-determining deprotonation step with subsequent or concomitant ionization to form the highly reactive cation 2 (Scheme 3). DFT minimization¹⁵ of the catalyst-bound oxy-allyl cation 2 (DFT-2) suggests that enantiodiscrimination is achieved via shielding of the oxy-allyl cation top face (as shown) by way of a cation– π interaction with one of the naphthalene rings on the catalyst framework. Subsequent addition of the indole

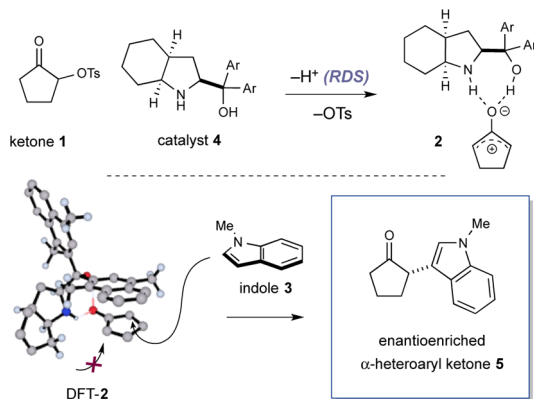
Scheme 1. Kinetic Isotope Effect Studies on Soft Enolization



Scheme 2. Competition Study Conducted in Common Vessel



Scheme 3. Proposed Mechanism of the Substitution Reaction



nucleophile 3 to the less sterically encumbered lower face should provide the enantioenriched α -heteroaryl ketone 5.¹⁶

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13041.

Crystallographic data for $C_{21}H_{20}BrNO_2$ (CIF)

Crystallographic data for $C_{66}H_{74}N_2O_{10}$ (CIF)

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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- At the current time, catalyst 4 is selective only for five-membered ring ketones; work is ongoing to develop a suitable catalyst for ketones of other ring sizes.
- DFT optimization used a B3LYP 6-31G basis set with benzene as the solvent.
- The absolute configuration of the *p*-bromobenzyl derivative of (*S*)-5 was unambiguously determined by X-ray crystallographic analysis, which lends further support for the proposed mechanism; see SI for crystallographic data.