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Oxy-Allyl Cation Catalysis: An Enantioselective Electrophilic Activation Mode

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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 bonding[1] or iminium catalysis[2] 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] cycloadditions[6] and Nazarov cyclizations[7] in a variety of natural 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.

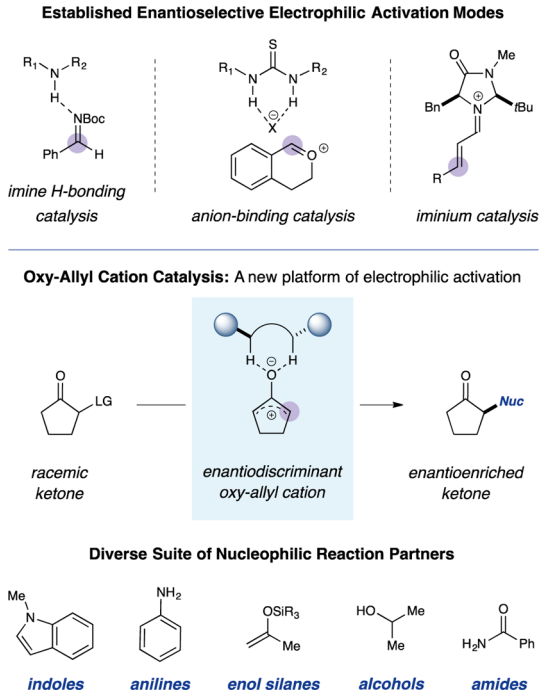

Figure 1. Accessing novel organocatalytic platforms of catalysis.

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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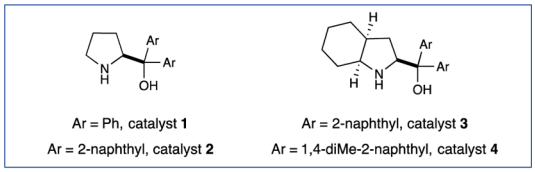
enolization/fragmentation to form enantiodiscriminant oxy-allyl cations. In this vein, we elected to evaluate a variety of amino alcohols given their capacity to function as carbonyl LUMO-lowering catalysts while at the same time being compatible with mildly basic conditions. Preliminary studies from 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 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.

Table 1. Initial Studies and Reaction Optimization



entry	catalyst	solvent	additive	yield[a]	ee[b]
1	**1**	C_6H_6	K_2HPO_4	58%	37%
2	**2**	C_6H_6	K_2HPO_4	50%	55%
3	**3**	C_6H_6	K_2HPO_4	54%	73%
4	**3**	1:1 C_6H_6/C_6F_6	K_2HPO_4	55%	79%
5	**3**	C_6F_6	K_2HPO_4	33%	81%
6[c]	**4**	C_6F_6	K_2HPO_4, H_2O[d]	**91%**	**92%**
7	none	C_6F_6	K_2HPO_4, H_2O[d]	0%	–
8	**4**	C_6F_6	H_2O	4%	–

[a]Yield determined by ^{1}H NMR. [b]Enantioselectivities determined by chiral HPLC. [c]Reaction time of 48 h. [d]1 equiv of H_2O.

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 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.

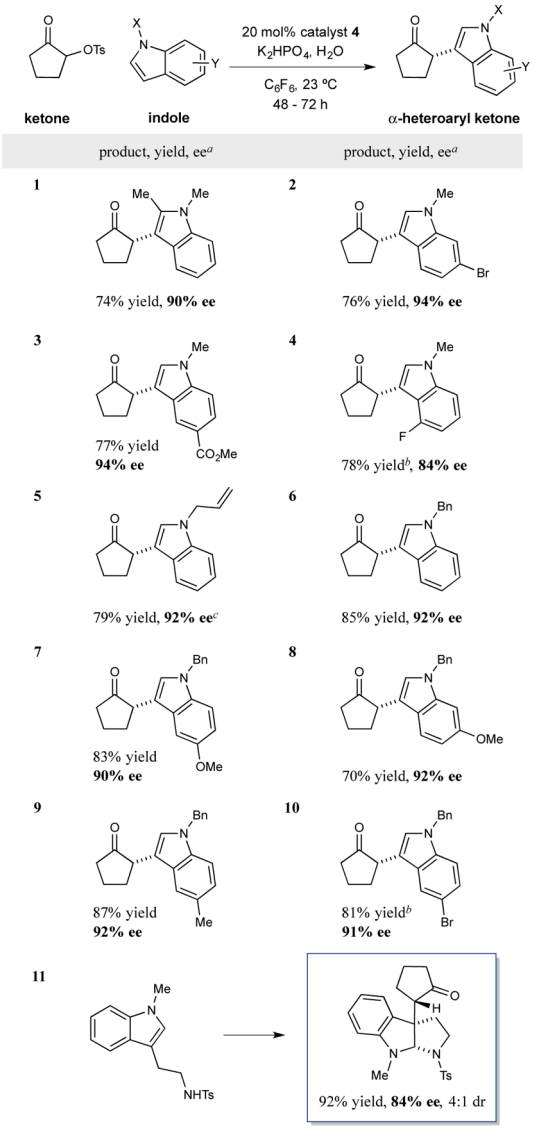


Figure 2. Scope of the indole nucleophile. [a] Isolated yields; see Supporting Information (SI) for experimental details. [b] Reaction time of 96 h. [c] Using 1,4-diOMe-2-naphthyloctahydroindolinol catalyst.

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

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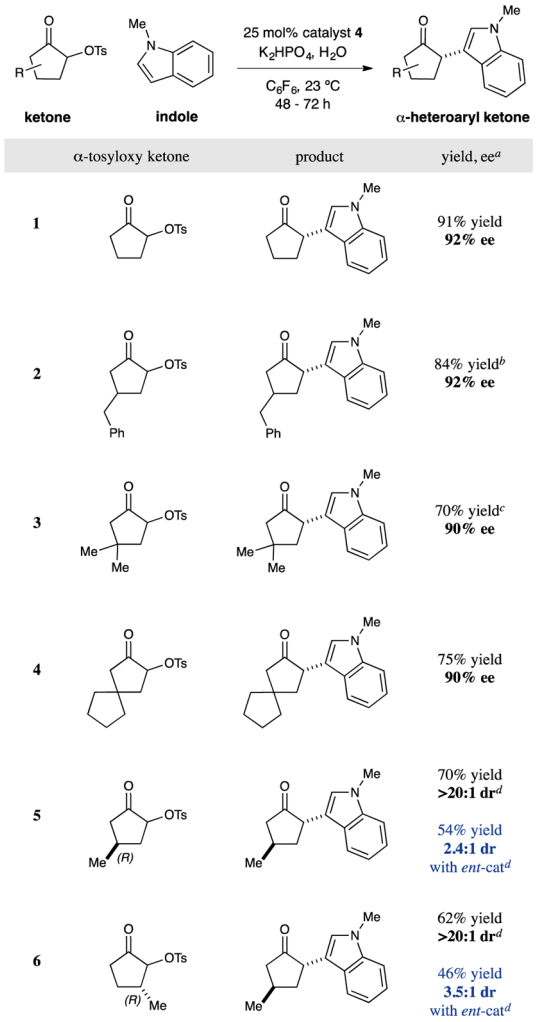

Figure 3. Scope of the ketone electrophile. [a] Isolated yields; see SI for experimental details. [b] 1:1 dr of product. [c] Reaction time of 96 h. [d] Using 1,4-diOMe-2-naphthyloctahydroindolinol catalyst.

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.

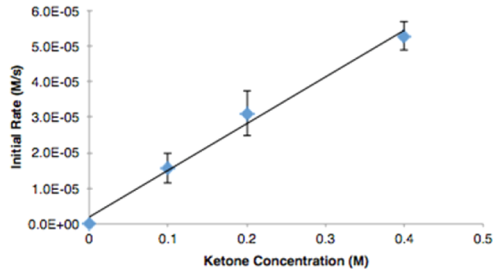

Figure 4. Plot of initial rate (M/s) versus [ketone] (M).

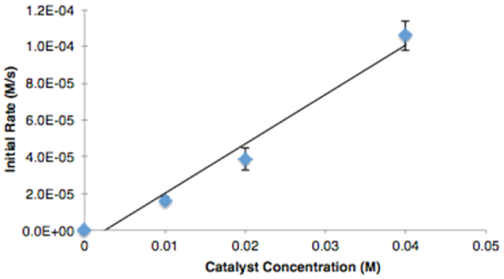

Figure 5. Plot of initial rate (M/s) versus [organocatalyst] (M).

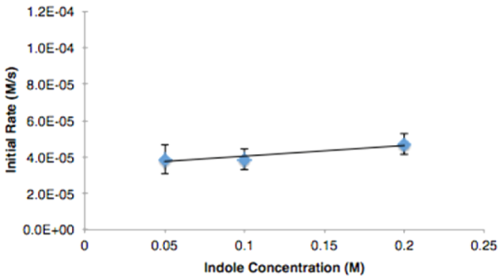

Figure 6. Plot of initial rate (M/s) versus [indole] (M).

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 minimization[15] 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

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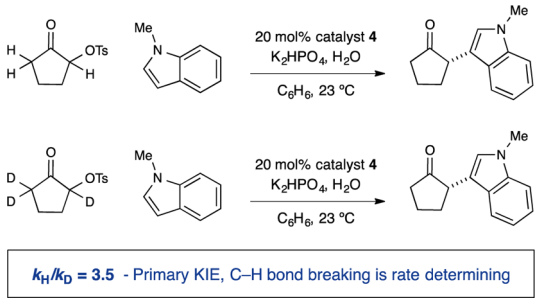
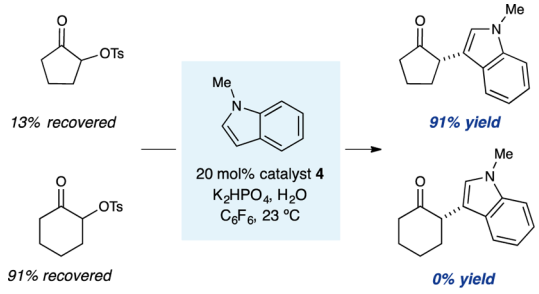
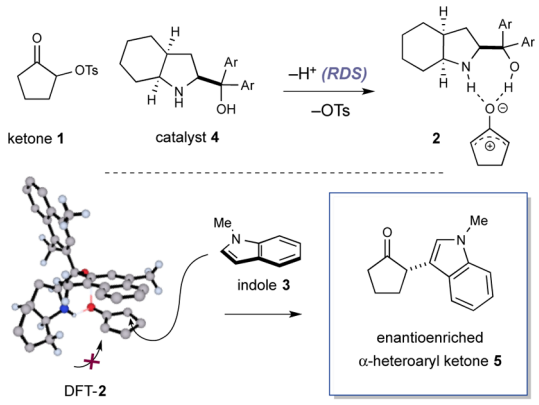
Scheme 1. Kinetic Isotope Effect Studies on Soft Enolization



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

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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(14) 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.

(15) DFT optimization used a B3LYP 6-31G basis set with benzene as the solvent.

(16) 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.

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