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Oxy-Allyl Cation Catalysis: An Enantioselective Electrophilic Activation Mode

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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

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Supporting Information

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Crystallographic data for C₂₁H₂₀BrNO₂ (CIF)

Crystallographic data for C₆₆H₇₄N₂O₁₀ (CIF)

Experimental procedures and spectral data (PDF)

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 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-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.

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.

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 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.

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 nucleophile **3** to the less sterically encumbered lower face should provide the enantioenriched α -heteroaryl ketone **5**.¹⁶

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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.

Established Enantioselective Electrophilic Activation Modes

Oxy-Allyl Cation Catalysis: A new platform of electrophilic activation

Diverse Suite of Nucleophilic Reaction Partners

Figure 1.
Accessing novel organocatalytic platforms of catalysis.

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.

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.

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).

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

Table 1

Initial Studies and Reaction Optimization

Ar = Ph, catalyst **1**

Ar = 2-naphthyl, catalyst **2**

Ar = 2-naphthyl, catalyst **3**

Ar = 1,4-diMe-2-naphthyl, catalyst **4**

20 mol% catalyst
additive

solvent, 23 °C, 24 h

ketone

indole

α-heteroaryl ketone

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 ^d	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	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.