Communication

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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. In this application, the enantioselectiveconversion of racemic α-tosyloxy ketonesto optically enrichedα-indolic carbonylshas been accomplished using a new amino alcohol catalystin the presence of electron-rich indole nucleophiles.Kinetic studiesreveal that the rate-determining stepin this S_N1 pathway is the catalyst-mediated α-tosyloxy ketone deprotonation step to form an enantiodiscriminant oxy-allyl cation prior to the stereodefiningnucleophilic addition event.The utility of this activation mode is further demonstrated by the rapid and enantioselective construction of natural product-like pyrroloindoline scaffolds.

Over the last 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 thatenables 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 enantioselectiveα-carbonyl functionaliz-ation might be accomplished using LUMO-loweringcatalysis, specifically founded upon a new oxy-allyl cation activation mode. As a critical design element, we recognized that the use of a LUMO-loweringpathway would allow for the implementation of nucleophilecoupling partnersin lieu of electrophiles,a strategy that should enablea dramaticincrease in the structure and scope of*α*-carbonyl products that would beaccessible 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 that might a)enable *α*-tosyloxy ketones to readily undergo soft catalyst enolization/fragmentationand 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.

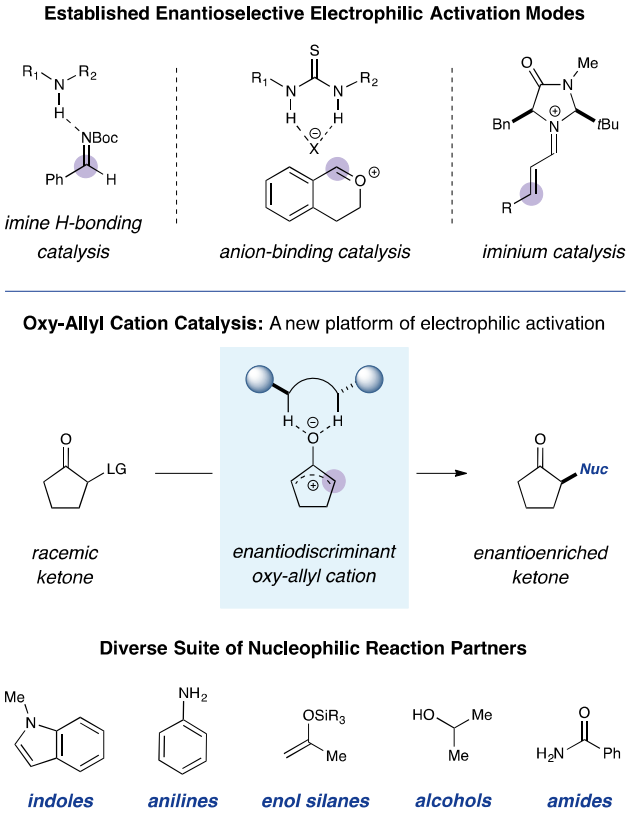
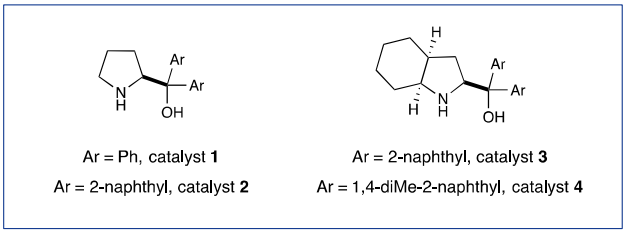
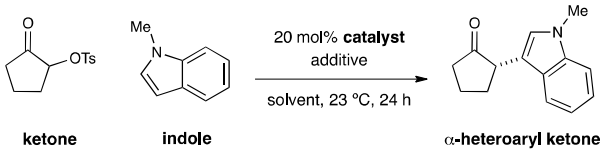


Figure 1. Accessing novel organocatalytic platforms of catalysis.

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-enolization/fragmentation to formenantiodiscriminantoxy-allyl cations.In this vein, we elected to evaluate a variety of amino alcoholsgiven 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*-methyl indolein 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,

Table 1. Initial studies and reaction optimization.





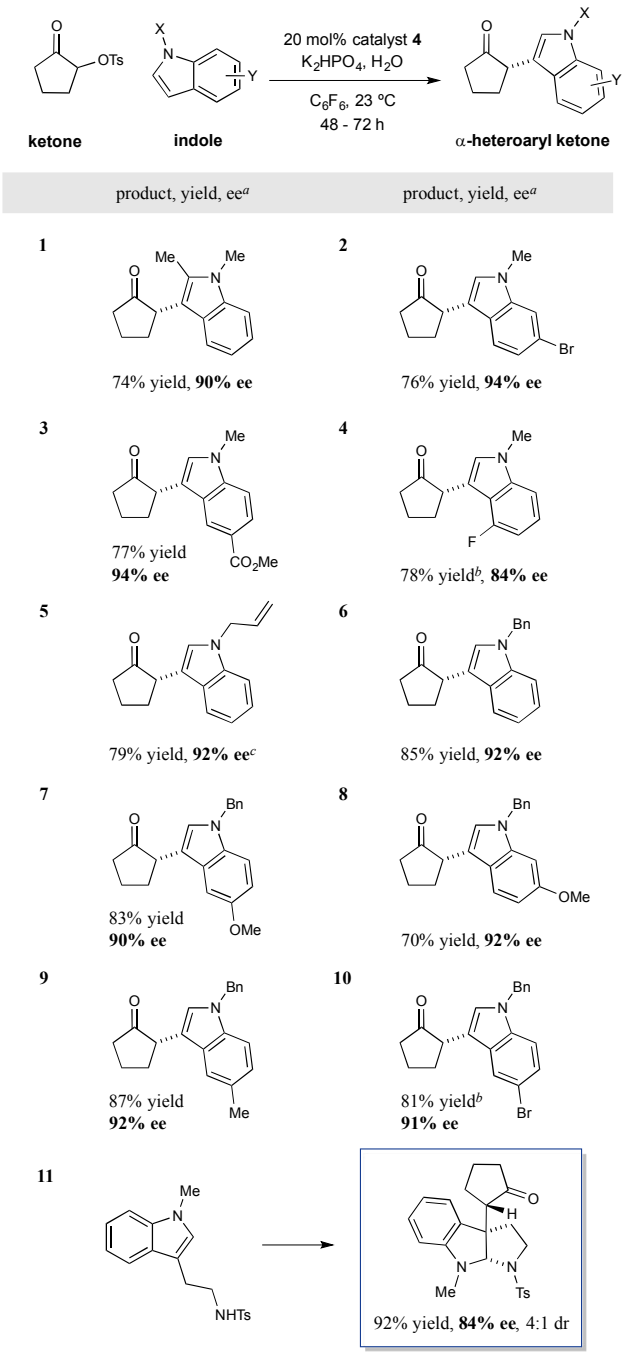
entry	catalyst	solvent	additive	yield[a]	ee[b]
1	**1**	C_6H_6	K_2HPO_4	58%	37%
2	**2**	C_6H_6	K_2HPO_4	50%	55%
3	**3**	C_6H_6	K_2HPO_4	54%	73%
4	**3**	1:1 C_6H_6: C_6F_6	K_2HPO_4	55%	79%
5	**3**	C_6F_6	K_2HPO_4	33%	81%
6[c]	**4**	C_6F_6	K_2HPO_4, H_2O[d]	**91%**	**92%**
7	None	C_6F_6	K_2HPO_4, H_2O[d]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

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, achange 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 catalystiscritical forthe reaction to proceed (entry 7), while the absence of K_2HPO_4 severely inhibits the overall efficiency (entry 8, 4% yield), indicating thesoft enolization step requires both 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, with the caveat that electron-deficient indoles require extended reaction times. Gratifyingly, substitution at the indole 2-position is tolerated (entry 1, 74% yield,90% ee) despite the attendant increase in nucleophile steric demand.[13] Electron-deficient *N*-methyl indoles can also be implemented and provide the desired indole addition adducts in high yield and enantioselectivity (entries 2–4, 76% – 78% yield, 84% – 94% ee). It should be noted that this asymmetric coupling operates equally well with allyl- and benzyl-protected indoles (entries 5 and 6, 79% yield, 92% ee; 85% yield, 92% ee respectively).[14] Moreover, a series of *N*-benzyl indoles of varying electronic description perform with almost uniform levels of efficiency and enantiocontrol, including electron-rich methoxy-, neutral methyl-, and electron-deficient bromo-substituted systems (entries 7–10, 70–87% yield, 90%–92% ee). Finally, we were able to extend this oxy-allyl cation activation mode to an iminium cascade sequence that

Figure 2. Scope of the indole nucleophile coupling partner.

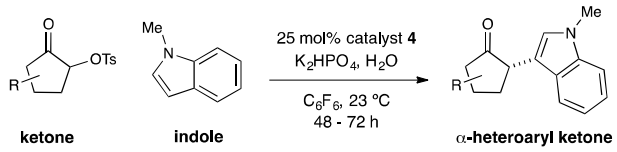


[a]Isolated yields,see SI for experimental details.[b]Reaction time of 96 h. [c]Using 1,4-diOMe-2-naphthyloctahydroindolinol catalyst.

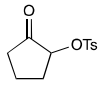
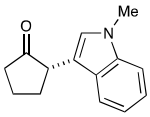
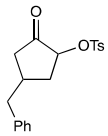
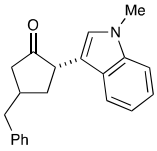
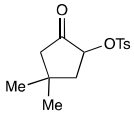
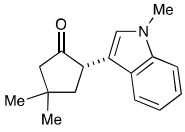
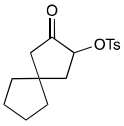
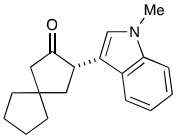
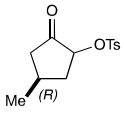
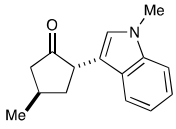
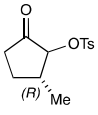
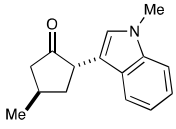
allows the rapid construction of a complex pyrroloindolines architecture, a motif commonly found among a variety of natural product classes.[15] As revealed in entry 11, the use of a tryptamine nucleophile with α-tosyloxy cyclopentanone in the presence of catalyst **4** leads to facile formation of the correspondingpyrroloindoline in 92% yield, 84% ee, and 4:1 dr.

We next evaluated the scope of α-tosyloxy ketones that are amenable to this new asymmetric oxy-allyl cation mechanism (Figure 3). The reaction is tolerant to substitution at the 4-position of the cyclopentyl substrate,including benzyl,dialkyl,and spirocyclic ring functionalities (entries 2–4, 70–84% yield, 90–92% ee). 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

Figure 3. Scope of the ketone electrophile coupling partner.



ketone indole α-heteroaryl ketone

	α-tosyloxy ketone	product	yield, ee[a]
1			91% yield **92% ee**
2			84% yield[b] **92% ee**
3			70% yield[c] **90% ee**
4			75% yield **90% ee**
5			70% yield **>20:1 dr**[d] 54% yield **2.4:1 dr** with *ent*-cat[d]
6			62% yield **>20:1 dr**[d] 46% yield **3.5:1 dr** with *ent*-cat[d]

[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.

6, 70% and 62% respectively). Not surprisingly, use of the mismatched (*R*)-catalyst lowers the diastereoselectivity (2.4:1 dr and 3.5:1 dr respectively), while regiocontrol remains high. As a useful mechanistic probe, the formation of the identical indoleaddition 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.[16]

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.[17] 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*-methyl indole was observed. These experiments are consistent with a pathway wherein the rate-determining step occurs prior to indole additionto the oxy-allyl cation. Moreover, as demonstrated in Scheme 1,

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

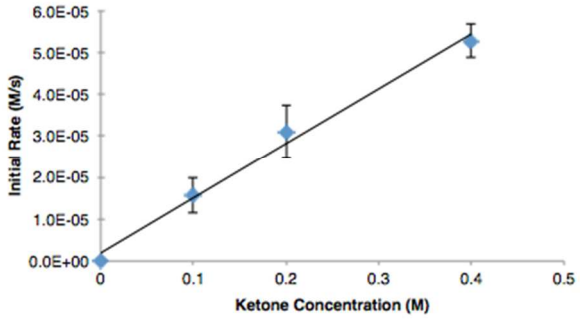


Figure 5. Plot of initial rate (M/s) versus [organocatalyst] (M).

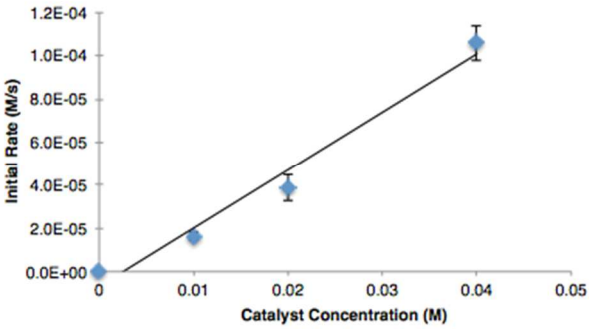
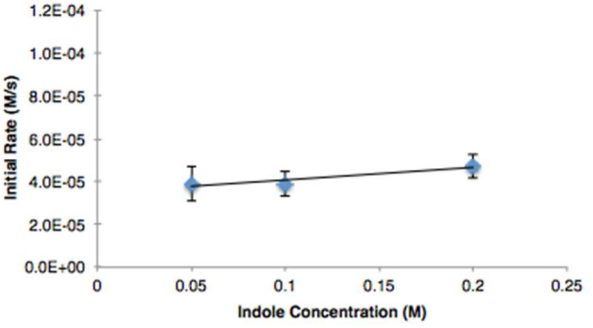
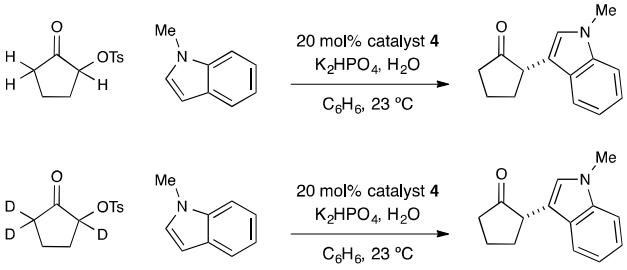


Figure 6. Plot of initial rate (M/s) versus [indole] (M).



Scheme 1. Kinetic isotope effect studies on soft enolization.

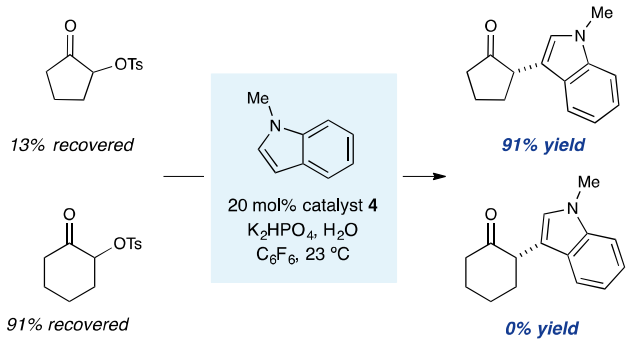


k_H/k_D = 3.5 - Primary KIE, C–H bond breaking is rate determining

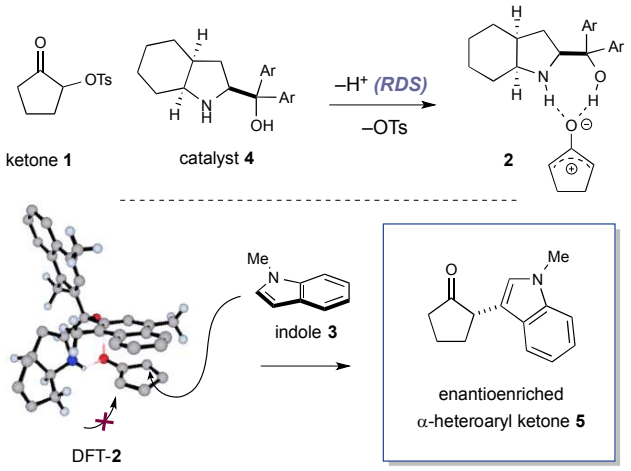
a primary KIE of 3.5 was found for *α*-tosyloxy ketones withproton vs. deuterium labels at the *α*-carbonyl positions. These studies provide insight that the deprotonation in the initialenolization step is rate-determining. At this stage we cannot state whether the fragmentation/ionization step happens inconcert 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

Scheme 2. Competition study conducted in common vessel.



Scheme 3. Proposed mechanism of the substitution reaction.



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 counterpartsdue 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 forα-tosyloxy cyclopentanone functionalizationwas observed, yielding 91% of thesmaller ring adduct and near quantitative recovery of the α-tosyloxy cyclohexanone (Scheme 2).[18]

Finally, a series of experiments were conducted using α-Br and α-OMs cyclopentanones to discriminate between two possible pathways forasymmetric 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 thatthe 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**toα-tosyloxy ketone **1**induces a rate-determining deprotonation step with subsequentor concomitant ionization to form the highly reactive cation**2**(Scheme 3). DFT minimization[19] 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 acation-π-interaction with one of the naphthalene rings on the catalyst framework. Subsequent addition of the indole **3**nucleophile to the less sterically encumbered lower face should provide the enantioenriched α-heteroaryl ketone **5**.[20]

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Supporting Information Available. Experimental procedures and spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The use of *N*-methylation or alcohol methylation analogues of catalyst **1** gave product formation with 0% and 16% ee respectively.

(11) A similar catalyst scaffold was employed in the following works: (a) Arceo, E.; Jurberg, I. D.; Alvarez-Fernandez, A.; Melchiorre, P. *Nat. Chem.* **2013**, *5*, 750. (b) Luo, R.; Weng, J.; Ai, H.; Lu, G.; Chan, A. S. C. *Adv. Synth. Catal.* **2009**, *351*, 2449.

(12) (a) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303. (b) Dougherty, D. A. *Science***1996**, *271*, 163.

(13) The use of 1,3-dimethyl indole result in [3+2] cycloaddition adducts (78% yield, 72% ee, 9:1 dr); major diastereomer as observed in reference 9c.

(14) The use of *N*-H indole in this reaction provided the corresponding product in 32% yield and 70% ee.

(15) For a review on the synthesis of pyrroloindolines and their reactivity, see: (a) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. For a review of pyrroloindoline-bearing natural products, see: (b) Steven, A.; Overman, L. E. *Angew. Chem. Int. Ed.* **2007**, *46*, 5488.

(16)Labeling studies employing catalyst **1** and $H_2{}^{18}O$ revealed no incorporation of ^{18}O into the product ketone, thus ruling out the possibility of enamine formation with subsequent tosylate ionization to furnish an amino-allyl cation.

(17) RPKA experiments were initially performed, but catalyst deactivation was observed (see SI for experimental results), thus necessitating the use of the method of initial rates. For a review on RPKA studies, see: Blackmond, D. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4302.

(18) At the current time, catalyst **4** is selective only for 5-membered ring ketones; work is ongoing to develop a suitable catalyst for ketones of other ring sizes.
(19) DFT optimization used a B3LYP 6-31G basis set with benzene as the solvent.
(20) 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.

Graphical Abstract