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Development of a generic activation mode: nucleophilic α-substitution of ketones *via* oxy-allyl cations†

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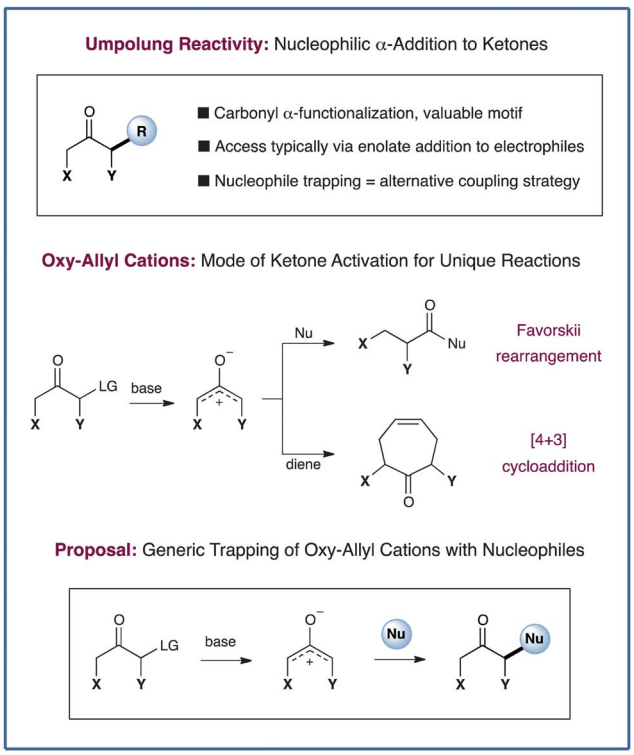
Oxy-allyl cations have been known as transient electrophilic species since they were first proposed as intermediates in the Favorskii rearrangement in 1894. Since that time, they also have been used as a mode of activation for [4 + 3] cycloadditions in a variety of natural product syntheses. In this manuscript, we describe a method for the interception of oxy-allyl cations with a diverse range of common nucleophiles, thereby demonstrating the value of this intermediate as a generic mode of activation. This simple, mild, room temperature protocol allows for the formation of a variety of high value carbon–carbon and carbon–heteroatom bonds that are readily incorporated within a series of cyclic and acyclic ketone systems. Initial efforts into the development of an enantioselective catalytic variant are also described.

Introduction

The carbonyl moiety remains among the most utilized and well-studied functional groups in all of organic chemistry. In particular, carbonyl α-functionalization *via* carbon–carbon or carbon–heteroatom bond formation has long been a mainstay transformation in chemical synthesis with broad application for the construction and coupling of complex organic architecture. From a traditional perspective, α-C=O functionalization typically involves the pregeneration or *in situ* formation of nucleophilic enols, enolates, or alkyl/silyl enol ethers, which readily combine with aryl, alkyl, heteroatom, or halogen-centered electrophiles.[1] Intriguingly, the capacity to effect the α-functionalization of carbonyls with nucleophilic coupling partners would provide an attractive pathway to generate a complementary series of α-carbonyl substituents and products. Such an umpolung strategy has been realized formally *via* the oxidative coupling of carbonyls with electron-rich olefins (*e.g.* silylketene acetals) wherein the formation of an enolate-derived radical cation allows for subsequent π-rich nucleophile addition at the α-carbonyl position.[2,3] This oxidative addition mechanism is limited, however, to π-nucleophiles that are capable of interacting through an open shell, radical pathway which generally excludes nitrogen- or oxygen-centered coupling partners. Recently, we sought to develop a new strategy for the direct α-functionalization of ketones that would couple enolates with nucleophiles that traditionally participate in closed shell, two-electron addition pathways (*e.g.* oxygen-, nitrogen-, carbon-, and halogen-type anions). Herein we describe a new transformation that is founded upon the generation and trapping of highly reactive oxy-allyl cations from a series of readily available α-tosyloxy ketones. Importantly, this mechanism allows for a diverse range of carbon- and heteroatom-based nucleophiles to participate in α-C=O bond formation under operationally simple conditions. While oxy-allyl cation intermediates have long been known for their utility in Favorskii reactions,[4] Nazarov cyclizations,[5] and [4 + 3] cycloadditions,[6] to our knowledge this is the first description of their application to bond formation with a broad series of common nucleophiles.[7,8]



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† Electronic supplementary information (ESI) available: Experimental procedures, structural proofs, and spectral data for all new compounds. See DOI: 10.1039/c3sc51266e

Design plan

Oxy-allyl cations have been known as transient electrophilic species since they were first proposed as intermediates in the Favorskii rearrangement in 1894.[9–11] In the classical Favorskii mechanism, the incipient oxy-allyl cation intermediate is intercepted by a variety of nucleophiles at the carbonyl *ipso* position to render an acylated nucleophile product after bond migration. Since these early reports, oxy-allyl cations have also been extensively studied in [4 + 3] cycloadditions to form seven-membered rings across a wide range of unique applications.[6] Additionally, oxy-allyl cations are known intermediates in interrupted Nazarov cyclizations and have been intercepted by π-rich nucleophiles in certain examples.[12] Remarkably, however, given the long history of these unique cations in organic synthesis, the direct coupling of α-halo ketones with nucleophilic partners at either of the α-carbonyl positions has not been reported as a general strategy for bond formation or fragment coupling.[7,8]

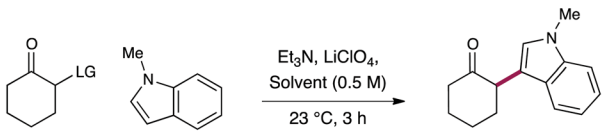
Under typical Favorskii rearrangement conditions, strong bases, such as hydroxide, induce oxy-allyl cation formation from an α-halo ketone and then subsequent nucleophilic addition to the resulting cyclopropyl ketone produces carboxylic acids and their derivatives.[13] With this in mind, we hypothesized that the development of mild, weakly basic conditions for the generation of oxy-allyl cations might allow the use of neutral heteroatoms or soft π-nucleophiles that should add directly to the non-traditional α-carbonyl cation position.[14] In practice, we proposed that ketone activation *via* coordination to a mild Lewis acid should allow weak, non-nucleophilic bases to induce enolate formation and thereafter allyl halide fragmentation to liberate the requisite oxy-allyl cation intermediate. As a central advantage to this "soft enolization" approach, we assumed that heteroatom and π-rich nucleophiles would be compatible with both the proposed mechanism and mild Lewis acids. It was encouraging to note that Lewis acid-mediated conditions have previously been utilized to promote oxy-allyl cation formation in the course of established [4 + 3] cycloadditions.[15] With this precedent in mind, we initiated studies to determine the feasibility and generality of the proposed α-functionalization of α-halo ketones with a diverse series of nucleophiles under soft enolization conditions.

Results and discussion

The proposed transformation was first examined using a variety of α-halo and α-pseudohalo cyclohexanones in the presence of 1-methylindole as the nucleophile, $LiClO_4$ as the Lewis acid, and Et_3N as the weak base. To our delight, a variety of substituted cyclohexanones yielded the desired α-ketone substituted indole in low to moderate yields (Table 1, entries 1–3, 20–42% yield) thereby demonstrating the feasibility of our proposal. We subsequently identified that solvent properties had a profound effect on the efficiency of this new reaction, with superior initial results being obtained with 2-tosyloxycyclohexanone as the source of oxy-allyl cation in the presence of 2,2,2-trifluoroethanol (TFE) (entries 3–7, 29–69% yield). To establish the role of $LiClO_4$ as a suitable Lewis acid for ketone activation, control experiments in the absence of this metal salt were performed. While the use of $LiClO_4$ was essential for product formation in THF (entries 6 and 8, 49% yield with $LiClO_4$, 0% yield without $LiClO_4$), remarkably, the use of trifluoroethanol as solvent gave the same product yield in the absence of Lewis acid (*cf.* entries 7 and 9, 69% yield). We assume that TFE is indeed functioning as a Lewis acid in both of these examples *via* hydrogen-bond activation of the ketone towards enol formation.[7c] Further investigation of substrate concentrations yielded optimal conditions to render the desired α-cyclohexanone indole product in 91% yield (entry 11).

With our preliminary studies complete, we next examined the scope of the ketone component in this new carbonyl α-functionalization protocol. We were delighted to find that a variety of α-tosyloxyketones functioned efficiently in this soft enolization/nucleophile trapping mechanism (Table 2). Importantly, the transformation is not limited to six-membered rings as both five-membered rings and macrocyclic ketones are competent substrates (Table 2, entries 2 and 3, 75% and 90% yield). Additionally, simple acyclic ketones are also highly effective in this coupling (entry 4, 72% yield). Evidence of the proposed delocalized allylic cation intermediate was gained with unsymmetrical ketones in that regioisomeric products were obtained (entries 6 and 8). From a synthetic utility perspective, the reaction exhibits sensitivity to steric constraints on the carbonyl-containing substrate, with nucleophilic substitution occurring preferentially at the less hindered position (entry 5, single regioisomer, 87% yield; entry 6, 2.5 : 1 rr, 82% yield). Finally, the mild conditions employed in this

Table 1 Nucleophilic α-ketone substitution: initial studies



ketone nucleophile α-heteroarylketone

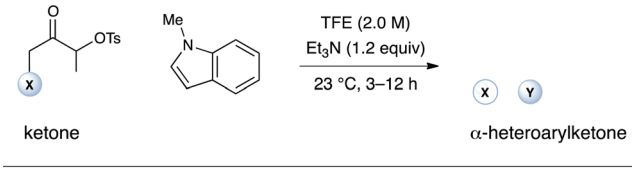
entry	LG	solvent	ketone (equiv)	Nu (equiv)	$LiClO_4$ (equiv)	% yield[a]
1	Cl	Ether	1	1.5	1	20
2	Br	Ether	1	1.5	1	42
3	OTs	Ether	1	1.5	1	41
4	OTs	MeCN	1	1.5	1	29
5	OTs	CH_2Cl_2	1	1.5	1	38
6	OTs	THF	1	1.5	1	49
7	OTs	TFE	1	1.5	1	69
8	OTs	THF	1	1.5	0	0
9	OTs	TFE	1	1.5	0	69
10[b]	OTs	TFE	1	1	0	78
11[c]	OTs	TFE	1.2	1	0	91

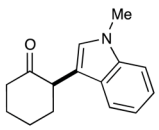
[a] NMR yield determined by ^1H NMR analysis of crude reaction *versus* nitrobenzene as an internal standard. [b] Reaction run at 2.0 M with 1.0 equiv. of Et_3N. [c] Reaction run at 2.0 M with 1.2 equiv. of Et_3N. THF = tetrahydrofuran, TFE = 2,2,2-trifluoroethanol.

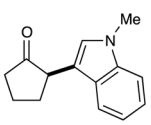
transformation allow for a diverse series of functional groups to be tolerated, a finding that is exemplified in both simple and complex structural settings (entries 7 and 8, 94% and 58% yield).

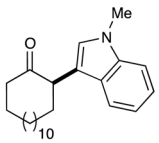
While the demonstrated ketone scope was found to be broad, we recognized that the general utility of this transformation would be dependent on the range of nucleophile types that could be successfully incorporated into this protocol. It was gratifying to find that our optimized reaction conditions were directly applicable to a range of aniline- and phenol-based nucleophiles including electron-rich and -deficient systems (Table 3, entries 1–4, 67–76% yield). The success of these substrates demonstrates the utility of this α-functionalization protocol given anilines and phenols are poor substrates for S_N2

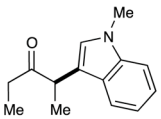
Table 2 Nucleophilic α-ketone functionalization: ketone scope[a,b]

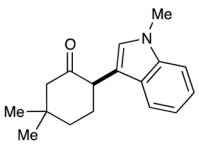


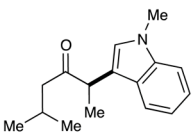
1

91% yield

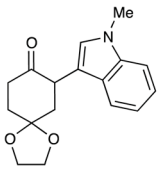
2

75% yield

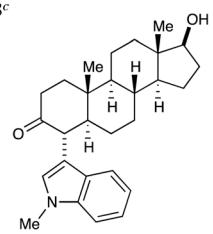
3

90% yield

4

72% yield

5

87% yield, single regioisomer

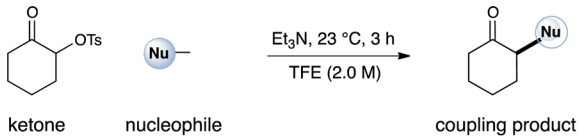
6

82% yield, 2.5:1 rr

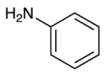
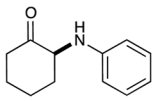
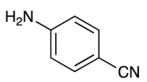
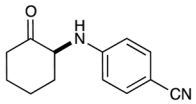
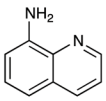
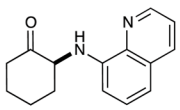
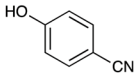
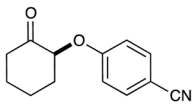
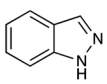
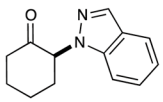
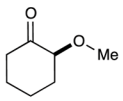
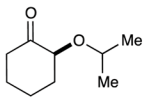
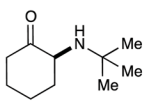
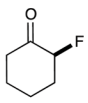
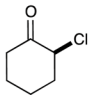
7

94% yield

8[c]

58% yield, 1.4:1 rr

[a] Reported as isolated yields on 1 mmol scale over the average of two experiments. [b] Regioisomeric ratio determined by ^{1}H NMR analysis. [c] Each regioisomer isolated as the single equatorial diastereomer.

Table 3 Ketone α-functionalization: nucleophile scope



entry	nucleophile	product	% yield[a]
1			71
2			76
3			67
4			73
5			62
6[b]			71
7[b]			82
8[b]			70
9[c]			62
10[c]			85

[a] Reported as isolated yields on 1 mmol scale over the average of two experiments. [b] Performed with 3 equiv. of nucleophile and 1 equiv. of Et_3N in HFIP as solvent. [c] Performed with 2 equiv. of nucleophile, 0.25 equiv. of TMSX as catalyst, 1 equiv. of Et_3N, and HFIP as solvent.

reactions. Remarkably, weakly nucleophilic species such as aromatic heteroatoms are also competent coupling partners (entry 5, 62% yield).

We next examined the use of alkyl alcohols and amines as nucleophiles and found that lower yields were observed due to competitive formation of 2-trifluoroethoxycyclohexanone as a reaction byproduct. This problem was readily overcome, however, by employing the less nucleophilic solvent 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). Using this alternative reaction medium, alkyl alcohols and amines functioned well as nucleophiles to provide the corresponding α-functionalized ketone adducts in good yield (entries 6–8, 70–82% yield).

During our investigations into the Ruppert–Prakash reagent ($TMSCF_3$) as a nucleophilic source of CF_3, we made a serendipitous discovery that the inclusion of CsF as an activating reagent resulted in formation of 2-fluorocyclohexanone in 44% yield (ESI Fig. 1†). Remarkably, when $TMSCF_3$ was withheld from the protocol, no conversion to 2-fluorocyclohexanone was observed. Based on this observation, we hypothesized that $TMSCF_3$ is facilitating fluoride group transfer from an oxygen-coordinated hexavalent silicate intermediate (see ESI Fig. 1†). Upon further exploration, it was discovered that TMSF could also function as the silicon source and was only necessary in catalytic quantities (Table 3, entry 9, 62% yield). We were gratified to find that these parameters were also directly applicable to formation of the corresponding α-chlorocyclohexanone product (Table 3, entry 10, 85% yield).

Due to the requirement for ketone activation using Lewis acids or hydrogen-bonding solvents, we hypothesized that the use of an enantiopure alcohol-based catalyst might enable an asymmetric variant of this new ketone α-functionalization protocol. Indeed, in preliminary studies we have found that prolinol based 1,2-hydroxyamines effectively catalyze the conversion of 2-tosyloxycyclopentanone to its corresponding 2-indole substituted adduct in good yield and moderate enantioselectivity (Fig. 1, 77% yield, 55% ee). The necessity of an insoluble inorganic base (K_2HPO_4) for catalytic turnover indicates that the prolinol catalyst is functioning as the required base in the reaction and enantioinduction is likely a result of association of the prolinol-derived ammonium ion to the oxy-allyl cation in the nucleophilic addition transition state.[16] Ongoing efforts towards the optimization of this asymmetric catalytic variant are underway and will be reported in due course from our laboratory.

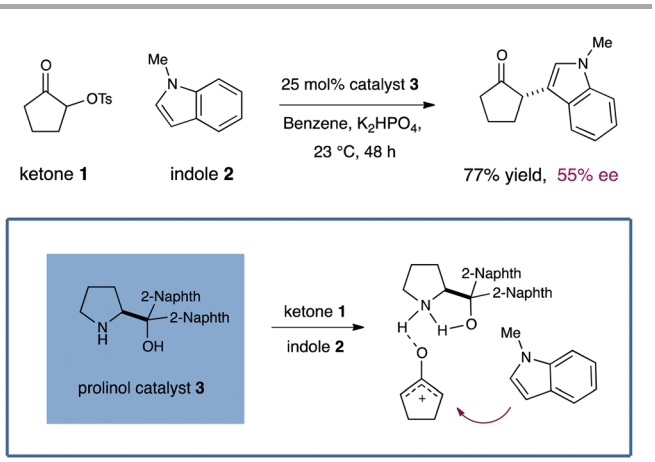


Fig. 1 Enantioselective catalytic additions: initial studies: reported as isolated yield on 1 mmol scale over the average of two experiments. Enantiomeric excess determined by chiral HPLC analysis.

Conclusions

We have detailed the development of a new substitution reaction for the addition of a broad range of high-value nucleophiles to α-tosyloxyketones. This process provides a general method for umpolung reactivity at the α-position of ketones and represents the first generic application of oxy-allyl cationic intermediates to simple nucleophilic substitution. Initial efforts towards an enantioselective variant of this transformation have provided encouraging results and further studies to define an optimal catalyst are currently underway.

Acknowledgements

Financial support was provided by NIHGMS (R01 GM078201-06) and kind gifts from Merck, Amgen, AbbVie Research Laboratories and Bristol-Myers Squibb.

Notes and references

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