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(3 + 3) Cycloaddition of Oxyallyl Cations with Nitrones: Diastereoselective Access to 1,2-Oxazinanes

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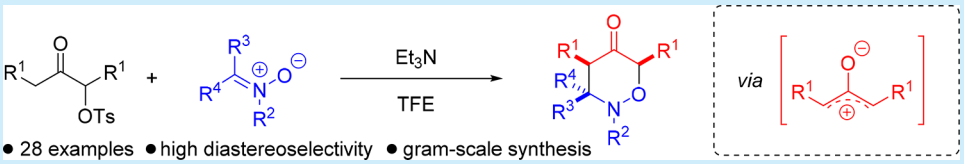
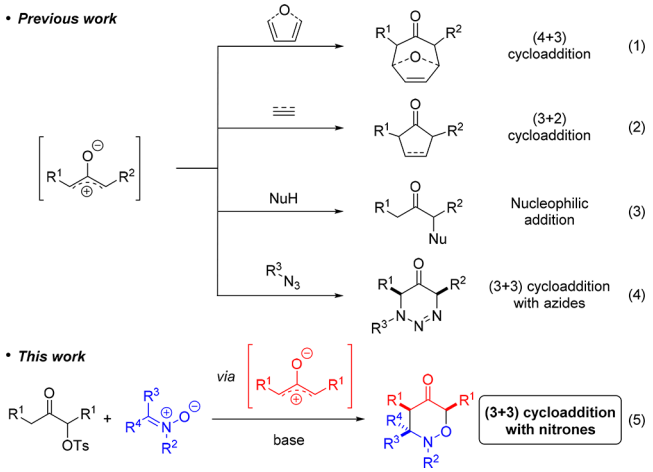
Supporting Information



ABSTRACT: Oxyallyl cations are prepared in situ from readily available α-tosyloxy ketones and act as transient electrophilic partners in (3 + 3) cycloaddition with nitrones. Under mild conditions, this method provides a chemoselective and diastereoselective route to polysubstituted 1,2-oxazinanes. A stepwise process is proposed to rationalize the diastereoselectivity of this transformation.

Oxyallyl cations are highly reactive electrophilic 2π systems that have been successfully engaged as 1,3-dipoles in numerous cycloaddition reactions. Since the pioneering work of Fort,[1] the (4 + 3) cycloaddition between oxyallyl cations and dienes or furans has become a dependable tool for the preparation of seven-membered rings [Scheme 1, eq 1].[2,3] This approach follows a symmetry-allowed [4π+2π] process and has been envisioned for numerous syntheses of biologically active natural products.[4] Various five-membered ring carbocycles can also be accessed via a stepwise (3 + 2) cycloaddition with alkenes or alkynes [Scheme 1, eq 2].[5−7] Recently, Chi[8] and MacMillan[9] reported an elegant application of oxyallyl cation chemistry to nucleophilic α-substitution of ketones before to develop an asymmetric version of this reaction [Scheme 1, eq 3].[10]

Scheme 1. Oxyallyl Cation Reactivity



While the (4 + 2) cycloaddition remains a method of choice for the preparation of six-membered N-heterocycles,[11] the 1,3-dipolar (3 + 3) cycloaddition between a stable nitrogen-based dipole and an all-carbon 1,3-dipole is currently growing as a reliable complementary alternative.[12−16] We envisioned that electrophilic oxyallyl cations could act as a 3C synthon in such transformations to generate polysubstituted six-membered heterocycles.

Only a few studies have been reported for the (3 + 3) cycloaddition of oxyallyl cations. Schultz[17] and West[18] demonstrated that the oxyallyl cation intermediate of a Nazarov cyclization could be trapped by an azide to furnish triazene compounds [Scheme 1, eq 4]. Inspired by recent findings by Wu and others on the reactivity of aza-oxyallyl cations,[19] this communication discloses a (3 + 3) cycloaddition between in-situ-generated oxyallyl cations and stable nitrones. Under mild conditions, polysubstituted 1,2-oxazinanes (tetrahydro-1,2-oxazines) are prepared with high diastereocontrol [Scheme 1, eq 5]. These six-membered heterocycles are found in numerous biologically active compounds[20] and their endocyclic N−O bond make them attractive synthetic intermediates.[21] To the best of our knowledge, this symmetry-allowed [4π+2π] process represents the first (3 + 3) cycloaddition between an oxyallyl cation intermediate and a nitrone.

To conduct our optimization study, we selected α-tosyloxy ketone **1a** and *N*-methyl-(*Z*)-aldonitrone **2a** as reference substrates. Gratifyingly, the use of a hydrogen-bond-donor (HBD) solvent such as 2,2,2-trifluoroethanol (2M)[3b] under mild conditions (Et_3N, room temperature (rt), 2.5 h) led to a single diastereomer of oxazinane **3aa** in good yield (Table 1, entry 1). The structure and the relative configuration of the three newly

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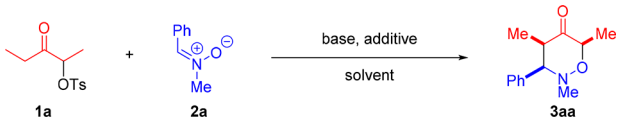
Table 1. Optimization of the Reaction Conditions[a,b]



entry	base	solvent	yield (%)[b]
1	**Et_3N**	**TFE**	**83, 77**[g]
2	Et_3N	HFIP	62
3[d]	Et_3N	DCM	traces
4[e]	Et_3N	THF	19
5[e]		TFE	nr[c]
6	4-DMAP	TFE	31
7	imidazole	TFE	20
8	*i*-Pr_2NEt	TFE	66
9	Cs_2CO_3	TFE	traces
10	Et_3N	TFE (0.1 M)	42
11[f]	Et_3N	TFE	59

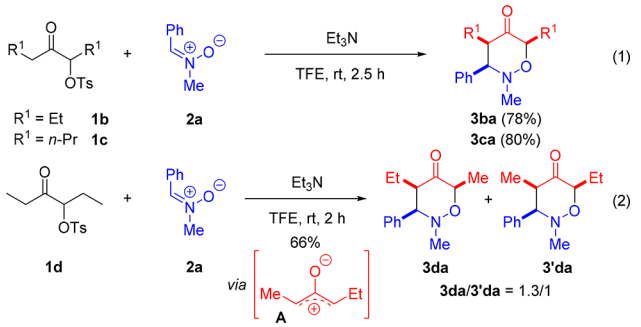
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), base (0.625 mmol) in solvent (0.25 mL) for 2.5 h at room temperature. [b]Isolated yields. [c]nr = no reaction. [d]$LiClO_4$ (1.5 equiv), solvent (0.75 mL). [e]Reaction time = 24 h. [f]**2a** (1 equiv). [g]**1a** (6 mmol), **2a** (12 mmol), Et_3N (7.5 mmol) in TFE (3 mL) for 2.5 h at room temperature.

formed stereocenters were confirmed by single-crystal X-ray analysis of the related compound **3af** bearing a *m*-OMe phenyl group (see Scheme 3, presented later in this work). The three substituents of this heterocycle are located on the same face of the ring. HFIP gave slightly deteriorated yield (Table 1, entry 2), and our investigations revealed the essential role of a strong HBD solvent as only a small amount of oxazinanone **3aa** was formed in the presence of $LiClO_4$ as a Lewis acid (1.5 equiv) and triethylamine in DCM or THF (Table 1, entries 3 and 4). While triethylamine appeared to be needed for the (3 + 3) cycloaddition to occur (Table 1, entry 5), a rapid survey of bases (4-DMAP, imidazole, *i*-Pr_2NEt and Cs_2CO_3) failed to improve the efficiency of the reaction (Table 1, entries 6−9). Finally, a 2:1 nitrone/ketone ratio along with a high concentration of the reaction mixture (2M) were necessary to isolate **3aa** in a good yield (Table 1, entries 10 and 11). To evaluate the robustness of our process, we conducted a gram-scale preparation of **3aa** in a similar good yield (77%), starting from 6 mmol of ketone.

With these optimized conditions in hand, we turned our attention to the scope of different ketones with *N*-methyl nitrone **2a**. Acyclic α-OTs ketones **1b** (R^1 = Et) and **1c** (R^1 = *n*-Pr) bearing aliphatic substituents were successfully converted into the corresponding oxazinanones **3ba** (78%) and **3ca** (80%) with complete diastereoselectivity [Scheme 2, eq 1]. The conversion of α-tosyloxy ketone **1d** afforded a 1.3/1 mixture of isomers **3da** and **3′da** and supported the formation of the putative unsymmetrical oxyallyl cation **A** as a transient intermediate [Scheme 2, eq 2].

The high diastereoselectivity of this (3 + 3) cycloaddition motivated us to investigate the reactivity of *N*-methyl (*Z*)-nitrones derived from various aromatic aldehydes in the presence of ketone **1a**. The electronic properties of the phenyl ring seems to have very little influence on the outcome of the transformation as aldonitrones **2b−2e** bearing either an electron-donating (Me, OMe) or an electron-withdrawing (F, Br) group in the *para* position were converted smoothly to the corresponding stereodefined oxazinanones **3ab−3ae** (73%−87%). Steric hindrance did not play a crucial role either as heterocycles

Scheme 2. Scope of α-OTs Ketone[a]



[a]Evidence for the formation of an oxyallyl cation.

3af−3aj bearing various substituents in the *meta* or *ortho* position can also be accessed from the corresponding nitrones in excellent yields (70%−85%). The presence of an allyl group did not affect the outcome of the transformation and nitrone **2k** yielded isomer **3ak** as the sole product of the transformation (70%). We next tackled a more challenging chemoselectivity issue by investigating the reactivity of heteroaromatic nitrones **2l** and **2m** bearing a furan and a free indole group, respectively. We were delighted to observe the exclusive formation of oxazinanes **3al** and **3am**, with no traces of $(4 + 3)^2$ or $(3 + 2)^5$ cycloaddition adduct. Styryl and alkyl groups were also well-tolerated and oxazines **3an−3ap** were prepared in high yields and diastereoselectivity. Interestingly, the in situ formation of the *N*-benzyl nitrone **2q** derived from formaldehyde yielded disubstituted heterocycle **3aq** bearing a methylene moiety. This oxazinanone was isolated in excellent yield (93%) as a mixture of diasteroisomers (diastereomeric ratio (dr) = 80:20). Finally, oxazinanes **3ar** and **3as** in which the nitrogen atom is protected by a benzyl group and a *para*-methoxybenzyl group, respectively, were obtained from their nitrone precursors with complete diastereoselectivity (see Scheme 3).

Because of their peculiar geometry, spiro compounds have recently emerged as valuable scaffolds for drug discovery.[22] We recognized that our strategy could provide a straightforward access to these structures and symmetrical ketonitrones **2t** and **2u** derived from cyclopentanone and cyclohexanone, respectively, delivered spiro oxazinanes **3at** (81%) and **3au** (89%) as single *cis*-diastereomers.

To shed light on the mechanism of this cycloaddition, we next turned our attention to the reactivity of cyclic (*E*)-nitrones. Gratifyingly, isoquinoline *N*-oxide **2v** underwent a stereocontrolled transformation leading to tricyclic oxazinane **3av**, in which the aromatic substituent is now located on the opposite side of the two methyl groups. The relative configuration of the three newly created stereocenters was ascertained by single-crystal X-ray analysis. Cycloadditions involving quinoline *N*-oxide **2w** and pyrroline tetrahydroisoquinoline *N*-oxide **2x** proceeded smoothly to yield the expected polycyclic heterocycles **3aw** and **3ax** (dr = 92:8), respectively (see Scheme 4).

The stereoselectivity of this cycloaddition prompted us to examine the behavior of the unsymmetrical ketonitrone **2y** arising from cyclohexenone. Two isomeric mixtures [(*E*)/(*Z*) = 13:1 and (*E*)/(*Z*) = 1:3] were subjected to the usual conditions, along with oxyallyl cation precursor **1a**. A rapid conversion generated the expected oxazinanes bearing a quaternary spiro center as a mixture of two diastereomers 3^E**ay** and 3^Z**ay**. In both cases, an erosion of the diastereoselectivity was observed and

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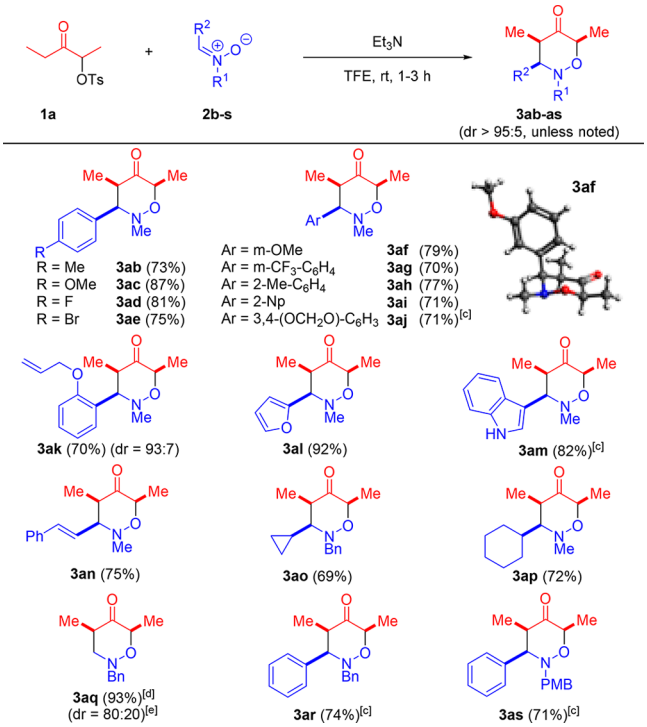
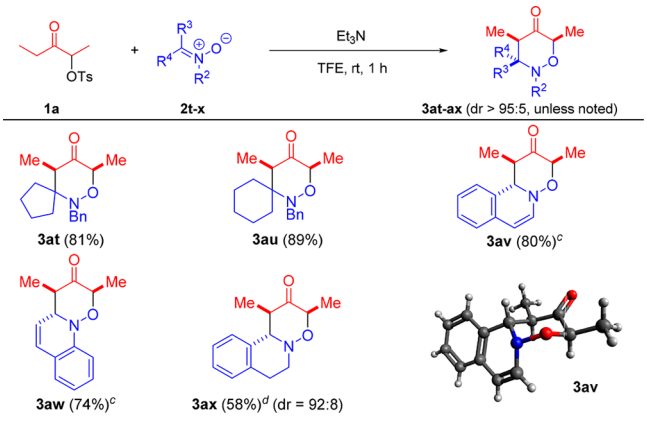
Scheme 3. Scope of Aldonitrones[a,b]



[a]Reaction conditions: ketone (0.5 mmol), nitrone (1 mmol), Et_3N (0.625 mmol) in TFE (0.25 mL) for 1−3 h at room temperature. The consumption of **1a** was monitored by TLC. [b]Isolated yields. [c]TFE (0.5 mL). [d]Nitrone **2q** was prepared in situ. [e]Isolated as a *cis*/*trans* mixture (cis/trans = 80:20) based on ^{1}H NMR analysis.

Scheme 4. Preparation of Spiro and Polycyclic Oxazinanes[a,b]

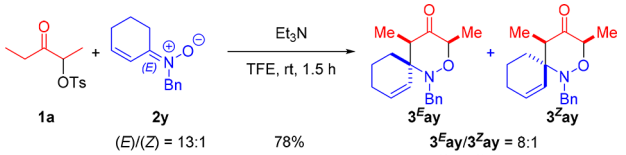


[a]Reaction conditions: ketone (0.5 mmol), nitrone (1 mmol), Et_3N (0.625 mmol) in TFE (0.25 mL) for 1 h at room temperature. The consumption of **1** was monitored by TLC. [b]Isolated yields. [c]TFE (0.5 mL).

3^E**ay**/3^Z**ay** mixtures were formed in 8:1 and 1:1.5 ratios, respectively (see Scheme 5).

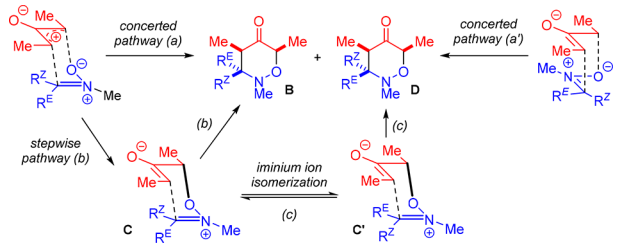
A mechanistic rationale was proposed to account for the diastereoselective formation of **B**. When aldonitrones participates in the transformation, this [4π+2π] cycloaddition often leads to a single isomer and could occur via a concerted pathway (*a*) involving an extended (exo) transition state or via a stepwise pathway (*b*) where the nucleophilic oxygen of the nitrone first attacks the electrophilic W-shaped[2a] oxyallyl cation to afford intermediate **C**. A rapid intramolecular Mannich reaction could

Scheme 5. Reactivity of an Unsymmetrical Ketonitrone



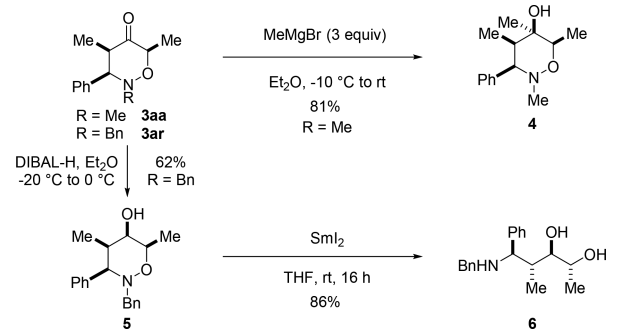
then yield the observed diastereomer **B**. However, the observation of isomer **D** (in the case of **3ak**, **3aq**, **3ax**, and **3ay**) could be better explained by a stepwise pathway (*b*) where intermediate **C** could undergo rapid iminium ion isomerization to **C′** before the ring-closing step. A competitive concerted pathway (a′) involving a compact (*endo*) transition state cannot be ruled out at this stage (see Scheme 6).

Scheme 6. Proposed Mechanism



The X-ray structure of **3f** (recall Scheme 3) prompted us to investigate further derivatization of these oxazinanones. Because of the bulky phenyl ring, one would expect a nucleophile following a Bürgi-Dunitz trajectory to attack the less-hindered face of the molecule exclusively. Gratifyingly, the treatment of oxazinanone **3aa** with MeMgBr (3 equiv, Et_2O, −10 °C to rt) afforded a single diastereomer of oxazinane **4** bearing four contiguous stereocenters, including one quaternary center. Ring-opening of heterocycle **3ar** by N−O bond cleavage could provide valuable aminoalcohols. After diastereoselective reduction of oxazinanone **3ar** (DIBAL-H, Et_2O, −20 to 0 °C), alcohol **5** (62%) underwent SmI_2-induced reductive N−O bond cleavage to afford the linear amine-diol **6** (86%) as a single diastereomer (see Scheme 7).

Scheme 7. Derivatization of Oxazinanones



To conclude, we have developed a (3 + 3) cycloaddition involving an oxyallyl cation intermediate. In the presence of a readily available nitrone as the nucleophilic partner, this transformation generates stereodefined oxazinanones after creation of two new σ bonds and three stereocenters. This strategy provides straightforward access to valuable N−O

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heterocycles bearing a vast array of functional groups as well as spiro and polycyclic compounds. An erosion of the diastereoselectivity observed with unsymmetrical ketonitrones led us to propose a stepwise pathway for this unprecedented cycloaddition. Further studies are ongoing in our laboratory to gain a better understanding of the mechanism and capitalize on the vast synthetic potential of oxyallyl cations in new cycloaddition reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00617.

Experimental procedures and NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1817917 and 1817918 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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