Communications

Nitrone Rearrangement

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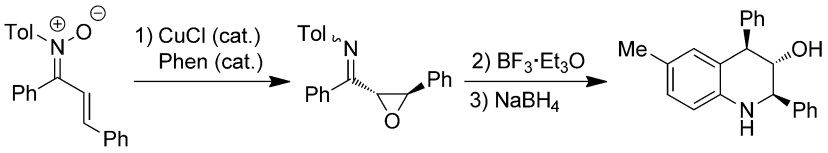
Copper-Catalyzed Rearrangement of *N*-Aryl Nitrones into Epoxyketimines



25 examples, 82–99%

77% from nitrone (one diastereomer)

Please pass the oxygen: A new method for the preparation of *trans*-α,β-epoxyketimines has been achieved through a copper-catalyzed rearrangement of (*E*)-α,β-unsaturated nitrones. The scope and tolerance of the method is evaluated and the synthetic utility of the products is demonstrated. The new transformation provides facile access to an unusual, densely functionalized intermediate that can be exploited for further synthetic application.

Nitrone Rearrangement

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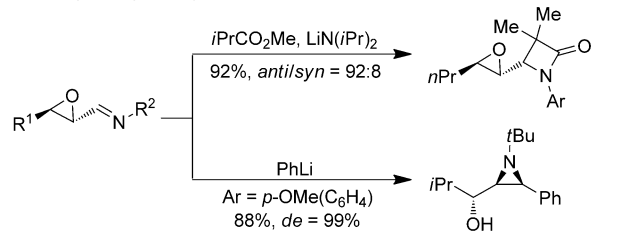
Copper-Catalyzed Rearrangement of *N*-Aryl Nitrones into Epoxyketimines**

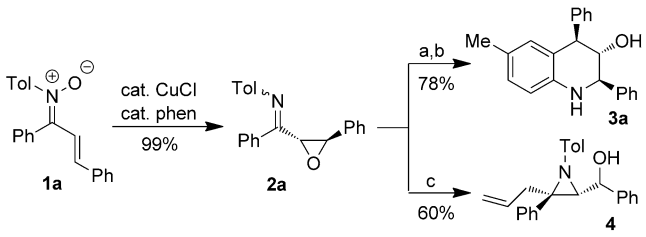
*Dong-Liang Mo and Laura L. Anderson**

α,β-Epoxyaldimines are densely functionalized intermediates that combine the reactivity of an epoxide with the electrophilicity of an aldimine within a three-carbon fragment. Accordingly, these compounds have been shown to be valuable precursors for the diastereoselective preparation of epoxy-substituted β-lactams, α-hydroxyaziridines, amino alcohols, oxazolidinones, and phytosphingosine lipid backbones (Scheme 1).[1] α,β-Epoxyaldimines are usually prepared by condensation of the corresponding epoxyaldehyde with an amine.[1,2] Unfortunately, corresponding methods for the preparation of α,β-epoxyketimines are sparse and few alternative methods have been reported.[3,4] Development of a simple and general method for the preparation of α,β-epoxyketimines would facilitate the exploration of the analogous reactivity of these highly substituted and densely functionalized intermediates.

Reactivity of α,β-epoxyaldimines [1d,e]



This work-preparation and functionalization of α,β-epoxyketimines

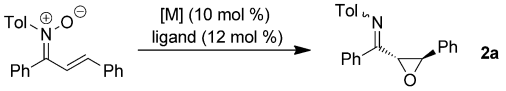


Scheme 1. Preparation and functionalization of α,β-epoxyketimines. a) $BF_3{\cdot}Et_2O$; b) $NaBH_4$; c) allyltributylstannane, $BF_3{\cdot}Et_2O$.

Recently, we reported the preparation of vinyl nitrones by the copper-mediated cross coupling of fluorenone oxime and vinyl boronic acids.[5] While testing the scope of this transformation, we observed that α,β-unsaturated *N*-aryl nitrones can also be prepared by the copper-mediated cross coupling of aryl boronic acids and α,β-unsaturated oximes.[6] Further exploration of the reactivity of these α,β-unsaturated aryl nitrones led to our discovery of a facile copper-catalyzed method for their conversion into α,β-epoxyketimines (Scheme 1). Herein, we describe the optimization of this copper-catalyzed intramolecular transfer of oxygen from a nitrone to an alkene, examine the scope of the method, and illustrate the synthetic utility of α,β-epoxyketimines, which are now easily accessible in two steps from oximes.

The conversion of arylnitrone **1a** into epoxyketimine **2a** was initially observed when **1a** was treated with a substoichiometic amount of $[(phen)Pd(OAc)_2]$ (phen = 1,10-phenanthroline). This palladium-catalyzed transformation was sensitive to the choice of ancillary ligand, as well as to the palladium(II) counterion (Table 1, entries 1–3). A more efficient conversion of **1a** to **2a** was observed when a mixture of CuCl

Table 1: Optimization of the O-atom transfer reaction.



only trans observed
E/*Z* ca. 2:1

Entry	[M]	Ligand	Solvent	Yield [%][a]
1	$Pd(OAc)_2$	phen	C_6H_6	59[b]
2	$Pd(OAc)_2$	bipy	C_6H_6	13[b]
3	$Pd(OBz)_2$	phen	C_6H_6	32[b]
4	CuCl	phen	C_6H_6	71
5	CuCl	phen	THF	90
6	CuCl	phen	DCE	n.r.
7	CuCl	phen	DMSO	76
8	CuCl	phen	MeCN	99
9	CuI	phen	MeCN	89
10	$Cu(OAc)_2$	phen	MeCN	97
11	Cu(OTf)·Tol	phen	MeCN	80
12	$Cu(OTf)_2$	phen	MeCN	75
13	CuCl	none	MeCN	58
14	CuCl	bipy	MeCN	98
15	CuCl	Py	MeCN	70

[a] Yield determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [b] $[LPdX_2]$ complex prepared separately. Ac = acetyl, bipy = bipyridine, Bz = benzoyl, DCE = 1,2-dichloroethane, DMSO = dimethylsulfoxide, phen = 1,10-phenanthroline, Py = pyridine, n.r. = no reaction, Tf = trifluoromethanesulfonyl, Tol = tolyl.

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and 1,10-phenanthroline was used as a catalyst (Table 1, entry 4). The yield of this transformation was dependent upon the choice of reaction medium, copper salt, and N-donor ligand. Benzene, THF, and dimethylsulfoxide (DMSO) were tolerated as solvents, but the most efficient transformation was observed in acetonitrile (Table 1, entries 4–8). Several copper(I) and copper(II) salts were observed to catalyze the oxygen transfer in the presence of phenanthroline, but CuCl was shown to be the optimal (Table 1 entries 8–12). The copper catalyst required the presence of a N-donor ligand for an efficient process and 1,10-phenanthroline was shown to provide the highest yield (Table 1, entries 8 and 13–15). The conversion of **1a** into **2a** can be achieved at 25–80 °C under the conditions shown in Table 1, entry 8; however, 80 °C was chosen as the preferred reaction temperature, as lower temperatures required longer reaction times. Compound **2a** was consistently isolated as a mixture of imine isomers, but the diastereoselectivity of the oxygen transfer reaction was excellent and only the *trans* isomer of **2a** was observed.

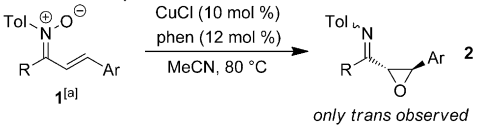
Once optimal conditions for the conversion of aryl nitrone **1a** into α,β-epoxyketimine **2a** were determined, the scope of the transformation was investigated. The electronic and steric preferences of the oxygen-transfer reaction were initially tested by varying the styrenyl group of chalcone-derived nitrones (Table 2, entries 1–7). As shown in Table 2, both electron-rich and electron-poor styrenyl functional groups, with *ortho*, *meta*, and *para* substitution patterns, were tolerated by the reaction conditions and provided the desired α,β-epoxyketimines in excellent yields.[7] Both electron-rich and electron-poor aryl groups were also screened for the imine substituent, and were observed to undergo equally efficient transformations (Table 2, entries 8–11). Alkyl-substituted α,β-unsaturated nitrones such as **1m** were unreactive under the optimized reaction conditions, but this stark change in reactivity does not appear to be due to the fact that these substrates favor the opposite imine isomer to the chalcone-derived nitrones.[8] A control experiment showed that a 1:1 *E*/*Z* mixture of **1a** gave the desired product in high yield. Finally, dibenzylidene acetone substrates were shown to be tolerated by the copper-catalyzed transformation, but unsymmetrical examples did not exhibit an electronic preference for oxygen transfer (Table 2, entries 13–14).

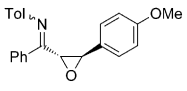
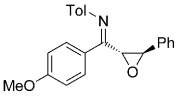
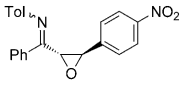
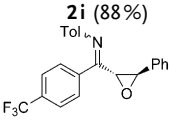
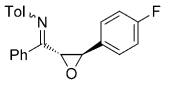
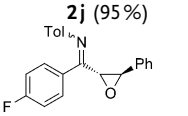
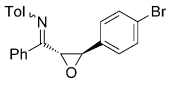
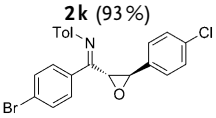
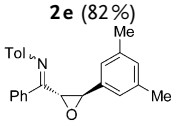
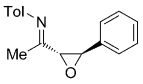
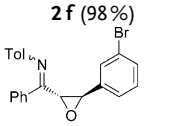
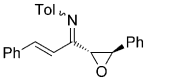
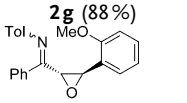
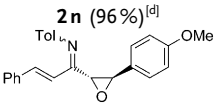
In addition to the carbon backbone of the nitrones, the *N*-aryl substituent was varied to determine its effect on the copper-catalyzed preparation of α,β-epoxyketimines from α,β-unsaturated arylnitrones. Both electron-rich and electron-poor *N*-aryl groups with either *meta* or *para* substituents provided the desired products in high yield. We were pleased to observe that aryl groups with bromide, vinyl, and ester functional groups were compatible with the reaction conditions, as these substituents further enhanced the potential synthetic utility of these densely functionalized products (Table 3, entries 4, 7, and 10).

A proposed mechanism for the rearrangement of α,β-unsaturated arylnitrones into α,β-epoxyketimines is illustrated in Scheme 2. An initial copper-catalyzed attack of the nitrone at the styrenyl group could precipitate a subsequent N–O bond cleavage to form **2**. This mechanism is similar to a pathway proposed for gold-catalyzed intramolecular oxygen transfer from benzaldehyde-derived nitrones to *o*-alkynyl functionalites for the preparation of enones.[9,10] Although the intermediacy of an isoxazoline was not observed in the copper-catalyzed transformations described above, spectral evidence for this intermediate was observed in the product mixtures of the less efficient palladium-catalyzed transformations discussed in Table 1.[11] Ring openings of 2-isoxazolines of this type are unknown; however, related 4-isoxazoline rearrangements to form α,β-aziridinyl ketones have been previously reported.[12]

With a variety of α,β-epoxyketimines in hand, we decided to investigate the synthetic utility of these compounds for initial comparison to their α,β-epoxyaldimine analogues. As shown in Scheme 3, **2a** was shown to readily undergo a variety of regioselective reductions. Treatment of **2a** with $LiAlH_4$ proceeded under steric control to give 1,3-aminoalcohol **5** as a single diastereomer. In contrast, treatment of **2a** with diisobutylaluminium hydride (DIBAL-H) proceeded under electronic control to give 1,2-aminoalcohol **6** as a 4:1 mixture

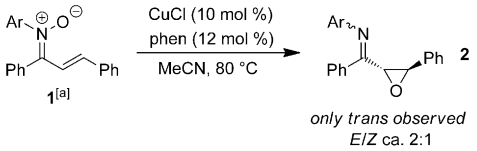
Table 2: Tolerance of epoxide formation to nitrone substitution.

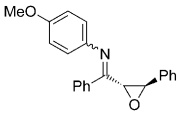
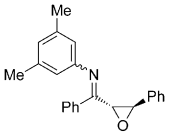
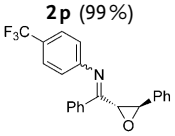
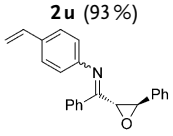
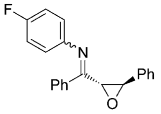
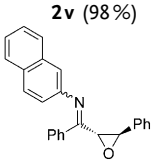
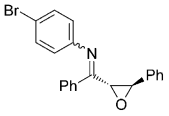
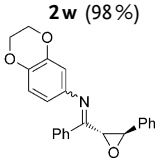
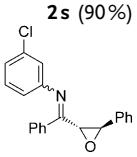
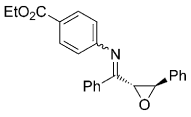


Entry	Product[b]	Entry	Product[b]
1	 **2b** (97%)	8	 **2i** (88%)
2	 **2c** (99%)	9	 **2j** (95%)
3	 **2d** (99%)	10	 **2k** (93%)
4	 **2e** (82%)	11	 **2l** (92%)
5	 **2f** (98%)	12	 **2m** (0%)[c]
6	 **2g** (88%)	13	 **2n** (96%)[d]
7	 **2h** (83%)	14	 **2o** (90%, 1:1)[d]

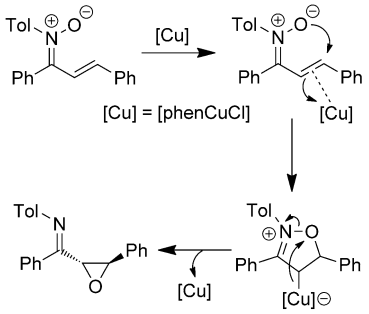
[a] *E* nitrones were subjected to the reaction conditions. [b] Data in parentheses are yields of isolated products. [c] **1m** was used as a 3.5:1 mixture of *E*/*Z* nitrone isomers. [d] $Cu(OAc)_2$ was used.

Table 3: Tolerance of epoxide formation to substitution of the *N*-aryl group.



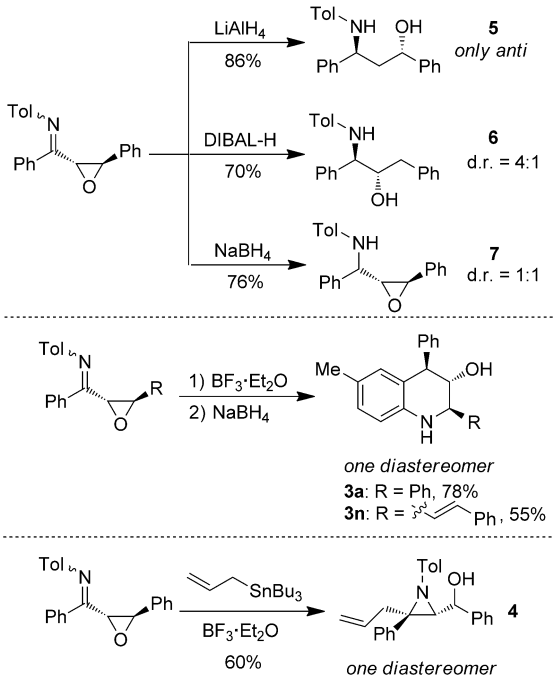
Entry	Product[b]	Entry	Product[b]
1	 **2p** (99%)	6	 **2u** (93%)
2	 **2q** (95%)	7	 **2v** (98%)
3	 **2r** (91%)	8	 **2w** (98%)
4	 **2s** (90%)	9	 **2x** (94%)
5	 **2t** (85%)	10	 **2y** (93%)

[a] *E* nitrones were subjected to the reaction conditions. [b] Data in parentheses are yields of isolated products.



Scheme 2. Proposed mechanism for nitrone rearrangement.

of diastereomers. Reduction of **2a** with $NaBH_4$ chemoselectively targeted the imine and left the epoxide intact to give α-aminoepoxide **7** as a 1:1 mixture of diastereomers. Surprisingly, sequential treatment of **2a** and **2n** with $BF_3{\cdot}Et_2O$ and $NaBH_4$ provided tetrahydroquinolines **3a** and **3n** by a Friedel–Crafts-type epoxide opening followed by imine reduction. This transformation provides an interesting alternative



Scheme 3. Synthetic utility of α,β-epoxyketimines. DIBAL-H = diisobutylaluminium hydride.

to the Povarov reaction or intramolecular amination for the preparation of highly substituted derivatives of these important heterocycles.[13] Exposure of **2a** to an allylic nucleophile in the presence of $BF_3{\cdot}Et_2O$ gave trisubstituted aziridine **4** as a single diastereomer, in analogy to the use of α,β-epoxyaldimines for the preparation of disubstituted aziridines illustrated in Scheme 1.[1d] The use of α,β-epoxyketimines for the preparation of *N*-aryl trisubstituted aziridines is appealing owing to the challenges involved with the preparation of these compounds and the fact that alternative methods to N-atom transfer and carbene insertion are desirable.[14,15]

In summary, we have shown that α,β-epoxyketimines can be synthesized in high yield and excellent diastereoselectivity from α,β-unsaturated nitrones through a copper-catalyzed oxygen-atom transfer reaction. When this transformation is used in combination with a copper-mediated boronic acid coupling developed by our group for the preparation of α,β-unsaturated nitrones, α,β-epoxyketimines can be easily accessed in two steps from simple oximes. The new method provides a facile entry into the study of the reactivity of α,β-epoxyketimines. Towards this goal, we have demonstrated that α,β-epoxyketimines can be used to access tetrahydroquinolines and *N*-aryl trisubstituted aziridines with high diastereoselectivity. Ongoing work in our laboratory is focused on developing a better understanding of the mechanism of the oxygen transfer process and further investigating the reactivity of α,β-epoxyketimines.

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Keywords: aryl nitrones · epoxidation · epoxyketimines · oxygen transfer · rearrangements

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[6] See the Supporting Information for experimental details regarding the preparation of α,β-unsaturated *N*-aryl nitrones from the corresponding oximes.

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[10] Although the proposed mechanism proceeds through a formally disfavored 5-*endo*-trig cyclization, we believe this pathway is still possible, as an alternative 5-*exo*-trig pathway is not available; also, the oxygen nucleophile will not be able to attack through the preferred Burgi–Duntz angle, which will increase the likelihood of a violation of Balwin's rules.

[11] The product mixture in Table 1, entry 3 contained 8% of an isoxazoline intermediate.

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