

## Cycloadditions

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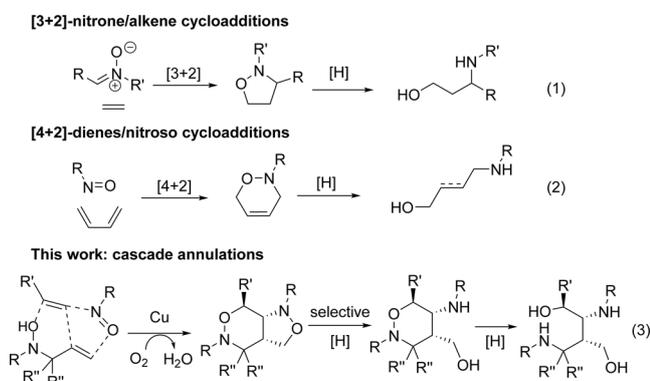
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## Copper-Catalyzed Three-Component Annulations of Alkenes, Nitrosoarenes, and N-Hydroxyallylaminates to Form Fused Oxazinane/Isoxazolidine Heterocycles

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**Abstract:** One-pot cascade annulations among nitrosoarenes, alkenes, and N-hydroxyallylaminates have been achieved with CuCl/O<sub>2</sub> catalysts, forming fused oxazinane/isoxazolidine heterocycles with excellent diastereoselectivity (*d.r.* > 20:1). To enhance the synthetic utility, we developed a successive cleavage of the two N–O bonds of the resulting heterocycles. A mechanism involving dipolar [3+2] cycloadditions of nitron intermediates with their tethered alkenes is postulated for formation of these heterocycles.

Heterocycles containing N–O bonds, such as derivatives of isoxazolidines and 1,2-oxazinanes, are important structural cores in many naturally occurring compounds.<sup>[1]</sup> Among numerous methods developed toward the synthesis of these two N–O-containing rings,<sup>[2]</sup> the dipolar [3+2] cycloadditions of nitrones with alkenes,<sup>[3,4]</sup> and [4+2] cycloadditions of dienes with nitroso groups represent the two most prominent systems.<sup>[5,6]</sup> Importantly, their stereo- and enantioselective versions have been satisfactorily achieved with suitable catalysts; a facile cleavage of the N–O bonds<sup>[7]</sup> of the resulting products affords useful 1,3- and 1,4-aminoalcohols efficiently.



Many bioactive molecules comprise not only one N–O ring, but also amino and alcohol functionalities; selected examples **I–VI** are depicted in Figure 1.<sup>[8]</sup> Stereoselective

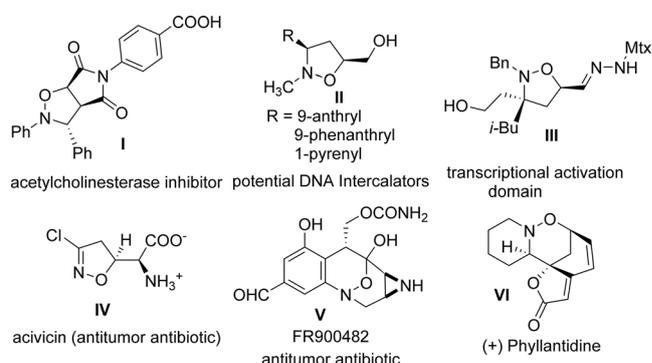


Figure 1. Representative bioactive molecules.

synthesis of these bioactive molecules is challenging because several stereogenic centers are present in the structures. We envisage that one-pot stereoselective construction of a bicyclic ring bearing two N–O bonds is a viable route. This work describes Cu-catalyzed oxidative annulations among nitrosoarenes, alkenes, and N-hydroxyallylaminates to deliver bicyclic 1,2-oxazinane/isoxazolidine fused rings (Equation (3)). To enhance the utility, a successive cleavage of two N–O bonds is developed to provide two different products, highly functionalized isoxazolidines and acyclic aminoalcohols [Eq. (3)].

The unique aspect of this work utilizes nitrosoarenes as diradical precursors to develop the first three-component annulations.<sup>[9a]</sup> In nitroso–ene reactions, nitroxyl diradicals seem to be viable intermediates according to theoretical studies.<sup>[9b–c]</sup>

Table 1 optimizes catalytic annulations among N-hydroxyallylaminates **1a** (1.0 equiv),<sup>[10]</sup> styrene **2a** (2.0 equiv), and nitrosobenzene **3a** (1–2 equiv) over various catalysts. In a typical operation, nitrosobenzene **3a** was slowly added to a mixture of **1a/2a**/catalyst in hot toluene (60 °C) over a period of 2 h to furnish the reactions. With nitrosobenzene at two-fold excess, two bicyclic heterocycles **4a** and **5a** were isolated in 35% and 36% yields, respectively; here, the undesired **6** arose from a metal-free reaction of nitrosobenzene **3a** with styrene **2a**.<sup>[9a]</sup> A low loading of nitrosobenzene (1 equiv) greatly improved the yield of bicyclic species **4a** to 68%. Among other Cu catalysts (entries 3–7), only CuCl<sub>2</sub> and CuBr gave the desired heterocycle **4a** in satisfactory yields (58–59%, entries 4 and 7). Under N<sub>2</sub>, compound **4a** was also produced with 35% yield; this outcome will be rationalized in the mechanistic discussion. Notably, in the absence of a catalyst, the reaction still afforded heterocycles **4a** and **5a** in 7–8% yields, together with unreacted **1a** in a 63%

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**Table 1:** Three-component annulation over various catalysts.

Entry	3 a (n equiv)	Catalyst (10 mol %)	t [h]	Yields [%] <sup>[b]</sup>			
				4 a	5 a	6	7
1	2	CuCl	6	35	35	12	10
2	1	CuCl	8	68	—	—	6
3	1	IPrCuCl	12	30	26	7	8
4	1	CuBr	9	58	12	6	18
5	1	CuI	14	33	34	4	15
6	1	(CuOTf) <sub>2</sub> L	14	24	6	4	14
7	1	CuCl <sub>2</sub>	7	59	5	—	4
8	1	CuCl <sup>[c]</sup>	12	35	4	12	14
9	1	— <sup>[d]</sup>	40	7	8	4	16

IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. L = benzene.

[a] [1 a] = 0.19 M. [b] Product yields are reported after purification from a silica column. [c] N<sub>2</sub> at 1 atm. [d] 1 a was recovered in 63%.

recovery. This observation is helpful to the reaction mechanism (entry 9). The molecular structures of two bicyclic heterocycles **4a** and **5a** are inferred from X-ray diffractions of their relatives **4f** and **5d**;<sup>[11]</sup> only one diastereomeric product was formed for each product (d.r. > 20:1).

We assessed the scope of the reactions using various styrenes and nitrosoarenes under the same conditions as depicted in Table 2. In all of the cases, resulting heterocycles **4a–4k** were produced as single diastereomeric products (d.r. > 20:1). In some entries, other heterocycles **5c–5d** and **5i** were produced in minor portions. Species **1** bear a dimethyl substituent to avoid ArN(OH)–CH to become a nitrene

**Table 2:** Reactions of various styrene derivative.

Entry	4 a	5 a	Yields [%]
(1) <b>4a</b> (X = H, 68%, 8h) <sup>[b]</sup>	(4) <b>4d</b> (X = F, 67%, 7h), <b>5d</b> (11%, X-ray)	(7) <b>4g</b> (66%, 6h)	
(2) <b>4b</b> (X = Me, 66%, 8h)	(5) <b>4e</b> (X = Cl, 68%, 7h)		
(3) <b>4c</b> (X = OMe, 51%, 10h), <b>5c</b> (12%)	(6) <b>4f</b> (X = NO <sub>2</sub> , 73%, 6h, X-ray)		
(8) <b>4h</b> (61%, 7h)	(9) <b>4i</b> (41%, 10h), <b>5i</b> (21%)	(10) <b>4j</b> (X = Me, 60%, 10h), <b>4k</b> (X = Cl, 52%, 9h)	

[a] [1 a] = 0.19 M. [b] Product yields are reported after purification from a silica column.

under this aerobic oxidation. These annulations were compatible not only with electron-rich styrene derivatives **2b–2c** (X = Me, OMe), but also with their electron-deficient analogues **2d–2f** (X = F, Cl, and NO<sub>2</sub>), affording compounds **4a–4f** in 51–73% yields. Electron-deficient styrenes seem to be more efficient than their electron-rich analogues (entries 2–6). For 3- and 2-thienylethenes **2g** and **2h**, their corresponding products were obtained with 61–66% yields (entries 7–8). The reaction is applicable to 2-pyridinylethene **2i** to afford desired **4i** in 41% yield together with side product **5i** in 21% yield (entry 9). Other nitrosobenzenes **3b–3c** (X = Me, Cl) were also suitable for these annulations to afford compounds **4j** and **4k** in 60% and 52% yields, respectively (entries 10–11).

The scope of these reactions is significantly expanded with variable N-hydroxyallylamines bearing an electron-withdrawing group (Table 3). We did not isolate any competitive

**Table 3:** Reactions of various N-hydroxyallylamines.

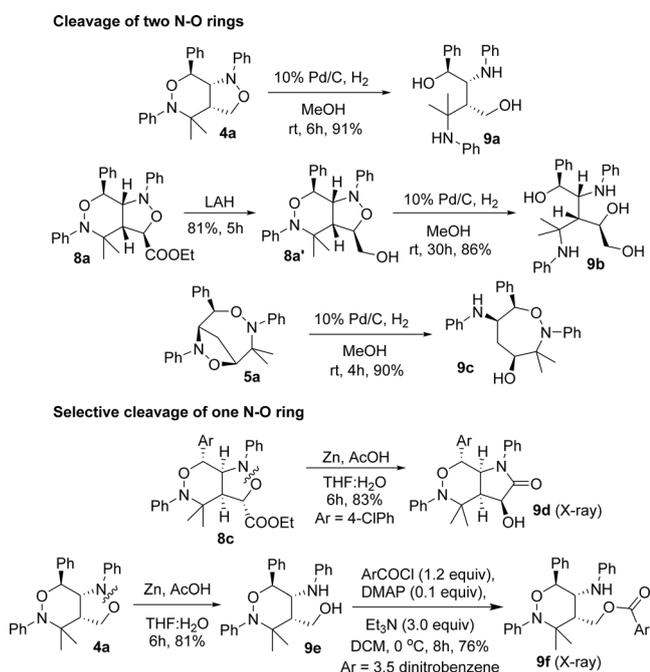
Entry	Structure	Yields [%]
(1) <b>8a</b>	X = H	63%, 9h <sup>[b]</sup>
(2) <b>8b</b>	X = Me	67%, 8h
(3) <b>8c</b>	X = Cl	61%, 9h
(4) <b>8d</b>	X = F	54%, 8h
(5) <b>8e</b>	X = S	64%, 10h
(6) <b>8f</b>	X = S	69%, 8h, X-ray
(7) <b>8g</b>	X = S	58%, 10h
(8) <b>8h</b>	R = Bn	65%, 10h
(9) <b>8i</b>	R = <sup>t</sup> Bu	62%, 10h
(10) <b>8j</b>	R = Ph	31%, 11h
(11) <b>8k</b>	R = Me	65%, 12h
(12) <b>8l</b>	R = <sup>n</sup> C <sub>6</sub> H <sub>13</sub>	48%, 9h
(13) <b>8m</b>	X = Me	54%, 10h
(14) <b>8n</b>	X = Cl	59%, 10h

[a] [1 d] = 0.13 M. [b] Product yields are reported after purification from a silica column.

heterocycle such as species **5**. Nitrosoarenes were used with 1.5 equivimolar proportion because byproducts **6** were produced with minor proportions (yields < 20%). Resulting heterocycles **8a–8n** were obtained as single diastereomers (d.r. > 20:1), despite there being four stereogenic centers. The structures were elucidated by X-ray diffraction of one representative **8f**.<sup>[11]</sup> In the reaction of unsaturated ester **1d** with styrene derivatives (X = Me (**2b**), Cl (**2c**), and F (**2d**))

and nitrosobenzene, their corresponding products were produced with reasonable yields (54–67%, entries 1–4). The same reactions with 2- and 3-thienylethenes **2e–2f** afforded desired compounds **8e** and **8f** in 64% and 69% yields, respectively (entries 5–6). For a cyclopentyl-bridged N-hydroxyallylamine **1g**, its corresponding annulation yielded species **8g** in 58% yield (entry 7). Other N-hydroxyaminoallyl esters **1h** and **1i** were also applicable substrates to afford desired **8h** and **8i** (R = benzyl and *tert*-butyl) in 62–65% yields (entries 8–9). We also prepared unsaturated ketones **1j–1l** to deliver our targets **8j–8l** (R = Ph, Me, *n*-hexyl) in 31–65% yields (entries 10–12). Other nitrosobenzenes **3b** and **3c** were applicable to these annulations to produce compounds **8m–8n** in 54–59% yields (entries 13–14).

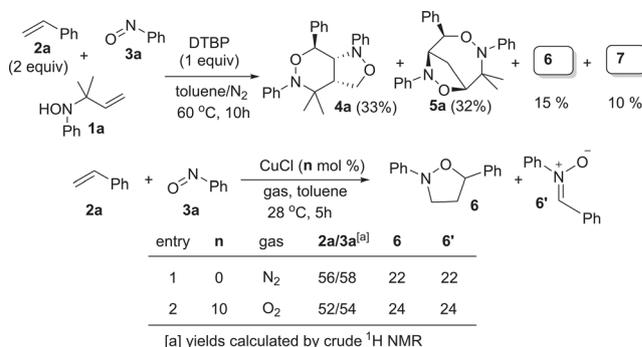
The utility of annulation products **4** and **8** is highlighted by their chemical transformations to various N- and O-functionalized motifs (Scheme 1). In a reductive cleavage of two N–O



**Scheme 1.** Single and double cleavages of N–O bonds.

rings, model molecule **4a** was subjected to Pd/C/H<sub>2</sub> in MeOH,<sup>[12a]</sup> yielding acyclic 2-methylhydroxy-1,3-diamino-4-ol **9a** as a single diastereomer (d.r. > 20:1). For an ester **8a**, its initial reduction with LiAlH<sub>4</sub> afforded the alcohol **8a'** that was transformed into 3-methylamino-4-amino-1,2,5-triols **9b** efficiently. We also performed a reductive cleavage on compound **5a** to afford a seven-membered heterocycle **9c** stereoselectively; the structure was assigned based on a comparison with the <sup>13</sup>C NMR data of compounds **9a** and **9b**. To increase their utility, we developed a selective N–O cleavage of these products using Zn/AcOH in THF,<sup>[12b]</sup> as manifested by compounds **8c** and **4a**, which undergo a single N–O cleavage selectively at their isoxazolidine ring to form products **9d** and **9f** stereoselectively. These structures were confirmed by X-ray diffraction.<sup>[11]</sup>

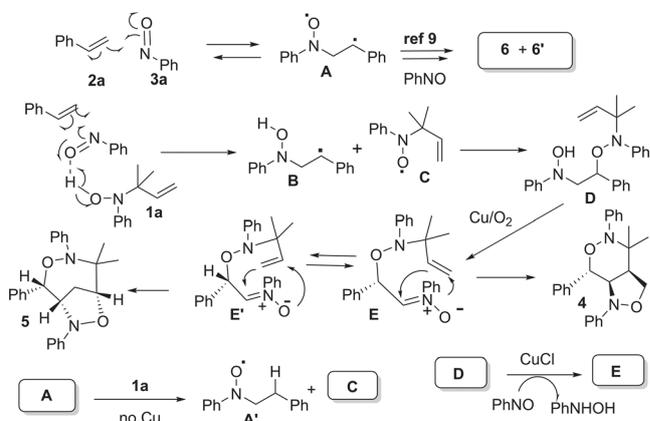
We noted that heterocycles **4a** and **5a** were obtained in low yields (7–8%) in the absence of a catalyst (Table 1, entry 9). We treated these three reactants with DTBP (di-*tert*-butylperoxide, 1 equiv) under N<sub>2</sub> without any catalyst, yielding compounds **4a** and **5a** to 33% and 32% yields, respectively (Scheme 2). Accordingly, CuCl/O<sub>2</sub> is an oxidant but affects



**Scheme 2.** Control experiments.

the **4a/5a** product ratio. Among styrene, nitrosobenzene, and N-hydroxyallylamine, only the styrene/nitrosobenzene pair showed noticeable reactions in the presence of CuCl/O<sub>2</sub>. At a standard 5 h, this mixture in toluene yielded isoxazolidine **6** and nitrone **6'** and unreacted **2a/3a** in 22%, 22%, and 56/58%, respectively, consistent with a literature report (entry 1).<sup>[9]</sup> In the presence of CuCl/O<sub>2</sub>, the product yields of compounds **6** and **6'** remained nearly unaffected. These results suggest that N-hydroxyallylamines **1a** affects the chemoselectivity of the nitroso/styrene reaction, in order to deliver new heterocycles **4a** and **5a**.

Scheme 3 shows a consistent mechanism for the formation of desired heterocycles **4** and **5**, which strongly indicates the intermediacy of nitrone species **E**. The reaction of nitrosobenzene with styrene was reported to yield isoxazolidine **6** and nitrone **6'** via a postulated diradical **A**.<sup>[9a]</sup> This radical pathway was supported by theoretical studies of nitroso–ene reactions.<sup>[9b–c]</sup> Diradical **A** is unaffected by CuCl/O<sub>2</sub> (Scheme 2), but its interception with N-hydroxyallylamine is expected to give two persistent nitroso radicals **A'** and **C**. This



**Scheme 3.** A postulated mechanism for three-component annulations.

pathway fails to yield our observed products. In our mechanism, N-hydroxyallylamine **1a** might complex with nitrosobenzene through a hydrogen bonding. Because N-hydroxyallylamine is a good hydrogen donor,<sup>[10]</sup> we envisage that radical reactions between styrene and this reactant pair likely give benzylic radical **B** and nitroso radical **C**, allowing a radical–radical coupling to form species **D**.<sup>[13]</sup> An oxidation of species **D** with Cu<sup>I</sup>/O<sub>2</sub> is expected to yield nitrone **E** or **E'**<sup>[14]</sup> that can undergo two *endo*-[3+2]-nitrone/alkene cycloadditions to yield bicyclic nitroso products **4** or **5** stereoselectively. The latter was present as a minor isomer because its transition state **E'** is sterically hindered. Notably, this Cu-catalyzed annulation under N<sub>2</sub> still rendered bicyclic nitroso species **4** in 35% yield (entry 8, Table 1). CuCl likely catalyzed the oxidation of species **D** with nitrosobenzene to yield nitrone **E** (or **E'**) and N-hydroxyaniline.

In summary, we report new cascade Cu-catalyzed annulations of styrenes, nitrosobenzene, and N-hydroxyallylamines to yield fused 1,2-oxazinane/isoxazolidine heterocycles with excellent stereoselectivity. To highlight the synthetic utility, we have developed single and double N–O cleavages of these bicyclic products, allowing efficient production of highly functionalized 1,2-oxazinanes, acyclic 2-methylhydroxy-1,3-diamino-4-ols, and new bicyclic heterocycles. We postulated a prior interaction of nitrosobenzenes with N-hydroxyallylamine before their radical reactions with styrene; the final step involves dipolar [3+2]-cycloaddition of nitrone intermediates with their tethered alkenes.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** amino alcohols · annulations · copper catalysis · dipolar [3+2]-cycloadditions · heterocycles

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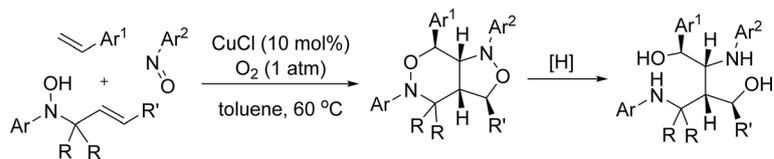
## Communications



## Cycloadditions

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Copper-Catalyzed Three-Component  
Annulations of Alkenes, Nitrosoarenes,  
and N-Hydroxyallyl amines to Form Fused  
Oxazinane/Isoxazolidine Heterocycles



**One-pot cascade annulations** among nitrosoarenes, alkenes and N-hydroxyallyl amines with CuCl/O<sub>2</sub> catalysts are

described, forming fused oxazinane/isoxazolidine heterocycles with excellent diastereoselectivity.