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Enoldiazosulfones for Highly Enantioselective [3 + 3]-Cycloaddition with Nitrones Catalyzed by Copper(I) with Chiral BOX Ligands

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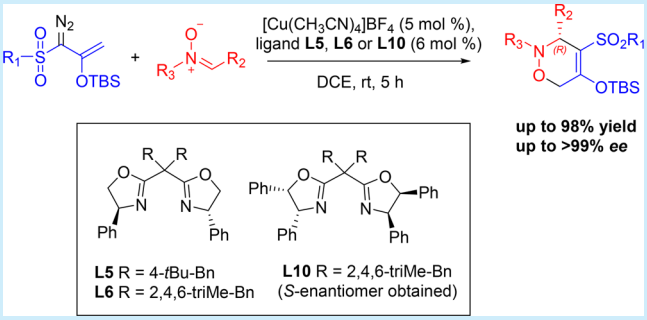
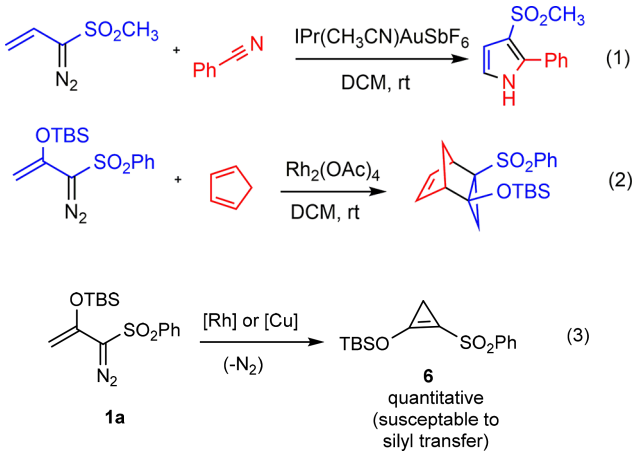
Supporting Information

ABSTRACT: Enoldiazosulfones undergo [3 + 3]-cycloaddition with nitrones when catalyzed by copper(I) catalysts, but not with dirhodium(II) catalysts. Under mild reaction conditions with chiral bisoxazoline ligands, copper(I) catalysts produce 1,2-oxazine-sulfone derivatives in high yields and enantioselectivities. Dirhodium(II) catalysts form stable donor–acceptor cyclopropenes that undergo uncatalyzed [3 + 2]-cycloaddition reactions with nitrones.

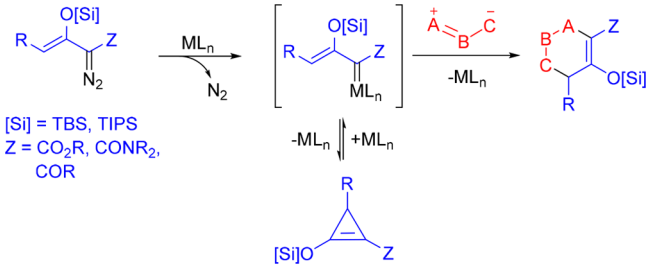


Organosulfones are a valuable class of sulfur containing molecules owing to their versatility as useful intermediates in organic synthesis.[1] They have a wide spectrum of biological properties that are recognized in natural products, pharmaceuticals, and agrochemicals.[2] However, despite their availability for more than 50 years,[3] diazosulfones have not been widely used in catalytic reactions involving metal carbenes.[4] Although the construction of these structures extends from tosyldiazomethanes to *β*-keto-*α*-diazosulfones, only two examples of cycloaddition reactions have been reported in which a vinyldiazosulfone has been used for the preparation of



sulfonyl-bearing frameworks (eq 1 and 2), and one of them the probable uncatalyzed [4 + 2]-cycloaddition by the donor–acceptor TBSO-cyclopropenesulfone formed from the diazo compound by dinitrogen extrusion.[5,6]

Scheme 1. Metal-Catalyzed [3 + 3]-Cycloaddition Reaction of Enoldiazo Compounds with Stable Dipoles



We have successfully employed silyl-protected enoldiazoacetates,[7] -acetamides,[8] and -ketones[9] in [3 + 3]-cycloaddition reactions with a variety of stable dipolar reactants (Scheme 1). These reactions occur with competitive formation of the donor–acceptor cyclopropene generated intramolecularly by dinitrogen extrusion.[10] In previous studies the donor–acceptor cyclopropene was found to be a resting state for the vinylcarbene that, once regenerated, undergoes [3 + 3]-cycloaddition.[11] High enantioselectivities were achieved using chiral dirhodium(II)[11] and, more recently, copper(I)[8] catalysts. We were intrigued with the possible application of enoldiazosulfones to [3 + 3]-cycloaddition reactions. We expected that they would be conveniently available from *β*-keto-*α*-diazosulfones by silyl transfer to the enolate,[12] but we were uncertain of their viability for [3 + 3]-cycloaddition because of the anticipated stability of the donor–acceptor cyclopropene.[6] We now report that the

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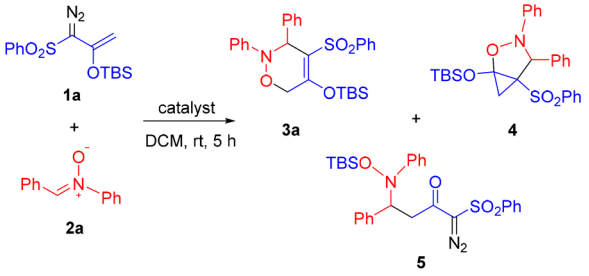
Table 1. Metal-Catalyzed Divergent Addition Reactions of Enoldiazosulfone 1a and Nitrone 2a: Catalyst Screening[a]



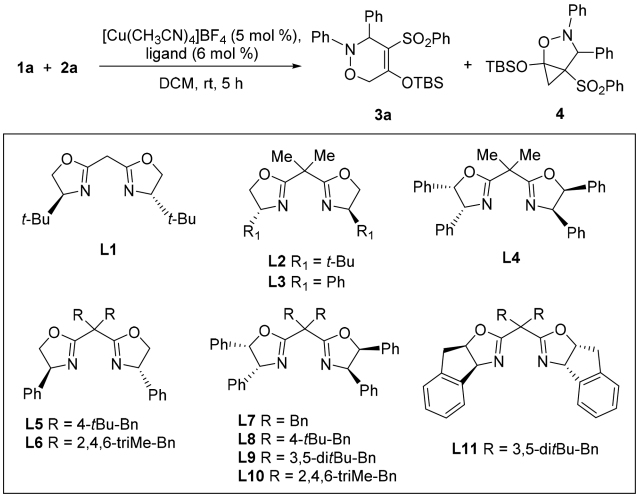
entry	catalyst (x mol %)	yield (%) 3a	4	5
1	$Rh_2(OAc)_4$ (2)		73[b]	
2	$Rh_2(oct)_4$ (2)		74[b]	
3	$[Cu(CH_3CN)_4]BF_4$ (5)	77[c]	trace	
4	$Cu(OTf)\cdot Tol_{1/2}$ (5)	33[b]	14[b]	37[b]
5	$[Au(JohnPhos)(CH_3CN)]SbF_6$ (5)			92[c]
6	$AgSbF_6$ (5)			76[c]
7	$Pd(PhCN)_2Cl_2$ (5)	15[b]	41[b]	

[a]All reactions were carried out on a 0.20 mmol scale in 4.0 mL of DCM: **2a** (0.20 mmol) and **1a** (0.30 mmol). [b]Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [c]Isolated yield after flash-chromatography.

sulfone group stabilizes the cyclopropene formed by dinitrogen extrusion, rendering dirhodium(II) catalysts ineffective to reform the metal-carbene. Chiral copper(I) catalysts, however, are able to overcome this limitation to effect [3 + 3]-cycloaddition in high yields and excellent enantiocontrol.

Silyl-protected enoldiazosulfones were prepared in high yields from the corresponding β-ketosulfones by diazo transfer and subsequent enolization/silyl transfer.[12] To determine metal catalyst suitability *tert*-butyldimethylsilyl (TBS)-protected enoldiazosulfone **1a** was treated with *N*,α-diphenylnitrone **2a** in dichloromethane (DCM) at room temperature (Table 1). Dirhodium(II) catalysts generated the product from [3 + 2]-cycloaddition (**4**) between the nitrone and the donor−acceptor cyclopropene formed from **1a** (entries 1 and 2), whereas copper(I) tetrafluoroborate $[Cu(CH_3CN)_4]BF_4$ formed the product from [3 + 3]-cycloaddition (**3a**) in 77% isolated yield (entry 3). Unlike previously documented [3 + 3]-cycloaddition reactions of enoldiazo compounds with nitrones,[9,13] where a slight molar excess of nitrone over the diazo compound provided optimum results, reactions with **1a** required an excess of the enoldiazosulfone over nitrone to achieve optimum yields. The yield of **3a** decreased with increasing the amounts of nitrone [copper(I) catalysis]: 0.7 equiv of **2a** (77% **3a**), 1.0 equiv of **2a** (37% **3a**), and 2.0 equiv of **2a** (19% **3a**). This was due to a facile silyl transfer from the donor−acceptor cyclopropene to the nitrone that was competitive with cycloaddition (see Supporting Information for NMR spectra) and probable subsequent ring opening of cyclopropene.[6] Other catalysts that are known to form metal carbenes from diazo compounds, specifically, gold(I) hexafluoroantimonate $[Au(JohnPhos)(CH_3CN)]SbF_6$[14] and silver(I) hexafluoroantimonate,[7b] completely shifted the reaction chemoselectivity to the formation of the Mukaiyama−Mannich addition product affording **5** in 92% and 76% yields, respectively (entries 5 and 6). Use of copper(I) triflate $[Cu(OTf)\cdot Tol_{1/2}]$ and bis(benzonitrile)palladium(II) chloride $[Pd(PhCN)_2Cl_2]$, however, resulted in a mixture of **3a**, **4**, and **5** (entries 4 and 7). In the absence of nitrone $[Cu(CH_3CN)_4]BF_4$, $Rh_2(OAc)_4$, and $Rh_2(oct)_4$ formed the hydrolytically unstable donor−acceptor cyclopropene **6** quantitatively within 10 min (eq 3).

Table 2. Copper(I)-Catalyzed [3 + 3]-Cycloaddition of Enoldiazosulfone 1a and Nitrone 2a: Chiral Ligand Optimization[a]



entry	ligand	3a yield (%)[b]	3a *ee* (%)[c]	4 yield (%)[d]
1	**L1**	40	28	17
2	**L2**	42	32	<10
3	**L3**	82	66	
4	**L4**	85	79	
5	**L5**	83(92)[e]	96(99)[e,f]	
6	**L6**	84(88)[e]	97(98)[e]	
7	**L7**	80	59	
8	**L8**	82	85	
9	**L9**	81	72	trace
10	**L10**	85	87	
11	**L11**	72	97	26

[a]All reactions were carried out on a 0.20 mmol scale in 4.0 mL of DCM: the copper(I) catalyst consisting of 5 mol % of $[Cu(CH_3CN)_4]BF_4$ and 6 mol % of chiral ligand was stirred in 1.0 mL of DCM at room temperature for 1 h, and the **2a** (0.20 mmol) and **1a** (0.30 mmol) were added in sequence. [b]Isolated yield after flash-chromatography. [c]Enantiomeric excesses were determined by chiral HPLC analysis. [d]Determined by ^1H NMR spectral analysis using 1,3,5-trimethoxybenzene as the internal standard. [e]Results in DCE as reaction solvent are shown in parentheses. [f]Lowering the catalyst loading from 5.0 to 2.0 to 1.0 mol % showed minimal effect on enantioselectivity.

Control experiments were conducted with preformed donor−acceptor cyclopropene **6** to confirm the role of the catalysts in the formation of **3a** and **4**. When cyclopropene **6** was treated with an equivalent amount of nitrone **2a** in the absence of catalyst, the [3 + 2]-cycloaddition product **4** was obtained in a yield comparable with that from the dirhodium(II)-catalyzed reactions (Table 1). However, when cyclopropene **6** was added to a solution of nitrone **2a** and $Cu(CH_3CN)_4BF_4$ under standard reaction conditions, the [3 + 3]-cycloaddition product **3a** was obtained in 71% yield without evidence for the formation of **4**. These results are consistent with initial metal−carbene formation with the enoldiazosulfone, followed by irreversible formation of the donor−acceptor cyclopropene with dirhodium(II) catalysts but either direct [3 + 3]-cycloaddition

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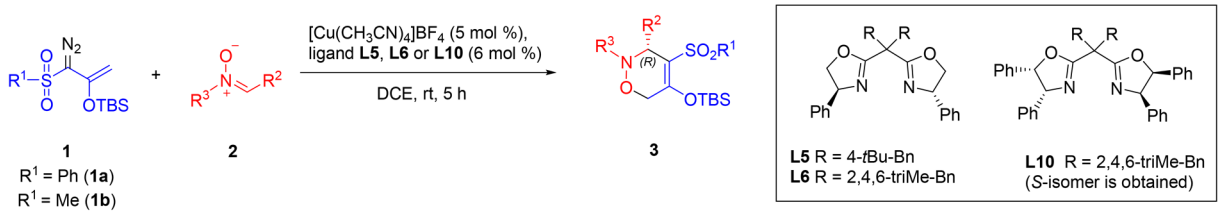
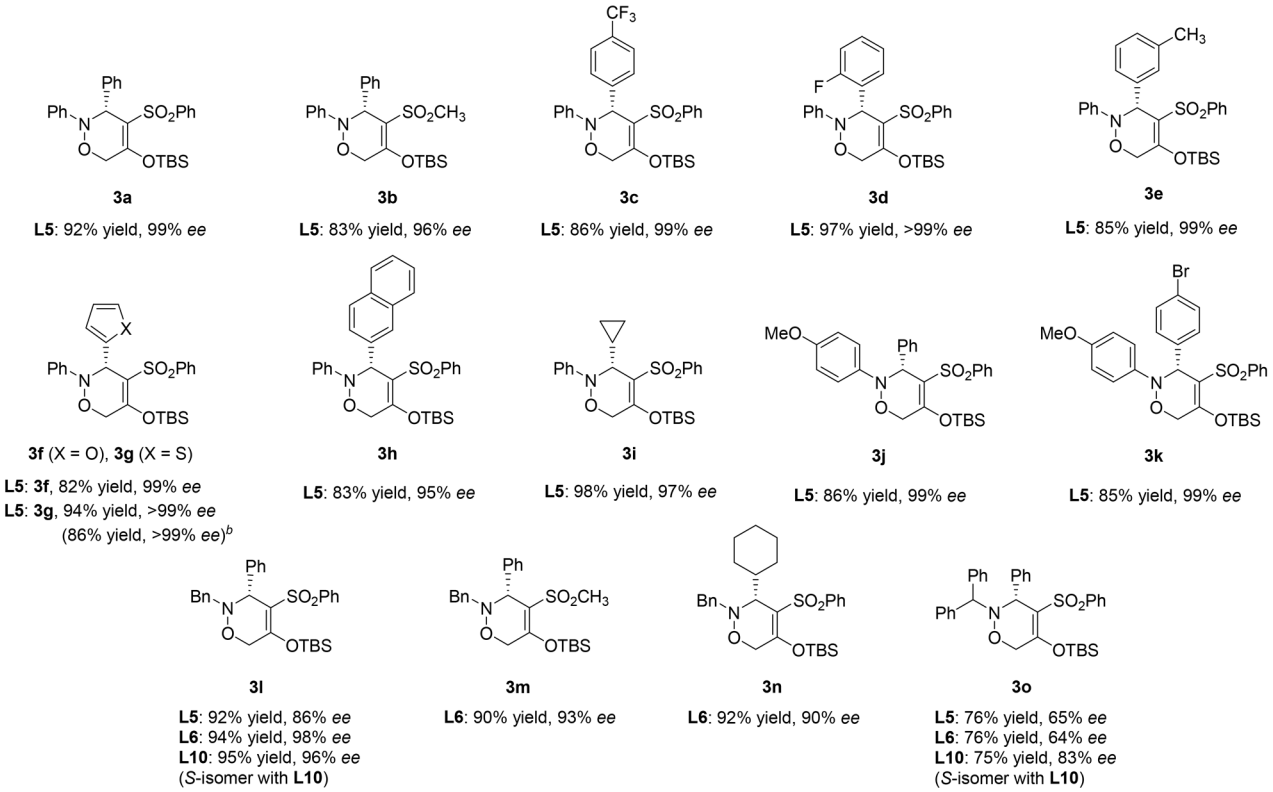
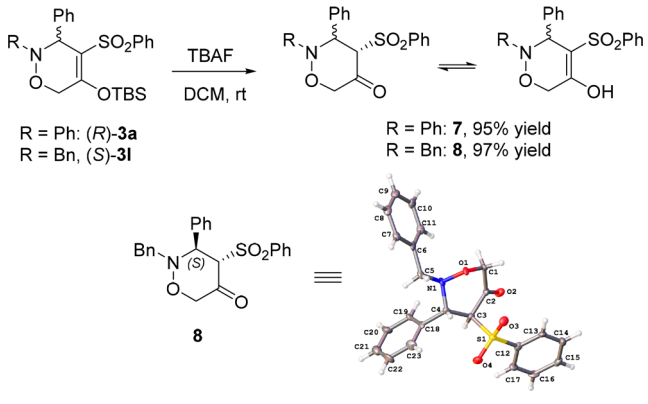
Scheme 2. Copper-Catalyzed [3 + 3]-Cycloaddition of Enoldiazosulfones 1 with Nitrones 2: Substrate Scope[a]





[a]All reactions were carried out on a 0.2 mmol scale in 4.0 mL of DCE: copper(I) catalyst (5 mol % of $[Cu(CH_3CN)_4]BF_4$ and 6 mol % of chiral ligand stirred in 1.0 mL of DCE at room temperature for 1 h; **2** (0.20 mmol), **1** (0.30 mmol). [b]Reaction was carried out on a 2.0 mmol scale of **2g**.

Scheme 3. TBS-Group Removal from 3a and 3l[a]



[a]X-ray structure of **8** with 50% thermal ellipsoid probability.

of the metal carbene or reversible formation of the donor–acceptor cyclopropene with copper(I) catalysts.

Enantiocontrol in the copper(I)-catalyzed cycloaddition process was examined with a set of chiral BOX ligands **L1**–**11** (Table 2). **L1** and **L2** were unsuitable due to low conversion to products and competing formation of **4** (entries 1 and 2). However, promising results were provided by ligands **L3** and **L4**, which gave improved yields of **3a** without observable formation of **4**. Further ligand screening was carried out with side-armed bisoxazoline (sabox) ligands in which substituents at the bridgehead carbon are known to influence catalyst selectivity.[9,15] Ligands **L5** and **L6** gave further enhancements with enantioselectivities of 96% and 97% *ee*, respectively. Although **L11** gave the desired product with 97% *ee*, its yield did not exceed 72% due to formation of **4** (26% yield).

Solvent variation using ligand **L5** showed minimal effect on reaction outcome (see Supporting Information), although modest increases in both yield and *ee* values were observed in 1,2-dichloroethane (DCE). Using **L5** in DCE as a solvent gave **3a** in 92% yield and 99% *ee* (entry 5), while ligand **L6** in DCE afforded **3a** in 88% yield and 98% *ee* (entry 6). Thus, ligand **L5** in DCE was selected to extend the scope of the reaction. Lowering the catalyst loading from 5.0 to 2.0 to 1.0 mol % showed minimal effect on enantioselectivity; however, prolonged reaction time (48 h) was required for 1.0 mol % catalyst loading to achieve a yield comparable to that for 5.0 mol % loading.

A diverse set of *N*,*α*-disubstituted nitrones was employed to investigate the scope of the reaction with **1** in the presence of $[Cu(CH_3CN)_4]BF_4$/**L5** in DCE (Scheme 2). In all cases, the

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catalytic system generated the corresponding [3 + 3]-cycloaddition products **3a**−**o** in good yields and excellent enantioselectivities. Neither electron withdrawing nor electron donating substituents at *ortho*-, *meta*-, or *para*-positions of the α-phenyl affected the outcome of the reaction. Also, nitrones with 2-furyl (**3f**), 2-thiophenyl (**3g**), 2-naphthyl (**3h**), or even cyclopropyl (**3i**) at the α-positions, as well as those with the *p*-MeO-substituent on the *N*-phenyl ring (**3j** and **3k**), gave the 1,2-oxazine cycloaddition products in good yields with high enantiocontrol. Replacing the phenyl group of the enoldiazosulfone with a methyl group also resulted in the corresponding [3 + 3]-cycloaddition product (**3b**), which occurred in 86% yield with 96% *ee*. The substrate scope also highlighted the important influence of the nitrone *N*-group to affect optimal enantioselectivity (Scheme 2). Compared to the *N*-phenyl group, *N*-benzyl and *N*-diphenylmethyl variants afforded lower enantioselectivities when **L5** was employed (86% and 65% *ee* for **3l** and **3o**, respectively). However, ligand screening showed that high enantiocontrol toward **3l** can be restored by using either **L6** or **L10**, returning excellent yields with 98% and 96% *ee*, respectively. Enantioselectivity for the reactions of nitrone with a bulkier *N*-diphenylmethyl group was enhanced to 83% *ee* only by switching from **L5** to **L10**. The absolute configuration of the newly created stereocenter in **3l** by (4*R*,4′*R*,5*S*,5′*S*)- and (4*R*,4′*R*)-bisoxazoline ligands was confirmed to be (*S*) by X-ray crystallographic analysis after removal of the TBS-protecting group (Scheme 3).

In summary, the [3 + 3]-cycloaddition reaction of silyl-protected enoldiazosulfones with nitrones occurs in high yields and enantioselectivities using chiral bisoxazoline-ligated copper(I) catalysts. Although formation of the donor−acceptor cyclopropene occurs rapidly, copper catalysts are able to return the cyclopropene to the metallo-enolcarbene to effect [3 + 3]-cycloaddition. In contrast to previously reported systems, the sulfone group stabilizes the cyclopropene so that the less Lewis acidic dirhodium(II) catalysts are unable to reform the metallo-enolcarbene and, instead, the TBSO-cyclopropene-sulfone undergoes [3 + 2]-cycloaddition with the nitrone.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03421.

Screening tables, experimental procedures, compound characterization data, NMR spectra, and HPLC traces (PDF)

Accession Codes

CCDC 1863663 contains 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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