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Lewis base-catalyzed diastereoselective [3 + 2] cycloaddition reaction of nitrones with electron-deficient alkenes: an access to isoxazolidine derivatives†

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A Lewis base-catalyzed [3 + 2] cycloaddition reaction of nitrones with electron-deficient alkenes has been achieved under mild reaction conditions, affording various functionalized isoxazolidine derivatives as single diastereomers in moderate to excellent yields.

Nucleophilic phosphine-catalyzed cycloaddition reactions provide important access to various synthetically useful or biologically important carbo- and heterocyclic compounds¹ and serve as the key step for the total synthesis of some natural products.² During the past several decades a wide range of cycloaddition reactions have been developed.^{3–11} A variety of phosphine acceptors such as activated allenes, alkynes and alkenes and electrophilic coupling partners such as aldehydes, alkenes, imines, and aziridines have been exploited for these reactions.¹ In the past five years, 1,3-dipoles such as *N,N'* or *C,N*-cyclic azomethine imines and azomethine ylides have been used as versatile electrophilic coupling partners for phosphine-catalyzed [3 + 2],¹² [3 + 3],^{12,13} [4 + 3]^{12,14} and [3 + 2 + 3]¹² cycloadditions with activated allenes, alkynes, alkenes and MBH carbonates, producing biologically important nitrogen-containing heterocycles, such as tetrahydropyrazolopyrazolone, tetrahydropyranzolo-pyridazinone, tetrahydropyrazolodiazepinone, tetrahydropyrazolo-diazocinone, tricyclic dihydroisoquinoline and tetrahydro-isoquinoline derivatives.^{12–14} Although these dipoles have displayed diverse reactivities in the phosphine-catalyzed cycloadditions, the scope of 1,3-dipoles is still limited to azomethine imines and azomethine ylides. Other kinds of 1,3-dipoles have received little attention and have not been explored in phosphine-catalyzed cycloadditions. In this context, we tried to develop novel cycloaddition reactions based on other 1,3-dipoles, such as nitrones.¹⁵ Nitrones are readily accessible and stable compounds and

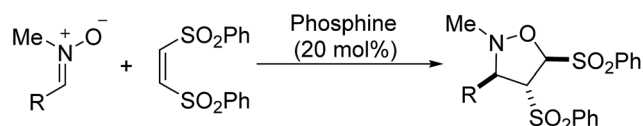
worked as efficient 1,3-dipoles in various cycloadditions to provide diverse cyclic compounds,¹⁵ which are important precursors for synthesis of bioactive compounds, natural products and other useful compounds.¹⁶ Herein, we present the first phosphine-catalyzed [3 + 2] cycloaddition reaction of various nitrones with electron-deficient alkenes for synthesis of functionalized isoxazolidines, which are potential scaffolds for the synthesis of pharmacologically active molecules (Scheme 1).

In our initial investigation, the reaction of *N*-methyl-1-phenylmethanimine oxide **1a** with (*Z*)-1,2-bis(phenylsulfonyl)ethylene **2** was chosen as the model reaction (Table 1). The reaction of **1a** and **2** was carried out in dichloromethane at room temperature in the absence of catalyst for 48 h, no new spots was observed by TLC monitoring (Table 1, entry 1). In the presence of 20 mol% PPh₃, the nitrone **1a** was treated with the alkene **2** in dichloromethane at room temperature for 48 h, leading to a desired [3 + 2] cycloaddition product isoxazolidine derivative **3a** as a single diastereomer in 99% yield (entry 2). The relative configuration of the product isoxazolidine derivative **3a** was unequivocally determined through the related X-ray crystallographic data of the homologous compound **3b** in Table 2.¹⁷ Several nucleophilic phosphines such as PBu₃, Me₂PPh, MePPh₂, EtPPh₂, *n*-PrPPh₂, *i*-PrPPh₂, *t*-BuPPh₂ and CyPPh₂ were next screened. Among these phosphines, both Me₂PPh and MePPh₂ were identified as the most effective catalysts for this reaction (entries 4 and 5). Other phosphines including PBu₃, EtPPh₂, *n*-PrPPh₂, *i*-PrPPh₂ and CyPPh₂ could also promote the reaction, but

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Scheme 1 Lewis base-catalyzed [3 + 2] cycloaddition of nitrones with electron-deficient alkene.



Table 1 Screening of the reaction conditions^a

Entry	Catalyst	Yield ^b (%)
1 ^b	—	0
2	PPh ₃	99
3	PBu ₃	60
4	Me ₂ PPh	95
5	MePPh ₂	97
6	EtPPh ₂	77
7	<i>n</i> -PrPPh ₂	89
8	<i>i</i> -PrPPh ₂	68
9	<i>t</i> -BuPPh ₂	Trace
10	CyPPh ₂	37
11	Et ₃ N	66
12	DABCO	36
13	DBU	99
14	DMAP	99
15 ^c	PPh ₃	50
16 ^d	PPh ₃	32

^a Reactions of **1** (0.1 mmol), **2** (0.12 mmol) and catalyst (0.02 mmol) were carried out in 2.5 mL of CH₂Cl₂ at room temperature for 48 h. ^b Without catalyst. ^c 10 mol% catalyst was used. ^d 5 mol% catalyst was used.

giving the corresponding product in lower 37–89% yields (entries 3, 6–8, and 10). With the use of *t*-BuPPh₂ as the catalyst, only trace of [3 + 2] cycloaddition product was obtained. Some tertiary amines, such as trimethylamine (Et₃N), 1,4-diazobicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 4-dimethylamino-pyridine (DMAP), have also been examined and displayed moderate to excellent catalytic activity (entries 11–14). The DBU and DMAP led to 99% yield of the product **3a** (entries 13 and 14). In the presence of Ph₃P, the catalyst loading was attempted to be decreased to 10 mol% and 5 mol%, but the yield was reduced to 50% yield and 32% yield, respectively (entries 15 and 16).

With the optimal reaction conditions in hand, we next investigated the scope of the Lewis base-catalyzed [3 + 2] cycloaddition of nitrones with alkenes. With 20 mol% of PPh₃ or DMAP as the catalyst, various nitrones **1** underwent [3 + 2] cycloaddition reaction with (*Z*)-1,2-bis(phenylsulfonyl)ethylene **2** in dichloromethane at rt for 48–120 h, providing a variety of 4,5-bis(phenylsulfonyl)isoxazolidine derivatives (**3a–3v**) in moderate to excellent yields (Table 2, entries 1–22). Nitrones bearing whether electron-donating or withdrawing groups on the benzene ring worked smoothly to afford the corresponding products in satisfactory yields (entries 2–21). The methoxy-substituted nitrones were not very active, requiring longer reaction time (entries 7–12). Those nitrones having di and trisubstituted aryl groups were also tolerated, leading to good yields of the [3 + 2] cycloadducts (entries 5–6, 10–12). Particularly, the cycloaddition of 2-naphthyl-

Table 2 Scope of nitron 1^a

Entry	Cat.	R	t/h	3	Yield (%)
1	Ph ₃ P	C ₆ H ₅ (1a)	48	3a	99
2	DMAP	2-MeC ₆ H ₄ (1b)	48	3b	81
3	DMAP	3-MeC ₆ H ₄ (1c)	48	3c	74
4	DMAP	4-MeC ₆ H ₄ (1d)	48	3d	69
5	Ph ₃ P	2,4-Me ₂ C ₆ H ₃ (1e)	48	3e	90
6	Ph ₃ P	3,4-Me ₂ C ₆ H ₃ (1f)	48	3f	87
7	Ph ₃ P	2-MeOC ₆ H ₄ (1g)	120	3g	76
8	Ph ₃ P	3-MeOC ₆ H ₄ (1h)	120	3h	80
9	Ph ₃ P	4-MeOC ₆ H ₄ (1i)	120	3i	63
10	DMAP	2,3-(OMe) ₂ C ₆ H ₃ (1j)	120	3j	77
11	Ph ₃ P	2,4-(OMe) ₂ C ₆ H ₃ (1k)	120	3k	75
12	Ph ₃ P	2,3,4-(OMe) ₃ C ₆ H ₂ (1l)	120	3l	78
13	Ph ₃ P	4-NMe ₂ C ₆ H ₄ (1m)	48	3m	65
14	Ph ₃ P	2-FC ₆ H ₄ (1n)	48	3n	51
15	Ph ₃ P	2-ClC ₆ H ₄ (1o)	48	3o	91
16	DMAP	3-ClC ₆ H ₄ (1p)	48	3p	62
17	DMAP	4-ClC ₆ H ₄ (1q)	48	3q	61
18	Ph ₃ P	2-BrC ₆ H ₄ (1r)	48	3r	83
19	DMAP	3-BrC ₆ H ₄ (1s)	48	3s	41
20	Ph ₃ P	4-BrC ₆ H ₄ (1t)	48	3t	62
21	DMAP	4-PhC ₆ H ₄ (1u)	48	3u	75
22	Ph ₃ P	2-Naphthyl (1v)	48	3v	99

^a Reactions of **1** (0.2 mmol), **2** (0.24 mmol) and the catalyst (0.04 mmol) were carried out in 5 mL of CH₂Cl₂ at room temperature.

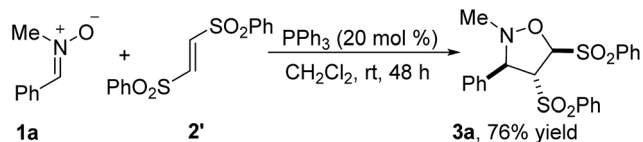
substituted nitron (**1v**) proceeded efficiently to give the product **3v** in 99% yield (entry 22).

The reaction of nitron **1a** with (*E*)-1,2-bis(phenylsulfonyl)ethylene **2'** has also been performed, producing 76% yield of the identical product **3a** with the reaction of (*Z*)-1,2-bis(phenylsulfonyl)ethylene **2** (Scheme 2). It indicated that the stereoselectivity of the reaction was not influenced by the configuration of carbon-carbon double bond in the alkene **2** and **2'**.

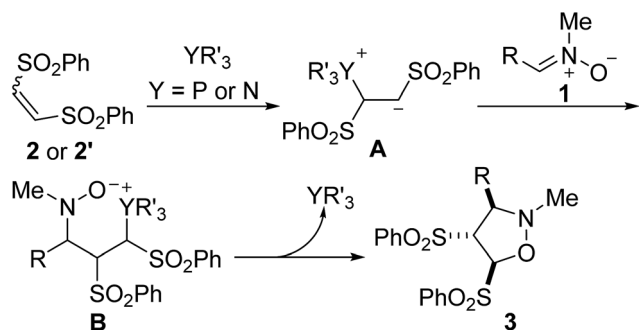
The proposed mechanism for [3 + 2] cycloaddition of the nitron **1** with 1,2-bis(phenylsulfonyl)ethylene **2** is presented in Scheme 3. Conjugate addition of the phosphine or tertiary amine to the alkene **2** or **2'** gives the zwitterion intermediate **A**, which then attacks nitron **1** to give the intermediate **B**. It undergoes an intramolecular nucleophilic attack to accomplish the [3 + 2] cyclization to give the product **3** with simultaneous regeneration of the catalyst. Since whether (*Z*)-alkene **2** or (*E*)-alkene **2'** produced the identical intermediate **A**, the stereochemistry of the reaction cannot be influenced by the configuration of the alkene.

The present reaction is quite robust. The reaction of 0.81 g of nitron **1e** with alkene **2** still worked efficiently to produce the desired product **3e** in 78% yield (Scheme 4). To further demonstrate the reaction could be a practical tool for the synthesis of other valuable compounds, some synthetic transformations of

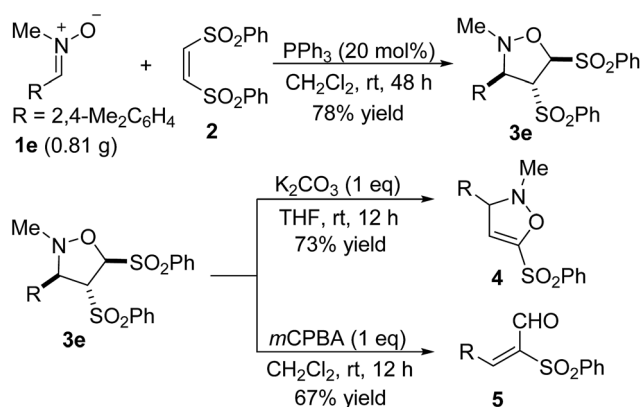




Scheme 2 PPh₃-catalyzed [3 + 2] cycloaddition of nitron **1a** with (E)-1,2-bis(phenylsulfonyl)ethylene **2'**.



Scheme 3 Proposed mechanism for the [3 + 2] cycloaddition.



Scheme 4 Gram-scale synthesis and further transformations of the cycloadduct.

cycloadduct **3e** were tried (Scheme 4). Treatment of the product **3e** with 1 equiv. K₂CO₃ in THF resulted in elimination of one of two phenylsulfonyl groups, affording the derivative **4** in 73% yield. The oxidation of **3e** with 1 equiv. of mCPBA in dichloromethane gave an α,β -unsaturated aldehyde **5** in 67% yield.

Conclusions

We have developed a Lewis base-catalyzed [3 + 2] cycloaddition reaction of nitrones with electron-deficient alkene, giving various functionalized isoxazolidine derivatives in moderate to excellent yields. A variety of nitrones underwent the reaction smoothly under the mild reaction conditions. The scaled-up reaction and further transformation of the cycloadducts demonstrated that the reaction could be a practical tool for organic synthesis.

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