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Organocatalytic Enantioselective Dipolar [3+2] Cycloadditions of Acetylenic Aldehydes with Nitrones for the Formation of Chiral 4-Isoxazolines

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Abstract: The first organocatalytic enantioselective protocol has been developed for the dipolar [3+2]cycloaddition between acetylenic aldehydes and nitrones through an iminium activation pathway. This protocol uses L-α,α-bis(3,5-ditrifluoromethylphenyl)prolinol as catalyst and 3,5-dinitrobenzoic acid as additive and is friendly for one-pot operation for the nitrone formation and the subsequent cycloaddition. It also exhibits a broad substrate scope and allows for the highly efficient production of chiral 4-isoxazolines with various substituents under mild conditions in high yields (68–92%) with high enantioselectivities (up to 96% *ee*).

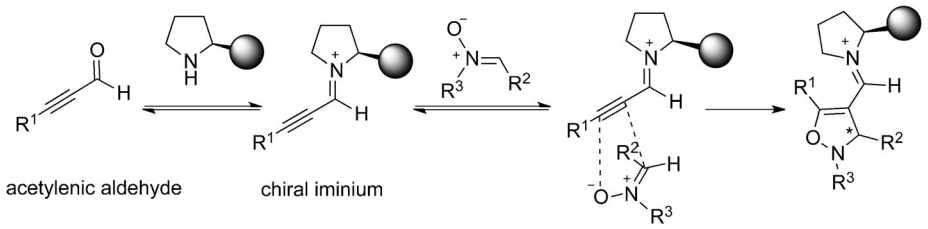
Keywords: acetylenic aldehydes; dipolar [3+2]cycloadditions; enantioselectivity; iminium activation; nitrones

The catalyitc asymmetric Diels–Alder reaction represents the most important and efficient transformation for the synthesis of chiral cyclic molecules. The development of highly effective methods to implement this transformation has attracted extraordinary attention in past decades.[1] So far numerous reports have appeared in the literature presenting different types of successful enantioselective Diels–Alder reactions with double-bond type dienophiles such as olefins, aldehydes, and imines.[1,2] However, there have been only a few successful examples of catalytic enantioselective Diels–Alder reactions with triple-bond type dienophiles such as alkynes.[3]

Recently, Ishihara reported the first highly enantioselective dipolar [3+2]cycloaddition of acetylenic derivatives with nitrones using a chiral copper complex as the Lewis acid catalyst, which resulted in the efficient production of a set of chiral 4-isoxazolines (2,3-dihydroisoxazoles) with different substitutents.[4] The indispensible presence of a pyrazoyl functionality in the acetylenic substrates for high enantioselectivity, however, is a serious limitation to the application of this method. Herein, we present a new method enabling the highly enantioselective dipolar [3+2]cycloadditions of various acetylenic aldehydes with nitrones using a chiral secondary amine as catalyst.

The activation of α,β-unsaturated carbonyl compounds by chiral secondary amines through an iminium intermediate has proven to be a viable strategy for asymmetric catalysis and has seen wide applications in methodological development in recent years.[5] This strategy, however, is mostly limited to the activation of olefinic aldehydes and ketones. Very recently, MacMillan demonstrated that this strategy is also applicable to the activation of acetylenic aldehydes and developed an efficient novel approach to furnish the total synthesis of a structurally complex natural product *via* a highly enantioselective intramolecular [4+2]cycloaddition with an acetylenic aldehyde as the dienophile.[6] Wang and Alemán also used this strategy to activate acetylenic aldehydes for oxo-Michael addition and successfully developed two cascade protocols that led to the highly enantioselective production of polyfunctionalized chiral 4*H*-chromenes.[7]

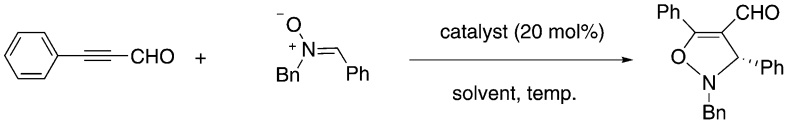
On the basis of the acetylenic aldehyde activation strategy using a chiral secondary amine as catalyst, we envisioned that a highly enantioselective dipolar [3+2]cycloaddition of nitrones with acetylenic aldehydes could be implemented (Scheme 1).[8] If successful, it could provide a practical and novel approach for the synthesis of chiral 4-isoxazolines.

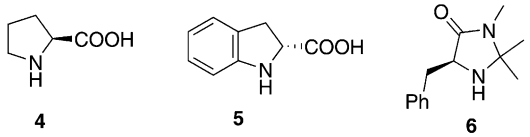


Scheme 1. Iminium-activation of acetylenic aldehyde and asymmetric dipolar [3+2] cycloaddition with nitrone.

Thus, we set out to check the 1,3-dipolar cycloaddition of phenylacetylenyl aldehyde **1a** with nitrone **2a** using different types of known catalysts (**4**–**10**). As shown in Table 1, L-proline **4** catalyzed the reaction to give the desired 4-isoxazoline product **3a** in good yield but with poor enantioselectivity (Table 1, entry 1). When 4,5-benzo-L-proline **5** was used as catalyst, both the reactivity and the enantioselectivity were significantly enhanced (Table 1, entry 2). Interestingly, while the imidazolidine catalyst **6** gave poor results (Table 1, entry 3,), the α,α-diarylprolinol catalysts **7** and **8** both exhibited a good level of enantioselectivity (81% and 83% *ee*, respectively, Table 1, entries 4 and 5), whereas their TMS ethers **9** and **10** completely lost the reactivity (Table 1, entries 6 and 7). Thus, catalyst **8** with the best overall performance was selected for further studies.

Table 1. Catalyst screen for the dipolar [3+2] cycloadditions of **1a** and **2a**.[a]

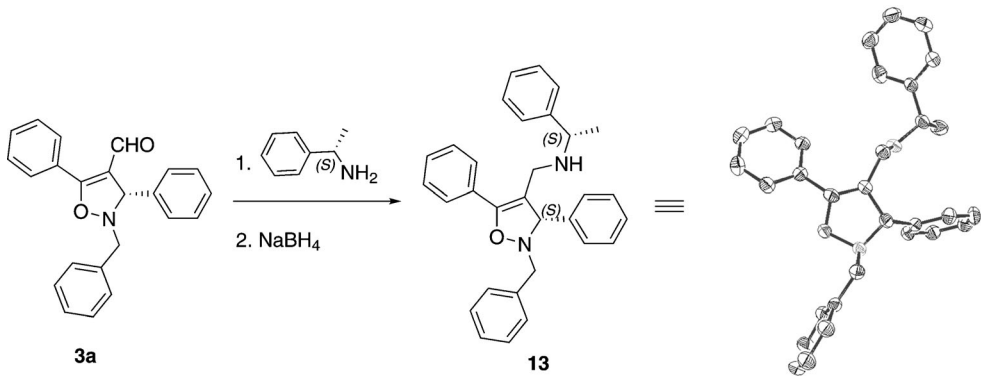




7 Ar = Ph, R = H
8 Ar = 3,5-$(CF_3)_2C_6H_3$, R = H
9 Ar = Ph, R = TMS
10 Ar = 3,5-$(CF_3)_2C_6H_3$, R = TMS

Entry	Catalyst	Solvent	Additive	Temperature [°C]	Yield [%][b]	*ee* [%][c]
1	**4**	toluene	–	−10	70	5
2	**5**	toluene	–	−10	90	−63
3	**6**	toluene	–	−10	17	53
4	**7**	toluene	–	−10	46	81
5	**8**	toluene	–	−10	60	83
6	**9**	toluene	–	−10	<5	–
7	**10**	toluene	–	−10	<5	–
8	**8**	$CHCl_3$	–	−10	76	88
9	**8**	$CHCl_3$	TFA	−10	51	78
10	**8**	$CHCl_3$	benzoic acid	−10	86	92
11	**8**	**$CHCl_3$**	**3,5-dinitrobenzoic acid**	**−10**	**92**	**95**
12	**8**	toluene	3,5-dinitrobenzoic acid	−10	80	93
13	**8**	DCM	3,5-dinitrobenzoic acid	−10	89	95
14	**8**	THF	3,5-dinitrobenzoic acid	−10	68	82
15	**8**	$CHCl_3$	3,5-dinitrobenzoic acid	−20	84	94
16	**8**	$CHCl_3$	3,5-dinitrobenzoic acid	0	89	85

[a] Reactions were carried out with **1a** (0.20 mmol), **2a** (0.24 mmol), additive (0.04 mmol) and the catalyst (0.04 mmol) in the indicated solvent (1 mL). The reaction mixture was stirred for 24 h at the temperature indicated.
[b] Yield of the isolated product.
[c] Determined by chiral HPLC.

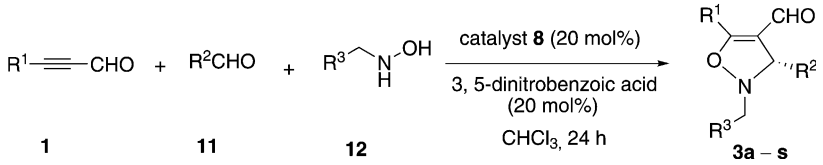


Scheme 2. Determination of the absolute stereochemistry of **3a** through derivatization.

Different reaction conditions were tested to optimize the catalytic efficacy of **8**. When toluene was changed to $CHCl_3$ as solvent, slightly improved yield and *ee* values were obtained (Table 1, entry 8). Benzoic acid as additive was found to have beneficial effects on both the enantioselectivity and the reactivity, affording 86% yield and 92% *ee* (Table 1, entry 10). Its analogue 3,5-dinitrobenzoic acid with stronger Brønsted acidity further enhanced the *ee* value to 95% and the yield to 92% (Table 1, entry 11). Either lowering or raising the reaction temperature had harmful impacts on the catalytic outcome (Table 1, entries 15 and 16).

To simplify the operation, we also tried to run the dipolar [3+2] cycloaddition of **1a** in a one-pot fashion with *in situ* prepared nitrone **2a**. *N*-Benzylhydroxylamine was mixed with benzaldehyde in chloroform at room temperature and stirred for 1 h. The resulting solution was then cooled to −10 °C and catalyst **8**, 3,5-dinitrobenzoic acid, and aldehyde **1a** were added se-

Table 2. Scope of the organocatalytic three-component reaction.[a]



Entry	R^1	R^2	R^3	Product	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	Ph	**3a**	92	95
2	Ph	4-Me-C_6H_4	Ph	**3b**	90	90
3	Ph	3-Me-C_6H_4	Ph	**3c**	92	94
4	Ph	4-MeO-C_6H_4	Ph	**3d**	82	91
5	Ph	3-MeO-C_6H_4	Ph	**3e**	75	95
6	Ph	2-naphthyl	Ph	**3f**	80	96
7	Ph	2-furyl	Ph	**3g**	68	87
8	Ph	1-propenyl	Ph	**3h**	70	82
9	Ph	3-Cl-C_6H_4	Ph	**3i**	80	87
10	Ph	4-CF_3-C_6H_4	Ph	**3j**	81	88
11	4-Me-C_6H_4	Ph	Ph	**3k**	90	90
12	4-MeO-C_6H_4	Ph	Ph	**3l**	90	94
13	4-CF_3-C_6H_4	Ph	Ph	**3m**	80	88
14	*n*-C_4H_9	Ph	Ph	**3n**	76	82
15	Ph	Ph	4-Me-C_6H_4	**3o**	83	96
16	Ph	Ph	4-MeO-C_6H_4	**3p**	81	95
17	Ph	Ph	4-F-C_6H_4	**3q**	89	95
18	Ph	Ph	4-CF_3-C_6H_4	**3r**	85	95
19	Ph	Ph	*n*-C_4H_9	**3s**	70	77

[a] *Reactions conditions*: **1** (0.20 mmol), **11** (0.40 mmol), **12** (0.32 mmol) and the catalyst **8** (0.04 mmol) in $CHCl_3$ (1 mL) at −10 °C for 24 h.
[b] Yield of the isolated product.
[c] Determined by using chiral HPLC.

quentially. To our delight, this reaction gave similar results as the one using performed nitrone **2a** (Table 2, entry 1).

Having established the optimal conditions, we explored the substrate scope of the **8**-catalyzed one-pot dipolar [3+2]cycloaddition. As shown in Table 2, this reaction exhibited a broad substrate tolerance. Different aldehydes **11** with various substituents reacted with *N*-alkylhydroxyamines **12** and subsequently with ynals **1** to furnish the desired chiral 4-isoxazolines **3** in good to high yields. Generally, a high level of enantioselectivity (87–96% *ee*) was obtained with **1**, **11**, and **12** – all having the variable substituents (R^1, R^2 and R^3, respectively) as aryl groups. Relatively electronic-rich aryl R^2 (Table 2, entries 1–6) and R^1 (Table 2, entries 11 and 12) groups led to higher enantioselecitivities than their electronic-deficient counterparts, whereas the electronic property of aryl R^3 had little effect on the enantioelectivity (Table 2, entries 15–18). Non-aryl R^1 (Table 2, entry 14), R^2 (Table 2, entry 8) and R^3 (Table 2, entry 19) groups could also be tolerated. The corresponding products were obtained in good yields, albeit only with moderate enantioselectivities.

To determine the absolute stereochemistry of products **3**, **3a** was derivatized with (*S*)-1-phenylethylamine through reductive amination (Scheme 2). An X-ray crystallographic analysis of the resulting product **13** revealed that the chiral carbon in the 4-isoxazoline ring has the *S* configuration.[9,10] This stereochemical outcome could be easily rationalized by stereoselective addition of the activated chiral iminium dipolarophile to the *Re*-face of the nitrone *via* the plausible transition state depicted in Scheme 3.

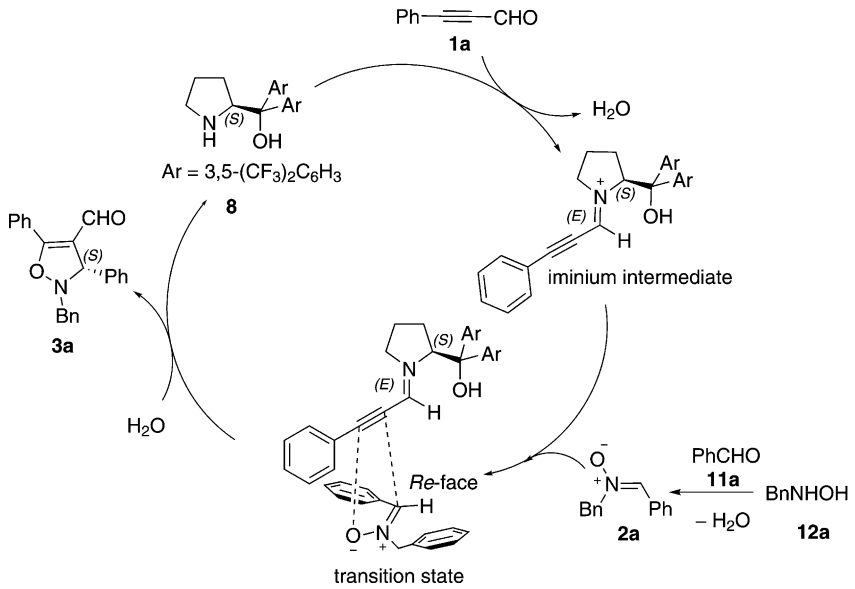
In summary, we have developed a highly effective catalytic enantioselective protocol for the dipolar [3+2]cycloaddition between acetylenic aldehydes and nitrones that are *in situ* formed from *N*-alkylhydroxylamines and aldehydes in one-pot. Under the catalysis of L-α,α-bis(3,5-ditrifluoromethylphenyl)prolinol with the assistance of 3,5-dinitrobenzoic acid, a variety of substrates underwent the cycloaddition under mild conditions to afford chiral 4-isoxazolines with various substituents in high yields (up to 92%) with excellent enanoselectivities (up to 96% *ee*).

Experimental Section

All starting materials were of the highest commercially available grade and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use.

General Procedure for the 8-Catalyzed Asymmetric Dipolar [3+2]Cycloaddition of Acetylenic Aldehyde 1 with Nitrone 2 *in situ* Formed from Hydroxylamine 12 and Aldehyde 11

To a stirred solution of aldehyde **11** (0.40 mmol) in $CHCl_3$ (1 mL) was added *N*-alkylhydroxylamine **12** (0.32 mmol, 1.6 equiv.). After stirring at room temperature for 1 h, the reaction mixture was cooled to −10 °C, and then catalyst **8** (0.05 mmol), 3,5-dinitrobenzoic acid (0.05 mmol), and alkynals **1** (0.2 mmol) were added sequentially. The reaction was stirred at −10 °C for 24 h. The reaction mixture was then concentrated under vacuum. The residue was subjected to purification by column chromatography (silica gel, hexane/EtOAc), affording pure 4-isoxazolines **3**. The *ee* values were determined by HPLC with chiral stationary phases.



Scheme 3. Proposed mechanism and catalytic cycle.

(*S*)-2-Benzyl-3,5-diphenyl-2,3-dihydroisoxazole-4-carbaldehyde (3a): yield: 92%; 95% *ee*; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 9.72$ (s, 1H), 7.58 (d, $J = 7.02$ Hz, 2H), 7.49 (t, $J = 7.50$ Hz, 1H), 7.41 (t, $J = 7.71$ Hz, 2H), 7.36 (d, $J = 7.02$ Hz, 2H), 7.31–7.21 (m, 7H), 7.18 (t, $J = 7.26$ Hz, 1H), 5.36 (s, 1H), 4.38 and 4.10 [d (AB-system), $J = 13.02$ Hz, 2H]; ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 185.6$, 168.6, 140.5, 135.1, 132.3, 129.4, 129.0, 128.6, 128.5, 128.1, 127.8, 127.1, 126.3, 116.6, 71.2, 63.4; $[\alpha]_D^{25}$: +254.4 (*c* 0.9, EtOH); HR-MS (ESI): $m/z = 342.1493$, calcd. for $C_{23}H_{20}NO_2$ $[M+H]^+$: 342.1494.

Acknowledgements

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