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Controlling Asymmetric Remote and Cascade 1,3-Dipolar Cycloaddition Reactions by Organocatalysis

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Supporting Information

ABSTRACT: The regio- and stereoselective control of cycloaddition reactions to polyconjugated systems has been demonstrated by applying asymmetric organocatalysis. Reaction of 2,4-dienals with nitrones allows for a highly regio- and stereoselective 1,3-dipolar cycloaddition in the presence of an aminocatalyst. The first cycloaddition on the remote olefin can be followed either by a cascade reaction or by other selective reactions of the remaining olefin. The chiral products are obtained in good to high yields and excellent diastereo- and enantioselectivities. The remote selective concept has been extended to 2,4,6-trienals by means of a novel enantioselective triple cascade 1,3-dipolar cycloaddition reaction. The formation of chiral poly 1,3-amino alcohols is also demonstrated.

Control of cycloaddition reactions of polyconjugated systems is a challenge, as multiple reaction sites are available. For polyenals, the challenge is to control not only which olefin reacts in the cycloaddition but also the stereoselectivity in such cycloadditions at, e.g., the distant olefin. Remote reactions will allow for further activation and selective functionalization of the remaining olefin(s) which are still in conjugation with the aldehyde. This concept is outlined for 2,4-dienals and 2,4,6-trienals in Figure 1. For 2,4-dienals (Figure 1, left), the first cycloaddition can proceed selectively to the distant olefin by reaction with **A**. This will allow for either a cascade reaction[1] with **A** or a reaction with another reagent (**B**) at the next olefin. The concept can potentially be extended to 2,4,6-trienals, and a triple cascade reaction might be possible (Figure 1, right). This will, in the case of enantioselective cycloaddition reactions, generate multiple stereocenters in highly-substituted and stereochemically dense compounds.

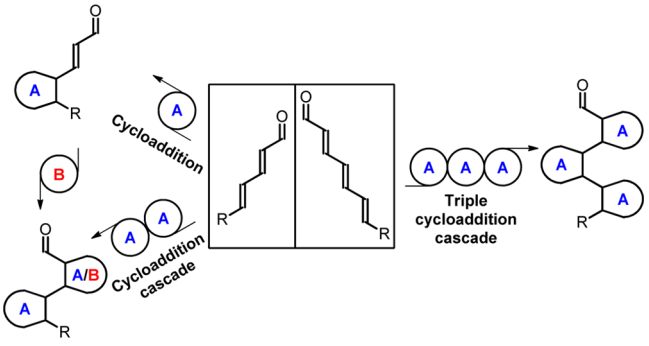

Figure 1. Stereoselective remote cycloaddition and cycloaddition cascade reactions of 2,4-dienals (left). Triple cycloaddition cascade reactions with 2,4,6-trienals (right).

We decided to try to develop novel regio- and stereoselective cycloaddition reactions based on the concepts in Figure 1. It was envisioned that this might be possible by choosing a suitable 4π-system for the cycloaddition, such as a nitrone.[2] Nitrones can react as 1,3-dipoles with the nucleophilic oxygen interacting with the electrophilic carbon generated in either the δ- or ζ-position of the 2,4-dienal or 2,4,6-trienal, respectively, by vinylogous[3] or bis-vinylogous iminium-ion activation with a chiral organocatalyst.

Enantioselective 1,3-dipolar cycloaddition reactions of nitrones with olefins is a very useful methodology for the formation of isoxazolidines.[4] These heterocycles are present in different bioactive compounds[5] and have been applied as precursors for the asymmetric synthesis of natural products.[6] In addition, the isoxazolidine ring can be converted into a chiral 1,3-amino alcohol,[7] very often applied in organic chemistry.[8]

Herein we describe a highly regio- and stereoselective 1,3-dipolar cycloaddition of nitrones to the remote olefin of 2,4-dienals, which can be followed either by a cascade reaction at the remaining olefin or by its functionalization with another reagent (Figure 1, left). This regioselective strategy to functionalize conjugated olefins is based on vinylogous iminium-ion activation of 2,4-dienals and represents the first vinylogous cycloaddition reaction utilizing LUMO-lowering activation with an aminocatalyst.[9] Moreover, we introduce unprecedented examples of bis-vinylogous iminium-ion-mediated 1,3-dipolar cycloadditions of 2,4,6-trienals generating a $\zeta,\varepsilon,\delta,\gamma,\beta,\alpha$-functionalized product with 9 contiguous stereocenters (Figure 1, right). Finally, we will present a transformation which affords chiral poly 1,3-amino alcohols.[10]

Preliminary results have shown that the *ortho*-methyl-phenyl-substituted nitrone **2a** is a promising substrate for the remote 1,3-dipolar cycloaddition with 2,4-dienals. Therefore, we initiated our studies by reacting hexa-2,4-dienal **1a** with nitrone **2a** applying 5 mol % of TfOH and 20 mol % of (*R*)-2-(diphenyl-(trimethylsilyloxy)methyl)-pyrrolidine **3a** as the catalyst in $CHCl_3$ at room temperature. Disappointingly, no product formation was observed after 40 h (Table 1, entry 1). Studies have revealed that the trifluoromethyl-substituted diarylprolinol-silyl ether is a more reactive catalyst than the diphenylprolinol-silyl ether in iminium-ion/neutral nucleophilic reactions.[11] We

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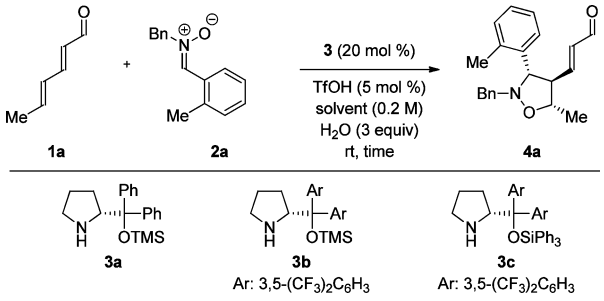
Table 1. Remote 1,3-Dipolar Cycloaddition of Nitrone 2a to 2,4-Dienal 1a. Screening Results[a]



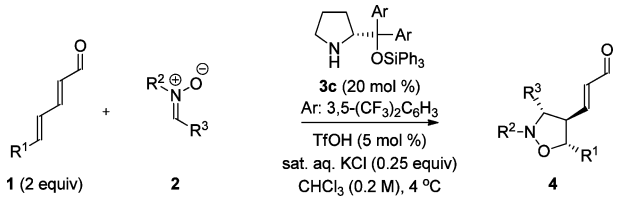
entry	3	solvent	conv.[b] (%)	time	dr[c]	ee[d] (%)
1	**3a**	$CHCl_3$	nr	40 h	–	–
2	**3b**	$CHCl_3$	83	40 h	2:1	62
3	**3c**	$CHCl_3$	94	40 h	9:1	85
4	**3c**	CH_2Cl_2	100	40 h	5:1	80
5	**3c**	EtOAc	100	40 h	7:1	78
6	**3c**	MeCN	46	40 h	1:2	55
7	**3c**	toluene	100	40 h	20:1	76
8[e]	**3c**	$CHCl_3$	88	48 h	20:1	89
9[e,f]	**3c**	$CHCl_3$	100	5 d	14:1	93

[a]Reactions were performed on a 0.1 mmol scale using **1a** (2 equiv) and **2a** (1 equiv). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by UPC^2 analysis (see SI). [e]0.25 equiv of sat. aq. KCl was used instead of water. [f]Performed at 4 °C.

therefore tested catalyst **3b** under the same reaction conditions, and delightfully, conversion to the desired single addition product **4a** was observed albeit with poor enantio- and diastereoselectivity (entry 2). Notably, complete selectivity for the remote double bond was obtained without formation of any detectable amount of regioisomeric products. Catalyst **3c**, protected with a more bulky silyl group, resulted in both improved stereoselectivity and conversion for the isoxazolidine product **4a** (entry 3). Performing the reaction in other solvents, as those shown in entries 4–7, gave addition of **2a** to both olefins in **1a**, and **4a** was obtained with lower enantioselectivity. We were pleased to observe that exchanging water with sat. aq. KCl provided **4a** in a highly stereoselective manner (entries 8, 9). It should be noted that performing the reaction applying a nitrone having a *C*-phenyl substituent, rather than the *ortho*-methyl-phenyl-substituted nitrone **2a**, gave a mixture of the single and double addition products, without being able to control the remote selectivity exclusively (*vide infra*). The *ortho*-substituent in **4a** is expected to introduce steric bulk near the remaining double bond in the single addition product making the second cycloaddition reaction less favorable.

The reaction conditions developed in Table 1 allowed us to direct the stereoselective 1,3-dipolar cycloaddition of nitrones to the remote olefin of 2,4-dienals. Some representative results are presented in Table 2. It should be noted that no regioisomeric products were observed in the ^{1}H NMR analysis of the crude reaction mixtures. Hexa-2,4-dienal **1a** reacted smoothly with different *C*-aryl-*N*-benzyl nitrones. The *ortho*-methyl-phenyl-substituted nitrone **2a** gave the isoxazolidine **4a** in high yield, excellent diastereomeric ratio (dr), and 93% enantiomeric excess (ee) (entry 1). Similar results were obtained for nitrones having *C*-naphthyl substituents bearing electron-donating and electron-withdrawing substituents (entries 3–5). Replacing the *N*-benzyl substituent with *N*-methyl provided the isoxazolidine **4f** in good

Table 2. Scope of the Remote 1,3-Dipolar Cycloaddition Reaction of Nitrones to 2,4-Dienals[a]



entry	R^1	R^2, R^3	yield (%)	dr[b,c]	ee[d] (%)
1	Me (**1a**)	Bn, *o*-MeC_6H_4 (**2a**)	**4a**-80	20:1 (14:1)	93
2	Me (**1a**)	Bn, *o*-BrC_6H_4 (**2b**)	**4b**-56	20:1 (3:1)	81
3	Me (**1a**)	Bn, 1-naphthyl (**2c**)	**4c**-73	20:1 (20:1)	92
4	Me (**1a**)	Bn, 4-MeO-1-naphthyl (**2d**)	**4d**-85	20:1 (20:1)	94
5	Me (**1a**)	Bn, 1-Br-2-naphthyl (**2e**)	**4e**-63	6:1 (6:1)	88
6	Me (**1a**)	Me, *o*-MeC_6H_4 (**2f**)	**4f**-66	20:1 (5:1)	93
7	Me (**1a**)	Ph, *o*-MeC_6H_4 (**2g**)	**4g**-99	20:1 (20:1)	47
8	*n*-hexyl (**1b**)	Bn, *o*-MeC_6H_4 (**2a**)	**4h**-60	20:1 (7:1)	89
9	Ph-C_2H_4 (**1c**)	Bn, *o*-MeC_6H_4 (**2a**)	**4i**-72	20:1 (20:1)	90
10	Ph-C_2H_4 (**1c**)	Bn, 4-MeO-1-naphthyl (**2c**)	**4j**-78	20:1 (20:1)	93

[a]Reactions were performed on a 0.1 mmol scale. [b]Determined by ^{1}H NMR analysis of the isolated product. [c]Ratio in parentheses refer to the dr determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by UPC^2 analysis (see SI).

diastereoselectivity and 93% ee (entry 6). The remote 1,3-dipolar cycloaddition reaction allowed also for varying the substituent in the 2,4-dienal as presented in entries 8–10, providing the corresponding isoxazolidines **4h–j** in good yields, high diastereo-, and enantioselectivities. An exception is for nitrone **2g** having phenyl and *ortho*-methyl phenyl substituents as R^2 and R^3, respectively (entry 7), for which 47% ee is obtained. This low ee is remarkable compared with the cascade reaction (*vide infra*) which proceeds with high stereoselectivity (Table 3).

Encouraged by the good regioselectivity observed for the single 1,3-dipolar cycloaddition reaction, we decided to investigate the possibility of the subsequent functionalization of the remaining olefin in the substrate. We envisioned a stereoselective cascade reaction functionalizing both olefins in the 2,4-dienals applying an additional equivalent of nitrone relative to the amount of aldehyde. Gratifyingly, reacting *C*-phenyl nitrone **2h** with hexa-2,4-dienal **1a** under the conditions for the single addition reaction provided the chiral bi-isoxazolidine product **5a** as one diastereoisomer in 73% yield and 99% ee without formation of regioisomeric products (Table 3, entry 1). In spite of the generation of six stereocenters, we were pleased to observe that only one stereoisomer was formed. Nitrones having different substituents in the *C*-phenyl ring were examined in the reaction. It was found that both electron-donating and -withdrawing groups in the *para*-position were well tolerated and the corresponding products **5b**,**c** were formed in good yields and excellent stereoselectivities (entries 2, 3). Interestingly, nitrones with *ortho*- and *meta*-substituents also reacted smoothly in the cascade cycloaddition reaction (entries 4, 5). Employing 2-naphthyl-substituted nitrone **2m** afforded product **5f** in good yield as a single stereoisomer (entry 6). In a similar manner the *N*-methyl- and *N*-phenyl-*C*-phenyl nitrones **2n**,**o** reacted with **1a** to give **5g**,**h** in very high diastereoselectiv-

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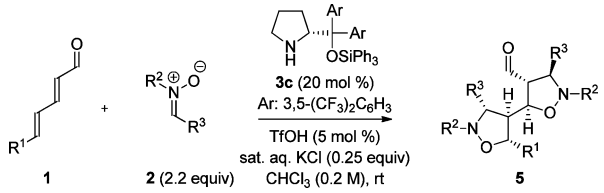
Table 3. Scope of the 1,3-Dipolar Cycloaddition Cascade Reaction of Nitrones to 2,4-Dienals[a]



entry	R^1	R^2, R^3	yield (%)	dr[b]	ee[c] (%)
1	Me (**1a**)	Bn, Ph (**2h**)	**5a**-73	20:1	99
2	Me (**1a**)	Bn, *p*-$MeOC_6H_4$ (**2i**)	**5b**-52	20:1	99
3	Me (**1a**)	Bn, *p*-BrC_6H_4 (**2j**)	**5c**-60	20:1	99
4	Me (**1a**)	Bn, *o*-$MeOC_6H_4$ (**2k**)	**5d**-60	20:1	99
5	Me (**1a**)	Bn, *m*-MeC_6H_4 (**2l**)	**5e**-60	20:1	99
6	Me (**1a**)	Bn, 2-naphthyl (**2m**)	**5f**-61	20:1	99
7	Me (**1a**)	Me, Ph (**2n**)	**5g**-56	20:1	92
8	Me (**1a**)	Ph, Ph (**2o**)	**5h**-86	12:1	99
9	*n*-hexyl (**1b**)	Bn, Ph (**2h**)	**5i**-47	20:1	99
10	Ph-C_2H_4 (**1c**)	Bn, Ph (**2h**)	**5j**-72	20:1	99

[a]Reactions were performed on a 0.1 mmol scale. [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]Determined by UPC^2 analysis (see SI).

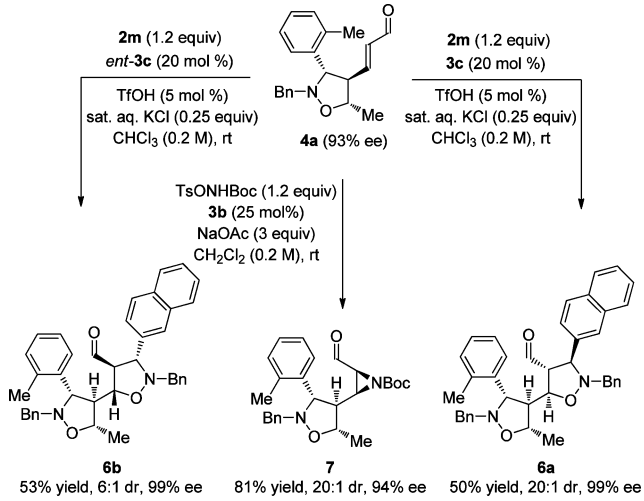
ities and up to 99% ee (entries 7, 8). The high stereoselectivity in entry 8 is remarkable compared to the result in Table 2, entry 7. We attribute the lower enantioselectivity in Table 2, entry 7, either to the *ortho*-methyl-phenyl substituent present in nitrone **2f** or that the reaction proceeds faster leading to lower selectivity. The substituted 2,4-dienals **1b,c** also underwent the stereoselective cascade reaction with nitrone **2h** providing the double 1,3-dipolar cycloaddition products **5i,j** in moderate to good yields and excellent stereoselectivities (entries 9, 10).

The absolute configuration of the products is determined by X-ray analysis of the alcohol of **5c**, and the stereochemistry of the remaining compounds is based on analogue (see Supporting Information (SI)).

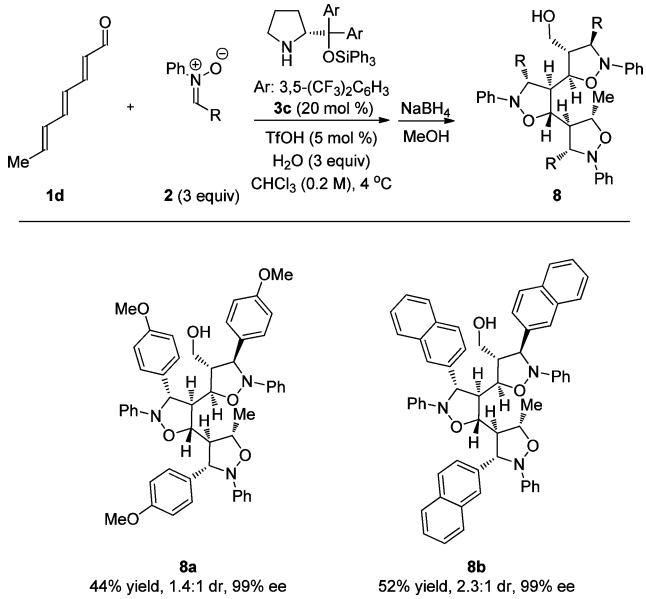
The olefin present in the isoxazolidine-substituted enal **4** can not only react in cascade cycloadditions with one type of nitrone but is also reactive toward different nitrones as well as other nucleophiles. First, a diastereodivergent reaction of **4a** with the 2-naphthyl-substituted nitrone **2m** was demonstrated affording the diastereomeric products **6a** and **6b** in decent yields and 99% ee (Scheme 1). Some degree of match/mismatch is observed as the products are obtained in very good, but slightly different diastereomeric ratios. Second, the product **4a** was reacted with TsONHBoc in an organocatalytic aziridination reaction.[12] The product **7** was obtained in good yield and excellent stereoselectivity using catalyst **3b** (Scheme 1).

We wanted to extend the disclosed concept to the functionalization of trienes in conjugation with an aldehyde. Reactions of all three double bonds are only possible if the first cycloaddition proceeds at the most distal double bond. We anticipated that this challenge could be solved by activating the system as a bis-vinylogous iminium-ion intermediate. To the best of our knowledge, this will be the first time this activating mode has been described.[13] In order to test this concept, we applied the general conditions developed to the reaction between 2,4,6-trienal **1d** and 3 equiv of *N*-phenyl-*para*-substituted nitrone **2p** (Scheme 2). Satisfyingly, the three conjugated olefins in **1d** participated in a triple cascade of 1,3-dipolar cycloadditions, generating the desired product **8a** in excellent ee, albeit with low

Scheme 1. Diastereodivergent 1,3-Dipolar Cycloaddition and Aziridination of Product 4a



Scheme 2. Triple 1,3-Dipolar Cycloaddition Cascade Reaction of Nitrones to Octa-2,4-6-trienal



diastereoselectivity. Similar results were obtained when the *C*-naphthyl nitrone **2q** was reacted with aldehyde **1d**.

The isoxazolidine ring formed in the described 1,3-dipolar cycloaddition reactions is a common precursor for the formation of 1,3-amino alcohols. Therefore, the chiral highly functionalized isoxazolidine rings in the products **5** and **8** are interesting for the synthesis of poly 1,3-amino alcohols which contain 6 and 9 stereocenters, respectively. Treatment of product **5c** with SmI_2 led to the chiral poly 1,3-amino alcohol **9** with no loss of enantiomeric purity as outlined in Scheme 3.

In conclusion we have demonstrated a novel reaction concept by which aminocatalysis is applied for the regio- and stereoselective control of the cycloaddition reaction to the remote olefin in polyenals. It has been shown that reaction of 2,4-dienals with nitrones in the presence of a diarylprolinol-silyl ether catalyst allows for a highly regio- and stereoselective remote 1,3-dipolar cycloaddition reaction with enantioselectivities up to 94% ee. This cycloaddition can be followed either by a cascade

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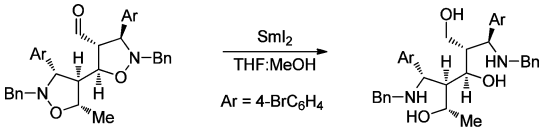
Scheme 3. Formation of 1,3-Amino Alcohols by Reaction of Bi-isoxazolidine 5c with SmI_2



5c
99% ee, 20:1 dr

9
99% ee, 20:1 dr, 54% yield

reaction or by other selective reactions of the remaining olefin. In the case of the addition of 2 equiv of the nitrones by a cascade reaction, the chiral bi-isoxazolidines are obtained in good yields, up to 20:1 dr, and 99% ee. It is also demonstrated that the remaining olefin can react in a diastereodivergent organocatalytic 1,3-dipolar cycloaddition and aziridination reaction giving 99% and 94% ee, respectively. The remote selective concept was extended to 2,4,6-trienals demonstrating for the first time an enantioselective triple cascade 1,3-dipolar cycloaddition reaction giving the tri-isoxazolidine product in 99% ee. Finally, a reductive ring-opening reaction of both isoxazolidine rings in one of the chiral bi-isoxazolidines providing a chiral poly 1,3-amino alcohol maintaining the ee was facilitated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03546.

Experimental details and data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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