Organocatalysis

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Organocatalytic Strategy for the Enantioselective Cycloaddition to Trisubstituted Nitroolefins to Create Spirocyclohexene-Oxetane Scaffolds

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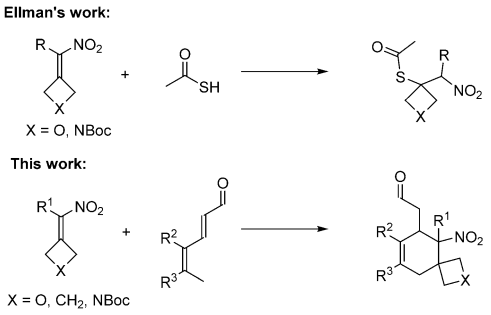
Abstract: *The first catalytic enantioselective cycloaddition reaction to α,β,β-trisubstituted nitroolefins is reported. For this purpose, nitroolefin oxetanes were employed in the reaction with 2,4-dienals promoted by trienamine catalysis. This methodology provides a facile and efficient strategy for the synthesis of highly functionalized chiral spirocyclohexene-oxetanes with two adjacent tetrasubstituted carbon atoms in high yields and excellent selectivities. This strategy also enabled access to chiral spirocyclohexene-cyclobutanes and -azetidines. Additionally, the obtained scaffolds can undergo diverse transformations leading to complex structures with up to four stereocenters, and we demonstrate that the nitro group, under nucleophilic conditions, can be applied for ring-opening of the oxetane.*

While enantioselective additions of nucleophiles to β-monosubstituted and α,β-disubstituted nitroolefins have been thoroughly investigated,[1] analogous reactions employing α,β,β-trisubstituted nitroolefins are highly challenging,[2] and have thus only been presented very recently by Ellman and co-workers (Scheme 1).[3] In this context, oxetane- and azetidine-containing nitroolefins were demonstrated to be useful building blocks, as they allow for enhanced reactivity owing to the release of ring strain in the transition state upon the attack of the nucleophile.

We envisioned that α,β,β-trisubstituted nitroolefins could be employed as 2π-components[4] in cycloaddition reactions by integrating trienamine organocatalysis applying 2,4-dienals (Scheme 1).[5] This would furnish densely functionalized chiral oxetane-cyclohexene frameworks bearing two adjacent tetrasubstituted carbons, one of which is stereogenic. The synthesis of quaternary stereocenters has been considered to be a challenge in contemporary organic chemistry.[6]



Scheme 1. Enantioselective additions to α,β,β-trisubstituted nitroolefins.

The presented development also has one further dimension as it enables the stereoselective synthesis of spirocyclic scaffolds incorporating oxetane and related ring systems into chiral cyclohexene derivatives. Oxetanes, and to a lesser extent azetidines, are of great importance. These structures are currently, after pioneering studies by Carreira et al.,[7] attracting significant attention from the pharmaceutical industry (Figure 1).[8] The reason for this is two-fold: Owing to their unprecedented nature, these frameworks enable access to unique intellectual property space, while, at the same time, the incorporation of oxetane and azetidine units allows for fine-tuning of physicochemical and pharmacokinetic properties.[9] However, as a result of novelty, strategies for the stereoselective assembly of complex spirocyclic, four-membered ring-containing scaffolds are scarce.[10]

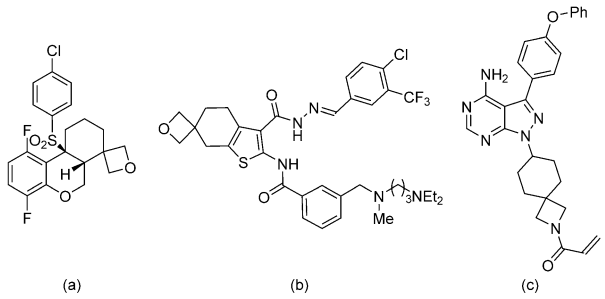


Figure 1. Examples of drug candidates containing the oxetane or azetidine ring: a) γ-secretase inhibitor (Merck Sharp & Dohme Corp.),[8a] b) phosphate uptake inhibitor (Kyowa Hakko Kirin Co., Ltd.),[8e] and c) Bruton's tyrosine kinase inhibitor (Beta Pharma Canada Inc.).[8f]

To study the applicability of α,β,β-trisubstituted nitroolefins in trienamine-mediated cycloaddition reactions, we investigated the reaction between 3-(1-nitroethylidene)oxetane **1a** and 4-phenylhexa-2,4-dienal **2a** (Table 1). Attempts to apply the sterically shielding TMS-protected prolinol catalyst **4a** gave only traces of the desired product, regardless of the use of bases and acids as additives under different reaction conditions. Therefore, we turned our attention towards bifunctional hydrogen-bonding aminocatalysts. Among the investigated catalysts, thiourea-based variant **4d**

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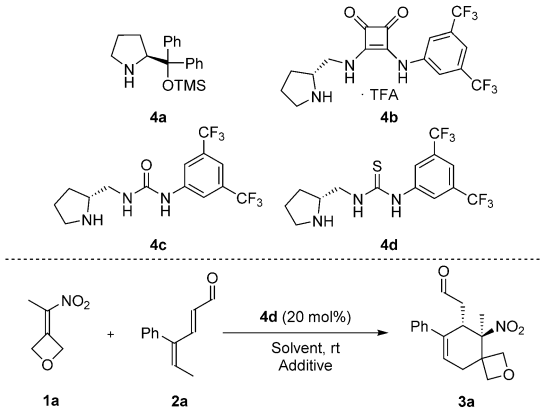
Table 1: Optimization of the reaction conditions for the cycloaddition between trisubstituted nitroolefin **1a** and dienal **2a** in the presence of **4d** as the catalyst.



Entry	Solvent	Additive (mol%)	*t* [h]	Conv [%][b]/ Yield [%][c]	d.r.[d]	*ee* [%][e]
1	Toluene	None	48	80/60	>20:1	82
2	Toluene	DABCO (20)	20	>99/22	>20:1	87
3	Toluene	TFA (20)	48	12/0	–	–
4	Toluene	BzOH (20)	48	42/15	>20:1	n.d.
5	Toluene	PA (20)	48	46/22	>20:1	n.d.
6	Toluene	DABCO (20) PA (20)	16	>99/59	>20:1	89
7	Toluene	DABCO (10) PA (15)	5	>99/70	>20:1	92
8	Toluene	DMAP (10) PA (15)	7	>99/63	>20:1	90
9	Toluene	Et_3N (10) PA (15)	7	>99/68	>20:1	94
10	CH_2Cl_2	Et_3N (10) PA (15)	8	>99/78	>20:1	92
11	Anisole	Et_3N (10) PA (15)	7	>99/82	>20:1	96
12	THF	Et_3N (10) PA (15)	20	>99/23	>20:1	n.d.

[a] Reactions were performed with **1a** (0.15 mmol), **2a** (0.1 mmol), **4d** (0.02 mmol) at rt. [b] Determined by ^{1}H NMR spectroscopy using TES as internal standard. [c] Yield of isolated product after FC. [d] Determined by ^{1}H NMR spectroscopy on the crude mixture. [e] Determined by chiral ultra-performance convergence chromatography (UPC^2) using a chiral stationary phase. PA = propionic acid.

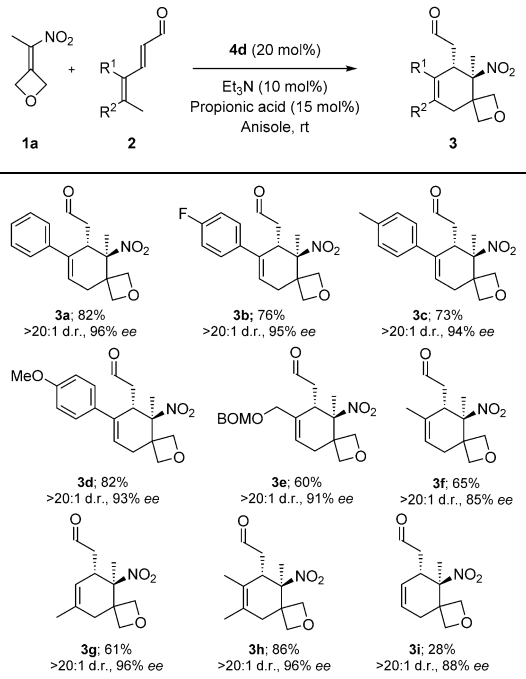
gave the best combination of yield and stereoselectivity (Table 1, entry 1), while squaramide-catalyst **4b** gave a very slow reaction and we did not observe any conversion with the urea-catalyst **4c**.

The addition of basic additives such as DABCO afforded **3a** with high enantioselectivity (87% *ee*), but in low yield owing to the lability of 3-(1-nitroethylidene)oxetane **1a** under basic conditions (Table 1, entry 2).[2b] We then assessed the effect of an acid on the reaction. Using TFA suppressed the reactivity (Table 1, entry 3), whereas employing weaker acids, such as benzoic acid and propionic acid, gave the spirocyclohexene-oxetane product **3a** in very low yield (Table 1, entries 4,5). We were curious to examine the reaction in the presence of both acid and base additives simultaneously (Table 1, entries 6–9). Gratifyingly, the combination of 20 mol% of DABCO and propionic acid afforded **3a** in good yield and 89% *ee* (Table 1, entry 6). Both yield and enantioselectivity were improved after fine-tuning the stoichiometry of the additives, obtaining the best results with 10 mol% of DABCO and 15 mol% of propionic acid (Table 1, entry 7). Additional base screening was carried out. The utilization of DMAP did not improve our previous results, whereas Et_3N led to a similar yield (68%), but a better enantioselectivity of 94% *ee* (Table 1, entry 9). We finally found out that the reaction proceeded in very good yield (82%) and high enantioselectivity (96% *ee*) in anisole (Table 1, entries 10–12).

With optimized conditions in hand, we explored the substrate scope with respect to the aldehyde (Table 2). 2,4-Dienals bearing an aromatic ring in the γ-position afforded the corresponding chiral cyclohexene-oxetanes in high yields (73–82%) and enantioselectivities (93–96% *ee*), regardless of the electronic nature of the substituent. The *para*-fluoro-substituted aldehyde **2b** gave product **3b** in 76% yield and excellent enantioselectivity (95% *ee*). Electron-donating substituents were also well tolerated leading to compounds **3c** and **3d** in 73% and 82% yield, respectively, and high enantiomeric excess (94% and 93% *ee*, respectively).

A 2,4-dienal with a BOM-protected hydroxy group is also compatible with the reaction conditions furnishing **3e** in good yield (60%) and high enantioselectivity (91% *ee*). The reaction proved to be suitable for the utilization of γ- and δ-alkyl-substituted aldehydes, affording **3f** and **3g** in moderate yields (65% and 61%, respectively) and good to high enantioselectivity. Dimethyl-substituted spirocyclohexene-

Table 2: Scope of dienals **2** with trisubstituted nitroolefin **1a**.



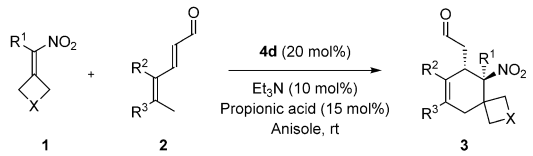
Reactions performed on a 0.1 mmol scale (see the Supporting Information for details). Yields of isolated products after FC. The d.r. was determined by ^{1}H NMR spectroscopy on the crude mixture. The *ee* values were determined by UPC^2 using a chiral stationary phase.

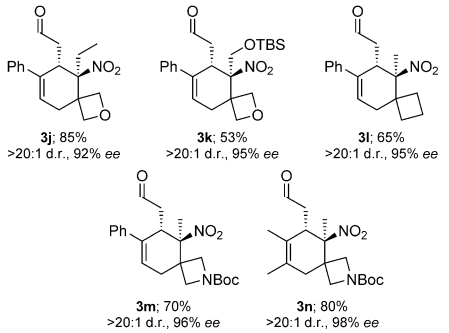
oxetane **3h** was obtained with 86% yield and excellent enantioselectivity (96% *ee*). We have also performed the reaction with the simplest dienal, 2,4-hexadienal **2i**. This reaction proceeded with high enantioselectivity (88% *ee*); however, a low yield of **3i** was obtained.

We have found that a slight decrease in the enantiomeric excess of the products could be observed over time in the presence of catalyst **4d** under the reaction conditions. Based on these observations, we performed stability studies of one of the products (**3a**) in the presence of **4d**. It was found that after 48 h the enantiomeric excess has decreased to 89% *ee*, while the diastereomeric excess still was >20:1. Leaving **3a** and **4d** together in the reaction mixture for 96 h resulted in a slight decrease in both enantiomeric and diastereomeric excess (see the Supporting Information for further details). Presumably, this is the result of a catalyst-mediated retro reaction. However, as the reaction time generally is <10 h, these observations have no influence on the results obtained.

Differently trisubstituted nitroolefins were also evaluated (Table 3). The reaction proceeded efficiently when 3-(1-nitropropylidene)oxetane was reacted with dienal **2a**, affording the corresponding product **3j** in 85% yield and 92% *ee*. The TBS-protected nitroolefin oxetane led to the formation of **3k** with moderate yield (53%), but high enantioselectivity (95% *ee*).

Table 3: Scope of trisubstituted nitroolefins **1** and dienals **2**.





Reactions performed on a 0.1 mmol scale (see the Supporting Information for details). Yields of isolated products after FC. The d.r. was determined by ^{1}H NMR spectroscopy on the crude mixture. The *ee* values were determined by UPC^2 using a chiral stationary phase.

Because we wanted to expand the strategy to the synthesis of chiral cyclobutane- and azetidine-containing spirocycles, we performed the reaction with (1-nitroethylidene)cyclobutane and *N*-Boc-protected 3-(1-nitroethylidene)azetidine (Table 3). Spirocyclobutane **3l** was formed in 65% yield and 95% *ee*. The reaction also proved to be unbiased toward the type of heteroatom in the four-membered ring. Thus, chiral cyclohexene-azetidine compounds **3m** and **3n** were obtained with excellent diastereoselectivity and enantioselectivity (96% *ee* and 98% *ee*, respectively) in good yields (70% and 80%, respectively).

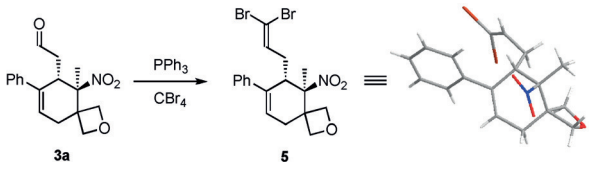
Notably, we demonstrated the robustness of the reaction as it can be scaled up to a 5.0 mmol scale, maintaining high yield, diastereoselectivity, and enantioselectivity (Table 4).

Single-crystal X-ray analysis of compound **5**,[11] obtained by a Ramirez olefination, allowed us to establish the absolute configuration of **3a** (Scheme 2). The configurations of the other chiral spirocyclohexene derivatives were assigned by analogy.

Table 4: Scale up of the reaction between trisubstituted nitroolefin **1a** and dienal **2a**.

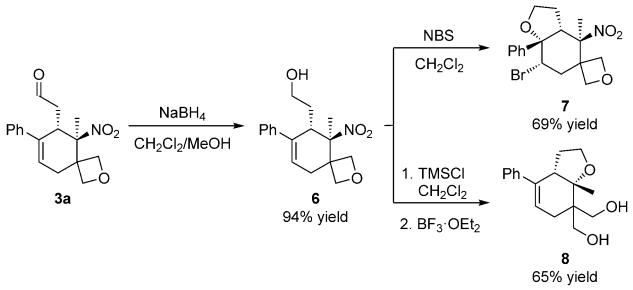
Entry	**1a** (mmol)	*t* [h]	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	0.1	7	82	>20:1	96
2	1.0	8	73	>20:1	97
3	5.0	6	74	>20:1	94

[a] Yield of isolated product after FC. [b] Determined by ^{1}H NMR spectroscopy on the crude mixture. [c] Determined by UPC^2 using a chiral stationary phase.



Scheme 2. Ramirez olefination of chiral cyclohexene-oxetane **3a** and X-ray structure of compound **5**.

To demonstrate the synthetic utility of the obtained chiral cyclohexene-oxetane products toward useful molecular scaffolds, a series of transformations were carried out (Scheme 3). Our intention with the transformations was to demonstrate that we could apply the olefin and oxetane functionality in the product for synthetic manipulations. The synthetic utility of the olefin was demonstrated by first treatment of **6** with NBS followed by a ring-closure reaction to generate an octahydrobenzofurane. The reaction proceeded well and afforded the desired product **7**, containing four consecutive stereocenters, in 69% yield. We were pleased to find that treatment of **6**



Scheme 3. Transformation of product **3a** into alcohol **6** and ring-closure reactions utilizing the olefin and oxetane moieties. The structure of **7** and **8** were confirmed by X-ray analysis.[12]

with TMSCl and $BF_3{\cdot}OEt_2$ provided **8** in 65% yield. This reaction is remarkable as we propose that $BF_3{\cdot}OEt_2$ promotes the oxetane ring-opening by the adjacent nitro group, involving a nucleophilic attack of the hydroxy group.[13] Thus, we have demonstrated that the hydroxy group in **6** can be involved in different reaction courses depending on the reaction set-up.

In conclusion, we have developed the first catalytic enantioselective cycloaddition reaction to α,β,β-trisubstituted nitroolefins. The reaction was made possible by employing nitroolefin oxetanes and 2,4-dienals promoted by trienamine catalysis. The reaction provides a facile and efficient strategy for the synthesis of highly functionalized chiral spirocyclohexene-oxetanes with two adjacent tetrasubstituted carbon atoms in high yields and up to 96% *ee*. This reaction concept has been extended to chiral spirocyclohexene-cyclobutanes and -azetidines with the same high stereoselectivities. Finally, it is demonstrated that the obtained scaffolds can undergo diverse transformations leading to complex structures with up to four stereocenters. In one of these transformations, we demonstrated that the nitro group adjacent to the oxetane can be applied for ring-opening of the oxetane under nucleophilic conditions.

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Keywords: cycloaddition reactions · oxetanes · spirocycles · trienamine catalysis · trisubstituted nitroolefins

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[11] CCDC 1434118 (**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[12] CCDC CCDC 1435327 (**7**), and 1437702 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[13] Carreira et al. have observed a ring-opening reaction of oxetene intermediates by a nitro group for the formation of isoxazoles; see Ref. [2b].

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