

Direct Access to Multifunctionalized Norcamphor Scaffolds by Asymmetric Organocatalytic Diels–Alder Reactions

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Abstract: A general organocatalytic cross-dienamine activation strategy to produce chiral multifunctionalized norcamphor compounds having a large diversity in substitution pattern is presented. The strategy is based on a Diels–Alder reaction of an amino-activated cyclopentenone reacting with most common classes of electron-deficient olefins, such as nitro-, ester-, amide-, and cyano-substituted olefins, chalcones, conjugated malononitriles, CF_3 -substituted enones, and fumarates. The corresponding norcamphor derivatives are formed in good yield, excellent enantioselectivities, and with complete diastereoselectivity. Furthermore, it is demonstrated that quaternary stereocenters and spiro norcamphor compounds can be formed with high stereoselectivity. The present development provides a simple, direct, and efficient approach for the preparation of important norcamphor scaffolds.

The Diels–Alder reaction is one of the most important synthetic transformations known and it provides easy access to six-membered carbo- and heterocycles in a chemo-, regio-, and stereoselective manner.^[1] Considerable effort has been devoted to the development of catalytic asymmetric versions of this reaction, with most examples focusing on a LUMO-lowering strategy through activation of electron-deficient dienophiles with chiral Lewis acids.^[2] The HOMO-activation strategy is mainly dominated by organocatalytic approaches focused on enamine-,^[3] dienamine-,^[4] and trienamine^[5] activation of alkyl- and vinyl aldehydes and ketones with chiral aminocatalysts.

The bicyclo[2.2.1]heptane scaffold is an important molecular entity and a Reaxys substructure search on this scaffold returned more than 100 000 hits, of which more than 15 000 compounds have shown bioactivity.^[6] A vast number of bioactive compounds have been applied within all areas of the life sciences and a few examples are shown in Figure 1. Sordarins, a new class of selective antifungal agents, and camphor are natural products containing the bicyclo[2.2.1]heptane scaffold.^[7] Numerous synthetic drugs and drug candidates have been created based on the bicyclo[2.2.1]heptane scaffold. Both Setrobuvir and LMV-601 are antiviral agents displaying activity against hepatitis C and HPV respectively.^[8] The library of uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonists are potential new drugs as this receptor has been targeted for the treatment of

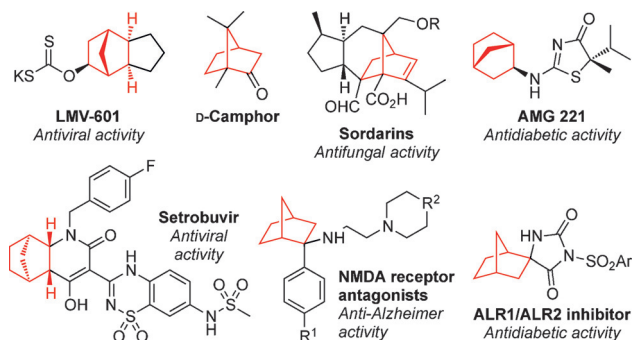


Figure 1. A few selected bioactive compounds containing the bicyclo[2.2.1]heptane scaffold.

Alzheimer's disease, but is also implicated in a range of other neurological and neuropsychiatric diseases.^[9] AMG 221, an inhibitor of 11 β -HSD1, has entered clinical trials for the treatment of type II diabetes, while the ALR1/ALR2 inhibitors also show promising in vivo antidiabetic activity.^[10]

We envisioned that organocatalysis could be used to develop a simple, direct, and efficient approach for the preparation of this very important molecular scaffold, providing a method that was diversity oriented, both in terms of substrates and substituents. Diels–Alder reactions of linear dienamines yield allylic amines, which cannot undergo hydrolysis. Thus, to achieve catalytic turnover, the amino-catalyst needs to be excluded in another manner (for example by E1cB elimination).^[4a] A more direct strategy for the Diels–Alder reaction can be achieved by applying cross-dienamines which directly results in hydrolyzable enamines and thus catalytic turnover.^[11]

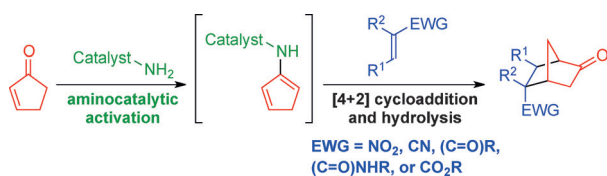
Surprisingly, organocatalytic cross-dienamine-activated Diels–Alder reactions of cyclopentenones have been almost completely ignored, whereas numerous examples have been reported on the reactions of open-chain vinyl ketones,^[12] cyclohexenones,^[12d,13] and cycloheptenones.^[13b–g] In fact, only three papers have been published, each containing a single entry, on the Diels–Alder reaction of cyclopentenone with for example, electron-deficient polyenes (with modest results),^[13f–h] whereas several papers report unsuccessful attempts.^[13a–c] This stands in stark contrast to the importance of the bicyclo[2.2.1]heptane scaffold.

Herein, we will present the asymmetric aminocatalytic reaction of cyclopentenone with a variety of different dienophiles and investigate its versatility towards the diversification of privileged structures (Scheme 1).

Initially, we focused our attention on the development of the Diels–Alder reaction between cyclopentenone **2** and nitrostyrene **3a**. The reaction was found to proceed in the

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Scheme 1. Aminocatalytic Diels–Alder reactions providing multifunctionalized norcamphor scaffolds.

presence of catalyst **1a**, but the desired product **4a** was only formed in 9% yield as a nearly racemic mixture (5% *ee*; Table 1, entry 1). It was observed that the conversion was much higher than the corresponding yield, which was ascribed to a polymerization of **3a**. Improved yield (26%) and enantioselectivity (28% *ee*) were obtained when primary aminocatalyst **1b** was employed (Table 1, entry 2). In an attempt to improve yield and enantiocontrol, the bifunctionalized catalyst **1c**, derived from **1b**, was employed. However, only the racemate of **4a** was obtained in a very low yield (entry 3). The quinine-based catalyst **1d**^[14] was found to be superior to all other catalysts applied, producing **4a** in good

Table 1: Screening of the reaction conditions for the Diels–Alder reaction of cyclopentenone **2** and nitrostyrene **3a**.

Reaction scheme showing the conversion of cyclopentenone (**2**) and nitrostyrene (**3a**) to a bicyclic product (**4a**) using a catalyst (20 mol%), additive (20 mol%), and solvent at 40 °C for 18 h.

Chemical structures of catalysts **1a**, **1b**, **1c**, and **1d**/**1e**.

1a: A quinine derivative with a phenyl group and a pyridine ring.

1b: A primary amine derivative with a phenyl group and a pyridine ring.

1c: A bifunctionalized amine derivative with a phenyl group, a pyridine ring, and a trifluoromethyl group.

1d R = OMe
1e R = H

Entry ^[a]	Cat.	Solvent	Additive	Conv./Yield [%] ^[c]	d.r. ^[c]	ee [%] ^[d]
1	1a	CDCl ₃	EtCO ₂ H	50/9	> 20:1	–5 ^[f]
2	1b	CDCl ₃	EtCO ₂ H	67/26	> 20:1	–28 ^[f]
3	1c	CDCl ₃	EtCO ₂ H	42/5	> 20:1	1
4	1d	CDCl ₃	EtCO ₂ H	79/49	> 20:1	83
5	1d	Toluene	EtCO ₂ H	91/52	> 20:1	90
6	1d	THF	EtCO ₂ H	35/17	> 20:1	91
7	1d	Heptane	EtCO ₂ H	100/18	> 20:1	82
8	1d	Toluene	PhCO ₂ Na	68/20	> 20:1	91
9	1d	Toluene	PhCO ₂ H	100/51	> 20:1	90
10	1d	Toluene	SA	90/44	> 20:1	91
11	1d	Toluene	<i>p</i> -NBA	90/34	> 20:1	87
12	1d	Toluene	TFA	62/14	> 20:1	90
13	1e	Toluene	EtCO ₂ H	73/39	> 20:1	84
14 ^[b]	1d	Toluene	EtCO ₂ H	89/65 ^[e]	> 20:1	90

[a] Reactions were performed with **2** (0.2 mmol), **3a** (0.1 mmol), **1** (0.02 mmol), and additive (0.02 mmol) in solvent (0.1 mL). [b] **2** (0.15 mmol) and 30 h reaction time. [c] Determined by ¹H NMR spectroscopy on the crude reaction mixture with 1,3,5-tris(trifluoromethyl)benzene as the internal standard. [d] Determined by ultra-performance convergence chromatography (UPC²) on a chiral stationary phase. [e] **4a** was isolated in 62% yield after flash column chromatography on silica gel. [f] Negative *ee* values indicate that the opposite enantiomer of **4a** was formed preferentially. *p*-NBA = *p*-nitrobenzoic acid, SA = salicylic acid, TFA = trifluoroacetic acid.

yield (49%) and high enantioselectivity (83% *ee*; entry 4). A solvent screening revealed that enantiocontrol could be enhanced in toluene (90% *ee*) while maintaining the same yield as in CDCl₃ (entries 4–7). Several additives were evaluated and found only to have minor influences on the enantioselectivity of the reaction (87–91% *ee*; Table 1, entries 8–12). The reaction performed best in weakly acidic mediums, whereas bases or stronger acids reduced the yield of **4a** (entries 8, 11, 12). Finally, the yield could be improved by increasing the reaction time to 30 h (entry 14).

To evaluate the generality of the reaction, a series of nitrostyrenes **3** were subjected to the reaction with cyclopentenone **2** (Table 2). Both electron-donating and electron-

Table 2: Scope of the Diels–Alder reaction of cyclopentenone **2** with nitrostyrenes **3**.

Reaction scheme showing the conversion of cyclopentenone (**2**) and a nitro-substituted alkene (**3**) to a bicyclic product (**4**). The reaction conditions are: **1d** (20 mol%), EtCO₂H (20 mol%), Toluene, 40 °C.

Entry ^[a]	R	Product	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	Ph	4a	62	> 20:1	90
2	<i>p</i> -Me(C ₆ H ₄)	4b	50	> 20:1	90
3	<i>p</i> -F(C ₆ H ₄)	4c	56	> 20:1	89
4	<i>p</i> -Br(C ₆ H ₄)	4d	56	> 20:1	92
5	<i>o</i> -Cl(C ₆ H ₄)	4e	81	> 20:1	95
6	<i>o</i> -MeO(C ₆ H ₄)	4f	79	> 20:1	95
7	<i>m</i> -MeO(C ₆ H ₄)	4g	48	> 20:1	90
8	<i>p</i> -MeO(C ₆ H ₄)	4h	48	> 20:1	86
9	2-naphthyl	4i	49	> 20:1	89
10	2-furyl	4j	59	> 20:1	84
11	PhCH=CH	4k	41	9:1	87

[a] Reactions were performed with **2** (0.15 mmol), **3** (0.1 mmol), **1d** (0.02 mmol), and propionic acid (0.02 mmol) in toluene (0.1 mL). [b] Yield of isolated product. [c] Determined by ¹H NMR spectroscopy on the crude reaction mixture. [d] Determined by UPC² on a chiral stationary phase.

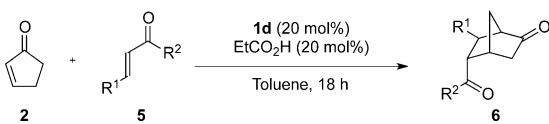
withdrawing substituents on the aromatic system were well-tolerated (entries 2–8), whereas aliphatic nitroolefins or very electron-poor nitro-substituted nitrostyrenes primarily lead to polymerization of the nitroolefin.^[15] Nitrostyrenes **3f–h**, with a methoxy group placed in each position on the aromatic ring, were evaluated (entries 6–8). Both yields and enantioselectivities followed the order *ortho* > *meta* > *para* and **4f–h** could be obtained in 48–79% yield and 86–95% *ee*. This trend was also apparent for the halide-substituted nitrostyrenes **3c–e** (entries 3–5). Polyaromatic, as well as heteroaromatic moieties, could be implemented in the products **4i** and **4j** in good yields and with high enantioselectivities (entries 9, 10). In a final reaction, the less reactive nitrodiene **3k** was reacted with **2** and product **4k** was obtained with 87% *ee*, but in a lower yield relative to the other entries (entry 11).

During the study of the scope of nitrostyrenes **3**, we realized that chalcones **5** also readily underwent a Diels–Alder reaction with cyclopentenone **2** under identical reaction conditions. This type of cross-enone reaction has previously been deemed difficult as a result of self-condensation of the starting materials.^[12a,16] Generally, chalcones **5**

were found to be slightly less reactive than **3**, but also more stable towards polymerization. As a result, most reactions were performed at higher temperatures. Thus, it turned out that the present catalytic method could be expanded to also include chalcones providing access to new classes of differently substituted norcamphor compounds.

In the first experiment, chalcone **5a** was reacted with cyclopentenone **2**. The desired cycloadduct **6a** was obtained in 79 % yield and 93 % *ee* (Table 3, entry 1). Both weakly and strongly electron-withdrawing groups were well-tolerated on

Table 3: Scope of the Diels–Alder reaction of cyclopentenone **2** with chalcones **5**.

							
Entry ^[a]	R ¹ /R ²	Product	T [°C]	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]	
1	Ph/Ph	6a	60	79	> 20:1	93	
2	<i>p</i> -Br(C ₆ H ₄)/Ph	6b	60	66	> 20:1	96	
3	<i>m</i> -NO ₂ (C ₆ H ₄)/Ph	6c	40	63	> 20:1	96	
4	<i>p</i> -NO ₂ (C ₆ H ₄)/Ph	6d	40	52	> 20:1	99	
5	<i>o</i> -MeO(C ₆ H ₄)/Ph	6e	60	75	> 20:1	99	
6	<i>m</i> -MeO(C ₆ H ₄)/Ph	6f	80	52	> 20:1	96	
7	<i>p</i> -MeO(C ₆ H ₄)/Ph	6g	100	38	> 20:1	87	
8	2-furyl/Ph	6h	80	62	> 20:1	87	
9	2-thiophenyl/Ph	6i	80	58	> 20:1	91	
10	2-naphthyl/Ph	6j	80	47	> 20:1	91	
11	Ph/ <i>p</i> -NO ₂ (C ₆ H ₄)	6k	60	85	> 20:1	96	
12	<i>p</i> -Br(C ₆ H ₄)/ <i>p</i> -NO ₂ -(C ₆ H ₄)	6l	40	91	> 20:1	99	
13 ^[e]	Me/Ph	6m	40	32	> 20:1	91	
14 ^[f]	Ph/Me	6n	60	19	> 20:1	92	

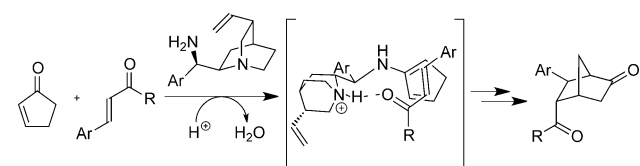
[a] Reactions were performed with **2** (0.2 mmol), **5** (0.1 mmol), **1d** (0.02 mmol), and propionic acid (0.02 mmol) in toluene (0.1 mL).

[b] Yield of isolated product. [c] Determined by ¹H NMR spectroscopy on the crude reaction mixture. [d] Determined by UPC² on a chiral stationary phase. [e] Reaction time 50 h. [f] Reaction time 72 h.

the aromatic rings (entries 2–4, 11, 12). The nitro-substituted chalcones **5c,d** having the nitro group in the *meta* and *para* positions readily underwent reactions with **2** to form products **6c** and **6d** in good yields and with almost perfect enantioselectivities (entries 3, 4).^[17] Electron-donating groups in *ortho*, *meta*, and *para* positions were also evaluated and, as for the nitrostyrenes **3f–h**, both yields and enantioselectivities followed the order *ortho* > *meta* > *para* for **5e–g** (entries 5–7). It should be noted that a temperature of 100 °C was necessary for the reaction with **5g**. Although the product could only be obtained in a low yield (38 %), it still performed well in terms of enantioselectivity (87 % *ee*) considering the high reaction temperature. Polyaromatic and heteroaromatic moieties could also be incorporated in the products **6h–j** in 47–62 % yields and 87–91 % *ee* (entries 8–10). Additionally, it was demonstrated that substituents on the other aromatic ring (R²) could also be present when using chalcone compounds **5k** and **5l**, giving the desired products **6k** and **6l** in 85–91 % yields and 96–99 % *ee* (entry 11, 12). With aliphatic groups in

either the R¹ or R² position, vinyl ketones **5m** and **5n** underwent the reaction with excellent stereoselectivities (>20:1 d.r., 91–92 % *ee*), albeit in low yield (19–32 %). It should be noted that the reaction of enone **5n** may pose a potential challenge, as two cross-dienamines are possible. However, only one product **6n** was formed in the reaction.

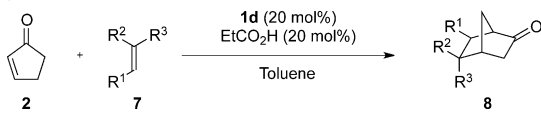
A recent paper by Houk and Lam described the mechanistic aspects of an organocatalytic intramolecular aldol reaction catalyzed by cinchona alkaloid primary amines.^[18] Based on the reaction mechanism proposed by the authors, we suggest a related transition state for this intermolecular aminocatalyzed Diels–Alder reaction (Scheme 2). Initially,



Scheme 2. Proposed reaction pathway for the aminocatalyzed cycloaddition reaction.

the cinchona alkaloid aminocatalyst condenses with cyclopentenone to form a cross-dienamine intermediate. By protonation of the quinuclidine part of the catalyst, the dienophile is activated and directed into the appropriate position by hydrogen bonding. After the cycloaddition step, the formed enamine is hydrolyzed to the corresponding ketone while liberating the aminocatalyst. Based on the diastereoselectivity obtained, we propose that the reaction might proceed via an asynchronous concerted cycloaddition, as more than 20:1 d.r. is obtained for all products except two (Table 2, entry 11 and Table 4, compound **8b** (see below)). However, we cannot exclude that a stepwise mechanism

Table 4: Scope of the Diels–Alder reaction of cyclopentenone **2** with dienophiles **7**.^[a]

					
Entry	Dienophile	Product	Yield [%]	d.r.	ee [%]
1	Ph	8a	53%	>20:1	42%
2	Ph	8b	62%	19:1	83%
3	Ph	8c	71%	>20:1	98%
4	MeO ₂ C	8d	74%	>20:1	65%
5	Ph	8e	79%	>20:1	80%
6	Ph	8f	84%	>20:1	87%
7	Ph	8g	27%	>20:1	90%

[a] Reactions were performed with **2** (0.2 mmol), **3** (0.1 mmol), **1d** (0.02 mmol), and propionic acid (0.02 mmol) in toluene (0.1 mL). In each case, the yield given is that of the isolated product. The d.r. values were determined by ¹H NMR spectroscopy on the crude reaction mixture, and ee values were determined by UPC² on a chiral stationary phase.

might also be operating for some dienophiles, such as those in which the reacting olefin is in conjugation with another olefin.

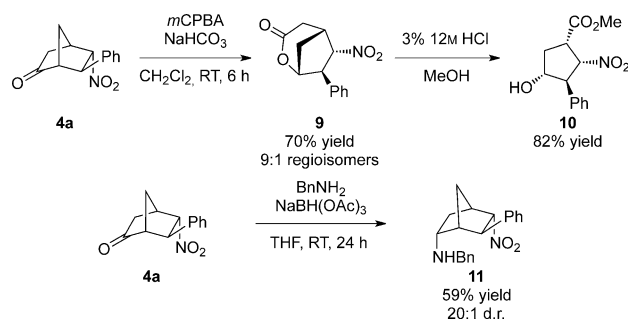
Normally, bifunctionalized catalysts are sensitive towards small variations of the hydrogen-bond acceptor groups of the electrophiles and extensive screenings need to be performed for each electrophile applied. Since the present reaction performed well for both nitrostyrenes and chalcones under identical reaction conditions, we were curious to see how well the reaction would perform towards different types of dienophiles. It turned out that the organocatalytically activated cyclopentenone shows unique general reactivity, as it reacts with most common classes of electron-deficient olefins. Furthermore, it allows for the formation of quaternary stereocenters and spirocyclic compounds. Table 4 shows an example of each of these reactions, without outlining all of the different substituent patterns as shown for the nitroolefins (Table 2) and chalcones (Table 3), and shows that varying the substituents does not change the diastereoselectivity of the reaction significantly. The following reactions were performed without further optimization of the reaction conditions used for the nitroolefins and chalcones.

Although the reaction with malononitrile **7a** only produced the cycloadduct **8a** in moderate enantioselectivity (42% *ee*), the reaction with the polyconjugated malononitrile **7b** afforded **8b** in good yield and high enantioselectivity (62% yield, 83% *ee*). Pleasingly, the CF₃-substituted enone **7c** readily underwent the cycloaddition to produce **8c** in 71% yield and almost perfect enantioselectivity (98% *ee*). The cycloadduct **8d** (from reaction of *trans*-dimethyl fumarate) could easily be generated in high yield but with modest enantiomeric excess. It was also demonstrated that quaternary stereocenters could be incorporated into the bicyclo[2.2.1]heptane scaffold by reaction of cyclopentenone **2** with cyanoacrylate **7e** or cyanoacrylamide **7f** to produce the desired cycloadducts **8e** and **8f** in high yield and enantioselectivities (79–84% yield, 80–87% *ee*). Finally, the spiro norcamphor **8g** could also be obtained with high enantiomeric excess, albeit in low yield under these nonoptimized reaction conditions. The examples in Table 4 highlight the generality of the catalytic system, since different types of dienophiles **7** can be applied under identical conditions as for nitrostyrenes **3** and chalcones **5**.

A few selected transformations were performed on **4a** to demonstrate the synthetic potential of the substituted norcamphor products. First, a Baeyer–Villiger oxidation led to the lactone **9** which could be ring-opened under acidic conditions to provide the highly substituted cyclopentane **10** containing four contiguous stereocenters (Scheme 3, top). Many bioactive products contain an amine moiety attached to the bicyclo[2.2.1]heptane scaffold (Figure 1). Therefore, we demonstrated a diastereoselective reductive amination of **4a** to form compound **11**, containing an additional stereocenter, in good yield (59%; Scheme 3, bottom).

The absolute configurations of compounds **6l** and **11** were unambiguously determined by single-crystal X-ray diffraction and the configurations of all remaining products were assigned by analogy.^[19]

In conclusion, we have demonstrated a straightforward procedure for the generation of a variety of 5,6-substituted



Scheme 3. Synthetic transformations of cycloadduct **4a**. mCPBA = *meta*-chloroperbenzoic acid.

norcamphor derivatives by means of an asymmetric organocatalytic reaction. Remarkably, the reaction conditions turned out to be very general allowing most common electron-deficient olefins to be applied in the cycloaddition without further optimizations. The norcamphor scaffolds are obtained in generally good to high yields and high to excellent stereoselectivities, providing a simple and efficient process for the preparation of an important class of privileged structures. Additionally, a few selected transformations were demonstrated to show that an additional stereocenter could be introduced by a diastereoselective reductive amination and that the norcamphor products could undergo an oxidative ring-opening reaction to generate highly substituted cyclopentanes.

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