



Amine-catalyzed direct self Diels–Alder reactions of α,β -unsaturated ketones in water: synthesis of pro-chiral cyclohexanones

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Received 27 June 2002; revised 18 July 2002; accepted 22 July 2002

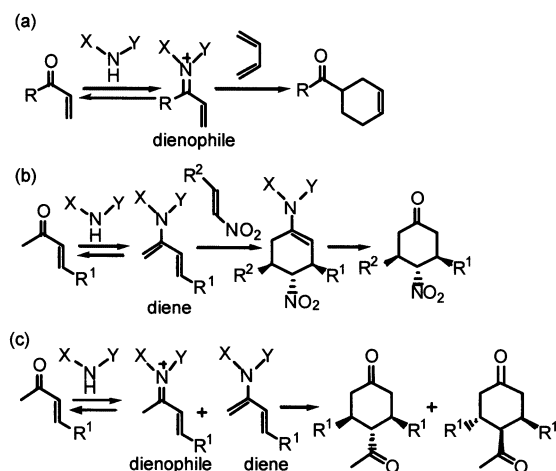
Abstract—Amine-catalyzed direct self Diels–Alder reactions of α,β -unsaturated ketones have been developed. (*S*)-1-(2-Pyrrolidinyl-methyl)pyrrolidine, L-proline and pyrrolidine catalyzed the reaction of α,β -unsaturated ketones to provide cyclohexanone derivatives with good yield (up to 80%) in a single step via in situ-generation of 2-amino-1,3-butadienes and iminium ion-activated enones. Pro-chiral cyclohexanones were selectively prepared with pyrrolidine catalysis in water. © 2002 Published by Elsevier Science Ltd.

The Diels–Alder reaction is one of the most important transformations in synthetic chemistry for the construction of six-membered ring systems and many strategies to catalyze this reaction have been studied.¹ Recently, organoamines have been applied as catalysts of Diels–Alder reactions involving α,β -unsaturated carbonyl compounds in a LUMO-lowering strategy based on imine formation (Scheme 1a).² Extending our studies of organoamine-catalyzed aldol,³ Michael,⁴ Mannich,⁵ and related reactions⁶ founded on enamine catalysis, we have reported the first direct asymmetric Diels–Alder reactions of α,β -unsaturated ketones with nitro olefins. This strategy involved in situ generation of 2-amino-1,3-butadienes with amine catalysts **1** or **2** providing for the synthesis of cyclohexanones (Scheme 1b).⁷

In this report we demonstrate the utility of amine-catalyzed self Diels–Alder (or double Michael) reactions of α,β -unsaturated ketones providing for the synthesis of pro-chiral acyl-substituted cyclohexanones (Scheme 1c). In this reaction, we envisioned amine activation of the α,β -unsaturated ketone as a dienophile together with in situ generation of a 2-amino-1,3-butadiene diene. This strategy would combine the iminium ion-based route of MacMillan,² with our enamine-based activation strategy.⁷ This type of catalytic Diels–Alder reaction affords

an attractive single-step route to cyclohexanone derivatives.⁸

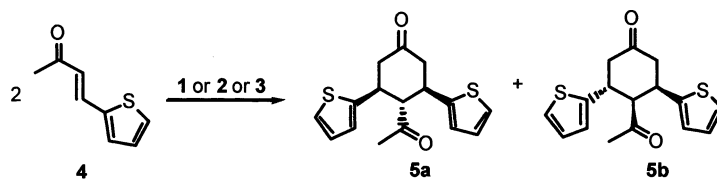
Initially, we studied a variety of reaction conditions involving amine catalysts for the self Diels–Alder reaction of α,β -unsaturated ketone. Since chiral amines (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **1** and L-Proline **2** provide enamine intermediates as described above,^{3–6} we tested these amines along with pyrrolidine **3** as catalysts for the self Diels–Alder reaction of α,β -unsaturated ketone **4** to form cyclohexanone derivatives **5a** and **5b**.⁹ The results are shown in Table 1.



Scheme 1.

Keywords: amines; cyclohexanones; Diels–Alder reactions; organocatalysis; enamines; imines; aqueous media.

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Table 1. Amine-catalyzed self Diels–Alder reaction of α,β -unsaturated ketone **4**

Entry	Enone (mmol)	Catalyst	Solvent	Temperature, reaction time	Conversion ^a	Yield (%) ^b	Ratio ^c 5a:5b
1	0.5	1 (0.3 equiv.)	Neat	rt, 24 h	58	50	1.6:1
2 ^d	0.5	1 (0.3 equiv.)	THF	40°C, 24 h	83	68	1.0:1
3 ^d	0.5	2 (0.3 equiv.)	EtOH	rt, 5 days	70	52	4.5:1
4 ^d	0.5	2 (0.3 equiv.)	MeOH	40°C, 24 h	54	47	3.5:1
5 ^d	0.5	3 (0.3 equiv.)	THF	40°C, 8.5 h	100	63	2.0:1
6 ^e	0.5	3 (0.3 equiv.)	H ₂ O	40°C, 23 h	90	70	6.0:1
7 ^f	0.5	3 (0.3 equiv.)- <i>p</i> -TSA	H ₂ O	40°C, 23 h	90	65	6.0:1

^a Conversion based on the ratio of **4** and **5**, determined by ¹H NMR analysis.

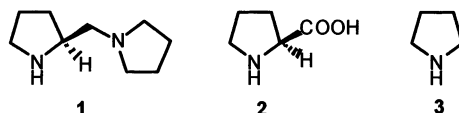
^b Combined isolated yield of **5a** and **5b**.

^c The ratio of diastereoisomers of **5** was determined by ¹H NMR.

^d The reaction was performed using **4** (0.5 mmol) and catalyst (0.15 mmol) in solvent (0.05 mL).

^e The reaction was performed using **4** (0.5 mmol) and catalyst (0.15 mmol) in H₂O (0.5 mL).

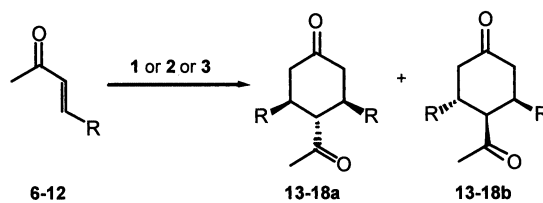
^f The reaction was performed using **4** (0.5 mmol), *p*-TSA (0.075 mmol) and catalyst (0.15 mmol) in H₂O (0.5 mL).



We were pleased to find that the reaction of enone **4** with amine **1** in neat conditions at room temperature for 24 h furnished a 1.6:1 diastereomeric mixture of Diels–Alder products **5a** and **5b** in 50% yield (entry 1). The same reaction in THF at 40°C for 24 h furnished cyclohexanones **5a** and **5b** in 68% yield as a 1:1 diastereomeric mixture (entry 2). Next, L-proline **2** was tested for the self Diels–Alder reaction of enone **4**. Performing the reaction under proline catalysis (30 mol% of **2**) in ethanol at room temperature for 5 days furnished products **5a** and **5b** in 52% yield with an enhanced 4.5:1 diastereomeric ratio (entry 3). The same reaction in methanol at 40°C for 24 h furnished products **5a** and **5b** with slightly reduced yield (entry 4). Since the chiral amines **1** and **2** provided the pro-chiral cyclohexanone derivative **5a** as the major product, we studied simple pyrrolidine as an achiral amine catalyst of this reaction. Accordingly, the reaction of enone **4** (0.5 mmol) with pyrrolidine **3** (0.15 mmol) in THF (0.05 mL) at 40°C for 8.5 h furnished the Diels–Alder products **5a** and **5b** in a 2:1 ratio and in 63% yield (entry 5). Next, we performed the reaction in water (0.5 mL) at 40°C for 23 h in an attempt to alter the stereoselectivity of the reaction. We were pleased to find that under these conditions Diels–Alder products **5a** and **5b** could be isolated in 70% yield with improved *exo*–*endo* selectivity (6:1) (entry 6). An attempt to further improve this reaction by addition of 15 mol% *p*-TSA as a co-catalyst to facilitate equilibration between imine and enamine intermediates during the reaction, resulted in slightly reduced yield with conservation of stereoselectivity (entry 7).

Examination of the scope of our amine-catalyzed reactions with a variety of α,β -unsaturated ketones is presented in Table 2. Amines **1**, **2** and **3** catalyzed the self Diels–Alder reaction of α,β -unsaturated ketones **6**–**12** to provide cyclohexanone derivatives **13**–**18** with isolated yields of 47–80%.¹⁰ The diastereoselectivity of these reactions varied depending on the amine catalyst, the reactants, as well as the reaction conditions. In four examples of catalysis using water as the solvent (entries 2, 3, 5 and 6), selectivity towards the *exo* product was uniformly increased. The amine-catalyzed self Diels–Alder reactions of α,β -unsaturated ketones in water provided the pro-chiral *exo*-product as the major product. While an *endo* selectivity is typically expected with enone dienophiles due to secondary orbital interactions, an *exo* selectivity is likely the result of more favorable iminium ion solvation and hydrophobic interactions¹¹ in the transition state as compared to those possible with an *endo*-transition state. There appear to be some steric limitations to this reaction. *trans*-4-(4-Methoxyphenyl)-3-methyl-but-3-en-2-one **19** proved to be unreactive with pyrrolidine under the standard reaction conditions after 48 h. Comparison of this reaction with simple α,β -unsaturated ketone **8** (entry 5, Table 2) suggests that **19** is too sterically demanding for the imine–enamine based Diels–Alder reaction mechanism proposed here.

Our amine-catalyzed Diels–Alder reaction provides for the scalable preparation of pro-chiral cyclohexanone derivatives using water as solvent. Cyclohexanone derivatives **13a** and **13b** were readily prepared on a 1.5 g scale from enone **6** under very mild conditions (Scheme 2).

Table 2. Amine-catalyzed self Diels–Alder reactions of a variety of α,β -unsaturated ketones

Entry	R	Catalyst	Solvent	Temperature, reaction time	Product	Yield (%) ^a	Ratio ^b a:b
1 ^c	Ph (6)	1	THF	40°C, 60 h	13a, 13b	75	2.0:1
2 ^d	Ph (6)	3	THF	40°C, 48 h	13a, 13b	70	1.3:1 (6.0:1) ^e
3 ^f	2-Furyl (7)	3	THF	40°C, 24 h	14a, 14b	52	1.5:1 (2.5:1) ^e
4 ^e	2-Furyl (7)	1	THF	40°C, 39 h	14a, 14b	47	2.0:1
5 ^f	4-CH ₃ OC ₆ H ₄ (8)	3	THF	40°C, 18 h	15a, 15b	75	1.0:2 (8.0:1) ^e
6 ^f	1-Naphthyl (9)	3	THF	40°C, 15 h	16a, 16b	75	1.4:1 (2.5:1) ^e
7 ^f	4-NO ₂ -C ₆ H ₄ (10)	3	THF	40°C, 5 h	17a, 17b	80	1.1:1
8 ^f	CO ₂ Me (11)	2	CH ₃ OH	rt, 16 h	18a, 18b	55	1:1.3
9 ^f	CO ₂ Me (11)	3	THF	rt, 38 h	18a, 18b	58	1:2.3
10 ^f	H (12)	3	THF	rt, 2 h; 40°C, 2 days	No reaction	–	–

^a Isolated yield of diastereoisomers.

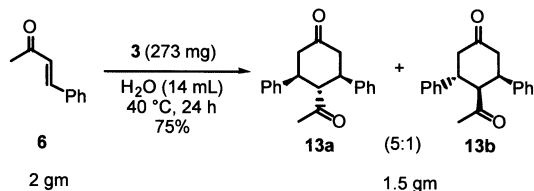
^b The ratio was determined by ¹H NMR of the extracted reaction mixture.

^c The reaction was performed using enone (**6**, 0.5 mmol) and **1** (0.15 mmol) in THF (0.15 mL) at 40°C. After 50% completion, *p*-TSA (0.075 mmol) was added to the reaction mixture.

^d The reaction was performed using enone **6** (0.5 mmol) and **3** (0.15 mmol) in THF (0.5 mL) at 40°C. After 24 h, *p*-TSA (0.075 mmol) was added to the reaction mixture.

^e Obtained using enone (0.5 mmol) and **3** (0.15 mmol) in H₂O (0.5 mL) at 40°C for 15 h.

^f The reaction was performed using enone (0.5 mmol) and catalyst (0.15 mmol) in solvent (0.05 mL).

**Scheme 2.**

Cyclohexanone **13a** was then obtained in pure form by recrystallization from EtOAc–hexane.

In summary, we have demonstrated for the first time amine-catalyzed direct self Diels–Alder reactions of α,β -unsaturated ketones to furnish cyclohexanone derivatives via the in situ formation of dienes and dienophiles in the form of 2-amino-1,3-butadienes and iminium activated enones, respectively, from simple α,β -unsaturated ketones. Currently, we have no formal proof that the mechanism exclusively involves an iminium-activated α,β -unsaturated ketone as a dienophile since α,β -unsaturated ketones are themselves reactive in some Diels–Alder reactions. Precedence for the efficacy of an iminium ion-based activation mechanism with α,β -unsaturated ketones is found in the recent studies of MacMillan.² Therefore, the possibility exists that both pathways could be operative in our reactions. While the reactions reported herein are enantioselective with respect to the minor *endo* product (entry 3, **5b**, 23%

ee),¹² further studies might yield highly enantio- and diastereoselective variants of this reaction.

Acknowledgements

This study was supported in part by the NIH (CA27489) and The Skaggs Institute for Chemical Biology.

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9. Relative stereochemistry was assigned by the coupling constant of the α -acyl-hydrogen. Spectral data for **5a**: ^1H NMR (399 MHz, CDCl_3): δ 7.20 (1H, ddd, $J=5.2, 1.2$ and 0.8 Hz), 6.91 (1H, dd, $J=5.2$ and 3.6 Hz), 6.81 (1H, ddd, $J=3.6, 1.2$ and 0.4 Hz), 3.64 (1H, dt, $J=11.2$ and 6.4 Hz), 3.33 (1H, t, $J=11.2$ Hz), 2.85–2.70 (2H, m), 1.52 (3H, s, COCH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 210.5 (C, C=O), 205.4 (C, C=O), 144.3 (C, C=CH), 127.0 (CH), 125.2 (CH) and 124.2 (CH) [3 \times aromatic CH], 64.3 (CH), 48.7 (CH_2), 42.0 (CH), 33.2 (CH_3 , COCH_3); HRMS (MALDI-FTMS): $\text{C}_{16}\text{H}_{16}\text{O}_2\text{S}_2$ [MH^+] $^+$ calcd 305.0664, found 305.0669. **5b**: ^1H NMR (399 MHz, CDCl_3): δ 7.23 (1H, dd, $J=5.2$ and 0.8 Hz), 7.18 (1H, dd, $J=5.2$ and 0.8 Hz), 6.96–6.90 (2H, m), 6.89 (1H, td, $J=3.6$ and 0.8 Hz), 6.77 (1H, td, $J=3.6$ and 0.8 Hz), 3.92 (1H, dd, $J=11.6$ and 6.0 Hz), 3.79 (1H, td, $J=10.8$ and 4.0 Hz), 3.55 (1H, t, $J=4.8$ Hz), 3.23–3.10 (2H, m), 2.76 (2H, dt, $J=16.0$ and 5.6 Hz), 1.95 (3H, s, COCH_3); HRMS (MALDI-FTMS): $\text{C}_{16}\text{H}_{16}\text{O}_2\text{S}_2$ [MNa^+] $^+$ calcd 327.0484, found 327.0487.
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12. Enantiomeric excess was determined by chiral-phase HPLC analyses. Absolute stereochemistry was not determined.