# Amine-catalyzed direct Diels–Alder reactions of α,β-unsaturated ketones with nitro olefins

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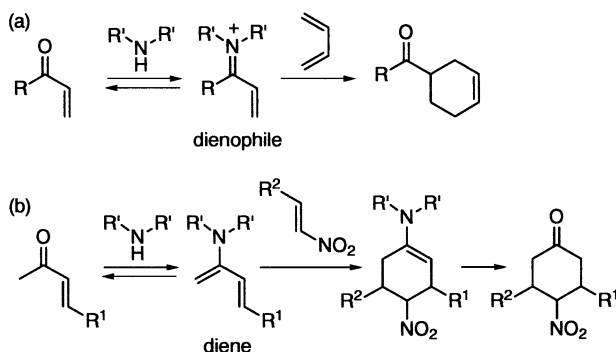
**Abstract**—Amine-catalyzed Diels–Alder reactions of α,β-unsaturated ketones with dienophiles have been developed. Either (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine or L-proline catalyzed the in situ-generation and reaction of 2-amino-1,3-dienes to provide cyclohexanone derivatives in good yield (up to 87%) in one step with modest enantioselectivity. © 2002 Published by Elsevier Science Ltd.

The Diels–Alder reaction is one of the most important synthetic transformations and many strategies have been devised to catalyze this reaction.[1] Recently, amines have been applied as catalysts of Diels–Alder reactions wherein α,β-unsaturated carbonyl compounds are activated as dienophiles in a LUMO-lowering strategy based on imine formation (Scheme 1a).[2] An alternative strategy involving the in situ-generation of 2-amino-1,3-dienes from α,β-unsaturated ketones has not been exploited in Diels–Alder reactions, although enamine intermediates have been exploited as nucleophiles in amine-catalyzed aldol,[3] Michael,[3b,4] Mannich,[3b,5] and

related reactions.[6] Here we report amine-catalyzed Diels–Alder reactions (or double Michael reactions) between α,β-unsaturated ketones and nitro olefin dienes (Scheme 1b). This type of catalytic Diels–Alder reaction provides an efficient single-step route to the synthesis of cyclohexanone derivatives.[7] Significantly, prior synthesis and isolation of 2-amino-1,3-diene[7] reactants is not required for this transformation.

Since (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (**1**) and L-proline (**2**) have proven to be effective catalysts in the enamine-based reactions described above,[3–6] we studied the potential of these amines as Diels–Alder catalysts of the reaction of nitro olefin **3** and α,β-unsaturated ketone **4** to provide cyclohexanone derivatives **5a** and **5b**.[8,9] The results of these studies are shown in Table 1.

Application of amine **1** as a Diels–Alder catalyst was initially studied by mixing **3** (0.5 mmol) with **4** (2.5 mmol) and **1** (0.5 mmol) in THF (1 mL) at room temperature (rt). Diels–Alder products **5a** and **5b** were obtained in good yield after 1 day (entry 1). The same reaction with a catalytic amount of **1** (50 and 30 mol% based on **3**) also provided the desired products in good yield within a few days (entries 2 and 3). The diastereomeric ratio of the products was 4:1 under these conditions, and was not effected by the amount of catalyst used. When the reaction was performed with 1.2 equiv. of **4**, the reaction rate became sluggish (entries 4–6), but provided the desired products in similar yield.



**Scheme 1.**

**Table 1.** Amine-catalyzed Diels–Alder reaction of nitro olefin **3** and α,β-unsaturated ketone **4**
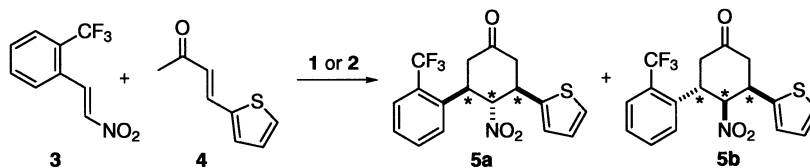


| Entry | **4**[a] (equiv.) | Catalyst[b] | Solvent | Temperature, reaction time | Yield (%) | Ratio[c] **5a:5b** |
|---|---|---|---|---|---|---|
| 1[d] | 5 | **1** (1.0 equiv.) | THF | rt 24 h | 62 (**5a**), 16 (**5b**)[e] | 4.0:1 |
| 2[d] | 5 | **1** (0.5 equiv.) | THF | rt 2 days | 73 (**5a**), 14 (**5b**)[e] | 4.0:1 |
| 3[d] | 5 | **1** (0.3 equiv.) | THF | rt 3 days | 69 (**5a**), 18 (**5b**)[e] | 4.0:1 |
| 4[d] | 1.2 | **1** (1.0 equiv.) | THF | rt 5 days | 60 (**5a**), 18 (**5b**)[e] | 3.6:1 |
| 5[d] | 1.2 | **1** (0.5 equiv.) | THF | rt 5 days | 67 (**5a**), 14 (**5b**)[e] | 3.2:1 |
| 6[d] | 1.2 | **1** (0.3 equiv.) | THF | rt 7 days | 52 (**5a**), 12 (**5b**)[e] | 4.6:1 |
| 7 | 5 | **1** (0.2 equiv.) | Neat | rt 4 h, 40°C 1 h | [100][f] | 2.9:1 |
| 8 | 1.0 | **1** (0.2 equiv.) | Neat | 40°C 2 h | [85][f] 73[g] | 3.0:1 |
| 9[h] | 1.0 | **1** (0.2 equiv.) | $H_2O$ | 40°C 2 h | [95][f] | 3.4:1 |
| 10[h] | 1.0 | **1** (0.2 equiv.) | Toluene | 40°C 2 h | [70][f] | 2.8:1 |
| 11[i] | 1.0 | **2** (0.2 equiv.) | $CH_3OH$ | rt 22.5 h | [24][f] | 3.6:1 |
| 12[i] | 1.0 | **2** (0.2 equiv.) | $CH_3OH$ | 40°C 22.5 h | [75][f] | 3.6:1 |
| 13 | 1.0 | **2** (0.2 equiv.) | Neat | 40°C 17 h | [35][f] | 3.0:1 |
| 14[h] | 1.0 | **2** (0.2 equiv.) | $H_2O$ | 40°C 24 h | No reaction | – |
| 15[h] | 1.0 | **2** (0.2 equiv.) | Toluene | 40°C 23 h | [<5][f] | – |
| 16 | 5 | – | Neat | 40°C 2 h, rt 7 days | No reaction | – |

[a] Equivalents of **4** to nitro olefin **3**.
[b] Equivalents of catalyst to nitro olefin **3** are shown in parentheses.
[c] The diastereomeric ratio of **5** was determined by ${}^1H$ NMR of the extracted reaction mixture.[8]
[d] The reaction was performed using **3** (0.5 mmol), **4**, and catalyst in solvent (1 mL).
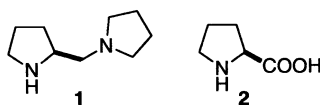[e] Isolated yield of **5a** and **5b**.
[f] Conversion based on the ratio of **3** and **5**, determined by ${}^1H$ NMR, is shown in square brackets.
[g] Combined isolated yield of **5a** and **5b**.
[h] The reaction was performed using **3** (0.5 mmol), **4**, and catalyst in solvent (0.025 mL).
[i] The reaction was performed using **3** (0.5 mmol), **4**, and **2** in solvent (0.5 mL).



To increase the reaction rate, neat conditions and heating were examined (entries 7 and 8). When the reaction was performed neat at rt, the reaction mixture solidified, preventing the reaction from proceeding to completion. Mild heating, however, proved sufficient to drive the reaction to completion. Reaction of **3** (0.5 mmol) with **4** (0.5 mmol) and 0.2 equiv. of **1** (neat) at 40°C afforded the desired products in good yield after only 2 h but with slightly reduced diastereoselectivity (entry 8).

This reaction could also be performed with water (entry 9) or toluene (entry 10) as solvents. Dichloromethane and diethyl ether were also good solvents for this reaction (data not shown). The amine catalyst was essential for this Diels–Alder reaction since reaction of **3** with **4** in the absence of catalyst did not provide **5** (entry 16). Furthermore, the reaction was neither catalyzed nor accelerated by water (entry 14).

L-Proline (**2**) catalyzed this reaction in methanol (entries 11 and 12). When this reaction was performed with **2** under neat conditions, solidification of the reaction mixture prevented significant conversion to product even after the application of heat, 40°C (entry 13). No reaction or very slow reaction was observed with **2** in water (entry 14), toluene (entry 15), or THF (data not shown).

The scope of this type of amine-catalyzed reaction was studied using a variety of nitro olefins and α,β-unsaturated ketones (Table 2). Both catalysts **1** and **2** catalyzed the reactions between **4** and nitro olefins **6**–**8**, between **9** and **3**, **7**, or **6**, and between **10** and **6** to provide cyclohexanone derivatives **11**–**17**. All reactions shown in Table 2 gave the desired Diels–Alder products as the main products with isolated yields of 32–75%.[10]

The diastereoselectivity of these reactions varied depending on the amine catalyst, the reactants, as well as the reaction conditions. For example, the reaction of **4** and **6** with amine **1** afforded **11a:11b** in a 8:1 ratio (entry 1), while the same reaction with L-proline provided the products in a 2:1 ~ 2.4:1 ratio (entries 2–4).

**Table 2.** Amine-catalyzed Diels–Alder reactions using various nitro olefins and α,β-unsaturated ketones
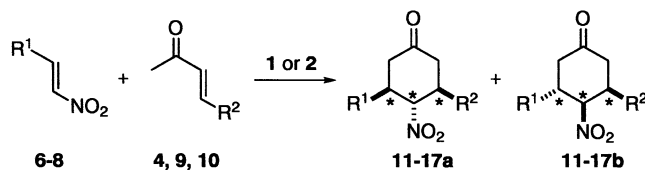


| Entry | $R^1$ | $R^2$ | Catalyst | Solvent | Temperature, reaction time | Product | Yield (%)[a] | Ratio[b] **a:b** |
|---|---|---|---|---|---|---|---|---|
| 1[c] | Ph (**6**) | 2-Thienyl (**4**) | **1** | THF | rt 24 h | **11a, 11b** | 45 | 8.0:1 |
| 2[d] | Ph (**6**) | 2-Thienyl (**4**) | **2** | $CH_3OH$ | rt 4 days | **11a, 11b** | 41 | 2.0:1 |
| 3[e] | Ph (**6**) | 2-Thienyl (**4**) | **2** | $CH_3OH$ | 40°C 4 h | **11a, 11b** | [63][f] | 2.0:1 |
| 4[g] | Ph (**6**) | 2-Thienyl (**4**) | **2** | $CH_3OH$ | 40°C 4 h | **11a, 11b** | 67 | 2.4:1 |
| 5[c] | 4-$CH_3OC_6H_4$ (**7**) | 2-Thienyl (**4**) | **1** | THF | rt 24 h | **12a, 12b** | 52 | 3.9:1 |
| 6[g] | 4-$CH_3OC_6H_4$ (**7**) | 2-Thienyl (**4**) | **2** | $CH_3OH$ | 40°C 5.5 h | **12a, 12b** | 60 | 1.8:1 |
| 7[c] | 1-Naphthyl (**8**) | 2-Thienyl (**4**) | **1** | THF | rt 24 h | **13a, 13b** | 75 | 3.6:1 |
| 8[g] | 1-Naphthyl (**8**) | 2-Thienyl (**4**) | **2** | $CH_3OH$ | 40°C 4 h | **13a, 13b** | 71 | 2.0:1 |
| 9[d] | 2-$CF_3C_6H_4$ (**3**) | Ph (**9**) | **1** | THF | rt 4 days | **14a, 14b** | 34 | 4.0:1 |
| 10[d] | 2-$CF_3C_6H_4$ (**3**) | Ph (**9**) | **2** | $CH_3OH$ | rt 4 days | **14a, 14b** | 32 | 4.0:1 |
| 11[d] | 4-$CH_3OC_6H_4$ (**7**) | Ph (**9**) | **1** | THF | rt 4 days | **15a, 15b** | 37 | 2.0:1 |
| 12[d] | 4-$CH_3OC_6H_4$ (**7**) | Ph (**9**) | **2** | $CH_3OH$ | rt 4 days | **15a, 15b** | 40 | 3.0:1 |
| 13[d] | Ph (**6**) | Ph (**9**) | **1** | THF | rt 4 days | **16a** | 64[h] | Nd[i] |
| 14[d] | Ph (**6**) | 2-Furyl (**10**) | **1** | THF | rt 4 days | **17a, 17b** | 35 | 4.0:1 |

[a] Isolated yield of a mixture of the diastereomers except for entries 3 and 13. The diastereomers were not separated by silica gel column chromatography.
[b] The ratio was determined by $^1H$ NMR of the extracted reaction mixture.
[c] The reaction was performed using nitro olefin (0.5 mmol), **4** (2.5 mmol), and **1** (0.15 mmol) in THF (0.5 mL).
[d] The reaction was performed using nitro olefin (1.0 mmol), **4** (5 mmol), and **2** (0.2 mmol) in solvent (10 mL).
[e] The reaction was performed using nitro olefin (0.5 mmol), **4** (2.5 mmol), and **2** (0.15 mmol) in $CH_3OH$ (0.04 mL).
[f] Conversion based on the ratio of nitro olefin and Diels–Alder products.
[g] The reaction was performed using nitro olefin (0.5 mmol), **4** (1.5 mmol), and **2** (0.45 mmol) in $CH_3OH$ (0.15 mL).
[h] Isolated yield of **16a**.
[i] Not determined.

In summary, we have demonstrated for the first time amine-catalyzed direct Diels–Alder reactions of α,β-unsaturated ketones with dienophiles to provide cyclohexanone derivatives. Traditionally, reactions of the type reported here have been performed by first synthesizing and isolating 2-amino-1,3-butadienes.[7] We demonstrate here that this requisite enamine can be generated in situ and reacted with nitro olefin dienes under amine catalysis. The enantioselectivity of the reactions described here was moderate (up to 38% ee),[11] however, we hope that further studies will result in highly enantio- and diastereoselective variants of this reaction. Enamine-based catalysis of Diels–Alder reactions could be relevant in Nature and a search for Diels–Alderase enzymes that exploit this mechanism can now be considered.

## Acknowledgements

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8. Relative stereochemistry was assigned using the coupling constant of the $\alpha$-$NO_2$-hydrogen.[7a–d] Purification by silica gel column chromatography provided **5a** and **5b**. **5a**: $^1$H NMR $\delta$ 7.68–7.59 (m, 3H), 7.41 (t, $J = 7.5$ Hz, 1H), 7.28 (dd, $J = 4.7$ Hz, 1.2 Hz, 1H), 6.96–6.93 (m, 2H), 5.37 (t, $J = 11$ Hz, 1H), 4.24–4.11 (m, 2H), 3.03–2.81 (m, 3H), 2.63 (t, $J = 14$ Hz, 1H). **5b**: $^1$H NMR $\delta$ 7.70 (d, $J = 7.9$ Hz, 1H), 7.58 (t, $J = 7.9$ Hz, 1H), 7.44–7.39 (m, 2H), 7.29 (d, $J = 5.0$ Hz, 1H), 6.99 (dd, $J = 5.0$ Hz, 3.5 Hz, 1H), 6.85 (d, $J = 3.5$ Hz, 1H), 5.49 (dd, $J = 9.1$ Hz, 4.4 Hz, 1H), 4.47–4.39 (m, 2H), 3.19–2.99 (m, 3H), 2.58 (dd, $J = 11$ Hz, 16 Hz, 1H).

9. Absolute stereochemistry was not determined.

10. Moderate yields originate primarily due to product losses that result from their low solubility. Reaction conversion was typically excellent.

11. Enantiomeric excess was determined by chiral phase HPLC analyses. The best enantioselectivity was obtained for **15a** in Table 2 entry 11.