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Iminium ion catalysis: Use of the α-effect in the acceleration of the Diels–Alder reaction†

Julie L. Cavill,[a] Jens-Uwe Peters[b] and Nicholas C. O. Tomkinson*[a]

[a] *Department of Chemistry, Cardiff University, PO Box 912, Cardiff, UK CF10 3TB. E-mail: tomkinsonnc@cardiff.ac.uk; Fax: 029 2087 4030; Tel: 029 2087 4068*

[b] *F. Hoffmann-La Roche Ltd, Pharmaceuticals Division, CH-4070 Basel, Switzerland*

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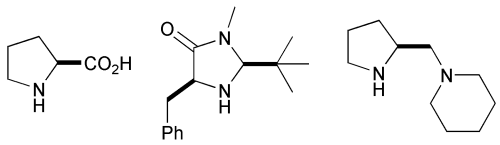
The α-effect can be used in the acceleration of the Diels–Alder reaction between a series of dienes and electron deficient dienophiles using iminium ion catalysis, providing a novel molecular scaffold capable of performing this class of catalytic process.

There has recently been significant interest in the use of Organocatalysis™ as a powerful method for accelerating asymmetric transformations.[1] Particularly noteworthy amongst these is the use of secondary amines by the groups of MacMillan, List and Yamamoto who have reported the use of proline **1**, the imidazolidinone **2**, and the diamine **3**, amongst others, to be effective catalysts for enantioselective Diels–Alder cycloadditions,[2] [3 + 2] cycloadditions,[3] alkylations,[4] Mannich reactions[5] and aldol condensations.[6]



1 **2** **3**

Examination of the structures of those compounds reported to be efficient in this area of Organocatalysis™ (such as **1**, **2** and **3**) show them all to posses a five membered amine containing heterocycle. It has been suggested than in order to gain effective catalytic turnover within these reactions it is necessary to have a highly nucleophilic nitrogen atom to accelerate the formation of the active iminium ion, which is thought to be the rate determining step of the catalytic cycle.[7]

It is well established that the nucleophilicity of a heteroatom can be greatly increased by the introduction of an adjacent heteroatom. Known as the α-effect,[8] and rationalised by frontier molecular orbital theory,[9] it has been used to explain the reactivity of a number of systems and has previously been exploited to accelerate synthetic transformations.[10] We believed that we could depart from the constraints inherent to this five membered ring system by taking advantage of the α-effect, and develop effective acyclic amine catalysts capable of high catalytic turnover, thus providing the opportunity to greatly diversify the previously reported structures and provide the ability to design and investigate other systems to probe this exciting and fundamental area of research.

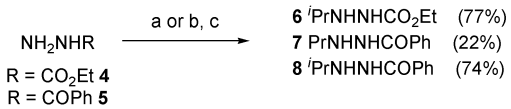
The initial results for the catalysis of the Diels–Alder reaction between cinnamaldehyde and cyclopentadiene with a variety of secondary amines posessing an α-heteroatom are outlined in Table 1. In the absence of any catalyst the reaction proceeds to just 7% completion inside 48 hours with the *endo* isomer predominating (entry 1). Use of dimethylamine hydrochloride as the catalyst increases the rate of reaction slightly and reverses the *endo*/*exo* selectivity similar to those observed by MacMillan, suggesting iminium ion catalysis is occurring albeit slugishly (entry 2). We then went on to examine a series of secondary amines that possessed an α-hetero atom, to discover if the α-effect did indeed accelerate the rate of reaction. We were delighted to discover that the use of *N*,*O*-dimethylhydroxylamine hydrochloride as the catalyst led to significant rate acceleration (65% completion, 48 hours) and a reversal of the *endo*/*exo* selectivity (entry 3). This suggests that it is possible to catalyse these reactions by taking advantage of the α-effect and represents a novel acyclic scaffold capable of catalysing this type of organocatalytic® transformation. Extending the reaction time to 72 hours increases formation of the Diels–Alder adduct to 80%, with the *endo*:*exo* ratios remaining at 34:66. Further evaluation of a series of readily available secondary amines possessing an α-heteroatom showed similar trends to be observed as well as lower conversion rates being revealed when the α-hetero atom was nitrogen (*e.g.* entries 5 and 6).

Table 1 Diels–Alder cycloaddition between cinnamaldehyde and cyclopentadiene[a]

Entry	Catalyst	Time	*endo*:*exo* Ratio[d]	% Yield
1	None	48	64:36	7
2[b]	$NHMe_2$	48	38:62	22
3[b]	MeNHOMe	48	34:66	65
4[b]	MeNHOMe	72	34:66	80
5[c]	MeNHNHMe	72	68:32	48
6[c]	PhNHNHPh	48	38:62	33

[a] Carried out in methanol:water (19:1) at room temperature with 10mol% catalyst. [b] Catalyst used as HCl salt. [c] Catalyst used as bis-HCl salt. [d] Ratio determined by ^{1}H NMR.

After extensive attempts to increase the reactivity of our systems we eventually prepared a series of secondary hydrazines derived from ethyl carbazate **4** and benzoic hydrazide **5** by a two step condensation-reduction protocol,[11] furnishing the hydrazine derivatives **6**–**8** in respectable yields (Scheme 1).‡



Scheme 1 *Reagents and conditions*: (a) CH_3CH_2CHO, AcOH, rt, 48 h; (b) $(CH_3)_2CO$, AcOH, rt, 48 h; (c) PtO_2, H_2, EtOH, AcOH, rt, 48 h.

Introduction of these electron withdrawing groups onto the α-heteroatom greatly increased the reactivity of our systems, with the Diels–Alder reaction between cinnamaldehyde and cyclopentadiene going to completion when catalysed by the HCl salt of the hydrazine derivatives **6**–**8**. The results obtained are outlined in Table 2. As observed with *N*,*O*-dimethylhydroxylamine similar *endo*:*exo* ratios to those reported by others were obtained within these reactions, which suggests that use of iminium ion catalysis for the acceleration of the Diels–Alder reaction will reverse the selectivity often observed and provide a viable alternative to the Lewis acid catalysed process which tends to favour the *endo* isomer.[12]

In order to test the generality of our system and prove we had genuinely discovered a novel molecular scaffold for iminium ion catalysis, we carried out a series of Diels–Alder reactions

† Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR, IR and MS spectra. See http://www.rsc.org/suppdata/cc/b2/b212239a/

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Table 2 Diels–Alder reaction between cyclopentadiene and cinnamaldehyde using ethyl carbazate and benzoic hydrazide derived catalysts

Entry[a]	Catalyst[b]	*exo*:*endo*	% Yield
1	**6**	65:35	94
2	**7**	67:33	97
3	**8**	67:33	93

[a] All reactions carried out for 48 h in methanol:water (19:1) at room temperature with 10 mol% catalyst. [b] As HCl salt.

using the hydrazide **8** as the catalyst, with acrolein **9**, methacrolein **10** and crotonaldehyde **11** as the dienophiles and cyclopentadiene **12** and 2,3-dimethyl butadiene **13** as the dienes. The results obtained are shown in Table 3.

Table 3 Diels–Alder cycloaddition catalysed by **8**[a]

Entry	Diene	Dienophile	*Exo*:*Endo*[b]	% Yield
1	**12**	**9**	41:59	98
2	**12**	**10**	83:17	98
3	**12**	**11**	54:46	98
4	**13**	**9**	—	97
5	**13**	**10**	—	98
6	**13**	**11**	—	89

[a] All reactions carried out for 48 h in methanol:water (19:1) at room temperature with 10 mol% **8** as HCl salt. [b] Ratio determined by ^{1}H NMR analysis of the crude reaction mixtures.

The results show that once again the use of the α-effect greatly accelerates the rates of reaction and this class of catalyst appears to be general for the Diels–Alder reaction of α,β-unsaturated aldehydes with both cyclic and acyclic dienes.

Finally, we investigated the optimal nature of the acid salt of the catalyst. After scanning a number of systems we discovered, in accordance with previous findings, that use of the perchlorate salt was most effective for catalytic turnover. For example, the use of 10 mol% of perchloric acid,[13] in the presence of 10 mol% of the amine catalyst **8** gave the Diels–Alder adduct between cyclopentadiene and cinnamaldehyde in 86% yield in just 24 h. The *exo*:*endo* ratios were 65:35, which is consistent with our previous observations. Lowering the catalyst loading to just 1 mol% catalyst as its perchlorate salt gave the adduct in a very pleasing 54% yield (*exo*:*endo* ratio 61:39) which greatly adds to the usefulness of this procedure and bodes well for future catalyst development.

In summary, we have shown that use of the α-effect as a handle to promote iminium ion catalysed Diels–Alder reactions between a variety of dienes and electron deficient dienophiles provides an effective platform from which to approach catalyst design. Of particular note is the fact that introduction of an electon withdrawing group on the α-hetero atom greatly enhances the catalytic activity whilst maintaining the stereochemical outcome of these reactions. The ability to carry out these reactions with acyclic catalysts will be of particular significance in the design of asymmetric variants of this and other OrganoCatalytic™ reactions. Our findings in these and related areas will be reported shortly.

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Notes and references

‡ Typical experimental procedure for the preparation of **8**: Benzoic hydrazide (5.00 g, 36.7 mmol) was added to a mixture of acetone (22 ml) and acetic acid (40 μl, 0.69 mmol) and stirring was continued at room temperature for 48 h. The reaction mixture was diluted with water (30 ml) and extracted with diethyl ether (3 × 30 ml). The extracts were washed with brine, dried ($MgSO_4$) and concentrated to give benzoic acid isopropylidine hydrazide as a colourless solid (5.57 g, 31.6 mmol, 86%). mp 141–143 °C; IR (Nujol mull) 3221, 1655 (C=O), 1638 (C=N), 1578, 1531, 1490, 718, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H, NH), 7.79 (d, 2H, J = 6.8 Hz, ArH), 7.52 (t, 1H, J = 7.2 Hz, ArH), 7.44 (dd, 2H, J = 7.6 and 7.3 Hz, ArH), 2.15 (s, 3H, CH_3), 1.97 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.6 (C), 156.9 (C), 134.1 (C), 132.1 (CH), 129.0 (CH), 127.6 (CH), 26.0 (CH_3), 17.3 (CH_3); *m*/*z* (GC-MS) 176 (M^+, 8%), 161 (50), 105 (100), 77 (31); HRMS (found 176.0950; $C_{10}H_{12}N_2O$ requires 176.0950).

Ethanol (12 ml) and acetic acid (6 ml) were added to platinum oxide (0.68 g, 0.3 mmol) under an atmosphere of nitrogen. Benzoic acid isopropylidine hydrazide (2.50 g, 14.2 mmol) was added and the flask charged with hydrogen. The reaction mixture was stirred at room temperature for 48 h, filtered through Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated to give **8** as a colourless powder (2.18 g, 12.2 mmol, 86%). mp 110–112 °C; IR (Nujol mull) 3289, 1640 (C=O), 1537, 725, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 3H, NH and ArH), 7.46 (t, 1H, J = 7.3 Hz, ArH), 7.38 (dd, 2H, J = 7.7 and 7.1 Hz, ArH), 4.81 (s, 1H, NH), 3.18 (hept, 1H, J = 6.2 Hz, $CH(CH_3)_2$) 1.05 (d, 6H, J = 6.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (C), 132.9 (C), 131.9 (CH), 128.7 (CH), 126.9 (CH), 51.4 (CH), 20.9 (CH_3); *m*/*z* (GC-MS) 178 (M^+, 3%), 163 (9), 122 (13), 105 (100), 77 (34), 58 (20); HRMS (found 178.1105; $C_{10}H_{14}N_2O$ requires 178.1106).

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13 **Caution**: Solutions of perchloric acid should be prepared and handled with the utmost care.