

Auxiliary Accelerated Reactions: Transition-metal Promoted Diels–Alder Cycloadditions

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Rate enhancements for the Diels–Alder reaction of (2-pyridyl)methyl propenoate **2** over benzyl propenoate **1** are observed in the presence of transition-metal promoters, particularly copper(II) and zinc(II) triflate.

The issue of acceleration and selectivity enhancement of Diels–Alder reactions is a topic of considerable current interest in organic synthesis,¹ primarily because of the fundamental importance and widespread usage of this pericyclic reaction for the highly diastereo- and enantio-selective construction of six-membered rings.² Many examples concerning the acceleration of Diels–Alder reactions by common Lewis acids³ such as TiCl₄, BF₃·Et₂O, Et₂AlCl, SnCl₄ and lanthanide complexes are known, and recent studies of rate enhancement in lithium perchlorate–diethyl ether have been reported.⁴

As part of a programme directed towards the development of auxiliary accelerated reactions in synthesis, we wish to report the rate acceleration of (2-pyridyl)methyl propenoate **2**† over benzyl propenoate **1** in competition experiments for Diels–Alder cycloaddition carried out in the presence of transition-metal promoters chosen for their high affinity for nitrogen in pyridyl-based systems.⁵

It was anticipated that for substrate **2**, the 2-pyridyl group would bind to a suitable transition-metal species, and thereby accelerate the Diels–Alder reaction with respect to **1** via chelation, as represented for a generalised case in Fig. 1.

Simple transition-metal promoters with a known affinity for nitrogen donors⁵ were examined for their ability to discriminate between **1** and **2**. Competition experiments between **1** and **2** were conducted as follows: to an equimolar mixture of **1** and **2** in dichloromethane was added 1 equiv. of promoter under dry nitrogen. After stirring at room temp. for 15 min, the reaction mixture was cooled to –10 °C and excess cyclopentadiene monomer (5 equiv.) was added followed by stirring at this temperature for 16–18 h (Scheme 1). The results of this study are shown in Table 1, in which the ratios of reisolated starting materials (**1**:**2**) and products (**4**:**3**) are provided for the different promoters examined.‡ It was found that conducting the competition experiments at room temperature in dichloromethane was inappropriate, since at this temperature the non-selective background reaction (in the absence of transition-metal) was too fast (overall conversion 21% after 18 h). The lower temperature of –10 °C, was therefore used in all subsequent experiments.

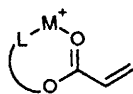
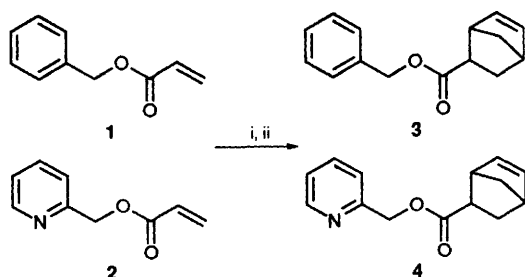


Fig. 1 Auxiliary acceleration via chelate delivery of a Lewis acid



Scheme 1 Reagents and conditions: i, cyclopentadiene (5 equiv.), catalyst, solvent (see Tables), –10 °C, 16–18 h; ii, aq. EDTA workup

Several interesting points arise from inspection of Table 1. The experiment conducted in the absence of transition-metal species gave no rate enhancement for reaction of **2** over **1**. This was gratifying, since this meant that any subsequent rate accelerations observed were due to the metal reagent involved. Rate enhancements were found to occur for the copper(II) triflate⁶ and zinc(II) triflate promoted cycloadditions (entries 2 and 3). However, competition experiments conducted in the presence of the other transition-metal promoters examined (entries 4–7) gave less impressive results, probably due in some cases (e.g. entries 4 and 7) to the low solubility of the transition-metal complex in the reaction medium. Magnesium bromide etherate (entry 8) enhanced the reactivity of both **1** and **2** but without significant discrimination, as expected for a Lewis acid with a high affinity for oxygen donors such as esters.

These experiments indicated that copper(I) reagents^{7,8} were good candidates for further study, and we examined a range of alternative counterions. The best levels of rate enhancement were found using copper(II) triflate, although the corresponding nitrate, tetrafluoroborate and perchlorate all provided significant rate enhancements in the Diels–Alder reactions.

Competition experiments were performed using copper(II) triflate in more coordinating solvents than dichloromethane. It was anticipated that a more coordinating solvent would compete with benzyl propenoate for binding sites at copper, and would thereby enhance the rate discrimination between **1** and **2**. The results of this study are shown in Table 2, which indicates that the highest levels of discrimination were in fact observed in dichloromethane.

Table 1 Effect of metal catalyst on Diels–Alder competition reactions between **1** and **2**

Entry	Catalyst	Ratio 1 : 2 ^a	Ratio 4 : 3 ^b	Conversion (%) ^c
1	None	1.0:1	1.0:1	9
2	Cu(OTf) ₂	3.6:1	7.6:1	44
3	Zn(OTf) ₂	2.0:1	6.6:1	35
4	HgI ₂	1.0:1	1.0:1	9
5	AgBF ₄	1.6:1	2.6:1	25
6	FeCl ₃	1.6:1	1.3:1	53
7	Ni(NO ₃) ₂ ·6H ₂ O	1.1:1	1.0:1	14
8	MgBr ₂ ·OEt ₂	1.4:1	1.1:1	64

^a Ratio **1**:**2** refers to the ratio of reisolated starting materials. ^b In each case, the *endo* isomer was formed as the major product. ^c Conversion refers to the amount of both products (**3** and **4**) formed.

Table 2 Solvent effect on Diels–Alder competition reactions between **1** and **2**

Entry	Solvent	Ratio 1 : 2 ^a	Ratio 4 : 3 ^b	Conversion (%) ^c
1	CH ₂ Cl ₂	3.6:1	7.6:1	44
2	Et ₂ O	2.5:1	1.5:1	59
3	THF	2.1:1	4.6:1	22
4	Me ₂ CO	2.3:1	3.9:1	23
5	MeOH	1.4:1	1.6:1	24

^a Ratio **1**:**2** refers to the ratio of reisolated starting materials. ^b In each case, the *endo* isomer was formed as the major product. ^c Conversion refers to the amount of both products (**3** and **4**) formed.

In summary, we have demonstrated that copper(II) and zinc(II) triflate provide rate discrimination⁹ in the Diels–Alder cycloaddition of either (2-pyridyl)propenoate or benzylpropenoate with cyclopentadiene, perhaps *via* coordination of the pyridyl nitrogen with the transition-metal species. Thus, (2-pyridyl)methanol behaves as a reaction-accelerating auxiliary. The design of bidentate and enantiomerically pure auxiliaries based on the above systems is currently under investigation.

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Footnotes

† All new compounds were characterized by ¹H and ¹³C NMR (250 MHz), and IR spectroscopy, MS and HRMS accurate mass or microanalysis.

‡ Ratios and conversions were calculated using gas chromatography (BP1 column from SGE) after calibration with standards.

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