Indium trichloride ($InCl_3$) catalysed Diels–Alder reaction in water

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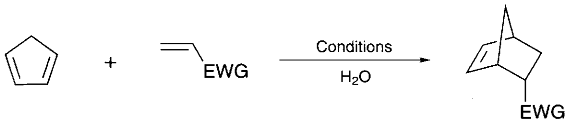
Indium trichloride ($InCl_3$) is found to catalyse the Diels–Alder reaction in water; the catalyst can be easily recovered from water after the reaction is completed and can be reused.

In recent years, aqueous Diels–Alder reactions have become of significant interest due to the increased reactivity rates experienced in water, especially when catalysed by a Lewis acid. Breslow and co-workers and Grieco and co-workers[1] first popularised the use of this reaction in water without a catalyst; this was followed by the development of Diels–Alder reactions with water-stable Lewis acids such as $Yb(OTf)_3$, $Sc(OTf)_3$ (Tf = trifluoromethanesulfonate) and lanthanide bis(trifluoromethanesulfonyl)amide $[(CF_3SO_2)_2N]_3Ln$. In some cases, where chiral Lewis acids were used, moderate stereoselectivity was obtained.[2]

In such water-catalysed reactions the Lewis acid must possess stability in water, a high coordination numbers and a fast coordination–dissociation equilibrium, and preferably be reusable. Indium trichloride trihydrate fulfills these properties as demonstrated by our recent research showing that indium trichloride is an excellent catalyst for promoting the Mukaiyama aldol reaction in water.[3] This result and subsequent studies on indium trichloride's stability in water suggest its untapped potential as a Lewis acid for enhancing carbon–carbon bond formations in aqueous media. This paper describes indium trichloride catalysed Diels–Alder reactions between various dienes and dienophiles in water. Preliminary studies have also shown moderate diastereoselectivity with a chiral dienophile.

Indium trichloride (available from Aldrich) was first tested for its effectiveness as a Lewis acid in the Diels–Alder reactions of acrolein (acrylaldehyde) and methyl acrylate with cyclopentadiene in water. Competitive experiments were carried out with and without $InCl_3$ in D_2O.† The results are summarised in Table 1.

Table 1 Effect of catalyst[a]

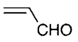
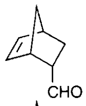
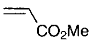
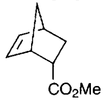
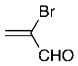
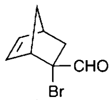
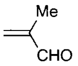
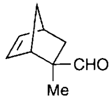
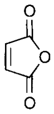
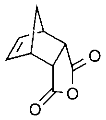
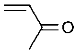
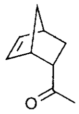
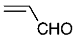
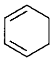
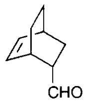
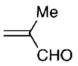
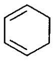
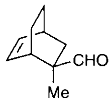
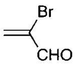
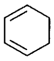
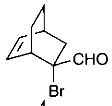
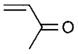
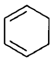
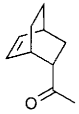
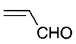
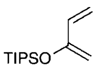
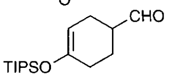
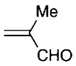
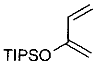
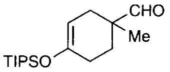
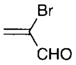
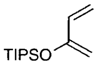
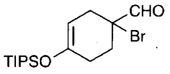


Entry	EWG	Conditions	Yield of product (%)	*endo* : *exo*
1	CHO	$InCl_3$ (20 mol%),[b] 2 h	100	91 : 9
2	CHO	2 h	60	74 : 26
3	CO_2Me	$InCl_3$ (20 mol%), 4 h	100	90 : 10
4	CO_2Me	4 h	70	75 : 25 (84 : 16–90 : 10)[4]

[a] All reactions were carried out in D_2O at room temp. and monitored by ^1H NMR spectroscopy. [b] Use of 10 mol% $InCl_3$ also increases the rate of the reaction, albeit more slowly.

The reaction of acrolein with cyclopentadiene in the presence of $InCl_3$ was completed in 2 h. However, the control reaction without any catalyst only went to 60% completion confirming

Table 2 $InCl_3$ catalysed Diels–Alder reactions[a]

Dienophile	Diene[b]	Major product	Yield (%)[c]	*endo* : *exo*[d]
			89[e]	91 : 9
			86[f]	90 : 10
			85[e]	90 : 10
			81[f]	90 : 10
			91	9 : 91
			93	10 : 90
			99	100 : 0
			84	87 : 13
			88	90 : 10
			94	4 : 96
			95	5 : 95
			87	90 : 10
			88 87 89	[g] [g] [g]

[a] All reactions were carried out on a 0.5–1 mmol scale. [b] TIPSO = triisopropylsilyloxy. [c] Isolated yield. [d] *Endo* : *exo* ratio determined by ^1H NMR spectroscopy. [e] First run. [f] Second run. [g] One regioisomer.

the effectiveness of $InCl_3$ as a catalyst for the aqueous Diels–Alder reaction. The reaction with the catalyst showed a high *endo* to *exo* selectivity of 91 : 9 compared with 74 : 26 in the absence of catalyst.

Similar results were observed when methyl acrylate was used as dienophile: a higher yield and *endo* : *exo* selectivity was observed in the presence of $InCl_3$. Having ascertained the ability of $InCl_3$ to catalyse these Diels–Alder reactions, several dienes were reacted with various dienophiles at ambient temperature in water as solvent in the presence of 20 mol% of $InCl_3$ as catalyst. The results of these experiments are summarised in Table 2.‡

In general, the reactions were clean and the desired Diels–Alder adducts were obtained in good to excellent yields. The reaction works with either the cyclic or non-cyclic dienes. $InCl_3$ can also be recovered for reuse after the reaction is completed; the Diels–Alder adduct was extracted with diethyl ether and the aqueous phase, containing the catalyst, was reused for a second round of the reaction, showing the same catalytic effect.

When the Diels–Alder reaction was carried out with chiral dienophile[5] **1** with cyclopentadiene in the presence of $InCl_3$, we obtained the corresponding adduct in good yield with moderate selectivity (73 : 27) (Scheme 1).

Further work to increase the diastereoselectivity is in progress. Since the Diels–Alder reaction is one of the most powerful structural transformations in organic synthesis, this methodology will undoubtedly provide an easy entry to a wide variety of natural products.

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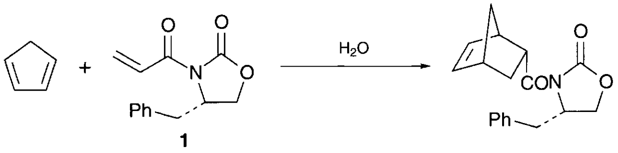

Scheme 1 No catalyst: 74% yield, 12% de (*endo*:*exo* 85 : 15); $InCl_3$ (20 mol%): 94% yield, 28% de (*endo* : *exo* 95 : 5); $InCl_3$ (120 mol%): 95% yield, 46% de (*endo*:*exo* 96/4)

Footnotes

† Experiments were carried out with acrolein (4 mg, 0.07 mmol), cyclopentadiene (14 mg, 0.21 mmol) and $InCl_3$ (3 mg, 0.014 mmol) in 1.0 ml of D_2O.

‡ A typical reaction procedure is as follows. Cyclopentadiene (0.25 ml, 198 mg, 3 mmol) was added to a stirred solution of methyl acrylate (0.09 ml, 86 mg, 1 mmol) and $InCl_3$ (44.2 mg, 0.2 mmol) in 5 ml of H_2O. The mixture was stirred at room temp. for 4 h, and then the product was extracted with dichloromethane. After the usual workup, the crude product was chromatographed on silica gel to give the pure adduct in 85% yield (129 mg).

References

1 For examples of Diels–Alder reactions in water without catalyst, see D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816; S. D. Larsen and P. A. Grieco, *J. Am. Chem. Soc.*, 1985, **107**, 1768; P. A. Grieco and S. D. Larsen, *Org. Synth.*, 1990, **68**, 206; P. A. Grieco, S. D. Larsen and W. F. Fobare, *Tetrahedron Lett.*, 1986, **27**, 1975; P. A. Grieco, D. T. Parker, W. F. Fobare and R. Ruckle, *J. Am. Chem. Soc.*, 1987, **109**, 5859; P. A. Grieco and A. Bahsas, *J. Org. Chem.*, 1987, **52**, 5746; P. A. Grieco and J. D. Clark *J. Org. Chem.*, 1990, **55**, 2271.

2 For examples of lanthanide(III) catalysed Diels–Alder reactions in aqueous media, see K. Mikami, O. Kotera, Y. Motoyama and H. Sakaguchi, *Synlett*, 1995, 975; H. Sasai, T. Suzuki, N. Itoh, K. Tanaka, T. Date, K. Okamura and M. Shibazaki, *Tetrahedron Lett.*, 1993, **34**, 851; L. Yu, D. Chen and P. G. Wang, *Tetrahedron Lett.*, 1996, **37**, 2169; S. Kobayashi, I. Hachiya, M. Araki and H. Ishitani, *Tetrahedron Lett.*, 1993, **34**, 3755; S. Kobayashi, I. Hachiya, T. Takahori, M. Araki and H. Ishitani, *Tetrahedron Lett.*, 1992, **33**, 6825.

3 Recently, we have found that $InCl_3$ is an excellent catalyst for the Mukaiyama aldol reaction in water, see T.-P. Loh, J. Pei and G.-Q. Cao, *Chem. Commun.*, 1996, 1819.

4 The *endo* : *exo* ratio of the product is known to vary according to the concentration of the dienophile, see J. A. Berson, Z. Hamlet and W. A. Mueller, *J. Am. Chem. Soc.*, 1962, **84**, 297; R. Breslow, U. Maitra and D. Rideout, *Tetrahedron Lett.*, 1983, **24**, 1901; A. A.-Z. Samii, A. deSavignac, I. Rico and A. Lattes, *Tetrahedron*, 1985, **41**, 3683.

5 D. A. Evans, K. T. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238 and references cited therein. Experimental detail will be reported in due course.

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