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LETTERS

Indium Triflate-An Efficient Catalyst For Hetero Diels-Alder Reactions

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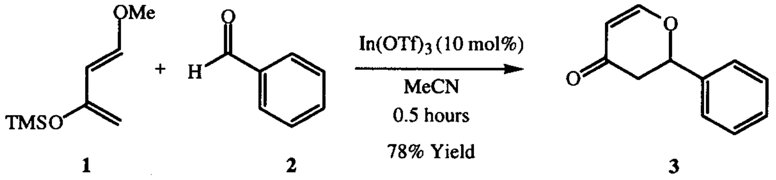
Abstract: At a loading as low as 0.5 mol% indium triflate has been found to catalyse the hetero Diels-Alder reaction. A three component coupling reaction between aldehydes, amines and Danishefsky's diene to afford tetrahydropyridine derivatives proceeds similarly in high yield.

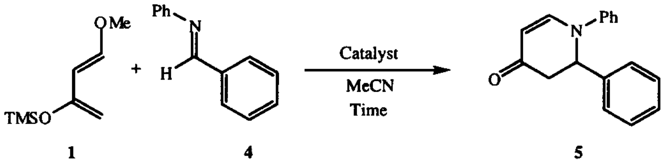
Keywords. Indium triflate; Catalysis; Hetero Diels-Alder; Library synthesis.

The organic chemistry community has witnessed the increased utility of indium reagents in recent years. For example, organoindium reagents have been used in a variety of transformations including allylations, Reformatsky reactions and cyclopropanations.[1] Indium metal has also been found to be an effective reducing agent.[2] Of particular significance to this report is the emergence of indium (III) halide complexes as efficient Lewis acid catalysts, to include applications in; Mukaiyama aldol reactions, Friedel-Crafts acylation reactions and Diels-Alder cycloadditions.[3] In a program of research directed towards the discovery of novel catalysts for pericyclic reactions we have noted the high activity of indium triflate in the hetero Diels-Alder reaction.



Scheme 1

In a preliminary experiment we examined the reaction between benzaldehyde **2** and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) **1**. This is an established transformation and is catalysed by a wide-range of Lewis acids including main group and transition metal halides,[4] $BF_3.Et_2O$,[5] lanthanide triflates[6] and ruthenium complexes.[7] In the presence of 10 mol% of indium (III) triflate the two components reacted smoothly to afford the product **3** in just thirty minutes at –20°C (Scheme 1).

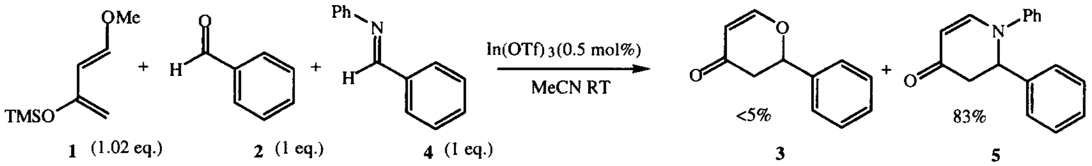


Catalyst	Time (Hours)	Yield (%)
None	24	<5
$Sc(OTf)_3$ (10 mol%)	20	83
$In(OTf)_3$ (10 mol%)	0.5	89
$In(OTf)_3$ (0.5 mol%)	0.5	93

Scheme 2

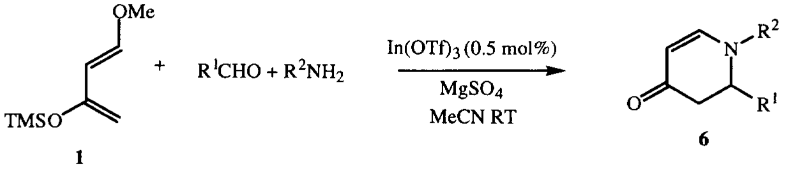
PII: S0040-4039(99)01045-X

The imino Diels-Alder reaction is a popular tool for heterocycle synthesis despite commonly requiring stoichiometric quantities of Lewis acids.[8] The efficiency of the indium catalysed process compared with other reported Lewis acids prompted us to investigate the reaction between imines and Danishefsky's diene **1** (Scheme 2). In the absence of any catalyst there was only a trace (<5%) of product after 24 hours at room temperature. Initial experiments revealed that the addition of 10 mol% of indium (III) triflate promoted the efficient formation of the product **5** in less than thirty minutes at room temperature.[9] Remarkably, the catalyst loading could be lowered to 0.5 mol% and the reaction was still complete in under thirty minutes to afford an isolated yield of 93% of product.[10] To confirm the reaction was being promoted by the indium and not adventitious triflic acid, we performed a series of experiments with added quantities of triflic acid, up to 30 mol%. No product was observed, the most notable occurrence not surprisingly was the hydrolysis of Danishefsky's diene to the corresponding enone.



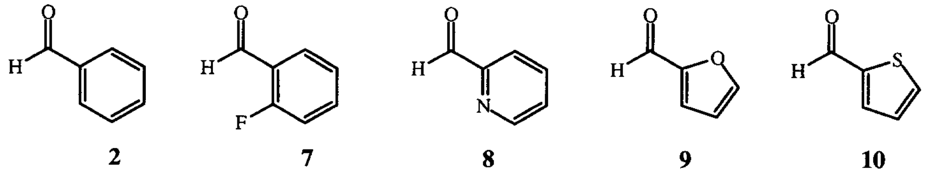
Scheme 3

A competition experiment illustrated that indium (III) triflate could preferentially activate imines in the presence of aldehydes (Scheme 3). When Danishefsky's diene **1** was added to a 1:1 mixture of benzaldehyde **2** and N-benzilideneaniline **4** in the presence of 0.5 mol% of indium (III) triflate, the product arising from reaction with the imine was isolated in 83% yield. The chemoselectivity of this process along with the precedent that imine formation could be promoted by the same catalyst suggested that an efficient three component coupling reaction would be possible (Scheme 4). This strategy has been employed previously using lanthanide and scandium triflates but at much higher catalyst loadings (10 mol%).[11]



Scheme 4

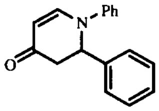
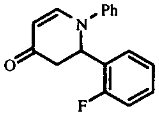
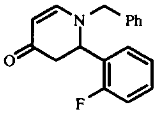
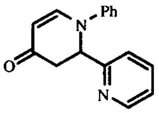
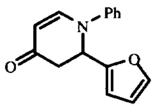
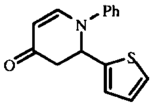
We examined the coupling reaction of Danishefsky's diene **1** with imines derived *in situ* from aromatic aldehydes (Scheme 5) and the primary amines aniline **11** and benzylamine **12.**



Scheme 5

In the presence of just 0.5 mol% of the Lewis acid the reaction proceeded smoothly to afford reasonable yields of aryl and heteroaryl substituted tetrahydropyridine products with the exception of 2-thiophene carboxaldehyde **10** (Table 1). Given the commercial availability of different reaction components and the efficiency of the coupling, this methodology would allow the parallel synthesis of large numbers of structurally diverse compounds.[12]

Table 1: Indium catalysed three component coupling reaction

Entry	*Aldehyde*	*Amine*	*Product*	*Yield (%)*
1	**2**	**11**		51%
2	**7**	**11**		84%
3	**7**	**12**		50%
4	**8**	**11**		95%
5	**9**	**11**		61%
6	**10**	**11**		No reaction

In conclusion, indium (III) triflate has been identified as a superior Lewis acid for the hetero Diels-Alder reaction of Danishefsky's diene and imines. Reactions are complete within thirty minutes at room temperature and a three component coupling of aldehyde, amine and diene was also successfully executed. The catalyst retains activity at very low loadings in the presence of water and primary amines demonstrating the advantageous stability and utility of indium complexes in organic synthesis.

Acknowledgments

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References and Notes

1. For a review see: Cintas, P., *Synlett*, **1995**, 1087.; For recent reports see: Lloyd-Jones, G. C.; Russell, T., *Synlett*, **1998**, 903.; Capps, S. M.; Lloyd-Jones, G. C.; Murray, M.; Peakman, T. M.; Walsh, K. E, *Tetrahedron Lett.*, **1998**, 39, 2853.; Höppe, H. A. F., Lloyd-Jones, G. C.; Murray, M.; Peakman, T. M.; Walsh, K. E, *Angew. Chem. Int. Ed.*, **1998**, 37, 1545.; Isaac, M. B.; Paquette, L. A., *J. Org. Chem*, **1997**, 62, 5333.; Loh, T.-P.; Li, X. R., *Angew. Chem. Int. Ed.*, **1997**, 36, 980.
2. Moody, C. J.; Pitts, M. R., *Synlett*, **1998**, 1028; Moody, C. J.; Pitts, M. R., *Synlett*, **1998**, 1029.
3. For recent applications see: Loh, T.-P.; Xu, K.-C.; Sook-Chiang Ho, D.; Sim, H. –K., *Synlett*, **1998**, 369.; Loh, T. –P.; Pei, J.; Cao, G. –Q., *J. Chem. Soc. Chem. Commun.*, **1996**, 1819.; Loh, T. –P.; Pei, J.; Lin, M., *J. Chem. Soc. Chem. Commun.*, **1996**, 2315.; Li, X. –R.; Loh, T. –P., *Tetrahedron: asymmetry*, **1996**, 7, 1535.; Loh, T. –P.; Li, X. –R., *J. Chem. Soc. Chem. Commun.*, **1996**, 1929.
4. Danishefsky, S.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P., *J. Am. Chem. Soc.*, **1985**, 107, 1256.; Danishefsky, S.; Kerwin, J. F.; Kobayashi, S., *J. Am. Chem. Soc.*, **1982**, 104, 358.
5. Danishefsky, S.; Larsen, E.; Springer, J. P., *J. Am. Chem. Soc.*, **1985**, 107, 1274.
6. Kobayashi, S., *Synlett*, **1994**, 689.
7. Faller, J. W.; Smart, C. J., *Tetrahedron Lett.*, **1989**, 30, 1189.
8. Boger, D. L.; Weinreb, S. M., *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press: New York, **1987**, Chapters 2 and 9.
9. For comparison with lanthanide and scandium triflates see; Kobayashi, S.; Ishitani, H.; Nagayama, S., *Chem. Lett.*, **1995**, 423.
10. Typical experimental procedure: To a stirring suspension of In(OTf)$_3$ (0.5 mol%) in acetonitrile (1ml) was added the imine **4** (0.5 mmol) in acetonitrile (1.5ml) at room temperature. The reaction mixture was allowed to stir for 5 minutes then Danishefsky's diene **1** (0.75 mmol) was added dropwise. After 30 minutes or when TLC showed the reaction to be complete, the reaction was quenched with aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The crude product was chromatographed on silica gel to afford the product **5** in 93% yield.

    ^{1}H NMR δ_H (270MHz, CDCl$_3$) 2.77 (ddd, 1H, J=1.3, 3.3, 16.5 Hz), 3.29 (dd, 1H, J= 7.3, 16.5 Hz), 5.27 (dd, 2H, J=1.1, 7.6 Hz), 6.99-7.35 (m, 10H), 7.67 (dd, 1H, J= 1.1, 7.6 Hz).

    ^{13}C NMR δ_C (270MHz, CDCl$_3$) 43.3, 61.4, 102.7, 118.3, 124.2, 125.9, 127.6, 128.8, 129.3, 137.7, 144.4, 148.1, 190.0.
11. Kobayashi, S.; Ishitani, H.; Nagayama, S., *Synthesis*, **1995**, 1195.
12. Kobayashi, S., *Chem. Soc. Rev.*, **1999**, 28, 1.