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LETTERS

$InCl_3$: A New Lewis Acid Catalyst for Reactions with α-Diazocarbonyl Compounds

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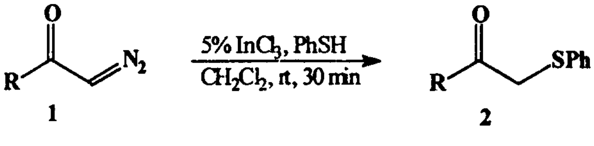
Abstract: The use of $InCl_3$ as a Lewis acid catalyst in diazocarbonyl S-H insertion reactions, nitrile cyclizations and addition reactions to aldehydes and ketones is described.

Catalyzed reactions of α-diazocarbonyl compounds *e.g.* cyclopropanation reactions, C-H & X-H insertion reactions, ylid formation, cyclization reactions, *etc.* have found widespread applications in organic synthesis.[1] These reactions are particularly attractive due to their mild and neutral conditions which allow chemoselective formation of new bonds in high yields. Recently, asymmetric versions of diazocarbonyl reactions have also emerged providing new opportunities in the synthesis of enantiomerically pure compounds.[1b]

Although reactions involving diazocarbonyl compounds are nowadays typically catalyzed by Rh and Cu salts, new catalyst systems are being continuously explored in search of improved efficiencies and cost-effectiveness (Rh salts are expensive). Several new metal salts, notably those of Ru,[2] Os[3] and Pt[4] have recently been investigated towards these ends. On the other hand, it is also known that certain diazocarbonyl reactions *viz.* X-H insertion reactions, addition reactions to aldehydes and ketones and π-cyclization reactions can be effectively catalyzed by Lewis acids ($BF_3.Et_2O$, $SnCl_2$, *etc.*). In these cases also, new Lewis acid catalysts have been regularly scanned in order to carry out reactions under milder and more effective conditions. $Sc(OTf)_3$ has been the latest addition to this list as a new Lewis acid catalyst for X-H insertion reactions of α-diazoketones.[5] In view of the recent surge in activity on the use of $InCl_3$ as a Lewis acid in various organic transformations,[6] we wished to study its catalytic effect in some diazocarbonyl reactions and in this Letter, describe our preliminary findings.



Scheme 1

$InCl_3$ turned out to be an excellent catalyst for intermolecular S-H insertion reaction of α-diazoketones. Thus, in presence of 5 mol% of this catalyst, a number of α-diazoketones (**1a-e**) reacted readily with PhSH to produce the respective α-phenylthio ketones **2a-e** within 45 min at ambient temperature (Scheme 1, Table 1).[7] The product yields are uniformly high (80-95%) and are comparable, if not better, to those obtained under Rh-catalyzed conditions.[8] Notably, a number of enantiopure α-amino diazoketones (**1b-e**),[1b,c] derived from the amino acid chiral pool, smoothly participated in these insertion reactions without any interference (ylid formation, intra-

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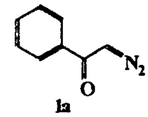
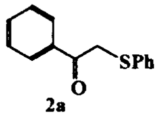
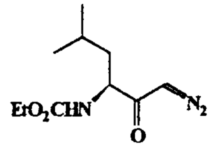
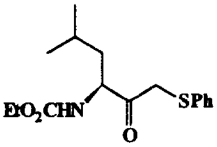
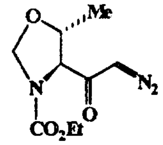
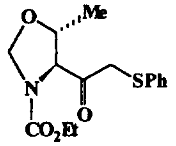
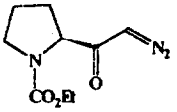
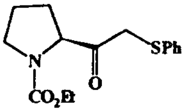
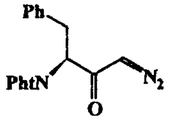
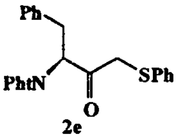
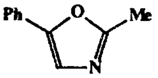
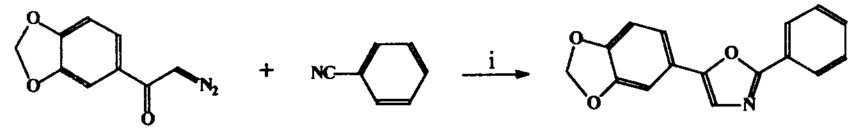
Table 1. $InCl_3$ Mediated Reactions of α-Diazoketones[a]

Entry	α-Diazoketone	Reactant	Product	Yield (%)	$[\alpha]_D^{27}$ (in $CHCl_3$)
1	 **1a**	PhSH	 **2a**	86	
2	 **1b**	"	 **2b**	93 (60)[b]	−11.6 (*c* 2.3)
3	 **1c**	"	 **2c**	90 (0)[b]	−58.7 (*c* 2.7)
4	 **1d**	"	 **2d**	95	−12.1 (*c* 3.4)
5	 **1e**	"	 **2e**	80	−82.6 (*c* 2.9)
6	**1a**	CH_3CN[c,d]	 **3**	50	

[a] 5% $InCl_3$, CH_2Cl_2, rt, 30 min–1h; [b] with $BF_3.Et_2O$; [c] 3 equiv. of $InCl_3$; [d] as solvent, rt, 12h.

molecular N-H insertion reactions) from the neighbouring functional groups to produce the highly useful enantiopure α-amino-α'-sulfenyl ketones **2b-e** in high yields (Table 1, entries 2-5). For comparison, we have also carried out $BF_3.Et_2O$ mediated insertion reaction of the α-amino diazoketones **1b** & **c** with PhSH. While **1b** gave a much reduced yield of the α-sulfenyl ketone **2b** (60%), the threonine derived α-diazoketone **1c** underwent decomposition, perhaps due to the sensitivity of the oxazolidine ring of the latter towards $BF_3.Et_2O$ (Table 1, entries 2 & 3). These results demonstrate the mildness and superiority of $InCl_3$ over other catalysts in S-H insertion reactions with functionalized α-diazoketones. Unfortunately, intermolecular O-H insertion reactions of α-diazoketones with alcohols and phenols have so far failed with $InCl_3$ as the catalyst, perhaps due to strong complexation of the catalyst with these reagents which considerably diminish its Lewis acidity.

$InCl_3$ can also be used for cyclization reactions of α-diazoketones with nitriles to produce 2,5-disubstituted oxazoles (Table 1, entry 6). However, as has been observed with other Lewis acid catalysts for similar cyclization reactions,[9] 2-3 equivs. of $InCl_3$ was necessary in this case for complete consumption of the α–diazoketone and to suppress α-chloro ketone formation.



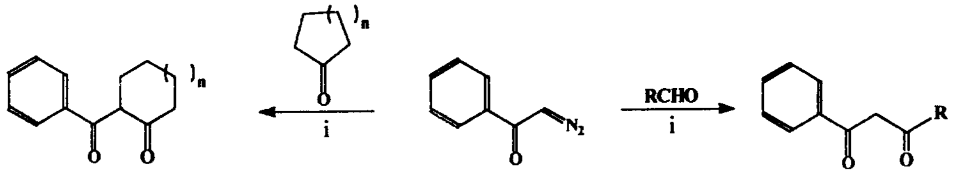
1f

Texamine (**4**, 53%)

Scheme 2. $InCl_3$ (3 equiv.), CH_2Cl_2, rt, 12h.

Based on this procedure, the oxazole alkaloid texamine (**4**),[10] isolated from the roots of *amyris texana*, was easily synthesized *via* the $InCl_3$ promoted cyclization reaction of the piperonylic acid derived α-diazoketone **1f** with excess benzonitrile (5 equiv.) (Scheme 2).

Lewis acid catalyzed addition reactions of diazocarbonyl compounds to aldehydes and ketones constitute a versatile synthetic route to β-dicarbonyl compounds.[11,12] $InCl_3$ was also found to be an effective mediator for such reactions. Thus, in presence of one equiv. of $InCl_3$, the α-diazoketone **1a** reacted with aliphatic aldehydes to produce the respective β-diketones **5a,b** in good yields within 30 min at room temperature (Scheme 3). A full equivalent of $InCl_3$ was found to be essential for these reactions, perhaps due to its strong complexation with the product β-diketones *via* their enol forms. Reaction of **1a** with benzaldehyde, an aromatic aldehyde, expectedly,[11] produced a poor yield of the β-diketone **5c**(15%) together with 35% of phenacyl chloride. Interestingly, it was observed that $InCl_3$ converts α-diazoketones to their corresponding α-chloro ketones in near quantitative yields within 45 min at room temperature.



n=1, **6a** (45%)
n=2, **6b** (40%)

1a

R = Et, **5a** (70%)
= *n*-Pr, **5b** (81%)
= Ph, **5c** (15%)

Scheme 3. $InCl_3$ (1 equiv.), CH_2Cl_2, rt, 30 min.

Addition reaction of **1a** to ketones (cyclopentanone, cyclohexanone) can also be carried out with $InCl_3$ to produce the 2-benzoyl cycloalkanones **6a,b** in 40-45% yields. Similar additions of ethyl diazoacetate to cyclopentanone, on the other hand, produced a 73% yield of ethyl cylohexanone-2-carboxylate. Although the yields of **6a,b** are only moderate and are being further investigated for improvement, these are quite significant results, especially since complete failure had previously been reported for Lewis acid catalyzed intermolecular addition reactions of α-diazoketones to ketones.[11] Indeed, a survey of the literature revealed that Lewis acid catalyzed diazocarbonyl addition reactions to ketones are primarily restricted to the reactions of α-diazoesters only.[11,12] In view of these, $InCl_3$ promoted successful addition reactions of **1a** to ketones is undoubtedly a notable methodological improvement having broad synthetic ramifications and points to the superior efficacy of $InCl_3$ over other Lewis acids for such reactions.

Further studies on the use of $InCl_3$ in α–diazocarbonyl reactions are in progress.

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