Synthetic Methods

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Nucleophilic Addition to *N*-Phosphinylimines by Rare-Earth-Metal Triflate/Trifluoroacetic Anhydride Activation**

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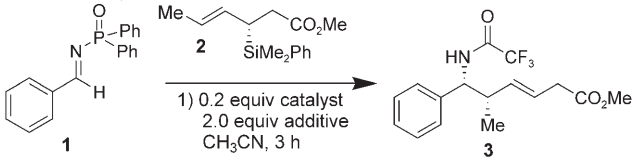
The asymmetric addition of allyl metal and related reagents to C=N bonds is an active area in chemical synthesis.[1] Methodologies include allylation of imines with allyl boronates,[2] allyl stannanes,[3] and chiral silanes.[4] Recently, *N*-diphenylphosphinylimines have emerged as useful acylimine equivalents in a variety of asymmetric C–C bond-forming reactions,[5] and we therefore considered their utility in asymmetric crotylations.[6] Herein, we report the addition of chiral organosilanes and other carbon nucleophiles to *N*-diphenylphosphinylimines using rare-earth-metal triflate/trifluoroacetic anhydride activation to unexpectedly afford trifluoroacetamide products as well as preliminary mechanistic studies to probe the reaction course.

We initiated our studies with the asymmetric crotylation of *N*-diphenylphosphinylimine **1**[7] using chiral organosilane **2**. After failed attempts in an initial evaluation of several Lewis acids (see Table 1, entries 1–3), we considered alternative, milder methods for activation of *N*-phosphinylimines. Previous studies by Yamamoto and co-workers have demonstrated the effectiveness of scandium triflate ($Sc(OTf)_3$) as a catalyst for acylation of alcohols with acetic anhydride.[8] Thus, we conducted studies probing the utility of $Sc(OTf)_3$/TFAA[9] for the activation of phosphinylimine **1** by acylation. Initial results revealed that catalytic amounts of $Sc(OTf)_3$ and TFAA (2.0 equiv) (Table 1, entry 4) were effective for the activation of *N*-phosphinylimine **1** towards addition of crotylsilane **2** and unexpectedly afforded trifluoroacetamide product **3** (56% yield). Control experiments established that both $Sc(OTf)_3$ and TFAA were required and that CH_3CN was an optimal solvent. Moreover, experiments[10] employing 0.2 equivalents of triflic acid[11] for the crotylation provided **3** in 27% yield after 48 h, thus establishing the importance of the rare-earth-metal catalyst.

Table 1: Catalyst evaluation.



Entry	Additive	Catalyst	Yield of **3** [%][a]
1[b]	–	$BF_3{\cdot}OEt_2$	0
2[b]	–	$TiCl_4$	0
3[b]	–	$Sc(OTf)_3$	0
4[b]	TFAA	$Sc(OTf)_3$	56
5[b]	TFAA	$Sm(OTf)_3$	37
6[b]	TFAA	$La(OTf)_3$	50–75
7[c]	TFAA	$La(OTf)_3$	86
8[c,d]	TFAA	$La(OTf)_3{\cdot}n\,H_2O$	93

[a] Yield of isolated product after purification by chromatography on silica gel. [b] Reaction was carried out in anhydrous CH_3CN. [c] ACS-grade CH_3CN was employed. [d] $La(OTf)_3{\cdot}n\,H_2O$ purchased from Aldrich. TFAA = trifluoroacetic anhydride.

To optimize the crotylation process, we next evaluated a range of rare-earth-metal triflates.[12] While $Sm(OTf)_3$ (Table 1, entry 5) afforded a modest yield (37%) of **3**, we found that $La(OTf)_3$ produced **3** in moderate to good yields (Table 1, entry 6).[10] Optimization studies later indicated that use of ACS-grade acetonitrile (2400 ppm water)[13] cleanly afforded **3** in 86% yield (Table 1, entry 7). Further optimization led to the identification of $La(OTf)_3{\cdot}n\,H_2O$,[14] which catalyzed the reaction to afford **3** in 93% yield after 2 h (Table 1, entry 8; d.r. > 20:1, e.r. > 97:3). The relative stereochemistry of homoallylic trifluoroacetamide **3** was determined by conversion into a known crotylation product[4a,10] and the absolute stereochemistry confirmed through conversion into the corresponding mandelamide derivatives.[10,15,16]

The liberation of the phosphinate moiety from the *N*-phosphinylimine substrate and formation of a trifluoroacetamide product were not anticipated in the transformation. The reaction outcome is consistent with in situ generation and subsequent crotylation of a highly activated trifluoroacetylimine[17] or its corresponding hydrate.[18] Unfortunately, attempts to generate aryl aldehyde-derived trifluoroacetylimines using reported methods have thus far been unsuccessful.[19] Initial mechanistic studies were undertaken to elucidate details of the $La(OTf)_3$/TFAA activation of *N*-phosphinylimines. ^1H NMR studies[10] indicate rapid loss of the phosphinylimine proton resonance (^1H NMR, CD_3CN, $\delta = 9.33$ ppm, $J_{P,H} = 32.1$ Hz) within 10 min to afford an unidentified intermediate (^1H NMR, CD_3CN, br, $\delta = 8.80$ ppm). To further probe this phenomenon, we carried out mass spectrometry experiments (ESI+),[14b,20] which confirmed rapid

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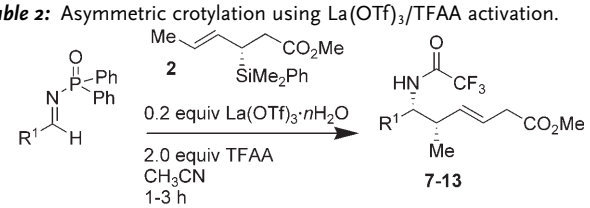
consumption of phosphinylimine **1** and suggested the presence of both hydrated species **4b** and **5** (Scheme 1).[10] Furthermore, upon addition of crotyl silane **2**, direct-injection mass spectral data supports the consumption of species **5**.[10] Based on our preliminary experimental data, we propose the general reaction mechanism for activation of the phosphinylimine **1** as shown in Scheme 1. Phosphinylimine acylation with TFAA may be promoted by lanthanum triflate through either direct N-acylation[21] or acylation of the phosphinyl oxygen atom with subsequent O-to-N acyl transfer.[22] Hydration of **4a** affords the observed tetrahedral intermediate **4b**,[18] which may be followed by loss of diphenylphosphinic acid ($HOPOPh_2$) to yield the lanthanum-coordinated intermediate **5**.[18b,c,23] ^{31}P NMR and mass spectrometry experiments (ESI+)[10] also suggest that symmetrical (diphenylphosphinic anhydride)[24] or mixed anhydrides (trifluoroacetic diphenylphosphinic anhydride)[25] derived from the liberated diphenylphosphinic acid and TFA become ligated to La^{III} as the reaction progresses.[26]

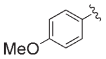
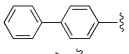
With an optimized protocol for crotylation in hand, we next evaluated the scope of the substrate (Table 2). Electron-rich aryl groups were found to be workable substrates in the crotylation, affording good yields of homoallylic amide products **7**–**9** (Table 2, entries 1–3). Electron-withdrawing aryl groups were tolerated and generally afforded moderate to good yields of crotylation products **10**–**11** (Table 2, entries 4 and 5). The aryl framework was also extended to cinnamaldehyde-derived phosphinylimines (Table 2, entry 6). A cyclopropanecarboxaldehyde-derived phosphinylimine substrate also produced a moderate yield of **13** (Table 2, entry 7). Attempts to perform the crotylation using other aliphatic phosphinylimines were unsuccessful likely owing to competing imine–enamine tautomerization.[27]

Further reactions employing the $La(OTf)_3$/TFAA catalytic system were investigated using alternative carbon nucleophiles (Scheme 2). Treatment of *N*-phosphinylimine **14**[10] with $La(OTf)_3$/TFAA in the presence of excess furan (microwave, 60 °C) led to efficient formation of the Friedel–Crafts[28] product **15** (88%). Alternatively, use of methylenecyclopentane as the nucleophile afforded the imino (aza)-ene[29] product **16** in high yield (91%). These initial studies illustrate the high reactivity of intermediates produced by lanthanum triflate/anhydride activation of *N*-phosphinylimines towards a range of nucleophiles, underscoring the significant potential for this catalyst system.

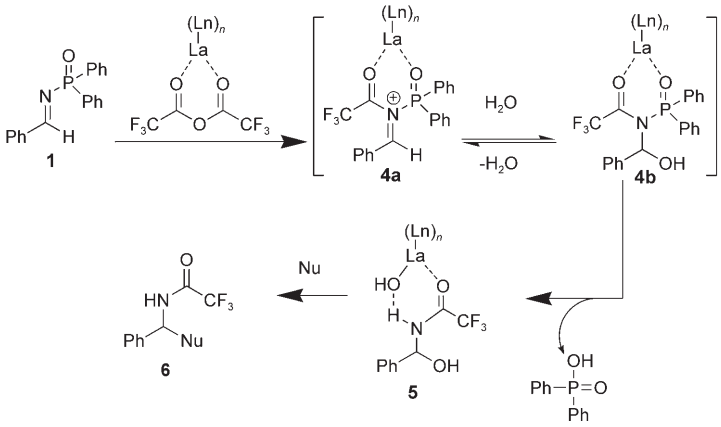
In summary, hydrated lanthanum triflate has been shown to be an effective and highly active Lewis acid catalyst for nucleophilic addition to *N*-phosphinylimines in the presence of trifluoroacetic anhydride. Unexpectedly, trifluoroacetamide products are produced in a novel process which likely involves consecutive acylation/hydration of *N*-phosphinylimine substrates and subsequent nucleophilic addition. In initial studies, asymmetric crotylation, Friedel–Crafts, and (aza)-ene reactions have been demonstrated with this activation system. Further development of additional

Table 2: Asymmetric crotylation using $La(OTf)_3$/TFAA activation.

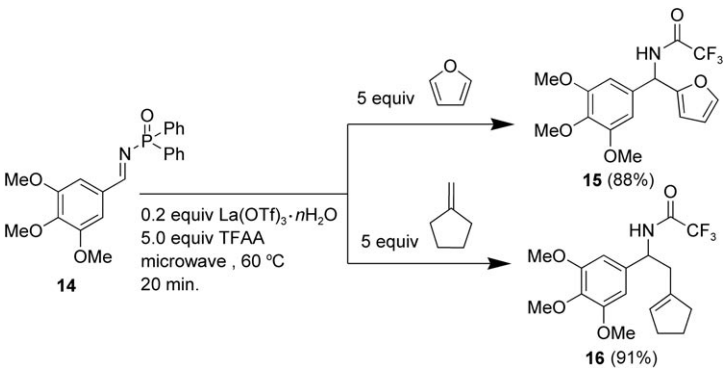


Entry	R^1	Product	Yield [%][a]	d.r.[b]	e.r.[c]
1		**7**	75	10:1	93:7
2		**8**	71	>20:1	96:4
3		**9**	87	15:1	89:11
4		**10**	99	15:1	96:4
5		**11**	87	15:1	99:1
6		**12**	80	10:1	91:9
7		**13**	53	10:1	99:1

[a] Yield of isolated product after chromatography on SiO_2. [b] Diastereomeric ratios determined using ^1H NMR integration. [c] Enantiomeric ratios determined by chiral HPLC analysis.



Scheme 1. Proposed mechanism for activation and nucleophilic addition of *N*-phosphinylimines.



Scheme 2. Friedel–Crafts and (aza)-ene reactions.

reaction processes using rare-earth-metal triflate/trifluoroacetic anhydride activation is ongoing in our laboratories and will be reported in due course.

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