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BF_3-Mediated Additions of Organolithiums to Ketimines: X-ray Crystal Structures of BF_3−Ketimine Complexes

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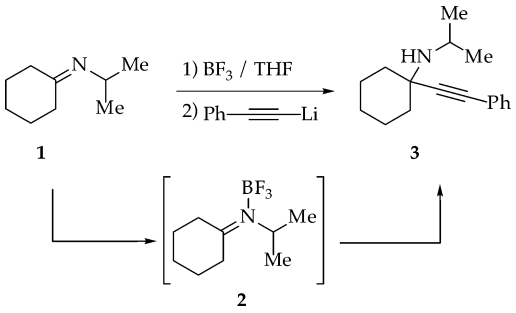
Additions of lithium acetylides and *n*-BuLi to *N*-alkyl ketimines mediated by BF_3−Et_2O in THF afford hindered *tert*-alkylamines in moderate to good yields. Stereochemical results and crystal structures of three BF_3−imine complexes suggest that allylic strain strongly influences conformation and may be an important determinant of reactivity and selectivity.

BF_3 has been used to facilitate reactions of organolithium reagents with a wide range of electrophiles.[1−5] The accelerating effects of BF_3 can be spectacular, allowing reactions that are sluggish at room temperature to proceed instantaneously at −78 °C. Spectroscopic and rate studies for the addition of lithium acetylides to aldimines mediated by BF_3−R_3N complexes showed that BF_3 and lithium acetylides do *not* condense before 1,2-addition.[2,6]

Although BF_3-mediated organolithium additions to aldimines are well documented,[3] analogous additions to ketimines appear to have been reported only for specialized cases.[4] We provide herein representative examples of BF_3-mediated 1,2-additions to simple *N*-alkylketimines; these reactions occur in respectable yields and display odd stereochemistries. Several X-ray crystal structures of BF_3−ketimine complexes suggest that $A_{1,3}$-strain may be an important stereochemical determinant.[7,8]

We previously reported that the crystalline, air-stable BF_3−*n*-Bu_3N complex mediates additions to aldimines. Attempts to extend this protocol to the addition of lithium phenylacetylide (PhCCLi) to ketimines, however, afford only $(PhCC)_3B(n\text{-}Bu_3N)$.[2,6c] Returning to the more traditional procedure,[3] treating ketimine **1** with 1.0 equiv of BF_3−THF complex (generated in situ from BF_3−Et_2O) affords a mixture of free and BF_3-complexed imine (**2**) as evidenced by IR absorbances of the C=N moieties at 1659 and 1630 cm^{-1}, respectively.[9] Monitoring the reaction of complex **2** with 3.0 equiv of lithium phenylacetylide with in situ IR spectroscopy reveals the instantaneous loss of complex **2** and no measurable disappearance of the free imine. The yield of the 1,2-addition correlates with the extent of observable BF_3−imine complexation. The optimum yields required 2.0 equiv of BF_3−THF and 3.0 equiv of PhCCLi at 4.0 M THF concentration in toluene. The low THF concentration renders complexation of the imine to BF_3 more competitive. This protocol was used for all subsequent 1,2-additions without further optimization.



The yields and affiliated stereoselectivities for 1,2-additions of *n*-BuLi, EtCCLi, and PhCCLi are summarized in Table 1 (eq 1). The ketimines were prepared and characterized with standard procedures as described in the Supporting Information. The mixtures resulting from syn−anti isomerism have been studied and discussed previously.[10] Stereochemistries were assigned by

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(9) IR spectroscopic studies of imine−BF_3 complexes: Samuel, B.; Snaith, R.; Summerford, C.; Wade, K. *J. Chem. Soc. A* **1970**, 2019.

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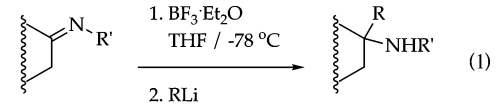
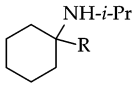
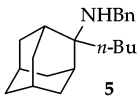
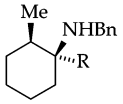
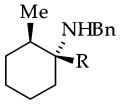
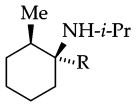
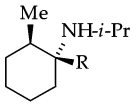
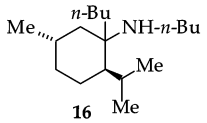
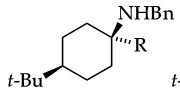
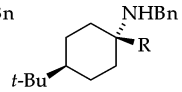
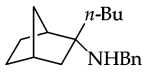
TABLE 1. 1,2-Additions of Organolithiums to Ketimines



(1)

Entry	Product		ratio	yield
				
1	**3**, R = CCPh		---	63%
2	**4**, R = *n*-Bu		---	46%
				
3	**5**		---	80%
				
4	**6**, R = *n*-Bu	**7**, R = *n*-Bu	1:3	69%
5	**8**, R = CCEt	**9**, R = CCEt	8:1	92%
6	**10**, R = CCPh	**11**, R = CCPh	(5:1)[a]	81%
				
7	**12**, R = *n*-Bu	**13**, R = *n*-Bu	1:3	59%
8	**14**, R = CCPh	**15**, R = CCPh	(3:1)[a]	70%
				
9	**16**		one isomer	29%
				
10	**17**, R = *n*-Bu	**18**, R = *n*-Bu	>50:1	70%
11	**19**, R = CCEt	**20**, R = CCEt	1:1	87%
				
12	**21**		>20:1	60%

[a] Stereochemistry was assigned based on analogy with the EtCCLi adduct.

using a combination of $^1H,^{13}C$−HMQC, $^1H,^{13}C$−HMBC, $^1H,^1H$−COSY, $^1H,^1H$−NOESY, and ^1H and ^{13}C NMR spectroscopies or from X-ray crystallography on the amine hydrochloride salts. The butyne and *n*-butyl adducts were related by hydrogenation of the alkynyl moiety. The PhCCLi adducts were assigned by analogy to the EtCCLi adducts, an imperfect but reasonable method. In the most sterically congested cases, substitution at the boron of the imine−BF_3 complex may be a significant side reaction. For example, reaction of a menthone-derived imine (see entry 9) sequentially with

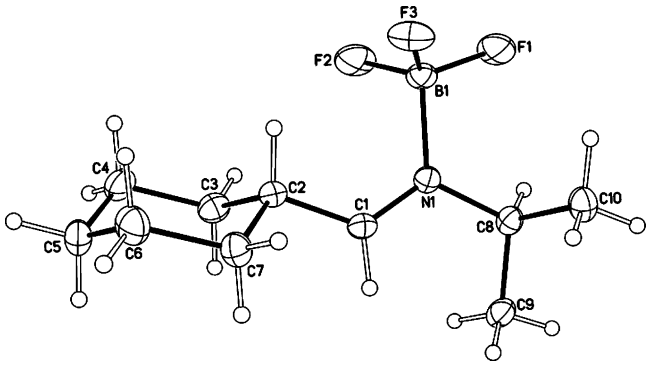


FIGURE 1. ORTEP of BF_3−imine complex **24** revealing syn-oriented BF_3.

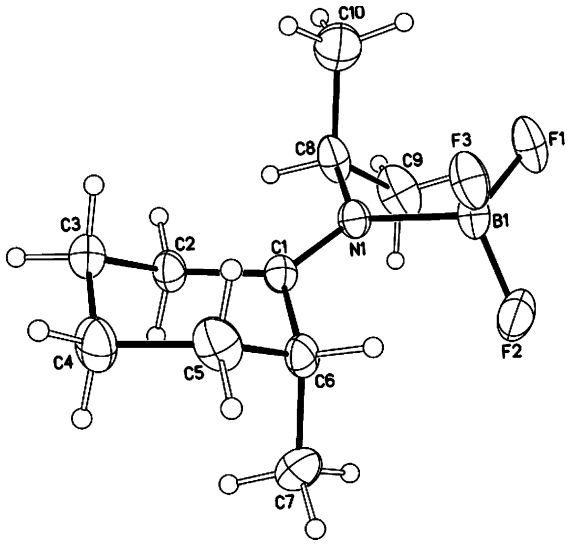
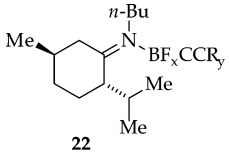
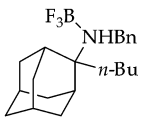


FIGURE 2. ORTEP of BF_3−imine complex **25** revealing syn-oriented BF_3 and axially disposed methyl.

BF_3−THF and lithium acetylides affords essentially no adduct, instead causing the C=N absorbance to increase due to what may be acetylide adducts of general structure **22**. Analogous reaction with *n*-BuLi affords *n*-butyl



22



23

adduct **16** in 29% purified yield as a single (uncharacterized) stereoisomer. In one instance, BF_3−adduct **23** survived a basic workup and flash chromatography;[11] a standard aqueous HCl workup afforded **5**.

Structures of BF_3−Imine Complexes. Crystal structures of BF_3−imine complexes **24**−**26** (Figures 1−3) provided some insights into the origins of the stereoselectivity. In all cases, the BF_3 group orients toward the more substituted side of the imine (as drawn), presumably because it is less sterically demanding than the *N*-alkyl groups. This orientation contrasts with several $B(C_6F_5)_3$/imine complexes reported by Piers and co-

(11) The ^1H NMR spectrum of adduct **23** displayed an AB quartet for benzylic protons.

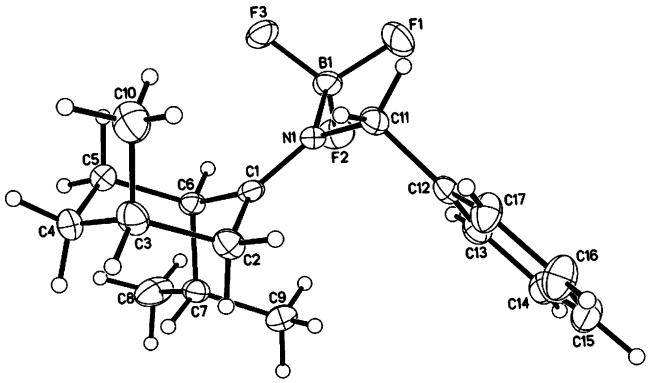
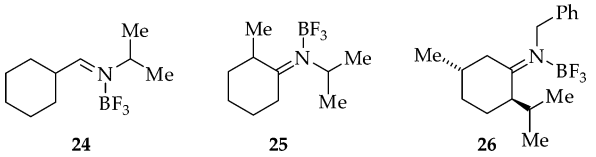


FIGURE 3. ORTEP of BF_3−imine complex **26** revealing syn-oriented BF_3 and diaxially disposed alkyl substituents.

workers in which the hindered BAr_3 orients to the less hindered side.[7] Marked A-strain is evidenced by the axially oriented methyl in **25** and the diaxially oriented alkyl groups in **26**. NMR spectroscopy suggests that **24** and **25** are representative of the bulk material. In fact, addition of a crystalline sample of **25** to solutions of *n*-BuLi or EtCCLi provides yields and selectivities similar to those obtained with the in situ protocol. In contrast, the isolated solid from which a crystal of **26** was obtained affords very complex NMR spectra consistent with a mixture of geometric isomers and diastereomers arising from epimerization. BF_3−imine complexes **24**−**26** displayed a reluctance to hydrolyze on brief exposure to laboratory atmosphere that was surprising given the sensitivity of the uncomplexed imines. This stability and ease of handling may prove synthetically useful.



24 **25** **26**

Stereochemistry. Although high reaction rates thwarted mechanistic studies, a few comments about the stereochemistry are warranted. It is curious that *n*-BuLi and EtCCLi add from opposite faces. This stereochemistry is reminiscent of that obtained in 1,2-additions to cyclohexanones in which opposing steric and electronic effects conspire to cause similar reversals.[12] Possibly the major *n*-BuLi adducts (**7** and **13**) represent the sterically more accessible approach. It seems likely that conformational control imparted by the allylic ($A_{1,3}$) strain[8,13] is important, although the details are far from obvious. The preference for adducts **7** and **13** is interesting given that *n*-BuLi addition in the absence of BF_3 affords complementary isomers (**6** and **12**, respectively), albeit slowly and in <10% yield. The origin of the inordinately high preference for equatorial attack to produce **17** is unclear.

Experimental Section

BF_3-Mediated Addition: A General Protocol. The in situ IR probe was inserted through a nylon adapter fitted with an O-ring seal into an oven-dried, cylindrical flask fitted with magnetic stir bar and T-joint. The T-joint was capped by a septum for injection and N_2 line. After evacuation under full vacuum and flushing with N_2, the flask was charged sequentially with 15 mL of 4.0 M THF in toluene and BF_3−Et_2O (0.19 mL, 0.10 mmol) and then cooled to −78 °C. After recording a background spectrum, a ketimine (0.05 mmol) was added neat. The lithium acetylide in THF or *n*-BuLi in pentane was added, and the reaction was monitored by recording IR spectra every 30 s for 3 min. The reaction was quenched with 20% aqueous NaOH (5 mL) and extracted with ether. The extracts were dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography.

Preparation of Crystalline BF_3−Imine Complexes: General Protocol. To a solution of imine (10.0 mmol) in pentane (20 mL) was added BF_3−Et_2O (12.0 mmol) at 0 °C. Stirring at 0 °C for 15 min typically affords an off-white to brown precipitate. Filtration under nitrogen and recrystallization from CH_2Cl_2/pentane affords the imine−BF_3 complex as a white or off-white crystalline solid displaying stability to limited exposure to the atmosphere.

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Supporting Information Available: Preparations of the imines, spectroscopic characterization of the 1,2-adducts, and crystallographic characterization of three BF_3−imine complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0480895

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(13) For stereoselective reductions of imines and iminium salts in which allylic strain appears to be consequential, see: Hutchins, R. O.; Su, W. Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *48*, 3412. See also: Meza-Leon, R. L.; Crich, D.; Bernes, S.; Quintero, L. *J. Org. Chem.* **2004**, *69*, 3976.

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