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Application of Arylboron Difluoride Lewis Acid Catalysts to the Diels-Alder Reaction: Convenient, Non-volatile Alternatives to Boron Trifluoride.

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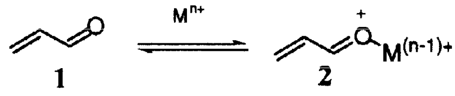
Abstract: Comparative studies were carried out on boron trifluoride etherate, phenylboron difluoride and *meta*-nitrophenylboron difluoride for the Lewis acid catalysed Diels-Alder reaction of cyclopentadiene and a range of standard dienophiles in tetrahydrofuran solution. Phenylboron difluoride showed remarkably similar reactivity in terms of yield and *endo* to *exo* selectivity to boron trifluoride, whereas *meta*-nitrophenylboron difluoride was more reactive than either boron trifluoride or phenylboron difluoride and showed more marked differences in *endo: exo* ratios. These results contrast to some extent with gas-phase semi-empirical calculations (PM3), which suggest that boron trifluoride and *meta*-nitrophenylboron difluoride should have similar reactivity; phenylboron difluoride being less reactive. However, since arylboron difluorides are easily prepared, these Lewis acids represent a group of potentially highly tuneable catalysts for Diels-Alder reactions.

Introduction.

The Diels-Alder reaction has long been recognised as one of the most useful synthetic reactions, due to its wide applicability and ability to generate two new carbon-carbon bonds in an essentially synchronous process, with up to four new chiral centres.[1] In addition, the power of the Diels-Alder process can be enormously increased by use of Lewis acid catalysts, which have the effect of causing substantial changes to: 1) the rates of reaction; 2) the regio-; and 3) stereo-selectivities.[2] The effects of adding such Lewis acids can be readily explained by frontier orbital effects,[3] *i.e.* that Lewis acids lower the LUMO energies of the dienophile (such as **1**) *via* an activated dienophile-Lewis acid complex of type **2** (**Equation 1**).

Equation 1.



Of all the Lewis acids which are commonly used for catalysing Diels-Alder reactions, boron trifluoride is one of the most used, being convenient for applications *via* the etherate solution. However, the effective relative Lewis acidity of boron trifluoride is lower than many other commonly used Lewis acids, such as aluminium trichloride and titanium tetrachloride, due to competing ether coordination.[4] While this is advantageous from the point of view of avoiding polymerisation processes, it also presents disadvantages due to the fact that relative Lewis acidity affects reactivity.[5] Additionally, since one can explain the stereoselectivity

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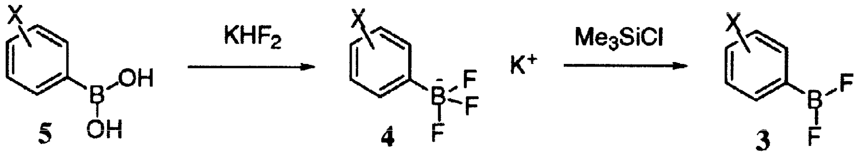
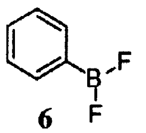
of a Lewis acid catalysed reaction by the structure of the Lewis acid-dienophile complex[6] and formation of an "early" transition-state[7], it is expected that boron trifluoride is not sufficiently sterically demanding to provide high levels of stereochemical control in many systems. We therefore became interested in examining alternative versions of boron trifluoride, which might offer: 1) tunability of Lewis acidity; 2) convenience of preparation; 3) improved stereochemical control; and 4) efficiency of reaction. In particular, our attention was drawn to arylboron difluorides **3**, since these structures are readily accessed from aryl boronic acids **5** *via* the arylboron trifluoride complex **4** (**Scheme 1**).[8]

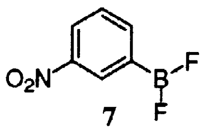
Scheme 1.



In this paper, we report our findings on the comparative reactivity and utility of two representative arylboron difluorides (phenyl- and *meta*-nitrophenyl difluoroborane, **6** and **7** respectively) for catalysing Diels-Alder reactions between cyclopentadiene and simple dienophiles.



6



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Results and Discussion.

The effects of the two arylboron difluorides **6** and **7** were compared under both stoichiometric and catalytic conditions, and compared with both thermal and boron trifluoride etherate mediated Diels-Alder reactions between cyclopentadiene and several dienophiles. The *endo:exo* ratios were measured after 1 hour at 0 °C (**Table 1a**) and these results were compared with identical reactions which were allowed to react for a further 3 hours at room temperature (**Table 1b**). The corresponding degree of conversion for both of these sets of experiments are summarised in **Table 2**.

The most striking observations that one can draw from **Tables 1a**, **1b** and **2**, are that: 1) Under identical conditions (stoichiometric Lewis acid:dienophile ratio, *Methods 2* and *3*) phenylboron difluoride **6** is very similar to boron trifluoride in terms of conversions, both at 0 °C and room temperature; 2) *Meta*-nitrophenylboron difluoride **7** produces consistently higher conversions under identical conditions than either boron trifluoride or phenylboron difluoride; 3) Stereoselectivities vary considerably with each Lewis acid, showing major dependence upon both the dienophile used and the reaction conditions. For example, the thermal reaction between crotonaldehyde and cyclopentadiene shows a strong thermal preference for the kinetic (*endo*) diastereoisomer, but conversion is low. Using *meta*-nitroarylboron difluoride **7** substantially improves the conversion. However, in order to maintain greatest preference for the *endo* product, catalytic quantities of Lewis acid are preferable. Methacrolein benefits most from using an arylboron difluoride; the selectivity can be improved from approximately 1:4 (*endo:exo*) to 1:10 at 95 % conversion, by use of catalytic **7**; 4) Where problems are encountered with Lewis acid catalysed polymerisation of the dienophile, arylboron difluorides can exhibit advantage by showing less susceptibility to induce polymerisation. For example, boron trifluoride produces polymerisation of cinnamaldehyde under stoichiometric conditions at room temperature. However, use of either phenylboron difluoride **6** or **7**, produces smooth conversion, the latter in approximately 50 % yield over 3 hours; 5) The degree of thermodynamic equilibration that takes place on the adducts can be adjusted by choice of the Lewis acid. For example, crotonaldehyde shows high susceptability to thermodynamic equilibration even at room temperature without Lewis acid (from 15:1 at 0 °C to 5.2:1 at room temperature). However, use of catalytic *m*-nitrophenylboron difluoride **7** produces an unexceptional 6.2:1 ratio of *endo:exo* adducts at 0 °C, but an improved 7.5:1 ratio at room temperature, and conversion is essentially quantitative.

Table 1a. *Endo:exo* ratios[a] of cycloadducts from the Diels-Alder reaction various dienophiles with cyclopentadiene after 1 hour at 0 °C.

Dienophile	*Method 1* no catalyst	*Method 2* $BF_3.Et_2O$ (1 equiv.)	*Method 3* $PhBF_2$ (1 equiv.)	*Method 4* $PhBF_2$ (cat.)	*Method 5* *m*-NO_2PhBF_2 (1 equiv.)	*Method 6* *m*-NO_2PhBF_2 (cat.)
Crotonaldehyde	15.0:1	7.1:1	4.6:1	11.4:1	3.0:1	6.2:1
Acrolein	4.2:1	4.6:1	5.5:1	5.8:1	6.3:1	6.1:1
Methyl acrylate	5.5:1	6.7:1	10.2:1	2.9:1	2.9:1	3.1:1
Methacrolein	1:4.1	1:7.3	1:2.1	1:6.4	1:8.2	1:3.2
Acrylamide	N	1:1	-	-	-	-
Maleic anhydride	1:0	1:0	1:0	1:0	1.8:1	1:0
Cinnamaldehyde	N	16.0:1	9.7:1	N	8.5:1	7.3:1

[a] *Endo:exo* ratios were determined by ^1H n.m.r.[9]

Key: N = No observable reaction; P = Polymerisation.

Table 1b. *Endo:exo* ratios[a] of cycloadducts from the Diels-Alder reaction various dienophiles with cyclopentadiene after 1 hour at 0 °C, followed by 3 hours at room temperature.

Dienophile	*Method 1* no catalyst	*Method 2* $BF_3.Et_2O$ (1 equiv.)	*Method 3* $PhBF_2$ (1 equiv.)	*Method 4* $PhBF_2$ (cat.)	*Method 5* *m*-NO_2PhBF_2 (1 equiv.)	*Method 6* *m*-NO_2PhBF_2 (cat.)
Crotonaldehyde	5.2:1	4.2:1	5.1:1	5.1:1	1.6:1	7.5:1
Acrolein	7.2:1	1.5:1	2.9:1	5.3:1	1.5:1	5.9:1
Methyl acrylate	3.1:1	6.4:1	4.0:1	9.1:1	3.3:1	3.4:1
Methacrolein	1:3.9	1:5.5	1:10.9	1:7.5	1:10.0	1:5.2
Acrylamide	N	1:1.1	-	-	-	-
Maleic anhydride	1:0	1:0	1:0	1:0	3.6:1	1:0
Cinnamaldehyde	N	P	7.1:1	10.2:1	10.1:1	9.8:1

[a] *Endo:exo* ratios were determined by ^1H n.m.r.[9]

Key: N = No observable reaction; P = Polymerisation.

Table 2. Total yield[a] of both *endo*- and *exo*-cycloadducts.

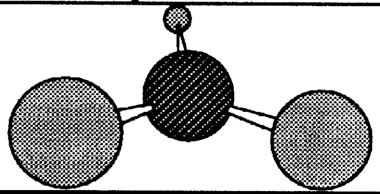
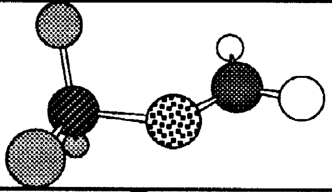
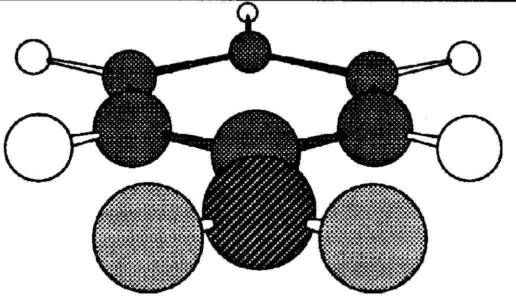
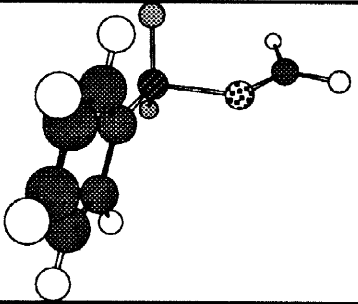
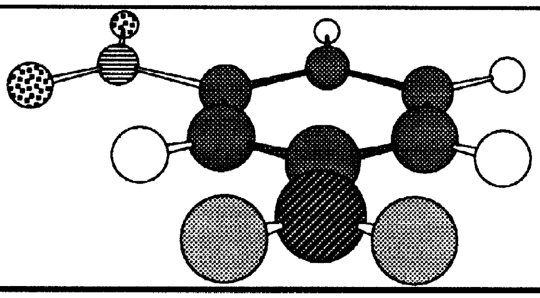
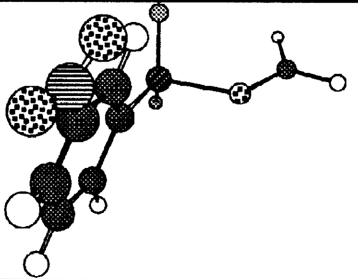
Dienophile	*Method 1* no catalyst		*Method 2* $BF_3.Et_2O$		*Method 3* $PhBF_2$ (1 equiv.)		*Method 4* $PhBF_2$ (cat.)		*Method 5* *m*-NO_2PhBF_2 (1 equiv.)		*Method 6* *m*-NO_2PhBF_2 (cat.)	
	1h 0 °C	+ 3h r.t.	1h 0 °C	+ 3h r.t.	1h 0 °C	+3h r.t.	1h 0 °C	+ 3h r.t.	1h 0 °C	+ 3h r.t.	1h 0 °C	+ 3h r.t.
Crotonaldehyde	17	21	60	67	54	65	14	51	99	> 95	99	98
Acrolein	20	82	44	32	70	72	89	89	98	98	94	99
Methyl acrylate	27	32	27	36	33	44	25	31	39	47	40	47
Methacrolein	76	81	100	100	84	93	83	88	95	95	89	96
Acrylamide	45	47	63	78	P	P	P	P	-	-	-	-
Maleic anhydride	95	97	97	95	98	97	98	98	97	92	97	93
Cinnamaldehyde	0	0	24	44	6	35	1	2	13	50	5	24

[a] Yields were determined by both g.c.[10] and ^1H n.m.r.[9]

Key: P = Polymerisation; - = reaction not attempted.

In order to explain why arylboron difluorides are either equally, or more reactive than boron trifluoride, we undertook PM3 semi-empirical calculations[11,12] to determine the structure of the activated Lewis acid complexes of both formaldehyde and acrolein, with boron trifluoride, phenylboron difluoride and *meta*-nitrophenylboron difluoride. The results of these calculations are summarised in **Tables 3** and **4**, with selected bond lengths and angles shown in **Table 5**.

Table 3. PM3 calculated structures for the uncomplexed and formaldehyde-complexed Lewis acids.

Entry	Uncomplexed Lewis acid	Formaldehyde complex
1		
2		
3		

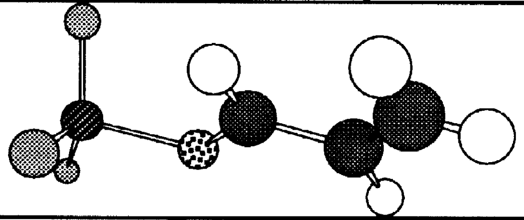
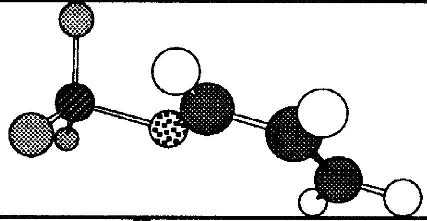
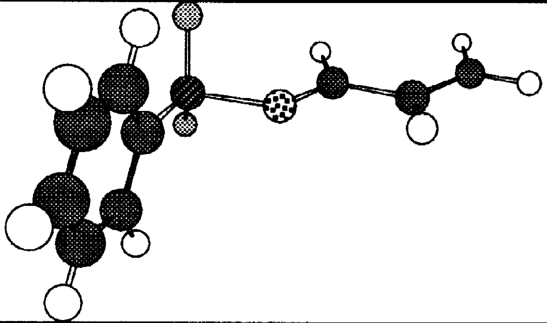
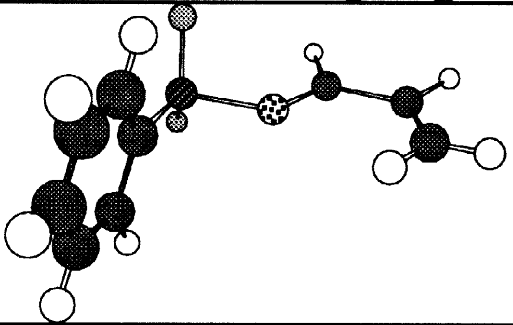
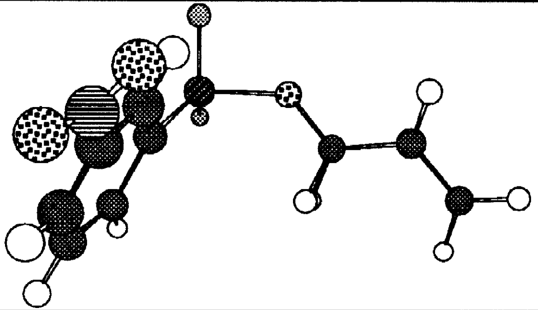
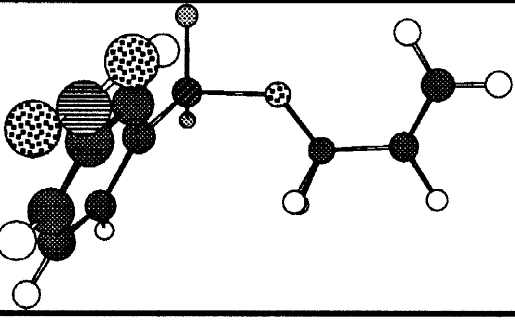
Symbols for **Tables 3** and **4.**

Hydrogen	○	Carbon	●	Oxygen	◌
Boron	▨	Fluorine	◍	Nitrogen	⊜

The overall results shown in **Tables 3 - 5** compare well with both theoretical *ab initio* calculations on boron trifluoride complexes of acetaldehyde and benzaldehyde,[13] X-ray derived experimental measurements[14] and other experimental results.[15] It is noticeable from these semi-empirical gas phase calculations that the boron-fluorine bond lengths for each of the three Lewis acids (Entries 1-3, **Table 5**) vary according to substitution, *i.e.* the boron-fluorine bond lengths are slightly longer for boron trifluoride than for either **6** or **7**, showing the effect of orbital overlap and stabilisation of the boron centre by the aryl groups. Comparison of the aryl-C-B bond lengths also shows that the *meta*-nitro substituent of **7** shows slightly less orbital overlap and therefore shortening of the aryl-carbon-boron bond, as expected for the effect of an electron withdrawing nitro function present. It is difficult to predict from these structures alone whether the arylboron difluorides should behave either as stronger or weaker Lewis acids than boron trifluoride, however it is expected that the arylboron difluoride systems should not be substantially different from boron trifluoride itself. Indeed, this fact is reinforced by comparing the complexes of each of the Lewis acids with formaldehyde (entries 6, 9 and

12, **Table 5**); the C=O bonds are obviously lengthened by Lewis acid complex formation with all three Lewis acids. One can also observe complimentary lengthening of the C=O bond, with the *meta*-nitro system **7** causing very similar effects to boron trifluoride. Most interesting is the fact that for all of the complexes with acrolein, the C=C bond of acrolein is lengthened to a very similar extent, with the phenyl system **6** being only very marginally less activating than either boron trifluoride or the nitro-phenyl system **7**.

Table 4. PM3 calculated structures for the acrolein complexed Lewis acids.

Entry	*S-Trans* acrolein complex	*S-Cis* acrolein complex
1		
2		
3		

Clearly it is not possible to extrapolate directly from results obtained from gas phase calculations of Lewis acid-dienophile complexes to those obtained from experimental condensed phase reactions. However, it is possible to see that boron trifluoride, phenylboron difluoride and *meta*-nitrophenylboron difluoride should not be substantially different in reactivity, with *meta*-nitrophenylboron difluoride exhibiting greatest reactivity, which is observed experimentally.

Summary.

There is an ever increasing need to derive new catalytic systems which have advantages of: 1) efficiency; 2) selectivity; 3) cost; and 4) environmental friendliness. It is clear that arylboron difluorides offer enormous scope for further development since they can offer significant advantages by manipulation of the aryl ring. The rational design of new arylborondifluorides using molecular modelling is possible and would be enhanced by higher level calculations. Studies along these lines are underway, together with the design and development novel supported versions of boron trifluoride[16] and further re-useable Lewis acid catalysts.

Table 5. PM3 calculated bond lengths and B-O-C bond angles for formaldehyde and acrolein complexes with borontrifluoride, phenyldifluoroborane and *m*-nitrophenyldifluoroborane.

Entry	System	C=C (Å)	C=O (Å)	C-B (Å)	B-F (Å)	B-O (Å)	C-B-O (°)	B-O-C (°)
1	OCH_2	-	1.220	-	-	-	-	-
2	$OCHCHCH_2$	1.321	1.190	-	-	-	-	-
3	BF_3	-	-	-	1.301	-	-	-
4	$PhBF_2$	-	-	1.551	1.315	-	-	-
5	m-NO_2PhBF_2	-	-	1.555	1.312	-	-	-
6	$BF_3.OCH_2$	-	1.227	-	1.331 1.338	1.619	-	123.04
7	$BF_3.OCHCHCH_2$ (s-trans)	1.334	1.243	-	1.333 1.340	1.594	-	121.96
8	$BF_3.OCHCHCH_2$ (s-cis)	1.335	1.245	-	1.334 1.340	1.589	-	122.28
9	$PhBF_2.OCH_2$	-	1.224	1.598	1.342	1.674	104.03	123.82
10	$PhBF_2.OCHCHCH_2$ (*s-trans*)	1.332	1.239	1.601	1.343	1.648	104.10	123.01
11	$PhBF_2.OCHCHCH_2$ (*s-cis*)	1.334	1.240	1.602	1.343	1.647	103.94	123.22
12	m-$NO_2PhBF_2.OCH_2$	-	1.226	1.602	1.341	1.660	104.18	123.71
13	m-$NO_2PhBF_2.OCHCHCH_2$ (*s-trans*)	1.333	1.240	1.611	1.344 1.338	1.615	108.71	124.96
14	m-$NO_2PhBF_2.OCHCHCH_2$ (*s-cis*)	1.335	1.242	1.611	1.344 1.338	1.613	108.98	125.00

Experimental.

PM3 semi-empirical calculations[11] were carried out using MacSpartan Plus 1.0.4., after initial minimisation using the Sybyl molecular mechanics force field within MacSpartan Plus. Structure files were converted into Chem3D Plus 3.1.1[17] structures for black and white visualisation.

THF was distilled under argon from benzophenone and sodium. Phenylboronic acid, *meta*-nitroboronic acid, chlorotrimethylsilane and potassium hydrogenfluoride were purchased from Aldrich. Potassium phenyltrifluoroborate was prepared as reported.[8c] All anhydrous reactions were carried out in glassware which was dried prior to use by storage in a glass oven maintained at 140 °C and cooled under a stream of argon. All organic extracts were dried with anhydrous magnesium sulfate or anhydrous sodium sulfate. Evaporations were carried out using a Buchi rotary evaporator or Buchi cold-finger rotary evaporator, followed by evaporation under high vacuum (typically at approximately 2 mmHg). M.p.'s were determined using an Electrothermal melting point apparatus and are uncorrected. ^1H spectra were recorded in $CDCl_3$, or D_6-DMSO/D_2O solutions at 200 or 400 MHz on a Bruker AC200 or AC400 n.m.r. spectrometer. I.r. spectra were recorded on a Perkin-Elmer 783 equiped with a PE600 data station. Fast atom bombardment (f.a.b.) spectra were recorded on a Kratos MS50, using a *meta*-nitrobenzylalcohol matrix and accurate mass determinations were carried out on a Kratos Concept IS spectrometer. Microanalyses were performed using a Carlo-Erba 1106 elemental analyser.

Preparation of potassium meta-nitrophenyltrifluoroborate.

To a solution of *meta*-nitrophenylboronic acid (3.785 g, 22.7 mmol) in water (30 ml) was added potassium hydrogen fluoride (3.540 g, 45.4 mmol). The mixture was heated for 15 minutes, cooled and the resulting crystalline salt was collected by filtration. Recrystallisation from water gave potassium *meta* nitrophenyltrifluorborate as a white solid (4.280 g, 82 %); υ_{max} (KBr) 1620, 1570, 1380, 1350, 1280, 1240, 1210, 1100, 1030, 1000-940, 900, 870, 810, 690 cm^{-1}; δ (^{1}H, D$_6$-DMSO) 7.43 (1H, t, *J* 7.5 Hz), 7.79 (1H, d, *J* 7.0 Hz), 7.96 (1H, ddd, *J* 8.0, 2.5, and 1.0 Hz), and 8.16 (1H, d, *J* 2.5 Hz); δ (^{13}C, D$_6$-DMSO) 120.6, 125.6, 128.2, 138.6 and 147.3; m/z (f.a.b.) 268 (base peak, M+K$^+$); Analysis, $C_6H_4NO_2BF_3K$ requires C, 31.5; H, 1.8; N, 6.1; F, 24.9; found C, 31.5; H, 1.6; N, 6.2; F, 25.0 %.

General procedures for Diels-Alder reactions.

Method 1: Thermal reaction.

To a solution of the dienophile (1.4 mmol) in dry tetrahydrofuran (2 ml) at 0 °C was added freshly distilled cyclopentadiene (0.46 ml, 7.0 mmol). After 1 h, the reactions were allowed to warm to room temperature and left for a further 3h. Monitoring of the reactions was carried out by removing aliquots of the reaction mixture and direct analysis by g.c.,[10] and by evaporation of the tetrahydrofuran and analysis by ^{1}H n.m.r.[9]

Method 2: Boron trifluoride etherate catalysed reaction.

This catalysed reaction was carried out in an identical manner to *Method 1*, except that boron trifluoride etherate (0.18 ml, 1.4 mmol) was added to the tetrahydrofuran prior to all other additions. Monitoring of the reactions was carried out by removing aliquots of the reaction mixture, quenching with dilute sodium hydrogen carbonate, extracting with chloroform, drying and evaporating. Direct analysis of the crude product was carried out by g.c.[10] and ^{1}H n.m.r.[9]

Method 3: Stoichiometric phenyldifluoroborane catalysed reaction.

This catalysed reaction was carried out in an identical manner to *Method 1*, except that potassium phenyltrifluoroborate (0.26 g, 1.4 mmol), followed by chlorotrimethylsilane (0.18 ml, 1.4 mmol) were added to the tetrahydrofuran prior to all other additions. Monitoring of the reactions was carried out by removing aliquots of the reaction mixture, diluting with chloroform, briefly washing with water, drying and evaporating. Direct analysis of the crude product was carried out by g.c.[10] and ^{1}H n.m.r.[9]

Method 4: Catalytic phenyldifluoroborane catalysed reaction.

This catalysed reaction was carried out in an identical manner to *Method 3*, except that potassium phenyltrifluoroborate (0.026 g, 0.14 mmol), followed by chlorotrimethylsilane (0.02 ml, 0.14 mmol) were added to the tetrahydrofuran prior to all other additions.

Method 5: Stoichiometric meta-nitrophenyldifluoroborane catalysed reaction.

This catalysed reaction was carried out in an identical manner to *Method 3*, except that potassium *meta*-nitrophenyltrifluoroborate (0.32 g, 1.4 mmol), followed by chlorotrimethylsilane (0.18 ml, 1.4 mmol) were added to the tetrahydrofuran prior to all other additions.

Method 6: Catalytic meta-nitrophenyldifluoroborane catalysed reaction.

This catalysed reaction was carried out in an identical manner to *Method 3*, except that potassium *meta*-nitrophenyltrifluoroborate (0.032 g, 0.14 mmol), followed by chlorotrimethylsilane (0.02 ml, 0.14 mmol) were added to the tetrahydrofuran prior to all other additions.

Acknowledgments.

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