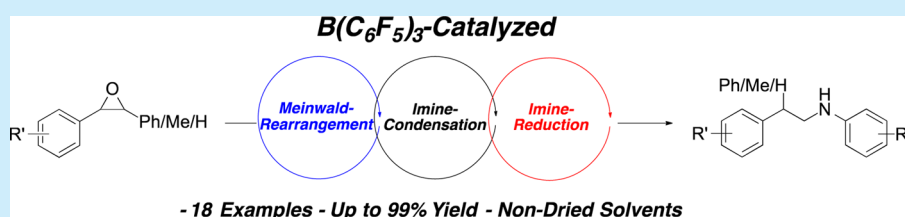# The B(C$_6$F$_5$)$_3$-Catalyzed Tandem Meinwald Rearrangement–Reductive Amination

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S *Supporting Information*

B(C$_6$F$_5$)$_3$-Catalyzed

- 18 Examples - Up to 99% Yield - Non-Dried Solvents

ABSTRACT: A system of three coupled catalytic cycles enabling the one-pot transformation of epoxides to amines via Meinwald rearrangement, imine condensation, and imine reduction is described. This assisted tandem catalysis is catalyzed by B(C$_6$F$_5$)$_3$ resulting in the first tandem Meinwald rearrangement–reductive amination protocol. The reaction proceeds in nondried solvents and yields β-functionalized amines. In particular, β-diarylamines are obtained in high yields.

Epoxides belong to the most versatile functional groups in organic chemistry. Their remarkable reactivity is caused by their ring strain, resulting in a wide-ranging chemistry. To date, many catalytic transformations of epoxides have been established, including synthetic approaches to alcohols,[1] cycloalkanes,[2] β-lactones,[3] succinic anhydrides,[4] thiiranes,[5] and carbonates.[6] Besides these reactions, the most typical transformations of epoxides are S$_N$-type ring openings leading to chlorohydrins, alcohols, or amino alcohols. These transformations of epoxides are usually mediated or catalyzed by Lewis or Brønsted acids. Acids are also capable of catalyzing aldehyde and ketone formation from epoxides via Meinwald rearrangements.[7]

Among many other Lewis acids, tris(pentafluorophenyl)-borane (B(C$_6$F$_5$)$_3$) is capable of catalyzing the Meinwald rearrangement.[8] To our knowledge B(C$_6$F$_5$)$_3$ has since then barely been used as a catalyst in Meinwald rearrangements.[7a] This is surprising, as, in recent years, many applications of B(C$_6$F$_5$)$_3$ as a catalyst for Frustrated Lewis pair type (FLP) reactions have been reported. Examples include its use as a hydrogenation catalyst for olefins,[9] carbonyl compounds,[10] and imines.[11] In addition, the B(C$_6$F$_5$)$_3$-catalyzed hydrosilylation has been reported by Piers and Parks.[12] Very recently, the B(C$_6$F$_5$)$_3$-catalyzed reductive amination of aldehydes that uses hydrosilanes as reducing agents has been reported by Ingleson and co-workers.[13]
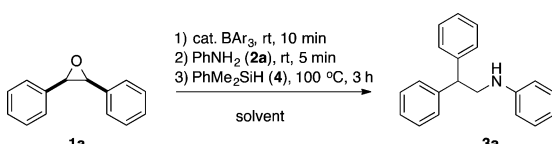
As both the Meinwald rearrangement and the reductive amination are known to be catalyzed by B(C$_6$F$_5$)$_3$, we wondered if both reactions could be performed in a one-pot tandem procedure. The products would be β-functionalized amines that are very interesting structural motifs with particularly high importance in drug design.[14] To the best of

our knowledge a tandem Meinwald rearrangement–reductive amination is unprecedented.

We started our investigations with *cis*-stilbene oxide (**1a**) as a substrate, as we anticipated that it would undergo a Meinwald rearrangement within a few minutes due to the high migration tendency of the phenyl substituents. We envisioned that aniline (**2a**) would form *in situ* an imine that would give the β-diarylamine **3a** after reduction (Table 1). Stirring **1a** in the presence of 5 mol % B(C$_6$F$_5$)$_3$ in chlorobenzene (PhCl) for 10 min, followed by the addition of 2.0 equiv of aniline (**2a**), resulted in a white suspension. Addition of 2.0 equiv of dimethylphenylsilane (**4**) and heating for 3 h at 100 °C gave amine **3a** in a very good isolated yield of 86% (entry 1). The stepwise addition of reagents is important to avoid B(C$_6$F$_5$)$_3$-catalyzed amino alcohol formation.[15] Notably, the presence of B(C$_6$F$_5$)$_3$ is crucial to obtain **3a**, as a control experiment without B(C$_6$F$_5$)$_3$ showed no product formation and only little conversion of **1a** to undefined compounds (entry 2). Similar to Ingleson and co-workers,[13] the solvent was used as provided from the supplier and has not been further dried (84.7 ppm water in PhCl as determined by Karl Fischer titration).

Knowing that the synthesis of **3a** from **1a** is possible in a one-pot procedure, we set out to optimize our reaction conditions (Table 1). First, we reduced the amount of **2a** and **4** from 2.0 to 1.2 equiv (entry 3). This resulted in a slight increase in yield to 88%. Similarly, by increasing the reaction time from 3 to 6 h 88% of **3a** were isolated (entry 4). We continued the following experiments with 1.2 equiv of **2a** and **4** and a 3 h reaction time, as a longer reaction time had only a slight effect on the isolated yield. Reducing the catalyst loading to 2.5 mol % resulted in a

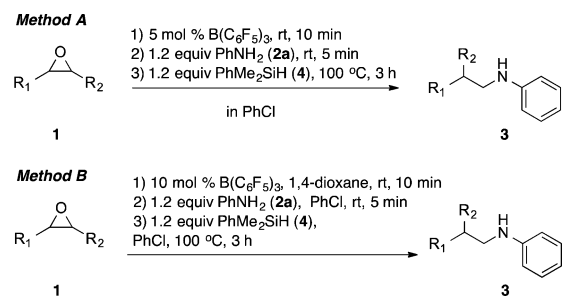## Table 1. Optimization of the Borane-Catalyzed Tandem Meinwald Rearrangement−Reductive Amination of 1a[a]

entry	BAr$_3$ (mol %)	equiv of 2	equiv of 4	solvent	yield [%]
1	B(C$_6$F$_5$)$_3$ (5)	2.0	2.0	PhCl	86
2	–	2.0	2.0	PhCl	0
3	B(C$_6$F$_5$)$_3$ (5)	1.2	1.2	PhCl	88
4[b]	B(C$_6$F$_5$)$_3$ (5)	2.0	2.0	PhCl	88
5	B(C$_6$F$_5$)$_3$ (2.5)	1.2	1.2	PhCl	79
6[c]	B(C$_6$F$_5$)$_3$ (5)	1.2	1.2	PhCl	15
7	B(C$_6$F$_5$)$_3$ (5)	1.2	1.2	1,2-DCE	80
8	B(C$_6$F$_5$)$_3$ (5)	1.2	1.2	toluene	76
9	B(C$_6$F$_5$)$_3$ (5)	1.2	1.2	1,4-dioxane	21
10	B(p-tol)$_3$ (5)	1.2	1.2	PhCl	0
11	B(C$_6$F$_5$)$_2$(Mes) (5)	1.2	1.2	PhCl	10

[a]Concentration after addition of all reagents = 0.125 M. [b]Reaction time = 6 h. [c]Reaction temperature = 60 °C; 1,2-DCE = 1,2-Dichlorethane; all yields are isolated yields.

small decrease in yield to 79% yield (entry 5). Reducing the temperature to 60 °C caused a dramatic decrease in yield to only 15% of **3a** (entry 6). Changing the solvent to 1,2-dichloroethane (1,2-DCE; entry 7) or toluene (entry 8) gave **3a** in 80% and 76% yield, while switching to 1,4-dioxane (entry 9) gave only 21% of **3a**. Other tris(aryl)borane Lewis acids tested, namely B(p-tol)$_3$ and B(C$_6$F$_5$)$_2$(Mes), have shown no or only very little activity under our conditions (entries 10 and 11).

With optimized reaction conditions in hand, we investigated the scope of amines in the reaction (Figure 1). To our delight, electron-rich anilines such as p-anisidine or p-toluidine can be employed, resulting in the formation of **3b** and **3c** in very good yields of 80% and 85%. Also electron-poor anilines such as 4-chloroaniline, 4-(trifluoromethyl)aniline, or ethyl 3-amino-benzoate are suitable substrates for this transformation, as they give the desired products **3d** (69%), **3e** (55%), and **3f** (69%) in good yields. Increasing the steric demand around nitrogen by employing 2,6-dimethylaniline as the substrate resulted in the formation of **3g** in a very good yield (84%). Interestingly, introducing a bromo substituent in the *para*-position by using 4-bromo-2,6-dimethylaniline as substrate resulted in the formation of **3h** in 58%. Naphtylamines can also be used as substrates. By employing 2- and 1-naphtylamine, the corresponding reaction products **3i** and **3j** could be obtained in good yields of 60% and 52%. Unfortunately, when using 2-aminopyridine as substrate, no reaction product **3k** could be observed. This might be due to catalyst inhibition caused by the chelating nature of the free amine and/or the formed imine. Furthermore, amines other than anilines gave at this point no desired reaction products. Examples include benzylamine and piperidine whose corresponding products **3l** and **3m** have not been formed according to NMR analysis of the crude reaction products.

After investigating the scope of suitable amines we turned our focus to study the scope of epoxides by using aniline **2a** as the amine component in all reactions (Table 2). Initially, we looked at substituted *cis*-stilbene oxides **1b−1e**. *tert*-Butyl
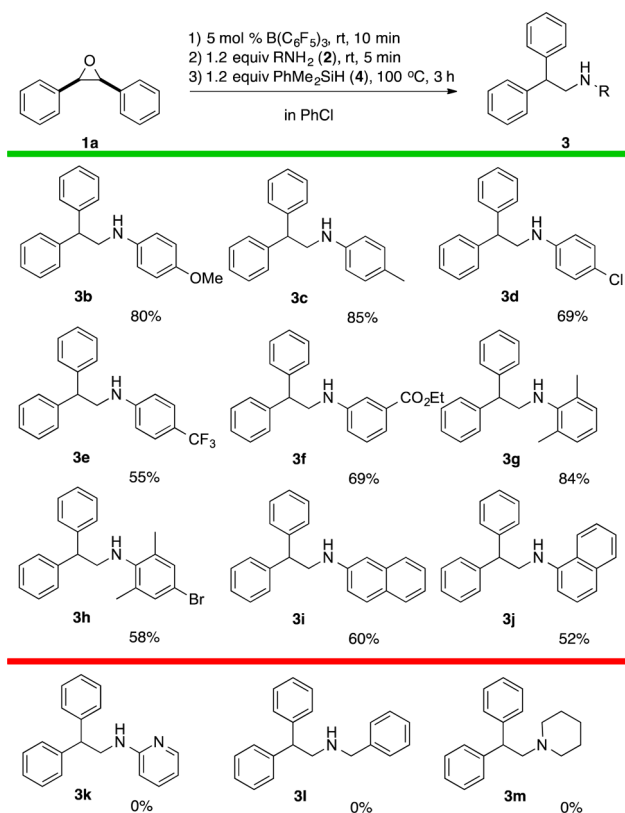
Figure 1. Amine scope of the B(C$_6$F$_5$)$_3$-catalyzed tandem Meinwald rearrangement−reductive amination of **1a**. All yields are isolated yields. The concentration after addition of all reagents is 0.125 M.

Table 2. Epoxide Scope of the B(C$_6$F$_5$)$_3$-Catalyzed Tandem Meinwald Rearrangement−Reductive Amination[a]

entry	R$_1$	R$_2$	cis/trans	substrate/product	yield [%]
1[b]	p-tert-BuC$_6$H$_4$	Ph	cis	1b/3n	99
2[b]	p-BrC$_6$H$_4$	Ph	cis	1c/3o	88
3[b]	p-ClC$_6$H$_4$	Ph	cis	1d/3p	87
4[b]	p-NO$_2$C$_6$H$_4$	Ph	cis	1e/3q	40
5[c]	Ph	Ph	trans	1f/3a	64
6[c]	Ph	H	–	1g/3r	30
7[c]	p-ClC$_6$H$_4$	H	–	1h/3s	26
8[c]	p-tert-BuC$_6$H$_4$	Me	mix[d]	1i/3t	24
9[c]	C$_3$H$_7$	C$_3$H$_7$	cis	1j/3u	0

[a]Concentration after addition of all reagents = 0.125 M. [b]Method A and isolated yields. [c]Method B and NMR yields. [d]cis/trans = 74:26.

substituted **1b** reacts under our optimized conditions to give **3n** in quantitative yield. The introduction of halogen substituents in **1c** and **1d** gave the corresponding β-diarylamines **3o** and **3p** in very good yields (88% and 87%). These yields are identical to the case of the nonsubstituted *cis*-stilbene oxide **1a**. Also

nitro-substituted **1e** reacted under our reaction conditions and gave **3q** in moderate yield (40%).

When moving from **1a** to the *trans*-isomer **1f** no product formation was observed under our optimized conditions. The case was similar when styrene oxides **1g**, **1h**, and **1i** were tested. As already reported by Yamamoto and co-workers,[8] the ability of an epoxide to undergo a $B(C_6F_5)_3$-catalyzed Meinwald rearrangement is solvent dependent. Indeed, when stirring **1f** in 1,4-dioxane in the presence of 10 mol % borane, followed by addition of 1.2 equiv **2a** in PhCl and 1.2 equiv **4** in PhCl, we observed the formation of **3a** in 64% yield. Also styrene oxides **1g**, **1h**, and **1i** reacted under our modified protocol to afford the desired β-arylamines **3r** (30%), **3s** (26%), and **3t** (24%). Unfortunately, the 1,2-dialkyl-substituted epoxide **1j** gave no product **3u** under our conditions. However, to the best of our knowledge, the catalytic results presented here are the first examples of a Meinwald rearrangement−reductive amination protocol yielding β-functionalized amines.

Based on our studies and reported mechanism for the Meinwald rearrangement[7g] and the $B(C_6F_5)_3$-catalyzed reductive amination,[13] we propose the overall mechanism depicted in Scheme 1. This mechanism consists of three coupled catalytic

Scheme 1. Proposed Mechanism of the $B(C_6F_5)_3$-Catalyzed Tandem Meinwald Rearrangement−Reductive Amination of 1a
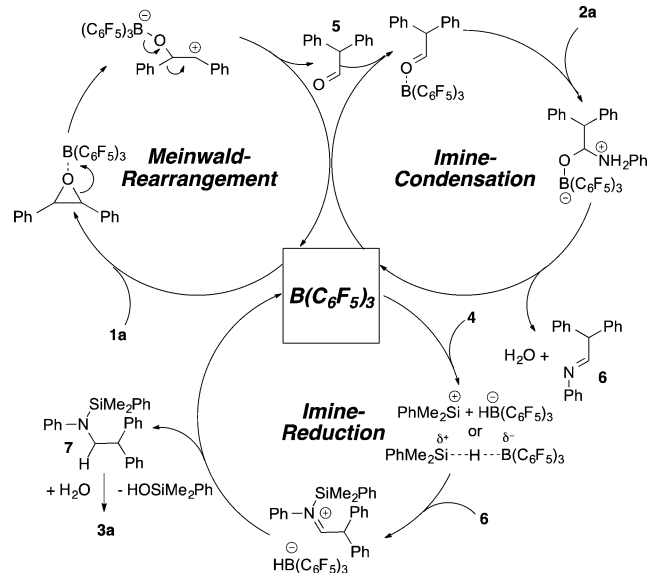
cycles that are all $B(C_6F_5)_3$-catalyzed. The first cycle is the Meinwald rearrangement where the catalyst activates **1a** via coordination. After ring opening a 1,2-migration occurs, resulting in the formation of aldehyde **5** and catalyst regeneration. The second cycle is the imine condensation where $B(C_6F_5)_3$ activates **5** for a nucleophilic attack of **2a**. After proton migration and water elimination, imine **6** is obtained and the catalyst is regenerated. The third cycle is the imine reduction. Here, first $B(C_6F_5)_3$ abstracts a hydride from silane **4** to generate $HB(C_6F_5)_3^-$ and $PhMe_2Si^+$. $PhMe_2Si^+$ is able to activate **6** for a hydride transfer from $HB(C_6F_5)_3^-$ resulting in the formation of "silyl amine" **7** and $B(C_6F_5)_3$. Alternatively, the formation of **7** could also proceed via a borane−silane complex, as reported by Piers, Tuononen and co-workers.[16] **7** is protonated by water to give **3a** and $HOSiMe_2Ph$. Very likely, $HOSiMe_2Ph$ is able to protonate a second equivalent of **7**

resulting in the formation of $O(SiMe_2Ph)_2$ which was also observed as a side product. The water that protonates **7** can originate either from the imine condensation or from the solvent, as nondried PhCl was used. To the best of our knowledge, assisted tandem catalysis consisting of three coupled catalytic cycles that employ the same precatalyst are rare.[17]

In conclusion, the one-pot transformation of arylepoxides to β-arylamines has been reported. The reactions are catalyzed by $B(C_6F_5)_3$ and proceed in easy to handle nondried solvents. Our protocol has been tested for the scope of epoxides and amines and is a complementary strategy to the classic Lewis acid mediated synthesis of amino alcohols from amines and epoxides. Therefore, it represents an important addition to the toolbox of synthetic chemists. We propose that the reaction occurs via an unprecedented Meinwald rearrangement− reductive amination tandem reaction that is catalyzed by $B(C_6F_5)_3$. We suggest that these metal-free transformations occur via three coupled catalytic cycles that are all catalyzed by $B(C_6F_5)_3$, highlighting the versatility of $B(C_6F_5)_3$. Current investigations in our laboratory focus on the development of an asymmetric protocol of this transformation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.6b01744.

> Experimental procedures, spectral data, and other characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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