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Chelation controlled reductive amination of cyclic ketones to *trans*-4-methoxycyclohexylamines: 9-BBN reduction mediated with $FeCl_3$

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ABSTRACT

A novel *trans*-diastereoselective reductive amination of 4-substituted cyclohexanones is described using 9-BBN as reducing agent in the presence of $FeCl_3$. The method permits efficient synthesis of structurally diverse 4-*trans*-alkoxycyclohexylamines.

Introduction

Reductive amination is an important synthetic tool in organic synthesis. Various reducing agents have been utilized to carry out this direct process,[1] for example, catalytic hydrogenation,[2] reduction using boranes or amine boranes,[3] sodium- or zinc borohydride in the presence of BrØnsted or Lewis acids,[4] sodium cyanoborohydride,[5] sodium triacetoxyborohydride,[6] silanes in the presence of Lewis acids[7] and organocatalytic reductive aminations.[8] However, few of these procedures targeted stereoselective reduction of in situ generated cyclohexylimines. Reductive amination of 4-substituted cyclohexanones usually affords a mixture of 1,4-*cis*- and 1,4-*trans* diastereomers without significant selectivity, which was attributed to the steric interaction of substituents on the nitrogen atom of the imine functionality.[9] Reductions of cyclohexanones are more amenable to generating alcohols with high *trans*-selectivity by varying the steric hindrance of the incoming hydrides (Fig. 1a). Relatively unhindered $LiAlH_4$, for example, will approach the ketone from the axial position to produce exclusively the *trans*-4-*tert*-butylcyclohexanol. Bulky hydrides such as LiBH(*sec*-Bu)$_3$ will attack from the less hindered equatorial side, leading to diastereoselective production of *cis*-4-*tert*-butylcyclohexanol. For cyclohexylimines, the least congested direction of hydride attack appears to be from the equatorial position due to steric hindrance induced by substitution on the nitrogen atom, therefore leading to the formation of *cis*-selective cyclohexylamines (Fig. 1b). In contrast to the well precedented diastereoselective reduction of substituted cyclohexanones, few *cis*-diastereoselective syntheses of 4-axial cyclohexylphenyl amines have recently been reported,[10] and one *trans*-selective reductive amination of 4-substituted cyclohexanones applying $Zn(BH_4)_2$ reduction supported on silica gel has been described.[4c]

Herein, we report highly *trans*-selective reductive amination of 4-alkoxycyclohexylamines using 9-borabicyclo(3,3,1)nonane (9-BBN) as reducing agent in the presence of $FeCl_3$. To our knowledge, 9-BBN has not been reported as the reducing agent in reductive amination reactions, even though it has been widely applied for the reduction of aldehydes and ketones.[11]

Reductive amination of the electron-deficient aniline methyl 2-aminobenzoate (**1a**) containing a labile *ortho* ester group was examined with 4-methoxycyclohexanone (**2a**). Ph_3SiH reduction catalyzed by $SnBu_2Cl_2$[7d] yielded 4-methoxycyclohexylamines in a *trans*/*cis* isomeric ratio of 35:65 (Table 1, entry 1) with *cis*-amine as the major product. However, *trans*-4-methoxycyclohexylamine was required for our current project. Different reducing agents were tested in an effort to increase the selectivity toward the *trans*-amine. No product formation was detected with metal borohydrides in the absence of Lewis acids even when dehydrating reagents such as activated molecular sieves or orthoformate was added to the reaction mixture (entry 2). Lewis acids are known to facilitate imine formation, therefore $BF_3{\cdot}Et_2O$ was examined.

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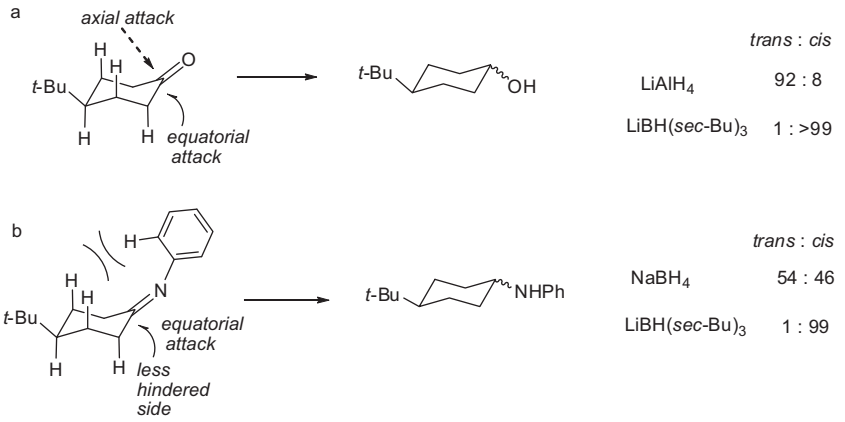
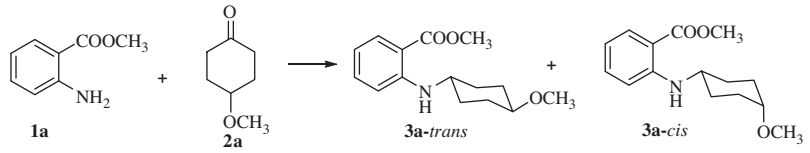


Figure 1. Reductions of ketone (a) and imine (b) with hydride reagents.[9]

Table 1
Screening of the reductive amination reactions



Entry	Reducing agent	Lewis acid[e] (or catalyst)	Additive	**3a** *trans*/*cis*[a,12]	Conv.[b]
1	$PhSiH_3$	$SnBu_2Cl_2$	—	35:65	100%[c]
2	$NaBH(OAc)_3$	—	4 Å	—	0[d]
3	$NaBH(OAc)_3$	BF_3Et_2O	HOAc	35:65	7%[d]
4	$NaBH(OAc)_3$	$FeCl_3$	HOAc	49:51	30%[d]
5	$tBuNH_2BH_3$	$FeCl_3$		65:35	45%[d]
6	9-BBN	—		—	Trace
7	**9-BBN**	**$FeCl_3$**		**82:18**	**100%**
8	9-BBN	$Fe(OTf)_3$		76:24	100%
9	9-BBN	$In(OTf)_3$		72:28	88%
10	9-BBN	BF_3Et_2O		74:26	100%
11	9-BBN	BH_3THF		52:48	100%
12	9-BBN	$TiCl_4$		55:45[f]	100%
13	9-BBN	$Ga(OTf)_3$		71:29	94%
14	9-BBN	$AlCl_3$		65:34	100%
15	BH_3THF	$FeCl_3$		52:48	100%

[a] Ratio and conv refer to HPLC analysis.
[b] 1.0 mmol aniline, 1.1 mmol ketone, 3.0 mmol reducing agent in THF at 0 °C for 3–6 h. 9-BBN was added as 0.5 M solution in THF.
[c] 1.2 mmol silane and 0.1 mmol $SnBu_2Cl_2$ in THF at 40 °C for 12 h.
[d] Room temperature for 12 h.
[e] 1.2 mmol Lewis acid was added unless specified otherwise.
[f] Same ratio was obtained with 1.0 mmol and 2.0 mmol of $TiCl_4$, respectively.

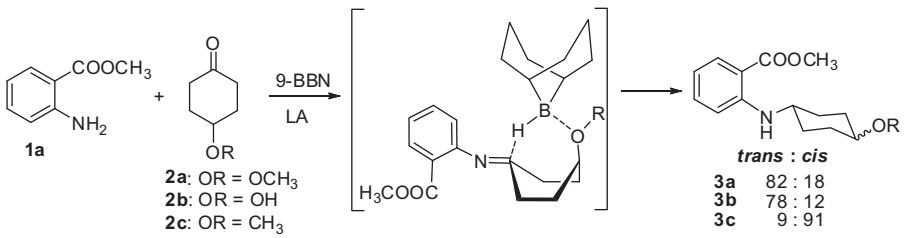
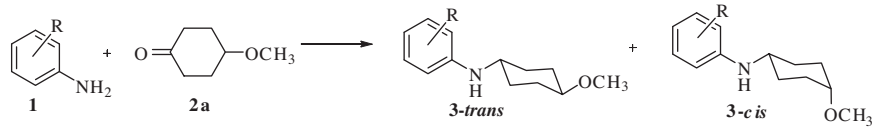
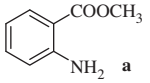
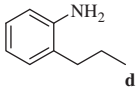
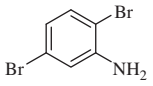
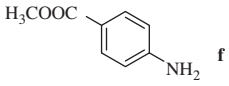
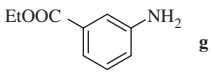
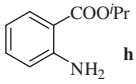
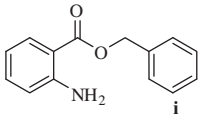
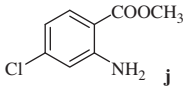
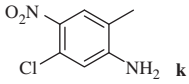
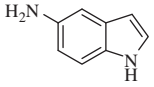
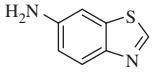
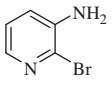
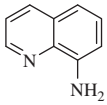


Figure 2. Proposed structure of the reaction intermediate.

Improved conversion was observed, however favoring the undesired *cis*-isomer (entry 3). Several Lewis acids were evaluated, among them $FeCl_3$ and $GaCl_3$ with $NaBH(OAc)_3$ produced a 1:1 mixture of *trans*/*cis*-amines (entry 4). Due to the hygroscopic nature of $GaCl_3$, $FeCl_3$ was selected for further optimization. Increased *trans*-selectivity was obtained when the reducing agent $tBu_2NH{\cdot}BH_3$ was used. *Trans*-4-methoxycyclohexylamine was obtained for the first time as the major product in a *trans*/*cis* ratio of 65:35 (entry 5). Incomplete reaction, however, was observed even after the addition of excess $tBu_2NH{\cdot}BH_3$. Other amine boranes such as $NH_3{\cdot}BH_3$,

Table 2
Reductive amination of aryl and heteroaryl amines with 4-methoxycyclohexylketone



Entry	Amine (**1**)	Ratio of *trans*/*cis* (**3**)	Yield[a,17] (%)
1	 **a**	82:18	94
2	 **d**	72:28	75
3	 **e**	86:14[b]	96
4	 **f**	82:18[b]	85
5	 **g**	82:18	86
6	 **h**	81:19	92
7	 **i**	83:17	93
8	 **j**	89:11[b]	90
9	 **k**	84:16[b]	95
10	 **l**	61/39	85
11	 **m**	79:21	67
12[c]	 **n**	75:25	89
13	 **o**	34:66	72

[a] Isolated overall yield.
[b] In MeTHF at 10 °C.
[c] *Trans*/*cis* ratio of 84:16 in MeTHF at 10 °C.

morpholine borane or picoline borane resulted in low selectivity of the *trans*-amine with low conversion. To our delight, 9-BBN was found to be the most selective reducing agent and an 82:18 *trans*/*cis* isomeric ratio was obtained in combination with $FeCl_3$ (entry 7). Various Lewis acids were then evaluated with 9-BBN. $FeCl_3$ produced the highest selectivity for *trans*-4-methoxycyclohexylamine. Recently $FeCl_3$ has been reported as catalyst for reductive amination of aldehydes using poly(methylhydrosiloxane) as a hydride source.[13] 9-BBN itself without additional Lewis acid was not effective enough to activate the ketone for imine formation (entry 6). Even though 9-BBN has been reported to reduce ketones[11d,e]; 4-methoxycyclohexanol was only observed in trace amounts if reactions were run at ambient temperature. Stronger Lewis acids $TiCl_4$ (entry 12) and $AlCl_3$ (entry 14) furnished complete conversion,

but low selectivity of *trans*-4-methoxycyclohexylamine was observed. Brown et al. have shown that 9-BBN has the ability to reduce $FeCl_3$ to a lower valence state,[14] however a test of $FeCl_2$ as Lewis acid resulted in no product formation, suggesting this is not the underlying mechanism.

The high percentage of *trans*-amine formation may be due to the coordination of the boron atom with the oxygen atom of 4-methoxy in cyclohexanone, so that the hydride has to approach the C=N bond from the same side of the OMe group, leading to *trans*-4-methoxycyclohexylamine as the preferred product. This hypothesis was supported by evaluating the reductive amination conditions on two additional ketones in the presence or absence of coordinating groups at the 4-position of the cyclohexanone (Fig. 2). Interestingly, –OMe or –OH substitution resulted in the *trans*-isomer as the major product, an 82:18 and 78:22 of *trans*/*cis* isomeric amines were obtained, respectively. When the coordinating atom was absent as in 4-methylcyclohexanone, the lack of chelation led to a preference for the hydride to approach from the least congested equatorial side, leading predominantly to the *cis*-4-methylcyclohexylamine in a *trans*/*cis* ratio of 9:91. The coordinating effect may explain the low *trans*-selectivity in the presence of strong Lewis acid such as $TiCl_4$ due to its stronger coordination to the 4-methoxy group, yielding equal amounts of *trans*- and *cis*-amines (Table 1, entry 12). Various boranes were evaluated for the reaction of aniline **1a** with ketone **2a**; inferior *trans*-selectivity compared to 9-BBN was found in all cases. Boranes that have low affinity to complex with the oxygen atom of the methoxy group in ketone **2a** resulted in low *trans*-selectivity. Pinacolborane generated a *trans*/*cis* ratio of 50:50, while *N*,*N*-diethylanilineborane and $BH_3{\cdot}NH_3$ gave isomeric ratios of 60:40 and 50:50, respectively. Boranes that are more prone to complex with the –OMe of ketone **2a** produced higher *trans*-amine formation, however steric hindrance of the borane reagent then interferes with the chelating effect and leads to lower selectivity when compared to 9-BBN: $(Ipc)_2BH$ gave a *trans*/*cis* ratio 70:30 and disiamylborane produced a similar ratio of 62:38. Interestingly, reductive amination with $BH_3{\cdot}THF$ resulted in low *trans*/*cis*-selectivity (Table 1, entry 15).[15]

The reductive amination occurred significantly faster in THF than in other solvents, which is attributed to the formation of the more reactive 9-BBN-THF complex.[6] Both commercially available solid $(9\text{-BBN})_2$ and 0.5 M 9-BBN in THF are effective. $(9\text{-BBN})_2$ has poor solubility in other solvents at 0 °C such as in CH_2Cl_2, toluene, and *tert*-butylmethyl ether, which leads to slower reaction rates. However, in MeTHF, higher *trans*-isomer ratios were observed for some amines, but a longer reaction time was required. $(9\text{-BBN})_2$ has low solubility in MeTHF, reactions need to be performed at a slightly higher temperature of 10 °C for completion after 12 h. Selectivity was marginally affected by the reaction temperature, and even when the reaction temperature was reduced to –78 °C in THF, an 85:15 *trans*/*cis* ratio was observed for the reaction of aniline **1a** and ketone **2a**. $Zn(BH_4)_2$ supported on silica gel has been reported to reduce *N*-phenyl-4-methylcyclohexylimine with high diastereoselectivity for the *trans* amine product.[4c] Reductive amination of **1a** and **2a** with silica-supported $Zn(BH_4)_2$ resulted in low *trans*-selectivity and poor conversion. At least three molar equivalents of 9-BBN were required for complete conversion,[11c,16] while theoretically only one molar equivalent was necessary for the reduction. We suspected that one equivalent of 9-BBN was decomposed by water generated from the imine formation, and a second equivalent of 9-BBN was required for complexation with Lewis bases in the reaction mixture. This was confirmed by the addition of two molar equivalents of ketone instead of one. In this case, four molar equivalents of 9-BBN instead of three were then required to achieve full conversion.

Highly *trans*-selective reductive amination of anilines with 4-methoxycyclohexanone was demonstrated on a series of aryl amines (Table 2). In all cases, good to high yields were achieved with the *trans*-amine as the major product. Reaction of **1a** with ketone **2a** produced a 94% overall yield of *trans*- and *cis*-amine in a ratio of 82:18 (Table 2, entry 1). 2-Propylaniline (**1d**) with an *ortho* alkyl group furnished a *trans*- to *cis*-amine ratio of 72:28 in a 75% overall yield, indicating no effect of the ester functionality (entry 2). Ester groups either *para* or *meta* to amine on the aminobenzoates are well tolerated, and the same ratio of *trans*/*cis* diastereomers 82:18 and overall yields of 85% were obtained (entries 4 and 5). Increasing the steric hindrance of the *ortho*-ester group did not affect the selectivity or reactivity when compared to the methyl ester (entries 6 and 7). Electron-poor anilines (**1j** and **1k**) produced high percentage of *trans*-amines; *trans*/*cis* isomeric ratios of 89:11 with a 90% yield and 84:16 with a 95% yield were obtained, respectively (entries 8 and 9). Less basic anilines with strong electron-withdrawing groups on the phenyl ring are usually unreactive for reductive amination with $NaBH(OAc)_3$.[6b] Unlike nucleophilic metal hydride reducing agents, 9-BBN is an electrophilic reducing reagent, therefore the conditions are tolerant of many different functional groups, such as halides and nitro groups (entries 3, 8 and 9), which are incompatible with other reducing methods. It has been reported that successful 9-BBN reductions were achieved in the presence of nitro and halogen functional groups.[6] One drawback of this methodology, however, is that the conditions are not tolerant of alkoxy groups on the aniline, probably due to the coordinating effect of alkoxy group with the boron atom of 9-BBN.

To expand the generality of this process, we examined the reductive amination conditions of heteroaryl amines with 4-methoxycyclohexanone. Similarly, moderate to good yields were obtained with the *trans*-amines as the major products. Reaction of 1*H*-indol-5-amine (**1i**) with 4-methoxycyclohexanone generates amines in a *trans*/*cis* diastereomeric ratio of 61:39 with a total yield of 85% in THF (Table 2, entry 10). Benzo[*d*]thiazol-6-amine produced *trans*/*cis* 4-methoxycyclohexylamines in a ratio of 79:21 with an overall yield of 67% (entry 11). 2-Bromopyridin-3-amine generated 75:25 of *trans*/*cis*-amines in an 89% yield. A higher *trans*/*cis*-amine ratio of 84:16 was generated in MeTHF at 10 °C, but with a compromised yield (entry 12). Most interestingly, contrary to *trans*-preferred reductive amination, 8-aminoquinoline produced the *cis*-amine as a major isomer in a *trans*/*cis* ratio of 34:66 (entry 13). We suspect this may be due to the chelating effect of the boron atom to the neighboring nitrogen atom, which limits its coordination with OMe group on the 4-substituted imine to result *cis* favored product.

In summary, we have developed a *trans*-selective reductive amination protocol to prepare 4-*trans*-methoxycyclohexylamines utilizing 9-BBN as the reducing agent in the presence of $FeCl_3$. This methodology is tolerant of many functional groups which otherwise are not stable under typical metal hydride reduction conditions. The initially observed preferential *cis*-selectivity using tin-catalyzed silane reduction was reversed to instead favor the *trans*-isomer through careful optimization. Taking advantage of the coordination of the 4-methoxy group with the boron atom of 9-BBN allowed for the preferred approach of the hydride from the same face of the methoxy group, furnishing the *trans*-amines as major products.

Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra of compounds **3a**–**3o** including both *cis*- and *trans*-amines) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.023.

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12. Ratio of two diastereomers was determined by HPLC analysis, Agilent Zorbax XDB-C8, 3.5 μM, 4.6 × 50 mm; A, H_2O with 0.5% formic acid; B, acetonitrile with 0.5% formic acid, 2 mL/min, 5% B–95% B in 3.5 min and hold at 95% B for 1 min. *Trans*-amines elute faster than *cis*-amines.
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17. All chemicals were of reagent grade and used as purchased. All the reactions were carried out under nitrogen atmosphere and monitored by HPLC. Representative procedure for the synthesis of methyl 2-(4-methoxycyclohexylamino) benzoate (**3a**): To a stirred solution of 194.6 mg (1.2 mmol) of $FeCl_3$ and 2 mL of anhydrous THF at 0 °C under nitrogen atmosphere were added 151.2 mg (1.0 mmol) of methyl 2-aminobenzoate (**1**) and 141.0 mg (1.1 mmol) of 4-methoxycyclohexanone (**2a**). 6.0 mL of 0.5 M 9-BBN in THF (3.0 mmol) was then added slowly to maintain internal temperature below 5 °C. The reaction mixture was further stirred at 0 °C for 2 h. After completion of the reaction (monitored by HPLC), 290 μL (3.0 mmol) of diethanolamine was added to the reaction mixture at 0 °C and stirred for 30 min to remove 9-BBN by forming an insoluble solid. After filtering out the precipitate, the crude mixture of **3a** was purified by column chromatography over silica gel using pure hexanes to 10% ethyl acetate in hexanes as eluent to give 247 mg of **3a** (0.94 mmol) as light yellow oil after drying. The corresponding *trans*-**3a** and *cis*-**3a** were further purified on silica gel.