Tetrahedron Letters 55 (2014) 1829–1834

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Direct reductive amination using triethylsilane and catalytic bismuth(III) chloride

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ARTICLE INFO

Article history:
Received 21 December 2013
Revised 23 January 2014
Accepted 28 January 2014
Available online 6 February 2014

Keywords:
Bismuth(0)
Bismuth(III) chloride
Catalysis
Direct reductive amination
Triethylsilane

ABSTRACT

Direct reductive amination (DRA) using triethylsilane (TESH) and catalytic bismuth(III) chloride ($BiCl_3$) is described for the first time. The use of TESH and $BiCl_3$ provides easy handling, low cost, non-toxicity, and a mild Lewis acid activity, thereby meeting the demand for green and sustainable chemistry. The developed DRA is highly chemoselective and applicable to less-basic amines. The experimental results of this study revealed that the developed DRA could be catalyzed by $BiCl_3$, which was gradually reduced to Bi(0) or bismuth with a low valency by TESH, but TESCl, Bi(0), and Bi(0) with TESCl catalyzed the DRA to some extent.

Because many biologically active and pharmaceutically relevant compounds include amines and their derivatives, amine preparation methods are important.[1] Therefore, a variety of preparation methods for amines have been reported, and the direct reductive amination (DRA) of aldehydes and ketones has been widely used for the preparation of primary, secondary, and tertiary amines, because it offers compelling advantages over other synthetic methods owing to brevity, wide availability of substrates and reagents, generally mild reaction conditions, and high functional group tolerance in some cases. DRA has another advantage in that intermediate imines do not need to be isolated. Thus, a mixture of an aldehyde or ketone and an amine is treated with a reducing reagent in a one-pot fashion. Therefore, DRA is not only useful but also effective for the reaction of aromatic amines with aliphatic carbonyl compounds that produce unstable imines. However, the reducing reagent should be carefully selected for a successful reaction because the reduction of aldehydes or ketones sometimes competes under the reaction conditions.

Catalytic hydrogenation with a platinum, palladium, or nickel catalyst has been used for DRA because it is an economical and effective method and has advantages in large-scale reactions.[2] However, this method has not been applied to the reaction of compounds containing carbon–carbon multiple bonds and reducible functional groups such as nitro and cyano groups.

DRA using sodium cyanoborohydride ($NaBH_3CN$)[3] and sodium triacetoxyborohydride [$NaBH(OAc)_3$][1c,4] offers the advantages of simplicity, wide availability of substrates, mild reaction conditions, and a tolerance to other functional groups. However, the former is highly toxic and generates toxic byproducts such as hydrogen cyanide (HCN) and sodium cyanide (NaCN). Moreover, it requires large quantities of excess amine. The latter requires corrosive acetic acid to carry out the reaction,[5] and it is not compatible with aromatic and unsaturated ketones.[4,6]

Several reagents for DRA other than those mentioned above have been developed, including sodium[6] or zinc borohydride with Brønsted acid or Lewis acid,[7] nickel boride,[8] pyridine·BH_3,[9] 2-picoline·BH_3,[10] 2,6-diborane·methanol,[11] dimethylamine·BH_3,[12] *t*-BuMe*i*PrN·BH_3,[13] 5-ethyl-2-methylpyridine·BH_3,[14] benzylamine·BH_3,[15] borohydride exchange resin (BER),[16] zinc–acetic acid,[17] sodium borohydride–magnesium perchlorate,[18] zinc borohydride–zinc chloride,[19] silica gel–zinc borohydride,[7d] and dibutyltin chloride hydride.[20] However, most of the reported DRAs call for filtration, aqueous workup, evaporation, or a combination of these techniques prior to purification. These operations typically serve to remove or decompose organic-insoluble metal salts introduced as reducing reagents such as $NaBH_3CN$ and $NaBH(OAc)_3$.

Therefore, it is reasonable that the use of organic-soluble reducing reagents such as organosilanes with efficient catalysts could streamline DRA.[21] It could also provide the advantage of multiple parallel solution phase synthesis, which requires a protocol with no pre-chromatography product manipulation. Although a variety of DRA have been reported, as described above, there have been

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http://dx.doi.org/10.1016/j.tetlet.2014.01.132
0040-4039/

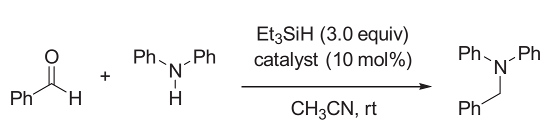
limited reports on DRA using organosilane as a reducing reagent. Organosilanes such as triethylsilane (TESH), in the presence of acid catalysts, are mild and useful reagent systems for reduction. However, trifluoroacetic acid (TFA)/TESH[22] is not compatible with acid labile functional groups. The use of $TiCl_4$/organosilane[23] is limited to aromatic aldehydes. $Bu_2SnCl_2/PhSiH_3$[24] is toxic, Ti(O*i*Pr)$_4$/polymethylhydrosiloxane (PMHS)[25] is water-sensitive, and organosilane with a hydrio-iridium complex[26] is not compatible with substrates containing reducible functionalities. Hence, the development of improved methods using organosilanes is still anticipated. We herein report DRA using TESH and catalytic bismuth(III) chloride ($BiCl_3$).

The preparation of aryl- and diarylamine derivatives is important in research on structure–activity relationships. The DRA of aryl- and diarylamines is a rational approach from the standpoint described above, and DRAs, which use organosilane and a catalytic amount of $Ga(OTf)_3$[27] or $InCl_3$,[28] have also been reported. However, both reagents are relatively expensive, and in the latter system, the unsaturated carbonyl compounds are potentially reduced.[29] Moreover, it has been reported that In(III) results in teratogenicity in rats.[30]

It has been reported that diarylamines are included in many biologically active and pharmaceutically relevant compounds,[31] as well as new materials,[32] but DRAs of aldehydes and diphenylamine have been limited. Therefore, we started to screen various Lewis acids as a catalyst for the DRA of benzaldehyde and diphenylamine using TESH and Lewis acid.[33]

The DRA was examined using a 1:1 ratio of benzaldehyde and diphenylamine in the presence of 3.0 equiv of TESH and 10 mol % Lewis acid in acetonitrile at room temperature (Table 1). $TiCl_4$ (59%, entry 1) and $SnCl_4$ (68%, entry 2) afforded the product in good yields. $SbCl_5$ (entry 3), $ZnCl_2$ (entry 4), $PbCl_2$ (entry 5), and $CeCl_3{\cdot}7H_2O$ (entry 6) did not afford any product, and $YCl_3{\cdot}6H_2O$ was almost ineffective (10%, entry 7). The yields in the reactions with Bi(III) were high, except BiF_3 (0%, entry 8). The yield was 99% when 10 mol % of $BiCl_3$ was used (entry 9), and use of the reduced amount (5 mol %) reduced the yield to 34% (entry 10). The yields when $BiBr_3$ and BiI_3 were used were 79% (entry 11) and 81% (entry 12), respectively. Interestingly, $Bi(OTf)_3$ (74%, entry 13), which is known to be a strong Lewis acid, was less effective than the other Bi(III) reagents (entries 9, 11, 12). The DRA catalyzed by $InCl_3$[28] proceeded faster and afforded the product with 95% yield (entry 14); however, $InCl_3$ is relatively expensive and has disadvantages, as described above. Consequently, the results listed in Table 1 indicate that the use of $BiCl_3$ (10 mol %) is the most effective and practical for the DRA of benzaldehyde and diphenylamine using TESH.

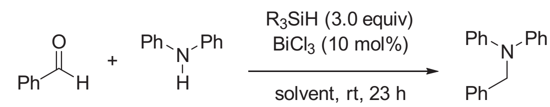
Table 1



Entry	Catalyst	Time (h)	Yield[a] (%)
1	$TiCl_4$	23	59
2	$SnCl_4$	23	68
3	$SbCl_5$	23	9
4	$ZnCl_2$	23	NR
5	$PbCl_2$	23	NR
6	$CeCl_3{\cdot}7H_2O$	13	NR
7	$YCl_3{\cdot}6H_2O$	13	10
8	BiF_3	13	NR
9	$BiCl_3$	13	99
10[b]	$BiCl_3$	13	34
11	$BiBr_3$	13	79
12	BiI_3	13	81
13	$Bi(OTf)_3$	13	74
14	$InCl_3$	10	95

[a] Isolated yield.
[b] $BiCl_3$ (5 mol %) was used.

Table 2



Entry	Organosilane	Solvent	Yield[a] (%)
1	Et_3SiH	CH_3CN	99
2	Et_3SiH	Toluene	Trace
3	Et_3SiH	Et_2O	Trace
4	Et_3SiH	CH_2Cl_2	NR
5	Et_3SiH	THF	NR
6	Et_3SiH	DMF	NR
7	Et_3SiH	DMSO	NR
8	Ph_3SiH	CH_3CN	NR
9	$(EtO)_3SiH$	CH_3CN	NR
10	$PhMe_2SiH$	CH_3CN	71
11	Et_2SiH_2	CH_3CN	72
12	Ph_2SiH_2	CH_3CN	42
13	$PhMeSiH_2$	CH_3CN	95
14	$PhSiH_3$	CH_3CN	97[b]

[a] Isolated yield.
[b] The reaction required 7 h to be completed.

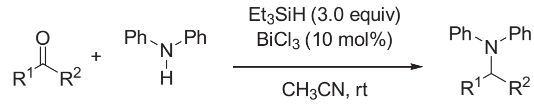
To the best of our knowledge, DRA using organosilanes and catalytic Bi(III) has never been reported. In addition, Bi(III) has been used as an efficient green catalyst because of its many advantages, including its easy handling, low cost, nontoxic nature, and mild Lewis acid activity.[34] Hence, we decided to study DRA using organosilanes and $BiCl_3$.

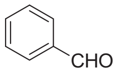
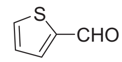
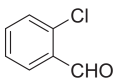
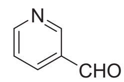
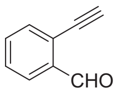
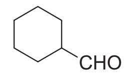
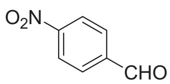
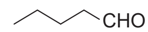
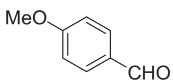
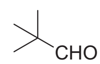
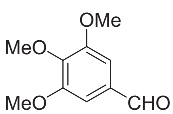
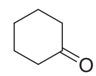
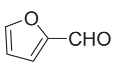
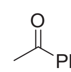
The reaction conditions for DRA using $BiCl_3$ were examined (Table 2). The DRAs of benzaldehyde and diphenylamine using TESH in various solvents were screened. Trace amounts of the product were obtained in toluene (entry 2) and diethyl ether (entry 3), but no reactions occurred in dichloromethane (entry 4), THF (entry 5), DMF (entry 6), and DMSO (entry 7). Reactions with some organosilanes were also examined, but no reaction occurred with Ph_3SiH (entry 8) and $(EtO)_3SiH$ (entry 9). The reactions with $PhMe_2SiH$ (entry 10), Et_2SiH_2 (entry 11), Ph_2SiH_2 (entry 12), $PhMeSiH_2$ (entry 13), and $PhSiH_3$ (entry 14) afforded the product in yields of 71%, 72%, 42%, 95%, and 97%, respectively. The results listed in Table 2 indicate that the DRA of benzaldehyde and diphenylamine exhibited the best performance when TESH or $PhSiH_3$ in the presence of catalytic $BiCl_3$ in acetonitrile as the solvent was used.

The DRAs of various aldehydes and ketones using TESH and $BiCl_3$ were examined, as summarized in Table 3. The substituent effect of substrates was observed in the DRAs of arylaldehydes with diphenylamine (Table 3). The yield was reduced in the DRAs of *o*-chlorobenzaldehyde (entry 2) and *o*-ethynylbenzaldehyde (entry 3), which can be attributed to the steric hindrance suffered from the *o*-substituent. The yield in the DRA of *p*-nitrobenzaldehyde (entry 4) was 90%, while that of *p*-methoxybenzaldehyde (entry 5) decreased to 35% and the starting material remained. This difference can be explained by the electronic effect of the substituent, that is the electron-donating *p*-substituent deactivated the benzaldehyde. This electronic effect well explains the DRA of 3,4,5-trimethoxybenzaldehyde (entry 6) in which the product was formed with a low yield and the starting material remained again.

The above substituent effect is consistent with a reaction mechanism via the formation of iminium by the nucleophilic attack of diphenylamine to aldehyde and the subsequent reduction of the imine. Chloride, nitro group, and alkyne, which are reducible

Table 3



Entry	Substrate	Time (h)	Product	Yield[a] (%)	Entry	Substrate	Time (h)	Product	Yield[a] (%)
1		13	**3a**	99	8		22	**3h**	46
2		22	**3b**	63	9		24	**3i**	NR
3		22	**3c**	69	10		3	**3j**	92
4		5	**3d**	90	11		22	**3k**	88
5		43	**3e**	35	12		24	**3l**	32
6		19	**3f**	39	13		24	**3m**	28
7[b]		22	**3g**	56	14		13	**3n**	NR

[a] Isolated yield.
[b] 30 mol % of $BiCl_3$ was used.

functionalities, remained intact in the DRA, indicating that the DRA proceeded chemoselectively.

The DRAs of heterocyclic aldehydes, 2-furfural (entry 7) and 2-thienal (entry 8), afforded products in moderate yields. The catalyst may be deactivated by the chelate formation with aldehydes; however, as shown later, the DRAs of 2-furfural and 2-thienal with ethyl carbamate afforded products in high yields. Therefore, the reason for the low yields in entries 7 and 8 is not clear at this stage. The DRA of 3-pyridinealdehyde (entry 9) did not proceed, probably because of the salt formation with the catalyst.

The DRAs of the aliphatic aldehydes (entries 10 and 11) afforded products in excellent yields, although sterically hindered pivalaldehyde afforded the product with a yield of 32% (entry 12). The DRAs of cyclohexanone (entry 13) and acetophenone (entry 14) were also examined; the yield of the former was 28%, and the latter did not proceed.

The DRAs of benzaldehyde with aniline and its derivatives were examined, as illustrated in Table 4. Aniline (entry 1) and its derivatives with no *o*-substituents (entries 2–5) afforded products with good to excellent yields (76%-quant). In the DRAs with *o*-substituted anilines, the yield depended on the substituent, that is the results in entries 6–10 indicate that the yield was reduced by a relatively large *o*-substituent because 2-nitroaniline (entry 6) and 2,4-dinitroaniline (entry 7) afforded the product in 50% and 0% yields, respectively. The different results for 2-chloroaniline (79%, entry 8) and 2-bromoaniline (52%, entry 9) are also explained by the size of the atoms. Notably, 2,4,6-trichloroaniline (entry 10) afforded the product in 68% yield, which was not prepared by the DRA with $NaBH(OAc)_3$. The result with aminopyridine (entry 11) was consistent with the result obtained with 3-pyridinealdehyde (Table 3, entry 9). No DRA occurred for morphorine (entry 12) and its hydrochloride (entry 13), *N*,*N*-diethylamine (entry 14), and *p*-anisidine (entry 15), and *N*-methylaniline (entry 16) afforded the product with only 9% yield probably because the increased basicity of amines could reduce the acidity of the catalyst or the reactivity of imines.

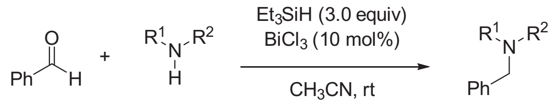
The results listed in Tables 3 and 4 also demonstrate the high chemoselectivity of the current DRA method, because the terminal alkyne, bromo, chloro, ester, fluoro, and nitro groups remained intact during the DRA. The results in Tables 3 and 4 also indicate that the DRAs of relatively weak amines such as non-*N*-alkylated arylamines and diaryl amines proceed with good to excellent yields.

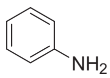
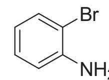
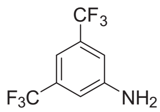
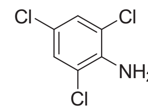
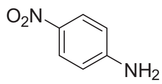
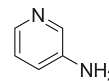
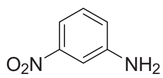
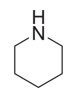
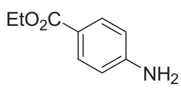
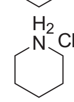
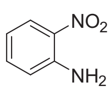
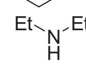
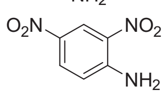
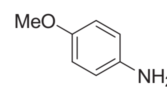
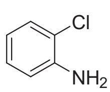
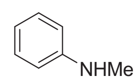
The DRAs of carbonyl compounds with less basic amines such as carbamates and amides were examined (Table 5). The DRA of benzaldehyde with ethyl carbamate (entry 1) afforded the product in 96% yield, and phenyl carbamate (entry 2) afforded the product in 75% yield. The yields of the DRAs of acetamide (entry 3) and phenylamide (entry 4) were relatively low, 13% and 23%, respectively. The p*K*a values of carbamates and amides are not very different; hence, the reason for the different yields is unclear at this stage.

Interestingly, the DRAs of cyclic carbamates (entries 5 and 6) did not proceed. The reaction of propionaldehyde with ethyl carbamate afforded the product in 85% yield (entry 7), and the DRAs of pivalaldehyde (entry 8) and cyclohexanecarbaldehyde (entry 9) afforded the products in 89% and 92% yields, respectively. The DRAs of heterocyclic aldehydes, 2-furfural (entry 10) and 2-thienal (entry 11), were also performed, and the corresponding products were obtained in 66% and 85%, respectively. Finally, the DRA of cyclohexanone (entry 12) was examined, and the yield was 66%, indicating the possibility of further extending the developed DRA.

As shown in Tables 3–5, in DRAs using TESH and $BiCl_3$ the reactions of less basic amines such as diarylamine, aniline derivatives, and carbamates proceeded in good to excellent yields, but it was difficult for the reactions of relatively basic amines such as piperidine and its hydrochloride salt, and *N*-methyl aniline, to proceed.

Table 4



Entry	Amine	Time (h)	Product	Yield[a] (%)	Entry	Amine	Time (h)	Product	Yield[a] (%)
1		18	**3o**	90	9		48	**3w**	52
2		11	**3p**	quant	10		23	**3x**	68
3		15	**3q**	97	11		20	**3y**	NR
4		22	**3r**	76	12		24	**3z**	NR
5		22	**3s**	91	13		24	**3aa**	NR
6		19	**3t**	50	14		21	**3ab**	NR
7		24	**3u**	NR	15		14	**3ac**	NR
8		20	**3v**	79	16		18	**3ad**	9

[a] Isolated yield.

This unique chemoselectivity is different from other DRAs reported thus far.[20,24,26–28,35,36]

Additional studies were pursued to acquire information about the reaction mechanism of the DRA. Because it has been reported that triethylsilylchloride (TESCl) is formed in the reaction of TESH and $BiCl_3$,[37] the DRA of benzaldehyde and diphenylamine with TESH was examined in the presence of TESCl (30 mol %) (Table 6, entry 2). As a result, the product was obtained with a yield of only 23%. This suggested that the DRA proceeded with TESCl to some extent, but the low yield indicated that TESCl did not play a major role in the DRA. It has also been suggested that Bi(0) is formed in the reaction of TESH and $BiCl_3$.[37] Indeed, black precipitates are formed in the reaction of TESH and $BiCl_3$ in acetonitrile, but the DRA using commercially available Bi(0) powder afforded the product only in 4% yield (entry 3). Interestingly, the use of Bi(0) powder and TESCl (entry 4) afforded the product in 69% yield.

We also examined the reduction of (*E*)-1-(4-chlorophenyl)-*N*-phenylmethanimine under the same reaction conditions in Table 6. As summarized in Table 7, the reductions were found to show the same trend in Table 6.

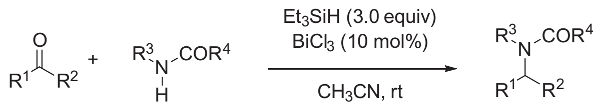
To the best of our knowledge, the DRA with TESH and the reduction of imine with TESH that were catalyzed by Bi(0) powder and TESCl have never been reported thus far. The mechanism of the DRA and the reduction catalyzed by Bi(0) powder and TESCl is interesting but is not clear at this stage; hence, further research on this reaction and its mechanism is now underway.

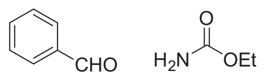
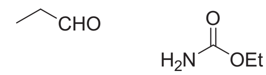
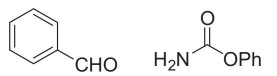
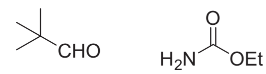
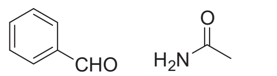
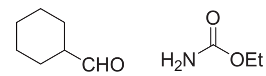
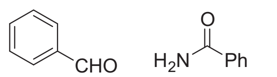
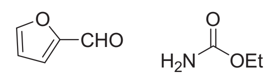
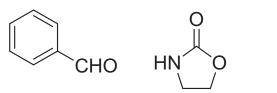
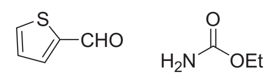
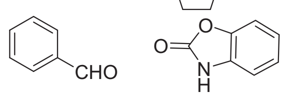
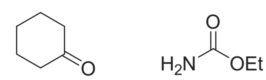
Wada et al. reported that the allylations of aldehydes using allylbromide and Bi(0) powder afford products in high to excellent yields.[38] Therefore, to examine the nature of the black precipitates, the allylation of benzaldehyde with allylbromide was carried out in the presence of the black precipitates formed by the reaction of TESH and $BiCl_3$ (indicated as Bi(0)* (time of the reaction)), that is after mixing TESH (10.0 equiv) and $BiCl_3$ (100 mol %) in acetonitrile at room temperature for 3 min, all the volatile materials, including TESCl, were removed under reduced pressure, and the resultant black precipitates (Bi(0)* (3 min)) were used for the allylation (Table 8, entry 1).

As a result, the allylated product was obtained in 27% yield using Bi(0)* (3 min), and the allylation using Bi(0)* (1 h) afforded the product in 98% yield (entry 2). These results suggest that Bi(0), or bismuth with a low valency, would be gradually formed by the reaction of TESH and $BiCl_3$. The results listed in Tables 6 and 7 indicate that $BiCl_3$ acted as the catalyst for the DRA, while the concomitant reduction of $BiCl_3$ with TESH gradually proceeded to afford Bi(0), but the DRA is catalyzed by TESCl and Bi(0) with TESCl in part.

In summary, we have developed a simple DRA procedure using TESH and catalytic $BiCl_3$.[39] The first use of $BiCl_3$ with TESH for the DRA demonstrated a high chemoselectivity, wherein only less basic amines such as diarylamine, aniline derivatives, and carbamates afforded the products in good to excellent yields. Interestingly, Wada et al. reported the reductive etherification of carbonyl compounds using TESH and catalytic $BiCl_3$.[40] Hence, the DRA reported herein proceeds faster than the reductive etherification. $BiCl_3$ has many advantages such as easy handling, low cost, nontoxic nature, and mild Lewis acid activity, meeting the demand of green and sustainable chemistry. Therefore, the DRA herein reported would be a good choice for certain cases. In this study,

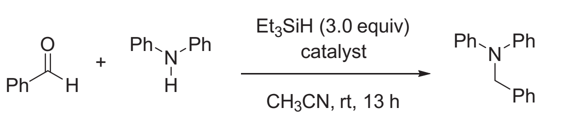
Table 5



Entry	R^1COR^2 / R^3NHCOR^4	Time (h)	Product	Yield[a] (%)	Entry	R^1COR^2 / R^3NHCOR^4	Time (h)	Product	Yield[a] (%)
1		24	**3ac**	96	7		14	**3ai**	85
2		24	**3ad**	75	8		24	**3aj**	89
3		19	**3ae**	13	9		29	**3ak**	92
4		22	**3af**	23	10		21	**3al**	66
5		24	**3ag**	NR	11		21	**3am**	85
6		24	**3ah**	NR	12		43	**3an**	66

[a] Isolated yield.

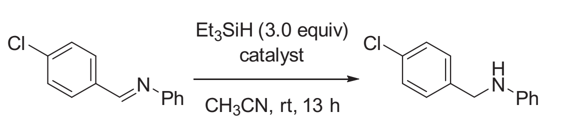
Table 6



Entry	Catalyst	Yield[a] (%)
1	$BiCl_3$ (10 mol %)	99
2	TESCl (30 mol %)	23
3	Bi (10 mol %)[b]	4
4	Bi (10 mol %)[b]+TESCl (30 mol %)	69

[a] Isolated yield.
[b] Commercially available bismuth powder.

Table 7

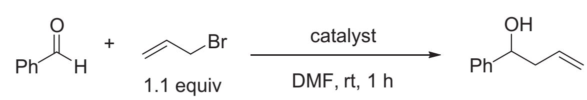


Entry	Catalyst	Yield[a] (%)
1	$BiCl_3$ (10 mol %)	86
2	TESCl (30 mol %)	29
3	Bi (10 mol %)[b]	17
4	Bi (10 mol %)[b]+TESCl (30 mol %)	89

[a] Isolated yield.
[b] Commercially available bismuth powder.

the experimental results indicated that Bi(0) would be formed by the reaction of TESH and $BiCl_3$, which has been suggested by other researchers, but Bi(0) thus formed was used for the allylation reported by Wada et al. for the first time. The experimental results in this study revealed that the developed DRA would be catalyzed by $BiCl_3$, which is gradually reduced to Bi(0) or bismuth with a low valency by TESH, but TESCl, Bi(0), and Bi(0) with TESCl catalyzed the DRA to some extent. Further mechanistic studies and applications of the developed DRA are now underway and will be reported in due course.

Table 8



Entry	Catalyst	Yield[a] (%)
1	Bi(0) (3 min)* (100 mol %)[b]	27
2	Bi(0) (1 h)* (100 mol %)[b]	98

[a] Isolated yield.
[b] Bismuth prepared from TESH (10.0 equiv) and $BiCl_3$ (100 mol %).

Acknowledgments

This work was financially supported in part by Waseda University Grant for Special Research Projects, The Grant-in-Aid for Scientific Research on Innovative Areas 'Organic Synthesis based on Reaction Integration, Development of New Methods and Creation of New Substances' (No. 2105), Grant for Scientific Research (B) (25293003), and Grants for Excellent Graduate Schools (Practical Chemical Wisdom), MEXT, Japan.

Supplementary data

Supplementary data (full characterization of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.132.

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39. *General Procedure:* To a stirred suspension of $BiCl_3$ (0.018 mmol) in CH_3CN (1 mL) was added TESH (0.53 mmol) at room temperature, and after 3 min, to the reaction mixture were added a solution of aldehyde (0.177 mmol) and a solution of aniline (0.177 mmol) in CH_3CN (1 mL) successively. The reaction mixture was stirred at room temperature under argon atmosphere. After starting material disappeared, to the reaction mixture was added saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography.
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