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PAPER

Selective *N*-alkylation of amines using nitriles under hydrogenation conditions: facile synthesis of secondary and tertiary amines†

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Nitriles were found to be highly effective alkylating reagents for the selective *N*-alkylation of amines under catalytic hydrogenation conditions. For the aromatic primary amines, the corresponding secondary amines were selectively obtained under Pd/C-catalyzed hydrogenation conditions. Although the use of electron poor aromatic amines or bulky nitriles showed a lower reactivity toward the reductive alkylation, the addition of NH_4OAc enhanced the reactivity to give secondary aromatic amines in good to excellent yields. Under the same reaction conditions, aromatic nitro compounds instead of the aromatic primary amines could be directly transformed into secondary amines *via* a domino reaction involving the one-pot hydrogenation of the nitro group and the reductive alkylation of the amines. While aliphatic amines were effectively converted to the corresponding tertiary amines under Pd/C-catalyzed conditions, Rh/C was a highly effective catalyst for the *N*-monoalkylation of aliphatic primary amines without over-alkylation to the tertiary amines. Furthermore, the combination of the Rh/C-catalyzed *N*-monoalkylation of the aliphatic primary amines and additional Pd/C-catalyzed alkylation of the resulting secondary aliphatic amines could selectively prepare aliphatic tertiary amines possessing three different alkyl groups. According to the mechanistic studies, it seems reasonable to conclude that nitriles were reduced to aldimines before the nucleophilic attack of the amine during the first step of the reaction.

Introduction

The selective *N*-alkylation of primary amines is a significant research goal because the resulting secondary and tertiary amines are some of the most important partial structures of biologically active compounds and functional materials.[1] Although a number of synthetic methods for secondary and tertiary amines have been reported,[2–15] few truly efficient and environmentally benign selective *N*-alkylation methods were involved.

The base-promoted *N*-alkylations of primary amines using alkyl halides have been recognized as conventional synthetic methods for secondary amines (eqn 1),[2] although their synthetic applications are quite limited due to over-alkylation giving tertiary amines and quaternary ammonium salts. Salvatore and co-workers reported that the over-alkylation was significantly suppressed by the addition of cesium hydroxide together with molecular sieves.[3,4]

Recently, Basu *et al.* reported the selective *N*-alkylations of amines promoted on activated silica gel.[5] Although such protocols might be useful as an *N*-monoalkylation method in the laboratory, the use of toxic and corrosive organic halides and the generation of equal amounts of inorganic salts as a by-product raise safety and environmental concerns in industrial applications.[6] On the other hand, the reductive alkylation using carbonyl compounds is efficient for the *N*-monoalkylation of primary amines (eqn 2)[7] and the nucleophilic addition to imine intermediates is also recognized as a useful synthetic method of secondary amines (eqn 3).[8] However, these reactions require the use of stoichiometric amounts of highly reactive carbonyl compounds (some carbonyl compounds are recognized as substances responsible for the sick house syndrome) and hydride reagents, such as $NaBH_4$ and $NaCNBH_3$. Although catalytic reductive alkylations using the heterogeneous Pd catalyst and a hydrogen source might be one of the solutions of such crucial issues,[9] by-products based on the over-alkylation of the resulting secondary amines to tertiary amines and the aldol reaction of aldehydes cause inevitable contaminations.[10] The catalytic alkylation of amines using alcohols as an alkylating agent is an attractive method because the reaction generates only water as a by-product (eqn 4);[11] however, the selectivity of the *N*-monoalkylation of primary amines is not always acceptable. The reduction of amides (eqn 5)[12,13] and the use of protecting groups (eqn 6)[14,15] are still used as secure synthetic methods for secondary

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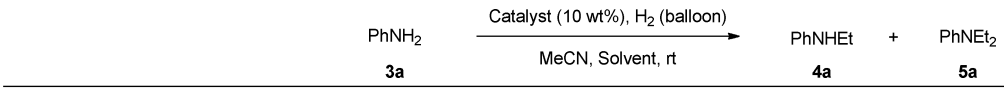
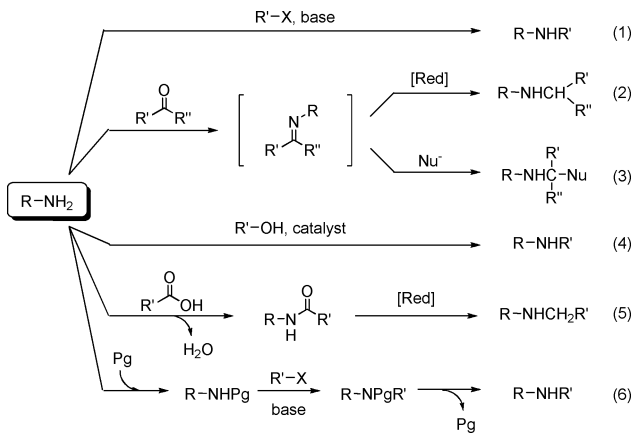
Table 1 Reductive *N*-monoalkylation of aniline (**3a**) using MeCN



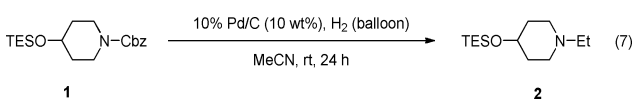
Entry	Catalyst	MeCN (equiv.)	Solvent	Time (h)	**3a** : **4a** : **5a**[a]	Yield (%)[b]
1	10% Pd/C	38	MeCN	24	0 : 99 : 1	—
2	10% Pd/C	5.0	MeOH	24	0 : 89 : 11	—
3	10% Pd/C	2.0	MeOH	25	0 : 100 : 0	85
4	5% Pd/$BaSO_4$	5.0	MeOH	24	96 : 4 : 0	—
5	5% Ru/C	5.0	MeOH	24	100 : 0 : 0	—
6	5% Pt/C	5.0	MeOH	24	82 : 18 : 0	—
7	5% Rh/C	5.0	MeOH	24	—[c]	—
8	10% Pd/C	5.0	*n*BuOH	24	0 : 100 : 0	—
9	10% Pd/C	5.0	THF	30	0 : 100 : 0	97
10	10% Pd/C	5.0	AcOEt	18	0 : 100 : 0	89
11	10% Pd/C	5.0	Toluene	13	0 : 99 : 1	—

[a] Determined by ^{1}H NMR. [b] Isolated yield of **4a**. [c] The reduction of an aromatic ring and the reductive coupling simultaneously occurred to give a complex mixture.

amines, although the harsh reduction step of the amide to amine functionalities[13] and the protection and deprotection steps are necessary. Therefore, the development of a direct, catalytic, environmentally benign and selective *N*-monoalkylation method of primary amines is still quite important.[16]



During the course of our studies[17] on the Pd/C-catalyzed reductive deprotection of the *N*-Cbz group of an *N*-Cbz-piperidine derivative (**1**) in MeCN, the corresponding *N*-ethylpiperidine (**2**) was isolated as the major product (eqn 7).[18] Since it is just conceivable that the unexpected product (**2**) was formed by the MeCN-mediated *N*-ethylation of the deprotected piperidine under hydrogenation conditions, nitriles could be used as an alkylating reagent. In this paper, we report the highly effective and selective Pd/C and Rh/C-catalyzed *N*-alkylation of amines under hydrogenation conditions using nitriles as alkylating agents, including the results of the comprehensive investigation of the selectivity, scope and limitation, additive effect and mechanistic studies.



Results and discussion

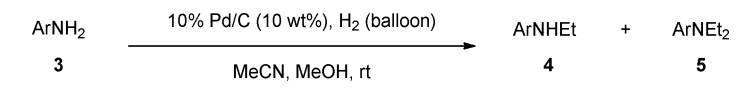
Selective *N*-monoalkylation of aromatic primary amines

Our initial study focused on the reductive alkylation of aromatic amines using nitriles. Interestingly, the reaction of aniline (**3a**) selectively gave the secondary amine, *N*-ethylaniline (**4a**), under Pd/C-catalyzed hydrogenation conditions in MeCN as the alkylating agent and solvent (Table 1, entry 1). Thus, we evaluated a wide variety of heterogeneous catalysts and solvents for the alkylation of **3a** using MeCN only as the alkylating agent (Table 1). Pd/C was the most effective catalyst for the reductive alkylation (entries 2 and 3), whereas Pd/$BaSO_4$ (entry 4), Ru/C (entry 5), Pt/C (entry 6) and Rh/C (entry 7) were much less effective. It is worth noting that MeOH was quite an effective solvent and the totally selective monoalkylation proceeded to afford **4a** as the sole product using only 2.0 equiv. of MeCN in MeOH (entry 3), while a significant over-alkylation was observed in the presence of 5.0 equiv. of MeCN (entry 2). The selective monoalkylation was also achieved in other solvents, such as *n*BuOH, THF, EtOAc and toluene, even though 5.0 equiv. of MeCN was used as the alkylating agent (entries 8–11).

Although it is well-known that the hydrogenation of nitriles over platinum metal catalysts under high pressure and temperature conditions gives symmetrical secondary and tertiary amines,[19] only a few synthetic methods of unsymmetrical amines using primary amines and nitriles have been reported in the literature,[20,22] while such previous procedures show a limited substrate scope and required a large excess amount of amines and elevated hydrogen pressure and/or higher temperature. Our reductive *N*-monoalkylation using nitriles can be quite useful as a synthetic method for secondary amines in organic synthesis because the reaction selectively proceeds under very mild (*ca.* 20 °C, under ambient pressure of hydrogen) conditions, and the catalytic reductive alkylation might be able to establish an environmentally benign process.[19,21]

The scope of the *N*-monoethylation of aromatic amines (**3**) with MeCN is summarized in Table 2. In general, 5.0 equiv. of MeCN and 10 wt% (10 weight percent of the substrate) of 10% Pd/C

Table 2 Reductive *N*-monoalkylation of various aromatic amines (**3**) using MeCN



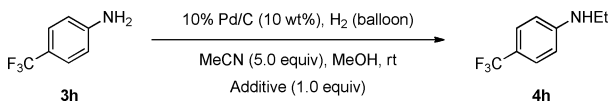
Entry	$ArNH_2$	3	MeCN (equiv.)	Time (h)	3 : 4 : 5[a]	4, 5	Yield (%)[b]
1	4-$MeOC_6H_4NH_2$	**3b**	5.0	18	0 : 40 : 60	**4b**, **5b**	—
2[c]	4-$MeOC_6H_4NH_2$	**3b**	5.0	24	0 : 99 : 1	**4b**, **5b**	99[d]
3	3,4,5-$(MeO)_3C_6H_2NH$	**3c**	2.0	22	0 : 100 : 0	**4c**, **5c**	100
4[e]	4-$MeCONHC_6H_4NH_2$	**3d**	5.0	12	0 : 99 : 1	**4d**, **5d**	97
5	4-$HO_2CC_6H_4NH_2$	**3e**	5.0	10	0 : 100 : 0	**4e**, **5e**	94
6	2-$HO_2CC_6H_4NH_2$	**3f**	5.0	26	0 : 100 : 0	**4f**, **5f**	91
7	4-$FC_6H_4NH_2$	**3g**	5.0	19	0 : 95 : 5	**4g**, **5g**	—
8[e]	4-$FC_6H_4NH_2$	**3g**	5.0	12	0 : 100 : 0	**4g**, **5g**	93
9	4-$CF_3C_6H_4NH_2$	**3h**	5.0	72	48 : 52 : 0	**4h**, **5h**	—
10	4-$MeOCOC_6H_4NH_2$	**3i**	5.0	48	22 : 78 : 0	**4i**, **5i**	—
11	2-*i*$PrC_6H_4NH_2$	**3j**	5.0	26	0 : 92 : 8	**4j**, **5j**	85
12	2-$PhC_6H_4NH_2$	**3k**	32[e]	24	0 : 98 : 2	**4k**, **5k**	95[d]
13	2,6-$Me_2C_6H_3NH_2$	**3l**	5.0	62	77 : 8 : 16	**4l**, **5l**	—
14	2-Naphthylamine	**3m**	32[e,f]	47	0 : 97 : 3	**4m**, **5m**	97[d]
15[g]	3-Aminopyridine	**3n**	5.0	58	11 : 89 : 0	**4n**, **5n**	79[h]

[a] Determined by ^1H NMR. [b] Isolated yield of **4**. [c] AcOEt was used as a solvent. [d] Product contaminated with a trace amount of diethylaniline derivative (**5**). [e] MeCN (32 equiv.) was used as the solvent. [f] 20 wt% of 10% Pd/C was used. [g] 30 wt% of 10% Pd/C was used. [h] Product was contaminated with 13% 3-aminopyridine (**3n**).

(1.0% as a Pd metal) were used in MeOH at ambient temperature and under ambient hydrogen pressure. For 4-methoxyaniline (**3b**), an electron-rich arylamine, the formation of a significant amount (60%) of the dialkylated product (**5b**) was observed in MeOH (entry 1), whereas the use of AcOEt as the solvent gave an excellent selectivity and yield (entry 2). The solvent effect was also important for the reaction of some electron-rich and fluorine-substituted aniline derivatives (**3d** and **3g**) (entries 4 and 8).[17] The reductive alkylation was appropriately depressed and controlled by AcOEt presumably because of the coordination of the oxygen lone pair or π electron of the ester moiety with the metallic palladium. Electron-poor substrates smoothly react with MeCN to form *N*-ethylaniline derivatives (**4**) in excellent yields (entries 5–8), while strongly electron-deficient aromatic amines have a poor reactivity under ordinary reaction conditions (entries 9 and 10). The reaction of the 2-substituted anilines went to completion (entries 6, 11 and 12), whereas 2,6-dimethylaniline (**3l**) was not a good substrate for the alkylation (entry 13). 2-Naphthylamine (**3m**) (entry 14) and 3-aminopyridine (**3n**) (entry 15) were also applicable substrates for the present reaction. Needless to say, the reaction conditions were compatible with various functional groups, such as alkoxy, amide, carboxylic acid, carboxylic ester, aryl fluoride and hetero aromatic functionalities.

To facilitate the alkylation of electron-deficient aromatic amines, such as 4-(trifluoromethyl)aniline (**3h**) and methyl 4-aminobenzoate (**3i**) (Table 2, entries 9 and 10), a variety of additives were evaluated using **3h** as a substrate as shown in Table 3. Although the conversion of **3h** to *N*-ethyl-4-(trifluoromethyl)aniline (**4h**) after 72 h was only 52% without additives (Table 3, entry 1, and also Table 2, entry 9), conversions were significantly improved by the addition of acidic additives (Table 3, entries 2–6) without over-alkylation to *N*,*N*-diethyl-4-(trifluoromethyl)amine (**5h**). In contrast, the addition of ammonia (NH_3), which is supposed to be generated by the reaction (*N*-alkylation) progress, suppressed the reaction (entry 7). The acceleration effect of acidic additives might be induced by the effect of quenching the generated NH_3, which is known as a typical catalyst poison of Pd/C. It is noteworthy that the reaction was also facilitated by the addition of ammonium acetate ($AcONH_4$), a nearly neutral additive (entry 8, 99% isolated yield). While ammonium formate (HCO_2NH_4) could have the dual role of an additive for the reaction acceleration and a hydrogen source (entry 9);[23] a significant delay in the reaction completion was observed in comparison to the case of $AcONH_4$ (compare entries 8 and 9).[6]

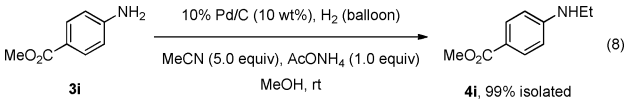
Table 3 Effect of additives toward the reductive *N*-monoalkylation of 4-trifluoromethylaniline (**3h**) using MeCN



Entry	Additives	Time (h)	3h : 4h[a]
1	None	72	48 : 52
2	HCl	27	13 : 87
3	TFA	18	0 : 100
4	AcOH	18	0 : 100
5	AcOH[b]	24	0 : 100
6	$PhCO_2H$	24	10 : 90
7	NH_3	30	89 : 11
8	$AcONH_4$	24	0 : 100[c]
9	HCO_2NH_4	48	0 : 100

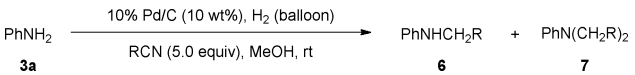
[a] Determined by ^1H NMR. [b] 0.50 equiv. of AcOH was added. [c] Secondary amine (**4h**) was isolated in 99% yield.

$AcONH_4$ was also a quite effective additive for the reaction of **3i** and MeCN (compare Table 2, entry 10 with eqn 8). Interestingly, over-alkylation was never observed in spite of the obvious enhancement of the reactivity for the *N*-monoalkylation (Table 3, entry 8 and eqn 8).



(8)

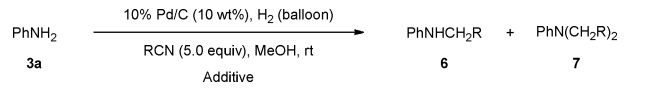
Table 4 Reductive *N*-monoalkylation of aniline (**3a**) using various nitriles



Entry	RCN	Time (h)	**3a** : **6** : **7**[a]	**6**, **7**	Yield (%)[b]
1	EtCN[c]	29	2 : 98 : 0	**6a**, **7a**	49
2	PrCN	42	5 : 95 : 0	**6b**, **7b**	—
3	dist. PrCN	19	0 : 99 : 1	**6b**, **7b**	78
4	BuCN	48	0 : 100 : 0	**6c**, **7c**	89
5	$Me(CH_2)_{10}CN$	46	67 : 33 : 0	**6d**, **7d**	—
6[d]	dist. $Me(CH_2)_{10}CN$	48	0 : 100 : 0	**6d**, **7d**	90
7	*i*PrCN	50	100 : 0 : 0	**6e**, **7e**	—
8	dist. *i*PrCN	6	0 : 100 : 0	**6e**, **7e**	88
9	*i*BuCN	48	89 : 11 : 0	**6f**, **7f**	—
10[d]	dist. *i*BuCN	49	5 : 95 : 0	**6f**, **7f**	85
11	dist. CyCN	46	40 : 60 : 0	**6g**, **7g**	—
12[e]	dist. CyCN	24	0 : 100 : 0	**6g**, **7g**	99
13	dist. *t*BuCN	48	81 : 19 : 0	**6h**, **7h**	—
14[e]	dist. *t*BuCN	24	0 : 100 : 0	**6h**, **7h**	80
15	$HO(CH_2)_2CN$	53	0 : 100 : 0	**6i**, **7i**	81
16	$(MeO)_2CH(CH_2)_2CN$	24	0 : 100 : 0	**6j**, **7j**	14[f]
17	BnCN	27	1 : 99 : 0	**6k**, **7k**	24[f,g]
18	$(CH_2CN)_2$	27	0 : 100 : 0	**6l**, **7l**	86[h]
19	PhCN	48	—[i]	**6m**, **7m**	—

[a] Determined by ^{1}H NMR. [b] Isolated yield of **6**. [c] 3.0 equiv. of the nitrile was used. [d] 20 wt% of 10% Pd/C was used. [e] 1.0 equiv. of $AcONH_4$ was added. [f] The low yield is due to isolation difficulties of **6**. [g] Product contaminated with 9% BnCN. [h] *N*-(3-Cyanopropyl)aniline (**6l**) was isolated as the sole product. [i] PhCN was smoothly reduced to benzylamine.

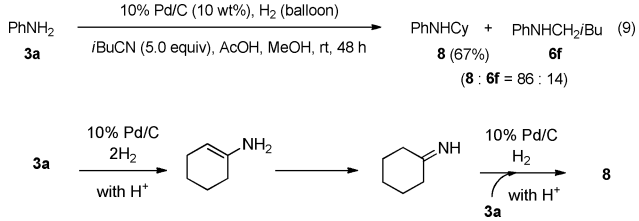
Table 5 Depression effect of the sodium cyanide and isonitriles



Entry	RCN	Additive (equiv.)	Time (h)	**3a** : **6** : **7**[a]
1	MeCN	NaCN (0.1)	24	100 : 0 : 0
2	MeCN	NaCN (0.01)	24	100 : 0 : 0
3	MeCN	*i*PrNC (0.1)	46	0 : 100 : 0
4	MeCN	*i*PrNC (2.0)	46	100 : 0 : 0
5	dist. *i*PrCN	*i*PrNC (0.1)	24	100 : 0 : 0
6	dist. *i*PrCN	*i*PrNC (2.0)	24	100 : 0 : 0

[a] Determined by ^{1}H NMR.

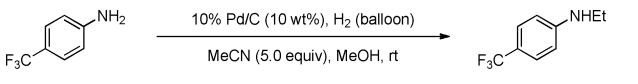
The alkylations of various nitriles as an alkylating reagent with aniline (**3a**) were also investigated (Table 4). For the relatively short and linear nitriles, such as EtCN, PrCN and BuCN, excellent selectivities to form *N*-monoalkylaniline (**6**) were achieved with good yields (entries 1–4). The comparatively low isolated yield of entry 1 was due to the volatile nature of the product. Although the use of the long chain (entry 5) and branched nitriles, such as *i*PrCN, *i*BuCN (entries 7 and 9) without distillation gave poor results, the simple distillation of nitriles solved the poor conversion to afford the corresponding secondary aromatic amines (**6**) in good yields (entries 6, 8 and 10). These results indicated that some impurities in commercial nitriles acted as a catalyst poison for the present alkylation (see Table 5).[24,25] More sterically demanding nitriles, such as cyclohexylnitrile (CyCN) and *t*BuCN, required the addition of $AcONH_4$ to obtain good conversions of **3a** (entries 12 and 14). On the other hand, the use of AcOH as an additive resulted in failure to produce a significant amount of by-product, *i.e.*, cyclohexylphenylamine (**8**, eqn 9),[26] which is produced by the partial hydrogenation of the aromatic nucleus of aniline (**3a**) and the subsequent reductive coupling with **3a** under acidic conditions (Scheme 1). The *N*-monoalkylation reaction was compatible with the hydroxyl group (entry 15), acetal (entry 16) and aromatic ring (entry 17). Interestingly, $(CH_2CN)_2$ possessing two cyano moieties within the molecule selectively reacted at only one cyano group with aniline to quantitatively form *N*-(3-cyanopropyl)aniline (**6l**) as the sole product (entry 18). However, the benzylation of **3a** using benzonitrile (PhCN) failed, because the aromatic nitrile group of PhCN was smoothly reduced to benzylamine under the hydrogenation conditions (entry 19).



Scheme 1 Mechanism of reductive homocoupling of aniline (**3a**) in the presence of acid.

We investigated the influence of NaCN and isonitriles as possible residual products in commercial nitriles because the reductive *N*-monoalkylation reaction proceeded efficiently in the distilled nitriles as shown in Table 4, entries 6, 8 and 10. A small amount of sodium cyanide (NaCN) completely inhibited the ethylation of **3a** (Table 5, entries 1 and 2) because the cyanide anion strongly coordinates to the palladium metal as a catalyst poison. Additionally, isonitriles also dose-dependently worked as catalyst poisons for the alkylation of **3a** (entries 3–6).

Table 6 Effect of temperature on the reductive *N*-monoalkylation of 4-trifluoromethylaniline (**3h**) using MeCN



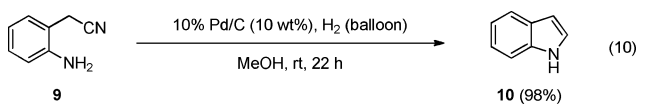
3h **4h**

Entry	*T*/°C	Time (h)	**3h** : **4h**[a]
1	0	24	92 : 8
2	rt (*ca.* 20 °C)	72	48 : 52
3	40	24	13 : 87
4	60	24	0 : 100
5	64	24	30 : 70
6	80	24	100 : 0

[a] Determined by ^{1}H NMR.

We next investigated the effect of the reaction temperature (Table 6). The total completion of the *N*-monoethylation using **3h** and MeCN was achieved at 60 °C without any additives (entry 4), although the suppression of the reaction progress was observed at a higher temperature (entries 5 and 6). The catalytic activity of Pd/C should be improved at higher temperature because of the enhancement of the kinetic energy of Pd/C and/or the reduction of the NH_3 concentration in the reaction mixture, while the solubility of hydrogen gas in MeOH might be temperature-dependently decreased. Thus, the balance between the catalyst activity and solubility of hydrogen gas would be the best at 60 °C.

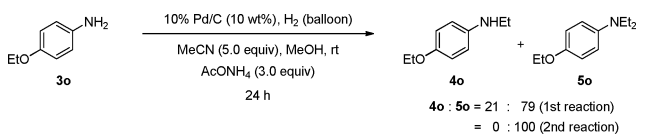
The nitrile-mediated *N*-monoalkylation of arylamines (**3**) can be applied to the intramolecular cyclization as an indole synthesis and the reaction of 2-cyanomethylaniline (**9**) smoothly and quantitatively proceeded to give the corresponding indole (**10**) under ambient hydrogenation conditions (eqn 10). The intramolecular alkylation of the aromatic amine caused by a nitrile would be applicable to the synthesis of various kinds of heteroaromatic derivatives.



9 **10** (98%) (10)

Selective *N*,*N*-dialkylation of aromatic primary amines

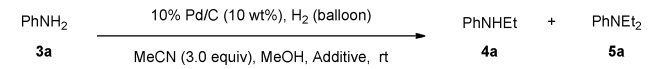
Next we applied the nitrile-mediated reductive alkylation to the synthesis of tertiary amines (**5**). The complete *N*-diethylation of the electron-rich *p*-phenetidine (**3o**) using 5.0 equiv. of MeCN was achieved in the presence of $AcONH_4$ to give *N*,*N*-diethyl-4-ethoxyaniline (**5o**) after the reaction was repeated twice under the same conditions (Scheme 2), although the *N*-dialkylation of the electron neutral aniline (**3a**) was impossible under similar reaction conditions (Table 7).



3o **4o** **5o**

Scheme 2 *N*,*N*-Dialkylation of *p*-phenetidine (**3o**).

Table 7 *N*,*N*-Dialkylation of aniline (**3a**)



3a **4a** **5a**

Entry	Additive	Time (h)	**3a** : **4a** : **5a**[a]
1	None	41	22 : 78 : 0
2	$AcONH_4$ (1.0 equiv.)	29	0 : 87 : 13
3	$AcONH_4$ (3.0 equiv.)	30	0 : 92 : 8
4	$AcONH_4$ (5.0 equiv.)	24	0 : 83 : 17

[a] Determined by ^{1}H NMR.

Direct synthesis of aromatic secondary amines from nitro compounds

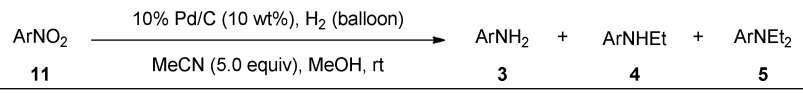
To expand the applicability of the present reductive monoalkylation, aromatic nitro compounds were used as the substrates for the synthesis of aromatic secondary amines through the *in situ* hydrogenolysis of nitro groups to the corresponding primary amino groups (Tables 8 and 9). The optimized reaction conditions developed for the alkylation of the aromatic primary amines (**3**) were successfully extended. The scope and limitations of the direct synthesis of **4** are summarized in Table 8. Nitrobenzene derivatives possessing an electron donating or withdrawing functionality on the aromatic ring, not to mention the simple nitrobenzene, were smoothly reduced to the corresponding amines under hydrogenation conditions, followed by the *N*-monoalkylation by MeCN to directly form aromatic secondary amines (entries 1–18). AcOEt, a depressing solvent based on the influence of its weak coordination effect toward Pd metal, effectively prevented the over-alkylation of the secondary amines (**4**) (entries 3, 5, 7, 9 and 12). The addition of $AcONH_4$ was effective for the enhancement of the reactivity (compare entries 13, 14 and 15, 16). Although the *ortho*-substituted nitrobenzenes, such as **11q**, **11f** and **11k**, could also be transformed into secondary amines (entries 8, 9, 11, 17 and 18), 2,6-dimethyl nitrobenzene (**11l**) and 1-nitronaphthalene (**11r**) gave the corresponding primary aromatic amines (**3l** and **3r**) as the major product because of the steric hindrance around the amino functionality and/or catalyst poison effects of the corresponding amine (entries 19 and 20).

Various nitriles were applied to the synthesis of secondary aromatic amines (**6**) from nitrobenzene (**11a**). The reactions of both linear (Table 9, entries 1–7 and 14–16) and branched nitriles (entries 8–13) produced *N*-monoalkylaniline derivatives in good to excellent yields. The use of distilled nitriles and/or the addition of $AcONH_4$ facilitate the reaction progress depending on the type of nitriles (entries 3, 5, 7, 9, 11 and 13). However, for the sterically hindered nitriles, such as *i*PrCN (entry 9) and *t*BuCN (entry 13), the conversions of the secondary amines were lower compared to the reactions using primary arylamines as the starting substrates (see Table 4).

Selective *N*-monoalkylation of aliphatic primary amines

Next, our attention turned to the *N*-alkylation of alkylamines using nitriles under hydrogenation conditions. We evaluated the effect of various heterogeneous catalysts on the *N*-ethylation of decylamine (**12a**, Table 10).[6] Quantitative formation of *N*,*N*-diethyldecylamine (**14a**) was observed using 5.0 equiv. of MeCN in

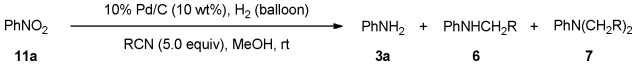
Table 8 Preparation of aromatic secondary amines (**4**) from nitroaromatic compounds (**11**)



Entry	$ArNO_2$	11	Time (h)	3 : 4 : 5[a]	3, 4, 5	Yield (%)[b]
1[c]	$PhNO_2$	**11a**	24	0 : 100 : 0	**3a**, **4a**, **5a**	92
2	$4\text{-MeOC}_6H_4NO_2$	**11b**	48	6 : 91 : 3	**3b**, **4b**, **5b**	—
3[d]	$4\text{-MeOC}_6H_4NO_2$	**11b**	5	0 : 100 : 0	**3b**, **4b**, **5b**	99
4	$4\text{-MeCONHC}_6H_4NO_2$	**11d**	44	0 : 75 : 25	**3d**, **4d**, **5d**	—
5[d]	$4\text{-MeCONHC}_6H_4NO_2$	**11d**	11	0 : 99 : 1	**3d**, **4d**, **5d**	97
6	$4\text{-MeC}_6H_4NO_2$	**11p**	48	0 : 67 : 33	**3p**, **4p**, **5p**	—
7[d]	$4\text{-MeC}_6H_4NO_2$	**11p**	12	0 : 100 : 0	**3p**, **4p**, **5p**	97
8	$2\text{-MeC}_6H_4NO_2$	**11q**	24	0 : 89 : 11	**3q**, **4q**, **5q**	81[e]
9[d]	$2\text{-MeC}_6H_4NO_2$	**11q**	24	7 : 93 : 0	**3q**, **4q**, **5q**	—
10	$4\text{-HO}_2CC_6H_4NO_2$	**11e**	27	0 : 100 : 0	**3e**, **4e**, **5e**	84
11	$2\text{-HO}_2CC_6H_4NO_2$	**11f**	24	0 : 97 : 3	**3f**, **4f**, **5f**	81[e]
12[d]	$4\text{-FC}_6H_4NO_2$	**11g**	8	2 : 98 : 0	**3g**, **4g**, **5g**	88[f]
13	$4\text{-CF}_3C_6H_4NO_2$	**11h**	42	59 : 41 : 0	**3h**, **4h**, **5h**	—
14[g]	$4\text{-CF}_3C_6H_4NO_2$	**11h**	29	0 : 100 : 0	**3h**, **4h**, **5h**	95
15	$4\text{-MeO}_2CC_6H_4NO_2$	**11i**	24	62 : 38 : 0	**3i**, **4i**, **5i**	—
16[g]	$4\text{-MeO}_2CC_6H_4NO_2$	**11i**	24	0 : 100 : 0	**3i**, **4i**, **5i**	100
17	$2\text{-PhC}_6H_4NO_2$	**11k**	48	51 : 49 : 0	**3k**, **4k**, **5k**	—
18[h]	$2\text{-PhC}_6H_4NO_2$	**11k**	24	15 : 85 : 2	**3k**, **4k**, **5k**	—
19	$2,6\text{-Me}_2C_6H_3NO_2$	**11l**	48	69 : 23 : 8	**3l**, **4l**, **5l**	—
20	1-Nitronaphthalene	**11r**	48	100 : 0 : 0	**3r**, **4r**, **5r**	—

[a] Determined by ^{1}H NMR. [b] Isolated yield of **4**. [c] Distilled MeOH was used as the solvent. [d] AcOEt was used as the solvent. [e] Product contaminated with a small amount of *N*,*N*-diethylaniline derivatives (**5**). [f] Product contaminated with 2% 4-fluoroaniline (**3g**). [g] 1.0 equiv. of $AcONH_4$ was added. [h] MeCN (38 equiv.) was used as the solvent.

Table 9 Preparation of *N*-monoalkylaniline derivatives (**6**) from nitrobenzene (**11a**)



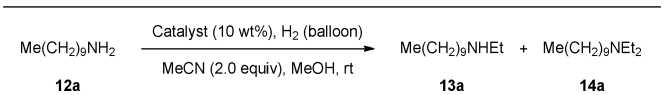
Entry	RCN	Time (h)	3a : 6 : 7[a]	6, 7	Yield (%)[b]
1	EtCN	24	0 : 98 : 2	**6a**, **7a**	81[c]
2	PrCN	48	40 : 60 : 0	**6b**, **7b**	—
3	dist. PrCN	20	0 : 96 : 4	**6b**, **7b**	75
4	BuCN	48	50 : 50 : 0	**6c**, **7c**	—
5	dist. BuCN	20	0 : 100 : 0	**6c**, **7c**	74
6	dist. $Me(CH_2)_{10}CN$	48	28 : 72 : 0	**6d**, **7d**	—
7[d]	dist. $Me(CH_2)_{10}CN$	24	0 : 100 : 0	**6d**, **7d**	100
8	*i*PrCN	68	100 : 0 : 0	**6e**, **7e**	—
9	dist. *i*PrCN	24	25 : 75 : 0	**6e**, **7e**	—
10	dist. *i*BuCN	48	53 : 47 : 0	**6f**, **7f**	—
11[d]	dist. *i*BuCN	44	0 : 100 : 0	**6f**, **7f**	85
12	dist. *t*BuCN	48	86 : 14 : 0	**6h**, **7h**	—
13[d]	dist. *t*BuCN	48	31 : 69 : 0	**6h**, **7h**	—
14	$HO(CH_2)_2CN$	48	20 : 80 : 0	**6i**, **7i**	—
15	BnCN	48	23 : 87 : 0	**6k**, **7k**	—
16[e]	BnCN	23	0 : 100 : 0	**6k**, **7k**	100

[a] Determined by ^{1}H NMR. [b] Isolated yield of **6**. [c] Product contaminated with 2% *N*,*N*-dipropylaniline (**7a**). [d] 1.0 equiv. of $AcONH_4$ was added. [e] 30 wt% of 10% Pd/C was used.

MeOH, although the reaction was not completed with 2.0 equiv. of MeCN (entries 1 and 2). After extensive studies, Pt/C was found to be a better catalyst for the *N*-monoalkylation of **12a** (entry 4). Finally, the reaction using 5% Rh/C in the presence of 2.0 equiv. of MeCN gave the desired *N*-ethyldecylamine (**13a**) in excellent selectivity and isolated yield (entry 6).

Under the optimized reaction conditions [10 wt% of 5% Rh/C (*ca.* 0.5% as an Rh metal), 2.0 equiv. of nitrile], the reactions between various amines and nitriles were explored (Table 11). Not only linear nitriles, such as EtCN, PrCN and BuCN, but also branched nitriles, such as *i*PrCN and *t*BuCN, were applicable for the *N*-monoalkylation to give the corresponding *N*-alkyldecylamines (**13b–f**) (entries 1–5). A range of primary amines (**12b–h**) could also be used for the monoalkylation to give secondary amines (**13g–m**) in good to excellent selectivities and yields (entries 6–13). The reaction conditions were tolerated by

Table 10 Catalyst screening of reductive *N*-monoalkylation of decylamine (**12a**) using MeCN



Entry	Catalyst	Time (h)	**12a** : **13a** : **14a**[a]
1[b]	10% Pd/C	24	0 : 0 : 100
2	10% Pd/C	24	7 : 18 : 75
3	5% Pd/$BaSO_4$	25	100 : 0 : 0
4	5% Pt/C	25	22 : 71 : 7
5	5% Ru/C	25	100 : 0 : 0
6	5% Rh/C	24	trace : 99[c] : trace
7	5% Rh/Al_2O_3	24	67 : 33 : 0

[a] Determined by ^{1}H NMR. [b] 5.0 equiv of MeCN was used. [c] 96% of **13a** was isolated.

the *N*-benzyl (entry 9) and hydroxyl groups (entry 13), although a double bond was reduced to give a saturated product (**13k′**) (entry 10). The amines (**12g** and **12h**) bearing chelating moieties within the molecule required a higher catalyst loading to achieve the *N*-monoalkylation (*ca.* 1% as Rh metal) (entries 11–13). From a mechanistic point of view, we realized the formation of a small amount of imines as by-products during the reaction of entries 8 and 12 (see Fig. 1), which were supposed to be intermediates of the Rh/C-catalyzed reductive *N*-monoalkylation.

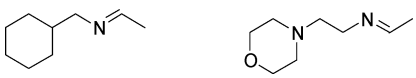
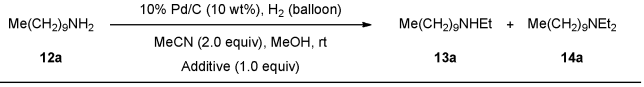


Fig. 1 Imines as intermediates.

Table 12 Reductive *N*,*N*-diethylation of decylamine (**12a**) using MeCN



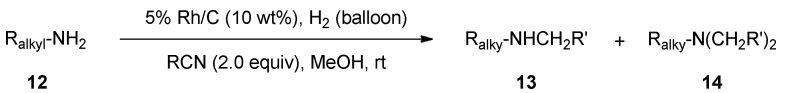
Entry	Solvent	Additive	Time (h)	**12a** : **13a** : **14a**[a]
1	THF	None	48	38 : 40 : 22
2	AcOEt	None	48	54 : 38 : 8
3	MeCN[b]	None	36	0 : 20 : 80
4	MeOH	*t*BuOK	48	100 : 0 : 0
5	MeOH	K_2CO_3	48	84 : 16 : 0
6	MeOH	TFA	48	25 : 14 : 61
7	MeOH	AcOH	27	30 : 25 : 45
8	MeOH	NH_4OAc	24	0 : 0 : 100 (97)[c]
9	MeOH	MS 13X (30 wt%)	24	0 : 0 : 100 (99)[c]

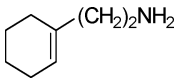
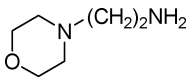
[a] Determined by ^{1}H NMR. [b] MeCN (38 equiv.) was used as the solvent. [c] Isolated yield.

N,*N*-Dialkylation of aliphatic primary amines

We next investigated the additive and solvent effect toward the *N*,*N*-dialkylation of aliphatic primary amines under Pd/C-catalyzed hydrogenation conditions using MeCN (Table 12). MeOH was the best solvent for this alkylation compared to THF, AcOEt and MeCN (Table 10, entry 2, and Table 12, entries 1–3). On the other hand, the dialkylation was effectively accelerated by the addition of $AcONH_4$ to provide the tertiary amine (**14a**) (Table 12, entry 8), while the addition of acids (TFA and AcOH) or bases (*t*BuOK and K_2CO_3) inhibited the reaction progress (entries 4–7). Interestingly, the addition of molecular sieves (MS 13X) was effective to provide complete conversion and an excellent isolated yield (entry 9).

Table 11 Reductive *N*-monoalkylation of alkylamine (**12**) using nitriles



Entry	R_{alkyl}–NH_2	**12**	R′CN	Time (h)	**12** : **13** : **14**[a]	**13**, **14**	Yield (%)[b]
1	$Me(CH_2)_9NH_2$	**12a**	EtCN	34	2 : 98 : 0	**13b**, **14b**	89
2	$Me(CH_2)_9NH_2$	**12a**	PrCN	34	3 : 97 : 0	**13c**, **14c**	82
3	$Me(CH_2)_9NH_2$	**12a**	BuCN	13	3 : 97 : 0	**13d**, **14d**	71
4	$Me(CH_2)_9NH_2$	**12a**	dist. *i*PrCN	59	9 : 91 : 0	**13e**, **14e**	39
5	$Me(CH_2)_9NH_2$	**12a**	dist. *t*BuCN	59	15 : 85 : 0	**13f**, **14f**	61
6[c]	$Ph(CH_2)_2NH_2$	**12b**	MeCN	48	5 : 94 : trace	**13g**, **14g**	80[d]
7	$Ph(CH_2)_4NH_2$	**12c**	MeCN	24	trace : 99 : trace	**13h**, **14h**	98
8	$CyCH_2NH_2$	**12d**	MeCN	36	0 : 99 : trace	**13i**, **14i**	56[e]
9	4-$MeOC_6H_4CH_2NH_2$	**12e**	MeCN	48	0 : 99 : trace	**13j**, **14j**	98
10		**12f**	MeCN	10	trace : 99 : trace	**13k′**, **14k′**	97[f]
11		**12g**	MeCN	48	26 : 73 : trace	**13l**, **14l**	—
12[g]		**12g**	MeCN	29	5 : 94 : trace	**13l**, **14l**	90[h]
13[g]	$HO(CH_2)_6NH_2$	**12h**	MeCN	46	trace : 99 : trace	**13m**, **14m**	99

[a] Determined by ^{1}H NMR. [b] Isolated yield of **13**. [c] 20 wt% of 5% Rh/C was used as the catalyst. [d] Product contaminated with 5% 2-phenylethylamine (**12b**). [e] Product contaminated with 5% corresponding imine. [f] *N*-(2-Cyclohexylethyl)-*N*-ethylamine (**13k′**) was obtained. [g] 5.0 equiv. of MeCN and 20 wt% of 5% Rh/C were used. [h] Product contaminated with 5% corresponding imine and 4% *N*-aminoethylmorpholine (**12g**).

The reductive *N*,*N*-dialkylations using linear alkylamines (**12**), such as decylamine (**12a**) and octylamine (**12i**), were efficiently performed with MeCN, EtCN, PrCN, BuCN to provide the corresponding tertiary amine (**14**) as the sole product (Table 13, entries 1–3 and 5–7). Other primary alkylamines, such as phenethylamine (**12b**), cyclohexanemethanamine (**12d**), cyclohexylamine (**12j**) and 6-hydroxy-1-hexylamine (**12h**), were also selectively converted to tertiary amines (**14**) (entries 8–11). The additions of $AcONH_4$ effectively achieved the completion of the reaction in most cases. On the other hand, only *N*-monoalkylation was selectively observed under the same reaction conditions when the bulky *i*PrCN was used as an alkylating agent (entry 4).

N-Alkylation of aliphatic secondary amines

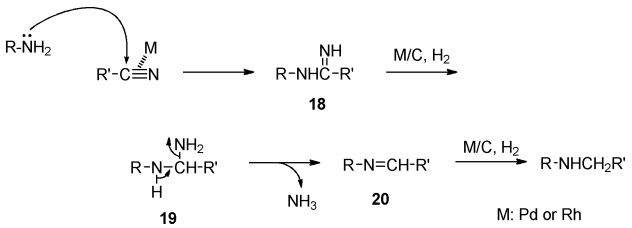
The alkylations of secondary amines (**15**) were also achieved under similar conditions to give the corresponding tertiary amines (**16**) in excellent conversions (Table 14). The results supported the conclusion that the Pd/C-catalyzed reductive alkylation of aliphatic amines using a nitrile is effective for the synthesis of tertiary amines.

Application to the synthesis of unsymmetrical tertiary amines

The combination of the Rh/C-catalyzed *N*-monoalkylation of aliphatic primary amines (Table 11) and Pd/C-catalyzed tertiary amine synthesis (Tables 13 and 14) using nitriles was applied to the synthesis of unsymmetrical tertiary amines possessing three different alkyl groups. First, the isolated *N*-butyldecylamine (**13c**), which was synthesized by the Rh/C-catalyzed alkylation of decylamine (**12a**) with PrCN (see Table 11, entry 2), was found to react with MeCN under Pd/C-catalyzed hydrogenation conditions to form *N*-butyl-*N*-ethyldecylamine (**17a**) in a 72% two-step total yield based on the starting **12a** (Table 15, entry 1). Next, we investigated the development of a tandem synthetic method of unsymmetrical tertiary amines (**17**) without isolation of the secondary amines (**13**) after simple filtration and evaporation to remove the 5% Rh/C and volatiles (entries 2–5). *N*-Ethyl-*N*-propyldecylamine (**17b**), *N*-ethyl-*N*-pentyldecylamine (**17c**), *N*-ethyl-*N*-propyl-2-phenetylamine (**17d**) and *N*-ethyl-*N*-pentyl-2-phenetylamine (**17e**) were readily prepared by the double sequential alkylation.

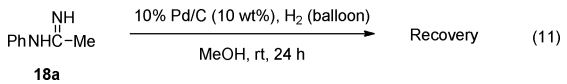
Mechanistic investigation

Two mechanisms can be envisioned for the catalytic reductive alkylation using nitriles. The first one is shown as Scheme 3. Amidine (**18**) is a key intermediate formed by the nucleophilic attack of amines on the metal-activated nitrile and may be reduced under catalytic hydrogenation conditions accompanying the elimination of ammonia to form the imine intermediate (**20**). The imines (**20**) were easily hydrogenated under the conditions to afford alkylated amines.



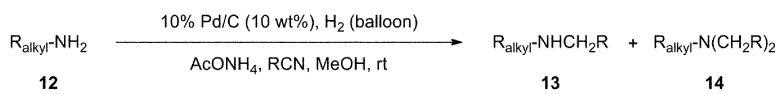
Scheme 3 Reaction mechanism *via* an amidine intermediate (**18**).

However, phenylacetoamidine (**18a**), which is the expected intermediate of the MeCN-mediated alkylation of aniline, was stable under the reaction conditions, and the unchanged **18a** was recovered even after 24 h (eqn 11). Thus, it is unlikely that the amidine intermediate (**18**) is formed during the alkylation reaction.



An alternative mechanism is shown in Scheme 4.[20,22] The key intermediates of this reaction are the imines (**21**), produced by the reduction of nitriles. After the formation of the imine (**21**) with no substituent on the nitrogen atom by the partial hydrogenation of the nitriles, the nucleophilic attack of the amines should occur on the electron-deficient imine carbon to produce another imine

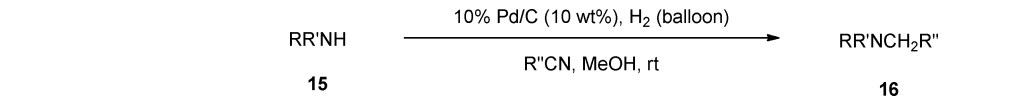
Table 13 Reductive *N*,*N*-dialkylation of primary alkylamine (**12**) using nitriles

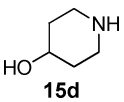
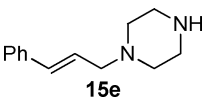


Entry	R_{alkyl}–NH_2	**12**	RCN	(equiv.)	$AcONH_4$ (equiv.)	Time (h)	**12** : **13** : **14**[a]	**13**, **14**	Yield (%)[b]
1	$Me(CH_2)_9NH_2$	**12a**	EtCN	(5.0)	1.0	47	0 : 0 : 100	**13b**, **14b**	89
2	$Me(CH_2)_9NH_2$	**12a**	PrCN	(5.0)	1.0	29	0 : 0 : 100	**13c**, **14c**	82
3	$Me(CH_2)_9NH_2$	**12a**	BuCN	(5.0)	1.0	13	0 : 0 : 100	**13d**, **14d**	71
4	$Me(CH_2)_9NH_2$	**12a**	*i*PrCN	(5.0)	1.0	46	23 : 77 : 0	**13e**, **14e**	—
5	$Me(CH_2)_7NH_2$	**12i**	MeCN	(3.0)	5.0	24	0 : 0 : 100	**13n**, **14n**	97
6	$Me(CH_2)_7NH_2$	**12i**	PrCN	(3.0)	3.0	31	0 : 0 : 100	**13o**, **14o**	100
7	$Me(CH_2)_7NH_2$	**12i**	BuCN	(3.0)	3.0	29	0 : 0 : 100	**13p**, **14p**	97
8[c]	$Ph(CH_2)_2NH_2$	**12b**	MeCN	(5.0)	1.0	24	0 : 0 : 100	**13g**, **14g**	90
9	$CyCH_2NH_2$	**12d**	MeCN	(5.0)	1.0	48	0 : 0 : 100	**13i**, **14i**	75
10	$CyNH_2$	**12j**	MeCN	(5.0)	None	40	0 : 7 : 93	**13q**, **14q**	69[d]
11	$HO(CH_2)_6NH_2$	**12h**	MeCN	(5.0)	1.0	34	0 : 0 : 100	**13m**, **14m**	quant.

[a] Determined by ^{1}H NMR. [b] Isolated yield of **14**. [c] 20 wt% of 10% Pd/C was used. [d] Product contaminated with 7% *N*-ethylaminomethylcyclohexane (**12j**).

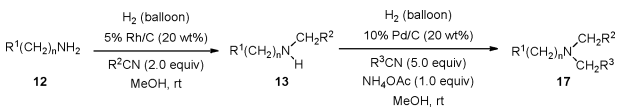
Table 14 Reductive *N*-alkylation of secondary amine (**15**) using nitriles



Entry	15	R″CN	(equiv.)	$AcONH_4$ (equiv.)	Time (h)	15 : 16[a]	16	Yield (%)[b]
1	Bu_2NH **15a**	MeCN	(5.0)	5.0	24	0 : 100	**16a**	76
2	 **15b**	MeCN	(3.0)	None	66	73 : 27	**16b**	—
3		MeCN	(3.0)	3.0	66	0 : 100	**16b**	76[c]
4	 **15c**	MeCN	(3.0)	3.0	66	0 : 100	**16c**	82[c]
5		PrCN	(3.0)	3.0	66	0 : 100	**16d**	51
6	 **15d**	MeCN	(5.0)	None	66	0 : 100	**16e**	98
7	 **15e**	MeCN	(5.0)	None	58	4 : 96	**16f′**	80[d]

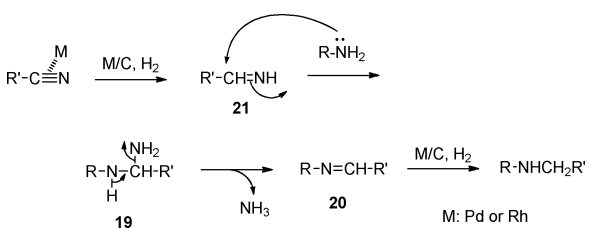
[a] Determined by ^1H NMR. [b] Isolated yield of **16**. [c] Determined by GC. [d] The product was contaminated with 4% 4-(3′-phenylpropyl)piperazine (**15e**').

Table 15 Preparation of unsymmetrical tertiary amines (**17**) *via* double alkylation



Entry	R^1	*n*	12	R^2	13	Yield (%) of 13	R^3	17	Yield (%) of 17[a]
1	Me	9	**12a**	Pr	**13c**	82	Me	**17a**	72
2	Me	9	**12a**	Et	**13b**	—[b]	Me	**17b**	69
3	Me	9	**12a**	Bu	**13d**	—[b]	Me	**17c**	53
4	Ph	2	**12b**	Me	**13g**	—[b]	Et	**17d**	94
5	Ph	2	**12b**	Bu	**13u**	—[b]	Me	**17e**	66

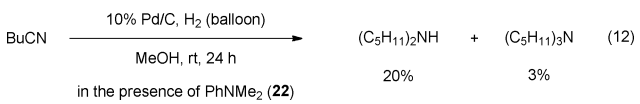
[a] Isolated yield based on starting material (**12**). [b] Without purification except for simple filtration and evaporation.



Scheme 4 Reaction mechanism *via* the imine intermediate (**21**).

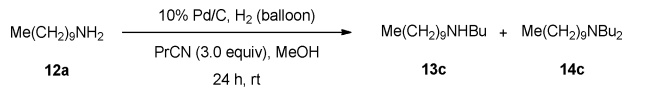
intermediate (**20**) bearing an alkyl substituent derived from the nitrile followed by the elimination of ammonia. The *N*-substituted imine (**20**) was then smoothly reduced to the corresponding alkylated amine. The imine intermediate (**20**) observed during the Rh/C-catalyzed alkylation of the amines supported these mechanisms (Fig. 1).

We also observed the partial reductive dimerization of BuCN under Pd/C-catalyzed hydrogenation conditions in the presence of *N*,*N*-dimethylaniline (**22**) (eqn 12). This result strongly suggests that nitriles would be reduced under the stated hydrogenation conditions and supports the first imine formation in Scheme 4.



We also examined the detailed effect of water on the present alkylation (Table 16). Although the acceleration effect by the addition of molecular sieves (MS 13X) was presented in Table 12, entry 9, it is quite difficult to explain this effect by the simple scavenging of water because the higher water content during the alkylation of **12a** also facilitated the reaction rate (compare Table 16, entries 1, 3 and 5). We suppose that the addition of MS 13X

Table 16 Effect of water and molecular sieves



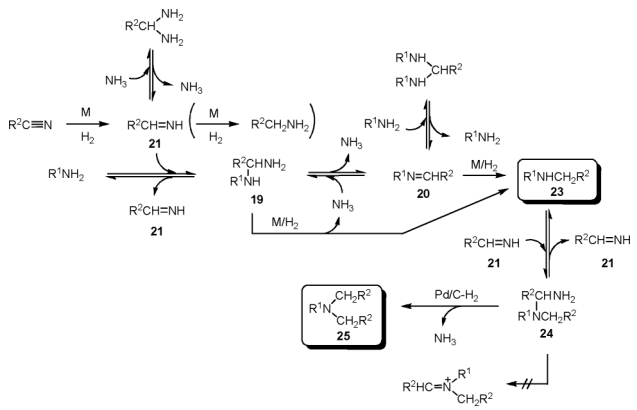
12a 13c 14c

Entry	Solvent	Additive: MS 13X[a]	Additive: H_2O	12a : 13c : 14c[b]
1	MeOH	None	None	0 : 45 : 55
2	MeOH	20 wt%	None	0 : 3 : 97
3	dist. MeOH	None	None	0 : 60 : 40
4	dist. MeOH	20 wt%	None	0 : 41 : 59
5	dist. MeOH	None	25 μL[c]	0 : 0 : 100
6	dist. MeOH	20 wt%	25 μL[c]	0 : 0 : 100

[a] MS 13X: Molecular sieves 13X. [b] Determined by ^{1}H NMR. [c] 1.4 equiv of H_2O.

accelerated the reaction by the scavenging effect of ammonia, a typical catalyst poison, by the macroporous MS 13X (entries 2, 4 and 6). However, the effect of water still remains to be elucidated.

Based on the proposed mechanism indicated in Scheme 4, we considered the difference between the Pd/C- and Rh/C-catalyzed reductive alkylations of the aliphatic amines (Pd/C-catalyzed dialkylation and Rh/C-catalyzed monoalkylation, Scheme 5). There are two routes for the formation of the secondary amine (**23**) as follows: (1) the sequential ammonia elimination from **19** and hydrogenation of the resulting imine (**20**), and (2) the direct hydrogenolysis of **19**. Although both routes are acceptable for the Pd/C- and Rh/C-catalyzed hydrogenations, only the cleavage of ammonia (hydrogenolysis) from **24** is available for the formation of tertiary amines (**25**) under neutral or basic hydrogenation conditions. The selective formation of a secondary amine using Rh/C and a nitrile can be rationalized by the inactivity of the Rh/C toward the hydrogenolysis of **24**, which is only achieved under the Pd/C-catalyzed hydrogenation conditions.



Scheme 5 Plausible total reaction mechanisms: difference between Pd/C and Rh/C.

Conclusions

In conclusion, we developed novel and environmentally friendly *N*-monoalkylation methods of both aromatic and aliphatic primary amines using nitriles as an alkylating reagent. The monoalkylation of aromatic primary amines smoothly proceeded in the presence of nitriles under 10% Pd/C-catalyzed hydrogenation conditions. The addition of ammonium acetate facilitated the alkylation reaction, no matter how bulky the nitriles and electron deficient aromatic amines were applied. Furthermore, the reaction was also used for the intramolecular cyclization in an indole synthesis and the direct transformation of aromatic secondary amines from aromatic nitro compounds. On the other hand, we have also demonstrated the 5% Rh/C-catalyzed reductive *N*-monoalkylation and the 10% Pd/C-catalyzed reductive *N*,*N*-dialkylation of aliphatic amines using nitriles as alkylating agents. The unsymmetrical tertiary amines possessing three different substituents were also easily prepared by the combination of the nitrile-mediated Rh/C- and Pd/C-catalyzed alkylations. These alkylation methods are particularly attractive as they do not use alkyl halides and carbonyl compounds.

Experimental section

General

All reagents, unless otherwise specified, were purchased from commercial sources (Aldrich, TCI, Wako, Kanto, Kishida, Nacalai, *etc.*) and used without further purification. dist. RCNs represent purified nitriles, the purification of which was achieved by washing commercial nitriles with half volume of conc. HCl and saturated $NaHCO_3$ solution, drying with $MgSO_4$ or K_2CO_3 and distilling from CaH_2 or P_4O_{10}. 10% Pd/C was purchased from Aldrich (20,569-9) or N.E. Chemcat (K type, NX type, BET2200 or K type wet). 5% Rh/C was obtained from WAKO (186–01011). MeOH for HPLC (WAKO 138-06473) was used without purification as a solvent. All reactions were monitored by thin-layer chromatography (TLC) on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm), *p*-anisaldehyde solution with subsequent heating. The silica gel (200–300 mesh) for column chromatography was purchased from the Merck. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ solution on a JEOL EX 400 and AL 400 instrument. Spectral data are reported in ppm relative to tetramethylsilane (TMS) as internal standard. Low and high-resolution mass spectra analysis (HRMS) data were measured on a JEOL JMS-SX 102A machine. Microanalyses were accomplished at the Microanalytical Laboratory of Gifu Pharmaceutical University, Japan. Melting points were determined on a Yanagimoto melting point apparatus and were uncorrected. All new compounds were further characterized by elemental analysis or HRMS. Compounds known in the literature were characterized by comparing their ^{1}H NMR data with the previously reported data.

General procedure for reductive alkylation of amines using nitriles

After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of the amine (1.0 or 0.50 mmol), metal-supported catalyst (10 wt% of the amine) and RCN (5.0 equiv.) [and additive (1.0 equiv.)] in MeOH (1.0 mL) was hydrogenated under ambient pressure (balloon) at room temperature (*ca.* 20 °C) for the appropriate time (see Tables). The reaction mixture was filtrated using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and the filtrate was concentrated under reduced pressure. [When

water soluble additive such as NH_4OAc, AcOH, *etc.* was added to the reaction, the residue was partitioned between Et_2O (10 mL) and water (10 mL). The aqueous phase was extracted with Et_2O (10 mL × 3), and then the combined organic phases were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.] The ratio of the primary amine, secondary amine and tertiary amine was confirmed by ^1H NMR of the crude mixture in $CDCl_3$. The crude mixture was purified by flash silica gel column chromatography, if necessary.

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Notes and references

1 (*a*) S. R. Sandler, W. Karo, *Organic Functional Group Preparations*, 2nd ed., Academic Press, New York, 1983, Chapter 13; (*b*) *The Chemistry of Amino, Nitroso, Nitro and Related Groups*, (Ed. S. Patai), Wiley, New York, 1996; (*c*) R. N. Salvatore, C. H. Yoon and K. W. Jung, *Tetrahedron*, 2001, **57**, 7785; (*d*) S. A. Lawrence, *Amines: Synthesis, Properties and Applications*, Cambridge University Press, Cambridge, 2004.

2 (*a*) R. C. Larock, *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, New York, 1999, pp. 789–792; (*b*) K. Mohri, K. Suzuki, M. Usui, K. Isobe and Y. Tsuda, *Chem. Pharm. Bull.*, 1995, **43**, 159.

3 (*a*) R. N. Salvatore, A. S. Nagle, S. E. Schmidt and K. W. J. Jung, *Org. Lett.*, 1999, **1**, 1893; (*b*) R. N. Salvatore, A. S. Nagle and K. W. Jung, *J. Org. Chem.*, 2002, **67**, 674.

4 Some recent papers on base-promoted selective *N*-monoalkylation of primary amines, see: (*a*) R. N. Salvatore, S. E. Schmidt, S. I. Shin, A. S. Nagle, J. H. Worrell and K. W. Jung, *Tetrahedron Lett.*, 2000, **41**, 9705; (*b*) J. H. Cho and B. M. Kim, *Tetrahedron Lett.*, 2002, **43**, 1273; (*c*) C. Chiappe and D. Pieraccini, *Green Chem.*, 2003, **5**, 193. For zeolite-mediated selective *N*-monoalkylation of aromatic primary amines, see: (*d*) M. Onaka, K. Ishikawa and Y. Izumi, *Chem. Lett.*, 1982, 1783; (*e*) M. Onaka, A. Umezono, M. Kawai and Y. Izumi, *J. Chem. Soc., Chem. Commun.*, 1985, 1202. For zeolite-mediated environmentally benign selective *N*-monoalkylation of aromatic amines using alkyl carbonate instead of alkyl halide, see: (*f*) M. Selva, A. Bomben and P. Tundo, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1041; (*g*) M. Selva, P. Tundo and A. Perosa, *J. Org. Chem.*, 2001, **66**, 677; (*h*) M. Selva, P. Tundo and A. Perosa, *J. Org. Chem.*, 2002, **67**, 9238.

5 B. Basu, S. Paul and A. K. Nanda, *Green Chem.*, 2009, **11**, 1115.

6 (*a*) Y. Ono, *Pure Appl. Chem.*, 1996, **68**, 367; (*b*) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford Science Publications, New York, 1998.

7 (*a*) R. C. Larock, *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, New York, 1999, pp. 835–846; (*b*) R. F. Borch, M. D. Bernstein and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897; (*c*) T. Suwa, E. Sugiyama, I. Shibata and A. Baba, *Synthesis*, 2000, 789; (*d*) E. Baxter, A. Reitz, *Organic Reactions*, Wiley, New York, 2002, Vol. 59, p.1; (*e*) E. M. Dangerfield, C. H. Plunkett, A. L. Win-Mason, B. L. Stocker and M. S. M. Timmer, *J. Org. Chem.*, 2010, **75**, 5470; (*f*) M. M. Dell'Anna, P. Mastrorilli, A. Rizzuti and C. Leonelli, *Appl. Catal., A*, 2011, **401**, 134.

8 (*a*) A. R. Katritzky, Q. Hong and Z. Yang, *J. Org. Chem.*, 1994, **59**, 7947; (*b*) D. Enders and U. Reinhold, *Tetrahedron: Asymmetry*, 1997, **8**, 1895; (*c*) R. Bloch, *Chem. Rev.*, 1998, **98**, 1407; (*d*) G. Alvaro and D. Savoia, *Synlett*, 2002, 651.

9 (*a*) W. S. Emerson and P. M. Walters, *J. Am. Chem. Soc.*, 1938, **60**, 2023; (*b*) W. S. Emerson and W. D. Robb, *J. Am. Chem. Soc.*, 1939, **61**, 3145; (*c*) H. Thies and H. Schonenberger, *Chem. Ber.*, 1956, **89**, 1918; (*d*) M. Giammaruco, M. Taddei and P. Ulivi, *Tetrahedron Lett.*, 1993, **34**, 3635; (*e*) F. Fache, F. Valot, A. Milenkovic and M. Lemaire, *Tetrahedron*, 1996, **52**, 9777; (*f*) S. Gomez, J. A. Peters and T. Maschmeyer, *Adv. Synth. Catal.*, 2002, **344**, 1037; (*g*) J. Bódis, L. Lefferts, T. E. Müller, R. Pestman and J. A. Lercher, *Catal. Lett.*, 2005, **104**, 23; (*h*) T. Mizuta, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 2005, **70**, 2195.

10 A. Skita and F. Keil, *Ber. Dtsch. Chem. Ges.*, 1928, **61**, 1452.

11 (*a*) R. G. Rice and E. J. Kohn, *J. Am. Chem. Soc.*, 1955, **77**, 4052; (*b*) Y. Tanigawa, S. Murahashi and I. Moritani, *Tetrahedron Lett.*, 1975, **16**, 471; (*c*) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, *J. Chem. Soc., Chem. Commun.*, 1981, 611; (*d*) Y. Watanabe, Y. Tsuji and Y. Ohsugi, *Tetrahedron Lett.*, 1981, **22**, 2667; (*e*) S. Murahashi, K. Kondo and T. Hakata, *Tetrahedron Lett.*, 1982, **23**, 229; (*f*) Y. Watanabe, Y. Tsuji, H. Ige, Y. Ohsugi and T. Ohta, *J. Org. Chem.*, 1984, **49**, 3359; (*g*) Y. Watanabe, Y. Morisaki, T. Kondo and T. Mitsudo, *J. Org. Chem.*, 1996, **61**, 4214; (*h*) F. Valot, F. Fache, R. Jacquot, M. Spagnol and M. Lemaire, *Tetrahedron Lett.*, 1999, **40**, 3689; (*i*) K. Fujita, Z. Li, N. Ozeki and R. Yamaguchi, *Tetrahedron Lett.*, 2003, **44**, 2687; (*j*) K. Yamaguchi, J. He, T. Oishi and N. Mizuno, *Chem.–Eur. J.*, 2010, **16**, 7199; (*k*) A. J. A. Watson and J. M. J. Williams, *Science*, 2010, **329**, 635; (*l*) G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2010, **110**, 1611.

12 R. C. Larock, *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, New York, 1999, pp. 869–874.

13 Recent example of the synthesis of secondary amine through amide reduction, see: (*a*) Y. Furusho, J. Shoji, N. Watanabe, N. Kihara, T. Adachi and T. Takata, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 139. Synthetic method of secondary amines *via* the reduction of α-aminoalkylphenyl sulfones using $NaBH_3OAc$, see: (*b*) M. Mataloni, M. Petrini and R. Profeta, *Synlett*, 2003, 1129.

14 (*a*) P. G. M. Wuts, T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, 4th ed., Wiley-Interscience, New York, 2007, pp. 696–926; (*b*) P. J. Kocienski, *Protecting Groups*, Thieme-Verlag, Stuttgart, 1994; (*c*) *Handbook of Reagents for Organic Synthesis; Activating Agents and Protecting Groups*, (ed.: A. J. Pearson, W. R. Roush), John Wiley & Sons, New York, 1999; (*d*) P. D. Croce, C. L. Rosa and A. Ritieni, *J. Chem. Research (S)*, 1998, 346.

15 Recently, nitrobenzenesulfonamides (Ns-amides), which can be removed under extremely mild conditions using a soft nucleophile, was reported as an efficient protective group for the synthesis of secondary amines. (*a*) S. Kobayashi, G. Peng and T. Fukuyama, *Tetrahedron Lett.*, 1999, **40**, 1519; (*b*) T. Kan and T. Fukuyama, *J. Synth. Org. Chem. Jpn.*, 2001, **59**, 779; (*c*) T. Kan and T. Fukuyama, *Chem. Commun.*, 2004, 353.

16 For some other recent papers on the selective *N*-monoalkylation of primary amines, see: (*a*) M. Selva, P. Tundo and A. Perosa, *J. Org. Chem.*, 2001, **66**, 677; (*b*) L. Blackburn and R. J. K. Taylor, *Org. Lett.*, 2001, **3**, 1637; (*c*) J. Zhang, H.-M. Chang and R. R. Kane, *Synlett*, 2001, 643.

17 (*a*) K. Hattori, H. Sajiki and K. Hirota, *Tetrahedron Lett.*, 2000, **41**, 5711; (*b*) K. Hattori, H. Sajiki and K. Hirota, *Tetrahedron*, 2001, **57**, 2109; (*c*) H. Sajiki, T. Ikawa, K. Hattori and K. Hirota, *Chem. Commun.*, 2003, 654; (*d*) T. Ikawa, K. Hattori, H. Sajiki and K. Hirota, *Tetrahedron*, 2004, **60**, 6901.

18 H. Sajiki, T. Ikawa and K. Hirota, *Org. Lett.*, 2004, **6**, 4977.

19 (*a*) P. N. Rylander, *Hydrogenation Methods*, Academic Press, London, 1985, pp. 94–103; (*b*) S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, Wiley-Interscience, New York, 2001, pp. 270–285; (*c*) A. Galan, J. De Mendoza, P. Prados, J. Rojo and A. M. Echavarren, *J. Org. Chem.*, 1991, **56**, 452.

20 K. Kindler and F. Hesse, *Arch. Pharm.*, 1933, **271**, 439.

21 (*a*) P. N. Rylander, L. Hasbrouck and I. Karpenko, *Ann. N. Y. Acad. Sci.*, 1973, **214**, 100; (*b*) F. Fülöp, I. Huber, G. Bernàth, H. Hönig and P. Seufer-Wasserthal, *Synthesis*, 1991, 43; (*c*) A. Rosowsky, C. E. Mota, J. E. Wright and S. F. Queener, *J. Med. Chem.*, 1994, **37**, 4522; (*d*) J. E. Gavagan, S. K. Fager, R. D. Fallon, P. W. Folsom, F. E. Herkes, A. Eisenberg, E. C. Hann and R. DiCosimo, *J. Org. Chem.*, 1998, **63**, 4792; (*e*) M. Graffner-Nordberg, K. Kolmodin, J. Åqvist, S. F. Queener and A. Hallberg, *J. Med. Chem.*, 2001, **44**, 2391; (*f*) A. Gangjee, O. O. Adair and S. F. Queener, *J. Med. Chem.*, 2003, **46**, 5074; (*g*) S. Ananthan, H. S. Kezar, III, S. K. Saini, N. K. Khare, P. Davis, C. M. Dersch, F. Porreca and R. B. Rothman, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 529.

22 Recently, an attractive example of the *N*-monoalkylation of primary amines using cyanohydrin and Pd/C accompanied by cyclization was investigated, see: M. K. S. Vink, C. A. Schortinghuis, A. Mackova-Zabelinskaja, M. Fechter, P. Pöchlauer, A. Marianne, C. F. Castelijns, J. H. van Maarseveen, H. Hiemstra, H. Griengl, H. E. Schoemaker and F. P. J. T. Rutjes, *Adv. Synth. Catal.*, 2003, **345**, 483.

23 R. Nacario, S. Kotakonda, D. M. D. Fouchard, L. M. V. Tillekeratne and R. A. Hudson, *Org. Lett.*, 2005, **7**, 471.
24 W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*, 5th ed., Butterworth-Heinemann, Amsterdam, 2003. Although the possible contaminants of commercial nitriles are the respective halides, alcohols (from hydrolysis), amines, amides, isonitriles, inorganic cyanides, etc., specific contaminants, which influence the reported reaction, have not yet been identified.
25 For example, the addition of only 1.0% of the cyanide anion (NaCN), which might be contained in commercial nitriles, shut down the reaction between aniline and MeCN.
26 When acetic acid was added to the reaction of aniline with isovaleronitrile, a significant amount of *N*-cyclohexylaniline was detected from the reaction mixture (eqn 9).[27] Using neutral ammonium acetate, this kind of by-product was not observed at all.
27 H. Alper and G. Vampollo, *Tetrahedron Lett.*, 1992, **33**, 7477.

