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Catalytic Carbon−Carbon Bond-Forming Reactions of Aminoalkane Derivatives with Imines

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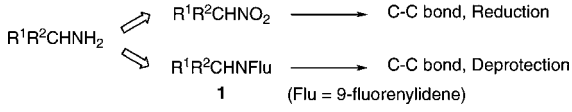
Aminoalkanes ($R^1R^2CHNH_2$) are readily available, simple, and attractive starting materials for the synthesis of nitrogen-containing compounds. As for C−C bond formation employing aminoalkanes as nucleophiles, carbanions are generally difficult to form directly because the acidity of the NH hydrogen is greater than that of the CH hydrogen.[1] Consequently, protection (activation) of the amino group is needed; however, successful examples of carbanion formation using protected aminoalkanes have been limited.[2,3] Although an alternative method using nitroalkanes ($R^1R^2CHNO_2$) is well-established (e.g., the Henry reaction),[4] reduction of the nitro groups is required to obtain amino groups.

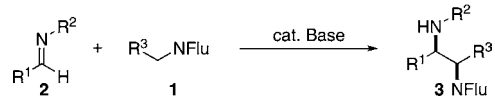
We focused on 9-fluorenylidene (Flu) as a protecting and activating group (Scheme 1). It has been used as an electron-withdrawing protecting group for primary amines[5] based on resonance stabilization by the 14π electron system of the fluorene moiety. Recently we reported that the fluorenone imines of glycine esters and their phosphonic acid analogues reacted with imines in the presence of a catalytic amount of weak base to afford the desired α,β-diamino compounds in high yields with high diastereoselectivities.[6] These results encouraged us to employ (9-fluorenylidene)aminoalkanes (**1**) as aminoalkane surrogates. Here we report the addition of **1** to imines under very mild conditions to afford C−C bond-forming products that are readily converted to free 1,2-diamines.

Scheme 1. Nitroalkanes and (9-Fluorenylidene)aminoalkanes (**1**) as Aminoalkane Surrogates



First, we investigated the addition of (9-fluorenylidene)benzylamine (**1**, R^3 = Ph)[7] to the Boc imine and the diphenylphosphinyl (Dpp) imine derived from benzaldehyde (Table 1). The desired addition reactions proceeded in the presence of a catalytic amount of potassium *tert*-butoxide (KO^tBu, 10 mol %). After optimization of the reaction conditions, the catalyst prepared from KO^tBu and 18-crown-6 was found to be more effective (entries 1 and 2).[8] Furthermore, it was found that Dpp imines were more suitable than Boc imines in terms of yields and diastereoselectivities (entries 1−4). Other imines, such as the 4-substituted benzaldehyde-derived imine, naphthyl imines, and 2-thiophenyl imine also reacted smoothly to afford the desired products in high yields with high syn selectivities (entries 5−8). Next, reactions of imines prepared from aliphatic aldehydes were investigated. It is known that aliphatic imines are easily converted to enamines by deprotonation of the α-position under basic conditions. In this system, however, it is noted that the desired products were obtained in good to high yields with high syn selectivities (entries 9−11). Other arylmethyl variants of **1** were examined, and in all cases, we were glad to find high yields and diastereoselectivities of the desired products (entries 12−15).

Table 1. Catalytic Addition of Benzylamine Derivatives (R^3 = Ar)[a]



entry	R^1	R^3	yield (%)[b]	syn/anti[c]
1[e]	Ph (**2a**)[d]	Ph (**1a**)	93	98:2
2	Ph (**2b**)	Ph (**1a**)	87	98:2
3[e]	2-furyl (**2c**)[d]	Ph (**1a**)	61	>99:1
4	2-furyl (**2d**)	Ph (**1a**)	98	97:3
5	4-BrC_6H_4 (**2e**)	Ph (**1a**)	81	96:4
6	2-thiophenyl (**2f**)	Ph (**1a**)	90	99:1
7	1-naphthyl (**2g**)	Ph (**1a**)	91	>99:1
8	2-naphthyl (**2h**)	Ph (**1a**)	94	91:9
9[f]	C_6H_{11} (**2i**)	Ph (**1a**)	quant.	>99:1
10[f]	^{i}Pr (**2j**)	Ph (**1a**)	61	98:2
11[f]	^{i}Bu (**2k**)	Ph (**1a**)	86	99:1
12	Ph (**2b**)	4-MeC_6H_5 (**1b**)	90	96:4
13	Ph (**2b**)	4-ClC_6H_5 (**1c**)	87	93:7
14	Ph (**2b**)	1-naphthyl (**1d**)	88	93:7
15	4-MeC_6H_4 (**2l**)	4-MeC_6H_5 (**1b**)	75	93:7

[a] The reaction was performed using **1** (0.20 mmol) and **2** (0.24 mmol) in 4:1 Et_2O/CH_2Cl_2 at 0 °C in the presence of KO^tBu (5 mol %) and 18-crown-6 (5−5.5 mol %) at 0.2 M, unless otherwise noted. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Boc imine (R^2 = ^{t}BuOCO) was used instead of Dpp imine [R^2 = $Ph_2P(O)$]. [e] Only Et_2O was used as a solvent. [f] **2** (0.3 mmol) was used.

We then examined the reactions of nonaromatic, simple primary aminoalkane derivatives. The α-protons of nonaromatic, primary alkylamines are much less acidic than those of arylmethyl amines. Interestingly, however, the reaction of aminoethane derivative **1e** (R^3 = Me) with imine **2b** proceeded to afford the desired adduct in high yield with high syn selectivity under the same reaction conditions shown in Table 1 (Table 2, entry 1).[9] We examined other imines (entries 2−8) and found that aromatic imines bearing electron-donating and -withdrawing groups also reacted smoothly to give the desired diamine derivatives in high yields with high selectivities. Additionally, heteroaromatic and naphthyl imines also worked well. Other aliphatic aminoalkanes **1f**−**i** with or without functional groups also reacted smoothly with **2b** in good yields with good to high diastereoselectivities (entries 9−12). Next we investigated the reaction of aminomethane derivative **1j** (R^3 = H). We treated **1j** with imine **2b** in the presence of the catalyst prepared from KO^tBu and 18-crown-6; however, the reaction did not proceed well under these conditions. After examination of the reaction conditions, we found that the desired compound was obtained in high yield when the reaction was conducted in *N*,*N*-dimethylformamide (DMF) in the presence of a catalytic amount of potassium 2,6-dimethylphenoxide prepared from KO^tBu and 2,6-dimethylphenol (entry 13). It was reasoned that this bulky base could suppress further deprotonation of the product, which might lead to undesired side reactions. The reactions of **1j** with other imines were surveyed,

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and good yields were obtained in almost all cases (entries 14−17). It is noted that the desired reactions of simple aminoalkane derivatives with imines proceeded well in the presence of a catalytic amount of base.

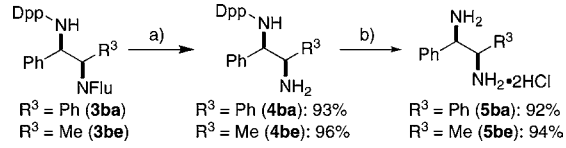
Table 2. Addition of Aminoalkane Derivatives[a]

entry	R^1	R^3	conditions[b]	yield (%)[c]	syn/anti[d]
1	Ph (**2b**)	Me (**1e**)	**A**	93	97:3
2	4-$MeOC_6H_4$ (**2m**)	Me (**1e**)	**A**	81	98:2
3	4-BrC_6H_4 (**2e**)	Me (**1e**)	**A**	72	94:6
4	4-ClC_6H_4 (**2n**)	Me (**1e**)	**A**	70	92:8
5	2-furyl (**2d**)	Me (**1e**)	**A**	91	98:2
6	2-thiophenyl (**2f**)	Me (**1e**)	**A**	73	>99:1
7	1-naphthyl (**2g**)	Me (**1e**)	**A**	95	98:2
8	2-naphthyl (**2h**)	Me (**1e**)	**A**	87	95:5
9	Ph (**2b**)	^{n}Pr (**1f**)	**A**	98	>99:1
10	Ph (**2b**)	**1g**[e]	**A**[h,i]	83	90:10
11	Ph (**2b**)	**1h**[f]	**A**[h]	80	81:19
12	Ph (**2b**)	**1i**[g]	**A**	83	93:7
13	Ph (**2b**)	H (**1j**)	**B**	86	−
14	4-$MeOC_6H_4$ (**2m**)	H (**1j**)	**B**	65	−
15	4-MeC_6H_4 (**2l**)	H (**1j**)	**B**	66	−
16	4-ClC_6H_4 (**2n**)	H (**1j**)	**B**	66	−
17	1-naphthyl (**2g**)	H (**1j**)	**B**	71	−

[a] The reaction was performed using **1** (0.20 mmol) and **2** (0.24 mmol) using conditions **A** or **B**. [b] Conditions **A**: KO^{t}Bu (10 mol %) and 18-crown-6 (11 mol %) were used. The reaction was performed in 4:1 Et_2O/CH_2Cl_2 (0.2 M) at 0 °C for 20 h. Conditions **B**: KO^{t}Bu (10 mol %) and 2,6-dimethylphenol (12 mol %) were used. The reaction was performed in DMF (0.4 M) at 0 °C for 20 h. [c] Isolated yield. [d] Determined by ^{1}H NMR analysis. [e] **1g**: $R^3 = CH_2CH(-OCH_2CH_2O-)$. [f] **1h**: $R^3 = (CH_2)_2COOEt$. [g] **1i**: $R^3 = (CH_2)_2OSiMe_2{}^tBu$. [h] At −10 °C for 36 h. [i] At 0.1 M.

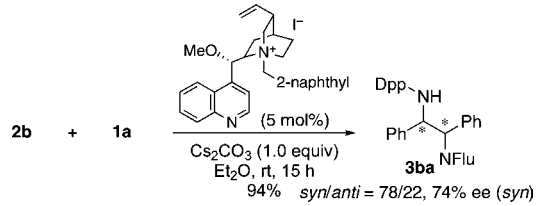
The fluorene parts of the products were readily removed under weakly acidic conditions (Scheme 2). Selective deprotection between Dpp and Flu was possible; treatment of **3ba** and **3be** with 0.5 M HCl/THF at 0 °C gave the monoamine products **4ba** and **4be** in 93% and 96% yields, respectively. After the deprotection, 9-fluorenone was recovered quantitatively, and the Dpp parts were completely inert in both cases. Further deprotection was performed at elevated temperature under more acidic conditions, and the desired diamines **5ba** and **5be** were obtained in high yields.

Scheme 2. Selective Deprotection[a]



[a] Conditions: (a) 0.5 M HCl/THF (1:9), 0 °C, 5 min, then sat. $NaHCO_3$; (b) conc. HCl/MeOH (1:6), rt, 1 h.

Scheme 3. Preliminary Study of Asymmetric Catalysis



Finally, a preliminary study of asymmetric catalysis was conducted. After a brief survey of chiral catalysts, a cinchonine derivative[10] was found to be effective for significant asymmetric induction (Scheme 3). In the presence of cesium carbonate, the desired reaction proceeded in high yield with good diastereo- and enantioselectivity.

In conclusion, catalytic C−C bond-forming reactions of aminoalkanes with imines were successfully performed using 9-fluorenylidene as a protecting and activating group of the nitrogen atom. The desired products were obtained in high yields with high diastereoselectivities using KO^{t}Bu/18-crown-6 or potassium 2,6-dimethylphenoxide as a catalyst. A wide substrate scope, including simple aminoalkanes and variety of imines, has been demonstrated. For the products obtained, selective deprotection was possible under acidic conditions to give the desired monoamine and diamine derivatives in high yields with quantitative recovery of 9-fluorenone. A preliminary trial of a catalytic asymmetric variant was also conducted, and promising enantioselectivity of the desired product was obtained. Further investigation of asymmetric reactions and application of the current reaction system to other carbon−carbon bond-forming reactions are in progress.

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Supporting Information Available: Experimental procedures, product characterization, and crystallographic data for **3ba** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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