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High Performance of *N*-Alkoxycarbonyl-imines in Triethylborane-Mediated Tin-Free Radical Addition

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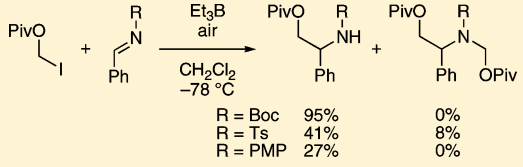
Supporting Information

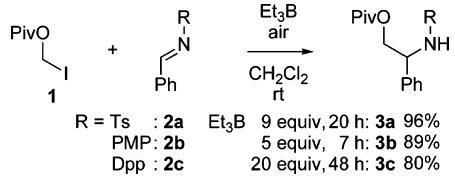
ABSTRACT: Triethylborane-mediated tin-free radical alkylation of *N*-alkoxycarbonyl-imines, such as *N*-Boc-, *N*-Cbz-, and *N*-Teoc-imines, proceeded smoothly at a low temperature (−78 to −20 °C) to give the corresponding adducts in high yield. Although the formation of isocyanate was the major unfavorable reaction at room temperature, a one-pot conversion of *N*-Boc-imine to *N*-ethoxycarbonyl-adduct was possible through the corresponding isocyanate generated in situ. The higher performance of *N*-alkoxycarbonyl-imine than those of *N*-Ts- and *N*-PMP-imines is rationalized by a moderate electron-withdrawing character of an alkoxycarbonyl group that makes both addition of alkyl radical and trapping of the resulting aminyl radical by triethylborane efficiently fast.



INTRODUCTION

The addition reaction of carbon nucleophiles to imines is one of the most versatile methodologies available for obtaining amines of chemical and/or biologic importance.[1,2] The selection of an *N*-activating−protecting group of imines, guaranteeing satisfactory reactivity and easy removal, is key to successful reactions. Among our approaches toward these types of reactions, we recently achieved radical acyloxymethylation of imines to obtain amino alcohols.[3] With iodomethyl pivalate (**1**), imines **2a**−**c**, bearing a Ts (tosyl), a PMP (4-methoxyphenyl), and a Dpp (diphenylphosphinoyl) group as an *N*-activating−protecting group, underwent pivaloyloxymethylation in the presence of triethylborane−air in dichloromethane at room temperature to give **3a**−**c** in 96, 89, and 80% yield, respectively (Scheme 1).[3] The removal of a Ts and a PMP group, however, usually requires rather harsh reductive and oxidative conditions, respectively.[4] Although a Dpp group is removable under mildly acidic conditions, its performance in pivaloyloxymethylation was moderate, and 20 equiv of triethylborane and 48 h were required for completion of the reaction. Besides, we met difficulty when we applied this reaction to sterically hindered *o*-tolualdimines (Scheme 2). The reactions of *N*-Ts-*o*-tolualdimine **2d** produced the corresponding adduct **3d** only in 33%, and dipivalate **4d** (R = Ts) was obtained in 12% yield. The production of **4d** is rationalized by the reaction of pivaloyloxymethyl radical (**8**)[5] and benzyl radical **7**, formed via 1,5-hydrogen shift of aminyl radical **5**, which indicates the slow conversion of **5** to borylamine **6** (R = Ts). Although the reaction of *N*-PMP-benzaldimine **2b** was faster than that of *N*-Ts analogue **2a** (Scheme 1), the reaction of *N*-PMP-*o*-tolualdimine **2e** was also sluggish, and adduct **3e** (R = PMP) was obtained in 58% yield after 23 h (Scheme 2). Importantly, dipivalate **4e** (R = PMP) was not detected in the products, although other unidentified byproducts were produced. These results suggest that the conversion of *N*-PMP-aminyl radical to *N*-boryl-*N*-PMP-amine with triethylborane is sufficiently fast, but the radical accepting ability of

Scheme 1. Previously Reported Pivaloyloxymethylation of Benzaldimines 2a−c



Scheme 2. Pivaloyloxymethylation of *N*-Ts- and *N*-PMP-*o*-tolualdimine 2d and 2e

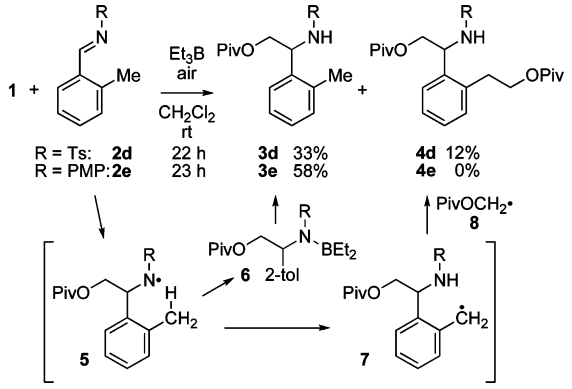


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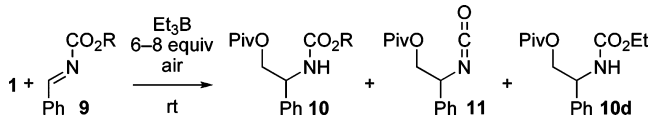
Table 1. Production of 10 and 11 in the Reaction of 1 and 9[a]



entry	9	R	solvent	time/h	10/%	11/%[b]	10d/%
1	**9a**	*t*-Bu	CH_2Cl_2	12	**10a**/42	18	9
2	**9b**	$(CH_2)_2TMS$	CH_2Cl_2	8	**10b**/42	32	7
3	**9c**	Me	CH_2Cl_2	8	**10c**/40	33	16
4	**9c**	Me	$PhCF_3$	9, 36[c]	**10c**/24	0	73
5	**9d**	Et	toluene	7, 3[d]		0	85

[a]After initial addition of Et_3B (3 equiv), Et_3B (1 equiv each) was added every 2 h. [b]Based on ^1H NMR of the crude materials. [c]At 100 °C. [d]Under reflux after addition of EtOH (17 equiv).

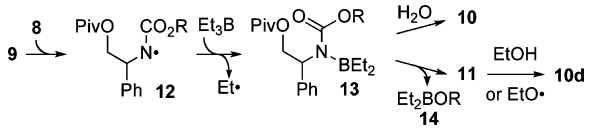
N-PMP-imine is unsatisfactory to overcome the steric hindrance of the *ortho*-methyl group in the addition of **8**. These limitations prompted us to search for a more reactive and easily removable *N*-activating group. We speculated that a more electron-accepting *N*-activating group should make the addition of radical faster but the following aminyl radical trap slower. On the basis of pK_a values of the corresponding N−H ($PhSO_2NH_2$ 16.1,[6a] $EtOCONH_2$ 24.2,[6b] $PhNH_2$ 30.6[6c]), *N*-alkoxycarbonyl-imines are expected to have moderate electron-accepting ability between those of *N*-Ts and *N*-PMP analogues, and thus both the addition step and the radical trap step might be sufficiently fast. We describe herein the high performance of *N*-alkoxycarbonyl-imines in the addition of alkyl radicals. Although oxime ethers,[7] hydrazones,[8] *N*-aryl-imines,[9] and *N*-sulfonyl-imines[10] were utilized as a radical accepting C=N compound, application of *N*-alkoxycarbonyl-imines,[11] such as *N*-Boc-, *N*-Cbz-, and *N*-(2-trimethylsilylethoxy)carbonyl (Teoc)-imines, in radical addition is rarely reported,[1,12] despite their easy removal.[4]

RESULTS AND DISCUSSION

Isocyanate Formation in the Pivaloyloxymethylation of *N*-Alkoxycarbonyl-imines. The reaction of iodomethyl pivalate (**1**) and *N*-Boc-benzaldimine **9a** (R = *t*-Bu) was conducted under the conditions[3] for *N*-Ts-imine **2a**; a 1.0 M hexane solution of triethylborane (3 mL, 3 mmol) was added to a solution of **1** (3 mmol) and **9a** (1 mmol) in dichloromethane (1 mL). The mixture was stirred at room temperature under normal atmosphere, and triethylborane (1 mL, 1 mmol) was added every 2 h. After a total addition of 8 equiv triethylborane, the mixture was stirred for another 2 h to give the expected adduct **10a** in 42% yield along with unexpected isocyanate **11** in 18% yield as well as ethyl carbamate **10d** in 9% yield (Table 1, entry 1). The use of dimethylzinc in hexane[13−15] in place of triethylborane produced a complex mixture, and no product could be identified. The reaction of *N*-Teoc-imine **9b** (R = $(CH_2)_2TMS$) and *N*-methoxycarbonyl-imine **9c** (R = Me) resulted in the similar formation of **10** as a major product in 42 and 40% yields and **10d** (7 and 16%), while isocyanate **11** was obtained in higher yields of 32 and 33%, respectively (Table 1, entries 2 and 3).

The unexpected production of isocyanate **11** is rationalized by the elimination of alkoxyborane **14** from *N*-Boc-borylamine **13** (Scheme 3).[16] The increasing tendency toward the formation of **11** by the reaction of **9b** and **9c**, having alkoxy groups with better leaving group ability than that of **9a**, supported this speculation. Isocyanate **11** then reacted with ethanol or ethoxyl, generated by the reaction of triethylborane or **14** with air,[17] to give ethoxycarbonylamine **10d**.

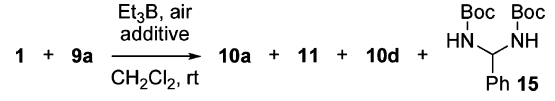
Scheme 3. Possible Pathway to 10−11 from 9



Prevention of the Isocyanate Formation. The above speculation was confirmed by the one-pot conversion of **9c** to **10d** in 73% yield (Table 1, entry 4). Thus, the addition reaction of **9c** with **1** was conducted at room temperature for 9 h in trifluoromethylbenzene and heated at 100 °C for 36 h, and **10d** was obtained in 73% yield along with **10c** in 24% yield without any residue of isocyanate **11**, indicating complete conversion of **11** to **10d**. *N*-Ethoxycarbonyl-imine **9d** was a useful imine; although the reaction in toluene at room temperature gave an almost 1:1 mixture of *N*-ethoxycarbonylamine **10d** and isocyanate **11** after 7 h, **10d** was obtained in 85% yield when the reaction mixture was heated for 3 h under reflux in the presence of ethanol (17 equiv) after the radical addition reaction was completed (Table 1, entry 5). This addition−elimination−addition sequence from **9** to **11** and then **10d** is applicable for preparing isocyanate, as the efficient conversion of *N*-ethoxycarbonylamine to isocyanate is documented.[16]

Scheme 3 also indicates that the protonation of **13** should prevent the elimination to **11** and selectively give **10**. Indeed, the reaction of **9a** with **1** at room temperature in the presence of 1 equiv of methanol and *tert*-butanol gave **10a** with improved yields of 60 and 73%, respectively (Table 2, entries 1 and 3). It

Table 2. Effect of Alkanol in the Reaction of 9a and 1[a]



entry	additive/equiv	time/h	10a/%	11/%	10d/%	15/%[b]
1	MeOH/1.0	10	60	0	0	4
2	*t*-BuOH/0.5	10	65	0	0	4
3	*t*-BuOH/1.0	8	73	0	0	11
4	*t*-BuOH/1.5	10	43	0	0	7

[a]After initial addition of Et_3B (3 equiv), Et_3B (1 equiv each) was added every 2 h. [b]Isolated yield after silica gel column chromatography with partial hydrolysis.

is noteworthy that neither isocyanate **11** nor ethoxycarbonyl-amine **10d** was produced, while *gem*-diamine **15** was formed by the reaction of **9a** and *tert*-butyl carbamate, generated by alcoholysis of **9a**. Indeed, almost complete conversion of **9a** and

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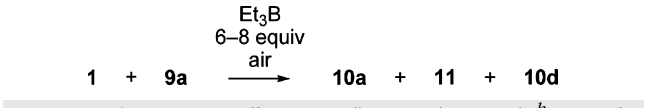
tert-butyl carbamate (0.5 mmol each) into **15** was observed by ^{1}H NMR in CD_2Cl_2 (0.6 mL) at room temperature for 15 min in the absence of any additives.[18]

Decreasing the temperature also effectively suppressed the elimination; the reaction at 0 °C provided **10a** in 67% yield (Table 3, entry 2). The reaction at −20 °C gave **10a** in 81%

Table 3. Temperature Dependence in the Reaction of 9a and 1[a]



entry	solvent	temp/°C	time/h	**10a**/%	**11**/%[b]	**10d**/%
1	CH_2Cl_2	rt	12	42	18	9
2	CH_2Cl_2	0	12	67	13	11
3	CH_2Cl_2	−20	6	81	0	0
4[c]	CH_2Cl_2	−20	6	95	0	0
5[c]	CH_2Cl_2	−78	10	95	0	0
6[c]	toluene	−20	10	97	0	0

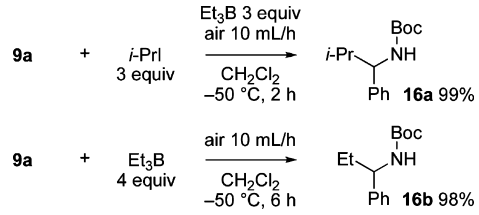
[a]After initial addition of Et_3B (3 equiv), Et_3B (1 equiv each) was added every 2 h. [b]Based on ^{1}H NMR of the crude materials. [c]Air was introduced into the reaction mixture at 10 mL/h.

yield without the formation of **11** and **10d** (Table 3, entry 3). These results clearly show that elimination of **14** from **13** requires a higher temperature, between −20 and 0 °C, than the radical addition and the following trap of **12** by triethylborane to give **13**. Air bubbling improved the yield of **10a** (Table 3, entry 4). The reaction proceeded even at −78 °C with the same level of efficiency (Table 3, entry 5). Toluene was also a good solvent to give **10a** in 97% yield (Table 3, entry 6). The high yield of the reactions at lower temperature sharply contrasted with the low yield at room temperature.

Scope of the Reaction of *N*-Alkoxycarbonyl-imines. The established conditions were successfully applied to pivaloyloxymethylation of other *N*-alkoxycarbonyl-imines at −20 or 0 °C (Table 4). *N*-Teoc-imine **9b** and *N*-Cbz-imine **9e** were also good acceptors to give the corresponding adducts in high yield (Table 4, entries 2 and 3). Interestingly, in the reaction of **9e**, isocyanate **11** was formed in 16% yield along with **10e** in 72% yield even at −40 °C, probably because of a higher ability of a benzyloxy group as a leaving group (pK_a in DMSO: BnOH 26.93,[19] EtOH 29.8, *t*-BuOH 32.2[20]). *N*-Boc-imine **9f**, having an electron-withdrawing 4-bromo substituent, gave **10f** in high 94% yield, and the bromo moiety was intact under the reaction conditions (Table 4, entry 4). Imine **9g**, bearing an electron-donating 4-methoxy substituent, reacted at 0 °C to give **10g** in 89% yield without the production of isocyanate and ethoxycarbonylamine (Table 4, entry 5). Similarly, **9h** reacted at −20 °C to give **10h** in 86% yield (Table 4, entry 6). The reaction of sterically hindered *o*-tolualdimine **9i** produced **10i** also in high yield (Table 4, entry 7), strikingly contrasting with poor results of *N*-Ts and *N*-PMP analogues in Scheme 2. Aliphatic imine **9j** reacted smoothly to give **10j** in 92% yield (Table 4, entry 8).

N-Boc-imine also performed well in a typical triethylborane-mediated addition reaction of an alkyl radical[10] (Scheme 4).

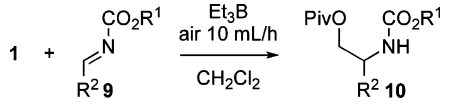
Scheme 4. Et_3B-Mediated Alkylation of 9a



The reactions of **9a** with and without 2-iodopropane (3 equiv) at −50 °C quantitatively afforded *N*-Boc isopropyl adduct **16a** and ethyl adduct **16b**, respectively. Isopropylation was much faster than ethylation and pivaloyloxymethylation probably because of the higher nucleophilicity of the isopropyl radical. Isopropylation also proceeded smoothly even at −78 °C to give **16a** in 92% yield after 2 h. These results clearly show the general applicability of *N*-Boc-imine as an excellent acceptor in triethylborane-mediated radical addition reactions at a low temperature. The reaction with and without 2-iodopropane at −20 °C provided the corresponding isocyanates in 27 and 10% yield with **16a** and **16b** in 68 and 73% yield, respectively. Thus, isopropylation and ethylation required a lower temperature than pivaloyloxymethylation to prevent isocyanate formation, suggesting that the pivaloyloxy functionality stabilizes the *N*-boryl intermediate **13**.

Comparison with the Reactions of *N*-Ts-imines and *N*-PMP-imines. *N*-Boc-imines have apparently high reactivity toward triethylborane-mediated radical addition; the addition to *N*-Boc-imine **9a** proceeded smoothly at −78 °C (Table 3, entry 5). The result shows that both the addition of

Table 4. Radical Pivaloyloxymethylation of *N*-Boc-imines 9[a]



entry	**9**	R^1	R^2	Et_3B/equiv	temp/°C	time/h	**10**	yield/%
1	**9a**	*t*-Bu	Ph	5	−20	6	**10a**	95
2	**9b**	$TMS(CH_2)_2$	Ph	6	−20	8	**10b**	89
3	**9e**	Bn	Ph	5	−60	6	**10e**	96
4	**9f**	*t*-Bu	4-BrC_6H_4	5	−20	6	**10f**	94
5	**9g**	*t*-Bu	4-$MeOC_6H_4$	7	0	10	**10g**	89
6	**9h**	*t*-Bu	4-MeC_6H_4	5	−20	6	**10h**	86
7	**9i**	*t*-Bu	2-MeC_6H_4	5	−20	6	**10i**	92
8	**9j**	*t*-Bu	$Ph(CH_2)_2$	4	−20	4	**10j**	92

[a]The reaction was conducted in a 20-mL 2-necked round-bottom flask with a NaOH drying tube. After initial addition of Et_3B (3 equiv), Et_3B (1 equiv each) was added every 2 h.

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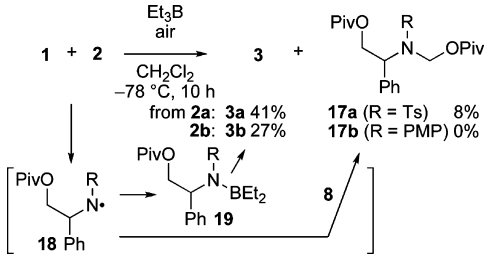
pivaloyloxymethyl radical (**8**) to **9a** and the trap of aminyl radical **12** by triethylborane (Scheme 3) are sufficiently fast even at −78 °C. In contrast, the reaction of *N*-Ts-benzaldimine **2a** under the same conditions gave the corresponding adduct **3a** in only 41% yield, along with **17a** in 8% yield, after 10 h (Scheme 5). The production of **17a** is probably due to the

Scheme 5. Reactions of *N*-Ts-benzaldimine 2a and *N*-PMP-benzaldimine 2b at −78 °C

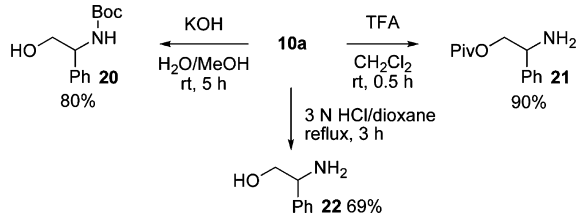


reaction of aminyl radical **18a** (R = Ts) with pivaloyloxymethyl radical (**8**),[21] indicating the slow conversion of **18a** to *N*-Ts-borylamine **19a** (R = Ts), as previously illustrated in Scheme 2. The formation of **17a** by the ionic nucleophilic substitution of **19a** with **1** could be excluded because **17a** was not produced at room temperature. The reaction of *N*-PMP-benzaldimine **2b** was also so inefficient at −78 °C that adduct **3b** was obtained in only 27% yield after 10 h with many unidentified byproducts, although no production of **17b** was observed (Scheme 5). This result indicates that the formation of borylamine **19b** from aminyl radical **18b** (R = PMP) and triethylborane is sufficiently fast, but **2b** is a poor radical acceptor at −78 °C due to less strong electron-withdrawing character of the PMP group. Importantly, *N*-Boc-*o*-tolualdimine **9i**, the counterpart of **2d** and **2e** (Scheme 2), reacted smoothly at −20 °C to give **10i** in 92% yield without forming the product corresponding to **4d** (Table 4, entry 7). This result also confirms that both the addition step and the aminyl radical trapping step are fast with *N*-Boc-imines.

Comparing the reaction of *p*-anisaldimine **9g** (Table 4, entry 5) with that of the *N*-Ts analogue, superiority of *N*-Boc-imine was further indicated. As previously reported,[3] the reaction of *N*-Ts-*p*-anisaldimine requires 9 equiv of triethylborane and 3 equiv of boron trifluoride to give the corresponding product in 94% yield within 22 h. Without boron trifluoride, the reaction failed to complete even after 60 h, and the yield of the product was decreased to 41%. In contrast, adduct **10g** was obtained in good yield at 0 °C after 10 h in the absence of boron trifluoride (Table 4, entry 5). These results seem to indicate that not only the aminyl radical trap but also the radical addition step of *N*-Boc-imines is faster than that of *N*-Ts-imines.

Selective Deprotection of the Adduct. Finally, we demonstrated selective deprotection of the adduct (Scheme 6). O-Deprotection of **10a** was selectively realized by our reported conditions (KOH, H_2O/MeOH),[3] and *N*-Boc-phenylglycinol **20** was obtained in 80% yield after 5 h. N-Deprotection was achieved by TFA treatment for 30 min to give **21** exclusively in 90% yield. It was important to liberate free amine **21** from the TFA salt using 10% NaOH at 0 °C to prevent undesired migration of the pivaloyl group; an 89:11 mixture of *O*- and *N*-pivaloyl-phenylglycinol was obtained at room temperature. N,O-Dual-deprotection was also possible by treatment with 3

Scheme 6. Selective Deprotection of 10a



N HCl in refluxing dioxane for 3 h,[22] and phenylglycinol (**22**) was directly obtained in 69% yield.

CONCLUSION

N-Alkoxycarbonyl-imines showed high performance in triethylborane−air-initiated tin-free radical alkylation. This high performance is likely due to mildly electron-withdrawing character of alkoxycarbonyl groups that keeps both the radical addition step and the aminyl radical trapping step sufficiently fast. The contrasting low performance at room temperature was attributed to isocyanate formation, which could account for the reported low efficiency of this class of imines.[12b] Not only the simple adduct but also the addition−elimination−addition sequence product was prepared in one pot. Because only mild conditions are required for removal of *N*-Boc, *N*-Cbz, and *N*-Teoc groups, the present finding that *N*-alkoxycarbonyl-imines are excellent radical acceptors expands the synthetic utility of radical reactions.

EXPERIMENTAL SECTION

General Methods. Imines **2a**,[23] **2b**,[24] **2d**,[25] **2e**,[26] **9a**,[27] **9b**,[28] **9c**,[29] **9d**,[30] **9e**,[31] **9f−i**,[27] and **9j**[32] were prepared according to the literature. $PivOCH_2I$ (**1**) was prepared by the reported procedure[33] and decolorized by being passed through Al_2O_3 prior to use. Anhydrous CH_2Cl_2, toluene, and $PhCF_3$, and hexane solutions of Me_2Zn and Et_3B were purchased and used as received. MeOH, EtOH, and *t*-BuOH were distilled from sodium prior to use. Column chromatography was performed using silica gel. All melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz, respectively. ^1H NMR spectra were measured at 55 or 58 °C in the cases that peaks were broadened at rt. Chemical shifts and coupling constants are presented in ppm δ relative to Me_4Si and Hz, respectively. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, and m = multiplet), coupling constants, integration, and assignment. ^{13}C peak multiplicity assignments were made on the basis of DEPT spectra. IR spectroscopy of oil and solid samples were measured as neat liquid films and KBr pellets, respectively. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}.

Typical Procedure (Table 4, Entry 1): 2-*tert*-Butoxycarbonylamino-2-phenylethyl pivalate (10a). A stirring bar and **9a** (205 mg, 1.0 mmol) were placed in a dry 20-mL two-neck round-bottom flask, which was filled with argon by three-time evacuation-and-refill using an argon balloon. To the flask were added CH_2Cl_2 (1 mL), iodomethyl pivalate (**1**) (0.50 mL, 3.0 mmol), and a hexane solution of Et_3B (1.0 M; 3.0 mL, 3.0 mmol) at −20 °C. After replacing the argon balloon with a NaOH drying tube, air was introduced into the stirred mixture through a syringe needle (10 mL/h), and the solution of Et_3B (1.0 mL, 1.0 mmol) was added every 2 h. After a total addition of 5.0 mmol Et_3B, the mixture was stirred for another 2 h, and saturated $NaHCO_3$ was added. The whole was extracted three times with EtOAc, and the combined organic layers were washed with 10% $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and then concentrated in vacuo. The resulting residue was purified by column chromatography (hexane/EtOAc 19/1) to afford the title compound (305 mg, 95%) as white solids of mp 107−108 °C (hexane): ^1H NMR (55 °C) 1.15

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(s, 9H), 1.41 (s, 9H), 4.25 (dd, J = 5.0, 11.5, 1H), 4.32 (dd, J = 6.5, 11.5, 1H), 4.9−5.1 (br m, 2H), 7.24−7.35 (m, 5H); ^{13}C NMR 27.0 (CH_3), 28.2 (CH_3), 38.7 (C), 53.8 (CH), 66.2 (CH_2), 79.6 (C), 126.6 (CH), 127.7 (CH), 128.6 (CH), 139.0 (C), 155.2 (C), 178.4 (C); IR 3402, 1728, 1690, 1520, 1142; FABMS m/z 322 (M + H), 266 (M − t-Bu), 206 (M − PivOCH$_2$), 150, 57 (t-Bu). Anal. Calcd. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.21; H, 8.35; N, 4.31.

***N*-(2-Methylbenzylidene)-*p*-anisidine (2e).** Pale yellow blocks of mp 50−51 °C (hexane): ^{1}H NMR 2.58 (s, 3H), 3.84 (s, 3H), 6.94 (d, J = 9.0, 2H), 7.19−7.25 (m, 3H), 7.27−7.37 (m, 2H), 8.06 (dd, J = 1.5, 8.0, 1H), 8.77 (s, 1H); ^{13}C NMR 19.4 (CH_3), 55.5 (CH_3), 114.3 (CH), 122.1 (CH), 126.3 (CH), 127.5 (CH), 130.7 (CH), 130.9 (CH), 134.3 (C), 138.3 (C), 145.6 (C), 157.1 (CH), 158.2 (C); IR 2908, 1597, 1504, 1242; EIMS m/z 225 (M$^+$); HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{15}H_{16}NO$, 226.1226, found 226.1229.

2-*p*-Toluenesulfonamido-2-*o*-tolylethyl Pivalate (3d) and 2-(2-Pivaloyloxyethyl)phenyl-2-(*p*-toluenesulfonamido)ethyl Pivalate (4d). The typical procedure at rt using **2d** in place of **9a** followed by column chromatography (toluene/EtOAc 19/1 to 3/1) afforded **3d** as colorless prisms of mp 106−107 °C (EtOAc): ^{1}H NMR 1.11 (s, 9H), 2.25 (s, 3H), 2.34 (s, 3H), 4.15 (d, J = 8.5, 2H), 4.93 (dt, J = 8.5, 8.5, 1H), 5.25 (br m, 1H), 6.99−7.04 (m, 2H), 7.07−7.12 (m, 4H), 7.53 (d, J = 8.5, 2H); ^{13}C NMR 19.0 (CH_3), 21.3 (CH_3), 27.0 (CH_3), 38.7 (C), 53.0 (CH), 65.6 (CH_2), 126.2 (CH), 126.4 (CH), 127.0 (CH), 127.8 (CH), 129.4 (CH), 130.5 (CH), 135.1 (C), 135.3 (C), 137.4 (C), 143.3 (C), 178.5 (C); IR 3279, 2978, 1728, 1597, 1458, 1327, 1281, 1165, 1088, 1034; EIMS m/z 274 (M − PivOCH$_2$), 155 (Ts), 118, 91 (tolyl). Anal. Calcd. for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.60. Found: C, 64.49; H, 6.91; N, 3.59. **4d** was also afforded as colorless oil: ^{1}H NMR 1.11 (s, 9H), 1.18 (s, 9H), 2.35 (s, 3H), 2.91 (m, 2H), 4.15−4.23 (m, 4H), 5.00 (dt, J = 6.5, 6.5, 1H), 5.35 (br m, 1H), 7.04−7.15 (m, 6H), 7.55 (d, J = 8.0, 2H); ^{13}C NMR 21.3 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 31.4 (CH_2), 38.6 (C), 38.7 (C), 52.6 (CH), 65.8 (CH_2), 65.9 (CH_2), 127.0 (CH), 127.0 (CH), 127.1 (CH), 127.9 (CH), 129.4 (CH), 130.0 (CH), 135.1 (C), 135.4 (C), 137.5 (C), 143.3 (C), 178.4 (C), 178.5 (C); IR 3279, 2970, 1728, 1481, 1350, 1288, 1157, 1088; FABMS m/z 504 (M + H), 402 (M − PivO), 388 (M − PivOCH$_2$); HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{27}H_{38}SNO_6$, 504.2420, found 504.2419.

2-*p*-Anisidino-2-*o*-tolylethyl Pivalate (3e). The typical procedure at rt using **2e** in place of **9a** followed by column chromatography (hexane/EtOAc 19/1) afforded the title compound as pale-yellow oil: ^{1}H NMR 1.18 (s, 9H), 2.49 (s, 3H), 3.69 (s, 3H), 4.11 (br s, 1H), 4.16 (dd, J = 8.5, 11.5, 1H), 4.32 (dd, J = 4.5, 11.5, 1H), 4.78 (dd, J = 4.5, 8.5, 1H), 6.43 (d, J = 9.0, 2H), 6.69 (d, J = 9.0, 2H), 7.13−7.22 (m, 3H), 7.47 (m, 1H); ^{13}C NMR 18.9 (CH_3), 27.0 (CH_3), 38.7 (C), 54.8 (CH), 55.4 (CH_3), 66.2 (CH_2), 114.3 (CH), 114.6 (CH), 126.0 (CH), 126.3 (CH), 127.3 (CH), 130.6 (CH), 135.2 (C), 137.3 (C), 141.3 (C), 152.1 (C), 178.4 (C); IR 3402, 2970, 1728, 1512, 1149; FABMS m/z 342 (M + H), 341 (M$^+$), 226 (M − PivOCH$_2$), 219 (M − NHC$_6$H$_4$OMe), 57 (t-Bu); HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{21}H_{28}NO_3$, 342.2064, found 342.2062.

2-Phenyl-2-(2-trimethylsilylethyl)carbonylaminoethyl Pivalate (10b). Purified by column chromatography (hexane/EtOAc 9/1). White solids of mp 59−61 °C (hexane): ^{1}H NMR (55 °C) 0.02 (s, 9H), 0.96 (dd, J = 7.5, 9.5, 2H), 1.14 (s, 9H), 4.12−4.20 (m, 2H), 4.27 (dd, J = 5.0, 11.5, 1H), 4.35 (dd, J = 7.5, 11.0, 1H), 5.02 (ddd, J = 5.0, 7.5, 7.5, 1H), 5.13 (br m, 1H), 7.24−7.36 (m, 5H); ^{13}C NMR −1.60 (CH_3), 17.6 (CH_2), 27.0 (CH_3), 38.8 (C), 54.3 (CH), 63.3 (CH_2), 66.2 (CH_2), 126.6 (CH), 127.9 (CH), 128.7 (CH), 138.8 (C), 156.1 (C), 178.5 (C); IR 3348, 2955, 1728, 1528, 1250; FABMS m/z 366 (M + H), 250 (M − PivOCH$_2$), 205 (M − NHCO$_2$C$_2$H$_4$TMS), 57 (t-Bu). Anal. Calcd. for $C_{19}H_{31}NO_4Si$: C, 62.43; H, 8.55; N, 3.83. Found: C, 62.13; H, 8.25; N, 3.82.

2-Methoxycarbonylamino-2-phenylethyl Pivalate (10c). Purified by column chromatography (hexane/EtOAc 9/1). Colorless oil: ^{1}H NMR (58 °C) 1.14 (s, 9H), 3.66 (s, 3H), 4.27 (dd, J = 4.5, 11.5, 1H), 4.36 (dd, J = 7.5, 11.5, 1H), 5.02 (m, 1H), 5.15 (br m, 1H), 7.26−7.37 (m, 5H); ^{13}C NMR 27.0 (CH_3), 38.8 (C), 52.2 (CH_3), 54.4 (CH), 66.1 (CH_2), 126.5 (CH), 127.9 (CH), 128.6 (CH), 138.5 (C), 156.4 (C), 178.4 (C); IR 3341, 2970, 1728, 1535; FABMS m/z 280 (M + H), 220 (M − CO$_2$Me), 205 (M − NHCO$_2$Me), 57 (t-Bu); HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{15}H_{22}NO_4$ 280.1543, found 280.1546.

2-Isocyanato-2-phenylethyl Pivalate (11). The yields were calculated on the basis of integration area of the ^{1}H NMR signals at 4.95 (CH of **11**) and 4.22−4.26 (overlapping PivOCH$_2$ of **10a** and **10d**) ppm of crude mixtures. After column chromatography (hexane/EtOAc 19/1), the title compound was isolated with 20−90% loss of the yield as colorless oil: ^{1}H NMR 1.23 (s, 9H), 4.09 (dd, J = 9.0, 11.5, 1H), 4.35 (dd, J = 4.0, 11.5, 1H), 4.95 (dd, J = 4.0, 9.0, 1H), 7.32−7.43 (m, 5H); ^{13}C NMR 27.0 (CH_3), 38.9 (C), 57.9 (CH), 68.3 (CH_2), 125.4 (C), 126.3 (CH), 128.6 (CH), 128.9 (CH), 136.7 (C), 178.1 (C); IR 2970, 2268, 1736, 1481; CIMS m/z 248 (M + H), 205 (M − NCO); HRMS−CI (m/z) [M + H]$^+$ calcd for $C_{14}H_{18}NO_3$, 248.1281, found 248.1280.

2-Ethoxycarbonylamino-2-phenylethyl Pivalate (10d). Table 1, Entry 5. The typical procedure was followed, except that toluene, instead of CH_2Cl_2, was used as solvent at rt using **9d** in place of **9a**. After a total addition of 6.0 mmol Et_3B, the mixture was stirred for another 1 h, and EtOH (1.0 mL, 17 mmol) was added. The mixture was heated under reflux for 3 h, cooled to rt, and diluted with EtOAc. The whole was washed with 10% $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and then concentrated in vacuo. The resulting residue was purified by column chromatography (hexane/EtOAc 9/1) to afford the title compound (249 mg, 85%) as colorless oil: ^{1}H NMR (55 °C) 1.14 (s, 9H), 1.22 (t, J = 7.0, 3H), 4.05−4.15 (m, 2H), 4.26 (dd, J = 5.5, 11.0, 1H), 4.36 (dd, J = 7.5, 11.0, 1H), 5.03 (ddd, J = 5.5, 6.0, 7.5, 1H), 5.13 (br m, 1H), 7.26−7.36 (m, 5H); ^{13}C NMR 14.5 (CH_3), 27.0 (CH_3), 38.8 (C), 54.5 (CH), 61.1 (CH_2), 66.2 (CH_2), 126.7 (CH), 127.9 (CH), 128.7 (CH), 138.9 (C), 156.1 (C), 178.4 (C); IR 3387, 1720, 1512, 1157; FABMS m/z 294 (M + H), 278 (M − Me), 221 (M + H − CO$_2$Et), 205 (M − NHCO$_2$Et), 178 (M − PivOCH$_2$), 57 (t-Bu); HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{16}H_{24}NO_4$, 294.1705, found 294.1710.

2-Benzyloxycarbonylamino-2-phenylethyl Pivalate (10e). Purified by column chromatography (hexane/EtOAc 19/1). White solids of mp 49−50 °C (hexane): ^{1}H NMR (55 °C) 1.12 (s, 9H), 4.28 (dd, J = 11.5, 5.0, 1H), 4.36 (dd, J = 11.5, 7.5, 1H), 5.00−5.15 (m, 3H), 5.24 (br m, 1H), 7.25−7.40 (m, 10H); ^{13}C NMR 26.8 (CH_3), 38.5 (C), 54.2 (CH), 65.9 (CH_2), 66.6 (CH_2), 126.4 (CH), 127.6 (CH), 127.90 (CH), 127.94 (CH), 128.2 (CH), 128.4 (CH), 136.2 (C), 138.4 (C), 155.7 (C), 178.2 (C); IR 3379, 2955, 1697, 1528, 1234, 1157; FABMS m/z 356 (M + H), 254 (M − t-BuCO$_2$), 240 (M − t-BuCO$_2$CH$_2$), 221 (M + H − PhCH$_2$OCO), 205 (M − PhCH$_2$OCONH). Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.84; H, 7.09; N, 3.92.

2-(4-Bromophenyl)-2-*tert*-butoxycarbonylaminoethyl Pivalate (10f). Purified by column chromatography (hexane/EtOAc 19/1). Colorless needles of mp 92−93 °C (hexane): ^{1}H NMR (55 °C) 1.15 (s, 9H), 1.41 (s, 9H), 4.22 (dd, J = 5.0, 11.5, 1H), 4.29 (dd, J = 7.0, 11.5, 1H), 4.92 (br m, 1H), 4.99 (br m, 1H), 7.17 (d, J = 8.5, 2H), 7.46 (d, J = 8.5, 2H); ^{13}C NMR 27.0 (CH_3), 28.2 (CH_3), 38.7 (C), 53.4 (CH), 65.9 (CH_2), 79.9 (C), 121.6 (C), 128.2 (CH), 131.6 (CH), 138.1 (C), 155.0 (C), 178.3 (C); IR 3348, 2978, 1728, 1681, 1535, 1157; FABMS m/z 402, 400 (M + H), 346, 344 (M − t-Bu), 302, 300, 285, 283 (M − NHBoc), 230, 228. Anal. Calcd. for $C_{18}H_{26}BrNO_4$: C, 54.01; H, 6.55; N, 3.50. Found: C, 54.03; H, 6.56; N, 3.44.

2-*tert*-Butoxycarbonylamino-2-(4-methoxyphenyl)ethyl Pivalate (10g). Purified by column chromatography (hexane/EtOAc 19/1). White solids of mp 76−76.5 °C (hexane): ^{1}H NMR (55 °C) 1.15 (s, 9H), 1.41 (s, 9H), 3.77 (s, 3H), 4.22 (dd, J = 5.5, 11.5, 1H), 4.28 (dd, J = 7.5, 11.5, 1H), 4.91 (br m, 1H), 5.06 (br d, J = 7.5, 1H), 6.86 (d, J = 8.5, 2H), 7.21 (d, J = 8.5, 2H); ^{13}C NMR 27.0 (CH_3), 28.3 (CH_3), 38.7 (C), 53.5 (CH), 55.2 (CH_3), 66.2 (CH_2), 79.5 (C), 114.1 (CH), 127.7 (CH), 131.3 (C), 155.1 (C), 159.2 (C), 178.2 (C); IR 3371, 2978, 1720, 1512, 1165; FABMS m/z 352 (M + H), 296 (M − t-Bu), 236 (M − PivOCH$_2$), 235 (M − NHBoc), 180. Anal. Calcd. for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99. Found: C, 64.77; H, 8.48; N, 4.06.

2-*tert*-Butoxycarbonylamino-2-*p*-tolylethyl Pivalate (10h). Purified by column chromatography (hexane/EtOAc 19/1). Colorless

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prisms of mp 75−75.5 °C (hexane): ^{1}H NMR (55 °C) 1.15 (s, 9H), 1.40 (s, 9H), 2.30 (s, 3H), 4.23 (dd, J = 5.5, 11.5, 1H), 4.28 (dd, J = 7.5, 11.5, 1H), 4.94 (br m, 1H), 5.27 (br m, 1H), 7.11 (d, J = 8.0, 2H), 7.18 (d, J = 8.0, 2H); ^{13}C NMR 20.7 (CH_3), 26.9 (CH_3), 28.2 (CH_3), 38.6 (C), 53.8 (CH), 66.2 (CH_2), 79.3 (C), 126.4 (CH), 129.0 (CH), 136.1 (C), 137.1 (C), 155.1 (C), 178.0 (C); IR 3363, 2978, 1736, 1681, 1528, 1150; FABMS m/z 336 (M + H), 280 (M − t-Bu), 236, 220 (M − PivOCH$_2$), 219 (M − NHBoc), 164. Anal. Calcd. for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.92; H, 8.95; N, 4.14.

2-*tert*-Butoxycarbonylamino-2-*o*-tolylethyl Pivalate (10i). Purified by column chromatography (hexane/EtOAc 19/1). Colorless needles of mp 113−114 °C (hexane): ^{1}H NMR (55 °C) 1.16 (s, 9H), 1.40 (s, 9H), 2.43 (s, 3H), 4.23 (d, J = 7.0, 2H), 4.97 (br d, J = 7.0, 1H), 5.22 (br m, 1H), 7.13−7.23 (m, 4H); ^{13}C NMR 19.2 (CH_3), 27.1 (CH_3), 28.4 (CH_3), 38.8 (C), 50.6 (CH), 65.6 (CH_2), 79.7 (C), 125.6 (CH), 126.2 (CH), 127.6 (CH), 130.8 (CH), 135.9 (C), 137.3 (C), 155.1 (C), 178.4 (C); IR 3309, 2978, 1736, 1674, 1550, 1288, 1142; FABMS m/z 336 (M + H), 280 (M − t-Bu), 220 (M − PivOCH$_2$), 219 (M − NHBoc), 164. Anal. Calcd. for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.00; H, 8.92; N, 4.12.

2-*tert*-Butoxycarbonylamino-4-phenylbutyl Pivalate (10j). Purified by column chromatography (hexane/EtOAc 19/1). Colorless needles of mp 69−70 °C (hexane): ^{1}H NMR (55 °C) 1.20 (s, 9H), 1.45 (s, 9H), 1.69−1.78 (m, 1H), 1.78−1.88 (m, 1H), 2.62−2.77 (m, 2H), 3.89 (br m, 1H), 4.03 (dd, J = 4.5, 11.0, 1H), 4.11 (dd, J = 5.5, 11.0, 1H), 4.45 (br m, 1H), 7.14−7.20 (m, 3H), 7.25−7.30 (m, 2H); ^{13}C NMR 26.9 (CH_3), 28.1 (CH_3), 31.9 (CH_2), 33.5 (CH_2), 38.5 (C), 49.2 (CH), 65.7 (CH_2), 78.9 (C), 125.7 (CH), 128.1 (CH), 128.2 (CH), 141.1 (C), 155.2 (C), 178.0 (C); IR 3333, 2963, 1728, 1690, 1535, 1173; FABMS m/z 350 (M + H), 294 (M − t-Bu), 250. Anal. Calcd. for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.64; H, 8.94; N, 4.03.

Di-*tert*-butyl Benzylidenedicarbamate (15). The typical procedure was followed in the presence of t-BuOH (1 equiv) at rt to afford **10a** (73%) along with the title compound (11%) as white solids of mp 140−142 °C (EtOAc): ^{1}H NMR (55 °C) 1.44 (s, 18H), 5.33 (br m, 2H), 6.09 (t, J = 7.5, 1H), 7.26−7.44 (m, 5H); ^{13}C NMR 28.3 (CH_3), 61.9 (CH), 80.1 (C), 125.8 (CH), 127.9 (CH), 128.5 (CH), 140.0 (C), 154.8 (C); IR 3317, 2978, 1697, 1504; FABMS m/z 345 (M + Na), 323 (M + H), 206 (M − NHBoc); HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{17}H_{27}N_2O_4$, 323.1965, found 323.1970.

***tert*-Butyl 2-Methyl-1-phenylpropylcarbamate (16a).** The typical procedure at −50 °C using 2-iodopropane in place of **1** followed by column chromatography (hexane/EtOAc 19/1) afforded the title compound in 99% yield as white solids of mp 107−107.5 °C (lit.[34] 61 °C): FABMS m/z 250 (M + H), 206 (M − i-Pr), 194 (M − t-Bu). ^{1}H and ^{13}C NMR and IR were identical to those reported.[34]

2-Methyl-1-phenylpropyl Isocyanate.[35] Purified by column chromatography (hexane/EtOAc 19/1). Colorless oil: ^{1}H NMR 0.92 (d, J = 6.5, 3H), 0.94 (d, J = 6.5, 3H), 2.03 (dqq, J = 6.0, 6.5, 6.5, 1H), 4.42 (d, J = 6.0, 1H), 7.24−7.40 (m, 5H); ^{13}C NMR 17.6 (CH_3), 19.7 (CH_3), 36.0 (CH), 65.5 (CH), 122.6 (C), 126.3 (CH), 127.7 (CH), 128.4 (CH), 140.3 (C); IR 2970, 2268, 1458; EIMS m/z 175 (M), 132 (M − i-Pr), 77 (Ph); HRMS−FAB (m/z) [M$^+$] calcd for $C_{11}H_{13}NO$, 175.0997, found 175.1000.

***tert*-Butyl 1-Phenylpropylcarbamate (16b).** The typical procedure at −50 °C without **1** followed by column chromatography (hexane/EtOAc 19/1) afforded the title compound in 98% yield as white solids of mp 91−92 °C (lit. 92−94 °C,[12b] 95 °C[36]): EIMS m/z 234 (M − H), 206 (M − Et), 178 (M − t-Bu), 150, 106. ^{1}H and ^{13}C NMR[12b] and IR[36] were identical to those reported.

1-Phenylpropyl Isocyanate. Not isolated. The production was confirmed on the basis of ^{1}H NMR (identical signals to those reported[37]), IR (2268 cm^{-1}), and EIMS (m/z = 161 [M$^+$]) of the crude material. The yield was based on integration area of the ^{1}H NMR signals at 1.82 (CH_2 of the title compound) and 1.77 (CH_2 of **16b**) ppm of the crude mixture.

2-Phenyl-2-(*p*-toluenesulfonamido)ethyl Pivalate (3a) and 2-Phenyl-2-(*N*-pivaloyloxymethyl-*p*-toluenesulfonamido)ethyl Pivalate (17a). The typical procedure at −78 °C using **2a** in place of **9a** followed by column chromatography (hexane/EtOAc 9/1) afforded **3a**[3] (41%) along with **2a** (24%), tosylamide (11%), and **17a** (8%) as colorless oil: ^{1}H NMR 1.05 (s, 9H), 1.06 (s, 9H), 2.44 (s, 3H), 4.29 (dd, J = 6.0, 11.5, 1H), 4.59 (dd, J = 8.5, 11.5, 1H), 5.10 (d, J = 12.5, 1H), 5.39 (dd, J = 6.0, 8.5, 1H), 5.64 (d, J = 12.5, 1H), 7.13−7.19 (m, 2H), 7.27−7.34 (m, 5H), 7.80 (d, J = 8.5, 2H); ^{13}C NMR 21.5 (CH_3), 26.8 (CH_3), 26.9 (CH_3), 38.5 (C), 38.6 (C), 58.3 (CH), 62.8 (CH_2), 70.2 (CH_2), 127.6 (CH), 128.0 (CH), 128.5 (CH), 128.7 (CH), 129.7 (CH), 134.9 (C), 137.6 (C), 144.0 (C), 177.4 (C), 177.9 (C); IR 2970, 1728, 1149; FABMS m/z 512 (M + Na), 388 (M − PivO), 374 (M − PivOCH$_2$), 260, 205 (M − PivOCH$_2$NTs); HRMS−FAB (m/z) [M + Na]$^+$ calcd for $C_{26}H_{35}NO_6SNa$, 512.2077, found 512.2088.

2-(4-Methoxyphenyl)amino-2-phenylethyl Pivalate (3b). The typical procedure at −78 °C using **2b** in place of **9a** followed by column chromatography (hexane/EtOAc 9/1) afforded the title compound[3] in 27% yield.

***tert*-Butyl *N*-(2-Hydroxy-1-phenylethyl)carbamate (20).** To a solution of **10a** (161 mg, 0.50 mmol) in MeOH (0.5 mL) was added 2 M KOH (0.5 mL) at rt, and the mixture was stirred for 5 h. The mixture was diluted with water (5 mL) and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by chromatography (hexane/EtOAc 4/1) gave the title compound (94.4 mg, 80%) as a white solid of mp 141−142 °C (lit.[38] 141−142 °C): IR 3310, 3225, 1674, 1558; FABMS (m/z) 238 (M + H), 206 (M − CH$_2$OH), 182 (M − t-Bu), 136 (M − Boc). ^{1}H and ^{13}C NMR were identical to those reported.[39]

2-Amino-2-phenylethyl Pivalate (21). To a solution of **10a** (161 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) was added TFA (1 mL) at rt. The mixture was stirred for 30 min and concentrated in vacuo. The residual TFA was removed by three-time azeotropic distillation with toluene. The residue, containing a TFA salt of the title compound, was dissolved in Et_2O (2 mL) and poured into stirred 10% NaOH cooled in an ice−water bath. The whole was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over K_2CO_3, and concentrated in vacuo to give the title compound (99.6 mg, 90%) as pale orange oil: ^{1}H NMR 1.19 (s, 9H), 1.59 (br s, 2H), 4.05 (dd, J = 7.5, 10.0, 1H), 4.23 (dd, J = 4.5, 10.0, 1H), 4.26 (dd, J = 4.5, 7.5, 1H), 7.27−7.42 (m, 5H); ^{13}C NMR 27.0 (CH_3), 38.6 (C), 54.5 (CH), 69.6 (CH_2), 126.6 (CH), 127.5 (CH), 128.4 (CH), 141.6 (C), 178.0 (C); IR 3379, 2970, 1728, 1481; FABMS m/z 222 (M + H), 205 (M − NH$_2$), 165 (M − t-Bu); HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{13}H_{20}NO_2$, 222.1489, found 222.1488.

Migration of a Pivaloyl Group: 2-Amino-2-phenylethyl Pivalate. The above procedure was followed to obtain a TFA salt of **21**, to which was added 10% NaOH (5 mL). The whole was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over K_2CO_3 and concentrated in vacuo to give a mixture of **21** and the title compound (89:11 based on ^{1}H NMR) as orange oil. The oil was dissolved in Et_2O (5 mL), and the solution was extracted three times with 10% HCl. The combined aqueous layers were washed three times with $CHCl_3$, basified with 10% NaOH, and extracted three times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (55.8 mg, 25%) as white solids of mp 143−144 °C: IR 3271, 2962, 1627, 1535; FABMS m/z 222 (M + H), 190 (M − CH$_2$OH), 136 (M − Piv). ^{1}H and ^{13}C NMR were identical to those reported for the (*S*)-enantiomer.[40]

2-Amino-2-phenylethanol (22). To a solution of **10a** (161 mg, 0.50 mmol) in dioxane (6 mL) was added 3 M HCl (12 mL). The mixture was heated under reflux for 3 h, cooled to rt, basified with 10% NaOH, and extracted three times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography (EtOAc/EtOH 1/1) to afford the title compound (48.4 mg, 69%) as white solids of mp 58−59 °C (lit.[41] 48.0−49.5 °C): IR 3333, 2870, 1605; FABMS m/z 138 (M + H). ^{1}H and ^{13}C NMR were identical to those reported.[42]

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■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Reviews on radical addition to C═N bonds: (a) Miyabe, H.; Yoshioka, E.; Kohtani, S. *Curr. Org. Chem.* **2010**, *14*, 1254. (b) Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695. (c) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461. (d) Naito, T. *Heterocycles* **1999**, *50*, 505. (e) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. Recent examples of radical addition to C═N bonds: (f) Friestad, G. K.; Ji, A.; Korapala, C. S.; Qin, J. *Org. Biomol. Chem.* **2011**, *9*, 4039. (g) Prosperini, S.; Pastori, N.; Ghilardi, A.; Clerici, A.; Punta, C. *Org. Biomol. Chem.* **2011**, *9*, 3759. (h) Ueda, M.; Miyabe, H.; Torii, M.; Kimura, T.; Miyata, O.; Naito, T. *Synlett* **2010**, 1341. (i) Valpuesta, M.; Munoz, C.; Diaz, A.; Torres, G.; Suau, R. *Eur. J. Org. Chem.* **2010**, 1934.

(2) Reviews on ionic addition to C═N bonds: (a) Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (d) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541. (e) Bräse, S.; Baumann, T.; Dahmen, S.; Vogt, H. *Chem. Commun.* **2007**, 1881. (f) Yamada, K.; Tomioka, K. *Chem. Rev.* **2008**, *108*, 2874.

(3) Yamada, K.; Nakano, M.; Maekawa, M.; Akindele, T.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3805.

(4) (a) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc: Toronto, Canada, 1999. (b) Kocieński, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: Stuttgart, Germany, 2005.

(5) Ethylene dipivalate was always observed in crude products of Et_3B−air-mediated radical reactions with **1**, indicating that **8** exists in the reaction mixtures in such a concentration that radical−radical coupling reactions can take place.

(6) (a) Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T. Y.; Satish, A. V.; Whang, Y. E. *J. Org. Chem.* **1990**, *55*, 3330. (b) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218. (c) Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 2964.

(7) (a) Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951. (b) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176. (c) Kim, S.; Song, H.-J.; Choi, T.-L.; Yoon, J.-Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2524.

(8) (a) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *122*, 8329. (b) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131.

(9) (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189. (b) Cannella, R.; Clerici, A.; Pastori, N.; Regolini, E.; Porta, O. *Org. Lett.* **2005**, *7*, 645.

(10) Ueda, M.; Miyabe, H.; Miyata, O.; Naito, T. *Tetrahedron* **2009**, *65*, 1321.

(11) Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238.

(12) (a) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509. (b) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2006**, *71*, 2099.

(13) (a) Akindele, T.; Yamada, K.; Sejima, T.; Maekawa, M.; Yamamoto, Y.; Nakano, M.; Tomioka, K. *Chem. Pharm. Bull.* **2010**, *58*, 265. (b) Yamada, K.; Maekawa, M.; Yamamoto, Y.; Nakano, M.; Akindele, T.; Tomioka, K. *Tetrahedron Lett.* **2009**, *50*, 6040. (c) Yamada, K.; Maekawa, M.; Akindele, T.; Yamamoto, Y.; Nakano, M.; Tomioka, K. *Tetrahedron* **2009**, *65*, 903. (d) Yamada, K.; Maekawa, M.; Akindele, T.; Nakano, M.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 9535 and references therein.

(14) (a) Maury, J.; Feray, L.; Perfetti, P.; Bertrand, M. P. *Org. Lett.* **2010**, *12*, 3590. (b) Feray, L.; Bertrand, M. P. *Eur. J. Org. Chem.* **2008**, 3164. (c) Bazin, S.; Feray, L.; Vanthuyne, N.; Siri, D.; Bertrand, M. P. *Tetrahedron* **2007**, *63*, 77 and references therein.

(15) (a) Akindele, T.; Yamada, K.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345. (b) Bazin, S.; Feray, L.; Bertrand, M. P. *Chimia* **2006**, *60*, 260.

(16) (a) Valli, V. L. K.; Alper, H. *J. Org. Chem.* **1995**, *60*, 257. (b) Butler, D. C. D.; Alper, H. *Chem. Commun.* **1998**, 2575.

(17) Formation of ethylcarbamate from isocyanate in the presence of Et_3B and air: Yoshimitsu, T.; Matsuda, K.; Nagaoka, H.; Tsukamoto, K.; Tanaka, T. *Org. Lett.* **2007**, *9*, 5115.

(18) Acid-catalyzed addition of amide to imine has been reported: Zhu, S.; Dong, J.; Fu, S.; Jiang, H.; Zeng, W. *Org. Lett.* **2011**, *13*, 4914 and references therein.

(19) Bordwell, F. G.; Liu, W.-Z. *J. Am. Chem. Soc.* **1996**, *118*, 8777.

(20) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295.

(21) Similarly, formation of *N*-ethyl ethyl-adduct in the reaction of **2a** with triethylborane was reported in reference 10.

(22) Fernandez, A.-M.; Plaquevent, J.-C.; Duhamel, L. *J. Org. Chem.* **1997**, *62*, 4007.

(23) Love, B. E.; Raje, P. D.; Williams, T. C. II *Synlett* **1994**, 493.

(24) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429.

(25) Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Org. Lett.* **2006**, *8*, 979.

(26) Chen, J.-H.; Liu, S.-R.; Chen, K. *Chem.—Asian J.* **2010**, *5*, 328.

(27) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

(28) Aggarwal, V. K.; Ferrara, M.; O'Brien, C. J.; Thompson, A.; Jones, R. V. H.; Fieldhouse, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1635.

(29) Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem.—Eur. J.* **1997**, *3*, 1691.

(30) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031.

(31) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117.

(32) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925.

(33) Knochel, P.; Chou, T.; Jubert, C.; Rajagopal, D. *J. Org. Chem.* **1993**, *58*, 588.

(34) Keller, L.; Beaumont, S.; Liu, J.-M.; Thoret, S.; Bignon, J. S.; Wdzieczak-Bakala, J.; Dauban, P.; Dodd, R. H. *J. Med. Chem.* **2008**, *51*, 3414.

(35) Potapov, V. M.; Gracheva, R. A.; Okulova, V. F. *Zh. Org. Khim.* **1989**, *25*, 348.

(36) Helene, L.; Olivier, L. *Org. Lett.* **2005**, *7*, 4107.

(37) Yoakim, C.; Ogilvie, W. W.; Cameron, D. R.; Chabot, C.; Guse, I.; Hachué, B.; Naud, J.; O'Meara, J. A.; Plante, R.; Déziel, R. *J. Med. Chem.* **1998**, *41*, 2882.

(38) Herranz, E.; Biller, S. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1978**, *100*, 3596.

(39) O'Brien, P.; Osborne, S. A.; Parker, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2519.

(40) Davies, S. G.; Sanganee, H. J.; Szolcsanyi, P. *Tetrahedron* **1999**, *55*, 3337.

(41) Newman, M. S.; Edwards, W. M. *J. Am. Chem. Soc.* **1954**, *76*, 1840.

(42) Periasamy, M.; Sivakumar, S.; Reddy, M. N. *Synthesis* **2003**, 1965.