HETEROCYCLES, Vol. 76, No. 2, 2008, pp. 1301 - 1312. © The Japan Institute of Heterocyclic Chemistry
Received, 4th April, 2008, Accepted, 13th May, 2008, Published online, 19th May, 2008. COM-08-S(N)95

DEVELOPMENT OF COLUMN-FREE ALKOXYCARBONYL, ARYLOXYCARBONYL, AND ACYL TRANSFER REAGENTS

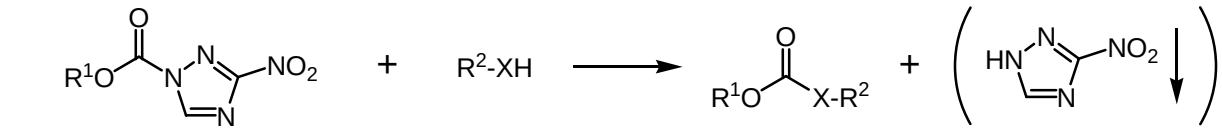
Mamoru Shimizu and Mikiko Sodeoka*

Synthetic Organic Chemistry Laboratory, RIKEN (The Institute of Physical and Chemical Research), 2-1, Hirosawa, Wako, 351-0198, Japan.
E-mail: sodeoka@riken.jp

Abstract – Easy-to-handle alkoxycarbonyl, aryloxycarbonyl, and acyl transfer reagents, which contain 3-nitro-1,2,4-triazole (NT) as a leaving group, were developed. With these reagents (NT reagents), which are stable nonhygroscopic crystalline materials, the reactions can be accomplished in about 5 min, and product can be isolated without tedious column chromatographic purification.

INTRODUCTION

In organic synthesis, protecting groups play an important role in permitting selective reaction at one reactive site in a multifunctional compound. For this purpose, many protecting groups have been, and are being, developed.[1] For example, carbamates are especially useful for the protection of amino groups. However, introduction of protecting groups does not always proceed selectively or in good yield. In some cases, products are difficult to separate from the reaction mixture. Furthermore, some commonly used introducing reagents are toxic and/or unstable, requiring careful handling and storage. Therefore, we have



NT reagents

R^1 = benzyl (**1a**), 2,2,2-trichloroethyl (**1b**), 9-fluorenylmethyl (**1c**), 2-(trimethylsilyl)ethyl (**1d**)

R^2-XH = amine, alcohol, or thiol

Scheme 1. Preparation of carbamates, carbonates, and thiocarbonates by using NT reagents

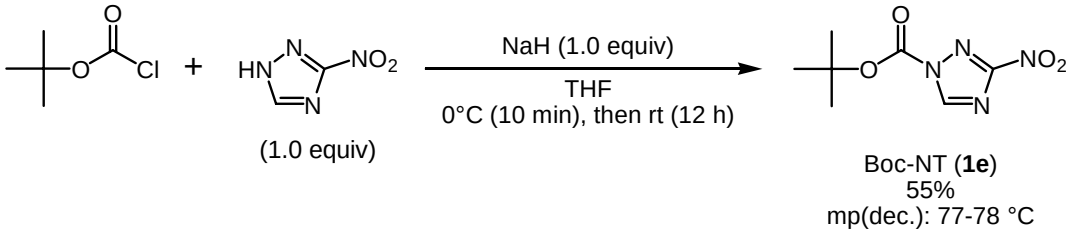
---

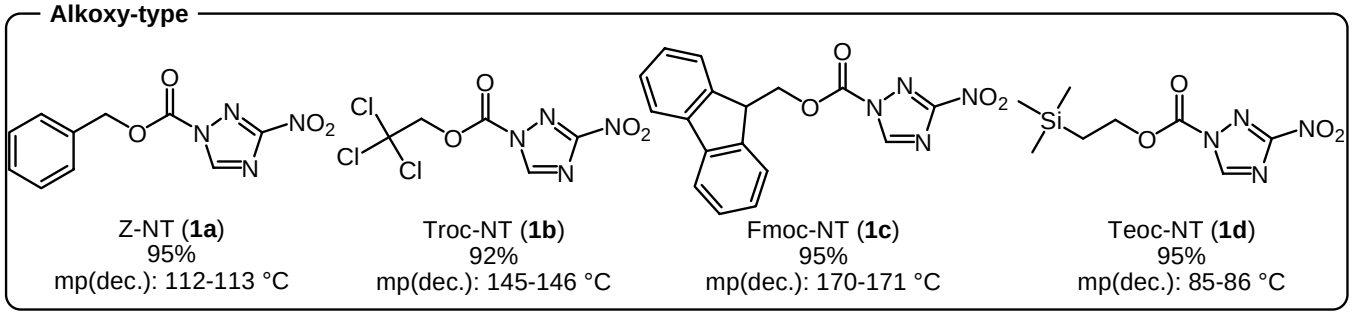
This paper is dedicated to Professor Ryoji Noyori on the occation of his 70th birthday.

recently reported a novel method to introduce protecting groups.[2] To provide a rapid and clean reaction system, we focused on the leaving group. We selected 3-nitro-1,2,4-triazole (NT),[3,4] as a crystalline compound that is expected to be a good leaving group, and developed novel reagents **1a-1d** (NT reagents). These reagents provide rapid access to protected substrates in highly pure forms without tedious purification (Scheme 1). Simply by dissolving amine and NT reagent in CH_2Cl_2 in an open flask, carbamate was quickly obtained (within 5 min) under neutral conditions, and highly pure products were obtained without the need for column chromatographic purification. To expand the scope of NT reagents, synthesis and reaction of other alkoxycarbonyl, aryloxycarbonyl, or acyl NT reagents were examined. In this paper, full details of these studies are reported.

RESULTS AND DISCUSSION

In addition to the previously reported NT reagents (**1a-1d**; their yields and melting points are summarized in Figure 1), we attempted to prepare a transfer reagent for *t*-butoxycarbonyl (Boc), which is widely used as an amino protecting group (Boc-NT (**1e**), Figure 1). Though $(Boc)_2O$ and Boc-Cl are usually used to protect amine with Boc, these reagents are susceptible to thermolysis and hydrolysis. Boc-Cl is especially unstable and must be prepared just before each use. By analogy with the reported NT reagents (**1a-1d**), Boc-NT was expected to be a stable crystalline solid. Therefore, Boc-NT was synthesized by the reaction





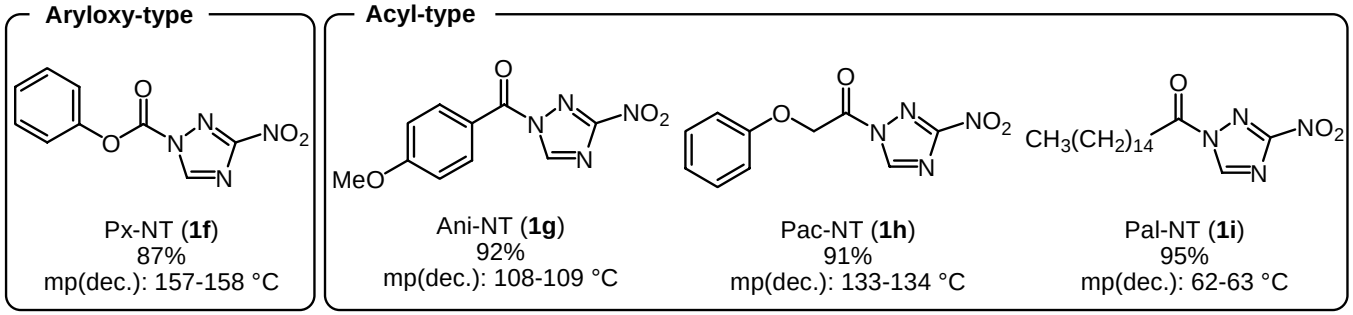


Figure 1. Synthesis of NT reagents

of Boc-Cl with the sodium salt of NT in THF, and as expected, Boc-NT was isolated as a crystalline material in 55% yield. The isolated yield was moderate due to the instability of Boc-Cl. Conversion yield based on recovered NT was almost quantitative. To introduce other commonly used protecting groups, we similarly synthesized aryloxycarbonyl- and acyl-type NT reagents, i.e., phenoxycarbonyl-NT (Px-NT, **1f**), anisoyl-NT (Ani-NT, **1g**), phenoxyacetyl-NT (Pac-NT, **1h**), and palmitoyl-NT (Pal-NT, **1i**) (Figure 1). In each case, pure NT reagent was obtained simply by filtration and subsequent recrystallization in excellent yield without difficulty. These newly synthesized compounds were all nonhygroscopic crystalline materials, stable at ambient temperature, and could be stored at 4 °C for a long period of time without decomposition.

With the various NT reagents in hand, we next examined their reactivity, using Z-NT as an example. First, to make a kinetic comparison of NT reagent with commercially available reagents, (*R*)-1-phenylethylamine (1 equiv) was allowed to react with Z-NT, benzyl chloroformate (Z-Cl), or benzyl succinimidyl carbonate (Z-OSu) in $CDCl_3$ at room temperature. The reactions were monitored by ^1H NMR (Figure 2). In the case of Z-Cl, the reaction was soon saturated at around 50%, and did not go to completion even after a prolonged reaction time. It is probably due to the formation of non-reactive (*R*)-1-phenylethylamine hydrochloride. For Z-OSu, the reaction was also rapid initially, but soon slowed down, and a long reaction time was required for completion. In contrast, reaction with Z-NT was rapid and reached completion in less than 5 min. Furthermore, the by-product NT is poorly soluble in $CDCl_3$, and simple filtration yielded the carbamate with >99% purity without any further purification.

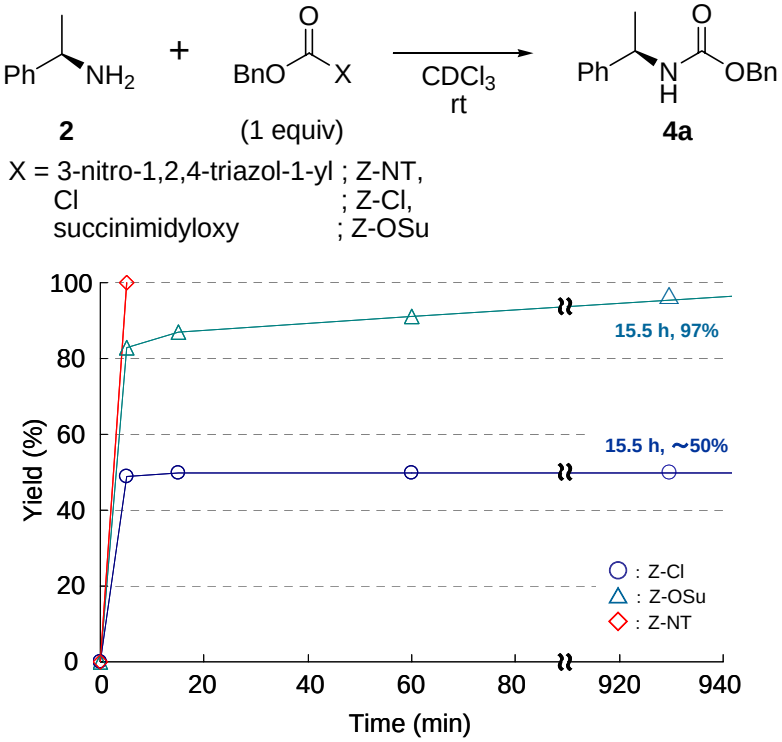
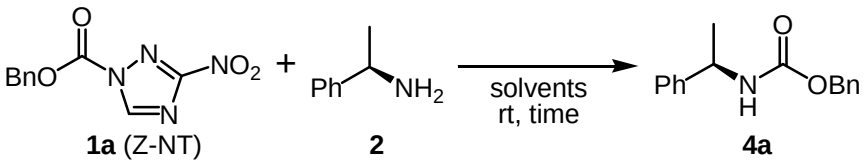


Figure 2. Comparison the reactivity of NT reagent with that of known reagents

Next, solvent effect was examined (Table 1). In addition to $CHCl_3$, CH_2Cl_2 was found to be a very effective solvent, because the by-product NT is almost insoluble in CH_2Cl_2. The reaction was completed within 5 min and highly pure product was obtained by simple filtration. Other organic solvents, such as THF and MeCN also worked without any problem. The reactions were completed in 15 min, affording

the carbamate in 94% and 96% yield, respectively (entries 2, 3). But in these cases, extraction with 5% aq. $NaHCO_3$ was necessary to remove NT from the reaction mixtures, since NT is soluble in THF and MeCN. In contrast, when EtOAc was used as a solvent, the reaction did not reach completion and only about 75% yield of carbamate was obtained even after a prolonged reaction time (entry 4). Methanol was not an appropriate solvent, because the NT reagents were almost insoluble in it at room temperature, and methyl carbonate was formed at elevated temperature.

Table 1. Preparation of carbamates using various solvents



1a (Z-NT) **2** **4a**

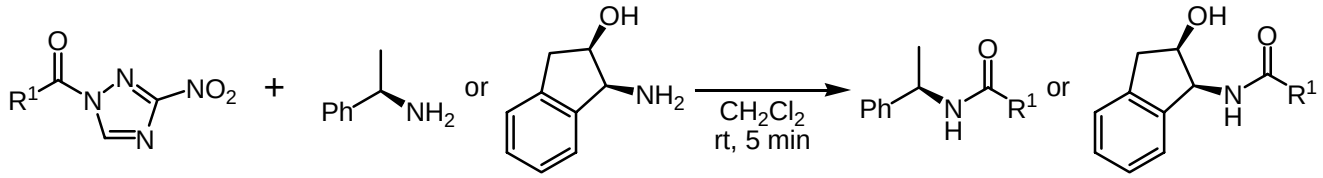
entry	solvent	time (min)	yield (%)
1	CH_2Cl_2	5	quant [a]
2	THF	15	94 [b]
3	MeCN	15	96 [b]
4	EtOAc	60	75 [c]

[a] Yield after filtration. [b] Yield after extraction with 5% aq. $NaHCO_3$. [c] Reaction did not go to completion.

Next, reactions of various NT reagents **1a**-**1i** with amine (**2**) and amino alcohol (**3**) were investigated. The results are summarized in Table 2. The reactions of amines with 1 equiv of **1a**-**1i** in CH_2Cl_2 proceeded quickly to give the corresponding carbamates and amides in >92% yield. In many cases, highly pure products (confirmed by ^1H and ^{13}C NMR analysis), were obtained by simple filtration and evaporation of CH_2Cl_2 (method A). Depending on the solubility of the products in CH_2Cl_2, they were sometimes contaminated with a small amount of NT. Though NT is almost insoluble in CH_2Cl_2, thorough washing with a considerable amount of CH_2Cl_2 to dissolve the products might also result in the dissolution of small amount of NT. In such cases, washing with 5% aq. $NaHCO_3$ was an effective way to remove the contaminating NT (method B), yielding highly pure (>99%) products without column chromatographic purification. In some cases (entries 4, 5, 13, 17), the reaction did not go to completion even after a prolonged reaction time. The details remain obscure, but we speculate that the reason for this may be partial formation of an insoluble salt between amine and NT. To prevent the formation of such non-reactive species, the use of a biphasic system (CH_2Cl_2 / 5% aq. $NaHCO_3$ (1:1, v/v)) was effective (method C), and the reaction was completed within 5 min in each case. After washing with 5% aq. $NaHCO_3$ and evaporation of the solvent, highly pure (>99%) products were obtained in 96-94% yield without column chromatographic purification. A noteworthy feature of the NT reagents is that they react selectively with the amino group of amino alcohol. Even when an excess amount of NT reagent (5 equiv) was used, no reaction with alcohol was seen under these conditions, even with primary alcohol.

Next, to demonstrate the usefulness of the NT reagents as esterification reagents, reaction of chloramphenicol (**6**) with Pal-NT (**1i**) was investigated. Palmitic acid is one of the most common saturat-

Table 2. Reactions of **1a-1i** with amines



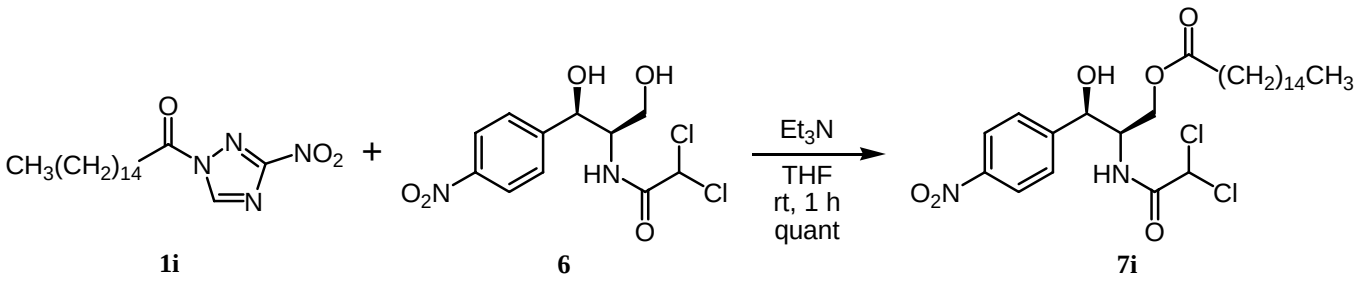
1a-1i **2** **3** **4a-4i** **5a-5i**

entry	reaction with amine **2**				entry	reaction with amine **3**			
	reagent	product	method [a]	yield (%)		reagent	product	method [a]	yield (%)
1	Z-NT (**1a**)	**4a**	A	quant	10	Z-NT (**1a**)	**5a**	A	95
2	Troc-NT (**1b**)	**4b**	A B	quant [b] 88	11	Troc-NT (**1b**)	**5b**	A B	95 [b] 92
3	Fmoc-NT (**1c**)	**4c**	A B	quant [b] 96	12	Fmoc-NT (**1c**)	**5c**	A B	quant [b] 94
4	Teoc-NT (**1d**)	**4d**	C	95	13	Teoc-NT (**1d**)	**5d**	C	96
5	Boc-NT (**1e**)	**4e**	C	94	14	Boc-NT (**1e**)	**5e**	A	92
6	Px-NT (**1f**)	**4f**	A B	quant [b] 95	15	Px-NT (**1f**)	**5f**	A B	quant [b] 90
7	Ani-NT (**1g**)	**4g**	A B	quant [b] 92	16	Ani-NT (**1g**)	**5g**	A B	quant [b] 92
8	Pac-NT (**1h**)	**4h**	A B	quant [b] quant	17	Pac-NT (**1h**)	**5h**	C	94
9	Pal-NT (**1i**)	**4i**	A B	quant [b] 93	18	Pal-NT (**1i**)	**5i**	A B	quant [b] 92

[a] See experimental section. [b] Containing a small amount of NT (<10%).

ed fatty acids in animals and plants, and palmitate-modified biologically/physiologically active substances and antibiotics are used as drugs and cosmetics.[5,6] Chloramphenicol (**6**)[6,7] is a natural antibiotic derived from a strain of *Streptomyces* isolated by Gottlieb. Though use of **6** for human therapy is limited (it can cause aplastic anemia), it is used in eye drops or in ointment to treat bacterial conjunctivitis. In the case of oral administration, **6** is usually used as the water-insoluble 3-*O*-palmitate ester in order to adjust plasma concentration. The methods previously reported for the synthesis of 3-*O*-palmitate ester of **6** are either enzymatic[8-10] or chemical,[11] but in each case, carefully controlled reaction conditions and a long reaction time, or tedious purification steps are essential. On the other hand, our new NT reagent made it possible to obtain the product more conveniently. As mentioned above, **1** did not react with alcohols in the absence of base; however, a stoichiometric amount of **1i** selectively and quickly reacted with the primary alcohol of **6** in the presence of Et_3N to afford **7i** in a highly pure form (>95% purity) without column chromatographic purification (Scheme 2).

In conclusion, we have developed new reagents which enable rapid and easy preparation of highly pure carbamates, amides, and esters without the need for column chromatographic purification. Characteristic



1i **6** **7i**

Scheme 2. Selective palmitoylation of chloramphenicol

features of these newly introduced reagents are: (1) they are highly stable and can be stored for long periods without decomposition; (2) since they are nonhygroscopic crystalline materials, they are easy to handle and weigh accurately even on a milligram scale; (3) the reactions can be carried out even in an open flask; (4) the co-product NT can be recycled; (5) generally, carbamate and amide formation proceeds quickly (within 5 min) under neutral conditions; (6) highly pure carbamates and amides can be obtained without tedious column chromatographic purification. An NT reagent also enabled simple, regioselective esterification of chloramphenicol in a highly pure form. In addition to the examples of acylation reported here, NT reagents are expected to be especially useful for the synthesis of polyfunctionalized compounds that are difficult to access by conventional procedures.[12]

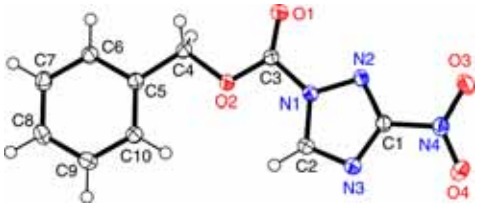
EXPERIMENTAL

General Information. ^{1}H NMR spectra were obtained at 300, 400, or 500 MHz with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were obtained at 100 or 125 MHz with $CDCl_3$ as an internal standard (δ 77.0) in $CDCl_3$, with CD_3CN as an internal standard (δ 1.3) in CD_3CN, or with CD_3COCD_3 as an internal standard (δ 29.8) in CD_3COCD_3. Thin layer chromatography (TLC) was performed on TLC plates silica gel 60 F254 (Merck, No. 5715). Silica gel column chromatography was carried out by using silica gel 60N (Cica-Reagent, 40-100 μm). Organic solvents were purified and dried by usual procedures.

Benzyl 3-nitro-1*H*-1,2,4-triazole-1-carboxylate (Z-NT: 1a).

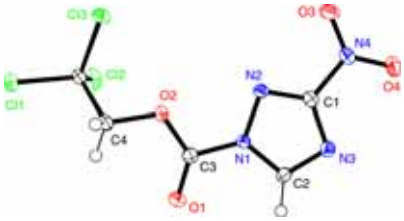
To powdery NaH (0.250 g, 10.4 mmol), prepared from NaH dispersion in mineral oil prior to use, was added a solution of 3-nitro-1,2,4-triazole (1.19 g, 10.4 mmol), which had been dried by repeated coevaporations with pyridine and toluene, in THF (30 mL) at 0 °C under an Ar atmosphere. The mixture was stirred for 10 min, then Z-Cl (1.48 mL, 10.4 mmol) was added dropwise with stirring. After 30 min, the solution was allowed to warm to rt and stirring was continued for 12 h. The insoluble solid was filtered off and thoroughly washed with EtOAc (ca. 50 mL). The combined filtrate was evaporated to give a residue, which was recrystallized from EtOAc to afford Z-NT (2.44 g, 95%) as a light yellow crystalline

solid. mp 112-113 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (1H, s), 7.55-7.42 (5H, m), 5.54 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 147.1, 146.0, 132.4, 129.9, 129.4, 129.0, 72.5; IR (neat) ν 3142, 1787, 1556, 1514, 1385, 1292, 1227, 1175, 1014 cm^{-1}; Anal. Calcd for $C_{10}H_8N_4O_4 \cdot 1/4H_2O$: C, 47.53; H, 3.39; N, 22.17. Found: C, 47.37; H, 3.32; N, 22.04. The crystallographic data of **1a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary no. CCDC 675625. This data can be obtained online free of charge. X-Ray structure of Z-NT (**1a**) is as follows.



2,2,2-Trichloroethyl 3-nitro-1*H*-1,2,4-triazole-1-carboxylate (Troc-NT: 1b).

This compound was obtained from Troc-Cl as a pale yellow crystalline solid (92% yield) in a similar manner to Z-NT. mp 145-146 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (1H, s), 5.17 (2H, s); ^{13}C NMR (125 MHz, CD_3CN) δ 164.2, 149.6, 146.1, 94.0, 78.0; IR (neat) ν 3114, 1783, 1553, 1523, 1438, 1390, 1276, 1238, 1019 cm^{-1}; Anal. Calcd for $C_5H_3Cl_3N_4O_4$: C, 20.75; H, 1.04; N, 19.36. Found: C, 20.68; H, 1.07; N, 19.65. The crystallographic data of **1b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary no. CCDC 675624. This data can be obtained online free of charge. X-Ray structure of Troc-NT (**1b**) is as follows.



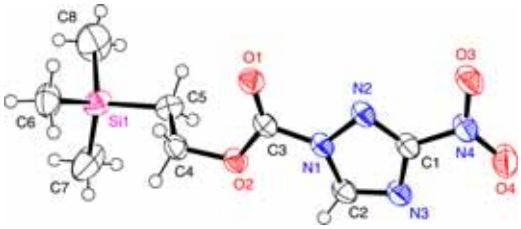
9-Fluorenylmethyl 3-nitro-1*H*-1,2,4-triazole-1-carboxylate (Fmoc-NT: 1c).

This compound was obtained from Fmoc-Cl as a pale yellow crystalline solid (95% yield) in a similar manner to Z-NT. mp 170-171 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (1H, s), 7.80 (2H, d, J = 7.3 Hz), 7.64 (2H, d, J = 7.3 Hz), 7.45 (2H, t, J = 7.3 Hz), 7.35 (2H, t, J = 7.3 Hz), 4.86 (2H, d, J = 7.1 Hz), 4.45 (1H, t, J = 7.1 Hz); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 164.1, 149.1, 147.1, 143.7, 142.1, 129.0, 128.2, 126.2, 121.0, 72.4, 47.1; IR (neat) ν 3130, 1789, 1563, 1512, 1386, 1360, 1293, 1263 cm^{-1}; Anal. Calcd for $C_{17}H_{12}N_4O_4$: C, 60.71; H, 3.60; N, 16.66. Found: C, 60.57; H, 3.69; N, 16.87.

2-(Trimethylsilyl)ethyl 3-nitro-1*H*-1,2,4-triazole-1-carboxylate (Teoc-NT: 1d).

This compound was obtained from Teoc-Cl[13] as a light yellow crystalline solid (96% yield) in a similar manner to Z-NT (instead of recrystallization, reprecipitation from *n*-hexane-EtOAc). mp 85-86 °C (dec.); ^{1}H NMR (500 MHz, CD_3CN) δ 8.97 (1H, s), 4.67-4.60 (2H, m), 1.27-1.20 (2H, m), 0.08 (9H, s); ^{13}C NMR (125 MHz, CD_3CN) δ 164.0, 148.8, 147.2, 70.8, 17.9, -1.7; IR (neat) ν 3137, 2958, 1777, 1564,

1514, 1290, 1230, 1170, 1015 cm^{-1}. The crystallographic data of **1d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary no. CCDC 675623. This data can be obtained online free of charge. X-Ray structure of Teoc-NT (**1d**) is as follows.



***t*-Butyl 3-nitro-1*H*-1,2,4-triazole-1-carboxylate (Boc-NT: 1e).**

This compound was obtained from Boc-Cl as a pale yellow crystalline solid (55% yield) in a similar manner to Z-NT. mp 77-78 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (1H, s), 1.71 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 146.6, 144.0, 90.5, 27.7. HRMS (FAB^+) *m/z* Calcd for $C_7H_{10}N_4NaO_4$ $[M+Na]^+$ 237.0600, found 237.0599; IR (neat) *ν* 3159, 2988, 1776, 1553, 1513, 1367, 1281, 1144, 1014 cm^{-1}.

3-Nitro-1-phenoxycarbonyl-1*H*-1,2,4-triazole (Px-NT: 1f).

This compound was obtained from phenoxycarbonyl chloride as a pale yellow crystalline solid (87% yield) in a similar manner to Z-NT. mp 157-158 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (1H, s), 7.56-7.49 (2H, m), 7.44-7.39 (1H, m), 7.37-7.32 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 149.3, 147.3, 144.6, 130.0, 127.7, 120.3. HRMS (FAB^+) *m/z* Calcd for $C_9H_7N_4O_4$ $[M+H]^+$ 235.0467, found 235.0469; IR (neat) *ν* 3126, 1779, 1553, 1513, 1482, 1437, 1370, 1239, 1186 cm^{-1}.

1-Anisoyl-3-nitro-1*H*-1,2,4-triazole (Ani-NT: 1g).

This compound was obtained from anisoyl chloride as a pale yellow crystalline solid (92% yield) in a similar manner to Z-NT. mp 108-109 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (1H, s), 8.36 (2H, d, *J* = 9.0 Hz), 7.06 (2H, d, *J* = 9.0 Hz), 3.95 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 162.5, 161.4, 146.7, 134.7, 119.3, 114.3, 55.7; MS (MALDI TOF) *m/z* Calcd for $C_{10}H_8N_4NaO_4$ $[M+Na]^+$ 271.04, found 271.00; IR (neat) *ν* 3139, 1721, 1589, 1510, 1424, 1346, 1288, 1240, 1173, 1012 cm^{-1}.

3-Nitro-1-phenoxyacetyl-1*H*-1,2,4-triazole (Pac-NT: 1h).

This compound was obtained from phenoxyacetyl chloride as a pale yellow crystalline solid (% yield) in a similar manner to Z-NT. mp 133-134 °C (dec.); ^{1}H NMR (400 MHz, CD_3CN) δ 9.10 (1H, s), 7.37-7.29 (2H, m), 7.08-6.98 (3H, m), 5.49 (2H, s); ^{13}C NMR (100 MHz, CD_3CN) δ 166.3, 163.4, 157.9, 146.7, 130.3, 122.7, 115.4, 66.7; MS (MALDI TOF) *m/z* Calcd for $C_{10}H_8N_4NaO_4$ $[M+Na]^+$ 271.04, found 270.90; IR (neat) *ν* 3133, 2905, 1788, 1562, 1491, 1421, 1393, 1345, 1287, 1233, 1195 cm^{-1}.

3-Nitro-1-palmitoyl-1*H*-1,2,4-triazole (Pal-NT: 1i).

This compound was obtained from parmitoyl chloride as a pale yellow crystalline solid (95% yield) in a similar manner to Z-NT. mp 62-63 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (1H, s), 3.18 (2H, t, *J* =

7.4 Hz), 1.82 (2H, quintet, *J* = 7.4 Hz), 1.47-1.22 (24H, m), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 162.5, 144.4, 34.3, 32.0, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.2, 28.9, 23.6, 22.8, 14.3. HRMS (FAB$^+$) *m/z* Calcd for $C_{18}H_{32}N_4NaO_3$ $[M+Na]^+$ 375.2372, found 375.2375; IR (neat) ν 3139, 2913, 2849, 1768, 1565, 1512, 1471, 1383, 1294, 1182 cm^{-1}.

General Procedure for the Preparation of Carbamate and Amide.

Method A

To a solution of **1** (100 μmol) in CH_2Cl_2 (500 μL) was slowly added substrate (100 μmol) at rt and the solution was stirred for 5 min. Insoluble NT was filtered off, and the filtrate was evaporated to give the desired compound.

Method B

To a solution of **1** (100 μmol) in CH_2Cl_2 (500 μL) was slowly added substrate (100 μmol) at rt and the solution was stirred for 5 min, then quenched with 5% aq. $NaHCO_3$ and diluted with CH_2Cl_2. The organic layer was washed with 5% aq. $NaHCO_3$ (3 mL x 3). The aqueous layer was back-extracted with CH_2Cl_2 (3 mL x 2), and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the desired compound.

Method C

To a solution of **1** (100 μmol) in CH_2Cl_2 (500 μL) and 5% aq. $NaHCO_3$ (500 μL) was slowly added substrate (100 μmol) at rt and the solution was stirred for 5 min. The organic layer was washed with 5% aq. $NaHCO_3$ (3 mL x 3). The aqueous layer was back-extracted with CH_2Cl_2 (3 mL x 2), and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the desired compound.

***t*-Butyl (*R*)-1-phenylethylcarbamate (4e).**

This compound was prepared by *Method C*: 94% yield; white powder. mp 81-82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.19 (5H, m), 4.92-4.67 (2H, m), 1.57-1.29 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 143.8, 128.4, 126.9, 125.7, 79.4, 50.2, 28.5, 22.8; MS (FAB) *m/z* Calcd for $C_{13}H_{19}NNaO_2$ $[M+Na]^+$ 244.13, found 243.95; IR (neat) ν 3382, 2983, 1687, 1514, 1448, 1363, 1311, 1245, 1170, 1059 cm^{-1}.

Phenyl (*R*)-1-phenylethylcarbamate (4f).

This compound was prepared by *Method A*: quantitative yield; *Method B*: 95% yield; white solid. mp 75-76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.06 (10H, m), 5.33 (1H, brs), 4.91 (1H, quintet, *J* = 7.0 Hz), 1.55 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 150.7, 142.8, 129.1, 128.6, 127.3, 125.9, 125.1, 121.4, 51.0, 22.3; MS (MALDI TOF) *m/z* Calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.12, found 241.93; IR (neat) ν 3319, 1711, 1530, 1493, 1207, 1032 cm^{-1}.

4-Methoxy-*N*-[(*R*)-1-phenylethyl]benzamide (4g).

This compound was prepared by *Method A*: quantitative yield; *Method B*: 92% yield; white powder. mp 154-155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* = 8.8 Hz), 7.44-7.21 (5H, m), 6.88 (2H, d, *J* = 8.8 Hz), 6.40 (1H, brd, *J* = 6.8 Hz), 5.31 (1H, quintet, *J* = 6.8 Hz), 3.82 (3H, s), 1.57 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 161.8, 143.1, 128.6, 128.5, 127.1, 126.7, 126.1, 113.5, 55.4, 49.1, 21.9; MS (MALDI TOF) *m/z* Calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.13, found 256.00; IR (neat) ν 3334, 1625, 1607, 1531, 1502, 1255, 1175, 1026 cm^{-1}.

2-Phenoxy-*N*-[(*R*)-1-phenylethyl]acetamide (4h).

This compound was prepared by *Method A*: quantitative yield; *Method B*: quantitative yield; white solid. mp 73-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.24 (7H, m), 7.07-7.01 (1H, m), 6.95-6.90 (2H, m), 6.82 (1H, d, *J* = 7.3 Hz), 5.25 (1H, quintet, *J* = 7.3 Hz), 4.53 (1H, d, *J* = 14.6 Hz), 4.48 (1H, d, *J* = 14.6 Hz), 1.54 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 156.9, 142.5, 129.6, 128.5, 127.3, 125.9, 122.0, 114.6, 67.4, 48.3, 21.9; MS (MALDI TOF) *m/z* Calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.13, found 256.00; IR (neat) ν 3295, 3063, 3023, 2974, 2936, 1659, 1599, 1529, 1493, 1442, 1239, 1060 cm^{-1}.

***N*-[(*R*)-1-Phenylethyl]palmitamide (4i).**

This compound was prepared by *Method A*: quantitative yield; *Method B*: 93% yield; white solild. mp 79-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.22 (5H, m), 5.78 (1H, brd, *J* = 7.1 Hz), 5.13 (1H, quintet, *J* = 7.1 Hz), 2.16 (2H, t, *J* = 7.7 Hz), 1.67-1.56 (2H, m), 1.48 (3H, d, *J* = 7.1 Hz), 1.34-1.18 (24H, m), 0.88 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 143.1, 128.4, 127.1, 126.0, 48.5, 37.0, 32.0, 29.8, 29.7, 29.7, 29.6, 29.4, 29.4, 25.8, 22.8, 21.8, 14.2; MS (MALDI TOF) *m/z* Calcd for $C_{24}H_{42}NO$ $[M+H]^+$ 360.33, found 360.30; IR (neat) ν 3308, 2916, 2849, 1641, 1547 cm^{-1}.

***t*-Butyl (2*R*,3*S*)-2,3-dihydro-2-hydroxy-1*H*-inden-3-ylcarbamate (5e).**

This compound was prepared by *Method A*: 92% yield; colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (4H, m), 5.19-5.02 (2H, m), 4.63-4.56 (1H, m), 3.13 (1H, dd, *J* = 16.6, 4.9 Hz), 2.93 (1H, brd, *J* = 16.6 Hz), 2.13 (1H, brs), 1.51 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 140.6, 139.6, 128.0, 127.0, 125.2, 124.3, 79.9, 73.7, 58.9, 39.5, 28.5; MS (MALDI TOF) *m/z* Calcd for $C_{14}H_{19}NNaO_3$ $[M+Na]^+$ 272.13, found 272.00; IR (neat) ν 3407, 2976, 2930, 1690, 1502, 1366, 1245, 1165, 1049 cm^{-1}.

Phenyl (2*R*,3*S*)-2,3-dihydro-2-hydroxy-1*H*-inden-3-ylcarbamate (5f).

This compound was prepared by *Method A*: quantitative yield; *Method B*: 90% yield; white solid. mp 111-112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.15 (9H, m), 5.80 (1H, d, *J* = 8.6 Hz), 5.14 (1H, dd, *J* = 8.6, 5.1 Hz), 4.62-4.55 (1H, m), 3.12 (1H, dd, *J* = 16.6, 5.1 Hz), 2.91 (1H, dd, *J* = 16.6, 2.0 Hz), 2.37 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 150.7, 140.1, 139.5, 129.2, 128.2, 127.1, 125.3, 125.2, 124.4, 121.4, 73.4, 59.3, 39.6; MS (MALDI TOF) *m/z* Calcd for $C_{16}H_{15}NNaO_3$ $[M+Na]^+$ 292.09, found 292.00; IR (neat) ν 3380, 3295, 2943, 2915, 1703, 1536, 1492, 1207 cm^{-1}.

***N*-[(2*R*,3*S*)-2,3-Dihydro-2-hydroxy-1*H*-inden-3-yl]-4-methoxybenzamide (5g).**

This compound was prepared by *Method A*: quantitative yield; *Method B*: 92% yield; white solid. mp 156-157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.72 (2H, m), 7.32-7.17 (4H, m), 6.91-6.82 (3H, m), 5.50 (1H, dd, *J* = 8.1, 5.2 Hz), 4.65 (1H, dt, *J* = 5.2, 2.2 Hz), 3.82 (3H, s), 3.17 (1H, dd, *J* = 16.6, 5.2 Hz), 3.03 (1H, brs), 2.95 (1H, dd, *J* = 16.6, 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 162.0, 140.7, 139.9, 128.8, 128.0, 127.0, 126.1, 125.1, 124.5, 113.6, 73.6, 57.9, 55.4, 39.9; MS (MALDI TOF) *m/z* Calcd for $C_{17}H_{18}NO_3$ $[M+H]^+$ 284.13, found 284.01; IR (neat) ν 3404, 3256, 2943, 2913, 2841, 1608, 1536, 1502, 1251, 1180, 1025 cm^{-1}.

***N*-[(2*R*,3*S*)-2,3-Dihydro-2-hydroxy-1*H*-inden-3-yl]-2-phenoxyacetamide (5h).**

This compound was prepared by *Method C*: 94% yield; white powder. mp 176-177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.15 (7H, m), 7.04-6.98 (1H, m), 6.93-6.87 (2H, m), 5.47 (1H, dd, *J* = 8.7, 5.1 Hz), 4.65 (1H, brs), 4.63 (1H, d, *J* = 14.9 Hz), 4.58 (1H, d, *J* = 14.9 Hz), 3.18 (1H, dd, *J* = 16.6, 5.1 Hz), 2.96 (1H, dd, *J* = 16.6, 2.0 Hz), 2.17 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 156.9, 139.9, 139.8, 129.6, 128.3, 127.1, 125.2, 124.3, 122.0, 114.6, 73.6, 67.4, 57.2, 39.9; MS (MALDI TOF) *m/z* Calcd for $C_{17}H_{18}NO_3$ $[M+H]^+$ 284.13, found 284.00; IR (neat) ν 3351, 3223, 2948, 2905, 2030, 1643, 1599, 1536, 1497, 1243 cm^{-1}.

***N*-[(2*R*,3*S*)-2,3-Dihydro-2-hydroxy-1*H*-inden-3-yl]palmitamide (5i).**

This compound was prepared by *Method A*: quantitative yield; *Method B*: 92% yield; white solid. mp 120-121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.23 (4H, m), 6.09 (1H, brd, *J* = 8.1 Hz), 5.41 (1H, dd, *J* = 8.1, 5.4 Hz), 4.65 (1H, dt, *J* = 5.4, 2.4 Hz), 3.19 (1H, dd, *J* = 16.5, 5.4 Hz), 2.95 (1H, dd, *J* = 16.5, 2.4 Hz), 2.31 (1H, brs), 2.30 (2H, t, *J* = 7.7 Hz), 1.75-1.60 (2H, m), 1.41-1.22 (24H, m), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 140.5, 139.7, 128.2, 127.1, 125.2, 124.4, 73.8, 57.5, 39.8, 37.0, 32.0, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 26.0, 22.8, 14.3; MS (MALDI TOF) *m/z* Calcd for $C_{25}H_{42}NO_2$ $[M+H]^+$ 388.32, found 382.33; IR (neat) ν 3448, 3312, 2917, 2849, 1639, 1615, 1547, 1462, 1047 cm^{-1}.

***threo*-(1*R*,2*R*)-1-(4-Nitrophenyl)-2-(dichloroacetamido)-1,3-propandiol 3-palmitate (7i).**

To a mixture of Pal-NT (**1i**) (35.2 mg, 100 μmol) and chloramphenicol (**6**) (32.3 mg, 100 μmol) in THF (1 mL) was added Et_3N (28.0 μL, 200 μmol) at rt and the solution was stirred for 1 h. The organic layer was washed with 5% aq. $NaHCO_3$ (4 mL x 3). The aqueous layer was back-extracted with CH_2Cl_2 (4 mL x 1), and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give **7i** in quantitative yield (>95% purity). For measurement of analytical data, **7i** was further purified by preparative thin layer chromatography (MeOH : CH_2Cl_2 = 5 : 95). 94% yield; white powder. mp 88-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 8.6 Hz), 7.56 (2H, d, *J* = 8.6 Hz), 6.89 (1H, d, *J* = 8.6 Hz), 5.76 (1H, s), 5.06 (1H, brs), 4.49-4.36 (2H, m), 4.20 (1H, dd, *J* = 10.9, 5.9 Hz), 3.41 (1H, d,

J = 4.2 Hz), 2.37 (2H, t, *J* = 7.6 Hz), 1.68-1.58 (2H, m), 1.36-1.25 (24H, m), 0.88 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 164.1, 147.4, 146.8, 126.6, 123.5, 70.7, 66.0, 62.4, 54.2, 34.2, 32.0, 29.8, 29.7, 29.7, 29.5, 29.5, 29.3, 29.2, 25.0, 22.8, 14.3; MS (MALDI TOF) *m/z* Calcd for $C_{27}H_{42}Cl_2N_2NaO_6$ $[M+Na]^+$ 583.23, found 583.40; IR (neat) ν 3476, 3315, 2916, 2849, 1732, 1678, 1518, 1467, 1350 cm^{-1}.

ACKNOWLEDGEMENTS

We thank Dr. Daisuke Hashizume (RIKEN) for obtaining X-ray crystallographic data, and Ms. Kumiko Harata (RIKEN) for obtaining HRMS data. This work was partially supported by a Grant-in-Aid for Scientific Reseach on Priority Areas from MEXT, and Special Project Funding for Basic Science.

REFERENCES AND NOTES

1. P. G. M. Wuts and T. W. Greene, 'Greene's Protecting Groups in Organic Synthesis', 4th ed., Wiley, New Jersey, 2007.
2. M. Shimizu and M. Sodeoka, *Org. Lett.*, 2007, **9**, 5231.
3. In '*Physical Methods in Heterocyclic Chemistry*', ed. by A. R. Katritsky, Academic Press: New York, 1963; Vol. 1.
4. E. J. Brown, *Aust. J. Chem.*, 1969, **22**, 2251.
5. (a) P. P. Fu, Q. Xia, M. D. Boudreau, P. C. Howard, W. H. Tolleson, and W. G. Wamer, *Vitam Horm*, 2007, **75**, 223. (b) L. Sangkil, L. Jaehwi, and W. C. Young, *Biol. Pharm. Bull.*, 2007, **30**, 393.
6. L. S. Goodman and A. Gilman, 'The Pharmacological Basis of Therapeutics', 5th ed. MacMillan Publishing Co., Inc., New York, 1975, pp. 1194-1198.
7. 'The Merck Index', 14th ed., Merck & Co., Inc., NJ, 2006, p. 2078 entry 2077.
8. T. A. El-Kersh and J. R. Plourde, *J. Antibiot.*, 1976, **29**, 292.
9. Y. Nakagawa, *Chem. Abstr.*, 1980, **93**, 62307j.
10. G. Ottolina, G. Carrea, and S. Riva, *J. Org. Chem.*, 1990, **55**, 2366.
11. (a) W. H. Edgerton, *Chem. Abstr.*, 1954, **48**, 12793e. (b) I. Farmaceutici, *Chem. Abstr.*, 1957, **51**, 10575g. (c) M. T. Goebel, *Chem. Abstr.*, 1959, **53**, 1650h. (d) G. Glazer and J. Neudorffer, *Chem. Abstr.*, 1961, **55**, 14387f. (e) I. Villax, *Chem. Abstr.*, 1965, **63**, 14948h.
12. Teoc-NT (**1d**) is now commercially available from Tokyo Chemical Industry Co., Ltd.
13. M. Sekine, M. Tobe, T. Nagayama, and T. Wada, *Lett. Org. Chem.*, 2004, **1**, 179.