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Radical Amination of C(sp^3)−H Bonds Using *N*-Hydroxyphthalimide and Dialkyl Azodicarboxylate

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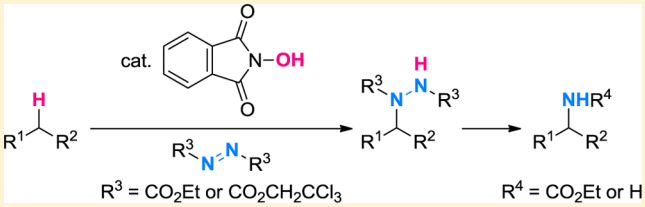
Supporting Information

ABSTRACT: A direct conversion of C(sp^3)−H bonds to C(sp^3)−N bonds has been achieved by utilizing catalytic *N*-hydroxyphthalimide (NHPI) and stoichiometric dialkyl azodicarboxylate. NHPI functions as a precursor of the electron-deficient phthalimide *N*-oxyl radical (PINO) to abstract hydrogens, and dialkyl azodicarboxylate acts as a trapping agent of the resultant carbon radical to generate the hydrazine derivatives. This C−H amination proceeds in a highly chemoselective manner with a wide applicability to functionalize benzylic, propargylic, and aliphatic C−H bonds. Furthermore, the obtained hydrazine compounds were readily converted to the corresponding carbamates or amines. Hence, the present protocol for direct introduction of the nitrogen functionality serves as a powerful tool for efficient construction of nitrogen-substituted natural products and pharmaceuticals.

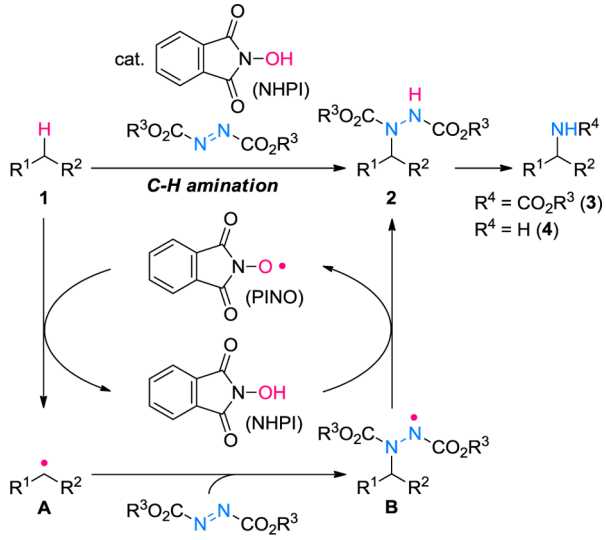


1. INTRODUCTION

C−H functionalization represents one of the ideal reactions in organic synthesis.[1] Direct C−H transformations eliminate preactivation steps for preparation of synthetic intermediates and thus dramatically simplify synthetic routes to multiply substituted molecules. Among such reactions, transformation of unreactive C(sp^3)−H bonds into C(sp^3)−C, C(sp^3)−O, and C(sp^3)−N bonds is especially desirable for efficient construction of highly complex natural products because their nonplanar architectures inevitably consist of a high ratio of sp^3-hybridized atoms and stereogenic centers.[2] However, selective functionalization of a particular C(sp^3)−H bond under mild conditions remains a challenging task given its intrinsic high bond dissociation energy and the ubiquity of other C(sp^3)−H bonds in organic substrates. Recently, we developed methodologies for chemoselective C(sp^3)−C and C(sp^3)−O formations from C(sp^3)−H bonds by employing highly reactive oxyl radicals as the key species to induce C(sp^3)−H cleavages.[3]

Amines and their derivatives are privileged structures for drug candidates and are prevalent in many natural products. As a result, development of C(sp^3)−N bond-forming reactions from C(sp^3)−H bonds is an intensively investigated field of the utmost importance.[4,5] We herein report an efficient method for direct intermolecular conversion of C(sp^3)−H bonds to C(sp^3)−N bonds by employing a reagent system composed of catalytic *N*-hydroxyphthalimide (NHPI)[6] and stoichiometric dialkyl azodicarboxylate (R^{3}O$_2$CN=NCO$_2$R^3) (Scheme 1). The present transformation is widely applicable to benzylic, propargylic and aliphatic C−H bonds (**1**), and generates the corresponding hydrazine derivatives **2** under neutral conditions in a highly chemoselective fashion. The derived adducts **2** were successfully converted to the corresponding carbamates **3** or amines **4**. Therefore, this methodology will serve as a powerful and versatile tool for efficient synthesis of complex nitrogen-substituted natural products and pharmaceutical agents.

Scheme 1. Radical C(sp^3)−H Amination Using *N*-Hydroxyphthalimide (NHPI) and Dialkyl Azodicarboxylate and Potential Reaction Mechanism



2. RESULTS AND DISCUSSION

Our envisioned catalytic cycle for the direct C(sp^3)−H amination is illustrated in Scheme 1. We planned to employ NHPI as an oxyl radical precursor and dialkyl azodicarboxylate

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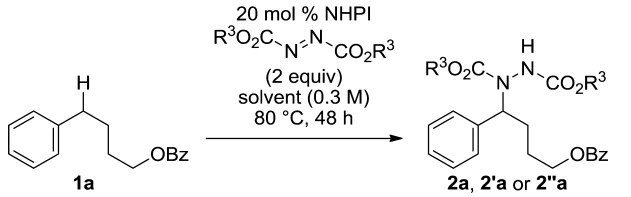
both as an oxidant and as a radical acceptor.[7,8] First, one-electron oxidation of NHPI with dialkyl azodicarboxylate would generate the phthalimide *N*-oxyl radical (PINO), a key reactive catalyst for C−H activation.[3e,6] Electron-deficient PINO then abstracts hydrogen from the electron-rich C(sp^3)−H bond of **1** to form carbon radical **A** and NHPI. Electron-rich carbon radical **A** would in turn react selectively with electron-deficient dialkyl azodicarboxylate, furnishing amidyl radical **B**. Abstraction of the hydrogen of NHPI by **B** would regenerate PINO and provide the hydrazinated product **2**. To realize the high-yielding transformation from **1** to **2**, high chemoselectivity of the C−H abstraction by PINO, facile trapping of **B** with dialkyl azodicarboxylate, and prevention of further abstraction of the Nα-CH bond of **2** by PINO would be the prerequisite factors. The generated **2** was planned to be converted to carbamate **3** or amine **4** through functional group manipulation.

First, we evaluated the outcome of the NHPI-catalyzed C(sp^3)-H amination of benzylic compound **1a** by varying two elements: the solvent and the alkyl group (R^3) of R^3O_2C−N=N-CO_2R^3 (Table 1). Treatment of **1a** with 20 mol % of NHPI

Table 1. Screening of Reaction Conditions for Direct Amination



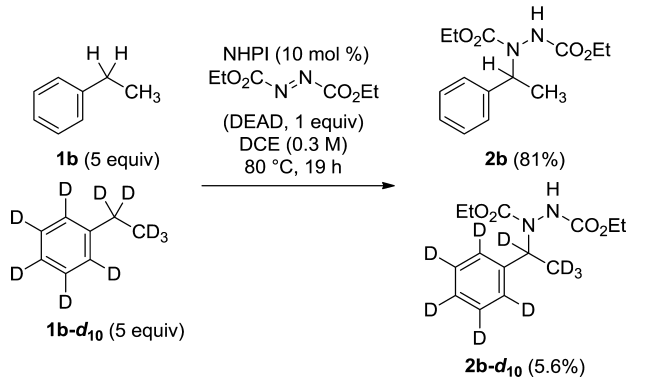
			yield[a] (%)	
entry	R^3	solvent	**2a**	recovery of **1a**
1	CH_2CH_3	CH_3CN	40[b]	54[b]
2	CH_2CH_3	*t*-BuOH	68[b]	22[b]
3	CH_2CH_3	EtOAc	92	
4	CH_2CH_3	benzene	88	
5	CH_2CH_3	DCE	93	
6[c]	CH_2CH_3	DCE	81[b]	8.2[b]
7[d]	CH_2CH_3	DCE	0[b]	100[b]
8	CH_2CCl_3	DCE	83 (**2'a**)	
9	$C(CH_3)_3$	DCE	57 (**2"a**)	35

[a]Isolated yield. [b]Yield was determined by NMR analysis of the crude mixture. [c]1.2 equiv of DEAD was used. [d]Absence of NHPI.

and 2 equiv of diethyl azodicarboxylate (DEAD) at 80 °C for 48 h in CH_3CN chemoselectively provided the desired product **2a** in 40% yield along with the recovered **1a** in 54% yield (entry 1).[3e,9] Although various solvents such as *t*-BuOH (entry 2), EtOAc (entry 3) and benzene (entry 4) were applicable for the present transformation, the most effective solvent in terms of the yield was found to be 1,2-dichloroethane (DCE) (93% yield, entry 5). While the product **2a** was formed in 81% yield in DCE even upon reducing the equivalents of DEAD from 2.0 to 1.2 (entry 6), no reaction occurred without addition of NHPI (entry 7).[10,11] The quantitative recovery of **1a** in the latter confirmed the requirement of NHPI for the present C−H functionalization. When bis(2,2,2-trichloroethyl) azodicarboxylate (TrocN=NTroc, BTCEAD) was used instead of DEAD (entry 8), the corresponding adduct **2'a** was obtained at the same level of efficiency (83% yield). However, the use of di-*tert*-butyl azodicarboxylate (BocN=NBoc) lowered the yield (57%) of **2"a**, presumably because the bulky *t*-Bu group decelerated the intermolecular reaction between the carbon radical and the azo compound. Nevertheless, consistent formation of the adducts under the varied solvents and reagents demonstrated the high reliability of the present system for C−H amination. In addition, stability of **2a**, **2'a** or **2"a** under the reaction conditions confirmed the low reactivity of the Nα−CH bond toward the abstraction, since it was proximal to the large and electron-withdrawing hydrazine group [−N(CO_2R^3)NHCO_2R^3].

The kinetic significance of the C−H abstraction step was probed by the following experiment (Scheme 2). Treatment of

Scheme 2. Kinetic Significance of the C−H Abstraction Step



DEAD with ethyl benzene **1b** (5 equiv) and its deuterated analogue **1b**-d_{10} (5 equiv) in the presence of 10 mol % of NHPI generated **2b** as the dominant product (81%) and **2b**-d_{10} as a minor product (5.6%).[12] Obviously, the product distribution of **2b** and **2b**-d_{10} was affected by the large rate difference of the C−H and C−D cleavages mediated by PINO (**1** → **A** in Scheme 1), indicating that the C−H abstraction is the product-determining step.[13] Therefore, it was expected that preferential C−H functionalization in the present protocol would occur at the most easily cleavable C−H bond in a given starting material, namely the C−H bond with the lowest bond dissociation energy. In fact, the C−H bond at the benzylic position generally possesses lower bond dissociation energy than the alkane C−H bonds, reflecting the high chemoselective transformation of **1a** to **2a**, **2'a** and **2"a**.

The secondary C−H bonds of the benzylic compounds **1a**−**n** having a variety of functional groups on the side chains were chemoselectively converted to the corresponding DEAD adducts **2a**−**n** (Table 2). Ethylbenzene **1b**, diphenylmethane **1c**, and *n*-butylbenzene **1d** were transformed to the aminated products **2b**, **2c**, and **2d**, respectively. As long as alcohol and amine functionalities were properly protected to avoid undesired nucleophilic reactions with highly electrophilic DEAD, the present reaction gave the expected benzylhydrazine derivatives in high yields. Namely, similar to benzoyl ester **2a**, TBDPS ether **2e**, phthaloyl (Phth) imide **2f**, and 2-nitrobenzenesulfonyl (Ns) amide **2g** were obtained. The reaction occurred without touching electrophilic methyl ester (**1h**), methyl ketone (**1i**), and cyanide (**1j**) moieties to provide **2h**, **2i**, and **2j**, respectively. Importantly, the C−H amination proceeded even in the presence of a free carboxyl group, resulting in formation of **2k**. The C−Br bond of **1l** was intact under these radical reaction conditions, furnishing the product **2l**. The benzoyloxy derivatives **2m** and **2n** were also formed, but the yield of **2n** (54%) was markedly lower than the yields of

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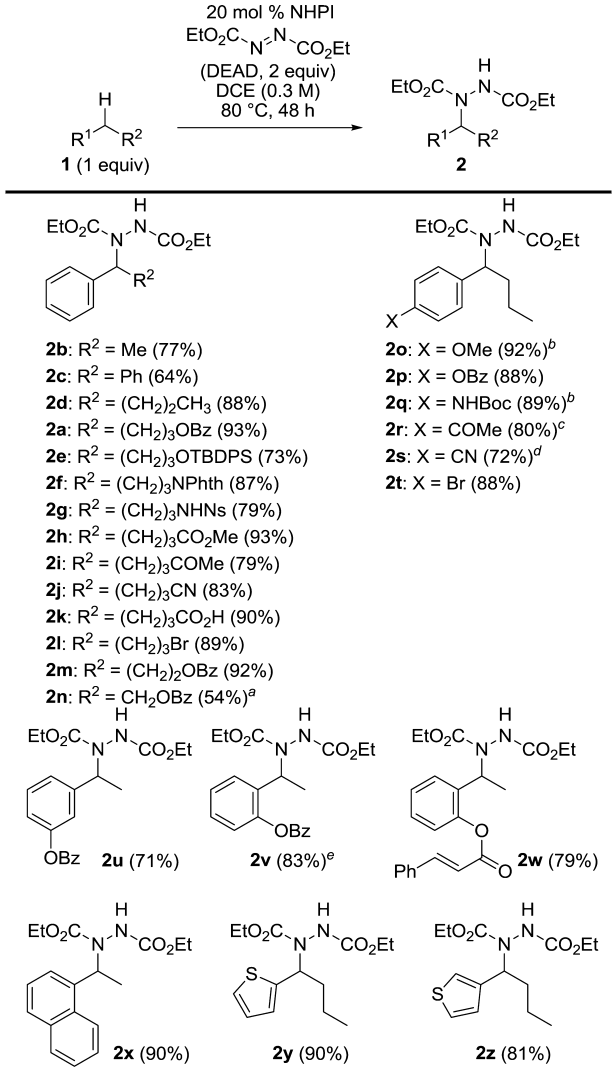
Table 2. Direct Amination of Secondary C−H Bonds at Benzylic Positions



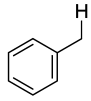
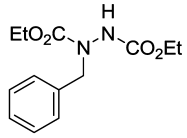
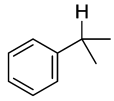
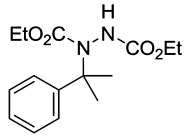
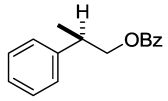
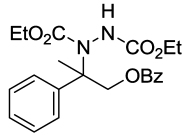
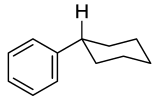
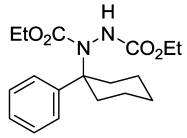
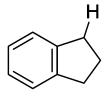
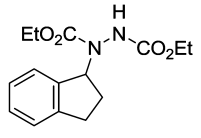
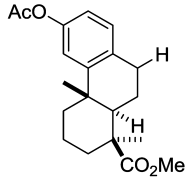
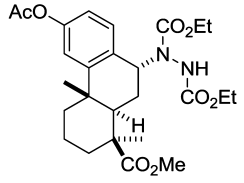
[a]Compound **1n** was recovered in 42% yield. [b]The reaction was complete within 24 h. [c]Compound **1r** was recovered in 12% yield. [d]Compound **1s** was recovered in 18% yield. [e]Compound **1v** was recovered in 12% yield.

2a (93%) and **2m** (92%). These results followed the general reactivity order of C−H transformations promoted by electrophilic reactants; electron-rich C−H bonds are more prone to be functionalized than electron-deficient ones.[3,14,15] Specifically, the lower yield of **2n** should originate from the more electron-poor nature of its benzylic C−H bond due to the shorter tether length between the benzyl methylene and the electron-withdrawing benzoyloxy group.

To further clarify the reactivity of the benzylic methylenes, the substrates **2o−z** having various aromatic rings were reacted using DEAD (Table 2). The *p*-methoxybutylbenzene derivative **2o** was formed in appreciably shorter time compared to formation of *p*-(benzoyloxy)butylbenzene derivative **2p**, again supporting the importance of the electron-richness of the benzylic C−H bonds for the reaction rates. While reaction acceleration was also observed for the Boc-protected aniline derivative **2q**, deceleration was noticed for derivatives with the electron-withdrawing acetyl (**2r**) and cyano (**2s**) functionalities. The C−Br bond on the aromatic ring (**1t**) was completely retained under the reaction conditions. The *m*- and *o*-substituted aromatic compounds afforded the corresponding adducts of the *m*-benzoyloxy **2u**, *o*-benzoyloxy **2v**, and *o*-cinnamoyloxy **2w** ethyl benzene derivatives. In addition, methylene groups adjacent to naphthalene and thiophene rings were smoothly functionalized as well to produce **2x**, **2y**, and **2z**. Clearly, formation of **2a−z** showed excellent functional group compatibility of the present benzylic C−H amination.

The broad scope of the present benzylic C−H amination was further demonstrated using a different set of substrates (Table 3). The primary C−H bond of **1aa** and the tertiary C−H bond of **1bb** were aminated using DEAD in the presence of catalytic

Table 3. Direct Benzylic C−H Amination Using Various Aromatic Compounds[a]

entry	starting material	product	yield, %
1	 **1aa**	 **2aa**	48[b]
2	 **1bb**	 **2bb**	92
3	 **1cc** (95% ee)	 **2cc** (11% ee)	46[c]
4	 **1dd**	 **2dd**	66
5[d]	 **1ee**	 **2ee**	72
6	 **1ff**	 **2ff**	62

[a]Reaction conditions: **1** (1 equiv), NHPI (20 mol %), DEAD (2 equiv), DCE (0.3 M), 80 °C, 48 h unless otherwise noted. [b]Compound **1aa** was recovered in 22% yield. [c]Compound **1cc** was recovered in 42% yield (93% ee). [d]DEAD (1.2 equiv) was employed.

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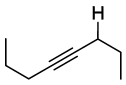
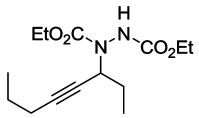
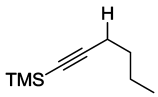
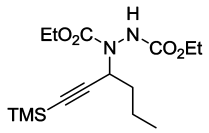
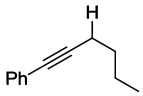
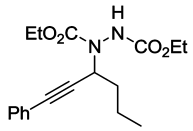
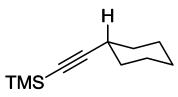
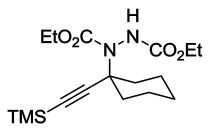
NHPI to produce **2aa** and **2bb**, respectively (entries 1 and 2). The yields of the aminated alkyl benzene derivatives **2aa** (48%), **2b** (Table 2, 77%), and **2bb** (92%) correlated to the number of the alkyl substituents at the reacting carbon, corroborating that the more electron-rich C−H bond was more easily functionalized.[3,14,15] The tertiary C−H bond of **1cc** (entry 3, Table 3) was functionalized similar to the secondary C−H bond of **2n** (Table 2) despite the increased steric interaction; however, its stereochemical information was lost during the radical reaction (95% ee → 11% ee).[16] Remarkably, a tetrasubstituted carbon center was introduced at the most hindered C−H bond on the cyclohexane ring of **1dd**, leading to **2dd** (entry 4). Moreover, the direct benzylic C−H amination occurred on fused carbocycles (entries 5 and 6). Thus, dihydroindene **1ee** was efficiently converted to the mono-DEAD adduct **2ee** using a reducing amount of DEAD (1.2 equiv). Finally, the C−H amination of more complex podocarpate derivative **1ff**[17] exhibited high chemoselectivity, delivering **2ff** as the sole stereoisomer. It is worthy of note that the C−H transformations in Tables 2 and 3 all took place at the benzylic position regardless of the steric environments and of the presence of other potentially reactive C−H bonds and polar functional groups.

We next investigated the direct C−H amination of propargylic compounds (Table 4).[18] Treatment of 4-octyne **1gg** (2 equiv) with DEAD (1 equiv) and a catalytic amount of NHPI chemoselectively afforded propargylic amine derivative **2gg** (entry 1). The reactions of both (trimethylsilyl)acetylene **1hh** and phenylacetylene **1ii** resulted in functionalization at their secondary C−H bonds, leading to the corresponding adducts **2hh** and **2ii** (entries 2 and 3). The tertiary C−H bond of cyclohexane structure **1jj** was also functionalized with similar efficiency to provide **2jj** with a tetrasubstituted carbon. Thus, the chemoselective propargylic C−H amination was achieved without affecting the C−C triple bond.

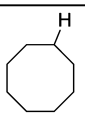
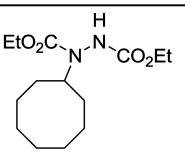
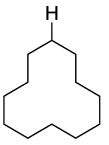
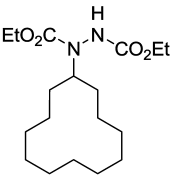
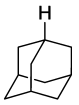
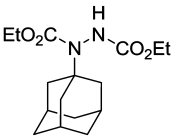
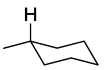
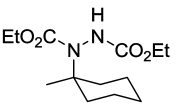
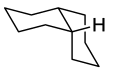
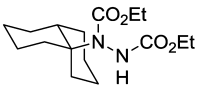
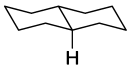
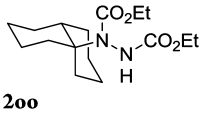
The protocol was then utilized for the direct amination of the C−H bonds of alkanes, which are known to be less reactive than those of benzylic and propargylic C−H bonds (Table 5). The secondary aliphatic C−H bonds of cyclooctane **1kk** and cyclododecane **1ll** underwent functionalization, providing the

Table 4. Direct Amination of Propargylic C−H Bonds[a]

entry	starting material	product	yield, %[b]
1[c]	 **1gg**	 **2gg**	69
2[d]	 **1hh**	 **2hh**	66
3[e]	 **1ii**	 **2ii**	67
4[d]	 **1jj**	 **2jj**	69

[a]Reaction conditions: **1** (2 equiv), NHPI (10 mol %), DEAD (1 equiv), DCE (0.3 M), 80 °C, 48 h unless otherwise noted. [b]Yields were calculated with respect to DEAD. [c]The reaction was complete within 24 h. [d]NHPI (20 mol %) was employed. [e]NHPI (30 mol %) was employed.

Table 5. Direct Amination of Aliphatic C−H Bonds[a]

entry	starting material	product	yield, %[b]
1[c]	 **1kk**	 **2kk**	87
2[d]	 **1ll**	 **2ll**	84
3[e]	 **1mm**	 **2mm**	74
4[f]	 **1nn**	 **2nn**	72
5[c,f]	 **1oo**	 **2oo**	74
6[f]	 **1pp**	 **2oo**	40

[a]Reaction conditions: **1** (5 equiv), NHPI (10 mol %), DEAD (1 equiv), DCE (0.3 M), 80 °C, 48 h unless otherwise noted. [b]Yields were calculated with respect to DEAD. [c]The reaction was complete within 24 h. [d]The reaction was complete within 36 h. [e]Compound **1mm** (2 equiv) was employed. [f]Compound **1** (10 equiv) was employed.

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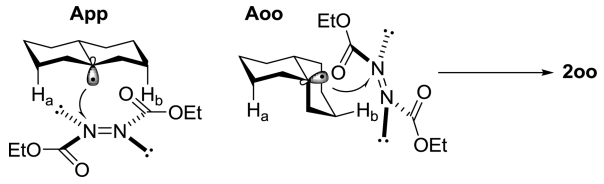
expected monoadducts **2kk** and **2ll** in high yields, respectively (entries 1 and 2). The reaction of adamantane **1mm** proceeded chemoselectively at the weaker tertiary C−H bond in the presence of the secondary counterparts to give aminated adamantane **2mm** as a single product (entry 3). High chemoselectivity toward the more substituted carbons was observed for the substituted cyclohexane derivatives (entries 4−6). While methyl cyclohexane **1nn** was aminated to generate the tetrasubstituted carbon of **2nn** (entry 4), the reaction of *cis*-decalin **1oo** chemo- and stereoselectively gave rise to the *cis*-fused compound **2oo** with the nitrogen functionality at the angular position (entry 5). When *trans*-decalin **1pp** was used as the starting material (entry 6), a configurational change of the bicyclic system occurred to produce the same **2oo** as the major isomer.[19] The origin of the *cis*-selectivity in entries 5 and 6 can be explained by the smaller steric interactions of the *cis*-decalyl radical **Aoo** during the addition in comparison with the equilibrating *trans*-counterpart **App**, whose axial-oriented H_a and H_b are proximal to the reacting DEAD (Scheme 3).[20]

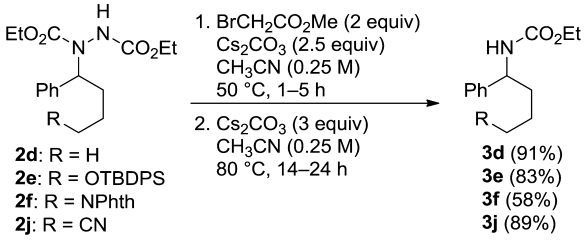
Scheme 3. Potential Mechanism of Stereoselective Formation of 2oo



Overall, the results in Tables 2−5 demonstrate the generality of the present methodology for construction of hydrazinated products from a variety of starting structures, and its efficiency for installation of tetrasubstituted carbons.

By taking advantage of the hydrazine structures, the DEAD adducts **2** thus obtained were transformed to carbamate derivatives **3** using the Magnus protocol[21] (Scheme 4).

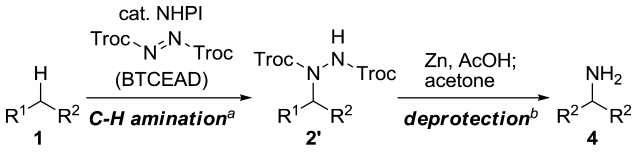
Scheme 4. Two-step Conversion of the Adducts to Amine Derivatives

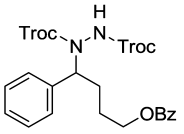
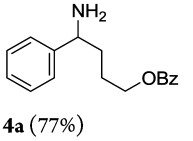
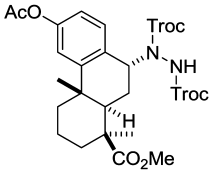
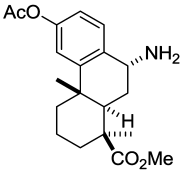
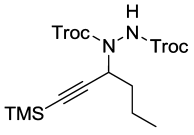
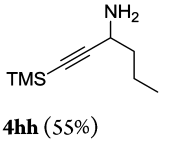
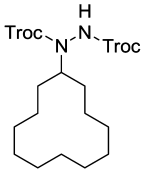
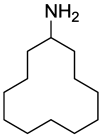


Alkylation of the nitrogen atom with methyl bromoacetate and subsequent cleavage of the N−N bond under basic conditions gave rise to variously functionalized carbamates **3d**, **3e**, **3f**, and **3j** in a range of 58−91% yields. Thus, ethyl carbamates **3** were prepared from the corresponding starting materials **1** in three steps.

Furthermore, we established a two-step procedure for construction of free amine derivatives from the starting materials **1** by applying BTCEAD (TrocN=NTroc) instead of DEAD (Table 6). The high generality of the process was demonstrated by four representative substrates, one each from Tables 2, 3, 4 or 5. Benzylic compounds **1a** and **1ff** (entries 1 and 2), propargylic compound **1hh** (entry 3), and aliphatic

Table 6. Direct C−H Amination under NHPI/BTCEAD Reagent System and One-Step Conversion of BTCEAD Adducts to Amine Derivatives



entry	compound **2'**	compound **4**
1	 **2'a** (83%)	 **4a** (77%)
2	 **2'ff** (76%)[c]	 **4ff** (60%)
3	 **2'hh** (71%)[d]	 **4hh** (55%)
4	 **2'll** (87%)[e]	 **4ll** (89%)

[a]Reaction conditions: **1** (1 equiv), NHPI (20 mol %), BTCEAD (2 equiv), DCE (0.3 M), 80 °C, 48 h unless otherwise noted. [b]Reaction conditions: **2′** (1 equiv), Zn (40 equiv), AcOH (0.07 M), room temperature, 1 h, then acetone (10 equiv), room temperature, 1 h. [c]The reaction was complete within 8 h. [d]**1hh** (2 equiv), BTCEAD (1 equiv) were employed. [e]**1ll** (5 equiv), NHPI (10 mol %), BTCEAD (1 equiv) were employed. The reaction was complete within 5 h.

compound **1ll** (entry 4) were all converted chemoselectively to the BTCEAD adducts **2′a**, **2′ff**, **2′hh**, and **2′ll**, respectively, in high yields. Treatment of **2′a**, **2′ff**, **2′hh**, or **2′ll** with Zn induced the reductive removal of the Troc group and cleavage of the N−N bond,[22] leading to the corresponding amines **4a**, **4ff**, **4hh**, or **4ll**. Remarkably, the Bz group (entry 1), the acetyl group and methyl ester (entry 2), and the acetylene group (entry 3) were left intact, showing the mildness of the present deprotection procedure.

3. CONCLUSION

In conclusion, we have developed a chemoselective C(sp^3)−H amination employing catalytic NHPI and stoichiometric DEAD or BTCEAD. This radical-based reaction is initiated by hydrogen abstraction by PINO generated from the oxidation of NHPI, and the carbon radical intermolecularly adds to

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DEAD or BTCEAD, resulting in installation of a nitrogen unit. The salient features of the present protocols are: (1) predictable chemoselectivity toward benzylic and propargylic C−H bonds and tertiary C−H bonds of aliphatic compounds; (2) wide applicability to various carboskeletons; (3) high compatibility with various functionalities including benzoyl- and silyl-protected alcohols, nosyl-, phth-, and Boc-protected amines, as well as carboxylic acids, cyanides, and bromides; and (4) expeditious transformation of the generated hydrazine derivatives to the corresponding carbamates and amines. Because of these advantages, the present methodology serves as a unique tool for the efficient synthesis of complex amine-substituted natural products and pharmaceuticals.

4. EXPERIMENTAL SECTION

General Information. All reactions sensitive to air or moisture were carried out under argon atmosphere and anhydrous conditions. Chemical shifts are reported in δ (ppm) with reference to residual solvent signals [^{1}H NMR: $CHCl_3$ (7.26); ^{13}C NMR: $CDCl_3$ (77.0)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

General Procedure for Amination of Benzylic C−H Bonds. To a solution of 4-phenylbutyl benzoate **1a** (92.6 mg, 0.364 mmol) and *N*-hydroxyphthalimide (11.9 mg, 0.0728 mmol) in 1,2-dichloroethane (1.2 mL) was added diethyl azodicarboxylate (127 mg, 0.728 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 48 h, and concentrated. The residue was purified with flash column chromatography (silica gel, hexane−EtOAc 3:1) to provide diethyl 1-[4-(benzoyloxy)-1-phenylbutyl]-1,2-hydrazinedicarboxylate **2a** in 93% yield (145 mg).

General Procedure for Amination of Propargylic C−H Bonds. To a solution of *N*-hydroxyphthalimide (4.9 mg, 0.030 mmol) in 1,2-dichloroethane (1.0 mL) were added 4-octyne **1gg** (66.1 mg, 0.600 mmol) and diethyl azodicarboxylate (52.2 mg, 0.300 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 24 h and concentrated. The residue was purified with flash column chromatography (silica gel, hexane−EtOAc 5:1) to provide diethyl 1-(4-octyn-3-yl)-1,2-hydrazinedicarboxylate **2gg** in 69% yield (58.7 mg).

General Procedure for Amination of Aliphatic C−H Bonds. To a solution of *N*-hydroxyphthalimide (4.9 mg, 0.030 mmol) in 1,2-dichloroethane (1.0 mL) were added cyclooctane **1kk** (168 mg, 1.50 mmol) and diethyl azodicarboxylate (52.2 mg, 0.300 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 24 h and concentrated. The residue was purified with flash column chromatography (silica gel, hexane−EtOAc 4:1) to provide diethyl 1-cyclooctyl-1,2-hydrazinedicarboxylate **2kk** in 87% yield (74.9 mg).

General Procedure for Synthesis of 3. To a solution of diethyl 1-(1-phenylbutyl)-1,2-hydrazinedicarboxylate **2d** (49.3 mg, 0.160 mmol) and Cs_2CO_3 (130 mg, 0.400 mmol) in CH_3CN (0.64 mL) was added methyl bromoacetate (29.5 μL, 0.320 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (×3). The extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified with flash column chromatography (silica gel, hexane−EtOAc 5:1) to provide the diethyl 1-[(methoxycarbonyl)methyl]-2-(1-phenylbutyl)-1,2-hydrazinedicarboxylate.

To a solution of the diethyl 1-[(methoxycarbonyl)methyl]-2-(1-phenylbutyl)-1,2-hydrazinedicarboxylate in CH_3CN (0.64 mL) was added Cs_2CO_3 (156 mg, 0.480 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 24 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (×3). The extracts were combined and washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified with flash column chromatography (silica gel, hexane−EtOAc 10:1) to provide ethyl 1-phenylbutylcarbamate **3d** in 91% yield (two steps, 32.1 mg).

General Procedure for Synthesis of 4. To a solution of bis(2,2,2-trichloroethyl) 1-[4-(benzoyloxy)-1-phenylbutyl]-1,2-hydrazinedicarboxylate **2′a** (57.7 mg, 0.0908 mmol) in glacial acetic acid (1.3 mL) was added zinc dust (238 mg, 3.63 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min, and then acetone (66.9 μL) was added. The mixture was stirred at room temperature for additional 30 min. Then CH_2Cl_2 was added and the resulting mixture filtered through a pad of Celite. The solvent was neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc (×3). The extracts were combined and washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified with flash column chromatography (silica gel, $CHCl_3$−MeOH 15:1) to provide 4-(benzoyloxy)-1-phenylbutylamine **4a** in 77% yield (18.8 mg).

Compound 2a: 93% yield (145 mg); colorless foam; IR (neat) 3296, 1753, 1715, 1602, 1584, 1496, 1276, 759, 714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.20−1.30 (6H, m), 1.84 (1H, m), 2.00−2.10 (2H, m), 2.19 (1H, m), 4.10−4.24 (4H, m), 4.37 (2H, t, J = 6.0 Hz), 5.35 (1H, m), 6.02 (1H, br), 7.26−7.35 (5H, m), 7.41 (2H, t, J = 7.5 Hz), 7.53 (1H, t, J = 7.5 Hz), 8.03 (2H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 25.9, 27.3, 60.8, 61.9, 62.6, 64.7, 128.0, 128.2 (×2), 128.6, 129.5, 130.5, 132.7, 138.8, 156.1, 156.6, 166.5; HRMS (ESI-TOF) calcd for $C_{23}H_{28}N_2NaO_6$ (M + Na)$^+$ 451.1840, found 451.1826.

Compound 2′a: 83% yield (96.4 mg); colorless foam; IR (neat) 3282, 1773, 1717, 1602, 1584, 1495, 1276, 1112, 811, 751, 712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.87 (1H, m), 2.05−2.15 (2H, m), 2.25 (1H, m), 4.38 (2H, m), 4.72 (2H, m), 4.81 (2H, m), 5.44 (1H, m), 6.40 (1H, br), 7.35−7.40 (5H, m), 7.43 (2H, t, J = 6.5 Hz), 7.55 (1H, t, J = 6.5 Hz), 8.03 (2H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 26.0, 27.3, 61.9, 64.5, 75.1, 75.8, 94.8, 94.9, 128.1, 128.3, 128.5, 128.8, 129.5, 130.4, 132.8, 137.7, 154.1, 154.5, 166.5; HRMS (ESI-TOF) calcd for $C_{23}H_{22}Cl_6N_2NaO_6$ (M + Na)$^+$ 656.9477, found 656.9477.

Compound 2″a: 57% yield (73.7 mg); colorless foam; mixture of rotamers; IR (neat) 3315, 1716, 1603, 1585, 1495, 1392, 1367, 1275, 1156, 757, 714, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.35−1.55 (18H, m), 1.82 (1H, m), 1.97−2.08 (2H, m), 2.15 (1H, m), 4.37 (2H, m), 5.31 (1H, m), 5.79 (1H, br), 7.27−7.33 (5H, m), 7.42 (2H, t, J = 7.2 Hz), 7.54 (1H, t, J = 7.2 Hz), 8.03 (2H, d, J = 7.2 Hz); detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 26.0, 27.5, 27.90, 27.94, 28.21, 28.25, 60.1, 64.8, 80.9, 81.4, 127.7, 128.0, 128.2, 128.4, 129.5, 130.5, 132.7, 139.5, 155.0, 155.6, 166.5; HRMS (ESI-TOF) calcd for $C_{27}H_{36}N_2NaO_6$ (M + Na)$^+$ 507.2466, found 507.2444.

Compound 2b (CAS: 94203-19-7):[21] 77% yield (97.2 mg); colorless foam; ^{1}H NMR (500 MHz, $CDCl_3$, at 50 °C) δ 1.24−1.29 (6H, m), 1.57 (3H, d, J = 6.0 Hz), 4.15−4.27 (4H, m), 5.50 (1H, m), 6.02 (1H, br), 7.26−7.34 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$, at 50 °C) δ 14.2, 14.4, 16.6, 56.4, 61.8, 62.3, 127.1, 127.5, 128.3, 140.6, 155.8, 156.6.

Compound 2c: 64% yield (87.5 mg); colorless foam; IR (neat) 3287, 1707, 1497, 760, 743, 725, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.10 (3H, m), 1.25 (3H, t, J = 6.9 Hz), 4.00 (2H, m), 4.23 (2H, q, J = 6.9 Hz), 6.16 (1H, s), 6.58 (1H, s), 7.26−7.35 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$, at 50 °C) δ 14.1, 14.3, 61.7, 62.7, 66.0, 127.5, 128.2, 128.7, 138.7, 155.8, 156.2; HRMS (ESI-TOF) calcd for $C_{19}H_{22}N_2NaO_4$ (M + Na)$^+$ 365.1472, found 365.1459.

Compound 2d: 88% yield (122 mg); colorless foam; IR (neat) 3290, 1705, 1312, 1228, 760, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.95 (3H, t, J = 7.3 Hz), 1.23−1.40 (8H, m), 1.85 (1H, m), 2.04 (1H, m), 4.08−4.26 (4H, m), 5.28 (1H, m), 5.92 (1H, br), 7.26−7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.7, 14.2, 14.3, 19.5, 32.6, 60.7, 61.7, 62.2, 127.6, 128.0, 128.3, 139.2, 156.0, 156.5; HRMS (ESI-TOF) calcd for $C_{16}H_{24}N_2NaO_4$ (M + Na)$^+$ 331.1628, found 331.1641.

Compound 2e: 73% yield (105 mg); colorless foam; IR (neat) 3280, 1757, 1709, 1588, 1110, 824, 760, 738, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.05 (9H, s), 1.20−1.29 (6H, m), 1.61 (1H, m), 1.72 (1H, m), 2.06 (2H, m), 3.66−3.75 (2H, m), 4.10−4.24 (4H, m), 5.27 (1H, m), 5.93 (1H, br), 7.27−7.42 (11H, m), 7.63−7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 19.2, 26.9,

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27.0, 29.4, 60.8, 61.8, 62.4, 63.6, 127.5, 127.7, 128.0, 128.4, 129.5, 134.0, 135.5, 139.2, 156.0, 156.5; HRMS (ESI-TOF) calcd for $C_{32}H_{42}N_2NaO_5Si$ $(M + Na)^+$ 585.2755, found 585.2751.

Compound 2f: 87% yield (127 mg); colorless foam; IR (neat) 3301, 1753, 1709, 772, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.10−1.32 (6H, m), 1.77 (1H, m), 1.83−2.02 (2H, m), 2.10 (1H, m), 3.75 (2H, t, J = 5.8 Hz), 3.95−4.25 (4H, m), 5.31 (1H, m), 5.91 (1H, br), 7.26−7.32 (5H, m), 7.68 (2H, dd, J = 4.8, 2.5 Hz), 7.82 (2H, dd, J = 4.8, 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.2, 14.3, 25.6, 28.0, 37.6, 60.7, 61.7, 62.4, 123.0, 127.8, 127.9, 128.3, 132.2, 133.6, 138.8, 155.9, 156.5, 168.1; HRMS (ESI-TOF) calcd for $C_{24}H_{27}N_3NaO_6$ $(M + Na)^+$ 476.1792, found 476.1787.

Compound 2g: 79% yield (109 mg); colorless foam; IR (neat) 3284, 1702, 1593, 1541, 1414, 1339, 1166, 853, 757, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.24−1.31 (6H, m), 1.65 (1H, m), 1.81 (1H, m), 1.98 (1H, m), 2.14 (1H, m), 3.18 (2H, m), 4.17−4.26 (4H, m), 5.26 (1H, m), 5.54 (1H, br), 5.89 (1H, br), 7.24−7.35 (5H, m), 7.68−7.71 (2H, m), 7.81 (1H, m), 8.11 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 26.1, 27.4, 43.4, 60.4, 62.2, 62.6, 125.0, 127.8, 128.0, 128.5, 130.9, 132.4, 133.3, 133.7, 138.7, 148.1, 156.1, 156.9; HRMS (ESI-TOF) calcd for $C_{22}H_{28}N_4NaO_8S$ $(M + Na)^+$ 531.1520, found 531.1512.

Compound 2h: 93% yield (104 mg); colorless foam; mixture of rotamers; IR (neat) 3293, 1735, 1710, 1225, 760, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.22−1.33 (6H, m), 1.47 (1H, m), 1.70 (1H, m), 1.92 (1H, m), 2.05 (1H, m), 2.37 (2H, t, J = 7.0 Hz), 3.66 (3H, s), 4.05−4.28 (4H, m), 5.28 (1H, m), 5.99 (1H, br), 7.26−7.33 (5H, m); Detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.2, 14.3, 21.7, 29.9, 33.5, 51.2, 51.3, 60.6, 61.7, 62.4, 127.9 (×2), 128.4, 138.8, 156.0, 156.5, 173.6; HRMS (ESI-TOF) calcd for $C_{18}H_{26}N_2NaO_6$ $(M + Na)^+$ 389.1683, found 389.1665.

Compound 2i: 79% yield (67.1 mg); colorless foam; IR (neat) 3287, 1753, 1710, 1496, 1412, 1381, 1226, 760, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.23−1.30 (6H, m), 1.49 (1H, m), 1.63 (1H, m), 1.76 (1H, m), 2.01 (1H, m), 2.12 (3H, s), 2.48 (2H, t, J = 7.0 Hz), 4.05−4.28 (4H, m), 5.27 (1H, m), 6.01 (1H, br), 7.26−7.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.2, 14.4, 20.6, 29.6, 29.9, 43.1, 60.7, 61.7, 62.4, 127.9 (×2), 128.4, 138.8, 156.0, 156.4, 208.3; HRMS (ESI-TOF) calcd for $C_{18}H_{26}N_2NaO_5$ $(M + Na)^+$ 373.1734, found 373.1725.

Compound 2j: 83% yield (89.4 mg); colorless foam; IR (neat) 3289, 2246, 1749, 1705, 1412, 1382, 1231, 759, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.25−1.29 (6H, m), 1.78 (1H, m), 1.98−2.10 (2H, m), 2.20 (1H, m), 2.35−2.49 (2H, m), 4.10−4.30 (4H, m), 5.31 (1H, m), 5.89 (1H, br), 7.27−7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 16.9, 22.5, 29.7, 60.2, 62.1, 62.7, 119.3, 127.9, 128.2, 128.7, 138.4, 156.0, 156.6; HRMS (ESI-TOF) calcd for $C_{17}H_{23}N_3NaO_4$ $(M + Na)^+$ 356.1581, found 356.1564.

Compound 2k: 90% yield (119 mg); colorless foam; IR (neat) 3273, 1711, 1414, 1382, 1229, 759, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.24−1.31 (6H, m), 1.71 (1H, m), 1.80−2.00 (2H, m), 2.09 (1H, m), 2.43 (2H, t, J = 7.1 Hz), 4.08−4.30 (4H, m), 5.29 (1H, m), 5.99 (1H, br), 7.22−7.33 (5H, m), CO_2-*H* missing; ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 21.6, 30.0, 33.5, 60.8, 62.0, 62.6, 128.0 (×2), 128.5, 138.8, 156.2, 156.8, 178.2; HRMS (ESI-TOF) calcd for $C_{17}H_{24}N_2NaO_6$ $(M + Na)^+$ 375.1527, found 375.1523.

Compound 2l: 89% yield (139 mg); colorless foam; IR (neat) 3283, 1753, 1706, 1411, 1382, 1060, 758, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.24−1.31 (6H, m), 1.95 (1H, m), 2.04−2.18 (3H, m) 3.45 (2H, m), 4.10−4.27 (4H, m), 5.31 (1H, m), 5.92 (1H, br), 7.27−7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.5, 29.3, 29.6, 33.6, 60.3, 62.0, 62.6, 128.0, 128.1, 128.6, 138.7, 156.1, 156.6; HRMS (ESI-TOF) calcd for $C_{16}H_{23}BrN_2NaO_4$ $(M + Na)^+$ 409.0739, found 409.0720.

Compound 2m: 92% yield (143 mg); colorless foam; IR (neat) 3294, 1752, 1716, 1602, 1584, 1494, 760, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.20−1.30 (6H, m), 2.37 (1H, m), 2.53 (1H, m), 4.13−4.25 (4H, m), 4.46 (1H, m), 4.53 (1H, m), 5.58 (1H, m), 6.03 (1H, br), 7.27−7.38 (5H, m), 7.43 (2H, t, J = 7.5 Hz), 7.55 (1H, t, J = 7.5 Hz), 8.03 (2H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.28, 14.34, 30.0, 58.1, 62.0, 62.1, 62.6, 128.0, 128.1, 128.2, 128.6, 129.5, 130.4, 132.7, 138.3, 155.9, 156.7, 166.4; HRMS (ESI-TOF) calcd for $C_{22}H_{26}N_2NaO_6$ $(M + Na)^+$ 437.1683, found 437.1672.

Compound 2n: 54% yield (86.2 mg); colorless foam; IR (neat) 3300, 1757, 1715, 1603, 1584, 1497, 1275, 760, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.05−1.25 (6H, m), 4.00−4.20 (4H, m), 4.62 (1H, m), 5.01 (1H, m), 5.75 (1H, m), 6.34 (1H, br), 7.32−7.47 (7H, m), 7.55 (1H, t, J = 7.5 Hz), 8.02 (2H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.2, 14.3, 59.7 (×2), 61.9, 62.7, 128.3 (×2), 128.4, 128.6, 129.7, 130.0, 133.1, 135.6, 156.0, 156.2, 166.5; HRMS (ESI-TOF) calcd for $C_{21}H_{24}N_2NaO_6$ $(M + Na)^+$ 423.1527, found 423.1515.

Compound 2o: 92% yield (142 mg); colorless foam; mixture of rotamers; IR (neat) 3287, 1756, 1707, 1612, 1586, 1514, 1249, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, at 50 °C) δ 0.94 (3H, t, J = 7.2 Hz), 1.18−1.55 (8H, m), 1.81 (1H, m), 2.01 (1H, m), 3.80 (3H, s), 4.10−4.25 (4H, m), 5.24 (1H, m), 5.91 (1H, br), 6.85 (2H, d, J = 8.8 Hz), 7.25 (2H, d, J = 8.8 Hz); Detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.6, 14.1, 14.3, 19.4, 32.8, 55.0, 55.1, 60.1, 61.6, 62.1, 113.6, 129.1, 131.3, 155.9, 156.5, 159.1; HRMS (ESI-TOF) calcd for $C_{17}H_{26}N_2NaO_5$ $(M + Na)^+$ 361.1734, found 361.1747.

Compound 2p: 88% yield (113 mg); colorless foam; IR (neat) 3288, 1736, 1707, 1601, 1585, 1508, 1265, 1205, 1063, 878, 760, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.97 (3H, t, J = 7.2 Hz), 1.23−1.45 (8H, m), 1.86 (1H, m), 2.03 (1H, m), 4.08−4.26 (4H, m), 5.32 (1H, m), 5.95 (1H, br), 7.19 (2H, d, J = 8.5 Hz), 7.41 (2H, d, J = 8.5 Hz), 7.51 (2H, t, J = 7.5 Hz), 7.64 (1H, t, J = 7.5 Hz), 8.20 (2H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.7, 14.2, 14.3, 19.5, 32.8, 60.1, 61.8, 62.3, 121.5, 128.4, 129.1, 129.5, 130.0, 133.4, 136.9, 150.5, 155.9, 156.6, 164.9; HRMS (ESI-TOF) calcd for $C_{23}H_{28}N_2NaO_6$ $(M + Na)^+$ 451.1840, found 451.1850.

Compound 2q: 89% yield (73.5 mg); colorless foam; IR (neat) 3304, 1705, 1614, 1598, 1529, 1415, 1315, 1236, 1161, 1055, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, at 50 °C) δ 0.94 (3H, t, J = 7.5 Hz), 1.23−1.50 (8H, m), 1.52 (9H, s), 1.83 (1H, m), 1.98 (1H, m), 4.10−4.25 (4H, m), 5.23 (1H, m), 5.89 (1H, br), 6.41 (1H, br), 7.25 (2H, d, J = 8.0 Hz), 7.31 (2H, d, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, at 50 °C) δ 13.7, 14.3, 14.4, 19.5, 28.3, 32.8, 60.3, 61.8, 62.3, 80.4, 118.6, 128.6, 133.7, 138.1, 152.8, 156.0, 156.6; HRMS (ESI-TOF) calcd for $C_{21}H_{33}N_3NaO_6$ $(M + Na)^+$ 446.2262, found 446.2249.

Compound 2r: 80% yield (126 mg); colorless foam; mixture of rotamers; IR (neat) 3287, 1754, 1709, 1685, 1608, 1574, 1517, 1268, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.96 (3H, t, J = 7.3 Hz), 1.20−1.50 (8H, m), 1.87 (1H, m), 2.06 (1H, m), 2.58 (3H, s), 4.10−4.25 (4H, m), 5.31 (1H, m), 5.97 (1H, br), 7.45 (2H, d, J = 8.1 Hz), 7.91 (2H, d, J = 8.1 Hz); detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.6, 14.1, 14.3, 19.4, 26.2, 26.3, 32.6, 60.4, 61.7, 62.4, 128.3 (×2), 136.5, 144.6, 155.8, 156.5, 197.4; HRMS (ESI-TOF) calcd for $C_{18}H_{26}N_2NaO_5$ $(M + Na)^+$ 373.1734, found 373.1746.

Compound 2s: 72% yield (57.9 mg); colorless foam; mixture of rotamers; IR (neat) 3290, 2229, 1754, 1709, 1609, 1505, 1412, 1382, 1312, 1220, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.96 (3H, t, J = 6.5 Hz), 1.18−1.50 (8H, m), 1.83 (1H, m), 2.04 (1H, m), 4.07−4.24 (4H, m), 5.28 (1H, m), 6.00 (1H, br), 7.47 (2H, d, J = 7.0 Hz), 7.62 (2H, d, J = 7.0 Hz); Detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.6, 14.2, 14.3, 14.4, 19.4, 32.6, 60.4, 62.0, 62.6, 111.7, 118.5, 128.9, 132.1, 144.8, 155.8, 156.5; HRMS (ESI-TOF) calcd for $C_{17}H_{23}N_3NaO_4$ $(M + Na)^+$ 356.1581, found 356.1575.

Compound 2t: 88% yield (144 mg); colorless foam; IR (neat) 3283, 1755, 1707, 1591, 1488, 1062, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.95 (3H, t, J = 7.3 Hz), 1.15−1.47 (8H, m), 1.81 (1H, m), 2.01 (1H, m), 4.07−4.25 (4H, m), 5.23 (1H, m), 5.93 (1H, br), 7.22 (2H, d, J = 8.2 Hz), 7.45 (2H, d, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.6, 14.2, 14.3, 19.4, 32.6, 60.2, 61.8, 62.4, 121.6, 129.8, 131.3, 138.3, 155.8, 156.5; HRMS (ESI-TOF) calcd for $C_{16}H_{23}BrN_2NaO_4$ $(M + Na)^+$ 409.0739, found 409.0728.

Compound 2u: 71% yield (69.5 mg); colorless foam; mixture of rotamers; IR (neat) 3288, 1736, 1715, 1588, 1263, 1227, 1062, 785, 762, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.20−1.30

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(6H, m), 1.59 (3H, d, J = 7.2 Hz), 4.12−4.27 (4H, m), 5.52 (1H, m), 6.08 (1H, br), 7.15−7.30 (3H, m), 7.39 (1H, t, J = 7.8 Hz), 7.52 (2H, t, J = 7.8 Hz), 7.64 (1H, t, J = 7.8 Hz), 8.20 (2H, d, J = 7.8 Hz); Detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 16.6, 56.1, 61.9, 62.5, 120.5, 120.6, 120.9, 124.7, 128.5, 129.4, 129.6, 130.1, 133.5, 142.5, 151.2, 155.7, 156.7, 165.0; HRMS (ESI-TOF) calcd for $C_{21}H_{24}N_2NaO_6$ $(M + Na)^+$ 423.1527, found 423.1511.

Compound 2v: 83% yield (79.5 mg); colorless foam; IR (neat) 3299, 1731, 1601, 1584, 1489, 1265, 1215, 1175, 1063, 757, 710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.96 (3H, t, J = 6.1 Hz), 1.21 (3H, t, J = 5.9 Hz), 1.59 (3H, d, J = 5.7 Hz), 3.67 (2H, m), 4.12 (2H, m), 5.69 (1H, m), 6.10 (1H, br), 7.13 (1H, d, J = 6.8 Hz), 7.30 (1H, t, J = 6.8 Hz), 7.39 (1H, t, J = 6.8 Hz), 7.46−7.52 (3H, m), 7.63 (1H, t, J = 7.0 Hz), 8.19 (2H, d, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, at 50 °C) δ 14.0, 14.3, 16.4, 51.5, 61.7, 62.0, 122.9, 126.2, 128.4, 128.6, 129.0, 129.1, 130.3, 131.9, 133.6, 149.4, 154.9, 156.6, 166.0; HRMS (ESI-TOF) calcd for $C_{21}H_{24}N_2NaO_6$ $(M + Na)^+$ 423.1527, found 423.1536.

Compound 2w: 79% yield (69.1 mg); colorless foam; IR (neat) 3300, 1722, 1635, 1578, 1142, 761, 709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.12 (3H, t, J = 7.0 Hz), 1.21 (3H, m), 1.59 (3H, m), 3.95−4.20 (4H, m), 5.70 (1H, m), 6.09 (1H, br), 6.63 (1H, d, J = 15.9 Hz), 7.11 (1H, d, J = 7.8 Hz), 7.28 (1H, d, J = 7.8 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.40−7.44 (3H, m), 7.46 (1H, d, J = 7.8 Hz), 7.57−7.61 (2H, m), 7.86 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, at 50 °C) δ 14.3 (×2), 16.4, 51.5, 61.7, 62.2, 116.9, 122.9, 126.0, 128.2, 128.5, 128.89, 128.93, 130.7, 131.8, 134.2, 146.9, 149.2, 155.1, 156.6, 166.1; HRMS (ESI-TOF) calcd for $C_{23}H_{26}N_2NaO_6$ $(M + Na)^+$ 449.1683, found 449.1676.

Compound 2x: 90% yield (59.2 mg); colorless foam; IR (neat) 3285, 1700, 1600, 803, 781, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.15−1.35 (6H, m), 1.72 (3H, d, J = 6.8 Hz), 4.05−4.32 (4H, m), 5.84 (1H, br), 6.29 (1H, m), 7.43−7.56 (4H, m), 7.80 (1H, d, J = 8.0 Hz), 7.86 (1H, d, J = 8.0 Hz), 8.20 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 17.0, 52.3, 61.7, 62.5, 123.4, 124.9, 125.0, 125.6, 126.5, 128.5, 128.7, 131.6, 133.9, 135.5, 155.4, 156.5; HRMS (ESI-TOF) calcd for $C_{18}H_{22}N_2NaO_4$ $(M + Na)^+$ 353.1472, found 353.1487.

Compound 2y: 90% yield (127 mg); colorless foam; mixture of rotamers; IR (neat) 3286, 1756, 1708, 1518, 1411, 1381, 1302, 1217, 760, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.96 (3H, t, J = 6.1 Hz), 1.19−1.30 (6H, m), 1.35−1.55 (2H, m), 1.85 (1H, m), 2.04 (1H, m), 4.10−4.38 (4H, m), 5.52 (1H, m), 6.02 (1H, br), 6.96 (1H, dd, J = 4.2, 3.0 Hz), 7.00 (1H, dd, J = 3.0, 1.0 Hz), 7.22 (1H, dd, J = 4.2, 1.0 Hz); Detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.5, 14.1, 14.3, 19.4, 34.6, 56.5, 61.7, 62.4, 124.57, 124.64, 125.5, 126.4, 142.4, 155.7, 156.4; HRMS (ESI-TOF) calcd for $C_{14}H_{22}N_2NaO_4S$ $(M + Na)^+$ 337.1192, found 337.1190.

Compound 2z: 81% yield (114 mg); colorless foam; IR (neat) 3285, 1755, 1706, 1412, 1381, 1302, 1218, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.96 (3H, t, J = 7.5 Hz), 1.15−1.55 (8H, m), 1.83 (1H, m), 1.99 (1H, m), 4.10−4.26 (4H, m), 5.36 (1H, m), 5.93 (1H, br), 7.06 (1H, d, J = 4.9 Hz), 7.19 (1H, s), 7.27 (1H, d, J = 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.6, 14.2, 14.3, 19.4, 33.5, 56.5, 61.7, 62.3, 122.6, 125.4, 127.2, 140.5, 155.9, 156.4; HRMS (ESI-TOF) calcd for $C_{14}H_{22}N_2NaO_4S$ $(M + Na)^+$ 337.1192, found 337.1202.

Compound 2aa (CAS: 16396-49-9)[23]: 48% yield (115 mg); colorless foam; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.25 (3H, t, J = 7.0 Hz), 1.29 (3H, t, J = 7.0 Hz), 4.18 (2H, q, J = 7.0 Hz), 4.24 (2H, q, J = 7.0 Hz), 4.69 (2H, s), 6.31 (1H, br), 7.26−7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 53.7, 61.9, 62.5, 127.6, 128.5 (×2), 136.4, 155.8, 156.2.

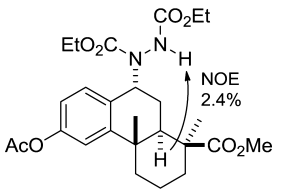
Compound 2bb: 92% yield (243 mg); colorless foam; 1:1 mixture of rotamers; IR (neat) 3295, 1716, 1603, 1497, 1261, 1240, 1095, 1057, 765, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.97 (3H, t, J = 7.1 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.61 (6/2H, s), 1.76 (6/2H, s), 3.95 (2H, m), 4.26 (2H, m), 6.45 (1H, br), 7.19 (1H, t, J = 7.2 Hz), 7.30 (2H, t, J = 7.7 Hz), 7.46 (2H, m); detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.8, 14.3, 27.7, 28.2, 61.7, 61.8, 64.2, 124.5, 126.1, 127.9, 148.0, 155.5, 157.3; HRMS (ESI-TOF) calcd for $C_{15}H_{22}N_2NaO_4$ $(M + Na)^+$ 317.1472, found 317.1467.

Compound 2cc: 46% yield (62.7 mg); colorless foam; mixture of rotamers; IR (neat) 3304, 1720, 1602, 1584, 1497, 1272, 763, 713, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.88−1.04 (3H, m), 1.25 (3H, m), 1.85 (3H, s), 3.98 (2H, m), 4.22 (2H, m), 4.75 (1H, d, J = 11.0 Hz), 4.86 (1H, d, J = 11.0 Hz), 6.64 (1H, br), 7.24 (1H, m), 7.34 (2H, t, J = 7.5 Hz), 7.38−7.48 (2H, m), 7.51−7.68 (3H, m), 7.97−8.03 (2H, m); detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.9, 14.0, 14.35, 14.38, 22.2, 24.5, 62.2, 65.9, 66.6, 68.9, 69.5, 125.0, 125.7, 126.9, 127.1, 128.3, 128.5, 129.6, 129.7, 130.0, 130.1, 132.9, 133.2, 143.3, 144.3, 155.3, 155.4, 156.9, 157.2, 166.0, 166.2; HRMS (ESI-TOF) calcd for $C_{22}H_{26}N_2NaO_6$ $(M + Na)^+$ 437.1683, found 437.1672. The enantiomeric excess of **2cc** was determined to be 11% ee by HPLC analysis. HPLC conditions: column: CHIRALCEL OD 10 × 250 mm; eluent: 90% hexane/10% *i*-PrOH; flow rate: 1.0 mL/min; detection: UV 254 nm; retention time: 9.9 min (major isomer) and 12.9 min (minor isomer).

Compound 2dd: 66% yield (133 mg); colorless foam; mixture of rotamers; IR (neat) 3290, 1713, 1498, 1376, 1331, 1241, 761, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.07 (3H, t, J = 7.0 Hz), 1.27 (3H, t, J = 7.0 Hz), 1.38−1.55 (4H, m), 1.66 (1H, m), 1.78 (1H, m), 2.23 (2H, m), 2.48 (2H, m), 3.99 (2H, m), 4.17 (2H, m), 6.19 (1H, br), 7.22 (1H, t, J = 7.5 Hz), 7.31 (2H, t, J = 7.5 Hz), 7.50 (2H, d, J = 7.5 Hz); detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.0, 14.3, 22.7, 23.0, 25.6, 35.3, 61.67, 61.72, 66.6, 126.6 (×2), 127.9, 144.3, 155.7, 157.1; HRMS (ESI-TOF) calcd for $C_{18}H_{26}N_2NaO_4$ $(M + Na)^+$ 357.1785, found 357.1800.

Compound 2ee: 72% yield (94.5 mg); colorless foam; mixture of rotamers; IR (neat) 3288, 1708, 1414, 1230, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.22 (3H, t, J = 7.1 Hz), 1.31 (3H, t, J = 7.1 Hz), 2.20 (1H, m), 2.42 (1H, m), 2.83 (1H, ddd, J = 16.0, 8.5, 7.5 Hz), 2.99 (1H, ddd, J = 16.0, 9.0, 4.7 Hz), 4.15 (2H, m), 4.27 (2H, m), 5.82 (1H, m), 6.05 (1H, br), 7.16−7.26 (4H, m); detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.39, 14.42, 28.9, 30.4, 61.8, 62.5, 63.5, 124.2, 124.8, 126.5, 128.0, 140.5, 144.0, 156.1, 156.5; HRMS (ESI-TOF) calcd for $C_{15}H_{20}N_2NaO_4$ $(M + Na)^+$ 315.1315, found 315.1323.

Compound 2ff: 62% yield (64.3 mg); colorless foam; mixture of rotamers; IR (neat) 3297, 1753, 1714, 1610, 1205, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.96 (3H, s), 1.05 (1H, m), 1.23 (3H, m), 1.26 (3H, s), 1.31 (3H, t, J = 7.1 Hz), 1.40 (1H, m), 1.63 (1H, m), 1.87 (1H, m), 1.98 (1H, m), 2.20−2.31 (5H, m), 2.43 (1H, m), 2.58 (1H, m), 3.66 (3H, s), 4.11 (2H, m), 4.27 (2H, m), 5.47 (1H, m), 5.99 (1H, br), 6.91 (1H, dd, J = 8.2, 2.2 Hz), 7.03 (1H, d, J = 2.2 Hz), 7.20 (1H, d, J = 8.2 Hz); detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.4 (×2), 19.8, 20.98, 21.00, 22.0, 26.5, 27.9, 37.8, 38.1, 39.0, 43.9, 46.4, 51.1, 51.2, 54.5, 61.8, 62.6, 118.0, 118.1, 119.4, 129.3, 130.2, 150.4, 151.4, 155.9, 156.1, 169.1, 177.6; HRMS (ESI-TOF) calcd for $C_{26}H_{36}N_2NaO_8$ $(M + Na)^+$ 527.2364, found 527.2342. The stereochemistry of **2ff** was determined by the NOE experiment.



Compound 2gg: 69% yield (58.7 mg); colorless foam; IR (neat) 3297, 2248, 1756, 1712, 1413, 1382, 1297, 1223, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.98 (3H, t, J = 6.1 Hz), 1.01 (3H, t, J = 6.1 Hz), 1.27 (3H, t, J = 6.0 Hz), 1.28 (3H, t, J = 6.0 Hz), 1.47−1.55 (2H, m), 1.68 (1H, m), 1.77 (1H, m), 2.16 (2H, t, J = 6.0 Hz), 4.15−4.26 (4H, m), 4.83 (1H, m), 6.31 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 10.6, 13.3, 14.33, 14.34, 20.6, 22.1, 27.1, 53.1, 61.8, 62.6, 76.9, 85.1, 155.7, 156.2; HRMS (ESI-TOF) calcd for $C_{14}H_{24}N_2NaO_4$ $(M + Na)^+$ 307.1628, found 307.1626.

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Compound 2hh: 66% yield (65.5 mg); colorless foam; IR (neat) 3298, 2177, 1758, 1713, 1414, 1382, 1303, 1251, 1064, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.15 (9H, s), 0.93 (3H, t, J = 7.2 Hz), 1.27 (3H, t, J = 7.0 Hz), 1.28 (3H, t, J = 7.0 Hz), 1.40−1.51 (2H, m), 1.63 (1H, m), 1.74 (1H, m), 4.12−4.27 (4H, m), 4.94 (1H, m), 6.32 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ −0.16, 13.4, 14.4 (×2), 19.2, 35.4, 51.5, 61.9, 62.7, 89.3, 102.5, 155.5, 156.2; HRMS (ESI-TOF) calcd for $C_{15}H_{28}N_2NaO_4Si$ $(M + Na)^+$ 351.1711, found 351.1719.

Compound 2ii: 67% yield (66.4 mg); colorless foam; IR (neat) 3293, 2234, 1755, 1711, 1598, 1572, 1517, 1413, 1482, 1228, 758, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.99 (3H, t, J = 6.3 Hz), 1.28 (3H, t, J = 6.0 Hz), 1.30 (3H, t, J = 6.5 Hz), 1.50−1.60 (2H, m), 1.78 (1H, m), 1.86 (1H, m), 4.15−4.27 (4H, m), 5.18 (1H, m), 6.38 (1H, br), 7.27−7.31 (3H, m), 7.42 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.5, 14.4 (×2), 19.3, 35.5, 51.5, 62.0, 62.7, 84.6, 86.3, 122.7, 128.2, 128.3, 131.7, 155.6, 156.3; HRMS (ESI-TOF) calcd for $C_{18}H_{24}N_2NaO_4$ $(M + Na)^+$ 355.1628, found 355.1641.

Compound 2jj: 69% yield (110 mg); colorless foam; mixture of rotamers; IR (neat) 3302, 2172, 1722, 1713, 1249, 867, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.14 (9H, s), 1.07−1.27 (7H, m), 1.54−1.70 (5H, m), 1.79 (1H, m), 1.86−2.05 (2H, m), 2.31 (1H, m), 4.10−4.22 (4H, m), 6.45 (1H, br); detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ −0.04, 14.37, 14.41, 23.4, 23.5, 25.2, 35.9, 61.8, 62.0, 62.7, 90.1, 106.2, 155.4, 156.7; HRMS (ESI-TOF) calcd for $C_{17}H_{30}N_2NaO_4Si$ $(M + Na)^+$ 377.1867, found 377.1854.

Compound 2kk: 87% yield (74.9 mg); colorless foam; IR (neat) 3288, 1735, 1710, 1692, 1310, 1214, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.26 (3H, t, J = 7.0 Hz), 1.28 (3H, t, J = 7.0 Hz), 1.50−1.62 (8H, m), 1.65−1.87 (6H, m), 4.14−4.28 (5H, m), 6.18 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 24.5, 26.1, 26.6, 30.9, 58.3, 61.7, 62.0, 155.6, 157.0; HRMS (ESI-TOF) calcd for $C_{14}H_{26}N_2NaO_4$ $(M + Na)^+$ 309.1785, found 309.1781.

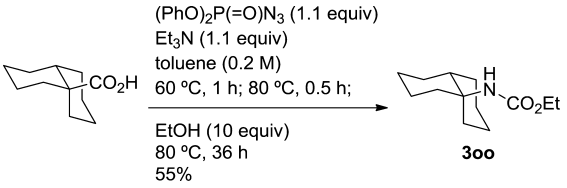
Compound 2ll: 84% yield (86.8 mg); colorless foam; IR (neat) 3286, 1739, 1710, 1225, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.24−1.65 (28H, m), 4.19 (4H, q, J = 7.5 Hz), 4.35 (1H, m), 6.11 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 22.4, 22.5, 23.0, 24.1, 24.3, 28.1, 53.4, 61.8, 62.1, 156.3, 157.0; HRMS (ESI-TOF) calcd for $C_{18}H_{34}N_2NaO_4$ $(M + Na)^+$ 365.2411, found 365.2397.

Compound 2mm: 74% yield (68.5 mg); colorless foam; IR (neat) 3301, 1712, 1692, 1376, 1336, 1277, 1228, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.25 (3H, t, J = 7.0 Hz), 1.28 (3H, t, J = 7.0 Hz), 1.60−1.75 (6H, m), 2.03−2.20 (9H, m), 4.06−4.26 (4H, m), 6.26 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.4, 14.5, 30.1, 36.3, 40.1, 60.6, 61.5, 61.7, 155.3, 157.2; HRMS (ESI-TOF) calcd for $C_{16}H_{26}N_2NaO_4$ $(M + Na)^+$ 333.1785, found 333.1799.

Compound 2nn: 72% yield (87.7 mg); colorless foam; mixture of rotamers; IR (neat) 3302, 1713, 1694, 1250, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.24 (3H, t, J = 7.0 Hz), 1.28 (3H, t, J = 7.0 Hz), 1.38−1.53 (9H, m), 1.58−1.68 (2H, m), 1.98 (1H, m), 2.19 (1H, m), 4.08−4.26 (4H, m), 6.30 (1H, br); Detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 22.6, 23.1, 23.5, 25.6, 35.9, 36.4, 61.5, 61.7, 62.6, 155.7, 157.1; HRMS (ESI-TOF) calcd for $C_{13}H_{24}N_2NaO_4$ $(M + Na)^+$ 295.1628, found 295.1615.

Compound 2oo: 74% yield (105 mg); colorless foam; IR (neat) 3302, 1752, 1736, 1712, 1373, 1322, 1230, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, at 50 °C) δ 1.17−1.58 (18H, m), 1.70−1.82 (2H, m), 1.99 (1H, m), 2.18 (1H, m), 2.45 (1H, m), 4.00−4.21 (4H, m), 6.40 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$, at 50 °C) δ 14.3, 14.4, 22.8, 22.9, 28.0, 28.8, 36.5, 61.5, 61.7, 66.6, 155.7, 157.2; HRMS (ESI-TOF) calcd for $C_{16}H_{28}N_2NaO_4$ $(M + Na)^+$ 335.1941, found 335.1926.

Compound 3oo: colorless oil; IR (neat) 3343, 1724, 1713, 1704, 1235, 1218, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.19 (3H, t, J = 6.0 Hz), 1.28−1.60 (12H, m), 1.65−1.72 (2H, m), 1.83−1.91 (3H, m), 4.02 (2H, q, J = 6.0 Hz), 4.53 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.6, 22.3, 23.0, 27.5, 32.1, 38.9, 55.3, 59.8, 154.8; HRMS (ESI-TOF) calcd for $C_{13}H_{23}NNaO_2$ $(M + Na)^+$ 248.1621, found 248.1627. The stereochemistry of **2oo** was unambiguously established by the data comparison of carbamate **3oo**, which was derivatized from **2oo** (70% yield, two steps, 44.4 mg) and from the known *cis*-fused carboxylic acid through Curtius rearrangement (55% yield, 89.5 mg).[24]



Compound 3d: 91% yield (two steps, 32.1 mg); colorless oil; IR (neat) 3321, 1692, 1605, 1586, 1537, 1252, 761, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 0.93 (3H, t, J = 7.2 Hz), 1.21 (3H, t, J = 7.0 Hz), 1.24−1.43 (2H, m), 1.67−1.80 (2H, m), 4.09 (2H, q, J = 7.0 Hz), 4.66 (1H, m), 4.91 (1H, br), 7.20−7.35 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 13.7, 14.5, 19.4, 39.0, 55.2, 60.7, 126.3, 127.2, 128.5, 143.1, 156.0; HRMS (ESI-TOF) calcd for $C_{13}H_{19}NNaO_2$ $(M + Na)^+$ 244.1308, found 244.1308.

Compound 3e: 83% yield (two steps, 45.6 mg); colorless oil; IR (neat) 3327, 1693, 1604, 1589, 1531, 1252, 1110, 823, 742, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, at 50 °C) δ 1.05 (9H, s), 1.21 (3H, t, J = 7.0 Hz), 1.57 (1H, m), 1.88 (1H, m), 1.83−1.91 (2H, m), 3.67 (2H, t, J = 6.3 Hz), 4.04−4.12 (2H, m), 4.65 (1H, m), 4.90 (1H, br), 7.22−7.43 (11H, m), 7.60−7.66 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$, at 50 °C) δ 14.5, 19.2, 26.9, 29.2, 33.1, 55.3, 60.8, 63.5, 126.3, 127.2, 127.6, 128.6, 129.6, 134.0, 135.6, 142.9, 156.0; HRMS (ESI-TOF) calcd for $C_{29}H_{37}NNaO_3Si$ $(M + Na)^+$ 498.2435, found 498.2430.

Compound 3f: 58% yield (two steps, 40.8 mg); colorless solid; mp 146−147 °C; IR (neat) 3331, 1770, 1709, 1529, 1397, 1245, 1046, 757, 720, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.20 (3H, t, J = 7.2 Hz), 1.63−1.87 (4H, m), 3.71 (2H, t, J = 6.5 Hz), 4.08 (2H, q, J = 7.2 Hz), 4.70 (1H, m), 4.91 (1H, br), 7.21−7.33 (5H, m), 7.70 (2H, dd, J = 5.2, 3.0 Hz), 7.83 (2H, dd, J = 5.2, 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.5, 25.5, 33.9, 37.6, 55.1, 60.8, 123.1, 126.3, 127.4, 128.6, 132.2, 133.8, 142.4, 155.9, 168.3; HRMS (ESI-TOF) calcd for $C_{21}H_{22}N_2NaO_4$ $(M + Na)^+$ 389.1472, found 389.1469.

Compound 3j: 89% yield (two steps, 24.1 mg); colorless oil; IR (neat) 3324, 2246, 1692, 1604, 1585, 1530, 1246, 1055, 764, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 50 °C) δ 1.23 (3H, t, J = 7.0 Hz), 1.65 (1H, m), 1.75 (1H, m), 1.88−2.02 (2H, m), 2.36 (2H, t, J = 7.0 Hz), 4.10 (2H, q, J = 7.0 Hz), 4.69 (1H, m), 4.84 (1H, br), 7.25−7.38 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 14.5, 16.8, 22.3, 35.5, 54.6, 61.0, 119.1, 126.3, 127.7, 128.8, 141.7, 156.0; HRMS (ESI-TOF) calcd for $C_{14}H_{18}N_2NaO_2$ $(M + Na)^+$ 269.1260, found 269.1268.

Compound 2′ff: 76% yield (47.6 mg); colorless foam; IR (neat) 3281, 1769, 1724, 1610, 1496, 1204, 813, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, at 50 °C) δ 0.95−1.08 (4H, m), 1.27 (3H, s), 1.39 (1H, m), 1.64 (1H, m), 1.85 (1H, m), 1.99 (1H, m), 2.20−2.33 (5H, m), 2.50 (1H, m), 2.64 (1H, m), 3.66 (3H, s), 4.63−4.95 (4H, m), 5.56 (1H, m), 6.47 (1H, br), 6.95 (1H, d, J = 8.0 Hz), 7.06 (1H, s), 7.25 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ 19.8, 21.1, 22.1, 26.7, 28.0, 37.8, 38.2, 39.0, 43.9, 46.5, 51.3, 55.9, 75.2, 75.9, 94.7, 95.1, 118.4, 119.8, 127.9, 130.4, 150.9, 151.7, 154.0, 154.1, 169.2, 177.4; HRMS (ESI-TOF) calcd for $C_{26}H_{30}Cl_6N_2NaO_8$ $(M + Na)^+$ 731.0026, found 730.9992.

Compound 2′hh: 71% yield (113 mg); colorless foam; IR (neat) 3302, 2177, 1780, 1732, 1407, 1251, 1203, 1107, 844, 717 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, at 50 °C) δ 0.18 (9H, s), 0.96 (3H, t, J = 7.2 Hz), 1.45−1.55 (2H, m), 1.73 (1H, m), 1.82 (1H, m), 4.70−4.87 (4H, m), 5.02 (1H, m), 6.80 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$, at 50 °C) δ −0.16, 13.4, 19.2, 35.5, 52.6, 75.3, 75.9, 90.7, 94.8, 94.9, 101.3, 153.6, 154.1; HRMS (ESI-TOF) calcd for $C_{15}H_{22}Cl_6N_2NaO_4Si$ $(M + Na)^+$ 554.9372, found 554.9356.

Compound 2′ll: 87% yield (143 mg); colorless foam; IR (neat) 3288, 1777, 1728, 1410, 1262, 1213, 1134, 1106, 1051, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, at 50 °C) δ 1.25−1.75 (22H, m), 4.45 (1H,

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m), 4.70−4.85 (4H, m), 6.80 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$, at 50 °C) δ 22.5 (×2), 23.0, 24.1, 24.2, 28.1, 55.0, 75.2, 75.9, 94.9, 95.0, 154.7, 155.1; HRMS (ESI-TOF) calcd for $C_{18}H_{28}Cl_6N_2NaO_4$ $(M + Na)^+$ 569.0072, found 569.0045.

Compound 4a: 77% yield (18.8 mg); colorless oil; IR (neat) 3371, 1715, 1602, 1584, 1493, 1451, 1275, 1116, 764, 712, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65−1.89 (6H, m), 3.95 (1H, t, J = 6.9 Hz), 4.30 (2H, t, J = 6.1 Hz), 7.22−7.36 (5H, m), 7.43 (2H, t, J = 7.8 Hz), 7.55 (1H, t, J = 7.8 Hz), 8.02 (2H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 35.8, 56.0, 64.8, 126.3, 127.1, 128.3, 128.6, 129.5, 130.3, 132.8, 146.0, 166.6; HRMS (ESI-TOF) calcd for $C_{17}H_{19}NNaO_2$ $(M + Na)^+$ 292.1308, found 292.1309.

Compound 4ff: 60% yield (9.2 mg); colorless foam; IR (neat) 3369, 1759, 1723, 1607, 1582, 1493, 1370, 1204, 823, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, s), 1.15 (1H, m), 1.27 (3H, s), 1.43 (1H, m), 1.64 (1H, m), 1.91 (1H, m), 1.96 (1H, m), 2.10 (1H, m), 2.17 (1H, m), 2.22−2.60 (7H, m), 3.66 (3H, s), 4.14 (1H, d, J = 3.5 Hz), 6.89 (1H, dd, J = 6.9, 2.0 Hz), 6.95 (1H, d, J = 2.0 Hz), 7.26 (1H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 21.1, 22.1, 28.3, 29.6, 37.4, 38.8, 38.9, 43.6, 45.3, 49.0, 51.3, 118.4, 119.5, 130.8, 135.3, 149.5, 149.9, 169.6, 177.7; HRMS (ESI-TOF) calcd for $C_{20}H_{27}NNaO_4$ $(M + Na)^+$ 368.1832, found 368.1831.

Compound 4hh: 55% yield (13.8 mg); colorless oil; IR (neat) 3366, 2164, 1458, 1251, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (9H, s), 0.93 (3H, t, J = 6.0 Hz), 1.40−1.59 (4H, m), 1.90 (2H, br), 3.54 (1H, t, J = 5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.02, 13.8, 19.2, 40.0, 43.9, 86.3, 110.0; HRMS (ESI-TOF) calcd for $C_9H_{19}NNaSi$ $(M + Na)^+$ 192.1179, found 192.1181.

Compound 4ll [CAS: 1502-03-0].[25] 89% yield (12.2 mg); colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20−1.45 (22H, m), 1.50−1.60 (2H, m), 2.89 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 23.38, 23.44, 23.8, 24.3, 33.2, 47.7.

Compound 1e: colorless oil; IR (neat) 1603, 1588, 1494, 1108, 823, 740, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (9H, s), 1.66 (2H, m), 1.78 (2H, m), 2.66 (2H, t, J = 6.0 Hz), 3.74 (2H, t, J = 6.5 Hz), 7.20−7.26 (3H, m), 7.30−7.35 (2H, m), 7.39−7.50 (6H, m), 7.70−7.75 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.9, 27.5, 32.1, 35.6, 63.7, 125.6, 127.6, 128.2, 128.4, 129.5, 134.1, 135.6, 142.6; HRMS (ESI-TOF) calcd for $C_{26}H_{32}NaOSi$ $(M + Na)^+$ 411.2115, found 411.2125.

Compound 1g: colorless solid; mp 73−75 °C; IR (neat) 3342, 1593, 1538, 1495, 1339, 1163, 781, 740, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50−1.68 (4H, m), 2.58 (2H, t, J = 7.5 Hz), 3.11 (2H, q, J = 6.5 Hz), 5.24 (1H, br), 7.10 (2H, d, J = 7.5 Hz), 7.18 (1H, t, J = 7.5 Hz), 7.26 (2H, t, J = 7.5 Hz), 7.72 (2H, dd, J = 6.0, 3.5 Hz), 7.84 (1H, dd, J = 6.0, 3.5 Hz), 8.11 (1H, dd, J = 6.0, 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 29.0, 35.1, 43.6, 125.3, 125.8, 128.26, 128.29, 130.9, 132.7, 133.5, 133.6, 141.6, 147.9; HRMS (ESI-TOF) calcd for $C_{16}H_{18}N_2NaO_4S$ $(M + Na)^+$ 357.0879, found 357.0878.

Compound 1q: pale yellow solid; mp 57−59 °C; IR (neat) 3332, 1702, 1595, 1524, 1162, 832 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.1 Hz), 1.34 (2H, m), 1.52 (9H, s), 1.57 (2H, m), 2.56 (2H, t, J = 7.5 Hz), 6.50 (1H, br), 7.26 (2H, d, J = 8.3 Hz), 7.09 (2H, d, J = 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.2, 28.3, 33.7, 34.9, 80.2, 118.7, 128.8, 135.9, 137.6, 152.9; HRMS (ESI-TOF) calcd for $C_{15}H_{23}NNaO_2$ $(M + Na)^+$ 272.1621, found 272.1613.

Compound 1w: colorless solid; mp 60−62 °C; IR (neat) 1727, 1633, 1578, 1488, 1449, 1139, 976, 764, 747, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, t, J = 7.6 Hz), 2.60 (2H, q, J = 7.6 Hz), 6.67 (1H, d, J = 16.0 Hz), 7.09 (1H, m), 7.19−7.31 (3H, m), 7.40−7.46 (3H, m), 7.58−7.63 (2H, m), 7.89 (1H, d, J = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 23.2, 117.1, 122.2, 126.1, 126.8, 128.2, 128.9, 129.4, 130.6, 134.1, 135.9, 146.5, 148.8, 165.3; HRMS (ESI-TOF) calcd for $C_{17}H_{16}NaO_2$ $(M + Na)^+$ 275.1043, found 275.1043.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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