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Hypervalent Iodine Catalyzed Hofmann Rearrangement of Carboxamides Using Oxone as Terminal Oxidant

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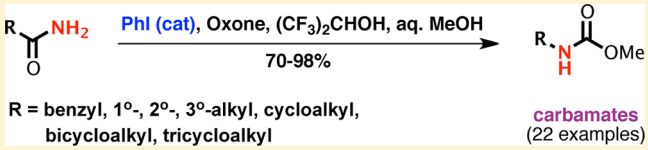
Supporting Information

ABSTRACT: Hofmann rearrangement of carboxamides to carbamates using Oxone as an oxidant can be efficiently catalyzed by iodobenzene. This reaction involves hypervalent iodine species generated in situ from catalytic amount of PhI and Oxone in the presence of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) in aqueous methanol solutions. Under these conditions, Hofmann rearrangement of various carboxamides affords corresponding carbamates in high yields.



In recent years, hypervalent iodine reagents have emerged as environmentally friendly and efficient oxidizing reagents for various synthetically useful oxidative transformations.[1] One of the most impressive recent achievements in the area of hypervalent iodine chemistry has been the development of numerous catalytic reactions utilizing organohypervalent iodine species in the iodine(I)/iodine(III) catalytic cycle. Most of these cycles, however, employ *m*-chloroperoxybenzoic acid (*m*-CPBA), which is a potentially explosive and environmentally unsafe stoichiometric oxidant. Herein, we report a new procedure for one of the key organic reactions, Hofmann rearrangement, using catalytic amount of PhI and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as an inexpensive and environmentally safe terminal oxidant.

Hypervalent iodine reagents are particularly important as oxidants for the Hofmann-type rearrangements, employed in numerous synthetic works.[2−6] The most common reagents for Hofmann rearrangement include (diacetoxyiodo)benzene,[2] [bis(trifluoroacetoxy)iodo]benzene,[3] [hydroxy(tosyloxy)]-iodobenzene,[4] *N*-tosyliminoiodane,[5] and their recyclable analogues.[6] Recently, Ochiai and co-workers have first reported the catalytic version of Hofmann rearrangement using aryliodides and *m*-CPBA as terminal oxidant.[8] Our group and Togo's group reported Hofmann rearrangement using stoichiometric organohypervalent iodine species generated in situ from PhI and appropriate oxidants.[7] However, catalytic Hofmann rearrangement using Oxone as the terminal oxidant remains unknown.

Previously, we have reported that activated iodine(III) species, hydroxy(phenyl)iodonium ion $[PhI(OH)]^+$, can be efficiently generated from PhI and Oxone in aqueous solution.[7a,9] This observation has also led us to the development of a synthetic procedure for preparation of [bis-(trifluoroacetoxy)iodo]arenes and [bis(trifluoroacetoxy)iodo]-perfluoroalkanes.[9b] Furthermore, we have also found that Oxone and the catalytic system PhI/Fe(III)-porphyrin can efficiently oxidize aromatic hydrocarbons.[9a,c] Several other groups reported catalytic hypervalent iodine reactions using Oxone in the iodine(III)/iodine(V) catalytic cycle.[10]

In a search for the organoiodine(III)-catalyzed Hofmann rearrangement, we have investigated the reactions of phenylacetamide **1a** using PhI (0.5 equiv) and Oxone (3 equiv) at 40 °C in different solvents (Table 1). The addition of small amount of water was required to dissolve Oxone in the reaction mixture. Out of several solvents tested (entries 1−11), we have found that the presence of a 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) in the mixture dramatically changes the outcome of this reaction leading to the formation of the carbamate **2a** in high yield (entry 4). The accelerating effect of fluoroalcohols, such as HFIP and 2,2,2-trifluoroethanol (TFE), on some reactions of hypervalent iodine species was previously reported by Kita and co-workers and several other groups.[11] Iodobenzene has the most pronounced catalytic effect; the use of other iodine containing precatalysts (2,4,6-$Me_3C_6H_2I$, 4-MeC_6H_4I, 4-$CF_3C_6H_4I$, 3-$HO_2CC_6H_4I$, Bu_4NI) instead of PhI gave poor results (entries 12−16). Decreasing amount of PhI from 50 to 20 mol % did not reduce the yields of products (entry 17); however, smaller amount of PhI (10 mol %) led to a slightly lower yield (89−93%) (entry 18). Under the same conditions in the absence of PhI, no reaction occurred (entry 19). In the absence of HFIP, reasonable yields of products (79−85%) could be obtained only using 50 mol % or greater amounts of PhI (entries 1 and 9).

Using the optimized condition with 20 mol % PhI, we have investigated the conversion of various substituted carboxamides **1** to the respective carbamates **2** (Table 2). In general, all benzylcarboxamides with either electron-donating or electron-withdrawing substituents afforded corresponding carbamates **2** in good yields (entries 2−8). As expected, various aliphatic amides, including primary, second, tertiary, and cyclic alkylcarboxamides, have also smoothly reacted under the same conditions giving respective carbamates **2** in good yields (entries 9−21). Compared to the previous method of Hofmann rearrangement with the stoichiometric hypervalent iodine

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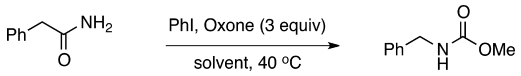
Table 1. Optimization of Catalytic Hofmann Rearrangement with Oxone[a]



1a **2a**

entry	time (h)	PhI (equiv)	solvents (ratio)	yields (%)[b]
1	3	0.5	MeOH–H_2O (10:1)	(79)
2	3	0.5	MeOH–CH_2Cl_2–H_2O (10:10:1)	(47)
3	3	0.5	MeOH–$CHCl_3$–H_2O (10:10:1)	(44)
4	3	0.5	MeOH–HFIP–H_2O (10:10:1)	98 (99)
5	3	0.5	MeOH–TFE–H_2O (10:10:2)	(82)
6	3	0.5	MeOH–THF–H_2O (10:10:1)	*c*
7	3	0.5	MeOH–Et_2O–H_2O (10:10:1)	(13)
8	3	0.5	MeOH–AcOEt–H_2O (10:10:1)	(1)
9	3	0.5	MeOH–hexane–H_2O (10:10:1)	(85)
10	3	0.5	MeOH–CH_3NO_2–H_2O (10:10:1)	(28)
11	3	0.5	MeOH–MeCN–H_2O (10:10:1)	(21)
12	3	0.5[d]	MeOH–HFIP–H_2O (10:10:1)	(13)
13	3	0.5[e]	MeOH–HFIP–H_2O (10:10:1)	(87)
14	3	0.5[f]	MeOH–HFIP–H_2O (10:10:1)	(30)
15	3	0.5[g]	MeOH–HFIP–H_2O (10:10:1)	(59)
16	3	0.5[h]	MeOH–HFIP–H_2O (10:10:1)	*c*
17	5	0.2	MeOH–HFIP–H_2O (10:10:1)	96 (99)
18	10	0.1	MeOH–HFIP–H_2O (10:10:1)	89 (93)
19	3	none	MeOH–HFIP–H_2O (10:10:1)	*c*

[a]All reactions were performed using 3 equiv of Oxone and 1 equiv of phenylacetamide **1a** at 40 °C. [b]Isolated yields (numbers in parentheses show yields determined from ^{1}H NMR spectra of reaction mixtures). [c]No reaction. [d]2,4,6-$Me_3C_6H_2I$ was used instead of PhI. [e]4-MeC_6H_4I was used instead of PhI. [f]4-$CF_3C_6H_4I$ was used instead of PhI. [g]3-$HO_2CC_6H_4I$ was used instead of PhI. [h]*n*-Bu_4NI was used instead of PhI.

species generated in situ, the new method affords carbamates **2** in similar yields.[7a]

In order to gain additional information about the mechanism of this catalytic reaction, we have investigated its stereochemistry. It is known from the literature that the rearrangement of amides to amines proceeds with retention of configuration at the migrating carbon.[3a,8] We have found that the reaction of bicyclic carboxamide **3** with endo configuration under our condition gave the corresponding carbamate **4** with retained endo configuration (Scheme 1). This result implied that the mechanism of the catalytic rearrangement is similar to that of the classical Hofmann rearrangement induced by hypervalent iodine species.

On the basis of the previously reported mechanistic studies of Hofmann rearrangement using hypervalent iodine reagents,[3a,4a,b,8] we propose that the active species **5** [hydroxy(phenyl)iodonium ion $[PhI(OH)]^+$ possibly activated by HFIP] generated from PhI and Oxone in aqueous HFIP further react with carboxamide **1** to give the hypervalent amidoiodane **6** via ligand exchange, which then undergoes the reductive elimination of iodobenzene and the 1,2-shift at the electron-deficient nitrenium nitrogen atom to give isocyanate **7** (Scheme 2). Subsequently, the addition of methanol to isocyanate **7** gives the final carbamate **2**. The regenerated PhI continues the catalytic cycle. The presence of HFIP may help to generate more electron-deficient active species **5** and **6** via ligand exchange with hydroxy(phenyl)iodonium ion or hypervalent aminoiodine, which help to accelerate further steps of the catalytic cycle, such as ligand exchange and 1,2-shift. A similar reaction mechanism of the catalytic Hofmann rearrangement of carboxamide in presence of *m*-CPBA was proposed by Ochiai and co-workers.[8]

In summary, we have developed a new procedure for the Hofmann rearrangement of various carboxamides using catalytic hypervalent iodine and Oxone as a terminal oxidant and HFIP as a co-solvent. This efficient procedure affords corresponding carbamates in high yields under mild conditions. The mechanism of this reaction probably involves the electron-deficient active species formed from hydroxy(phenyl)iodonium ion or hypervalent aminoiodane and HFIP.

EXPERIMENTAL SECTION

All reactions were performed under dry nitrogen atmosphere with flame-dried glassware. All commercial reagents were ACS reagent grade and used without further purification. Carboxamides **1** were from commercial sources (**1a**, **1b**, **1i**, **1j**, **1t**, **1u**) or prepared from corresponding carboxylic acids (Method A) or nitriles (Method B) according to modified literature procedures described below. Dichloromethane was distilled from CaH_2 immediately prior to use. Diethyl ether was distilled from Na/benzophenone. NMR spectra were recorded at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR). Chemical shifts (δ) are reported in parts per million and referenced relative to tetramethylsilane. High resolution mass spectra (ESI-HRMS) were obtained using mass spectrometer with TOF mass analyzer.

General Procedure for Synthesis of Carboxamides. *Method A.* A solution of substituted carboxylic acid RCO_2H (1000 mg) in excess thionyl chloride (5 mL) was refluxed for 3 h. After reaction, the resulting solution of RCOCl was cooled on ice, then aqueous NH_4OH (5 mL) was added, and the precipitate was filtered and dried to give crude carboxamide product. This product was recrystallized from ethanol to give pure amide **1**.

Method B. The substituted nitrile RCN (8.5 mmol) in concentrated hydrochloric acid (41 mmol) was stirred at 65–70 °C for 2 h. After reaction, the solution was cooled, and water (4 mL) was added. The precipitate was filtered and dried to give crude carboxamide product. This product was recrystallized from ethanol to give pure amide **1**.

2-(4-Fluorophenyl)acetamide ***1c***.[12] Reaction of 2-(4-fluorophenyl)acetic acid according to general procedure method A afforded 572 mg (58%) of product **1c**, isolated as colorless needles (recrystallized from ethanol): mp 157.2–157.6 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.49 (br s, 1H), 7.34–7.25 (m, 2H), 7.16–7.08 (br s, 1H), 6.90 (br s, 1H), 3.37 (s, 2H).

2-(4-Chlorophenyl)acetamide ***1d***.[13] Reaction of **2**-(4-chlorophenyl)acetonitrile according to general procedure method B afforded 803 mg (56%) of product **1d**, isolated as colorless needles (recrystallized from ethanol): mp 182.2–182.4 °C (lit.[13] mp 180–182 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.49 (br s, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.91 (br s, 1H), 3.45 (s, 2H).

2-(3-Chlorophenyl)acetamide ***1e***.[13] Reaction of 2-(3-chlorophenyl)acetonitrile according to general procedure method B afforded 873 mg (61%) of product **1e**, isolated as colorless needles (recrystallized from ethanol): mp 131.3–131.7 °C (lit.[13] mp 126.5–128 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.53 (br s, 1H), 7.44–7.18 (m, 4H), 6.95 (br s, 1H), 3.40 (s, 2H).

2-(2-Chlorophenyl)acetamide ***1f***.[13] Reaction of 2-(2-chlorophenyl)acetonitrile according to general procedure method B afforded 856 mg (59%) of product **1f**, isolated as colorless needles (recrystallized from ethanol): mp 172.8–173.3 °C (lit.[13] mp 168–172 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.46 (br s, 1H), 7.43–7.39 (m, 1H), 7.37–7.33 (m, 1H), 7.29–7.25 (m, 2H), 6.96 (br s, 1H), 3.55 (s, 2H).

2-(4-Bromophenyl)acetamide ***1g***.[14] Reaction of 2-(4-bromophenyl)acetonitrile according to general procedure method B afforded 923 mg (50%) of product **1g**, isolated as colorless needles

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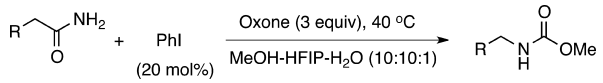
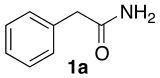
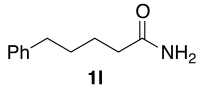
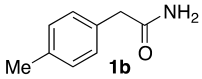
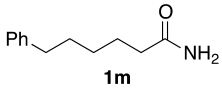
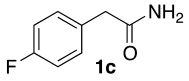
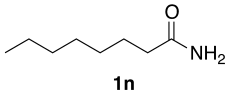
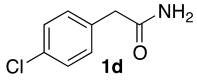
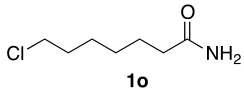
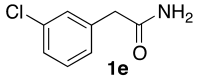
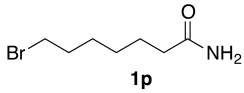
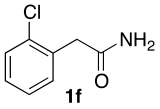
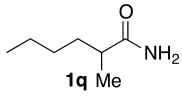
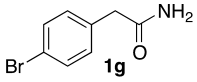
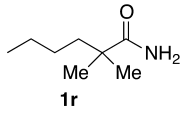
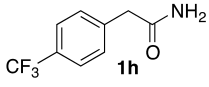
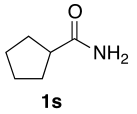
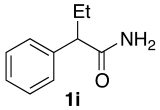
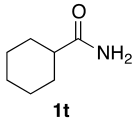
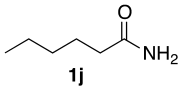
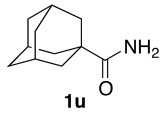
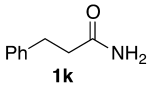
Table 2. Preparation of Carbamates by Hofmann Rearrangement under Catalytic Conditions[a]

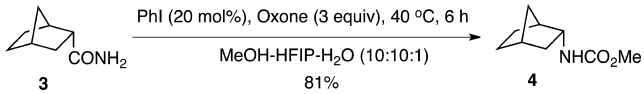


1 2

Entry	Time (h)	Carboxamide 1	Product 2	Yield (%)[b]	Entry	Time (h)	Carboxamide 1	Product 2	Yield (%)[b]
1	5	 1a	**2a**	96 (97)	12	7.5	 1l	**2l**	85
2	5	 1b	**2b**	96 (93)	13[c]	7.5	 1m	**2m**	84
3	7	 1c	**2c**	86	14	8	 1n	**2n**	86
4	7	 1d	**2d**	93	15	8	 1o	**2o**	85
5	7	 1e	**2e**	86	16	8	 1p	**2p**	78
6	7	 1f	**2f**	88	17	8	 1q	**2q**	73
7	7	 1g	**2g**	85	18	8	 1r	**2r**	70
8	9	 1h	**2h**	78	19	6	 1s	**2s**	83
9	5	 1i	**2i**	96	20	6	 1t	**2t**	92 (89)
10	8	 1j	**2j**	92 (100)	21	5	 1u	**2u**	98 (90)
11	7.5	 1k	**2k**	91					

[a]All reactions of amides **1** (1 equiv) were performed at 40 °C in the presence of PhI (0.2 equiv) and Oxone (3 equiv) in MeOH−HFIP−H_2O. [b]Isolated yields; the yields shown in parentheses correspond to the literature[7a] data for the synthesis of carbamates **2** from carboxamides **1** using PhI (1 equiv) and Oxone (2 equiv).

Scheme 1. Retention of Configuration in Hofmann Rearrangement under Catalytic Conditions



3 4

(recrystallized from ethanol): mp 194.1−194.7 °C (lit.[14] mp 197−198 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.55−7.44 (br s, 1H), 7.50 (d, J = 7.3 Hz, 2H), 7.23 (d, J = 7.3 Hz, 2H), 6.92 (br s, 1H), 3.37 (s, 2H).

2-[(4-Trifluoromethyl)phenyl]acetamide ***1h.***[8] Reaction of 2-(4-trifluoromethyl)acetonitrile according to general procedure method B afforded 866 mg (50%) of product **1h**, isolated as colorless blocks (recrystallized from ethanol): mp 149.9−150.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.66 (d, J = 8.0 Hz, 2H), 7.59 (brs, 1H), 7.49 (d, J = 8.0 Hz, 2H), 6.98 (br s, 1H).

5-Phenylpentanamide ***1l.***[15] Reaction of 5-phenylpentanoic acid according to general procedure method A afforded 147 mg (15%) of product **1l**, isolated as light brown needles (recrystallized from ethanol): mp 106.8−107.3 °C (lit.[15] mp 102−104 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.44−7.12 (m, 6H), 6.73 (br s, 1H), 2.80−2.50 (m, 2H), 2.50−2.00 (m, 2H), 1.75−1.45 (m, 2H).

6-Phenylhexanamide ***1m.***[16] Reaction of 6-phenylhexanoic acid (500 mg) according to general procedure method A afforded 228 mg (46%) of product **1m**, isolated as light brown needles (recrystallized from ethanol): mp 93.1−93.4 °C (lit.[16] mp 94−96 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.34−7.13 (m, 6H), 6.70 (br s, 1H), 2.56 (t, J = 7.8 Hz, 2H), 2.04 (t, J = 7.6 Hz, 2H), 1.62−1.46 (m, 4H), 1.27 (quint, J = 7.6 Hz, 2H).

Octanamide ***1n.***[17] Reaction of octanoic acid according to general procedure method A afforded 267 mg (27%) of product **1n**, isolated as light brown needles (recrystallized from ethanol): mp 103.7−103.9 °C

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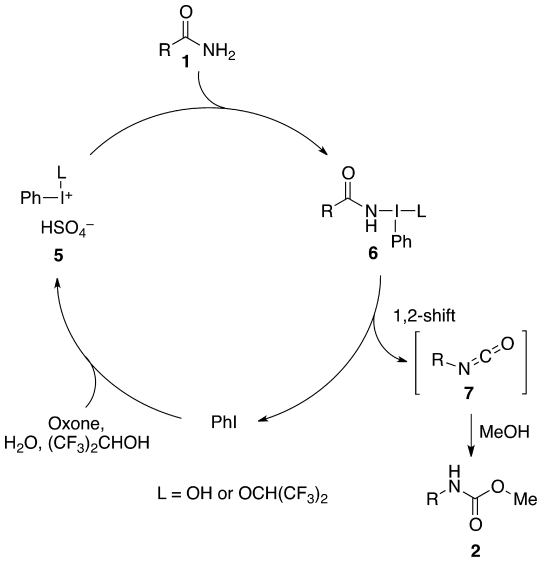
Scheme 2. Proposed Reaction Mechanism



(lit.[17] mp 109–110 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.23 (br s, 1H), 6.67 (br s, 1H), 2.02 (t, J = 7.3 Hz, 2H), 1.56–1.40 (m, 2H), 1.34–1.16 (m, 8H), 0.86 (t, J = 6.5 Hz, 3H).

7-Chloroheptanamide **1o**.[18] Reaction of 7-chloroheptanenitrile according to general procedure method B afforded 123 mg (11%) of product **1o**, isolated as colorless needles (recrystallized from ethanol): mp 81.9–82.6 °C (lit.[18] mp 82–83 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.21 (br s, 1H), 6.67 (br s, 1H), 3.62 (t, J = 7.5 Hz, 2H), 2.03 (t, J = 7.5 Hz, 2H), 1.76–1.65 (m, 2H), 1.53–1.43 (m, 2H), 1.42–1.32 (m, 2H), 1.30–1.21 (m, 2H).

7-Bromoheptanamide **1p**.[19] Reaction of 7-bromoheptanenitrile according to general procedure method B afforded 526 mg (48%) of product **1p**, isolated as colorless needles (recrystallized from ethanol): mp 83.2–83.6 °C (lit.[19] mp 84 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.21 (br s, 1H), 6.67 (br s, 1H), 3.52 (t, J = 7.8 Hz, 2H), 2.03 (t, J = 7.5 Hz, 2H), 1.84–1.74 (m, 2H), 1.54–1.43 (m, 2H), 1.42–1.33 (m, 2H), 1.31–1.20 (m, 2H).

2-Methylhexanamide **1q**.[20] Reaction of 2-methylhexanoic acid according to general procedure method A afforded 75 mg (8%) of product **1q**, isolated as light brown needles (recrystallized from ethanol): mp 62.2–62.8 °C (lit.[20] mp 68.5–69 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.19 (br s, 1H), 6.64 (br s, 1H), 2.23–2.13 (m, 1H), 1.54–1.40 (m, 1H), 1.32–1.13 (m, 5H), 0.96 (t, J = 6.5 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H).

2,2-Dimethylhexanamide **1r**.[21] Reaction of 2,2-dimethylhexanoic acid (500 mg) according to general procedure method A afforded 83 mg (17%) of product **1r**, isolated as colorless needles (recrystallized from ethanol): mp 92.5–92.9 °C (lit.[21] mp 93–93.5 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.97 (br s, 1H), 6.69 (br s, 1H), 1.42–1.37 (m, 2H), 1.28–1.19 (m, 2H), 1.18–1.09 (m, 2H), 1.03 (s, 6H), 0.86 (t, J = 7.3 Hz, 3H).

Cyclopentanecarboxamide **1s**.[22] Reaction of cyclopentanecarboxylic acid according to general procedure method A afforded 107 mg (11%) of product **1s**, isolated as light brown needles (recrystallized from ethanol): mp 171.3–172.2 °C (lit.[22] mp 174–175 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.29 (br s, 1H), 6.66 (br s, 1H), 1.82–1.68 (m, 2H), 1.66–1.54 (m, 4H), 1.54–1.43 (m, 2H).

Bicyclo[2.2.1]heptane-2-carboxamide **3**.[8] Reaction of norbornane-2-carboxylic acid (*endo* major isomer) according to general procedure method A afforded 94 mg (10%) of product **3**, isolated as white solid (*endo*:*exo* = 88:12); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.12 (br s, 1H), 6.71 (br s, 1H), 2.60–2.40 (m, 2H), 2.20–2.08 (m, 1H), 1.56–1.51 (m, 1H), 1.50–1.22 (m, 6H), 1.19–1.10 (m, 1H).

General Procedure for Catalytic Hofmann Rearrangement of Carboxamides. To a solution of amide **1** (0.25 mmol) in a solvent mixture of MeOH (0.75 mL), HFIP (0.75 mL), and H_2O (0.075 mL) were added Oxone (460 mg, 0.75 mmol) and PhI (10 mg, 0.05 mmol). The reaction was stirred at 40 °C for 5–9 h (reaction completion was controlled by TLC). After completion, the reaction mixture was filtered, the inorganic solids on the filter were washed with CH_2Cl_2, then 5% aqueous $Na_2S_2O_3$ (5 mL) was added to the filtrate, and the resulting solution was extracted with dichloromethane. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. Purification by preparative TLC (hexane–ethyl acetate = 2:1 or 3:1) afforded analytically pure carbamates **2**.

Methyl N-Benzylcarbamate **2a**.[7a] Reaction of 2-phenylacetamide **1a** (34 mg, 0.25 mmol) according to general procedure afforded 40 mg (96%) of product **2a**, isolated as colorless needles (recrystallized from dichloromethane–hexane): mp 62.2–62.9 °C (lit.[12] mp 63–65 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, J = 7.8 Hz, 2H), 7.31–7.25 (m, 3H), 4.98 (br s, 1H), 4.37 (d, J = 5.5 Hz, 2H), 3.70 (s, 3H).

Methyl N-(4-Methylbenzyl)carbamate **2b**.[7a] Reaction of 2-(*p*-tolyl)acetamide **1b** (37 mg, 0.075 mmol) according to general procedure afforded 43 mg (96%) of product **2b**, isolated as colorless needles (recrystallized from dichloromethane–hexane): mp 71.5–72.2 °C (lit.[7a] mp 68–70 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 7.5 Hz, 2H), 7.14 (d, J = 7.5 Hz, 2H), 4.92 (br s, 1H), 4.33 (d, J = 5.5 Hz, 2H), 3.7 (s, 3H), 2.34 (s, 3H).

Methyl N-(4-Fluorobenzyl)carbamate **2c**.[23] Reaction of 2-(4-fluorophenyl)acetamide **1c** (38 mg, 0.25 mmol) according to general procedure afforded 39 mg (86%) of product **2c**, isolated as colorless needles (recrystallized from dichloromethane–hexane): mp 70.7–71.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.21 (m, 2H), 7.25–6.98 (m, 2H), 5.09 (br s, 1H), 4.32 (d, J = 5.5 Hz, 2H), 3.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4 (d, J_{CF} = 245.9 Hz), 157.3, 134.6, 129.4 (d, $^3J_{CF}$ = 245.9 Hz), 115.7 (d, $^2J_{CF}$ = 21.6 Hz), 52.5, 44.6.

Methyl N-(4-Chlorobenzyl)carbamate **2d**.[24] Reaction of 2-(4-chlorophenyl)acetamide **1d** (42 mg, 0.25 mmol) according to general procedure afforded 46 mg (93%) of product **2d**, isolated as colorless needles (recrystallized from dichloromethane–hexane): mp 80.9–81.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 5.09 (br s, 1H), 4.33 (d, J = 5.5 Hz, 2H), 3.7 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 137.2, 133.2, 128.8, 128.8, 52.3, 44.4.

Methyl N-(3-Chlorobenzyl)carbamate **2e**.[25] Reaction of 2-(3-chlorophenyl)acetamide **1e** (42 mg, 0.25 mmol) according to general procedure afforded 43 mg (86%) of product **2e**, isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.22 (m, 3H), 7.16 (d, J = 6.0 Hz, 1H), 5.12 (br s, 1H), 4.34 (d, J = 5.5 Hz, 2H), 3.70 (s, 3H).

Methyl N-(2-Chlorobenzyl)carbamate **2f**.[24] Reaction of 2-(2-chlorophenyl)acetamide **1f** (42 mg, 0.25 mmol) according to general procedure afforded 44 mg (88%) of product **2f**, isolated as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.33 (m, 2H), 7.26–7.20 (m, 2H), 5.24 (br s, 1H), 4.44 (d, J = 6.5 Hz, 2H), 3.68 (s, 3H).

Methyl N-(4-Bromobenzyl)carbamate **2g**.[26] Reaction of 2-(4-bromophenyl)acetamide **1g** (54 mg, 0.25 mmol) according to general procedure afforded 52 mg (85%) of product **2g**, isolated as colorless needles (recrystallized from dichloromethane–hexane): mp 93.7–94.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 5.09 (br s, 1H), 4.31 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 137.7, 131.7, 129.2, 121.3, 52.3, 44.5.

Methyl N-(4-Trifluoromethylbenzyl)carbamate **2h**. Reaction of 2-[(4-trifluoromethyl)phenyl]acetamide **1h** (51 mg, 0.25 mmol) according to general procedure afforded 45 mg (78%) of product **2h**, isolated as colorless needles (recrystallized from dichloromethane–hexane): mp 88.5–89.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 5.22 (br s, 1H), 4.42 (d, J = 6.0 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 143.0, 130.0 (d, $^2J_{CF}$ = 32.6 Hz), 127.8, 125.8 (d, $^3J_{CF}$ = 3.9 Hz), 124.3 (q, J_{CF} = 272.1 Hz), 52.6, 44.8; HRMS (ESI): calcd for $C_{10}H_{10}F_3NO_2Na$ ($[M + Na]^+$): 256.0561, found: 256.0552.

Methyl N-(1-Phenylpropyl)carbamate **2i**.[5] Reaction of 2-phenylbutanamide **1i** (41 mg, 0.25 mmol) according to general procedure afforded 46 mg (96%) of product **2i**, isolated as a light brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.32–7.28 (m,

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3H), 5.11 (br s, 1H), 4.68−4.54 (m, 1H), 3.66 (s, 3H), 1.92−1.72 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H).

Methyl N-Pentylcarbamate ***2j***.[5] Reaction of hexanamide **1j** (29 mg, 0.25 mmol) according to general procedure afforded 33 mg (92%) of product **2j**, isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62 (br s, 1H), 3.66 (s, 3H), 3.22−3.06 (m, 2H), 1.49 (quint, J = 7.0 Hz, 2H), 1.38−1.24 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H).

Methyl N-(2-Phenylethyl)carbamate ***2k***.[27] Reaction of 3-phenylpropanamide **1k** (37 mg, 0.25 mmol) according to general procedure afforded 41 mg (91%) of product **2k** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 2H), 4.74 (br s, 1H), 3.65 (s, 3H), 3.52−3.34 (m, 2H), 2.81 (t, J = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 138.8, 128.9, 128.6, 126.5, 52.0, 42.2, 36.2.

Methyl N-(4-Phenylbutyl)carbamate ***2l***.[8] Reaction of 5-phenylpentanamide **1l** (44 mg, 0.25 mmol) according to general procedure afforded 44 mg (85%) of product **2l** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 7.5 Hz, 2H), 7.22−7.14 (m, 3H), 4.68 (br s, 1H), 3.65 (s, 3H), 3.24−3.10 (m, 2H), 2.62 (t, J = 7.3 Hz, 2H). 1.64 (quint, J = 7.3 Hz, 2H), 1.52 (quint, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 142.1, 128.4, 128.3, 125.8, 52.0, 40.9, 35.5, 29.6, 28.5.

Methyl N-(5-Phenylpentyl)carbamate ***2m***.[28] Reaction of 6-phenylhexanamide **1m** (46 mg, 0.25 mmol) according to general procedure afforded 46 mg (84%) of product **2m** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 7.5 Hz, 2H), 7.20−7.14 (m, 3H), 4.69 (br s, 1H), 3.65 (s, 3H), 3.20−3.06 (m, 2H), 2.61 (t, J = 7.5 Hz, 2H). 1.68−1.59 (m, 2H), 1.56−1.47 (m, 2H), 1.35 (quint, J = 7.5 Hz, 2H).

Methyl N-Heptylcarbamate ***2n***.[29] Reaction of octylamide **1n** (36 mg, 0.25 mmol) according to general procedure afforded 37 mg (86%) of product **2n**, isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (br s, 1H), 3.66 (s, 3H), 3.24−3.08 (m, 2H), 1.55−1.44 (m, 2H), 1.38−1.21 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H).

Methyl N-(6-Chloro)hexylcarbamate ***2o***.[30] Reaction of 7-chlorohexanamide **1o** (41 mg, 0.25 mmol) according to general procedure afforded 41 mg (85%) of product **2o**, isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (br s, 1H), 3.66 (s, 3H), 3.53 (t, J = 6.5 Hz, 2H), 3.18 (q, J = 6.5 Hz, 2H), 1.78 (quint, J = 7.5 Hz, 2H), 1.56−1.42 (m, 2H), 1.39−1.30 (m, 2H).

Methyl N-(6-Bromo)hexylcarbamate ***2p***.[31] Reaction of 7-bromohexanamide **1p** (52 mg, 0.25 mmol) according to general procedure afforded 47 mg (78%) of product **2p**, isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (br s, 1H), 3.66 (s, 3H), 3.41 (t, J = 7 Hz, 2H), 3.18 (q, J = 6.3 Hz, 2H), 1.86 (quint, J = 7 Hz, 2H), 1.57−1.41 (m, 4H), 1.39−1.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 52.2, 41.1, 34.0, 32.9, 30.1, 28.0, 26.1.

Methyl N-(2-Methyl)pentylcarbamate ***2q***. Reaction of 2-methylhexanamide **1q** (32 mg, 0.25 mmol) according to general procedure afforded 29 mg (73%) of product **2q**, isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (br s, 1H), 3.65 (s, 3H), 1.46−1.24 (m, 7H), 1.13 (d, J = 6.5 Hz, 3H), 0.90 (t, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 51.8, 47.1, 36.9, 28.1, 22.6, 21.3, 14.0; HRMS (ESI): calcd for $C_8H_{17}NO_2Na$ ($[M + Na]^+$) 182.1157, found: 182.1158.

Methyl N-(2,2-Dimethyl)butylcarbamate ***2r***. Reaction of 2,2-dimethylpentanamide **1r** (36 mg, 0.25 mmol) according to general procedure afforded 30 mg (70%) of product **2r**, isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (br s, 1H), 3.61 (s, 3H), 1.64−1.56 (m, 2H), 1.35−1.20 (m, 4H), 1.27 (s, 6H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 52.7, 51.4, 40.6, 27.0, 26.3, 23.1, 14.1; HRMS (ESI): calcd for $C_9H_{19}NO_2Na$ ($[M + Na]^+$) 196.1313, found: 196.1314.

Methyl N-Cyclopentylcarbamate ***2s***.[32] Reaction of cyclopentanecarboxamide **1s** (30 mg, 0.25 mmol) according to general procedure afforded 30 mg (83%) of product **2s**, isolated as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (br s, 1H), 3.97 (br s, 1H), 3.65 (s, 3H), 2.02−1.88 (m, 2H), 1.71−1.53 (m, 4H), 1.44−1.32 (m, 2H).

Methyl N-Cyclohexylcarbamate ***2t***.[7a] Reaction of cyclohexanecarboxamide **1t** (32 mg, 0.25 mmol) according to general procedure afforded 36 mg (92%) of product **2t**, isolated as colorless needles (recrystallized from dichloromethane−hexane): mp 74.6−75.2 °C (lit.[7a] mp 73.5−74.5 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (br s, 1H), 3.65 (s, 3H), 3.48 (br s, 1H), 1.98−1.86 (m, 2H), 1.75−1.65 (m, 2H), 1.64−1.56 (m, 1H), 1.4−1.28 (m, 2H), 1.22−1.06 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 51.8, 49.8, 33.5, 25.5, 24.8.

Methyl N-(1-Adamantanyl)carbamate ***2u***.[7a] Reaction of 1-adamantanecarboxamide **1u** (45 mg, 0.25 mmol) according to general procedure afforded 51 mg (98%) of product **2u**, isolated as colorless needles (recrystallized from dichloromethane−hexane): mp 118.4−118.9 °C (lit.[7a] mp 118−120 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.51 (br s, 1H), 3.61 (s, 3H), 2.08 (s, 3H), 1.93 (s, 6H), 1.67 (s, 6H).

endo-Methyl N-Bicyclo[2.2.1]-2-heptyl-carbamate ***4***.[33] Reaction of bicyo[2.2.1]heptane-2-carboxamide (*endo*:*exo* = 88:12) **3** (35 mg, 0.25 mmol) according to general procedure afforded 34 mg (81%; *endo*:*exo* = 88:12) of product **4**, isolated as white solid: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.71 (br s, 1H), 3.92 (br s, 1H), 3.66 (s, 3H), 2.46−2.31 (m, 1H), 2.20 (s, 1H), 2.14−1.98 (m, 1H), 1.66−1.06 (m, 6H), 0.69 (d, J = 13 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8, 52.3, 51.9, 40.4, 38.1, 37.9, 37.0, 29.9, 21.4.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra for all 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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