A Mild and Efficient Catalytic Mannich-Type Reaction as a Simple Access to *N*-Benzyloxycarbonyl β-Amino Ketones[1]

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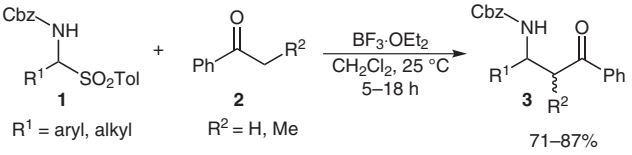
Abstract: *N*-Benzyloxycarbonylamino sulfones react with aromatic ketones in the presence of catalytic amount of boron trifluoride–diethyl ether at room temperature to afford the corresponding protected β-amino ketones in high yields (71–87%).

Key words: α-amido sulfones, stable imine precursors, aromatic ketones, $BF_3{\cdot}OEt_2$, Lewis acids, β-amino ketones



Scheme 1 Synthesis of *N*-benzyloxycarbonyl β-amino ketones from *N*-benzyloxycarbonylamino sulfones

β-Amino carbonyl compounds exhibit significant biological activity[2] and their skeleton is present in different medicinally important compounds.[3] They are also valuable building blocks for the synthesis of pharmaceuticals and bioactive natural molecules.[4] Paclitaxel, a prominent anticancer compound, contains a β-amino carbonyl function in its side chain, which is an important segment for its bioactivity.[5] The general protocol for the synthesis of β-amino carbonyl compounds is the Mannich-type reaction of aldehydes, amines (or directly imines), and enolizable ketones or silyl enolates. Several methods have been developed involving these reactions,[6] however, many of these methods have different drawbacks, such as the use of toxic reagents and expensive catalysts in excess, long reaction times, drastic conditions, and unsatisfactory yields. Moreover, several Lewis acid catalysts required to perform these Mannich-type reactions deactivate or decompose in the presence of amines and water produced during imine formation and many of the imines are unstable. Here, we report the application of *N*-benzyloxycarbonylamino sulfones for a simple and efficient synthesis of protected β-amino ketones.

In continuation of our work[7] on the development of useful synthetic methodologies using *N*-benzyloxycarbonylamino sulfones **1** (generally referred as α-amido sulfones) we have found that the treatment of these compounds with aromatic ketones **2** in the presence of a catalytic amount of boron trifluoride–diethyl ether complex afforded the corresponding protected β-amino ketones **3** at room temperature (Scheme 1).

Initially *N*-benzyloxycarbonylamino sulfone **1a** (R^1 = Ph) was treated with acetophenone (**2a**, R^2 = H) at 25 °C in the presence of various Lewis acids (Table 1). Consideration of the reaction time and yield identified boron trifluoride–diethyl ether complex (25 mol%) as the most effective catalyst. Subsequently this catalyst was used to prepare a series of Cbz-protected β-amino ketones **3** (Table 2) following the above procedure (Scheme 1); earlier methods for preparation of these compounds are limited.[6,8]

N-Benzyloxycarbonylamino sulfones **1** derived[9] from aromatic, heteroaromatic, and aliphatic aldehydes were employed in this conversion; the aromatic aldehydes contained both electron-donating and electron-withdrawing groups. The reaction times required for the conversion of the sulfones containing an aromatic ring with an electron-donating group into Cbz-protected β-amino ketones **3b–h** were 5–10 hours. However, the conversion of *N*-benzyloxycarbonylamino sulfones derived from aromatic aldehydes with electron-withdrawing group or from aliphatic aldehydes into Cbz-protected β-amino ketones **3i**,**j**,**m**,**n** required somewhat longer reaction times (15–18 h). The reaction conditions were mild and the products **3a–r** were formed in high yields (71–87%). Different functionalities, such as an ether, a halogen, and a nitro group, remained intact. The sulfone prepared from a sterically hindered aldehyde, such as 2-naphthaldehyde, underwent the conversion smoothly to give **3k** in 83% yield. When the reaction was carried out with propiophenone both *anti*- and *syn*-isomers were formed and these were carefully separated; the *anti*-isomer was the major isomer. The structures of all the products were confirmed by their spectral data [IR, ^{1}H and ^{13}C NMR, ESI-MS, and HRMS (ESI)]. The *anti*- and *syn*-isomers were characterized by comparison of their ^{1}H NMR spectral values with those of known or related compounds.[6,8,10] In the ^{1}H NMR spectrum the coupling constant between H2 and H3 for the *anti*-isomer is known to be 6–8 Hz while for a *syn*-isomer it is 3–5 Hz. The NH proton of the *anti*-isomer also resonates upfield (δ = 5.0–5.5) compared to that of the *syn*-isomer (δ = 6.5–7.0).

Additionally, the *anti*- and *syn*-isomers were directly compared with the authentic compounds prepared by our earlier reported method.[6f] The *N*-Cbz group of the products can easily be deprotected[11] to generate β-amino ke-

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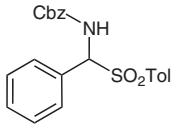
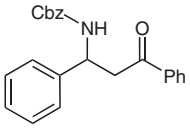
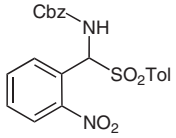
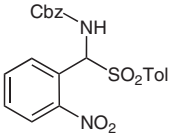
Table 1 Evaluation of the Catalytic Activity of Different Catalysts for the Preparation of *N*-Benzyloxycarbonyl β-Amino Ketones **3a**,**i**[a]

Entry	α-Amido sulfone	β-Amino ketone	Catalyst	Time (h)	Yield[b] (%)
1			$BF_3{\cdot}OEt_2$	8	87
			$Cu(OTf)_2$	15	61
			$Bi(OTf)_3$	15	67
			$Yb(OTf)_3$	15	65
			$Sc(OTf)_3$	15	63
			$La(OTf)_3$	15	59
			$FeCl_3$	24	51
			$InCl_3$	24	43
			$ZrCl_4$	24	39
			CuI	24	31
2			$BF_3{\cdot}OEt_2$	15	78
			$Cu(OTf)_2$	20	53
			$Bi(OTf)_3$	20	59
			$Yb(OTf)_3$	20	54
			$Sc(OTf)_3$	20	51
			$La(OTf)_3$	20	53
			$FeCl_3$	24	41
			$InCl_3$	24	39
			$ZrCl_4$	24	28
			CuI	24	19

[a] Reaction conditions: α-amido sulfone **1** (1.0 mmol), acetophenone (**2a**, 1.2 mmol), catalyst (25 mol%), CH_2Cl_2 (5 mL), 25 °C, N_2.
[b] Isolated yield.

tones. The free amine group can be utilized to synthesis different analogues of the compounds. To our knowledge, the present conversion is the first catalytic Mannich-type reaction of *N*-benzyloxycarbonylamino sulfones with aromatic ketones. The only other report of such reaction of these sulfones is known with silyl enolates in the presence of bismuth(III) triflate.[8,12]

N-Benzyloxycarbonylamino sulfones can be easily prepared[9] from aldehydes and are generally stable solids. They are known to be converted into the corresponding *N*-acyliminium ions **A** (containing a positively charged nitrogen atom) on treatment with an appropriate Lewis acid. Here, in the presence of boron trifluoride–diethyl ether complex, *N*-benzyloxycarbonylamino sulfones were converted into **A** which was then attacked by aromatic ketones in the enolic form to produce the Cbz-protected β-amino ketones (Scheme 2).

In conclusion, we have developed a simple, mild, and efficient method for the synthesis of protected β-amino ketones at room temperature and in high yields by treatment of *N*-benzyloxycarbonylamino sulfones (prepared from both aromatic and aliphatic aldehydes) with aromatic ketones in the presence of boron trifluoride–diethyl ether complex as a catalyst.

The spectra were recorded with the following instruments; IR: Perkin-Elmer RX1 FT-IR spectrophotometer; NMR: Varian Gemini 200 MHz (^1H) and 50 MHz (^{13}C) spectrometer; ESI-MS: VG-Autospec micromass; and HRMS: QSTAR XL, Hybrid MS system (Applied Biosystems). Column chromatography was performed over silica gel (BDH 100–200 mesh). Solvents were purified according to standard procedures. The silica gel F_{254} plates were used for TLC.

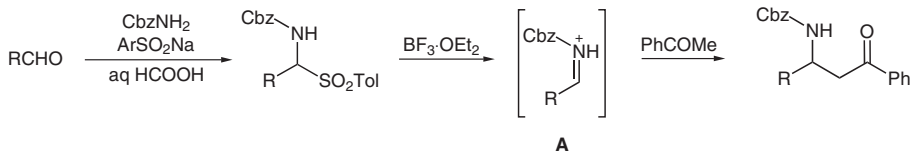
Benzyl 3-Oxo-3-diphenylpropylcarbamates 3; General Procedure

To a soln of *N*-benzyloxycarbonylamino sulfone **1** (1.0 mmol) in CH_2Cl_2 (5 mL) was added aromatic ketone (acetophenone or propiophenone) **2** (1.2 mmol) under an N_2 atmosphere. $BF_3{\cdot}OEt_2$ (0.25 mmol) was added dropwise to this mixture, which was stirred at r.t. (TLC monitoring). When the reaction was complete, the mixture was washed with cold H_2O (2 × 5 mL) and subsequently extracted with EtOAc (2 × 10 mL). The extract was dried (anhyd Na_2SO_4) and concentrated under vacuum. The residue was subjected to column chromatography (silica gel, 4–15% EtOAc–hexane) to give pure **3**.

Benzyl 3-Oxo-1,3-diphenylpropylcarbamate (3a)

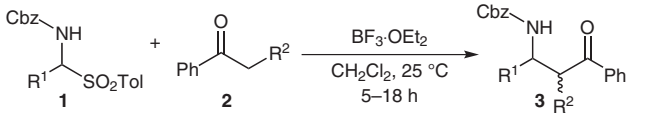
IR (KBr): 3371, 1721, 1680, 1525, 1449, 1290 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.0 Hz, 2 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.37–7.19 (m, 10 H), 5.85 (br s, 1 H), 5.30 (m, 1 H), 5.11 (d, *J* = 12.0 Hz, 1 H), 5.04 (d, *J* = 12.0 Hz, 1 H), 3.70 (br d, *J* = 14.0 Hz, 1 H), 3.42 (dd, *J* = 14.0, 6.0 Hz, 1 H).



Scheme 2 Formation of *N*-protected β-amino ketones through an *N*-acyliminium ion

Table 2 Synthesis of *N*-Benzyloxycarbonyl β-Amino Ketones **3** by the Reaction of Various α-Amido Sulfones and Aromatic Ketones in the Presence of $BF_3{\cdot}OEt_2$[a]



Entry	R^1	R^2	Product	Time (h)	Yield[b] (%)	Ratio[c] *syn*/*anti*
1	Ph	H	**3a**	8	87	–
2	4-FC_6H_4	H	**3b**	7	85	–
3	4-ClC_6H_4	H	**3c**	5	86	–
4	4-BrC_6H_4	H	**3d**	5	84	–
5	2-BrC_6H_4	H	**3e**	6	82	–
6	4-MeC_6H_4	H	**3f**	9	83	–
7	4-EtO-3-$MeOC_6H_3$	H	**3g**	10	82	–
8	3,4,5-$(MeO)_3C_6H_2$	H	**3h**	10	83	–
9	2-$O_2NC_6H_4$	H	**3i**	15	78	–
10	4-NCC_6H_4	H	**3j**	14	79	–
11	2-naphthyl	H	**3k**	10	83	–
12	2-thienyl	H	**3l**	9	81	–
13	cyclohexyl	H	**3m**	17	72	–
14	CH_2CHMe_2	H	**3n**	18	71	–
15	4-FC_6H_4	Me	**3o**	7	85	45:55
16	4-ClC_6H_4	Me	**3p**	7	87	39:61
17	3,4,5-$(MeO)_3C_6H_2$	Me	**3q**	10	81	48:52
18	2-naphthyl	Me	**3r**	10	82	45:55

[a] Reaction conditions: α-amido sulfone **1** (1.0 mmol), acetophenone or propiophenone **2** (1.2 mmol), catalyst (25 mol%), CH_2Cl_2 (5 mL), 25 °C, N_2.
[b] Isolated yield.
[c] Ratio *syn*/*anti*-isomers determined by ^{1}H NMR spectroscopy

^{13}C NMR (50 MHz, $CDCl_3$): δ = 196.8, 156.2, 141.5, 135.9, 135.8, 134.4, 129.1, 128.5, 127.3, 126.4, 66.6, 51.7, 43.9.

MS (ESI): *m*/*z* = 360 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{21}NNaO_3$: 382.1419; found: 382.1407.

Benzyl 1-(4-Fluorophenyl)-3-oxo-3-phenylpropylcarbamate (3b)

IR (KBr): 3337, 1691, 1510, 1451, 1225 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.0 Hz, 2 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 7.35–7.22 (br s, 7 H), 7.04–6.90 (m, 2 H), 5.89 (br s, 1 H), 5.29 (m, 1 H), 5.11 (d, *J* = 12.0 Hz, 1 H), 5.04 (d, *J* = 12.0 Hz, 1 H), 3.62 (dd, *J* = 14.0, 4.0 Hz, 1 H), 3.41 (dd, *J* = 14.0, 6.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.8, 155.2, 136.6, 135.5 (d, *J* = 10.0 Hz), 134.3, 128.0, 127.5, 126.8, 66.2, 50.3, 44.1.

MS (ESI): *m*/*z* = 378 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{20}FNNaO_3$: 400.1324; found: 400.1317.

Benzyl 1-(4-Chlorophenyl)-3-oxo-3-phenylpropylcarbamate (3c)

IR (KBr): 3334, 1696, 1499, 1250 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 2 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.36–7.19 (m, 9 H), 5.99 (d, *J* = 8.0 Hz, 1 H), 5.21 (m, 1 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 5.02 (d, *J* = 12.0 Hz, 1 H), 3.67 (br d, *J* = 14.0 Hz, 1 H), 3.22 (dd, *J* = 14.0, 6.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.2, 155.8, 140.0, 136.6, 136.5, 134.2, 134.0, 129.7, 128.6, 127.5, 127.2, 127.0, 66.2, 50.8, 44.3.

MS (ESI): *m*/*z* = 394, 396 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{20}ClNNaO_3$: 416.1029; found: 416.1015.

Benzyl 1-(4-Bromophenyl)-3-oxo-3-phenylpropylcarbamate (3d)

IR (KBr): 3318, 1682, 1534, 1491, 1251 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.0 Hz, 2 H), 7.53 (t, *J* = 8.0 Hz, 1 H), 7.46–7.35 (m, 4 H), 7.31–7.18 (m, 7 H), 5.89 (br s, 1 H), 5.20 (m, 1 H), 5.07 (d, *J* = 12.0 Hz, 1 H), 5.02 (d, *J* = 12.0 Hz, 1 H), 3.69 (br d, *J* = 14.0 Hz, 1 H), 3.34 (d, *J* = 14.0, 6.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.0, 155.1, 140.1, 135.8, 134.2, 130.7, 129.8, 128.0, 127.5, 127.3, 126.6, 66.2, 50.7, 44.6.

MS (ESI): *m*/*z* = 438, 440 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{20}BrNNaO_3$: 460.0524; found: 460.0508.

Benzyl 1-(2-Bromophenyl)-3-oxo-3-phenylpropylcarbamate (3e)

IR (KBr): 3330, 1695, 1541, 1450, 1275 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.0 Hz, 2 H), 7.60–7.21 (m, 11 H), 7.09 (t, *J* = 8.0 Hz, 1 H), 6.29 (br s, 1 H), 5.61 (m, 1 H), 5.11 (d, *J* = 12.0 Hz, 1 H), 5.02 (d, *J* = 8.0 Hz, 1 H), 3.72 (br d, *J* = 14.0 Hz, 1 H), 3.45 (dd, *J* = 14.0, 4.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.5, 155.2, 136.2, 134.2, 134.0, 129.8, 129.6, 129.5, 128.7, 127.9, 66.0, 51.4, 41.2.

MS (ESI): *m*/*z* = 438, 440 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{20}BrNNaO_3$: 460.0524; found: 460.0532.

Benzyl 3-Oxo-3-phenyl-1-(4-tolyl)propylcarbamate (3f)

IR (KBr): 3378, 1720, 1682, 1530, 1447, 1290 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.0 Hz, 2 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.79–7.28 (br s, 5 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 5.82 (br s, 1 H), 5.30 (m, 1 H), 5.11 (d, *J* = 12.0 Hz, 1 H), 5.02 (d, *J* = 12.0 Hz, 1 H), 3.70 (br d, *J* = 14.0 Hz, 1 H), 3.42 (dd, *J* = 14.0, 6.0 Hz, 1 H), 2.29 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.6, 155.4, 138.0, 136.8, 136.0, 135.9, 134.4, 129.8, 129.0, 128.1, 125.4, 66.2, 51.4, 44.6, 20.3.

MS (ESI): *m*/*z* = 374 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{23}NNaO_3$: 396.1575; found: 396.1572.

Benzyl 1-(4-Ethoxy-3-methoxyphenyl)-3-oxo-3-phenylpropylcarbamate (3g)
IR (KBr): 3343, 1716, 1593, 1513, 1454, 1260 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.0 Hz, 2 H), 7.51 (t, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.35–7.21 (br s, 5 H), 6.90–6.69 (m, 3 H), 5.74 (br s, 1 H), 5.20 (m, 1 H), 5.11 (d, *J* = 12.0 Hz, 1 H), 5.02 (d, *J* = 12.0 Hz, 1 H), 4.02 (q, *J* = 7.0 Hz, 2 H), 3.80 (s, 3 H), 3.69 (br d, *J* = 14.0 Hz, 1 H), 3.36 (dd, *J* = 14.0, 6.0 Hz, 1 H), 1.40 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.6, 156.8, 153.8, 148.0, 137.2, 134.8, 134.6, 127.6, 127.5, 127.3, 118.2, 112.5, 110.4, 66.0, 54.9, 55.1, 51.8, 44.9, 14.9.

MS (ESI): *m*/*z* = 434 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{27}NNaO_5$: 456.1786; found: 456.1768.

Benzyl 3-Oxo-3-phenyl-1-(3,4,5-trimethoxyphenyl)propylcarbamate (3h)
IR (KBr): 3357, 1694, 1593, 1507, 1458, 1237 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.0 Hz, 2 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.35–7.22 (br s, 5 H), 6.50 (s, 2 H), 5.80 (br s, 1 H), 5.16 (m, 1 H), 5.07 (s, 2 H), 3.79 (s, 6 H), 3.74 (s, 3 H), 3.61 (br d, *J* = 14.0 Hz, 1 H), 3.32 (dd, *J* = 14.0, 6.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.4, 155.2, 154.1, 137.5, 137.2, 136.9, 134.0, 129.5, 129.0, 128.3, 102.5, 66.2, 60.1, 55.8, 51.4, 43.4.

MS (ESI): *m*/*z* = 450 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{27}NNaO_6$: 472.1736; found: 472.1741.

Benzyl 1-(2-Nitrophenyl)-3-oxo-3-phenylpropylcarbamate (3i)
IR (KBr): 3328, 1688, 1524, 1338, 1264 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.00–7.89 (m, 3 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.65–7.52 (m, 2 H), 7.49–7.38 (m, 3 H), 7.36–7.25 (br s, 5 H), 6.38 (d, *J* = 8.0 Hz, 1 H), 5.80 (m, 1 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 5.01 (d, *J* = 12.0 Hz, 1 H), 3.72–3.59 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.5, 156.0, 148.2, 136.2, 135.8, 134.5, 134.2, 130.4, 129.3, 129.2, 129.0, 125.1, 65.9, 49.2, 42.3.

MS (ESI): *m*/*z* = 405 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{20}N_2NaO_5$: 427.1269; found: 427.1285.

Benzyl 1-(4-Cyanophenyl)-3-oxo-3-phenylpropylcarbamate (3j)
IR (KBr): 3421, 1691, 1528, 1452, 1254 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.0 Hz, 2 H), 7.64–7.29 (m, 12 H), 6.10 (br s, 1 H), 5.36 (m, 1 H), 5.11 (d, *J* = 12.0 Hz, 1 H), 5.03 (d, *J* = 12.0 Hz, 1 H), 3.70 (br d, *J* = 14.0 Hz, 1 H), 3.47 (dd, *J* = 14.0, 6.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.1, 155.2, 146.0, 135.2, 133.8, 132.2, 128.8, 128.2, 127.9, 127.5, 126.0, 118.7, 110.2, 66.0, 50.7, 44.1.

MS (ESI): *m*/*z* = 385 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{20}N_2NaO_3$: 407.1371; found: 407.1375.

Benzyl 1-(Naphthalen-2-yl)-3-oxo-3-phenylpropylcarbamate (3k)
IR (KBr): 3344, 1697, 1513, 1455, 1250 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.0 Hz, 2 H), 7.75–7.69 (m, 4 H), 7.54–7.20 (m, 11 H), 6.05 (d, *J* = 8.0 Hz, 1 H), 5.42 (m, 1 H), 5.10 (d, *J* = 12.0 Hz, 1 H), 5.02 (d, *J* = 12.0 Hz, 1 H), 3.77 (br d, *J* = 14.0 Hz, 1 H), 3.48 (d, *J* = 14.0, 6.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.2, 155.8, 139.1, 136.2, 136.1, 133.7, 133.2, 129.0, 128.1, 127.4, 126.3, 126.2, 125.2, 125.0, 66.4, 51.2, 42.8.

MS (ESI): *m*/*z* = 410 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{23}NNaO_3$: 432.1575; found: 432.1577.

Benzyl 3-Oxo-3-phenyl-1-(thiophen-2-yl)propylcarbamate (3l)
IR (KBr): 3339, 1692, 1522, 1450, 1223 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.0 Hz, 2 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.39–7.22 (br s, 5 H), 7.12 (m, 1 H), 6.93 (m, 1 H), 6.90 (m, 1 H), 5.95 (br s, 1 H), 5.54 (m, 1 H), 5.08 (s, 2 H), 3.76 (br d, *J* = 14.0 Hz, 1 H), 3.49 (dd, *J* = 14.0, 6.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.2, 155.1, 145.1, 135.8, 135.6, 138.3, 128.7, 127.8, 127.5, 126.4, 124.9, 66.2, 46.4, 44.8.

MS (ESI): *m*/*z* = 366 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{19}NNaO_3S$: 388.0983; found: 388.0988.

Benzyl 1-Cyclohexyl-3-oxo-3-phenylpropylcarbamate (3m)
IR (KBr): 3441, 1702, 1504, 1449, 1216 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.0 Hz, 2 H), 7.58 (t, *J* = 8.0 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 2 H), 7.35–7.28 (br s, 5 H), 5.32 (d, *J* = 8.0 Hz, 1 H), 5.04 (s, 2 H), 3.91 (m, 1 H), 3.33 (dd, *J* = 14.0, 6.0 Hz, 1 H), 3.12 (dd, *J* = 14.0, 4.0 Hz, 1 H), 1.90 (m, 1 H), 1.71–1.53 (m, 7 H), 1.32–1.11 (m, 2 H), 1.01 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.7, 156.1, 135.8, 134.2, 129.2, 129.0, 128.4, 66.0, 53.4, 40.6, 40.1, 30.1, 29.9, 29.8, 25.4, 25.2.

MS (ESI): *m*/*z* = 388 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{27}NNaO_3$: 388.1888; found: 388.1891.

Benzyl 5-Methyl-1-oxo-1-phenylhexan-3-ylcarbamate (3n)
IR (KBr): 3359, 1715, 1510, 1224 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.0 Hz, 2 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 8.0 Hz, 2 H), 7.39–7.30 (m, 5 H), 5.32 (d, *J* = 8.0 Hz, 1 H), 5.09 (s, 2 H), 4.21 (m, 1 H), 3.35 (dd, *J* = 14.0, 4.0 Hz, 1 H), 3.12 (dd, *J* = 14.0, 6.0 Hz, 1 H), 1.40 (m, 1 H), 1.29–1.16 (m, 2 H), 0.87 (d, *J* = 7.0 Hz, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 196.5, 155.7, 134.0, 130.1, 130.0, 129.9, 129.8, 128.4, 125.5, 65.7, 45.4, 43.8, 29.9, 25.1, 24.0, 21.3.

MS (ESI): *m*/*z* = 340 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{25}NNaO_3$: 362.1732; found: 362.1725.

Benzyl (1*S*,2*S*)-1-(4-Fluorophenyl)-2-methyl-3-oxo-3-phenylpropylcarbamate (*syn*-3o)
IR (KBr): 3357, 1692, 1533, 1448, 1262 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 2 H), 7.51 (t, *J* = 8.0 Hz, 1 H), 7.43–7.29 (m, 7 H), 7.25–7.20 (m, 2 H), 6.92 (t, *J* = 8.0 Hz, 2 H), 6.66 (br s, 1 H), 5.12 (d, *J* = 12.0 Hz, 1 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 5.03 (m, 1 H), 4.01 (m, 1 H), 1.33 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.8, 164.6, 160.1, 155.7, 135.8, 135.6, 134.1, 128.7, 128.2, 127.5, 115.0 (d, *J* = 10.0 Hz), 65.8, 56.1, 44.9, 15.2.

MS (ESI): *m*/*z* = 414 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{22}FNNaO_3$: 414.1481; found: 414.1484.

Benzyl (1*S*,2*R*)-1-(4-Fluorophenyl)-2-methyl-3-oxo-3-phenylpropylcarbamate (*anti*-3o)
IR (KBr): 3359, 1692, 1510, 1223 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.0 Hz, 2 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 7.35–7.20 (m, 7 H), 6.92 (t, *J* = 8.0 Hz, 2 H), 5.29 (t, *J* = 8.0 Hz, 1 H), 5.14 (t, *J* = 8.0 Hz, 1 H), 5.10 (d, *J* = 12.0 Hz, 1 H), 5.01 (d, *J* = 12.0 Hz, 1 H), 3.98 (m, 1 H), 1.23 (d, *J* = 8.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.2, 164.4, 160.1, 155.6, 136.4, 136.3, 132.8, 128.5, 128.2, 127.9, 115.1 (d, *J* = 10.0 Hz), 65.9, 55.2, 45.7, 14.5.

MS (ESI): *m*/*z* = 414 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{22}FNNaO_3$: 414.1481; found: 414.1496.

Benzyl (1*S*,2*S*)-1-(4-Chlorophenyl)-2-methyl-3-oxo-3-phenylpropylcarbamate (*syn*-3p)
IR (KBr): 3314, 1702, 1673, 1533, 1239 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 2 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.41–7.23 (m, 7 H), 7.20 (br s, 4 H), 6.62 (br s, 1 H), 5.10 (s, 2 H), 5.01 (m, 1 H), 4.00 (m, 1 H), 1.32 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.2, 155.8, 140.1, 135.6, 135.5, 134.1, 133.3, 129.0, 128.2, 127.5, 66.1, 56.3, 44.9, 15.4.

MS (ESI): *m*/*z* = 408, 410 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{22}ClNNaO_3$: 430.1185; found: 430.1178.

Benzyl (1*S*,2*R*)-1-(4-Chlorophenyl)-2-methyl-3-oxo-3-phenylpropylcarbamate (*anti*-3p)
IR (KBr): 3343, 1694, 1528, 1283, 1239 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.0 Hz, 2 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.34–7.12 (m, 9 H), 5.22 (br s, 1 H), 5.11–4.94 (m, 3 H), 3.93 (m, 1 H), 1.20 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.6, 155.8, 139.9, 135.7, 135.6, 133.6, 133.5, 129.1, 129.0, 128.4, 66.3, 55.8, 45.1, 14.2.

MS (ESI): *m*/*z* = 408, 410 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{22}ClNNaO_3$: 430.1185; found: 430.1199.

Benzyl (1*S*,2*S*)-2-Methyl-3-oxo-3-phenyl-1-(3,4,5-trimethoxyphenyl)propylcarbamate (*syn*-3q)
IR (KBr): 3350, 1685, 1592, 1508, 1457, 1239 cm^{-1}.

^{1}H NMR (200 MHz,$CDCl_3$): δ = 7.72 (d, *J* = 8.0 Hz, 2 H), 7.57–7.21 (m, 8 H), 6.60 (br s, 1 H), 6.39 (s, 2 H), 5.10 (s, 2 H), 4.91 (m, 1 H), 4.01 (m, 1 H), 3.71 (s, 9 H), 1.34 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.9, 155.6, 154.3, 137.0, 136.8, 136.7, 134.4, 130.8, 129.7, 129.6, 128.4, 128.2, 104.2, 66.2, 60.4, 57.7, 55.2, 44.9, 14.9.

MS (ESI): *m*/*z* = 464 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{29}NNaO_6$: 486.1887; found: 486.1910.

Benzyl (1*S*,2*R*)-2-Methyl-3-oxo-3-phenyl-1-(3,4,5-trimethoxyphenyl)propylcarbamate (*anti*-3q)
IR (KBr): 3337, 1682, 1588, 1529, 1456, 1244 cm^{-1}.

^{1}H NMR (200 MHz,$CDCl_3$): δ = 7.82 (d, *J* = 8.0 Hz, 2 H), 7.59–7.22 (m, 8 H), 6.39 (s, 2 H), 5.21–4.94 (m, 4 H), 3.96 (m, 1 H), 3.72 (s, 9 H), 1.21 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.8, 156.1, 154.2, 135.8, 135.7, 133.2, 130.8, 130.1, 130.0, 129.7, 129.5, 128.6, 128.5, 104.5, 66.0, 60.6, 57.2, 55.8, 45.6, 14.7.

MS (ESI): *m*/*z* = 464 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{29}NNaO_6$: 486.1887; found: 486.1899.

Benzyl (1*S*,2*S*)-2-Methyl-1-(naphthalen-2-yl)-3-oxo-3-phenylpropylcarbamate (*syn*-3r)
IR (KBr): 3420, 1685, 1533, 1452, 1242 cm^{-1}.

^{1}H NMR (200 MHz,$CDCl_3$): δ = 7.86–7.65 (m, 6 H), 7.51–7.22 (m, 11 H), 6.73 (br s, 1 H), 5.20 (m, 1 H), 5.08 (s, 2 H), 4.11 (m, 1 H), 1.32 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.7, 155.6, 139.3, 136.1, 136.0, 133.8, 133.7, 132.5, 129.0, 128.2, 128.0, 127.5, 127.2, 125.8, 125.7, 125.3, 124.9, 66.3, 58.2, 44.9, 15.6.

MS (ESI): *m*/*z* = 424 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{25}NNaO_3$: 446.1732; found: 446.1728.

Benzyl (1*S*,2*R*)-2-Methyl-1-(naphthalen-2-yl)-3-oxo-3-phenylpropylcarbamate (*anti*-3r)
IR (KBr): 3341, 1693, 1527, 1452, 1213 cm^{-1}.

^{1}H NMR (200 MHz,$CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 2 H), 7.81–7.67 (m, 4 H), 7.55–7.23 (m, 11 H), 5.40–5.24 (m, 2 H), 5.03 (d, *J* = 12.0 Hz, 1 H), 4.97 (d, *J* = 12.0 Hz, 1 H), 4.10 (m, 1 H), 1.22 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.6, 155.8, 135.6, 134.0, 133.8, 129.4, 129.1, 128.7, 128.6, 128.2, 125.9, 125.7, 125.1, 66.0, 56.2, 45.1, 14.2.

MS (ESI): *m*/*z* = 424 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{25}NNaO_3$: 446.1732; found: 446.1725.

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References

(1) Part 200 in the series 'Studies on Novel Synthetic Methodologies'.
(2) (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991.
(3) (a) Casimir, J. R.; Turetta, C.; Ettouati, L.; Paris, J. *Tetrahedron Lett.* **1995**, *36*, 4797. (b) Godfrey, A. C.; Brooks, D. A.; Hay, L. A.; Peters, M.; McCarthy, J. R.; Mitchell, D. *J. Org. Chem.* **2003**, *68*, 2623.
(4) (a) Kobayashi, S.; Ishitani, S. *Chem. Rev.* **1999**, *99*, 1069. (b) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (c) Joshi, N. S.; Whitaker, L. R.; Francis, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 15942.
(5) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A.-T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.
(6) (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (b) Xu,

L.-W.; Xia, C.-G.; Li, L. *J. Org. Chem.* **2004**, *69*, 8482. (c) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (d) Ollevier, T.; Nadeau, E. *J. Org. Chem.* **2004**, *69*, 9292. (e) Phukan, P.; Kataki, D.; Chakraborthy, P. *Tetrahedron Lett.* **2006**, *47*, 5523. (f) Das, B.; Majhi, A.; Chowdhury, N.; Reddy, K. R.; Ravikanth, B. *Chem. Lett.* **2007**, *36*, 1106. (g) Das, B.; Majhi, A.; Reddy, K. R.; Suneel, K. *J. Mol. Catal. A: Chem.* **2007**, *274*, 83. (h) Ollevier, T.; Nadeau, E. *Org. Biomol. Chem.* **2007**, *5*, 3126.

(7) (a) Das, B.; Damodar, K.; Sashikanth, B.; Srinivas, Y.; Kalavathi, I. *Synlett* **2008**, 3133. (b) Bas, B.; Damodar, K.; Bhunia, N. *J. Org. Chem.* **2009**, *74*, 5607.

(8) Ollevier, T.; Nadeau, E.; Eguillon, J.-C. *Adv. Synth. Catal.* **2006**, *348*, 2080.

(9) (a) Pearson, W. H.; Lindback, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622. (b) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970.

(10) Rao, I. N.; Prabhakaran, E. N.; Das, S. K.; Iqbal, J. *J. Org. Chem.* **2003**, *68*, 4079.

(11) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley: New York, **1999**, 235–236.

(12) (a) Petrini, M. *Chem. Rev.* **2005**, *105*, 3949. (b) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159.