

Efficient and selective cleavage of the *tert*-butoxycarbonyl (Boc) group under basic condition

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Abstract

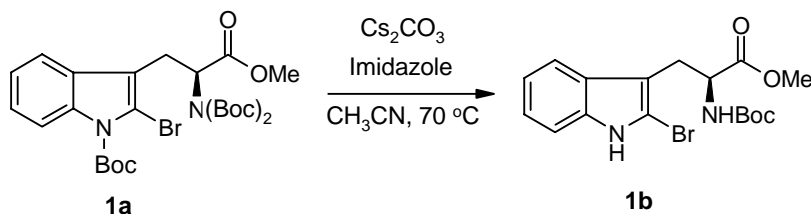
A simple, efficient and mild method for the selective cleavage of *tert*-butoxycarbonyl (Boc) from dicarbamates and a carbonyl or aromatic ring in conjugation with the nitrogen atom bearing the Boc-group is described under basic condition.

Keywords: α -Amino acids, di-*t*-butylimidodicarbonate, selective deprotection, celogenitins, racemization

Introduction

The natural and unnatural α -amino acids play a central role in chemistry and biology.¹ In addition, to their key biological roles as components of peptides, proteins, and other natural products, α -amino acids are utilized in the pharmaceutical, agrochemical, and related industries. The use of α -amino acids and their derivatives solely depend on the protecting group attached to the amine and acid functionality.² Among the various protecting groups for amine functionality, the *t*-butoxycarbonyl (Boc) group is one of the most frequently used in organic synthesis due to its chemical stability to basic and mildly acidic conditions and its ease of removal under specific conditions.³ However, selective cleavage of the di-*t*-butylimidodicarbonate, oftenly found as valuable intermediates in Mitsunobu⁴ and Gabriel type⁵ processes towards the synthesis of several bio-active molecules, protected α -amino acids to mono-Boc compounds still lacks efficient and milder methods. Numerous methods are available for the removal of the Boc-group,⁷ including trifluoroacetic acid,⁸ trimethylsilyl iodide,⁹ hydrochloric acid in ethyl acetate,¹⁰ ceric ammonium nitrate,¹¹ tin tetrachloride,¹² tetrabutylammonium fluoride,¹³ zinc bromide,¹⁴ boron trifluoride,¹⁵ thermolytic removal¹⁶ etc. However, there are very few methods for the selective cleavage^{17a-f} of the di-Boc protected α -amino acids to mono-Boc compounds. Still organic community seeks simple, efficient and milder methods for selective deprotection of the well known protecting groups by preserving the other functionalities.

During our investigation towards the synthesis of celogenitins,¹⁸ we tried to perform Suzuki coupling reaction at C-2 position of tryptophan derivative **1a** with imidazole in the presence of Cs₂CO₃ and catalytic amount of palladium reagent in acetonitrile at 70 °C. It is worthy to mention that, under various conditions of employing different palladium reagent, we could able to isolate only the Boc-protected product **1b** (Scheme 1).



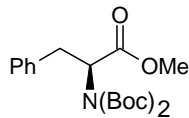
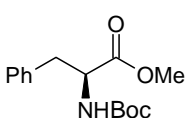
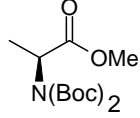
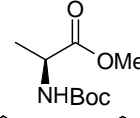
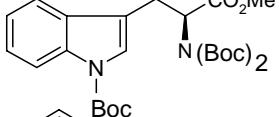
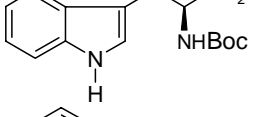
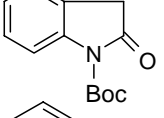
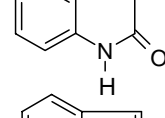
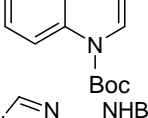
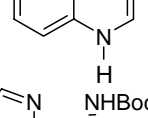
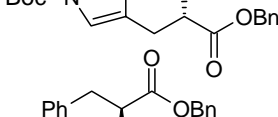
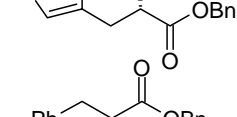
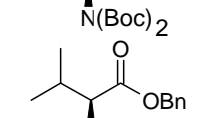
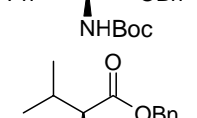
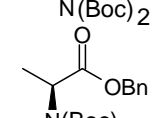
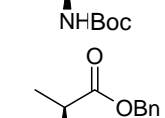
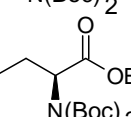
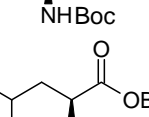
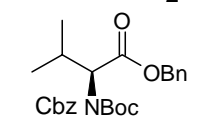
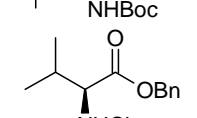
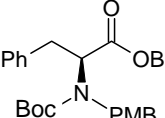
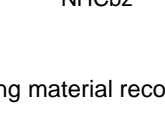
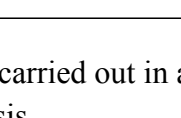
Scheme 1

We report herein a new and mild method for the deprotection of Boc-group from amino compounds under basic conditions, using Cs₂CO₃ and imidazole system, from di-*t*-butyldiimidodicarbonate as well as nitrogen atom conjugated to a carbonyl or aromatic system.

Results and Discussion

To explore the scope and limitations, we investigated a series of Boc-protected amino compounds with different protecting groups and functionalities, which are shown in Table 1. Although it is known that cleavage of the protecting groups in methyl *N*-Boc- α -amino esters gave the corresponding *N*-Boc-amino acids without racemization¹⁹ under basic condition, in our case, we were worried about such a possibility in the presence of an additional Boc group. To investigate this, we submitted compound **2**, **3**, and **4** to above basic conditions to cleave the Boc group. We found that the optical rotation of the product obtained changed with time, showing clearly that epimerization has occurred. Furthermore, chiral HPLC analysis of **2b** showed two peaks confirming the epimerization during the reaction.²⁰ In light of this result, we decided to convert the acid into its benzyl esters. To ensure the enantiomeric purity of such a product (**8b**), we again submitted for the chiral HPLC which showed single peak at the corresponding retention time and in addition, the rotation clearly confirmed no detectable racemization. With the retention of optical purity on amino acids, we applied the above method to other Boc-protected compounds. Boc-group attached to nitrogen atoms part of an aromatic system or in conjugation with a carbonyl group was removed in high yields. Simple aliphatic mono-Boc compounds were unaffected under above reaction conditions. In entry **12a**, where the nitrogen functionality is protected by Boc as well as Cbz group, we found that only Boc group was selectively cleaved from the nitrogen and Cbz group was untouched affording the product **12b** in 82% yield.

Table 1. Selective removal of Boc-group under basic condition

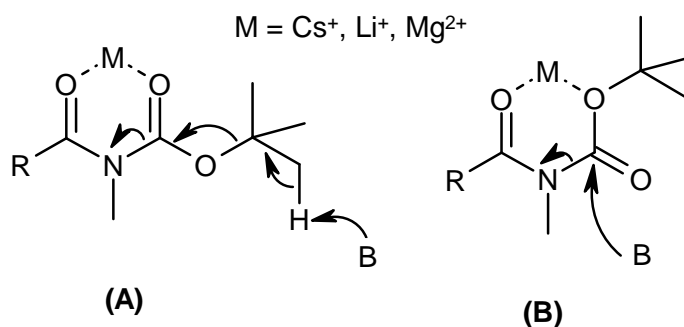
S. No	Starting Material (a)	Product (b)	Time (h)	Yield (%) ^{i,ii}
2			12	75
3			16	74
4			12	72
5			08	85
6			24	82
7			04	91
8			10	84
9			10	86
10			08	80
11			07	87
12			12	82
13		Starting material recovered	48	00

ⁱ All reactions were carried out in acetonitrile at 70 °C and the products characterized by NMR, IR, elemental analysis.

ⁱⁱ Isolated yield.

When the nitrogen functionality was doubly protected with an additional protecting group besides Boc (entry **13a**), such as *p*-methoxybenzyl (PMB) group, the deprotection of the Boc-group was not observed. Interestingly in case of **7a**, the *t*-butoxycarbonyl group attached to the ring nitrogen was cleaved selectively compare to the BOC group present on the aliphatic nitrogen atom to afford compound **7b** which is difficult to make directly from histidine in 91% yield. Next various organic solvents were tried and we found that in particular acetonitrile and THF were the solvents where better results were obtained. Another important point is that both the reagents are required in stoichiometric amount for the completion of the reaction.

The mechanism proposed by Stafford *et al.*^{16b} and Martin *et al.*^{16f} for the cleavage of *N*-Boc amines based on the formation of a six-membered chelate seems to be applicable to our method. We proposed that the initial chelation between the metal ion and two oxygen of the carbonyl group followed by abstraction of proton from the methyl group led to the loss of isobutene, CO₂ and formation of Boc-deprotected product. Our observation supports the structure **A**, in which both carbonyls are chelated with the cation.



Conclusions

In conclusion, we have described a simple, mild, and efficient protocol for the deprotection of the Boc group from Boc-protected carbamates, amides and nitrogen atom present in the aromatic ring under basic condition at 70 °C.

Experimental Section

General Procedures. Solvents were purified and dried by standard procedures before use. Column chromatography was carried out with silica gel (60-120 mesh). Infrared spectra were recorded with Shimadzu IR 420 and Perkin-Elmer 683 spectrometers. NMR spectra were recorded on Bruker AC-200 and Bruker DRX-500 machine in CDCl₃ with TMS as internal standard. Mass spectra were obtained with Finningen MAT 1210 mass spectrometer. Optical rotations were measured with digital polarimeter. Elemental analysis was done on elemental

analyzer model 1108 EA. All reactions were monitored on 0.25 mm E-Merck pre-coated silica gel (TLC) plates (60F-254) with UV or I₂, anisaldehyde reagent in ethanol. Petroleum ether refers to mixture of hexanes with bp 60-80 °C.

General experimental procedure for Boc deprotection

To a stirred solution of dicarbamates and a carbonyl or aromatic ring in conjugation with the nitrogen atom bearing the Boc-group (**1a-13a**) (1 mmol) in acetonitrile (5 mL), was added Cs₂CO₃ (1.5 mmol) and imidazole (1.5 mmol) and the reaction mixture was heated to 70 °C until the completion of the reaction [monitored by TLC, ethyl acetate: petroleum ether (1:9)]. The reaction mixture was then cooled to room temperature, filtered over celite and concentrated. The viscous liquid was purified by column chromatography (silica gel, ethyl acetate/petroleum ether) affording the product (**1b-13b**) in 72-91% yield.

Spectral data of compound 1a. Colorless liquid; R_f = 0.5 (5% ethyl acetate/petroleum ether); ¹H NMR (500 MHz, CDCl₃): δ 8.06 (d, 1 H, *J* = 5.7 Hz), 7.45 (d, 1 H, *J* = 5.7 Hz), 7.24 (m, 1 H), 7.18 (m, 1 H), 3.78 (s, 3 H), 3.49 (m, 2 H), 1.68 (s, 9 H), 1.31 (s, 9 H), 1.28 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) 170.4, 151.5, 148.8, 148.4, 136.9, 136.5, 129.2, 128.1, 124.4, 122.9, 119.1, 116.7, 82.6, 57.6, 52.2, 28.1, 27.6, 25.9; Anal. Calcd. for C₂₇H₃₇BrN₂O₈: C, 54.28; H, 6.24; N, 4.69. Found: C, 54.16; H, 6.08; N, 4.78.

Spectral data of compound 1b. Colorless liquid; R_f = 0.5 (20% ethyl acetate/petroleum ether); ¹H NMR (200 MHz, CDCl₃): δ 8.43 (br s, 1 H), 7.43-7.08 (m, 4 H), 5.16 (d, 1 H, *J* = 7.6 Hz), 4.63 (m, 1 H), 3.70 (s, 3 H), 3.19 (m, 2 H), 1.41 (s, 9 H); Anal. Calcd. for C₁₇H₂₁BrN₂O₄: C, 51.40; H, 5.33; N, 7.05. Found: C, 51.26; H, 5.31; N, 7.16.

Spectral data of compound 2a. Colorless liquid; R_f = 0.6 (5% ethyl acetate/petroleum ether); [α]_D²⁵ = - 89.7 (*c* 0.96, CHCl₃); IR (neat): 2979, 2935, 1795, 1744, 1703 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 7.18 (m, 5 H), 5.14 (dd, 1 H, *J* = 3.6, 7.3 Hz), 3.75 (s, 3 H), 3.37 (dd, 1 H, *J* = 3.5, 14.2 Hz), 3.25 (dd, 1 H, *J* = 10.2, 14.2 Hz), 1.38 (s, 18 H); ¹³C NMR (50 MHz, CDCl₃) 170.5, 151.3, 137.3, 129.2, 128.0, 126.2, 82.5, 59.1, 51.9, 35.9, 27.5; Anal. Calcd. for C₂₀H₂₉NO₆: C, 63.31; H, 7.70; N, 3.69. Found: C, 63.48; H, 7.66; N, 3.92.

Spectral data of compound 2b. Colorless liquid; R_f = 0.5 (15% ethyl acetate/petroleum ether); [α]_D²⁵ = + 18.4 (*c* 1.54, CHCl₃); lit^{17e} [α]_D²⁵ = + 42.5 (*c* 1.32, CHCl₃) (prepared by following standard procedure and took the rotation too); IR (neat): 3372, 3029, 2978, 1746, 1715 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 7.25-7.13 (m, 5 H), 4.94 (d, 1 H, *J* = 7.4 Hz), 4.59 (m, 1 H), 3.71 (s, 3 H), 3.07 (m, 2 H), 1.41 (s, 9 H); ¹³C NMR (50 MHz, CDCl₃) 172.0, 154.7, 135.9, 129.0, 128.2, 126.7, 79.3, 54.2, 51.7, 38.0, 28.0; Anal. Calcd. for C₁₅H₂₁NO₄: C, 64.50; H, 7.58; N, 5.02. Found: C, 64.78; H, 7.46; N, 4.89.

Spectral data of compound 3a. Colorless liquid; R_f = 0.5 (5% ethyl acetate/ petroleum ether); [α]_D²⁵ = -39.6 (*c* 1.0, CHCl₃); IR (CHCl₃): 3021, 2983, 1788, 1746, 1697 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 4.99-4.89 (q, 1 H, *J* = 6.82, 13.90 Hz), 3.72 (s, 3 H), 1.50 (br s, 21 H); ¹³C NMR (50 MHz, CDCl₃) 173.0, 151.4, 82.4, 53.5, 51.8, 27.7, 15.3; MS (MALDI TOF): *m/z* 304.18 (65, M⁺), 248.12 (100), 192.05 (91), 148.07 (80). Anal. Calcd. for C₁₄H₂₅NO₆: C, 55.43; H, 8.31; N, 4.62. Found: C, 55.41; H, 8.29; N, 4.64.

Spectral data of compound 3b. Colorless liquid; $R_f = 0.2$ (5% ethyl acetate/petroleum ether); $[\alpha]_D^{25} = -2.75$ (*c* 2.0, CHCl_3); IR (CHCl_3): 3440, 3378, 2981, 1744, 1709, cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 5.06 (br s, 1 H), 4.30 (m, 1 H), 3.75 (s, 3 H), 1.44 (s, 9 H), 1.38 (d, 3 H, $J = 7.2$ Hz); ^{13}C NMR (50 MHz, CDCl_3) 173.1, 154.5, 78.6, 51.4, 48.5, 27.6, 15.5; MS (MALDI TOF): m/z 226.11 (26, $\text{M}^+ + \text{Na}$), 204.12 (100, M^+), 148.07 (98). Anal. Calcd. for $\text{C}_9\text{H}_{17}\text{NO}_4$: C, 55.19; H, 8.43; N, 6.89. Found: C, 55.21; H, 8.41; N, 6.88.

Spectral data of compound 4a. $R_f = 0.5$ (5% ethyl acetate/petroleum ether); $[\alpha]_D^{25} = -75.2$ (*c* 1.0, CHCl_3); IR (neat): 3021, 2982, 2932, 1788, 1745, 1739, 1703 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 8.10 (d, 1 H, $J = 8.64$ Hz), 7.51 (d, 1 H, $J = 8.42$ Hz), 7.35-7.10 (m, 3 H), 5.14 (dd, 1 H, $J = 3.84, 11.53$ Hz), 3.76 (s, 3 H), 3.54-3.27 (m, 2 H), 1.64 (s, 9 H), 1.32 (s, 18 H); ^{13}C NMR (50 MHz, CDCl_3) 170.1, 151.3, 149.0, 135.1, 130.1, 123.9, 123.8, 122.1, 118.5, 116.0, 114.8, 82.7, 82.2, 57.7, 51.8, 27.7, 27.3, 25.1; Anal. Calcd. for $\text{C}_{27}\text{H}_{38}\text{N}_2\text{O}_8$: C, 62.53; H, 7.39; N, 5.40. Found: C, 62.36; H, 7.48; N, 5.62.

Spectral data of compound 4b. Colorless liquid; $R_f = 0.4$ (10% ethyl acetate/petroleum ether); $[\alpha]_D^{25} = +39.3$ (*c* 1.0, CHCl_3); IR (neat): 3478, 3433, 3019, 2981, 2954, 1739, 1705 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 8.45 (br s, 1 H), 7.55 (d, 1 H, $J = 8.50$ Hz), 7.25 (d, 1 H, $J = 8.44$ Hz), 7.15 (m, 1 H), 7.10 (m, 1 H), 6.90 (s, 1 H), 5.01 (m, 1 H), 4.60 (m, 1 H), 3.65 (s, 3 H), 3.25 (m, 2 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) 172.7, 155.2, 136.3, 122.8, 122.1, 119.5, 118.6, 111.2, 110.0, 80.0, 54.4, 52.0, 28.4; Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_4$: C, 64.14; H, 6.96; N, 8.79. Found: C, 64.29; H, 7.38; N, 8.81.

Spectral data of compound 5a. Light yellow oil; $R_f = 0.5$ (5% ethyl acetate/petroleum ether); IR (CHCl_3): 3021, 2930, 1789, 1766, 1730, cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 7.80 (d, 1 H, $J = 8.84$ Hz), 7.32-7.11 (m, 3 H), 3.64 (s, 2 H), 1.04 (s, 9 H); ^{13}C NMR (50 MHz, CDCl_3) 172.2, 148.9, 140.9, 127.7, 123.8, 122.9, 114.8, 83.6, 36.1, 27.8; Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.91; H, 6.39; N, 5.98.

Spectral data of compound 6a. Colorless liquid; $R_f = 0.4$ (4% ethyl acetate/petroleum ether); IR (CHCl_3): 2979, 2933, 1729, cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 8.12 (d, 1 H, $J = 7.96$ Hz), 7.58-7.50 (m, 2 H), 7.33-7.16 (m, 2 H), 6.54 (d, 1 H, $J = 3.66$ Hz), 1.67 (s, 9 H); ^{13}C NMR (50 MHz, CDCl_3) 149.4, 135.2, 130.5, 125.5, 123.9, 122.4, 120.7, 115.0, 107.0, 83.0, 27.9; MS (MALDI TOF): m/z 240.11 (100, $\text{M}^+ + \text{Na}$), 218.09 (10, M^+), 197.12 (96), 162.07 (49), 141.05 (41), 126.10 (98), 108.09 (34). Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.83; H, 6.95; N, 6.41.

Spectral data of compound 8a. Colorless liquid; $R_f = 0.6$ (5% ethyl acetate/petroleum ether); $[\alpha]_D^{25} = -56.6$ (*c* 2.45, CHCl_3); IR (neat): 3021, 2981, 1787, 1742, 1708 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 7.22 (m, 10 H), 5.19 (m, 3 H), 3.40 (dd, 1 H, $J = 5.05, 14.02$ Hz), 3.26 (dd, 1 H, $J = 10.23, 14.02$ Hz), 1.35 (s, 18 H); ^{13}C NMR (50 MHz, CDCl_3) 170.0, 151.6, 137.5, 135.5, 129.4, 128.3, 128.2, 128.0, 126.4, 82.6, 66.7, 59.3, 35.8, 27.7; MS (MALDI TOF): m/z 478.25 (83, $\text{M}^+ + \text{Na}$), 456.27 (100, M^+), 400.21 (86), 344.14 (49), 274.20 (48), 252.15 (54). Anal. Calcd. for $\text{C}_{26}\text{H}_{33}\text{NO}_6$: C, 68.55; H, 7.30; N, 3.08. Found: C, 68.74; H, 7.49; N, 3.42.

Spectral data of compound 8b. White crystalline solid, mp = 64.9 °C; $R_f = 0.6$ (10% ethyl acetate/petroleum ether); $[\alpha]_D^{25} = +14.9$ (*c* 1.00, CHCl_3); IR (neat): 3438, 3019, 2981, 1737,

1711 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.34-7.04 (m, 10 H), 5.14 (dd, 2 H, $J = 13.88, 24.67$ Hz), 4.96 (m, 1 H), 4.62 (m, 1 H), 3.08 (m, 2 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) 171.4, 154.7, 135.9, 135.2, 129.1, 128.2, 128.1, 126.7, 79.4, 66.7, 54.4, 38.1, 28.1; MS (MALDI TOF): m/z 378.18 (100, M^+Na), 356.20 (44, M^+), 274.20 (9), 252.15(11), 208.14 (16). Anal. Calcd. for $\text{C}_{21}\text{H}_{25}\text{NO}_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.58; H, 7.35; N, 3.68.

Spectral data of compound 9a. Colorless liquid; $R_f = 0.4$ (5% ethyl acetate/ petroleum ether); $[\alpha]_D^{25} = -32.9$ (c 1.0, CHCl_3); IR (CHCl_3): 3021, 2982, 1786, 1744, 1698 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 7.31 (s, 5 H), 5.14 (dd, 2 H, $J = 12.63, 23.12$ Hz) 4.52 (d, 1 H, $J = 9.35$ Hz), 2.58-2.40 (m, 1 H), 1.44 (s, 18 H), 1.16 (d, 3 H, $J = 6.44$ Hz), 0.88 (d, 3 H, $J = 6.95$ Hz); ^{13}C NMR (50 MHz, CDCl_3) 169.7, 152.1, 135.6, 128.0, 127.6, 127.5, 82.2, 65.9, 63.1, 27.5, 21.8, 18.6; MS (MALDI TOF): m/z 430.24 (6, M^+Na), 408.25 (10, M^+), 352.19 (9), 274.19 (8), 208.14 (8), 126.10 (98), 126.10 (100). Anal. Calcd. for $\text{C}_{22}\text{H}_{33}\text{NO}_6$: C, 64.84; H, 8.16; N, 3.44. Found: C, 64.79; H, 8.18; N, 3.42.

Spectral data of compound 9b. Colorless liquid; $R_f = 0.2$ (5% ethyl acetate/petroleum ether); $[\alpha]_D^{25} = -3.02$ (c 2.1, CHCl_3); IR (CHCl_3): 3442, 2972, 1744, 1712, 1501 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 7.34 (s, 5 H), 5.16 (dd, 2 H, $J = 12.25, 19.58$ Hz), 5.00 (d, 1 H, $J = 8.08$ Hz), 4.29-4.22 (m, 1 H), 2.22-2.10 (m, 1 H), 1.44 (s, 9 H), 0.93 (d, 3 H, $J = 6.82$ Hz), 0.84 (d, 3 H, $J = 6.94$ Hz); ^{13}C NMR (50 MHz, CDCl_3) 171.8, 155.3, 135.3, 128.3, 128.1, 79.2, 66.5, 58.3, 30.0, 28.1, 18.8, 17.3; MS (MALDI TOF): m/z 330.18 (10, M^+Na), 308.19 (15, M^+), 304.19 (24), 252.13 (18), 248.12 (73), 204.13 (69), 192.06 (100). Anal. Calcd. for $\text{C}_{17}\text{H}_{25}\text{NO}_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.40; H, 8.18; N, 4.53.

Spectral data of compound 10a. White powder, mp = 51.9 $^\circ\text{C}$; $R_f = 0.5$ (5% ethyl acetate /petroleum ether); $[\alpha]_D^{25} = -21.8$ (c 1.25, CHCl_3); IR (neat): 2980, 2941, 1794, 1750, 1701 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.34 (m, 5 H), 5.16 (s, 2 H), 5.02 (q, 1 H, $J = 7.33, 13.92$ Hz), 1.54 (d, 3 H, $J = 7.33$ Hz), 1.46 (s, 18 H); ^{13}C NMR (125 MHz, CDCl_3) 170.8, 151.8, 135.6, 128.3, 127.8, 82.8, 66.6, 53.8, 27.8, 15.2; MS (MALDI-TOF): m/z 402.21 (7, M^+Na), 380.22 (100, M^+), 324.16 (80), 280.17 (34), 224.10 (43), 180.11 (74). Anal. Calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}_6$: C, 63.31; H, 7.70; N, 3.69. Found: C, 63.16; H, 8.16; N, 3.60.

Spectral data of compound 10b. Colorless thick liquid; $R_f = 0.5$ (10% ethyl acetate /petroleum ether); $[\alpha]_D^{25} = -11.2$ (c 1.35, EtOH); IR (neat): 3367, 3066, 3034, 2979, 2935, 1742, 1716 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 7.35 (m, 5 H), 5.18 (d, 2 H, $J = 4.61$ Hz), 4.35 (m, 1 H), 1.44 (s, 9 H), 1.42 (d, 3 H, $J = 7.76$ Hz); ^{13}C NMR (50 MHz, CDCl_3) 172.9, 154.9, 135.4, 128.3, 127.9, 79.5, 66.6, 49.2, 28.1, 18.1; MS (MALDI TOF): m/z 302.21 (100, M^+Na), 280.17 (51, M^+), 252.14 (10), 224.10 (14), 180.11 (12). Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_4$: C, 64.49; H, 7.58; N, 5.02. Found: C, 64.25; H, 7.54; N, 4.90.

Spectral data of compound 11a. Colorless syrup; $R_f = 0.4$ (10% ethyl acetate/ petroleum ether); $[\alpha]_D^{25} = -30.1$ (c 1.0, CHCl_3); IR (CHCl_3): 3019, 2962, 1728, 1711, 1500 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 7.31 (s, 5 H), 5.14 (dd, 2 H, $J = 12.50, 15.79$ Hz) 4.94 (dd, 1 H, $J = 5.69, 8.85$), 1.93-1.84 (m, 1 H), 1.69-1.61 (m, 1 H), 1.44 (s, 18 H), 0.93 (d, 6 H, $J = 6.57$ Hz); ^{13}C NMR (50 MHz, CDCl_3) 171.1, 152.2, 128.4, 127.9, 82.7, 66.6, 56.6, 38.4, 27.9, 25.1, 23.3, 21.8; MS

(MALDI TOF): m/z 444.26 (7, M^+Na), 422.26 (4, M^+), 326.17 (9), 304.18 (41), 248.12 (100). Anal. Calcd. for $C_{23}H_{35}NO_6$: C, 65.54; H, 8.37; N, 3.32. Found: C, 65.51; H, 8.35; N, 3.39.

Spectral data of compound 11b. Colorless liquid; $R_f = 0.2$ (10% ethyl acetate/ petroleum ether); $[\alpha]_D^{25} = -13.5$ (c 2.0, $CHCl_3$); IR ($CHCl_3$): 3441, 3021, 1784, 1740, 1698 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$): δ 7.34 (s, 5 H), 5.15 (dd, 2 H, $J = 12.38, 15.53$ Hz) 4.90 (d, 1 H, $J = 8.34$), 4.40-4.29 (m, 1 H), 1.69-1.47 (m, 3 H), 1.43 (s, 9 H), 0.93 (d, 3 H, $J = 1.89$ Hz), 0.90 (d, 3 H, $J = 2.14$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 172.9, 155.1, 135.4, 128.3, 128.0, 127.9, 79.3, 66.5, 52.1, 41.4, 28.1, 24.5, 22.6, 21.7; MS (MALDI TOF): m/z 344.20 (6, M^+Na), 322.21 (4, M^+), 304.18 (53), 248.18 (97), 204.13 (38), 192.05 (99), 148.07 (100). Anal. Calcd. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.24; H, 8.45; N, 4.38.

Spectral data of compound 12a. Colorless liquid; $R_f = 0.3$ (10% ethyl acetate/ petroleum ether); $[\alpha]_D^{25} = -29.1$ (c 1.0, $CHCl_3$); IR ($CHCl_3$): 3031, 2971, 1791, 1747, 1701 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$): δ 7.29 (m, 10 H), 5.15 (d, 2 H, $J = 1.01$ Hz), 5.07 (d, 2 H, $J = 8.59$ Hz) 4.60 (d, 1 H, $J = 9.35$), 2.58-2.40 (m, 1 H), 1.38 (s, 9 H), 1.16 (d, 3 H, $J = 6.57$ Hz), 0.84 (d, 3 H, $J = 6.94$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 169.4, 153.72, 151.3, 135.5, 135.1, 128.2, 128.0, 127.8, 127.7, 83.0, 68.3, 66.2, 63.2, 28.2, 27.6, 27.5, 21.9, 18.6; MS (MALDI TOF): m/z 464.22 (100, M^+Na), 442.25 (46, M^+), 386.19 (53), 342.19(40). Anal. Calcd. for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17. Found: C, 67.98; H, 7.10; N, 3.15.

Spectral data of compound 12b. Colorless thick liquid; $R_f = 0.4$ (20% ethyl acetate/ petroleum ether); $[\alpha]_D^{25} = -2.7$ (c 1.1, $CHCl_3$); IR ($CHCl_3$): 3434, 3358, 3032, 2966, 1724, 1512 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$): δ 7.33 (m, 10 H), 5.29 (d, 1 H, $J = 8.84$ Hz), 5.15 (d, 2 H, $J = 4.17$ Hz), 5.09 (s, 2 H), 4.37-4.31 (dd, $J = 4.67, 9.09$ Hz), 2.25-2.09 (m, 1 H), 0.93 (d, 3 H, $J = 6.82$ Hz), 0.84 (d, 3 H, $J = 6.85$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 171.4, 155.8, 136.0, 135.0, 127.8, 127.8, 127.5, 127.4, 66.2, 58.6, 30.6, 18.4, 17.0; MS (MALDI TOF): m/z 364.16 (100, M^+Na), 342.18 (11, M^+), 304.19 (28), 248.12(42), 192.06 (45). Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.39; H, 6.75; N, 4.08.

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20. Enantiomeric purity of the product **2b** formed was verified by HPLC analysis. HPLC conditions: column, Chiralcel OD-25 cm; mobile phase, petroleum ether:IPA (90:10); flow rate, 1ml/min; UV detection at 254 nm (Retention time for racemic **2b** prepared by mixture of D- and L-phenyl alanine is 6.983 and 7.594 where as the product obtained from reaction showed retention time at 7.054 and 7.650; HPLC conditions: column, Chiralcel OD-25 cm; mobile phase, petroleum ether:IPA (98:2); flow rate, 1ml/min; UV detection at 254 nm retention time for racemic **8b** prepared by following standard procedure is 9.008 (D-phenyl alanine) and 9.908 (L-phenyl alanine) and the product from the reaction mixture showed at 10.106.