Chapter 5

$NaBH_4$ Induced Chemoselective Reduction of Amides to Alcohols and Amines under Catalyst Free Condition

5.1 Introduction

Reduction of carbonyls are among the most important and prevalent transformations in organic chemistry but the amide functionality being the most challenging to reduce. One of the favorable features of the amide functionality is the stability of this bond, which stems from the resonance stabilization. The C–N bond is of partial double-bond character due to the orbital overlap between the nitrogen lone pair and the anti-bonding orbital of the carbonyl group (**Figure 5.1**). This delocalization induces planarity of the amide bond and also diminishes the electrophilicity of the carbonyl carbon, making it less susceptible for nucleophilic attack (Magano et al. 2012, Volkov et al. 2016). The reactivity of the amidic bond can be improved by disturbing the resonance of this bond through destroying the planarity of the system. The planarity can be distorted by highly sterically hindered electron withdrawing N-substituents, which was taken as an advantage in the development of a mild substitution procedure in amides (Meng et al. 2016, Pace et al. 2016, Szostak et al. 2016, Liu et al. 2017, Gnanaprakasam et al. 2018, Meng et al. 2018).

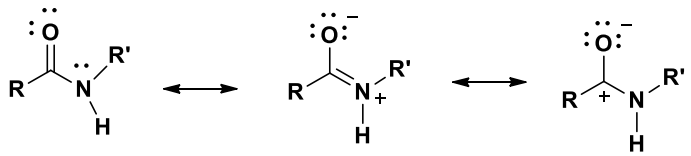

Figure 5.1: Resonance stability in amide.

Amide reduction enables the formation of a number of different important compounds. Amines, imines and enamines are accessible through C–O bond cleavage whereas aldehydes, alcohols and amines are formed via the C–N bond cleavage (**Figure 5.2**) (Dub et al. 2012). The majority of the reported chemoselective protocols are dealing with the reduction of amides into amines; however, some examples of the formation of aldehydes, alcohol, imines and enamines in the presence of sensitive functional groups have been demonstrated.

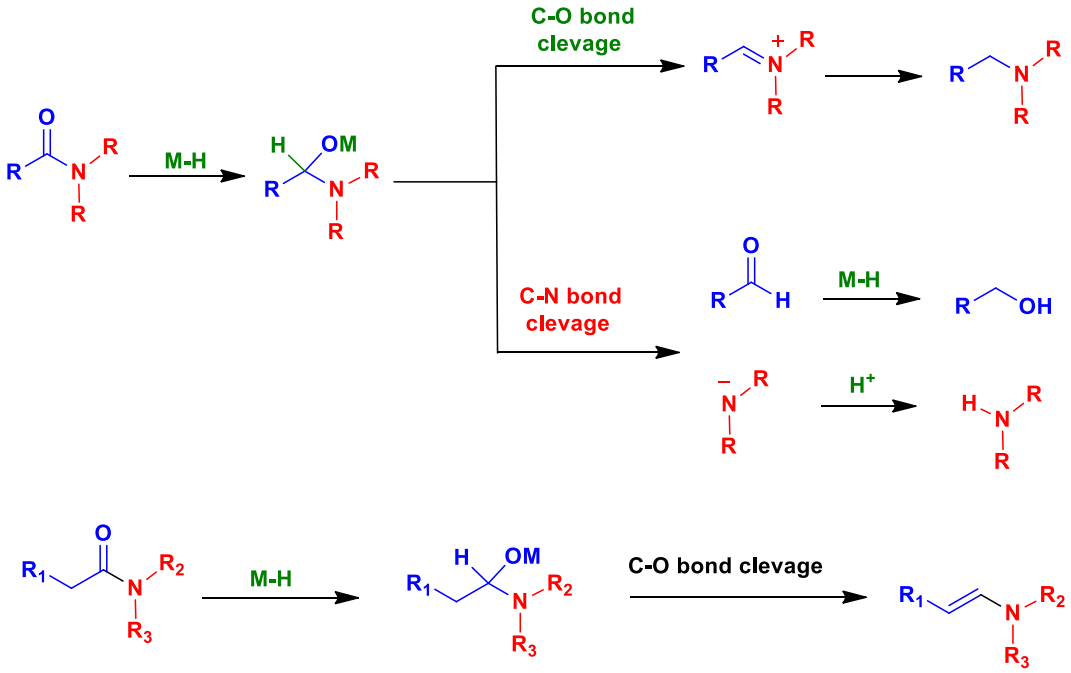

Figure 5.2: Reduction of amides via C–N and C–O bond cleavage.

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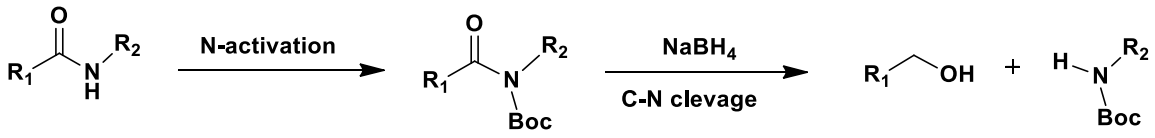
The main strategies adopted in amide reduction are the use of hydride reagents, hydrogenation or hydrosilylation. Lithium aluminium hydride (LAH), borane and silane were promptly found to be capable of reducing carboxamides but suffer the problem of functional group tolerance and chemoselectivity (Constable et al. 2007, Smith et al. 2014). Numerous heterogeneous and homogeneous catalysts for selective hydrogenation of amides via C–O bond cleavage were reported (Xie et al. 2018). The first example of homogeneously catalyzed hydrogenation of amides via C–N bond cleavage to produce amines and alcohols was reported in 2010 (Balaraman et al. 2010), thereafter, Ru (Ito et al. 2011, Miura et al. 2013, Cabrero-Antonino et al. 2015, Shi et al. 2017, Wang et al. 2017), Fe (Garg et al. 2016, Rezayee et al. 2016, Schneck et al. 2016), Mo (Krackl et al. 2012), Sm (Szostak et al. 2014) and Mn (Papa et al. 2017) homogeneous catalysts were reported for this reaction. Heterogeneous catalyst was first time used in 2018 for selective amide hydrogenation via and C–N bond cleavage (Xie et al. 2018).

Herein, we report the first example of selective amide hydrogenation via C–N bond cleavage using $NaBH_4$ at room temperature. $NaBH_4$ is a mild reducing agent and generally does not reduce carboxamides. This reduction process followed the two step mechanism in which the first step is nitrogen functionalization with *tert*-butyloxycarbonyl (Boc) group and in the second step it undergoes reduction with $NaBH_4$ to give corresponding primary alcohol and N-Boc activated amine via C–N bond cleavage (**Scheme 5.1**).

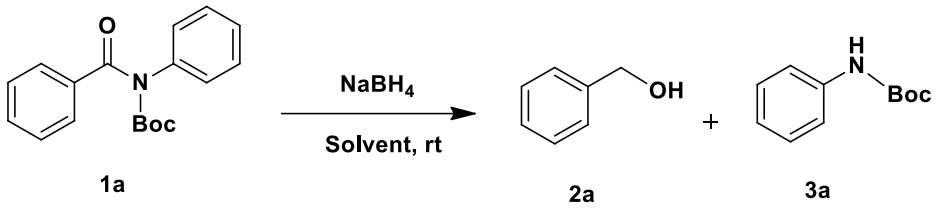


Scheme 5.1: $NaBH_4$ induced reduction of amides.

5.2 Results and Discussion

To standardize the reaction parameters, the reduction of *tert*-butyl benzoyl(phenyl) carbamate (**1a**) with $NaBH_4$ was selected as model substrate. It was observed that (**1a**) underwent efficient reduction in methanol to the corresponding alcohol (**2a**) and amine (**3**a) with 90% conversion and isolated yield of alcohol was 82%. With this exciting result in hand we have tested the model substrate for reduction using $NaBH_4$ in different polar and non-polar solvents. Among all the solvent tested (methanol, ethanol, isopropanol, *tert*-butanol, water, acetonitrile, acetic acid, tetrahydrofuran, 1,4-dioxane, benzene and toluene) only in the alcoholic solvents desired product was obtained and ethanol gave the best result with almost 100% conversion of amide to corresponding alcohol and N-Boc protected amine, and the isolated yield of corresponding alcohol i.e. benzyl alcohol is 93%. The results are summarized in **Table 5.1** on the basis of alcohol formed (**2a**).

Table 5.1: Optimization of solvent[a]



Entry	Solvent	Time (min)	Conversion (%)	Yield (%)[b]
1	Methanol	5	90	82
2	**Ethanol**	**1**	**100**	**93**
3	Isopropanol	15	90	83
4	*tert*-butanol	18	85	78
5	Water	30	--	NR
6	Acetonitrile	30	--	NR
7	Acetic acid	30	--	NR
8	Tetrahydrofuran	30	--	NR
9	Dioxane	30	--	NR
10	Benzene	30	--	NR
11	Toluene	30	--	NR

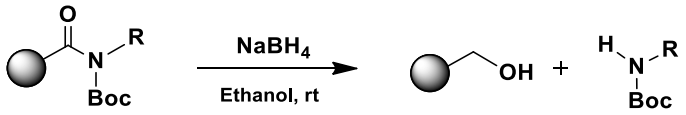
[a] **Reaction Condition:** N-Boc activated amide (**1a**) (1 equiv.) and $NaBH_4$ (1 equiv.) were stired in different solvents at room temperature for corresponding time. [b] Isolated yield (%).

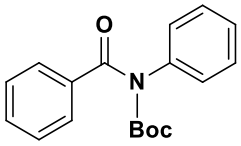
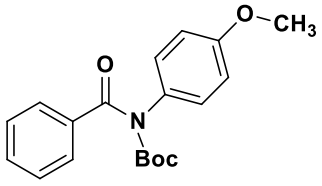
Having optimized reaction conditions for reduction of N-Boc activated amides in hand, the scope of this methodology were explored over different substrates (**1a**-**p**) *viz.* *tert*-butyl benzoyl(phenyl) carbamate (**1a**), *tert*-butyl benzoyl(4-methoxyphenyl)carbamate (**1b**), *tert*-butyl benzoyl(4-fluorophenyl)carbamate (**1c**), *tert*-butyl benzoyl(2-chlorophenyl)carbamate (**1d**), *tert*-butyl benzoyl(4-nitrophenyl)carbamate (**1e**), *tert*-butyl benzoyl(2-ethylphenyl)carbamate (**1f**), *tert*-butyl benzoyl(benzyl)carbamate (**1g**), *tert*-butyl benzoyl(methyl)carbamate (**1h**), *tert*-butyl benzoyl(cyclopropyl)carbamate (**1i**), *tert*-butyl (2-chlorobenzoyl)(phenyl)carbamate (**1j**), *tert*-butyl (3-nitrobenzoyl)(phenyl)carbamate (**1k**), *tert*-butyl benzyl(4-methoxybenzoyl)carbamate (**1l**), *tert*-butyl (4-nitrobenzoyl) (phenyl)carbamate (**1m**), *tert*-butyl benzyl(4-(trifluoromethyl)benzoyl)carbamate (**1n**), *tert*-butyl phenyl(pivaloyl)carbamate (**1o**) and *tert*-Butyl (cyclohexanecarbonyl)(phenyl) carbamate (**1p**). These gave the corresponding alcohols *viz.* Phenylmethanol (**2a**), (2-chlorophenyl)methanol (**2b**), (3-nitrophenyl)methanol **(2c),** (4-methoxyphenyl) methanol (**2d**)**,** (4-nitrophenyl)methanol (**2e**), (4-(trifluoromethyl)phenyl)methanol **(2f),** 2,2-dimethylpropan-1-ol (**2g**) and cyclohexyl-methanol (**2h**) in good to excellent yield.

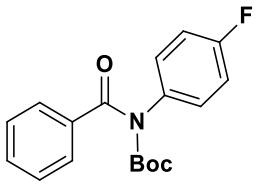
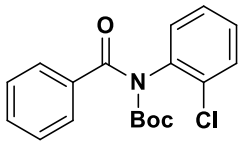
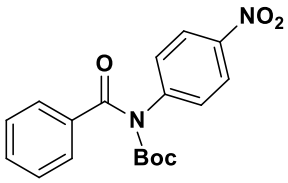
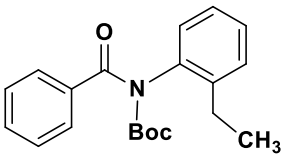
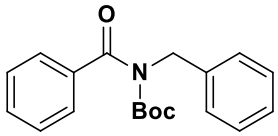
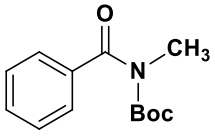
In the initial investigation, the reaction was performed with N-substituted benzanilides with electron donating and electron withdrawing substituents under optimized reaction conditions. It was observed that electron withdrawing groups like F, Cl and NO_2 (**Table 5.2, Entry 3**-**5**) gave slightly higher yield in lesser time in compare to the electron donating substituents like OMe and Et (**Entry 2, 6**). In case of amides with N-aliphatic

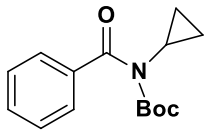
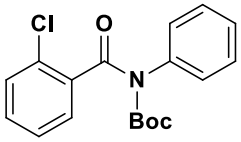
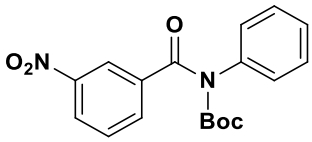
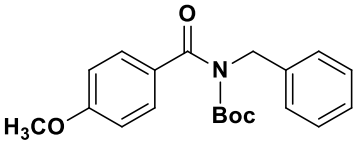
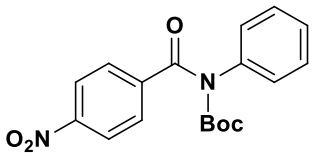
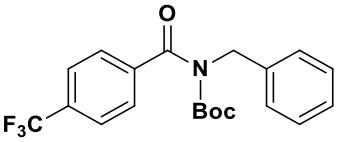
substituents *viz.* benzylamine (**Entry 7**), methylamine (**Entry 8**) and cyclopropylamine (**Entry 9**), the reaction went very well and it gave good to excellent yield of products (**Table 5.2**). Amides bearing aromatic acyl groups with different electron donating and electron withdrawing groups as well as aliphatic acyl groups were also screened. In case of electron withdrawing substituents (**Entries 10, 11, 13** and **14**), reduction were completed in shorter time than electron donating groups. In case of aliphatic acyl substituents (**1o** and **1p**) reduction underwent smoothly and gave good to excellent yield of products.

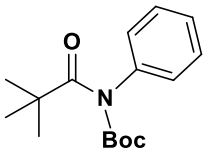
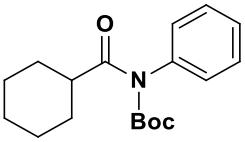
Table 5.2: $NaBH_4$ induced Reduction of amide **1**[a]



Entry	Amide	Time	Conversion (%)	Yield (%)[b]	
				Alcohol	Amine
1	 1a	1 min	>99	91	90
2	 1b	2 min	93	85	86

3	 1c	55 sec	98	92	90
4	 1d	50 sec	99	93	89
5	 1e	50 sec	98	92	89
6	 1f	2 min	94	85	87
7	 1g	1 min	97	91	92
8	 1h	65 sec	>99	95	90

9	 1i	1 min	98	91	89
10	 1j	1 min	96	88	83
11	 1k	70 sec	98	90	88
12	 1l	2.5 min	87	78	76
13	 1m	1.5 min	95	89	84
14	 1n	1.5 min	99	92	91

15	 1o	2 min	95	87	86
16	 1p	2 min	97	89	86

[a] **Reaction Conditions:** N-Boc activated amide (1 equiv.) and $NaBH_4$ (1 equiv.) were stir in ethanol at room temperature for corresponding time. [b] Reaction time. [c] Isolated yield (%).

5.3 Mechanistic studies

The proposed mechanism for the reduction of amide using $NaBH_4$ was shown in **Figure 5.3**. It follows two step mechanism, in the first step amide was activated with Boc group and in second step the N-Boc activated amide undergo nucleophilic attack by hydride followed by formation of corresponding alcohol and N-Boc activated amine via C-N bond cleavage. The formation of N-Boc activated amine and alcohol supports the proposed mechanism for $NaBH_4$ induced reduction of amide.

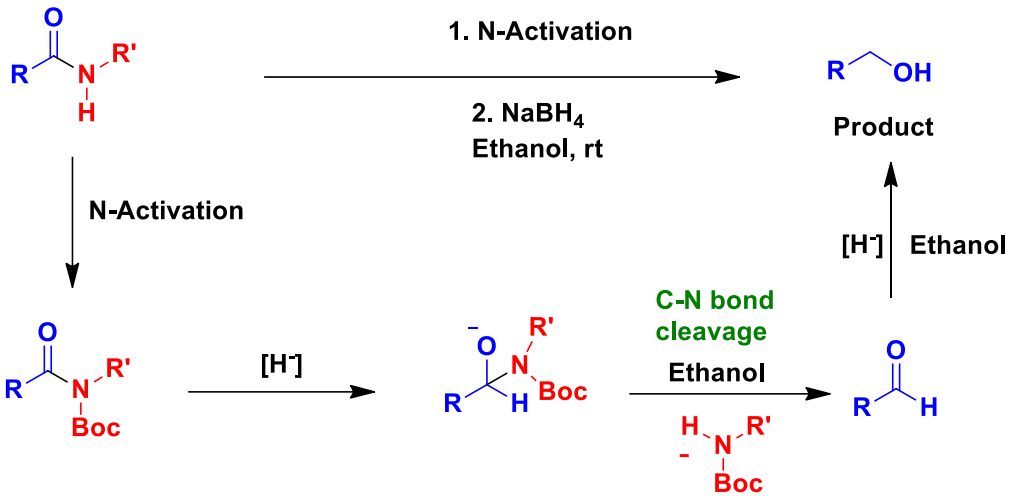


Figure 5.3: Plausible reaction mechanism of $NaBH_4$ induced reduction of amides.

5.4 Experimental section

5.4.1 General procedure for Synthesis of *N*-Boc activated amides from secondary amides (1a-p): N-Boc activated amides were synthesized according to the previously reported method (QináZhou 2015, Liu et al. 2017). To an oven dried round bottom flask, amide (1 equiv.), DMAP (0.1 equiv.) in dichloromethane (25 mL) was added, the reaction temperature was maintained to 0 ^{0}C and then dropwise Boc anhydride (1.5 equiv.) was added. After complete addition of Boc anhydride the reaction mixture was brought to the room temperature and allowed to stir at room temperature for 15-24 h. The progress of reaction was monitored by TLC.

5.4.2 General procedure of reduction of N-Boc activated amides to corresponding alcohols and amines: To N-Boc activated amide (1 equiv.) in ethanol, $NaBH_4$ (1 equiv.) was added and the reaction mixture was stirred at room temperature for the respective time. The progress of reaction was monitored by TLC and after completion of reaction the solvent was evaporated under reduced pressure. The reaction mixture was then extracted with ethyl acetate and washed with dilute HCl, brine and distilled water. The organic layer was dried over anhydrous sodium sulphate and evaporated to dryness to obtain alcohol which is pure enough. On the other hand, the crude compound was subjected to column chromatography (silica gel using ethyl acetate/hexane) to obtain the products in high purity. To separate amine and alcohol both the reaction was directly loaded over silica for column chromatography.

5.5 Analytical data

5.5.1 Analytical data of N-Boc activated amides

***tert*-Butyl benzoyl(phenyl)carbamate (1a).** White solid; yield 91%; m.p. 98-99 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.74 (d, 2 H), 7.53 (t, 1 H), 7.44 (q, 4 H), 7.35 (t, 1 H), 7.28 (d, 2 H), 1.24 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 172.91, 153.42, 139.21, 137.09, 131.83, 129.33, 128.40, 128.25, 128.07, 127.92, 83.62, 27.59.

***tert*-Butyl benzoyl(4-fluorophenyl)carbamate (1c).** White solid; yield 90%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.73 (dd, 2 H), 7.55 (s, 1 H), 7.47 (t, 2 H), 7.31 – 7.23 (m, 2 H), 7.13 (t, 2 H), 1.24 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 172.82, 163.01, 161.04, 153.29, 136.90, 135.03, 135.01, 131.94, 129.99, 129.92, 128.44, 128.20, 116.35, 116.17, 83.87, 27.57.

***tert*-Butyl benzoyl(2-chlorophenyl)carbamate (1d).** Yellow oil; yield 88%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.78 (dd, 2 H), 7.52 (d, 2 H), 7.45 (d, 2 H), 7.33 (dd, 3 H), 1.24 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 171.94, 152.37, 136.81, 136.67, 133.07, 131.72, 130.52, 130.29, 129.65, 128.29, 128.25, 127.76, 83.89, 27.51.

***tert*-Butyl benzoyl(2-ethylphenyl)carbamate (1f).** White solid; yield 85%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.79 (dd, 2 H), 7.61 – 7.54 (m, 1 H), 7.49 (dd, 2 H), 7.40 (dd, 2 H), 7.33 (ddd, 1 H), 7.25 (d, 1 H), 2.73 (q, J = 7.6 Hz, 2 H), 1.33 (t, J = 7.6 Hz, 3 H), 1.26 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 172.37, 153.32, 141.62, 137.44, 137.20, 131.48, 129.16, 128.83, 128.80, 128.27, 127.90, 126.85, 83.34, 27.44, 24.14, 14.21.

***tert*-Butyl benzoyl(benzyl)carbamate (1g).** White solid; yield 94%; m.p. 62-63 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.51 (d, 2 H), 7.47 – 7.42 (m, 3 H), 7.38 (t, 2 H), 7.33 (t, 2 H), 7.29 – 7.25 (m, 1 H), 4.99 (s, 2 H), 1.12 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 173.24, 153.61, 138.01, 137.88, 131.17, 128.59, 128.30, 128.20, 127.60, 127.54, 83.32, 49.01, 27.48.

***tert*-Butyl benzoyl(methyl)carbamate (1h).** Yellow oil; yield 94%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.47 – 7.38 (m, 2 H), 7.38 – 7.31 (m, 1 H), 7.31 – 7.21 (m, 2 H), 3.21 (s, 3 H), 1.05 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 173.34, 153.34, 137.81, 130.71, 127.85, 127.31, 127.27, 127.24, 82.75, 32.40, 27.15.

***tert*-Butyl benzoyl(cyclopropyl)carbamate (1i).** Yellow oil; yield 93%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.64 – 7.33 (m, 5 H), 2.94 – 2.78 (m, 1H), 1.19 (s, 9H), 1.06 – 0.95 (m, 2H), 0.80 – 0.70 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 174.90, 153.80, 137.79, 131.73, 128.22, 128.02, 82.78, 28.29, 27.62, 8.75.

***tert*-Butyl (2-chlorobenzoyl)(phenyl)carbamate (1j).** White solid; yield 91%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.51-7.46 (m, 3 H), 7.44 – 7.30 (m, 6 H), 1.21 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 169.69, 152.15, 138.40, 137.75, 130.83, 130.21, 129.51, 129.35, 128.80, 128.42, 128.38, 127.11, 84.04, 27.51.

***tert*-Butyl (3-nitrobenzoyl)(phenyl)carbamate (1k).** White solid; yield 94%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.47 – 8.43 (m, 1 H), 8.29 (d, 1 H), 7.95 (d, 1 H), 7.57 (t, 1 H), 7.38 (t, 2 H), 7.31 (t, 1 H), 7.21 – 7.17 (m, 2 H), 1.20 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 170.31, 152.92, 148.01, 138.45, 138.44, 133.79, 129.62, 129.47, 128.44, 128.12, 126.00, 123.03, 84.49, 29.81, 27.68.

***tert*-Butyl benzyl(4-methoxybenzoyl)carbamate (1l).** Yellow oil; yield 86%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.57 (d, 2 H), 7.45 (d, 2 H), 7.34 (t, 2 H), 7.27 (t, 1 H), 6.90 (d, 2 H), 4.99 (s, 2 H), 3.83 (s, 3 H), 1.21 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 172.64, 162.27, 153.74, 138.11, 130.01, 129.61, 128.43, 128.06, 127.32, 113.32, 82.83, 55.40, 49.14, 27.49.

***tert*-Butyl benzyl(4-(trifluoromethyl)benzoyl)carbamate (1n).** White solid; yield 94%; m.p. 78-79 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.67 (d, 2 H), 7.61 (d, 2 H), 7.43 (d, 2 H), 7.36 (t, 2 H), 7.32 – 7.27 (m, 1 H), 5.01 (s, 2 H), 1.16 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 171.86, 153.09, 141.25, 137.62, 128.68, 128.29, 127.75, 127.67, 125.28, 125.25, 84.02, 48.93, 27.51; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -62.89.

***tert*-Butyl phenyl(pivaloyl)carbamate (1o).** Colorless oil; yield 92%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.38 (t, 2 H), 7.28 (t, 1 H), 7.19 (d, 2 H), 1.48 (s, 9 H), 1.28 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 185.20, 153.27, 138.97, 129.01, 127.10, 126.93, 82.43, 44.04, 28.36, 28.00.

***tert*-Butyl (cyclohexanecarbonyl)(phenyl)carbamate (1p).** White solid; yield 91%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.40 (t, 2 H), 7.33 (t, 1 H), 7.08 (d, 2 H), 3.38 (tt, 1 H), 1.99 (d, 2 H), 1.86-1.79 (m, 2 H), 1.74-1.67 (m, 1 H), 1.58-1.48 (m, 2 H), 1.43 (d, 9 H), 1.40-1.22 (m, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 179.41, 152.78, 139.49, 128.90, 128.17, 127.56, 82.94, 44.57, 29.65, 27.86, 25.88, 25.71.

5.5.2 Analytical data of products

Phenylmethanol (2a). Colourless liquid; yield 91%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.42 – 7.07 (m, 5 H), 4.53 (s, 2 H), 2.49 (s, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 140.92, 128.59, 127.66, 127.07, 65.19.

(2-Chlorophenyl)methanol (2b). White solid; yield 93%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.53 – 7.46 (m, 1 H), 7.38 (dd, 1 H), 7.33 – 7.23 (m, 2 H), 4.80 (s, 2 H), 2.19 (s, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 138.27, 132.84, 129.47, 128.97, 128.86, 127.15, 62.97.

(3-Nitrophenyl)methanol (2c). Yellow oil; yield 90%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.21 (d, 2 H), 7.81 – 7.36 (m, 2 H), 4.83 (s, 2 H), 2.12 (s, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 148.31, 127.13, 123.87, 64.13.

(4-Methoxyphenyl)methanol (2d). Yellow oil; yield 78%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.34 – 7.11 (m, 2 H), 6.97 – 6.69 (m, 2 H), 4.50 (d, 2 H), 3.71 (d, 3 H), 1.98 (s, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 159.74, 133.28, 130.21, 128.71, 114.06, 114.02, 66.25, 55.36.

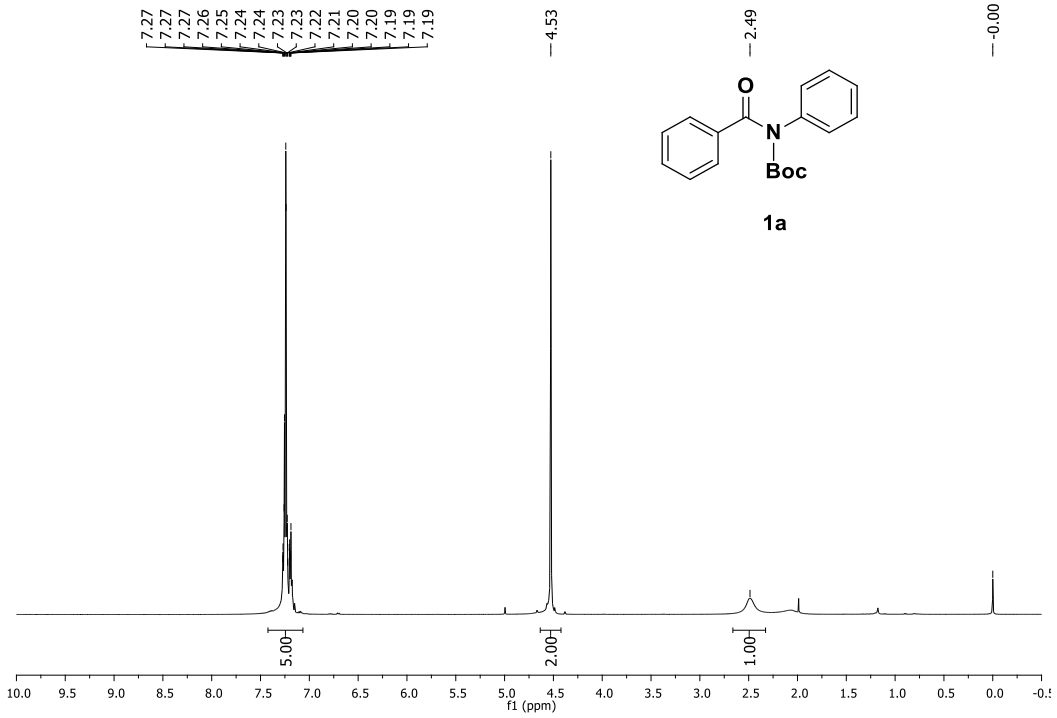
(4-Nitrophenyl)methanol (2e). Yellow solid; yield 89%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.21 (d, 2 H), 7.81 – 7.36 (m, 2 H), 4.83 (s, 2 H), 2.12 (s, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 148.31, 127.13, 123.87, 64.13.

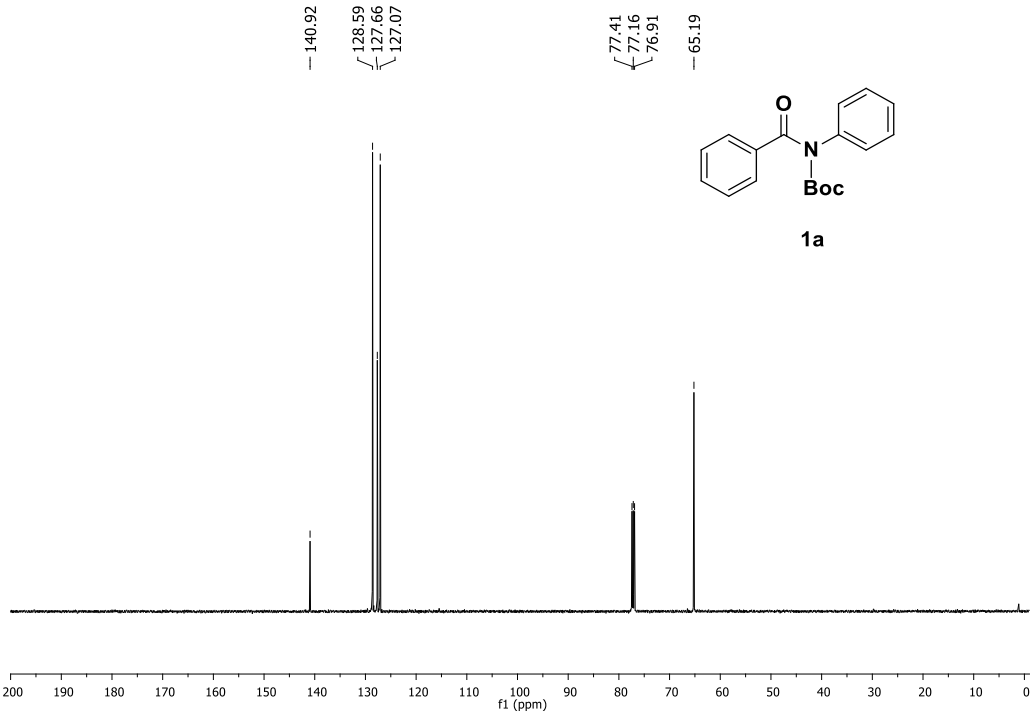
(4-(Trifluoromethyl)phenyl)methanol (2f). Yellow oil; yield 92%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.59 (d, 2 H), 7.45 (d, 2 H), 4.73 (s, 2 H), 2.25 (s, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 144.72, 129.74 (q), 126.83, 125.57 (q), 124.21 (q), 64.46.

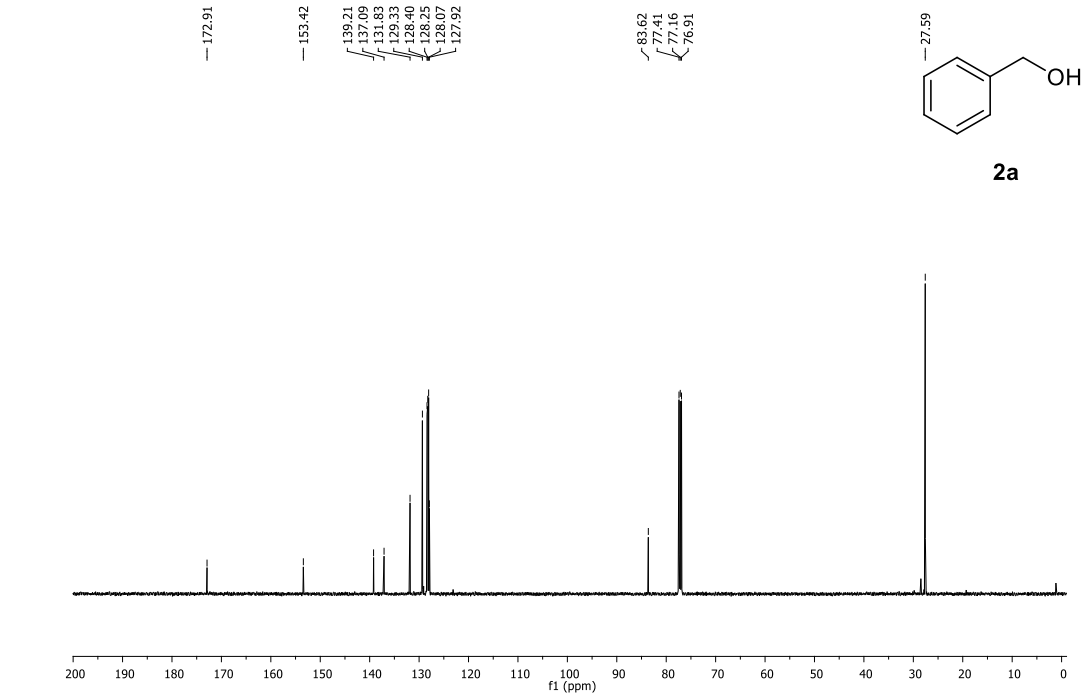
2,2-Dimethylpropan-1-ol (2g). Yellow oil; yield 87%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 3.25 (s, 2 H), 2.18 (s, 1H), 0.89 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 73.91, 33.10, 26.81.

Cyclohexyl-methanol (2h): Yellow oil; yield 89%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 3.44 (d, 2 H), 1.66 – 1.78 (m, 5 H), 1.12 – 1.55 (m, 5 H), 1.00 – 0.85 (m, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 68.83, 40.52, 29.56, 26.64, 25.83.

5.6 Spectral data



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137.09
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129.33
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127.92
83.62
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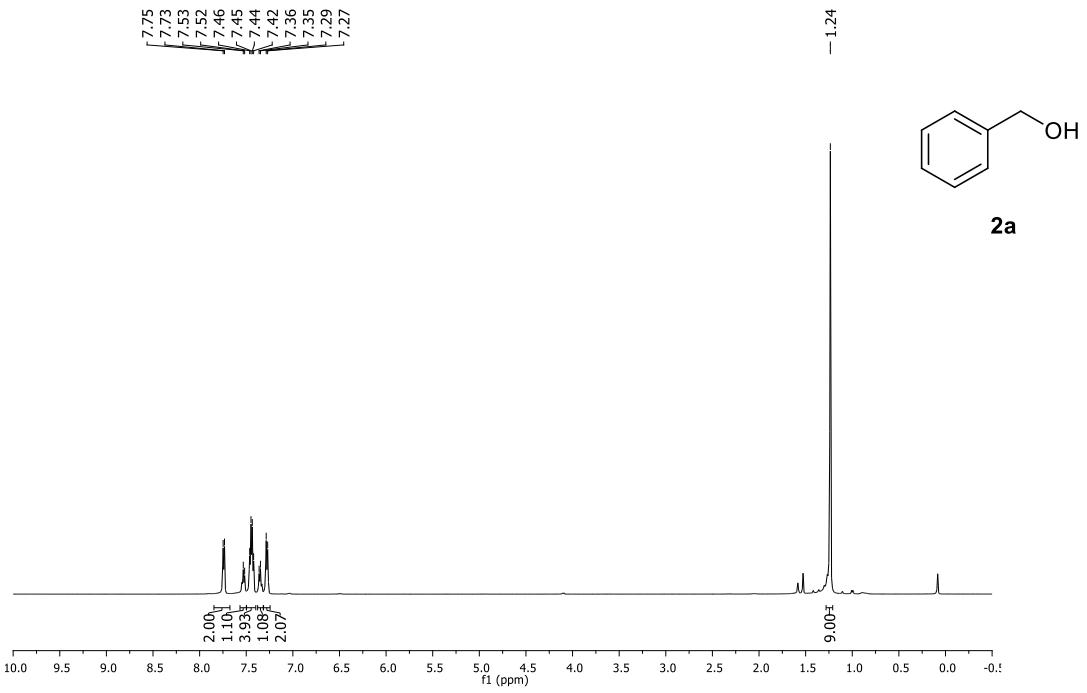
76.91
27.59
OH
2a
f1 (ppm)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7.53
7.52
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7.44
7.42
7.36
7.35
7.29
7.27
1.24
OH
2a
2.00
1.10
3.93
1.08
2.07
9.00
f1 (ppm)

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