Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700532

Link to VoR: http://dx.doi.org/10.1002/adsc.201700532

10.1002/adsc.201700532

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Efficient Approach to Amide Bond Formation with Nitriles and Peroxides: One-Pot Access to Boronated β-Ketoamides

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. An efficient, mild and practical approach for the synthesis of amides from nitriles and peroxides is reported in the presence of BF_3-ethereate. In this protocol, we utilized peroxides as C1 synthons for the amidation reaction. Also, we successfully prepared boron-incorporated β-ketoamides in a one-pot assembly from β-ketonitriles. A variety of functional groups were tolerated in moderate to good yields. Radical inhibition studies showed that the reaction proceeded via a non-radical pathway.

Keywords: nitriles; peroxides; amide; C1 synthon; BF_3-etherate

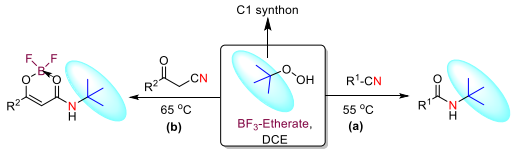
Introduction

Amides are privileged structural motifs because of their presence in many natural products, active pharmaceutical ingredients (API), and heterocycles.[1] They have also gained significant interest due to their wide range of applications in chemistry, including in proteins, peptides, and polymers.[2] The classical approach to construct amide bonds is through acid-amine coupling using activating reagents such as thionyl chlorides, HOBT, EDC·HCl, and T_3P.[3] Despite their success, some of these reported classical methods have certain drawbacks, such as harsh reaction conditions, elevated temperatures, the requirement of additives, complicated operations, the use of strong acids and the use of activating reagents, which has thus limited their applicability.

Since the discovery of the Ritter reaction,[4] several other non-classical routes have emerged for amidation by the discovery of various acids and amines as synthons.[5] For example, cross-coupling reactions of boronic acids with amines,[6] amidation via S-nitrosothioacid,[7] Lewis-acid-catalyzed reactions,[8] and unactivated ester-mediated amidation reactions[9] have been employed. Therefore, the identification of new methods to overcome the utilization of expensive coupling reagents is still an interesting area of research.

Peroxides have been utilized in various applications as oxidants/H-acceptors to activate C-H bonds[11] and as radical initiators,[12] but they have been less explored as alkylating reagents.[13] For example, Hock and Kornblum DelaMare reported the acid/base-catalyzed decomposition of peroxides for the synthesis of alcohols/ketones.[10]

Therefore, by considering these points and our current interest in nitriles as well as Lewis acid chemistry,[14] herein, we disclose a BF_3-etherate-mediated efficient protocol for the synthesis of amides from nitriles and peroxides (Scheme 1a). We also discovered the synthesis of boron-incorporated β-ketoamides from β-ketonitriles in presence of inexpensive organic peroxides (Scheme 1b) for the first time. However, after a brief literature survey, we found that Turner and co-workers patented the synthesis of amides from peroxides and nitriles using strong reaction conditions, which utilized an alcoholic acidic medium of H_2SO_4.[15] The potential drawback of this methodology is the poor functional group tolerance due to the strong acidic conditions. Herein, our reaction conditions are mild and applicable to a variety of nitrile derivatives, and in the case of β-ketonitriles, we prepared the BF_2-chelated compounds in a one-pot strategy. These compounds are known to possess potential biological activity.[16]



Scheme 1. Our Approach for Amide Bond Formation.

Results and Discussion

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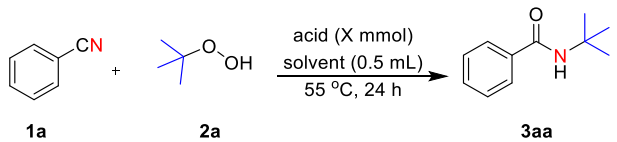
Table 1. Screening of the reaction conditions.[a]



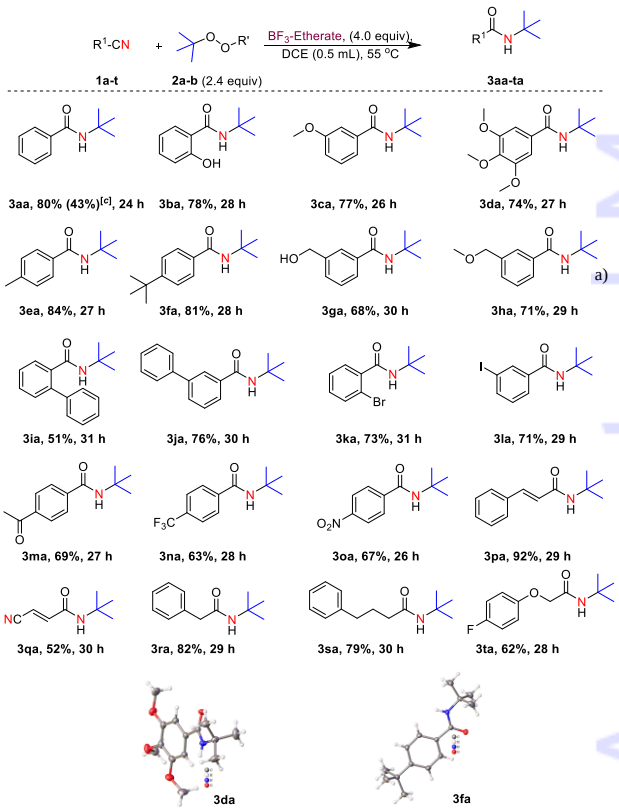
1a **2a** **3aa**

Entry	Acid (X mmol)	Reagent (Y mmol)	Solvent	Yield (%)[b]
1	$BF_3.OEt_2$ (1)	TBHP (2)	DCE	12
2	$BF_3.OEt_2$ (2)	TBHP (2)	DCE	30
3	$BF_3.OEt_2$ (3)	TBHP (2)	DCE	40
4	$BF_3.OEt_2$ (4)	TBHP (2)	DCE	66
5	$BF_3.OEt_2$ (4)	TBHP (2)	PhCl	63
6	$BF_3.OEt_2$ (4)	TBHP (2)	DMSO	-
7	$BF_3.OEt_2$ (4)	TBHP (2)	MeOH	-
8	$BF_3.OEt_2$ (4)	TBHP (2)	dioxane	29
9	$BF_3.OEt_2$ (4)	TBHP (2)	Toluene	52
10	$BF_3.OEt_2$ (4)	TBHP (2.4)	DCE	80
11	$BF_3.OEt_2$ (4)	TBHP (3)	DCE	68
12	$BF_3.OEt_2$ (4)	TBHP (4)	DCE	-
13	$Cu(OAc)_2$ (4)	TBHP (2.4)	DCE	-
14	CuI (4)	TBHP (2.4)	DCE	-
15	$Fe(OTf)_3$ (4)	TBHP (2.4)	DCE	-
16	AgOTf (4)	TBHP (2.4)	DCE	-
17	$AlCl_3$ (4)	TBHP (2.4)	DCE	34
18	$FeCl_3$ (4)	TBHP (2.4)	DCE	43
19[c]	$BF_3.OEt_2$ (4)	TBHP (2.4)	DCE	54
20	$BF_3.OEt_2$ (4)	DTBP (2.4)	DCE	43
21[d]	HCl (4)	TBHP (2.4)	DCE	-
22[e]	TFA (4)	TBHP (2.4)	DCE	-
23	TsOH (4)	TBHP (2.4)	DCE	62
24	Acetic acid (4)	TBHP (2.4)	DCE	28
25	HF (4)	TBHP (2.4)	DCE	-
26	HBF_4 (4)	TBHP (2.4)	DCE	Trace
27	-	TBHP (2.4)	DCE	-
28[f]	$BF_3.OEt_2$ (4)	TBHP (2.4)	DCE	53
29[g]	$BF_3.OEt_2$ (4)	TBHP (2.4)	DCE	69

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.4 mmol), acid (4.0 mmol) and solvent (0.5 mL) stirred for 24 h at 55 °C, unless otherwise noted. [b] Isolated yield. [c] TBHP in decane was used. [d] 35% of benzamide was formed. [e] Reaction decomposed. [f] Reaction was carried out at RT. [g] Reaction was carried out at 85 °C.

Our preliminary studies began with benzonitrile **1a** and *tert*-butyl hydroperoxide **2a** (70% aqueous) as model substrates (Table 1). To our surprise, we obtained *N*-(*tert*-butyl) benzamide **3aa** in 12% yield when these substrates were treated with BF_3-etherate (1.0 equiv.) in 1,2-DCE (0.5 mL) for 24 h at 55 °C (Table 1, entry 1). By varying the equivalents of BF_3-etherate (Table 1, entries 2-4), we obtained **3aa** in 66% yield with 4 equiv. of BF_3-etherate (Table 1, entry 4). Next, various solvents, including chlorobenzene (PhCl), DMSO, MeOH, 1,4-dioxane, toluene, were tested (Table 1, entries 5-9), but these solvents were found to be less favourable than 1,2-DCE (Table 1, entry 4). Furthermore, we tested various equivalents of TBHP (Table 1, entries 10-12), and interestingly, we obtained **3aa** in 80% yield with 2.4 equiv. of TBHP (Table 1, entry 10). Additionally, we tried different Lewis acids, such as $Cu(OAc)_2$, CuI, $Fe(OTf)_3$, and AgOTf, but none of these gave the desired product (Table 1, entry 13-16) except $AlCl_3$ and $FeCl_3$, albeit in low yield (Table 1, entry 17 and 18). Next, we examined other organic peroxides, such as TBHP in decane and DTBP (Table 1, entries 19-20), but none of these gave better yields than 70% using aq. TBHP (Table 1, entry 10). Different acids, such as HCl, TFA, *p*-toluenesulfonic acid (TsOH), acetic acid, HF and HBF_4, were then tested in the amidation reaction (Table 1, entries 21-26), and none of these acids were successful. Additionally, in the absence of BF_3-etherate, the reaction did not proceed to give **3aa** (Table 1, entry 27). This result confirms that BF_3-etherate is crucial for this transformation. Finally, lowering or increasing the temperature (Table 1, entries 28-29) resulted in a lower yield of **3aa**. Thus. Table 1, entry 10 was chosen as the optimum reaction conditions.

Table 2. Scope of nitriles with peroxides[a,b]



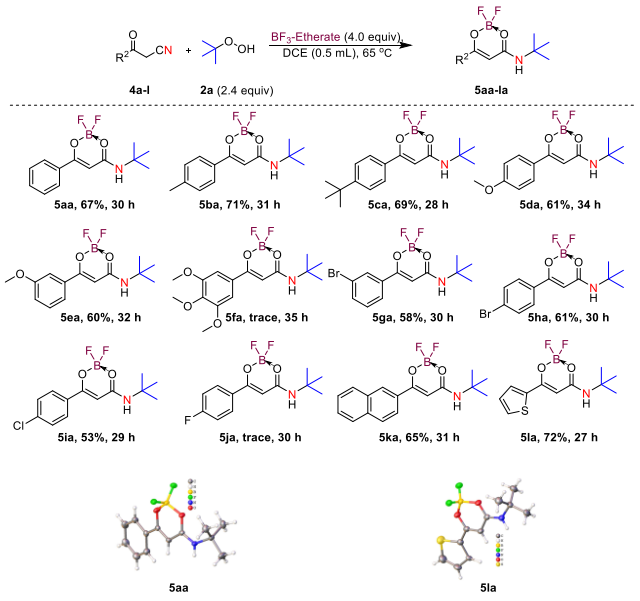
Reaction conditions: Compounds **1a-t** (1.0 mmol), DCE (0.5 mL), peroxide **2a-b** (2.4 equiv) and $BF_3.OEt_2$ (4.0 equiv) at 55 °C for the indicated time. [b] Isolated yields, [c] Instead of TBHP, DTBP was used.

With the optimized conditions in hand, the scope of nitriles **1a-t** with various R^1-functional groups was investigated with *tert*-butyl hydroperoxide **2a** (70% aqueous), as shown in Table 2. Electron-donating

nitriles, such as nitriles with *o*-OH (**1b**), *m*-OMe (**1c**), 3,4,5-trimethoxy (**1d**), *p*-Me (**1e**), *p*-*tert*-butyl (**1f**), *m*-hydroxymethyl (**1g**) and *m*-methoxymethyl (**1h**) groups, were reacted with TBHP under the standard conditions. To our delight, the corresponding *N*-*tert*-butyl amides **3ba-ha** were obtained in 68-84% yields.

Next, the reaction of *o*-Ph (**1i**) and *m*-Ph (**1j**) benzonitriles also gave the respective amides **3ia-ja** in 51-76% yields irrespective of the steric/electronic factors. Furthermore, halogenated nitriles, including *o*-Br (**1k**) and *m*-I (**1l**) nitriles, gave the desired amides **3ka-la** in 71-73% yields. Similarly, electron-withdrawing nitriles, such as *p*-acetyl (**1m**), *p*-CF_3 (**1n**) and *p*-NO_2 (**1o**) nitriles, were also smoothly tolerated to obtain the corresponding amides **3ma-oa** in 63-69% yields. Under the optimized conditions, next, we successfully achieved the amidation of nitriles bearing alkene (**1p-q**), alkane (**1r-s**) and ether (**1t**) functional groups to obtain the respective amides **3pa-ta** in 52-92% yields. Finally, DTBP (**2b**) was also treated with benzonitrile (**1a**) to obtain the respective amides **3aa** in 43% yields. The crystal structures of **3da** and **3fa** were unambiguously confirmed by X-ray crystallography.[17]

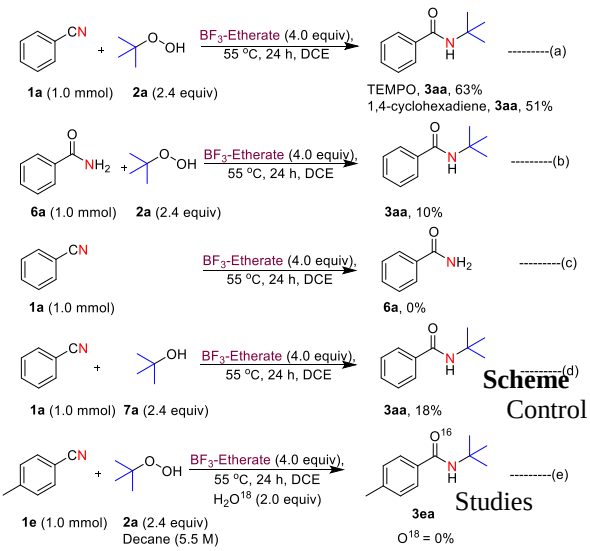
Table 3. Substrate scope of β-ketonitriles with a 70% aq. TBHP solution[a,b]



[a] Reaction conditions: Compound **4a**-l (1.0 mmol), DCE (0.5 mL), **2a** (2.4 equiv) and $BF_3.OEt_2$ (4.0 equiv) at 65 °C for the indicated time. [b] Isolated yields.

In light of the success with nitrile derivatives, we explored the scope of the reaction of β-ketonitriles under slightly modified conditions (Table 3). To our surprise, we prepared β-ketoamides with boron incorporated between the two oxygen atoms. Next, we elucidated the substrate scope with simple β-ketonitrile (**4a**) as well as electron-donating β-ketonitriles, such as those containing *p*-Me (**4b**), *p*-*tert*-butyl (**4c**), *p*-OMe (**4d**), and *m*-OMe (**4e**) groups. Interestingly, the expected products **5aa-ea** were isolated in 60-71% yields. Similarly, electron-withdrawing β-ketonitriles, such as those with *m*-Br (**4g**), *p*-Br (**4h**) and *p*-Cl (**4i**) groups, were also successfully applied to give the desired products **5ga-ia** in 53-61% yields. Finally, we successfully transformed naphthyl (**4k**) and thiophenyl (**4l**) β-ketonitriles to the desired products **5ka-la** in 65-72% yields. However, the reaction only gave trace product using 3,4,5-trimethoxy (**5fa**) or *p*-F (**5ja**) derivatives. The crystal structures of **5aa** and **5la** were unambiguously confirmed by X-ray crystallography.[17]

To understand the mechanism, some control experiments were performed, as shown in Scheme 2. Radical inhibition studies of **1a** under the optimized conditions with TEMPO and 1,4-cyclohexadiene gave **3aa** in 63% and 51% yields, respectively (Scheme 2a). These results ruled out the possibility of a radical intermediate. Furthermore, the reaction of benzamide (**6a**) under the standard conditions gave **3aa** only in 10% yield, along with some unidentified products (Scheme 2b). Then, the reaction of benzonitrile (**1a**) under the standard conditions without TBHP did not afford benzamide **6a** (Scheme 2c). Hence, the formation of a benzamide intermediate was also ruled out. Finally, the reaction of **1a** with *tert*-butanol **7a** under the standard conditions gave **3aa**, albeit in low yield (Scheme 2d). To further investigate the reaction mechanism, we performed the reaction with O^{18}-labelled H_2O and 5.5 M TBHP in decane (Scheme 2e). But there was trace of oxygen incorporation observed by LC-Mass analysis.[18] These results suggest that the oxygen atom could possibly come from TBHP.



Scheme 2. Control Studies

Based on the control studies and previous literature,[19] a plausible mechanism is proposed, as shown in Scheme 3. Initially, peroxide **2** will react with BF_3-etherate to form intermediate **A** after elimination of HF. Then, intermediate **A** will undergo nucleophilic addition with nitrile **1** to form a Zwitterionic intermediate **B**, followed by reaction with HF to form intermediate **C**. Finally,

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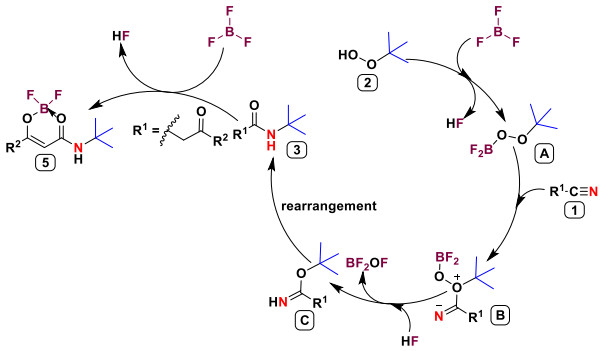
rearrangement of intermediate **C** from *O*-alkyl to *N*-alkyl will give the desired amide **3**. In the case of β-ketonitrile, the obtained product will further undergo reaction with BF_3-ethereate to form compound **5** via elimination of HF.



Scheme 3. Proposed Mechanism

Conclusion

In conclusion, we developed an amidation of nitriles and β-ketonitriles with peroxides as C1 synthons with the combination of a Lewis acid. This method broadens the application of peroxides under Lewis acidic conditions. Furthermore, β-ketonitriles were transformed to boron-incorporated β-ketoamides in a one-pot assembly, and their structures were confirmed by X-ray analysis. This protocol provided key advantages to avoid expensive amide coupling agents and strong acids, such as thionyl chloride and oxalyl chloride.

Experimental Section

General procedure for the synthesis of compounds 3aa-3ta. In a 15 mL oven-dried sealed tube, nitrile **1a-t** (1.0 mmol) in 1,2-dichoroethane (DCE, 0.5 mL) was added, and the solution was stirred at 0 °C. BF_3-etherate (4.0 mmol) was added dropwise to the solution for approximately 1 min at 0 °C, and the solution was maintained stirring at the same temperature for 10 min. To the same solution, peroxide **2a-b** (2.4 mmol) was added dropwise, and the solution was continued stirring at the same temperature for 30 min. Furthermore, the resultant reaction mixture was stirred at room temperature and then at 55 °C. The reaction was monitored by TLC until completion. The reaction was cooled to room temperature and quenched with aq. K_2CO_3. The aqueous layer was extracted with EA (3x10 mL), and the combined organic layers were washed with aq. K_2CO_3 (1x10 mL) followed by water (2x10 mL) and brine solution. The final solution was dried over Na_2SO_4 and concentrated under reduced pressure. Finally, the resultant crude mixture was purified by column chromatography using 5-20% EA/hexane to obtain the pure compounds **3aa-ta**.

***N*-(*tert*-butyl)benzamide (3aa):** White solid; Yield: 80% (141.81 mg); Mp 135-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.70 (m, 2H), 7.48-7.44 (m, 1H), 7.42-7.37 (m, 2H), 5.96 (brs, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.87, 135.89, 131.00, 128.40, 126.64, 51.54, 28.83; HRMS (ESI) calcd for $C_{11}H_{15}NONa$ $[M + Na]^+$: 200.1045; found: 200.1043.

***N*-(*tert*-butyl)-2-hydroxybenzamide (3ba):** White solid; Yield: 78% (151.73 mg); Mp 74-76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.48 (brs, 1H), 7.35 (ddd, J = 8.4, 7.2, 1.6 Hz, 1H), 7.28 (dd, J = 8.0, 1.6 Hz, 1H), 6.95 (dd, J = 8.0, 1.6 Hz, 1H), 6.80 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H), 6.11 (brs, 1H), 1.47 (s, 9H); ; Yield: ; Mp° C; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.78, 161.67, 133.81, 125.25, 118.65, 118.40, 115.13, 52.09, 28.82; HRMS (ESI) calcd for $C_{11}H_{16}NO_2$ $[M + H]^+$: 194.1176; found: 194.1172.

***N*-(*tert*-butyl)-3-methoxybenzamide (3ca):** Off-white solid; Yield: 77% (159.62 mg); Mp 114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.32 (m, 1H), 7.30-7.26 (m, 1H), 7.21 (dt, J = 7.6, 1.2 Hz, 1H), 7.01 (ddd, J = 8.4, 2.4, 0.8 Hz, 1H), 5.94 (brs, 1H), 3.84 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.70, 159.79, 137.40, 129.37, 118.35, 117.31, 112.12, 55.41, 51.61, 28.83; HRMS (ESI) calcd for $C_{12}H_{17}NO_2Na$ $[M + Na]^+$: 230.11515; found: 230.11514.

***N*-(*tert*-butyl)-3,4,5-trimethoxybenzamide (3da):** White solid; Yield: 74% (197.81 mg); Mp 126-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 2H), 5.86 (brs, 1H), 3.90 (s, 6H), 3.88 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.59, 153.09, 140.68, 131.42, 104.23, 60.87, 56.35, 51.67, 28.83; HRMS (ESI) calcd for $C_{14}H_{21}NO_4Na$ $[M + Na]^+$: 290.1362; found: 290.1361.

***N*-(*tert*-butyl)-4-methylbenzamide (3ea):** White solid; Yield: 84% (160.74 mg); Mp 115-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 5.91 (brs, 1H), 2.38 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.79, 141.33, 133.01, 129.05, 126.63, 51.44, 28.87, 21.34; HRMS (ESI) calcd for $C_{12}H_{18}NO$ $[M + H]^+$: 192.1382; found: 192.1383.

***N*,4-di-*tert*-butylbenzamide (3fa):** White solid; Yield: 81% (189.11 mg); Mp 164-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 5.93 (brs, 1H), 1.46 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.82, 154.45, 133.01, 126.46, 125.33, 51.44, 34.81, 31.14, 28.87; HRMS (ESI) calcd for $C_{15}H_{24}NO$ $[M + H]^+$: 234.1852; found: 234.1849.

***N*-(*tert*-butyl)-3-(hydroxymethyl)benzamide (3ga):** Colourless viscous oil; Yield: 68% (140.91 mg); Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 6.04 (brs, 1H), 4.68 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.19, 141.52, 136.03, 129.52, 128.61, 125.79, 125.03, 64.59, 51.72, 28.84; HRMS (ESI) calcd for $C_{12}H_{18}NO_2$ $[M + H]^+$: 208.1332; found: 208.1331.

***N*-(*tert*-butyl)-3-(methoxymethyl)benzamide (3ha):** Pale yellow solid; Yield: 71% (157.12 mg); Mp 54-55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 2H), 7.45-7.42 (m, 1H), 7.39 (t, J = 7.6 Hz, 1H), 5.97 (brs, 1H), 4.48 (s, 2H), 3.40, (s, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.75, 138.59, 136.09, 130.20, 128.56, 126.07, 125.74, 74.20, 58.24, 51.61, 28.82; HRMS (ESI) calcd for $C_{12}H_{20}NO_2$ $[M + H]^+$: 222.1489; found: 222.1484.

***N*-(*tert*-butyl)-[1,1'-biphenyl]-2-carboxamide (3ia):** White solid; Yield: 51% (129.2 mg); Mp 109-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 7.6, 1.6 Hz, 1H), 7.47-7.37 (m, 7H), 7.33 (dd, J = 7.6, 1.6 Hz, 1H), 4.98 (brs, 1H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.26, 140.50, 139.33, 136.78, 130.00, 129.77, 128.96, 128.90, 128.57, 127.70, 127.62, 51.31, 28.16; HRMS (ESI) calcd for $C_{17}H_{20}NO$ $[M + H]^+$: 254.1539; found: 254.1537.

***N*-(*tert*-butyl)-[1,1'-biphenyl]-3-carboxamide (3ja):** White solid; Yield: 76% (192.54 mg); Mp 122-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (t, J = 2.0 Hz, 1H), 7.70-7.65 (m, 2H), 7.67-7.63 (m, 2H), 7.49-7.43 (m, 3H), 7.39-7.35 (m, 1H), 6.00 (brs, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.95, 141.62, 140.34, 136.50, 129.75,

128.88, 128.82, 127.67, 127.18, 125.66, 125.34, 51.71, 28.86; HRMS (ESI) calcd for $C_{17}H_{20}NO$ [M + H]$^+$: 254.1539; found: 254.1533.

2-bromo-*N*-(*tert*-butyl)benzamide (3ka): Off-white solid; Yield: 73% (186.98 mg); Mp 99-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 8.0, 1.2 Hz, 1H), 7.48 (dd, J = 7.6, 1.6 Hz, 1H), 7.33 (td, J = 7.6, 1.2 Hz, 1H), 7.23 (td, J = 1.6 Hz, 1H), 5.73 (brs, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.06, 139.15, 133.30, 130.95, 129.42, 127.64, 119.24, 52.39, 28.89; HRMS (ESI) calcd for $C_{11}H_{15}NOBr$ [M + H]$^+$: 256.0332; found: 256.0330.

***N*-(*tert*-butyl)-3-iodobenzamide (3la):** White solid; Yield: 71% (215.23 mg); Mp 110-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (t, J = 1.6 Hz, 1H), 7.79 (ddd, J = 7.6, 1.6, 1.2 Hz, 1H), 7.66 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 5.90 (brs, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.25, 139.89, 137.91, 135.73, 130.11, 125.92, 94.15, 51.84, 28.77; HRMS (ESI) calcd for $C_{11}H_{15}NOI$ [M + H]$^+$: 304.0193; found: 304.0191.

4-acetyl-*N*-(*tert*-butyl)benzamide (3ma): White solid; Yield: 69% (151.3 mg); Mp 106-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H), 6.01 (brs, 1H), 2.62 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.42, 165.86, 139.79, 138.80, 130.11, 128.41, 128.24, 126.99, 51.92, 28.77, 26.76; HRMS (ESI) calcd for $C_{13}H_{18}NO_2$ [M + H]$^+$: 220.1332; found: 220.1331.

***N*-(*tert*-butyl)-4-(trifluoromethyl)benzamide (3na):** White solid; Yield: 63% (154.5 mg); Mp 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 8.4 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 5.97 (brs, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.59, 139.19, 132.80 (q, J_{CF3} = 33 Hz), 127.16, 125.49 (q, J_{CF3} = 3.7 Hz) 125.03, 122.32, 51.98, 28.76; HRMS (ESI) calcd for $C_{12}H_{15}NOF_3$ [M + H]$^+$: 246.1100; found: 246.1096.

***N*-(*tert*-butyl)-4-nitrobenzamide (3oa):** Off-white solid; Yield: 67% (148.9 mg); Mp 153-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.6 Hz, 2H), 7.87 (d, J = 7.6 Hz, 2H), 6.06 (brs, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.82, 149.26, 141.49, 127.88, 123.66, 52.24, 28.69; HRMS (ESI) calcd for $C_{11}H_{14}N_2O_3Na$ [M + Na]$^+$: 245.0896; found: 245.0898.

***(E)*-*N*-(*tert*-butyl)cinnamamide (3pa):** White solid; Yield: 92% (187.02 mg); Mp 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 15.6 Hz, 1H), 7.46-7.44 (m, 2H), 7.36-7.26 (m, 3H), 6.35 (d, J = 15.6 Hz, 1H), 5.59 (brs, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.21, 140.20, 134.99, 129.42, 128.74, 127.68, 122.02, 51.50, 28.88; HRMS (ESI) calcd for $C_{13}H_{17}NONa$ [M + Na]$^+$: 226.1202; found: 226.1203.

(*E*)-*N*-(*tert*-butyl)-3-cyanoacrylamide (3qa): White solid; Yield: 52% (79.14 mg); Mp 118-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, J = 16.0 Hz, 1H), 6.44 (d, J = 15.6 Hz, 1H), 5.72 (brs, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.68, 143.40, 116.30, 109.13, 52.39, 28.52; HRMS (ESI) calcd for $C_8H_{13}N_2O$ [M + H]$^+$: 153.1022; found: 153.1020.

***N*-(*tert*-butyl)-2-phenylacetamide (3ra):** White solid; Yield: 82% (156.84 mg); Mp 112-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (ddd, J = 8.4, 6.8, 0.8 Hz, 2H), 7.29-7.26 (m, 1H), 7.25-7.22 (m, 2H), 5.20 (brs, 1H), 3.48 (s, 2H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.24, 135.48, 129.26, 128.90, 127.12, 51.23, 44.89, 28.67; HRMS (ESI) calcd for $C_{12}H_{18}NO$ [M + H]$^+$: 192.1383; found: 192.1379.

***N*-(*tert*-butyl)-4-phenylbutanamide (3sa):** White solid; Yield: 79% (173.27 mg); Mp 68-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.20-7.16 (m, 3H), 5.24 (brs, 1H), 2.64 (t, J = 7.6 Hz, 2H), 2.08 (t, J = 7.6 Hz, 2H), 1.94 (quin, J = 7.6 Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.95, 141.58, 128.44, 128.28, 125.84, 51.03, 36.70, 35.05, 28.78, 27.07; HRMS (ESI) calcd for $C_{14}H_{22}NO$ [M + H]$^+$: 220.1696; found: 220.1692.

***N*-(*tert*-butyl)-2-(4-fluorophenoxy)acetamide (3ta):** Pale yellow solid; Yield: 62% (137.8 mg); Mp °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03-6.98 (m, 2H), 6.88-6.84 (m, 2H), 6.33 (brs, 1H), 4.33 (s, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.02, 157.89 (d, J_F = 238.3 Hz), 153.30, 116.16 (d, J_F =24 Hz), 115.85 (d, J_F = 8 Hz), 68.40, 51.25, 28.72; HRMS (ESI) calcd for $C_{12}H_{16}NO_2FNa$ [M+Na]$^+$: 248.1057; found: 248.1058.

General procedure for the synthesis of compounds 5aa-5la. In a 15 mL oven dried sealed tube was charged with respective β-ketonitrile **4a-l** (1.0 mmol) in 1,2-dichoroethane (DCE, 0.5 mL) and stirred the solution at 0 °C. To the solution was added BF_3-etherate (4.0 mmol) drop wise for around 1 min. at 0 °C and maintained stirring at same temperature for 10 min. To the same solution was added 70% aq. TBHP solution **2a** (2.4 mmol) drop wise and continued the stirring at same temperature for 30 min. Further, the resultant reaction mixture was stirred at room temperature and then at 65 °C. The reaction was monitored by TLC until the completion. The reaction mass was cooled to room temperature and quenched with aq. K_2CO_3. The aqueous layer was extracted with EA (3X10 mL), and combined organic layer was washed with aq. K_2CO_3 (1X10 mL) followed by water (2X10 mL) and brine solution. The final solution was dried over Na_2SO_4 and concentrated under reduced pressure. Finally, the resultant crude was purified by column chromatography using 5-20% EA/hexane to obtain the pure compounds **5aa-la**.

(*Z*)-*N*-(*tert*-butyl)-3-((difluoroboranyl)oxy)-3-phenylacrylamide (5aa): White solid; Yield: 67% (178.95 mg); Mp 191-193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.81 (m, 2H), 7.47 (ddd, J = 8.0, 4.0, 2.0 Hz, 1H), 7.39-7.33 (m, 2H), 6.25 (brs, 1H), 5.81 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.21, 169.16, 133.01, 132.15, 128.54, 126.87, 85.13, 54.58, 28.89; HRMS (ESI) calcd for $C_{13}H_{17}BNO_2F_2$ [M + H]$^+$: 268.13149; found: 268.13144.

(*Z*)-*N*-(*tert*-butyl)-3-((difluoroboranyl)oxy)-3-(p-tolyl)acrylamide (5ba): Pale yellow solid; Yield: 71% (199.59 mg); Mp 260-262 °C; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 8.32 (brs, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 5.91 (s, 1H), 2.39 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.24, 168.59, 141.98, 130.49, 128.91, 126.32, 84.84, 53.44, 28.60, 21.20; HRMS (ESI) calcd for $C_{14}H_{19}BNO_2F_2$ [M + H]$^+$: 282.14714; found: 282.14716.

(*Z*)-*N*-(*tert*-butyl)-3-(4-(*tert*-butyl)phenyl)-3-((difluoroboranyl)oxy)acrylamide (5ca): Pale yellow solid; Yield: 69% (223 mg); Mp 211-214 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 6.25 (brs, 1H), 5.80 (s, 1H), 1.47 (s, 9H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.26, 169.21, 155.91, 130.21, 126.79, 125.52, 84.57, 54.44, 34.99, 31.07, 28.92; HRMS (ESI) calcd for $C_{17}H_{25}BNO_2F_2$ [M + H]$^+$: 324.1941; found: 324.1942.

(*Z*)-*N*-(*tert*-butyl)-3-((difluoroboranyl)oxy)-3-(4-methoxyphenyl)acrylamide (5da): Off-white solid; Yield: 61% (181.24 mg); Mp 251-252 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 5.94 (brs, 1H), 5.66 (s, 1H), 3.84 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.25, 169.20, 162.96, 128.88, 113.91, 83.39, 55.42, 54.43, 29.03; HRMS (ESI) calcd for $C_{14}H_{17}BNO_3F_2$ [M - H]$^+$: 296.1264; found: 298.1271.

(*Z*)-*N*-(*tert*-butyl)-3-((difluoroboranyl)oxy)-3-(3-methoxyphenyl)acrylamide (5ea): White solid; Yield: 60% (178.27 mg); Mp 222-224 °C; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.38-7.36 (m, 2H), 7.26 (t, J = 8.0 Hz, 1H), 7.01 (ddd, J = 8.0, 2.4, 0.8 Hz, 1H), 6.35 (brs, 1H), 5.81 (s, 1H), 3.80 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.94, 169.11, 159.72, 134.47, 129.50, 119.23, 118.54, 111.58, 85.43, 55.39, 54.57, 28.87; HRMS (ESI) calcd for $C_{14}H_{19}BNO_3F_2$ $[M + H]^+$: 298.1421; found: 298.1421.

***(Z)*-3-(3-bromophenyl)-*N*-(*tert*-butyl)-3-((difluoroboranyl)oxy)acrylamide (5ga):** Off-white solid; Yield: 58% (200.67 mg); Mp 180-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (t, J = 1.6 Hz, 1H), 7.74 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H), 7.59 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 7.26 (t, J = 8.0, Hz, 1H), 6.24 (brs, 1H), 5.77 (s, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.01, 168.98, 134.96, 130.10, 129.84, 125.38, 122.75, 85.84, 54.85, 28.87; HRMS (ESI) calcd for $C_{13}H_{15}BNO_2F_2BrNa$ $[M + Na]^+$: 368.0239; found: 368.0236.

(*Z*)-3-(4-bromophenyl)-*N*-(*tert*-butyl)-3-((difluoroboranyl)oxy)acrylamide (5ha): Off-white solid; Yield: 61% (211.05 mg); Mp 159-160 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (brs, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 5.96 (s, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.86, 168.44, 132.33, 131.48, 127.87, 125.97, 85.88, 53.71, 28.57; HRMS (ESI) calcd for $C_{13}H_{15}BNO_2F_2BrNa$ $[M + Na]^+$: 368.0239; found: 368.0240.

(*Z*)-*N*-(*tert*-butyl)-3-(4-chlorophenyl)-3-((difluoroboranyl)oxy)acrylamide (5ia): White solid; Yield: 53% (159.81 mg); Mp 237-239 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (brs, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 6.10 (s, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.79, 167.52, 136.74, 131.74, 129.12, 127.98, 86.33, 53.47, 28.26; HRMS (ESI) calcd for $C_{13}H_{14}BNO_2F_2Cl$ $[M - H]^+$: 300.0769; found: 300.0777.

(*Z*)-*N*-(*tert*-butyl)-3-((difluoroboranyl)oxy)-3-(naphthalen-2-yl)acrylamide (5ka): Off-white solid; Yield: 65% (206.14 mg); Mp 242-243 °C; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 8.45 (d, J = 0.8 Hz, 1H), 8.06 (brs, 1H), 7.87 (dd, J = 7.6, 1.2 Hz, 1H), 7.81 (dd, J = 8.0, 0.8 Hz, 1H), 7.79-7.75 (m, 2H), 7.55-7.47 (m, 2H), 6.10 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.31, 168.79, 134.72, 132.58, 130.47, 129.06, 128.02, 127.69, 127.67, 127.46, 126.56, 122.67, 86.09, 53.88, 28.76; HRMS (ESI) calcd for $C_{17}H_{19}BNO_2F_2$ $[M + H]^+$: 318.1471; found: 318.1472.

(*Z*)-*N*-(*tert*-butyl)-3-((difluoroboranyl)oxy)-3-(thiophen-2-yl)acrylamide (5la): Light brown solid; Yield: 72% (196.64 mg); Mp 211-213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 3.6, 1.2 Hz, 1H), 7.50 (dd, J = 5.2, 1.2 Hz, 1H), 7.07 (dd, J = 5.2, 3.6 Hz, 1H), 6.07 (brs, 1H), 5.64 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.85, 167.03, 137.57, 131.15, 129.88, 128.20, 84.02, 54.60, 28.97; HRMS (ESI) calcd for $C_{11}H_{14}BNO_2SF_2$ $[M + H]^+$: 274.0879; found: 274.0878.

Acknowledgements

The authors gratefully acknowledge funding from the Ministry of Science and Technology (MOST), Taiwan and the Centre for Research and Development of Kaohsiung Medical University for 400 MHz NMR, LC-MS and GC-MS analyses. The authors also thankful for Dr. Vinoth Kumar Ponnusamy for H_2O^{18} LC-Mass analysis.

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FULL PAPER

Efficient Approach to Amide Bond Formation with Nitriles and Peroxides: One-Pot Access to Boronated β-Ketoamides

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