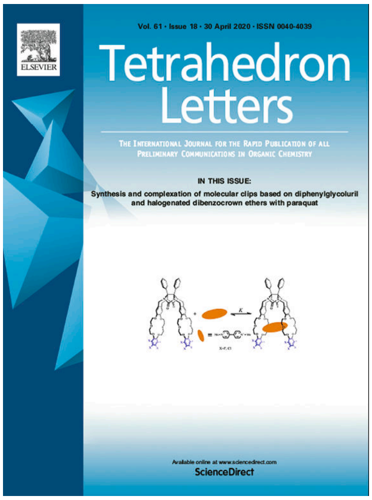

Ball-milling enables highly selective solvent-free N-tert-butoxycarbonylation for activation of amides

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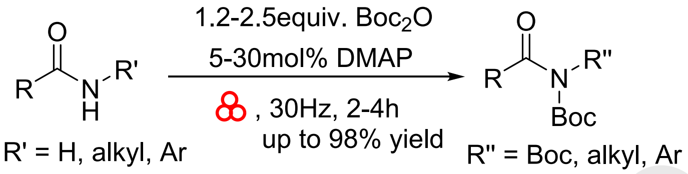

Solvent-free condition

High chemoselectivity

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Ball-milling enables highly selective solvent-free N-tert-butoxycarbonylation for activation of amides

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ABSTRACT

A ball-milling enabled chemoselective activation of amides via N-tert-butoxycarbonylation catalyzed by 4-dimethylaminopyridine is described under solvent-free conditions. High chemoselectivity with respect to NH acidity of amides has been observed. A one-pot two-step procedure for selective esterification of amides has been demonstrated in model reaction of benzamides with *p*-cresol and benzyl alcohol.

Introduction

With increasing concerns over environment and sustainable development, solvent-free synthetic technology as a green alternative to the conventional processes in organic solvents has been attracting interests [1-3]. In fact, solvent-free synthesis has proven not only environmentally benign but also economically feasible, profiting from the shorter reaction time and smaller batch-size because of the high reactant concentrations in the absence of solvents. The most common difficulty encountered in solvent-free organic synthesis lies in low mixing efficiency at molecular level, in particular, in the cases involving solid materials. Ball-milling, the simplest form of mechanochemistry, has a privilege of mixing solid materials under solvent-free conditions. Indeed, mechanochemical synthesis via ball-milling has recently attracted increasing attentions as an emerging synthetic methodology [4-13], showing not only environmental advantages but also capabilities to alter selectivities and / or reaction pathways [14] benefiting from the extremely short and localized yet high temperature and pressure spots generated by the unique mechanical impacts and/or the simple increase in mixing rates and thermal energy [15-17].

Amides generally represent the least reactive carboxylic acid derivatives because of the conjugation of electron pair on nitrogen with carbonyl group. Therefore, although they are abundant in natural and artificial sources, ranging from discrete small molecules to polymeric macromolecules [18], amides have been rarely used as acetyl reagents [19, 20]. Since the seminal reports on the nickel or palladium catalyzed cross-coupling of activated amides by Houk and Garg [21], Szostak [22], and ourselves [23], independently, in 2015, it has come to be recognized that, after conversion into imides, both primary and secondary amides could become a versatile acetyl source [24-32].

N-Sulfonylation and N-tert-butoxycarbonylation (Boc) of amides have proven to be the most feasible way to convert primary and secondary amides into bias imides to activate the target C(O)-N bond. Compared with N-sulfonylation, N-tert-butoxycarbonylation of amides by Boc_2O catalyzed by 4-dimethylaminopyridine (DMAP) is operationally simple yet powerful, capable of reaction with both primary and secondary amides affording the corresponding imides under open-flask conditions [33]. Conventionally, N-tert-butoxycarbonylation of amides requires use of environmentally hazardous solvents, e.g. CH_3CN and CH_2Cl_2 etc., in the presence of a tertiary amine as base or, at least, catalyst. With the rapid increase in applications of N-Boc-amides, it is important to develop an environmentally benign synthetic procedure. We report herein ball-milling enabled highly chemoselective solvent-free N-*tert*-butoxycarbonylation for amide activation and demonstration of its potential in sequential telescope transformations by selective esterification of *p*-cresol and benzyl alcohol.

Results and Discussion

Initially, when a mixture of benzamide (**1a**) with 1.2 equiv. Boc_2O was milled at 30 Hz for 2h in the presence of 10 mol% DMAP as catalyst to produce mono-Boc amide, N, N-di-Boc-benzamide (**2a**) was found to be the sole isolable product with about half amount of benzamide recovered (Table 1, entry 1). Under various ball-milling conditions, mono-butoxycarbonylation product, PhCONH(Boc), could not be isolated although it was reported that ArCONH(Boc) could be obtained in various yields via a similar procedure in common solvents, such as CH_2Cl_2 [34], and THF [35]. Neither mono- nor di-butoxycarbonylation occurred without DMAP catalyst. These results indicated that the second N-*tert*-butoxycarbonylation should take place much faster than the first one under ball-milling conditions, due to the higher NH acidity in the intermediate imide PhCONH(Boc) than that in amide $PhCONH_2$. In fact, N, N-di-Boc-benzamide could be obtained in excellent isolated yields (95-96%) with 2.5 equiv. Boc_2O using 5-10 mol% DMAP (Table 1, entries 3 and 4). Control experiments indicated that the reaction was cleaner and faster under the solvent-free ball-milling conditions than in conventional CH_3CN solution (Figure 1). The former completed in 2h while the later gave **2a** in 84% yield after 8h.

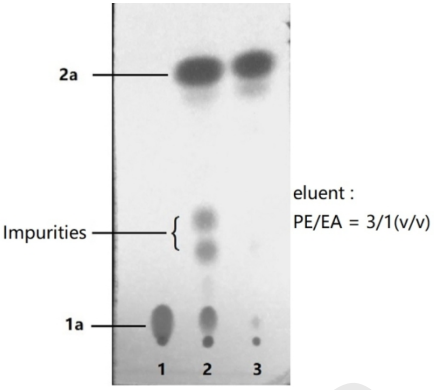
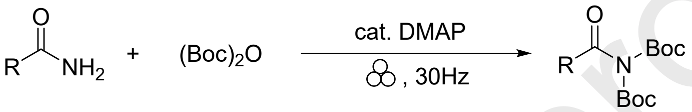
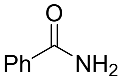
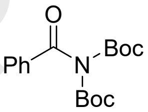
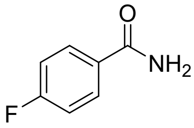
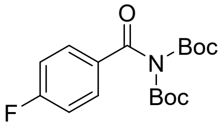
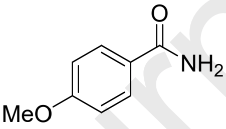
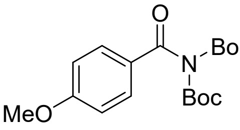
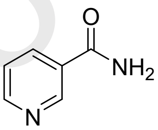
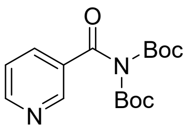
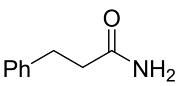
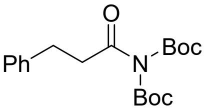
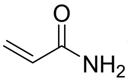
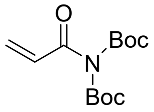


Figure 1. TLC of the control experiment in CH_3CN solution (2) vs solvent-free ball-milling (3) under otherwise identical conditions at 2h when the ball-milling reaction almost completed.

Table 1. DMAP catalyzed di-N-*tert*-butoxycarbonylation of primary amides under solvent-free ball-milling conditions[a]



Entry	Amide (**1**)	Boc_2O(equiv.)	DMAP(mol%)	Time(h)	Imide (**2**)	Yield(%)[b]
1	 (**1a**)	1.2	10	2	 (**2a**)	47
2	**1a**	2.2	10	2	**2a**	81
3	**1a**	2.5	10	2	**2a**	96
4	**1a**	2.5	5	2	**2a**	95
5	**1a**	2.5	1	4	**2a**	87
6	 (**1b**)	2.5	5	2	 (**2b**)	94
7	 (**1c**)	2.5	5	4	 (**2c**)	28
8	**1c**	2.5	10	4	**2c**	78
9	**1c**	4.0	5	4	**2c**	97
10	 (**1d**)	2.5	5	4	 (**2d**)	70
11	 (**1e**)	2.5	10	4	 (**2e**)	61
12	**1e**	4.0	10	4	**2e**	91
13	 (**1f**)	2.5	5	4	 (**2f**)	31
14	**1f**	4.0	10	4	**2f**	81

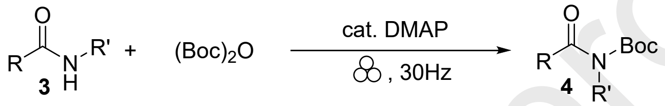
[a] Reaction run in 1 mmole scale in a planetary ball mill with 60 min on, 10 min off cycle to take sample for TLC analysis.

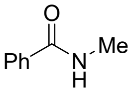
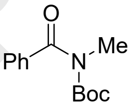
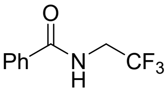
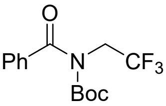
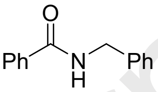
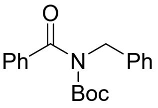
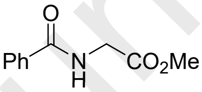
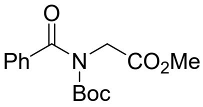
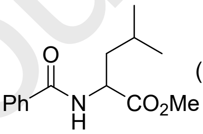
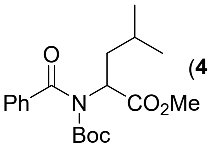
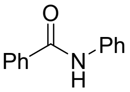
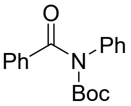
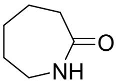
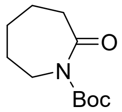
[b] Isolated yields

T [illegible] he solvent-free mechanochemical N-*tert*-butoxycarbonylation via ball-milling. For example, 4-fluorobenzamide (**1b**) reacted similarly to **1a** while 4-methoxybenzamide (**1c**) gave a low yield (28%) even after double reaction time. No remarkable conversion was observed after 4h, indicating a competitive decomposition of Boc_2O under ball-milling conditions. The reaction of less reactive **1c** could complete with high loading of Boc_2O (4.0 equiv.) to give **2c** in 97% yield (Table 1, entries 7-9). The relatively low yield (70%) with nicotinamide may be attributed to the competition of the pyridine moiety with the catalyst. Aliphatic amides, e.g. 3-phenylpropanamide (**1e**) and acrylamide (**1f**), reacted slower and gave lower yields than aromatic ones, requiring high loadings of both Boc_2O (4.0 equiv.) and catalyst DMAP (10 mol%) to achieve good yields (Table 1, entries 11-14).

A large electronic effect of the N-substituent in secondary amides has been observed. N-methyl benzamide (**3a**) reacted corresponding Boc derivative **4a** in only 50% yield. High loadings of both DMAP catalyst (30 mol%) and Boc_2O (2.0 equiv.) had to be used to obtain good yields (Table 2, entries 1-4). However, benzamides bearing an electron-withdrawing substituent on nitrogen, e.g. N-(2,2,2-trifluoroethyl) (**3b**) and N-phenyl (**3f**) benzamides as well as methyl benzoylglycinate (**3d**) showed remarkably high reactivities, giving the corresponding N-Boc amides in good to excellent yields (94-99%) with 10 mol% DMAP and 1.2 equiv. Boc_2O (Table 2, entries 5, 7 and 9). The low reactivity of methyl benzoylleucinate (**3e**) reflected the steric influence of N-substituent of benzamides (Table 2, entry 8), indicating that small steric hindrance could be negligible while large one could not be overcome by simply increasing the loadings of DMAP and Boc_2O. Caprolactam **3g** reacted readily, consistent with the high reactivity of lactams in acylation.

Table 2. Reactivities of secondary amides under solvent-free ball-milling conditions[a]



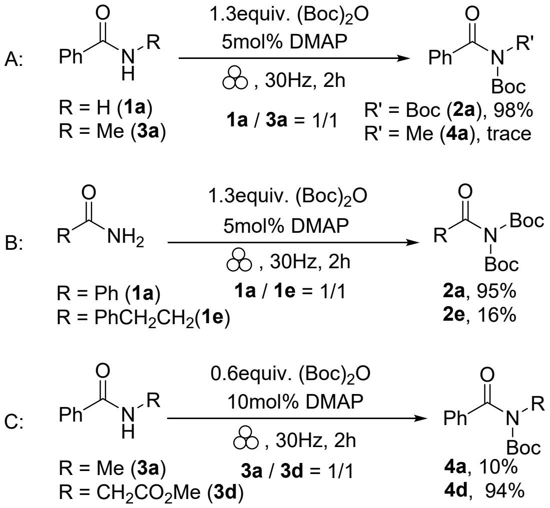
Entry	Amide (**3**)	Boc_2O(equiv.)	DMAP(mol%)	Time(h)	Imide (**4**)	Yield(%)[b]
1	 (**3a**)	1.2	10	4	 (**4a**)	50
2	**3a**	1.2	30	4	**4a**	74
3	**3a**	2.0	10	4	**4a**	72
4	**3a**	2.0	30	4	**4a**	90
5	 (**3b**)	1.2	10	4	 (**4b**)	98
6	 (**3c**)	2.0	10	4	 (**4c**)	81
7	 (**3d**)	1.2	10	4	 (**4d**)	94
8	 (**3e**)	2.0	30	4	 (**4e**)	35
9	 (**3f**)	1.2	10	4	 (**4f**)	99
10	 (**3g**)	1.2	10	4	 (**4g**)	95

[a] Reaction run in 1 mmole scale in a planetary ball mill with 60min on, 10min off cycle to take sample for TLC analysis.

[b] Isolated yields

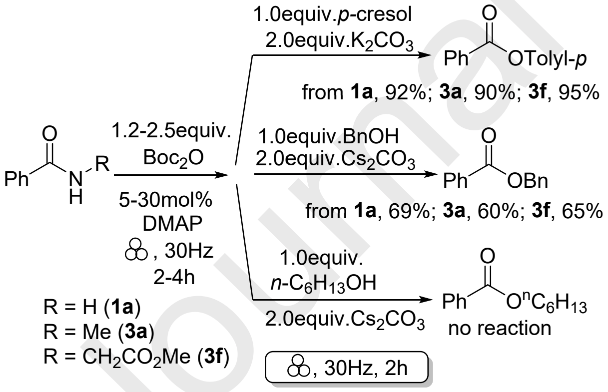
Given the strong influence of the NH acidity, it is envisaged that chemoselective N-*tert*-butoxycarbonylation could be feasible among electronically varied amides. Therefore, intermolecular competition of 3 pairs of amides was investigated, including primary / secondary benzamides, primary aromatic / aliphatic amides and secondary benzamides bearing N-electronically different substituents (Scheme 1). When a 1:1 (mole ratio) mixture of primary (**1a**) and secondary (**3a**) benzamides was milled with 1.3 equiv. Boc_2O in total (2.6 equiv. with respect to **1a**) and 5 mol% DMAP for 2h, N, N-di-Boc-benzamide (**2a**) was isolated in 98% yield while only trace **4a** could be detected by TLC, showing an excellent selectivity between primary and se

between primary aromatic (**1a**) and aliphatic (**1e**) amides as well as secondary benzamides **3a** and **3d** could be achieved, respectively.



Scheme 1. Competition of amides

Direct transamidation of N-Boc activated amides is known [20, 36]. Comparably, reaction of N-Boc activated amides with the less reactive oxygen-centered nucleophiles, i.e. phenols and alcohols, requires either use of pre-formed oxygen anions or assistance from catalysts [19-21, 37, 38]. We anticipated that, in high-yielding cases of the solvent-free N-*tert*-butoxycarbonylation, efficient one-pot two-step esterification of amides with the oxygen-centered nucleophiles should be feasible in telescope manner. Indeed, the amide activation / esterification sequential transformation could be efficiently effected in the model reaction of primary and secondary benzamides with *p*-cresol or benzyl alcohol under the solvent- and catalyst-free ball-milling conditions (Scheme 2).



Scheme 2. Demonstration of one-pot two-step chemoselective esterification of amides

In typical procedure, after milling a mixture of benzamide (**1a**) with 2.5 equiv. Boc_2O and 5 mol% DMAP for 2h, 1.0 equiv. *p*-cresol and 2.0 equiv. K_2CO_3 were added to the mixture and milled for another 2h to give the corresponding ester in 92% yield. Secondary amides (**3a**) and (**3f**) could also be used in the one-pot two-step esterification procedure although the first step of N-*tert*-butoxycarbonylation required longer reaction time (4h) and higher loadings of DMAP, 30 mol% and 10 mol%, respectively, to convert the secondary amides completely. The esterification of benzyl alcohol needed stronger base Cs_2CO_3 while no reaction occurred for *n*-hexanol unless use of Cs_2CO_3 in DMSO solvent [38].

In summary, we have demonstrated that mechanochemistry via ball-milling could not only enable an environmentally benign N-tert-butoxycarbonylation of amides under solvent-free conditions but also make the amide activation more chemoselective with respect to the NH acidity. Primary amides reacted to directly give di-Boc imides without isolable mono-Boc intermediates. Secondary amides reacted much more slowly than primary ones unless bearing an electron-donating group on NH moiety. Indeed, a high chemoselectivity could be effected not only between the primary and secondary amides, but also among secondary ones with NH substituted by electronically various substituents. Selective esterification of amides via one-pot two-step procedure has been demonstrated to be feasible in the model reaction of benzamides with *p*-cresol and benzyl alcohol under solvent-free ball-milling conditions.

Acknowledgments

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Supplementary Material

Experimental procedures, compound characterization and copies of NMR and HRMS (**4b**) spectra of products.

Highlights

Mechanochemical solvent-free N-tert-butoxycarbonylation of amides.

High chemoselectivity with respect to NH acidity.

Capable of one-pot two-step sequential transformations.

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