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A novel 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI)-catalyzed esterification of *N*-protected amino acids with nearly equimolar amounts of alcohols in the presence of Boc_2O

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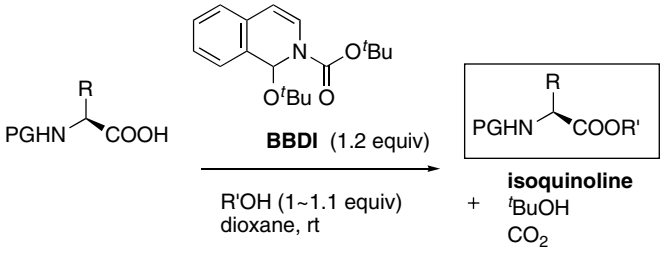
Abstract—A very mild, BBDI-catalyzed esterification using approximately equimolar amounts of N-protected amino acids and alcohols, in junction with Boc_2O is described.

Ester moieties constitute major backbones, as well as important functional groups, in numerous natural products and synthetic compounds.[1] In addition, ester groups are also useful protecting groups for carboxylic acids in chemical synthesis.[2] Esterification is defined as the transformation of carboxylic acids or their derivatives into esters. A major problem that is frequently encountered in esterification technology arises from equilibration. To shift the equilibrium to the product side, one of the reactants must be used in excess and/or one of the products must be continuously removed constantly during the reaction.

Accordingly, use of a non-equilibrium reaction approach, with the aid of activated reactants such as acid anhydrides and halides or alkoxides, can be effective in bypassing such a problem, on some occasions.[3] We recently reported on the simple and mild esterification of *N*-protected α-amino acids using approximately equimolar amounts of alcohols via *tert*-butoxycarbonyl esters using 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) (Scheme 1).[4] In pursuing our interest in the use of BBDI as a *tert*-butoxycarbonylation reagent in the organic synthesis,[5] further we describe the novel BBDI-catalyzed esterification of N-protected α-amino acids in the presence of Boc_2O herein.

It is noteworthy that isoquinoline is liberated form BBDI in the *tert*-butoxycarbonylation of carboxylic acid with BBDI (Scheme 1). We consider that BBDI is regenerated from isoquinoline with Boc_2O. On the basis of the



Scheme 1.

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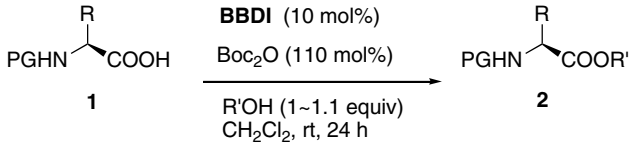
above consideration, the esterification of *N*-Cbz L-phenylalanine (**1a**) with allyl alcohol using a catalytic amount of BBDI (10 mol %) in the presence of Boc_2O (110 mol %) in dioxane for 24 h at room temperature was examined. As expected, the corresponding allyl ester **2a** was obtained in 57% yield. Fortunately, the yield was dramatically improved to 97%, when dichloromethane was used as a solvent, instead of dioxane. In addition, the screening experiments involving various reaction times were conducted for the reaction of **1a** and allyl alcohol as shown in Table 1 and the finding indicated that approximately 24 h was required for the completion of the reaction.

Thus, a variety of *N*-protected amino acids were treated with BBDI (10 mol %) in the presence of Boc_2O (110 mol %) in dichloromethane for 30 min, followed by the addition of various alcohols (1–1.1 equiv) for 24 h at room temperature.[6] The results are shown in Table 2.[7] The yields for most reactions are high, similar to cases in which 120 mol % of BBDI was used.[4] However, the yields using bulkier amino acids such as proline and valine (entries 11 and 12) accompanied with a couple of substrates (entries 5, 14 and 19) exhibited somewhat low yields (77–84%).

Furthermore, it was found that this esterification proceeded in the presence of alcohols to provide the corresponding esters in high yields. In a typical experiment, alcohols, Boc_2O and BBDI were sequentially added to a solution of **1a** in CH_2Cl_2 and the reaction mixture was stirred for 24 h. This procedure permits esterification to proceed in a single operation. The reaction mixture was concentrated, ethyl acetate added and the organic solvent washed with dilute HCl and brine. The reagent-derived byproducts are easily removed by a simple aqueous workup. The results are shown in Table 3.

In order to better understand the nature of this BBDI-catalyzed esterification, the following experiments were carried out (Table 4). First, in the absence of BBDI, the use of isoquinoline (10 mL%) provided **2a** in 66% yield (entry 1). It was found that isoquinoline, even without BBDI, could be reacted with Boc_2O to form BBDI and esterification proceeded though the reaction time was long. On the other hand, the use of quinoline in place of isoquinoline resulted in a low yield (16%) (entry 2).[8] The yield of esterified product with isoquinoline containing 4-dimethylaminopyridine (DMAP) (10 mol %) as an additive was improved slightly to 81% yield (entry 3). However, the use of only DMAP resulted in a very low yield (4%) (entry 4). Based on the above results, we propose the following reaction mechanism (Scheme 2). Isoquinoline liberated from BBDI is again reacted with Boc_2O to regenerate BBDI. A long reaction time (~24 h) would be required for the reformation of BBDI. *tert*-Butoxylation of carboxylic acid group with Boc_2O was not promoted by either quinoline or DMAP.[9] Accordingly, the formation of BBDI of isoquinoline with Boc_2O may be accelerated by DMAP.

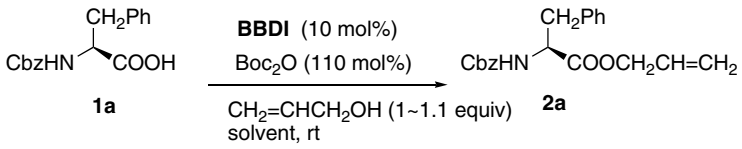
Table 2. Esterification of **1** with alcohols using BBDI (10 mol %) in the presence of Boc_2O



Entry	*N*-PG-AA	Alcohol	Ester	Yield (%)[a]
1	Cbz-Ala **1b**	Me	**2b**	89
2	Cbz-Ala **1b**	Et	**2c**	95
3	Cbz-Ala **1b**	Allyl	**2d**	89
4	Cbz-Ala **1b**	Ph	**2e**	88
5	Cbz-Ala **1b**	*p*-MeO-C_6H_4	**2f**	82
6	Cbz-Ala **1b**	$C_6H_5CH_2$	**2g**	98
7	Cbz-Ala **1b**	TMSE[b]	**2h**	90
8	Cbz-Phe **1a**	$C_6H_5CH_2$	**2i**	95
9	Cbz-Met **1c**	Allyl	**2j**	95
10	Cbz-Met **1c**	$C_6H_5CH_2$	**2k**	99
11	Cbz-Pro **1d**	Allyl	**2l**	82
12	Cbz-Val **1e**	Allyl	**2m**	77
13	Cbz-Phe **1a**	$(CH_3)_2CH$	**2n**	91
14	Boc-Ala **1f**	Allyl	**2o**	83
15	Boc-Ala **1f**	*p*-MeO-C_6H_4	**2p**	90
16	Boc-Ala **1f**	$C_6H_5CH_2$	**2q**	91
17	Boc-Phe **1g**	Allyl	**2r**	90
18	Boc-Phe **1g**	$C_6H_5CH_2$	**2s**	89
19	Boc-Met **1h**	Allyl	**2t**	84
20	Fmoc-Ala **1i**	Allyl	**2u**	88
21	Fmoc-Phe **1j**	Allyl	**2v**	93

[a] Isolated yield.
[b] TMSE = 2-$TMSCH_2CH_2$.

Table 1. Esterification of *N*-Cbz-Phe **1a** with allyl alcohol using BBDI (10 mol %)



Entry	Solvent	Time (h)	Ester	Yield (%)[a]
1	Dioxane	24	**2a**	57
2	CH_2Cl_2	24	**2a**	97
3	CH_2Cl_2	18	**2a**	61
4	CH_2Cl_2	10	**2a**	48
5	CH_2Cl_2	5	**2a**	23

[a] Isolated yield.

Table 3. Esterification of **1a** with BBDI in the coexistence of alcohols beforehand

Entry	N-PG-AA	R′	Ester	Yield (%)[a]
1	**1a**	Allyl	**2a**	94
2	**1a**	$C_6H_5CH_2$	**2i**	96
3	**1a**	$(CH_3)_2CH$	**2n**	92

[a] Isolated yield.

Table 4. Esterification of **1a** with allyl alcohol in the absence of BBDI under several conditions[a,b]

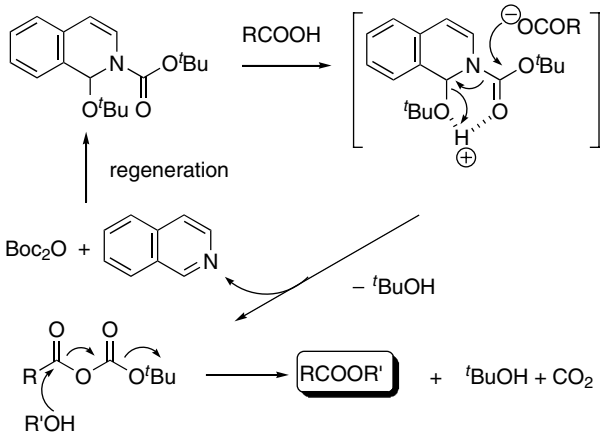
Entry	Catalyst (10 mol %)	Additive (10 mol %)	Ester	Yield (%)[c]
1	Isoquinoline	—	**2a**	66
2	Quinoline	—	**2a**	16
3	Isoquinoline	DMAP	**2a**	81
4	—	DMAP	**2a**	4

[a] Reaction time (24 h).
[b] Use of Boc_2O (110 mol %).
[c] Isolated yield.

The issue of whether the amounts of BBDI in the esterification of **1b** with allyl alcohol could be further reduced was next examined. The use of 5 mol % and 1 mol % of BBDI provided yields of 92% and 84% of **2d**, respectively. However, to achieve this, it was necessary to extend the reaction times to 48 h and 10 days, respectively.

The data presented herein show that no significant racemization of the chiral center on the α-carbon atom occurred during the synthesis.[10]

In conclusion, we developed a novel BBDI-catalyzed esterification of *N*-protected amino acids in the presence of Boc_2O under simple and mild conditions. Although a variety of methods for acid-catalyzed esterification reactions have been reported,[11] the use of a nearly neutral catalyst such as BBDI has not been extensively investigated.[12] This procedure has several advantages including the use of nearly equimolar amounts of alcohols, no requirement for additives, and no racemization occurs.



Scheme 2. Postulated mechanism of BBDI-catalyzed esterification.

Acknowledgements

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6. General procedure for esterification of N-protected amino acids with BBDI. BBDI (0.1 mmol) was added to a solution of N-protected amino acid (1 mmol) and Boc_2O (1.1 mol) in CH_2Cl_2 (5 mL) with stirring at room temperature. The reaction mixture was stirred for 30 min. Alcohol (1 or 1.1 mmol) was added to the reaction mixture and after the addition, the reaction mixture was stirred for 24 h, and then concentrated. After the addition of ethyl acetate, the organic phase was washed twice with 5% HCl and brine. The organic layers were dried ($MgSO_4$) and the solvent evaporated to give the crude compound, which was purified by chromatography on a short column using a mixture of *n*-hexane and ethyl acetate as eluant to yield N-protected amino acid ester.
7. N-Protected amino acid esters were used as chiral educts (a) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825–1872; (b) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*; John Wiley & Sons: New York, 1987.
8. The exposure of quinoline to Boc_2O gave no adduct (*tert*-butyl 2-*tert*-butoxyquinoline-1(2*H*)-carboxylate) similar to BBDI. Unpublished result.
9. Accordingly, DMAP, quinoline, and isoquinoline would be weak as bases for *tert*-butoxylation of carboxylic acid.
10. In fact, the enantiomeric purities of **2a**, **2b** and **2h** were >99% ee, as determined by chiral HPLC analysis (Chiralcel OD column, 95:5 hexane/2-propanol, 1.0 mL/min) for **2a**,**b** and (Chiralcel OJ column) for **2h**.
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