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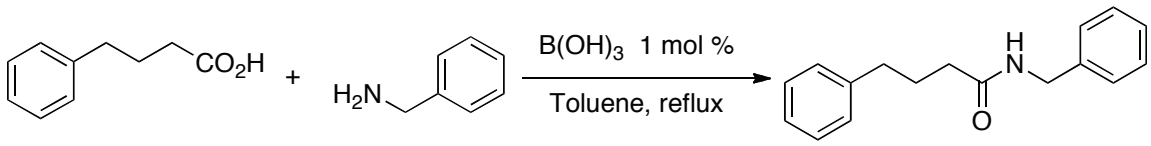
Discussion Addendum for: Boric Acid Catalyzed Amide Formation from Carboxylic Acids and Amines: *n*-Benzyl-4-phenylbutyramide



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In the last few years, boric acid catalyzed carboxylic amide formation directly from carboxylic acids and amines has attracted considerable attention because it has emerged as a viable alternative route to the indirect methods of preparing carboxamides. The standard methods employ carboxylic acid derivatives such as acid halides, anhydrides or activating agents[2] such as DCC/HOBt, EDC, BOP-Cl.[3] and others. These methods suffer from several disadvantages including environmental unfriendliness, poor selectivity, poor atom economy, poor step economy, and unsuitability for large-scale preparation.[4]

Scope of Boric Acid Catalyzed Amidation

Recent developments employing boric acid as a green, inexpensive and readily available catalyst have significantly expanded not only the scope of the direct formation of carboxamides from carboxylic acids and amines in general,[5,6] but also its application to the synthesis of a wide spectrum of compounds of industrial interest. Carboxamides are key components of a number of valuable intermediates for the pharmaceutical and other industries. By far, the most notable application of boric acid catalyzed amidation has been the synthesis of medicinally useful carboxamides, including carriers for drug delivery,[7] active pharmaceutical ingredients, and drug candidates.[8,9]

Boric acid catalyzed amidation was featured in the preparation of sterically hindered *N,N*-disubstituted amides, which are used as drug delivery agents, in 45–55% yield (Figure 1).[10] Mono-substituted α,β-unsaturated carboxamides such as *N*-furylmethylcinnamamides, which offer

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potential use as drug delivery agents and as biological models with antifungal and antiparasitic properties, were prepared by boric acid catalyzed amidation using a 2:1 cinnamic acid/amine molar ratio (Figure 1).[11]

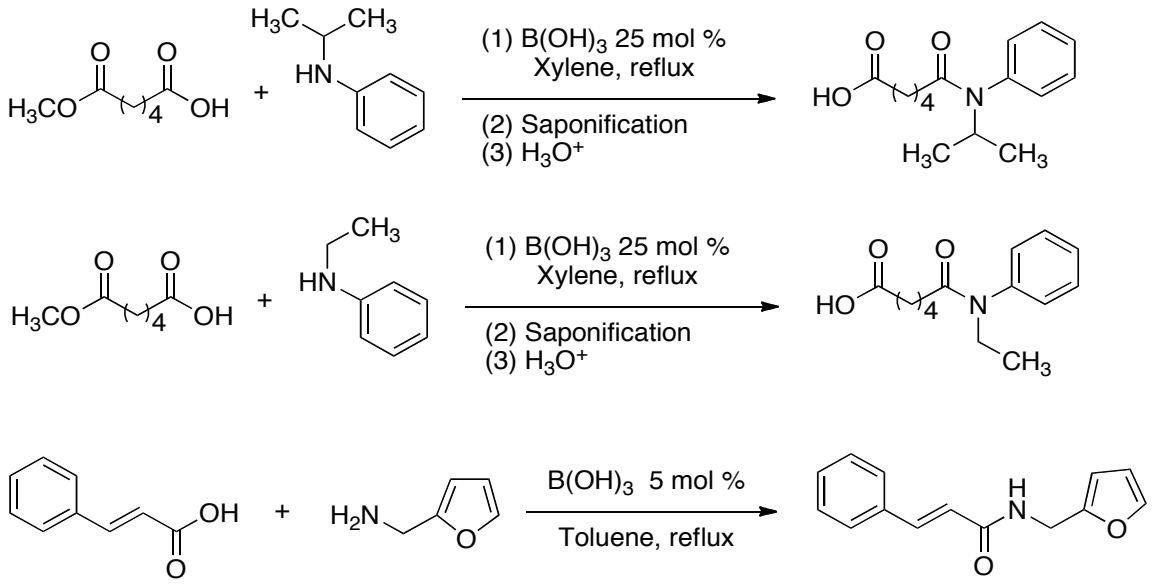

Figure 1. Boric acid catalyzed amidation

Bandichhor et al. employed this method to synthesize a number of active pharmaceutical ingredients (API).[8,9] When both primary and secondary amine functionalities are present in the same molecule, boric acid catalyzed amidation takes place chemoselectively at the primary amine functionality (Figure 2).[8]

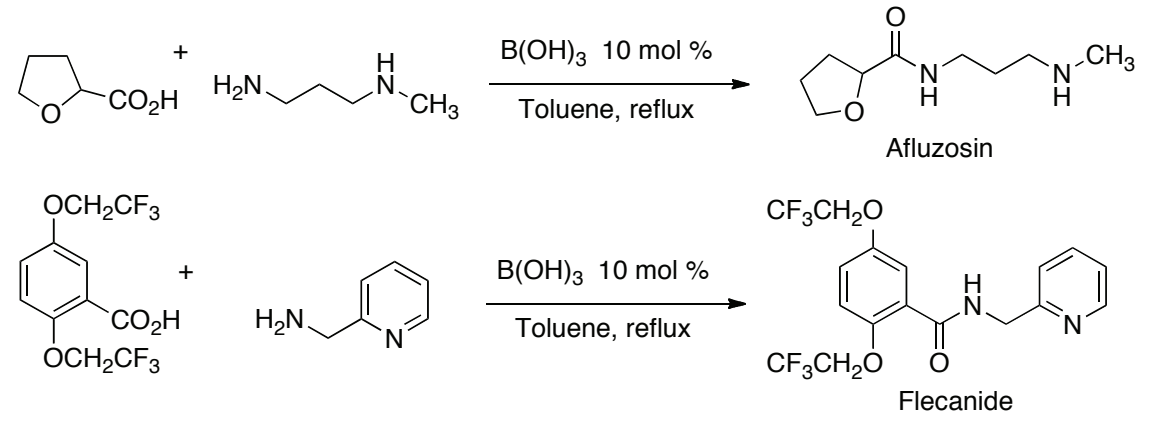

Figure 2. Boric acid catalyzed synthesis of various API intermediate.

The integrity of stereogenic centers either in the carboxylic acid and/or in the amine are preserved in the boric acid catalyzed amidation. No

epimerization is observed under the studied experimental conditions (Figure 3).[4,8,12]

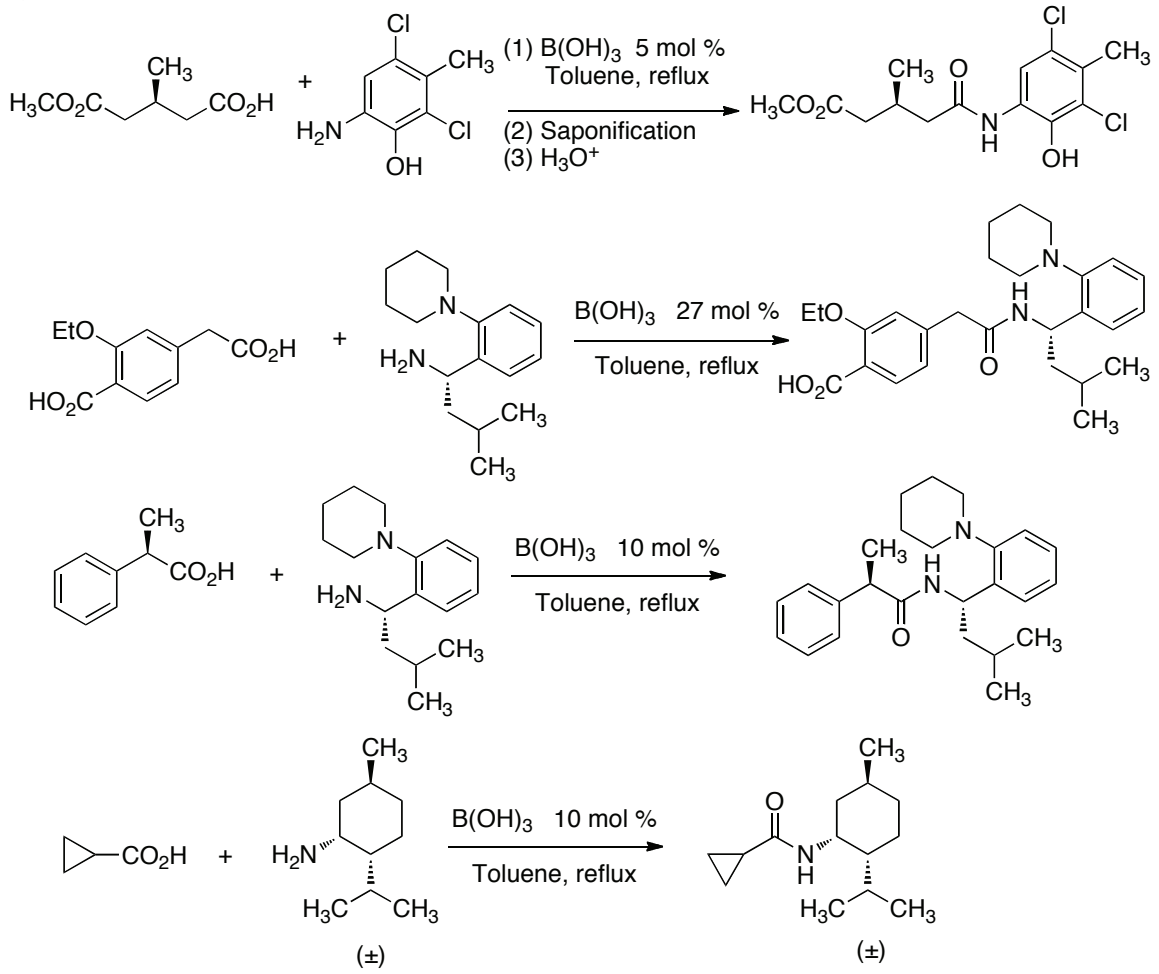

Figure 3. No racemization is observed in boric acid catalyzed amidation.

Using the same procedure in a one step reaction, the dihydroxamic acid ligands can be prepared from *N*-methylhydroxylamine and 1,3-phenylene diacetic acid (Figure 4).[13]

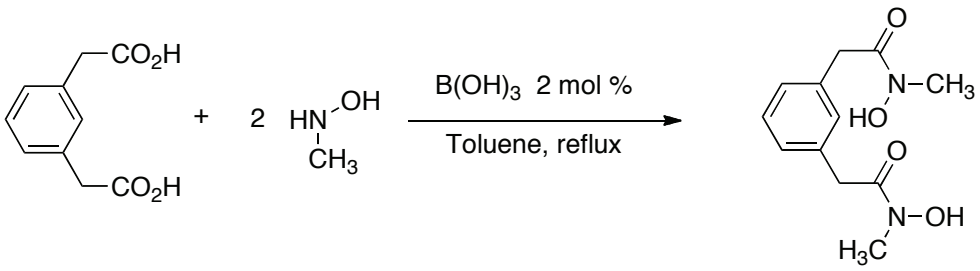

Figure 4. Boric acid catalyzed dicarboxylic amidation reactions.

Synergistic Catalytic Effect of Boric Acid and Other Compounds Containing at Least One Hydroxyl Functional Group

The ability of boric acid to form an ester or a complex with hydroxyl functionality has provided higher catalytic activity in the direct amidation reaction involving carboxylic acids and amines. This discovery allows a wider range of molecule partners to be incorporated into a cooperative catalytic system for enhancing the direct amidation. A study of the kinetics of the boric acid catalyzed amidation of 4-nitrobenzoic acid with ammonia showed that the amidation activity was enhanced by adding the co-catalyst polyethylene glycol (PEG). The latter forms a hypothetical PEG-boric ester complex with boric acid. The molecular weights of PEG have little effect on the yield of the final 4-nitrobenzamide product (Figure 5).[14] With PEG-400 as a co-catalyst, the optimal molar ratio between boric acid and PEG-400 in the amidation of 4- nitrobenzoic acid and ammonia was 1:(1.5-2.5).[14]

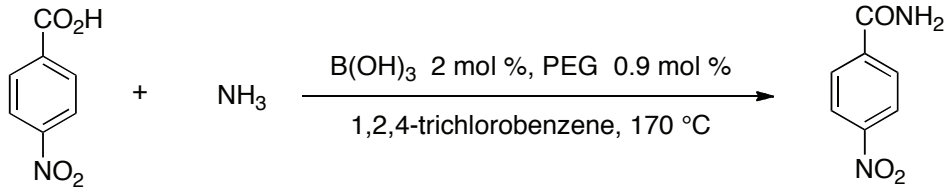

Figure 5. Synergistic catalytic effect of boric acid and polyethylene glycol (PEG).

For the preparation of amides from sterically demanding carboxylic acids and amines, such as tris(alkylsubstituted cyclohexylamide) that is used as a material for molding,[15] the catalytic activity of boric acid was enhanced when boric acid was converted *in-situ* to a boric acid ester. This conversion was achieved by means of a molecule bearing mono-hydroxyl or di-hydroxyl functional groups, such as cresol or tetrachlorocatechol prior to the addition of carboxylic acids and amines to the reaction vessel (Figure 6).[16,17]

We believe that in the near future many more applications to the synthesis of important carboxamides using this boric acid catalyzed amidation will be reported.

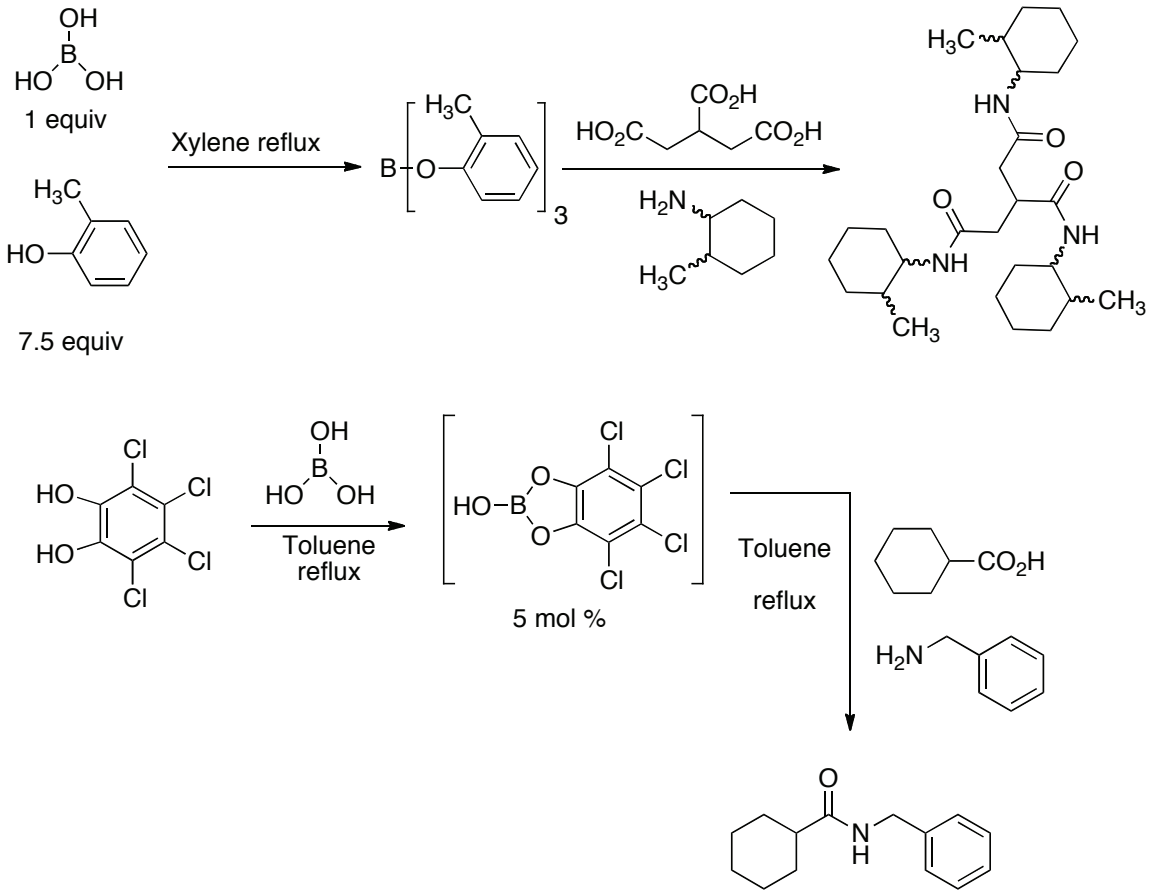

Figure 6. Amidation catalyzed by a boric acid ester prepared *in-situ* from boric acid and compounds containing hydroxyl functional groups.

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Pingwah Tang obtained his B. Sc., M. Sc., Dr. of Specialty in Organic Synthesis, and Dr. Sc. degrees from the University of Paris. After post-doctoral research at University of Montreal and Johns Hopkins University, he joined Eastman Kodak Company in Rochester, NY as a senior staff scientist (1978-1998) conducting R&D in photographic chemicals, dyes, polymers, API and novel organic synthetic methodology. He then held positions with Emisphere Technologies focusing on the research of carrier-mediated drug delivery and green chemistry. He is currently a visiting professor/research professor at Guangzhou Jinan University and Beijing University of Chemical Technology.