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"*Bor-Lewis-Säure-Katalyse: Amide atomeffizient synthetisieren*"

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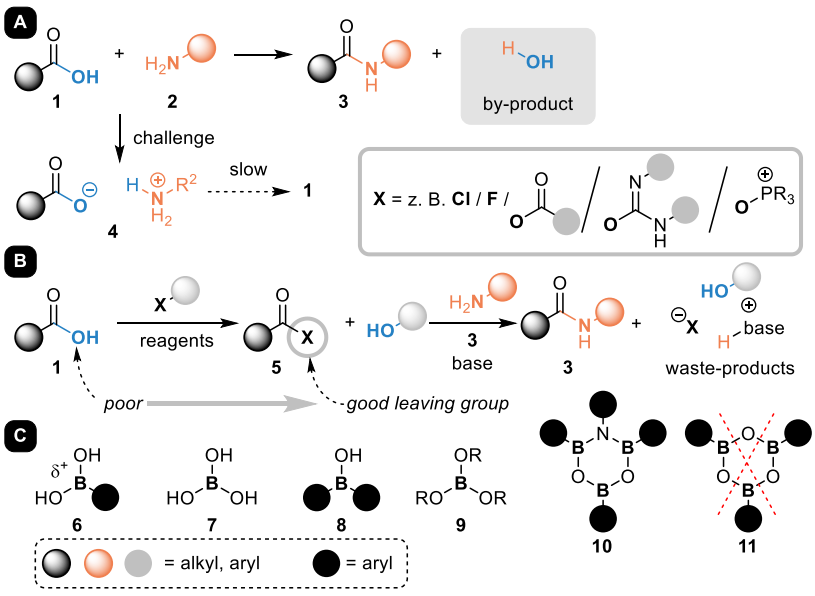
# Boron *Lewis* Acid Catalysis: How to Synthesize Amides Atom-Efficiently

## Abstract

Boron-containing *Lewis* acids such as boronic acids, borates and boric acid allow for the direct dehydrative condensation of carboxylic acids with amines to afford amides. These catalysts not only enable the formation of peptide C-N bonds without epimerization, but also tolerate acid labile functional groups.

Amides account to the most important functional groups. They are an essential structural motif in proteins, pharmaceuticals, crop protection products or polymers, for example. Albeit several strategies have been established for the synthesis of amides of type **3**,[1] the classical condensations of carboxylic acids **1** and amines **2** is still the most dominating (Scheme 1 **A**). Ideally, in this transformation only water would arise as by-product. However, acids react with basic amines inevitably to ammonium salts **4**, in which the *N* component bears no nucleophilic lone pair anymore. These salts can only be converted to the desired products **2** by heating to 110 to 300 °C. Due to the high temperatures, most structurally more complex amides are not accessible.




**Scheme 1. A** Ideal synthesis of amides **3**, **B** amide preparation in practice and **C** boron *Lewis* acid catalyst types for amidation reactions.

To enable amide bond formation under milder conditions and consequently ensure a broader applicability, a manifold array of reagents has been developed (Scheme 1 **B**). These agents allow for conversion of the OH group of acids **1** into an enhanced leaving group **X**, such as chloride, fluoride, carboxylates, ureas and phosphine oxides. Then, the resulting carboxylic acid derivate **5** is transformed with amines **2** into amides **3**. The necessity of stoichiometric reagents and bases inevitably effect formation of waste by-products. Therefore, these conventional protocols are typically neither atom-economic nor cost-efficient.

Particular boron based *Lewis* acids enable a solution to this problem, since they catalyse the direct condensation of acids **1** with amines **2** to afford amides **3** (Scheme 1 **C**).[2] Thereby, the *Lewis* acidity is reasoned by the vacant p-Orbital of the boron atom. Feasible catalysts are aryl boronic acids **6**, boric acid (**7**), diarylborinic acid **8**, borates **9** and dioxoazatriborinanes of type **10**. In contrast, boroxines **11**, which are in equilibrium with **6**, do not promote the condensation of amines with acids.

## How to Remove Water

In order to prepare amides by means of *Lewis* acid catalysis, the by-product water has to be removed. This is typically accomplished by either azeotropic reflux or by molecular sieves in the reaction mixture.

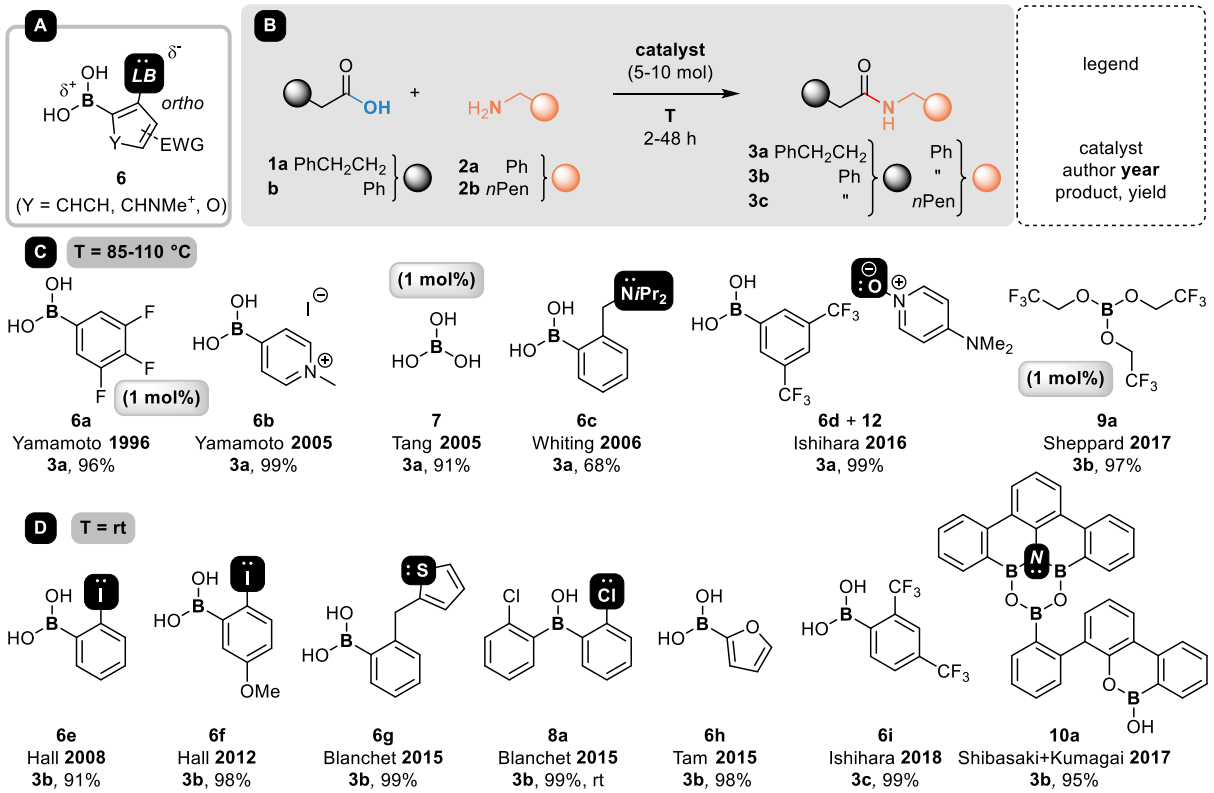
In the case of azeotropic reflux, water is separated with a *Dean Stark* and a *Soxhlet* apparatus filled with molecular sieves, respectively. The reaction temperature can be modified between 85 and 166 °C by selecting a solvent with the respective boiling point. Most commonly, fluorobenzene, *iso*-amylmethylether, toluene, xylene and mesitylene are employed as solvent.

The latest catalyst generation even allows the synthesis of amides at room temperature (rt), which permits water removal by azeotropic distillation. Thereby, water has to be adsorbed by solid drying agents added to the reaction mixture. This is best achieved through molecular sieves, whereby the optimal pore size varies between 3 and 5 Å. This specificity suggests that molecular sieves serve an additional purpose beyond simple drying of the reaction media.

## Boron Catalysts

To date, a plethora of catalysts have been developed for the dehydrative coupling of amines and acids (Scheme 2). Bifunctional boronic acids of type **6** containing an electron poor aryl portion with an additional *Lewis* basic function in *ortho*-position are most frequently encountered as catalysts (Scheme 2 **A**).

The applied boron catalyst can be divided into two classes based on the vital reaction temperature. In Scheme 2 **C** boron *Lewis* acids are depicted that require reaction under reflux. In contrast, in Scheme 2 **D** catalysts are compiled that allow for the amide synthesis at room temperature. Indeed, *Yamamoto* and co-workers reported for the first time on the catalytic activity of boron *Lewis* acids such as **6a** in the preparation of amides **3** without the need of stoichiometric agents in 1996.[3a,b]




**Scheme 2.** Most important examples for boron based catalysts for the synthesis of amides. EWG = electron withdrawing group. **T** = reaction temperature

Subsequently, they introduced pyridinium salt **6b** as recyclable catalyst, whereby an ionic liquid was engaged as co-solvent.[3c] Even, commercial boric acid (**7**) turned out to be a potent catalyst for the production of **3**.[4] Through the bifunctional amino boronic acid **6c** the reaction temperature could be decreased from 110 to 85 °C.[5]

DMAPO **12** in concert with boronic acid **6d** especially facilitate the condensation of less reactive aromatic carboxylic acids with sterically encumbered amines.[6a] As demonstrated by *Sheppard* and co-workers, boric acid ester **9a** also catalyses amide formation.[7] Additionally, tetrahydroydiborane and tetrakis(diamino) diborane promote the amidation of challenging aromatic acids of type **3**.[8]

## Mild Reaction Conditions

In particular *ortho*-substituted boronic acids of type **6** allow for amidation reactions at room temperature (Scheme 2 **D**). As pioneers in the field, the group of *Hall* implemented 2-iodophenylboronic acid (**6e**) followed by derivative **6d** as highly active catalysts.[9] Interestingly, analogues with a bromine, chlorine and fluorine atom instead of iodine were significantly less efficient.

As verified with boron compound **6g**, also a sulfur containing moiety can act as *Lewis* basic functionality.[10a] Furthermore, borinic acid **8a** was established as catalyst for the preparation of amides.[10b] Nevertheless, a recent report questioned, if **8a** is the actual catalytically active species.[11] Instead, **8a** could be converted via protodeboration to 2-Chlorophenyl boronic acid, which is a known catalyst for the synthesis of amides.[9a] Also 2-furanyl boronic acid (**6h**) is as effective as **6f**.[12]

However, aryl boronic acids such as **6e** and **6f** only allow for the preparation of amides derived from aromatic acids and sterically confined amines in moderate yields (up to 34%). This limitation has been recently overcome by boron compounds **6i**[10b] and **10a**[13]. Moreover, as verified with **6a**, **7** and **9a** as examples, catalysts loadings can be minimized from the common 5-10 mol% down to 1 mol%.

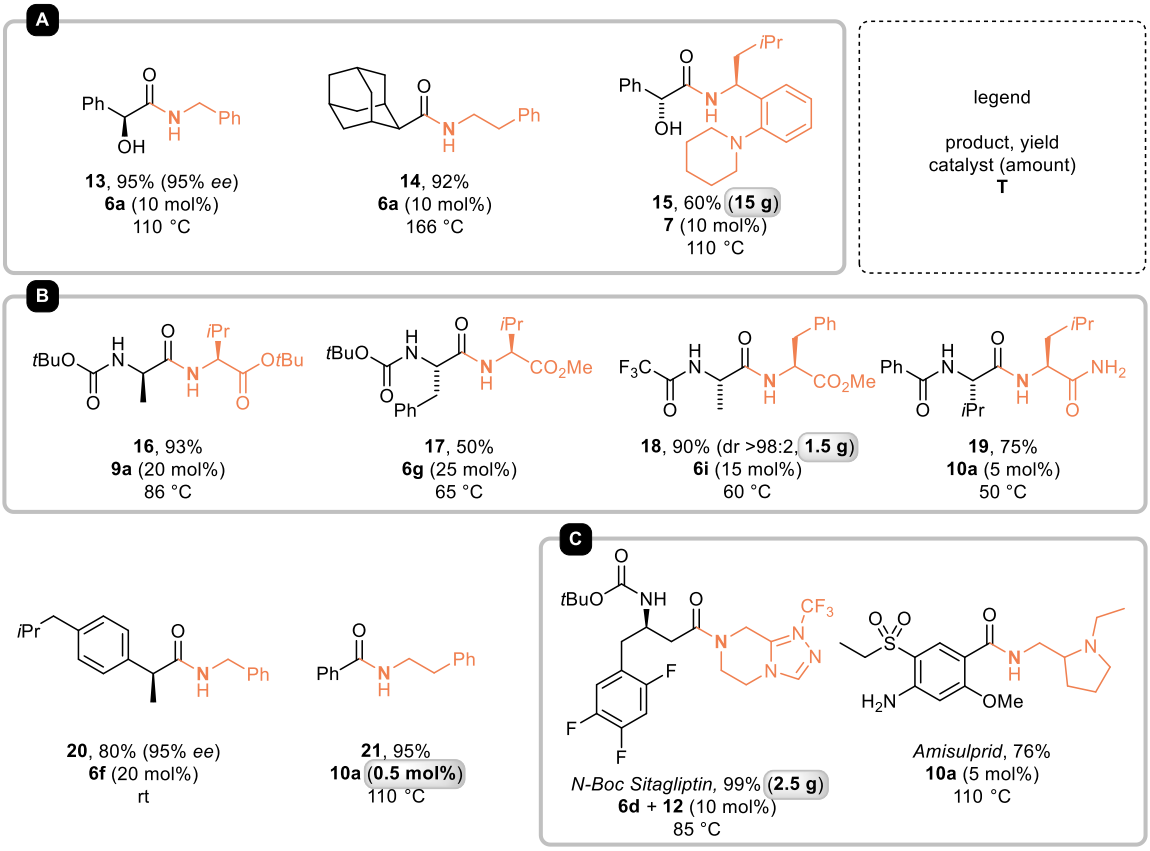
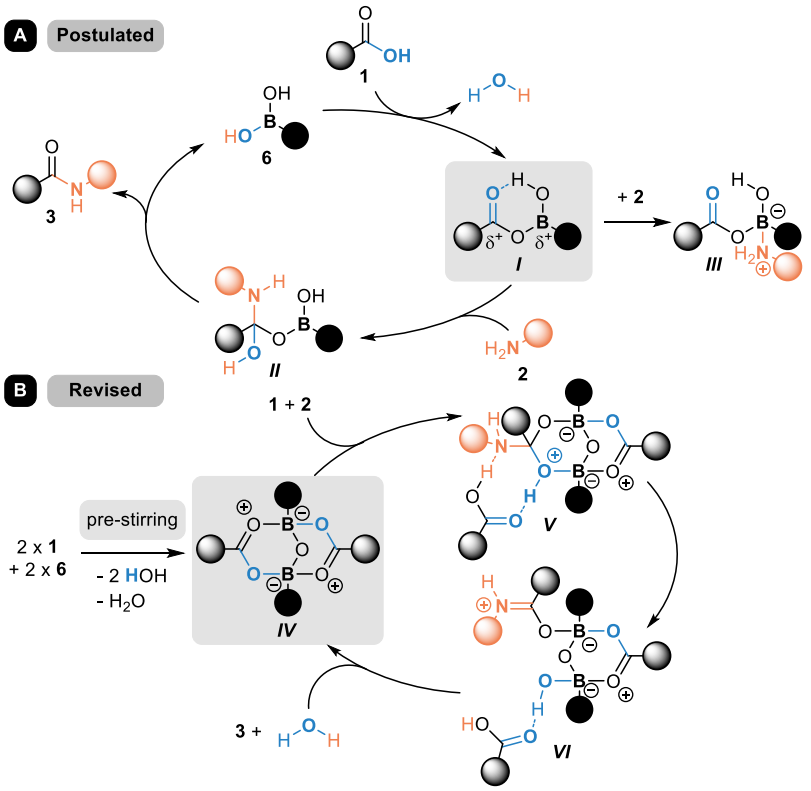



**Figure 1.** Selected amides produced by means of boron *Lewis* acid catalysis.

Importantly, the catalyst has to be pre-stirred with the acid **1** and molecular sieves for approximately 15 min, in order to access amides in synthetically useful yields ≥70%, (see e.g. [9,11,12]). In addition, the substrate **1** should be used in a slight excess with respect to the amine coupling partner **2**. Both aspects can be reasoned by the revised mechanism (see below).




**Scheme 3.** Simplified **A** originally proposed and **B** revised mechanism for the boronic acid catalyzed formation of amides.

## Substrate Scope

Figure 1 highlights representative amides synthesized through dehydrative coupling of amines with acids under boron catalysis. Already *Yamamoto* discovered the ability of boronic acids of type **6** to access α-chiral amides such as **13** in high stereoisomerical purity (Figure 1 **A**).[3a]. In the instance of **13**, the respective parent acid was used in 99%*ee*. As illustrated through the construction of **14**, sterically demanding carboxylic acids are accessible towards amidation, when the reaction is heated to 165 C.[3a] Plain boric acid (**7**) enables the assembly of amide **15** entirely without epimerization.[4c] Notably, boronic acids of type **6**,[6b,10b] borate **9a**[9a] and the boron heterocycle **10a**[13] facilitate the formation of C-N peptide bounds in the presence of acid-labile protecting groups without epimerization (*dr* ≥ 98:2, Figure 1 **B**). Remarkably, just 0.5 mol% of catalyst **10a** were necessary for the synthesis of aromatic amide **21**.[13]

Eventually, pharmaceuticals and precursors are accessible by means of boron *Lewis* acid catalysis (Figure 1 **C**).[6a,13a] A good scalability is attested by examples **15** and **18** and *N*-Boc protected *Sitagliptin*, which have been produced on a multigram scale.[6a]

## Complex Mechanism

Albeit the overall transformation of acids **1** and amines **2** into amides **3** appears to be simple, the crucial mechanism has yet not been fully elucidated. Originally, *Yamamoto* postulated activation via mixed anhydride intermediates of type ***I***, which are deduced from the acid **1** and catalyst **6** (Scheme 3 **A**).[3] This has been supported by several experimental and theoretical studies[5,14] Next, the intermediate ***I*** would be attacked on the carboxyl C-atom group by the nucleophilic amine **2**, of which the tetrahedral adduct ***II*** results. In the end, elimination would deliver the amide product **3** and boronic acid **6**. On closer examination of species ***I***, it is apparent that also the boron atom constitutes a strongly electrophilic centre. Addition of the amine to ***I*** could also deliver the *Lewis* acid base complex ***III***.

Indeed, adducts of type ***III*** derived from borinic acids **8** could not be converted to the respective amides.[11] In fact, reaction of boronic acids and carboxylic acids in the presence of molecular sieves yields complexes of type ***IV,*** which explains the recommended pre-stirring period (Scheme 3 **B**).[11] Based on kinetic and theoretical studies, intermediate ***IV*** has been proposed as acylation agent for amines **2**.[11]

Supported by simultaneous deprotonation with the aid of acid **1**, initially the tetrahedral intermediate ***V*** would arise. In the following, ring opening would furnish intermediate ***VI***. Release of product **3** and water elimination would afford complex ***IV*** and thereby establish a catalytic process. The predominance of *ortho*-substituted aryl boronic acids as optimal catalyst has been rationalized by destabilisation of unreactive boroxines of type **11**, which increases the amount of the active monomeric boronic acid **6**.[11] In addition, unproductive amine boron intermediates ***I*** would be less favourable due to steric repulsion.[6b]

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**Peter Huy**, born 1980, is leading a young researcher´s group as a *Liebig* fellow at the Saarland University since 2014. He pursued his PhD thesis in organic chemistry in the group of Prof. Hans-Guenther Schmalz at the University of Cologne. Subsequently, he joined the group of Prof. Ari Koskinen at the Aalto University in Helsinki and the group of Prof. Ben List at the Max-Planck Institute for Carbon Research in Muehlheim at Ruhr as a postdoctoral researcher. His research interests are committed towards homogenous catalysis and natural product synthesis. In the preparation of the current manuscript, he was supported by his master student **Ben Zoller**.