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A Lewis Acid Palladium(II)-Catalyzed Three-Component Synthesis of α-Substituted Amides

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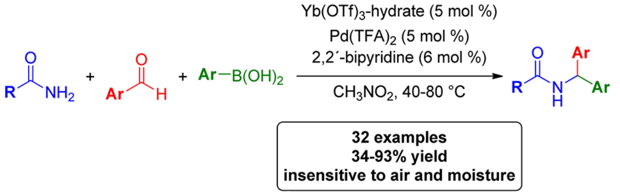
ABSTRACT



A Lewis acid palladium-catalyzed reaction of amides, aryl aldehydes, and arylboronic acids is described. This new method allows for a practical and general synthesis of α-substituted amides from simple, readily available building blocks.

The Petasis or Borono-Mannich reaction—a three-component reaction of an amine, an aldehyde, and a boronic acid—allows for a straightforward synthesis of various nitrogen-containing molecules (Scheme 1; classic Petasis reaction).[1,2] Due to the synthetic utility and biological activity of the resulting products, the accessibility of the starting materials and the rapid access to structural diversity, the Petasis reaction has become a powerful tool in drug discovery.

However, the classical Petasis method has two severe limitations.[2] In general, the reaction is restricted to activated aldehydes (e.g., glyoxalates) or aldehydes bearing a suitable boron-activating group, typically a free hydroxy group (e.g., α-hydroxyaldehydes or salicylaldehyde). In addition, the reaction usually proceeds well only with electron-rich vinyl- and (hetero)arylboronic acids. Successful examples with electron-poor, nonactivated boronic acids are rare and require special reagents and substrate combinations.[3,4]

In recent years, different approaches to overcome these limitations have been developed. Nucleophilic activation of the organoboron reagent with transition metal catalysts leads to a somewhat greater flexibility in the choice of starting materials, but there are still some limitations regarding the exact nature of the aldehyde or arylboronic acid (Scheme 1; transition metal catalyzed three-component reaction).[5,6] An alternative approach would be a similar electrophilic activation of the in situ formed imine (Scheme 1; addition of ArB(OH)$_2$ to acyl imines). Several,

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(1) (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. (c) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.

(2) (a) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169. (b) Ramadhar, T. R.; Batey, R. A. *Boronic Acids – Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; Vol. 2, Chapter 9, p 427.

(3) For rare exceptions with heteroarylaldehydes, see: (a) Schlienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron Lett.* **2000**, *41*, 1303. (b) Mandai, H.; Murota, K.; Suga, S. *Heterocycles* **2012**, *85*, 1655.

(4) For rare exceptions with arylboronic acids, see: Tremblay-Morin, J.-P.; Raeppel, S.; Gaudette, F. *Tetrahedron Lett.* **2004**, *45*, 3471 and ref 3b.

(5) (a) Yu, A.; Wu, Y.; Cheng, B.; Wei, K.; Li, J. *Adv. Synth. Catal.* **2009**, *351*, 767. (b) Frauenlob, R.; García, C.; Bradshaw, G. A.; Burke, H. M.; Bergin, E. *J. Org. Chem.* **2012**, *77*, 4445.

(6) For some examples of transition metal catalyzed additions of arylboronic acids to preformed imines or imine precursors, see: (a) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (b) Bolshan, Y.; Batey, R. A. *Org. Lett.* **2005**, *7*, 1481. (c) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789. (d) Beenen, M.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304. (e) Bakar, A.; Suzuki, Y.; Sato, M. *Chem. Pharm. Bull.* **2008**, *56*, 973. (f) Dai, H.; Lu, X. *Org. Lett.* **2007**, *9*, 3077. (g) Zhang, Q.; Chen, J.; Liu, M.; Wu, H.; Cheng, J.; Qin, C.; Su, W.; Ding, J. *Synlett* **2008**, *6*, 935. (h) Dai, H.; Lu, X. *Tetrahedron Lett.* **2009**, *50*, 3478. (i) Miyaura, N. *Synlett* **2009**, *13*, 2039. (j) Ma, G.-N.; Zhang, T.; Shi, M. *Org. Lett.* **2009**, *11*, 875. (k) Chen, J.; Lu, X.; Lou, W.; Ye, Y.; Jiang, H.; Zeng, W. J. *Org. Chem.* **2012**, *77*, 8541. (l) Johnson, T.; Lautens, M. *Org. Lett.* **2013**, *15*, 4043.

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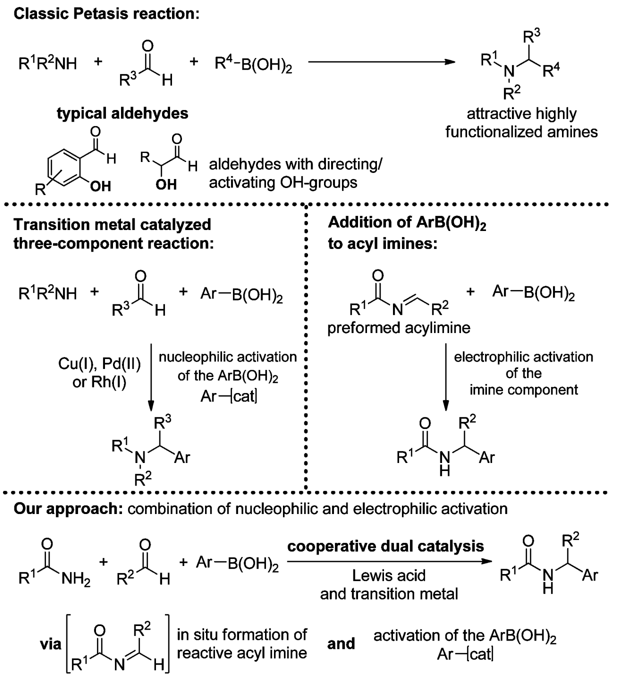
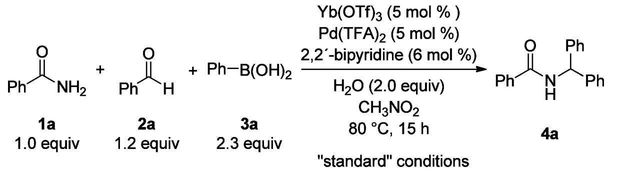
Scheme 1. Classical and Modified Petasis Reactions



even enantioselective, direct additions of boronates to preformed acyl imines or *N,O*-aminals have been reported.[7] However, there is only one example of a Petasis-type reaction utilizing such highly electrophilic acyliminium salts,[8] a copper-catalyzed three-component coupling of imines and acid chlorides with tetraarylboranes.[9]

Herein we want to report a new, more general "amide" version of the Petasis reaction using a cooperative dual catalyst system capable of combining nucleophilic and electrophilic activation.[10] Our initial idea was to generate the reactive acyl imine in situ via an acid-mediated condensation between an amide and an aldehyde[11] and to use a suitable transition metal to activate simple commercial available arylboronic acids for addition to the formed reactive imine derivative. As a starting point for our studies, we chose the reaction between benzamide (**1a**), benzaldehyde (**2a**), and phenylboronic acid (**3a**) (Table 1).

Table 1. Cooperative Dual Catalyzed Three-Component Reaction: Influence of Reaction Parameters[a]



entry	variation from the "standard" conditions	yield (%)[b]
1	none	**86**
2	no $Yb(OTf)_3$	–
3	no $Pd(TFA)_2$	–
4	no 2,2′-bipyridine	–
5	no H_2O	<10
6	no H_2O and $Yb(OTf)_3$-hydrate, instead of $Yb(OTf)_3$	83
7	no H_2O, with 5 mol % TfOH	86
8	+ 10 mol % 2,6-di-*tert*-butylpyridine	–
9	TfOH, instead of $Yb(OTf)_3$	–[c]
10	DCE, instead of CH_3NO_2	84
11	$Pd(OAc)_2$, instead of $Pd(TFA)_2$	50
12	$Pd(PPh_3)_4$, instead of $Pd(TFA)_2$	–
13	1.2 equiv of $PhB(OH)_2$, instead of 2.3 equiv	55

[a] Reactions run at 0.5 mmol scale. [b] Isolated yield of analytical pure product. [c] Benzhydrol was isolated in 67% yield. TFA = trifluoroacetate. DCE = 1,2-dichloroethane.

From a range of tested transition metal complexes (based on Cu, Rh and Pd), palladium(II)-salts proved to be the most active catalysts. While several Lewis acids could catalyze this reaction, the use of $Yb(OTf)_3$ gave the highest and most reproducible yields. Best results were obtained with $Yb(OTf)_3$ in combination with $Pd(TFA)_2$ (TFA = trifluoroacetate) and 2,2′-bipyridine, furnishing the desired product in 86% yield (Table 1, entry 1). In the absence of the Lewis acid $Yb(OTf)_3$, the transition metal $Pd(TFA)_2$, or 2,2′-bipyridine[12] no product is formed (entries 2–4). Interestingly, the presence of small amounts of water (typically 0.4–2.0 equiv) is crucial for obtaining a high yield. In the absence of water the yield drops dramatically (entry 5). The amount of water present in the hydrated form of $Yb(OTf)_3$ is usually sufficient for a high yielding reaction (entry 6).[13] Since metal triflates are known to hydrolyze to TfOH,[14a] we also investigated the

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(7) (a) Wu, T. R.; Chong, J. M. *Org. Lett.* **2006**, *8*, 15. (b) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398. (c) Bishop, J. A.; Lou, S.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4337.

(8) For some examples of acyliminium salts as highly electrophilic intermediates, see: (a) Zaugg, H. *Synthesis* **1984**, 85. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (d) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159. (e) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339.

(9) Morin, M. S. T.; Lu, Y.; Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2012**, *77*, 2013.

(10) For some examples using two catalysts to separately generate two or more active intermediates, see: (a) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309. (b) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (c) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (d) Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 7289. (e) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, *2*, 766. (f) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633. (g) Nahra, F.; Macé, Y.; Lambin, D.; Riant, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 2308.

(11) For recent examples utilizing an acid-catalyzed in situ generation of acyl imines, see: (a) Ba, T.; Ollevier, T. *Tetrahedron Lett.* **2003**, *44*, 9003. (b) Gandhi, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 2573. (c) Schneider, A.; Manolikakes, G. *Synlett* **2013**, *24*, 2057. (d) Halli, J.; Manolikakes, G. *Eur. J. Org. Chem.* **2013**, published online DOI: 10.1002/ejoc.201301349.

(12) We assume that 2,2′-bipyridine stabilizes the palladium(II) species. In the absence of ligand, rapid formation of Pd-black occurs.

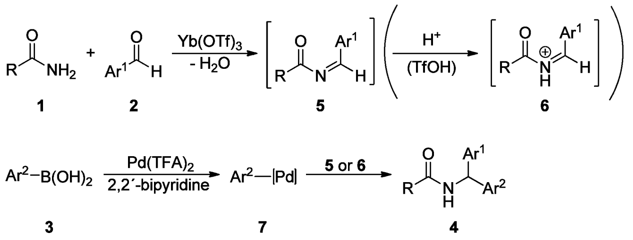
(13) For the exact water content of $Yb(OTf)_3$ and $Yb(OTf)_3$-hydrate, see Supporting Information.

(14) (a) Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem.—Eur. J.* **2004**, *10*, 484. (b) Dang, T. T.; Boeck, F.; Hintermann, L. *J. Org. Chem.* **2011**, *76*, 9353.

possibility of catalysis by an in situ formed Brønsted acid.[14b] Indeed, performing the reaction in the absence of water but with 5 mol % TfOH furnished the desired product in comparable yield (entry 7). Moreover, no product was formed, when 2,6-di-*tert*-butylpyridine, a proton scavenger,[14a] was added to the reaction (entry 8). On the other hand, performing the reaction with TfOH as the Brønsted acid catalyst led to the selective formation of benzhydrol, the direct addition product of phenylboronic acid to benzaldehyde (entry 9). These results indicate that both $Yb(OTf)_3$ and an in situ generated Brønsted acid are important for the catalytic system.[15] Comparable results were obtained with 1,2-dichloroethane as the solvent (entry 10). While the use of $Pd(OAc)_2$ as the palladium source led to considerable lower yields (entry 11), Pd(0)-species, such as $Pd(PPh_3)_4$, were generally ineffective (entry 12). Performing the reaction with less than 2.3 equiv of phenylboronic acid (**3a**) led to decreased yields of the desired amide **4** (entry 13).

Based on the results from Table 1, a plausible mechanism for the three-component reaction is shown in Scheme 2.

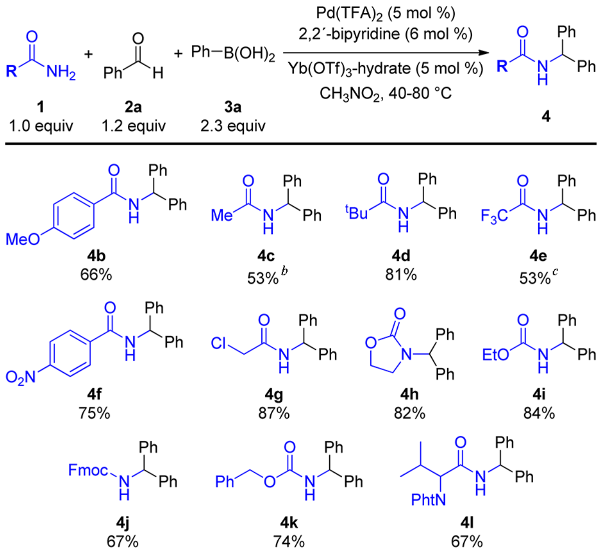
Scheme 2. Proposed Mechanism



A reactive acyl imine **5** is formed through a Lewis acid catalyzed condensation between the amide and the aldehyde. An in situ released Brønsted acid could then protonate the formed acyl imine to give an even more reactive acyliminium ion **6**. We assume that the Lewis acid can catalyze the acyl imine formation more efficiently.[16] Simultaneously, the dicationic palladium(II) complex reacts with the arylboronic acid to form a more nucleophilic arylpalladium(II) complex **7**. Those two catalytically generated active intermediates, acyl imine **5** (or acyliminium ion **6**) and arylpalladium(II) species **7**, can subsequently react with each other to form the desired product **4**. However, further investigations are necessary to elucidate the reaction mechanism and to confirm the formation of the reactive acyliminium ion.

With the optimized conditions established, the scope and limitations of the method were explored. As shown in Scheme 3, electron-rich and -poor aryl amides afforded the corresponding α-substituted aryl amides in good yields (**4b** and **4f**). Moreover, various alkyl amides, such as trifluoroacetamide, worked well and gave the desired products in 53–87% yield (**4c**–**4e** and **4g**). Using our standard conditions, secondary amides did not react with the exception of the cyclic carbamate 2-oxazolidone (**4h**). To our delight, carbamates could be used as an amide component, allowing the efficient preparation of various *N*-protected amines (**4i**–**4k**). As the deprotection of products from typical Petasis reactions is sometimes difficult,[2] our method could provide a more efficient approach to the often desired free amines. In addition, the reaction with *N*-phthalyl-protected valinamide furnished the product in 67% yield (**4l**).

Scheme 3. Variation of Amides[a]



[a] Reactions run at 0.5 mmol scale. Isolated yields of analytical pure products. [b] With $Yb(OTf)_3 + H_2O$ (2.0 equiv). [c] With 2.0 equiv of **1** and 1.0 equiv of **2a**. TFA = trifluoroacetate. Fmoc = 9-fluorenylmethyloxycarbonyl-. Pht = *N*-phthalyl-.

We next examined reactions with various aryl aldehydes (see Scheme 4). Aryl aldehydes bearing halogen or trifluoromethyl substituents in the *ortho*-, *meta*-, or *para*-position afforded the desired product in good to excellent yields (**4m**–**4r**). In some cases better yields were obtained with 4,4′-dinitro-2,2′-bipyridine as the ligand (**4q** and **4x**). Both electron-poor and -rich aryl aldehydes are compatible with our method, but electron-rich aldehydes, such as 4-methoxybenzaldehyde, just gave moderate yields (**4s**–**4u**). More importantly, *N*-heterocyclic aldehydes could be employed as an aldehyde component, furnishing the amides **4w** and **4x** in moderate yields.

Finally, an analogous series of reactions were performed with various arylboronic acids (see Scheme 5). *Ortho*-substituted or halogenated arylboronic acids provided the desired products in good to high yields (**4ab**, **4p**, and **4q**). Only in the case of the sterically very hindered di-*ortho*-substituted mesitylboronic acid a lower yield was obtained (**4z**). Reactions with highly electron-rich or -poor arylboronic acids, such as (4-methoxyphenyl)boronic acid and (4-(ethoxycarbonyl)phenyl)boronic acid, were also possible (**4u** and **4aa**). Although the yields are low,

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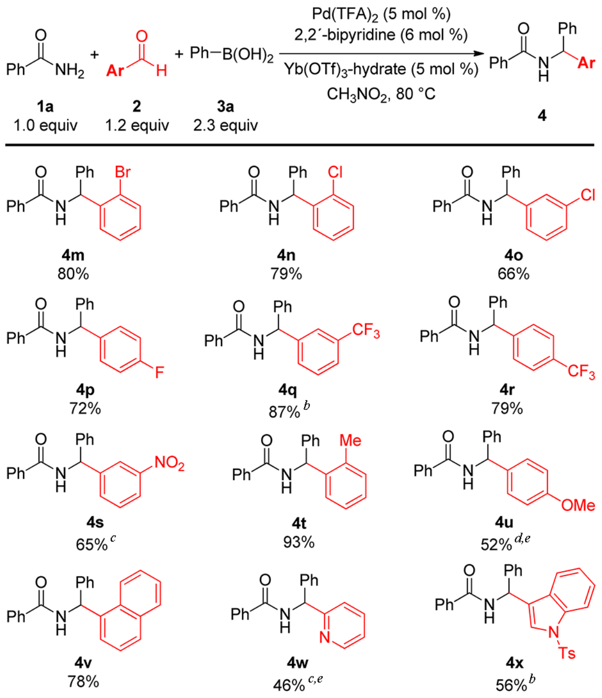
(15) Additional water might also facilitate the transmetalation of the boronic acid to palladium.

(16) Control experiments with preformed acyl imines lead to a rapid hydrolysis of the acyl imine under our standard reaction conditions.

Scheme 4. Variation of Aryl Aldehydes[a]



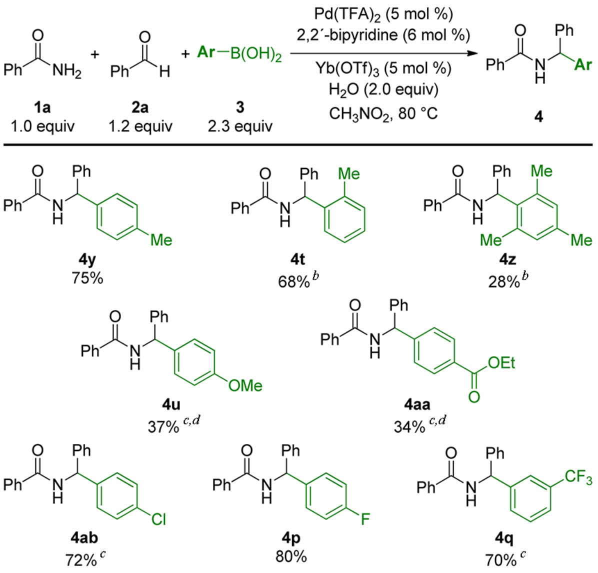
[a] Reactions run at 0.5 mmol scale. Isolated yields of analytical pure products. [b] With 6 mol % 4,4′-dinitro-2,2′-bipyridine as ligand. [c] With 10 mol % Yb(OTf)$_3$-hydrate. [d] With Yb(OTf)$_3$ + H_2O (2.0 equiv). [e] In 1,2-dichloroethane. TFA = trifluoroacetate.

this is, to the best of our knowledge, the first example of a Petasis-type reaction with an electron-deficient arylboronic acid.[17]

It has to be emphasized that this reaction is very simple to perform. It is not necessary to exclude air or moisture. All shown reactions were performed without an inert atmosphere in commercial grade solvents.

In summary, we have developed an efficient and practical three-component synthesis of α-substituted amides from readily available amides, aryl aldehydes, and arylboronic acids. A dual catalyst system, consisting of a Lewis acid (Yb(OTf)$_3$) and a palladium(II) salt, and the presence of water in the reaction are key to a successful transformation. This new method has a very broad scope and represents

Scheme 5. Variation of Arylboronic Acids[a]



[a] Reactions run at 0.5 mmol scale. Isolated yields of analytical pure products. [b] With 6 mol % 4,4′-dinitro-2,2′-bipyridine as ligand. [c] With Yb(OTf)$_3$-hydrate, no additional H_2O. [d] With Pd(OAc)$_2$, in 1,2-dichloroethane. TFA = trifluoroacetate.

a useful extension of the classical Petasis reaction. Further applications of this concept as well as the development of an enantioselective reaction are currently being investigated in our laboratory.

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Supporting Information Available. Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Using our standard conditions, alkenylboronic acids, such as *trans*-*β*-styreneboronic acid, did not react.

The authors declare no competing financial interest.