A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

Title: Merging Electron Transfer with 1,2-Metalate Rearrangement: Deoxygenative Arylation of Inert Amides with Arylboronic Esters

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202104359

Link to VoR: https://doi.org/10.1002/anie.202104359

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10.1002/anie.202104359

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RESEARCH ARTICLE

Merging Electron Transfer with 1,2-Metalate Rearrangement: Deoxygenative Arylation of Aromatic Amides with Arylboronic Esters

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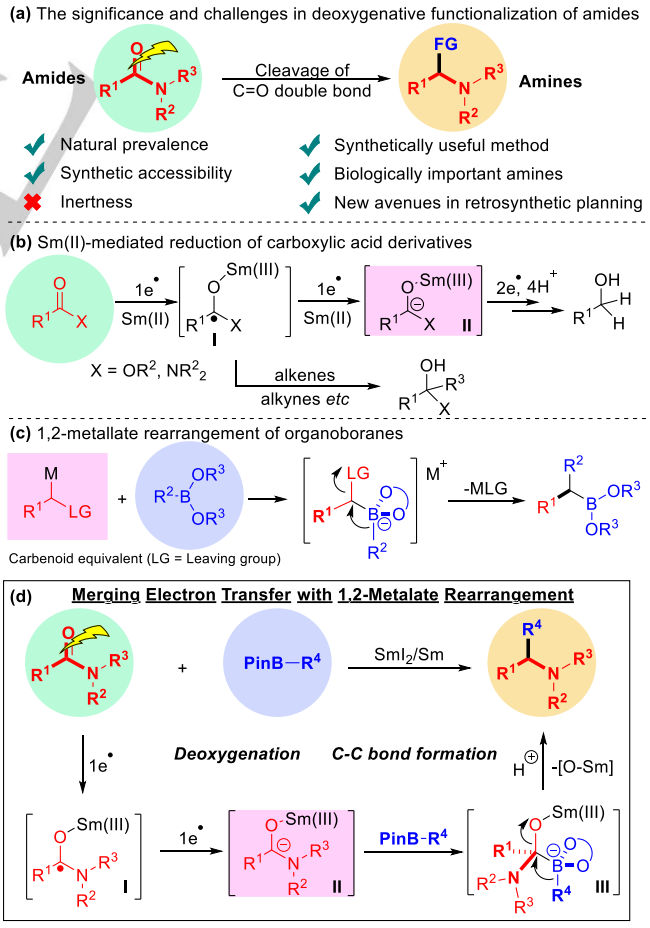
Abstract: Amides are essentially inert carboxyl derivatives in many types of chemical transformations. In particular, deoxygenative C-C bond formation of amides to synthetically important amines is a long-standing challenge for synthetic chemists due to the inertness of the resonance-stabilized amide C=O bond. Herein, it is disclosed that by merging electron transfer induced activation with 1,2-metalate rearrangement, a wide range of aromatic amides react smoothly with arylboron regents, affording a series of biologically relevant diarylmethylamines as deoxygenative C-C bond cross coupling products. With its simplicity and versatility, it shows great promise in synthesis of amines from amides, which may open up new avenues in retrosynthetic planning and find widespread use in academia and industry.

Introduction

The amide, a common functional group in organic chemistry is characterized by its high chemical stability and the low inherent reactivity of its carbonyl carbon due to the resonance-stabilized C-N bond.[1] On the other hand, amides are an under-exploited class of nitrogen-containing compounds, ubiquitous in the fine chemical, agrochemical and pharmaceutical industries, and their transformation to synthetically useful amines by deoxygenative C-C bond formation is a long-standing challenge for synthetic chemists (Scheme 1a).[2-7] Several methods involving electrophilic activation[3] or controlled hydride reduction[4-6] have been developed to achieve deoxygenative C-C bond forming reactions of amides. Notwithstanding these advances, multistep procedures, air/water sensitive organometallic reagents,[8] the use of strong base/acid[3] or special amides bearing directing groups,[9] are generally necessary, due to the considerably weak electrophilicity of the carbonyl carbon.

SmI_2, introduced by Kagan in 1977 has emerged as one of the most important reducing agents available in the laboratory and is now widely used for the effective reduction of various functional groups in organic synthesis.[10-12] For examples, electron transfer (ET) to carboxylic acid derivatives mediated by Sm(II) has been developed as a powerful strategy to invert the polarity of the carbonyl group, resulting in the formation of a carbon-centered radical **I** and/or a dianion **II** (Scheme 1b).[13-15] In addition, it has been revealed that a SmI_2/Sm mixed system can promote the deoxygenative dimerization of amides to provide *vic*-diaminoalkenes with an α-aminocarbene species as the proposed initermediate.[16] Therefore, it was envisioned that with the umpolung of the carbonyl carbon generated in the process of ET to amides, an active intermediate might be reactive in a deoxygenative C-C cross-coupling reaction with an appropriate reagent, providing a means of activating and functionalizing the inert amide.



Scheme 1. Merging electron transfer with 1,2-metalate rearrangement for the deoxygenative functionalization of amides.

The 1,2-metalate rearrangement of boronate complexes possessing an α-leaving group (Scheme 1c) provides a useful clue for the development of C-C cross-coupling reaction of amides,

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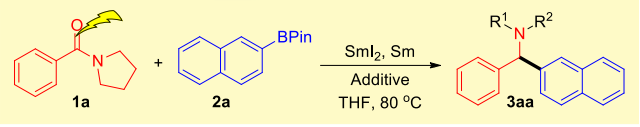
since intermediate **II** might be regarded as a carbenoid equivalent (α-aminocarbenoid) in the 1,2-metalate rearrangement.[17-20] A boronate complex **III** can be generated from the nucleophilic addition of anion **II** to a Lewis acidic organoboron compound (Scheme 1d). Due to the well-known high oxophilicity of Sm compounds,[21] 1,2-migration of **III** following the removal of an [O-Sm(III)] group and protodeboronation of the C-B bond could afford the corresponding deoxygenative C-C bond cross coupling product.[18-20] Herein, we report an unprecedented and highly efficient SmI_2/Sm mediated deoxygenative arylation of unactivated amides using air- and moisture-stable arylboron regents by the merging electron transfer with 1,2-metalate rearrangement (Scheme 1d). This reaction can be used for the facile reductive conversion of aromatic amides to biologically important diarylmethylamines, a synthetically useful transformation.

Results and Discussion

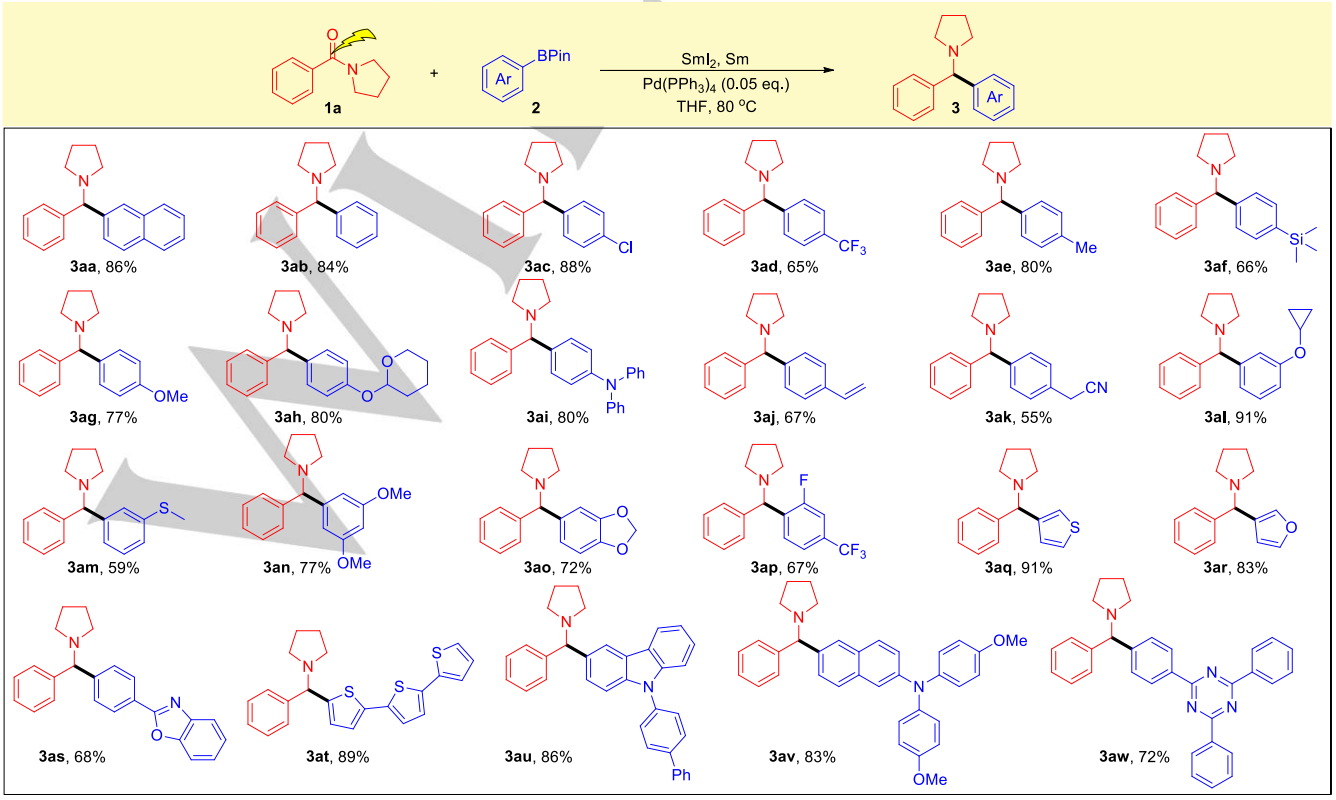
Diarylmethylamines are key constituents in many bioactive compounds and a variety of methods have been developed to synthesize these structures.[22,23] However, deoxygenative arylation of inert amides using bench-stable arylboron regents to access this important moiety remains a formidable challenge.[8,9] To implement this proposed reaction, an amide **1a** was first treated with 2.0 eq. of 2-naphthylpinacolboronate ester **2a** in the presence of SmI_2 (2.2 eq.) and Sm (2.0 eq.), and the reaction was continued in THF at 80 °C for 18 h (Table 1, entry 1). The desired product **3aa** was formed in 56% yield, confirming the feasibility of the transformation. Without Sm powder, the reaction only resulted in a 29% yield of **3aa** (entry 2). Moreover, the reaction failed to afford **3aa** in the absence of SmI_2 (entry 3), showing that SmI_2 is essential for the cross coupling. Although it is well known that the reactivity of SmI_2 can be enhanced by co-solvents and various metal salts,[24] only negative results were obtained from reactions performed in the presence of the commonly used co-solvents, such as HMPA, H_2O, MeOH or NEt_3 (entries 4-7). A range of Fe, Ni, Rh, Cu and Pd salts and/or complexes were also tested as additives. To our delight, most of them can obviously improve the yield of **3aa** (entries 9-14) and $Pd(PPh_3)_4$ was found to be the best additive, affording the product **3aa** in 86% isolated yield. Catalytic amount of SmI_2 (20 mol%) was also investigated together with Sm (5.0 eq.) and $Pd(PPh_3)_4$ (0.05 eq.) in the reaction. However, only

Table 1. Optimization of the deoxygenative arylation of amide[a]



Entry	Additive (co-solvents)	Yield (%)[b]	Entry	Additive (metal species) (0.05 eq.)	Yield (%)[b]
1	-	56	8	$FeCl_3$	30
2[c]	-	29	9	NiI_2	78
3[d]	-	0	10	$Ni(COD)_2/PPh_3$	74
4	HMPA (5% V)	42	11	$Rh_2(OAc)_4$	67
5	H_2O (5% V)	0	12	CuI	67
6	MeOH (5% V)	0	13	$Pd_2(dba)_3/PPh_3$	77
7	NEt_3 (2.0 eq.)	8	14	$Pd(PPh_3)_4$	91 (86)[e]

[a] Reaction conditions: The mixture of **1a** (0.1 mmol), **2a** (0.2 mmol), SmI_2 (2.2 eq., 0.1 M in THF), Sm powder (2.0 eq.) and additive was stirred at 80 °C for 18 h. [b] GC yield. [c] Without Sm. [d] Without SmI_2. [e] Isolated yield on 0.2 mmol scale. HMPA = hexamethylphosphoramide; COD = 1,5-Cyclooctadiene; THF = Tetrahydrofuran. For more details, see the Supporting Information.



Scheme 2. The scope of aryl boron reagents.

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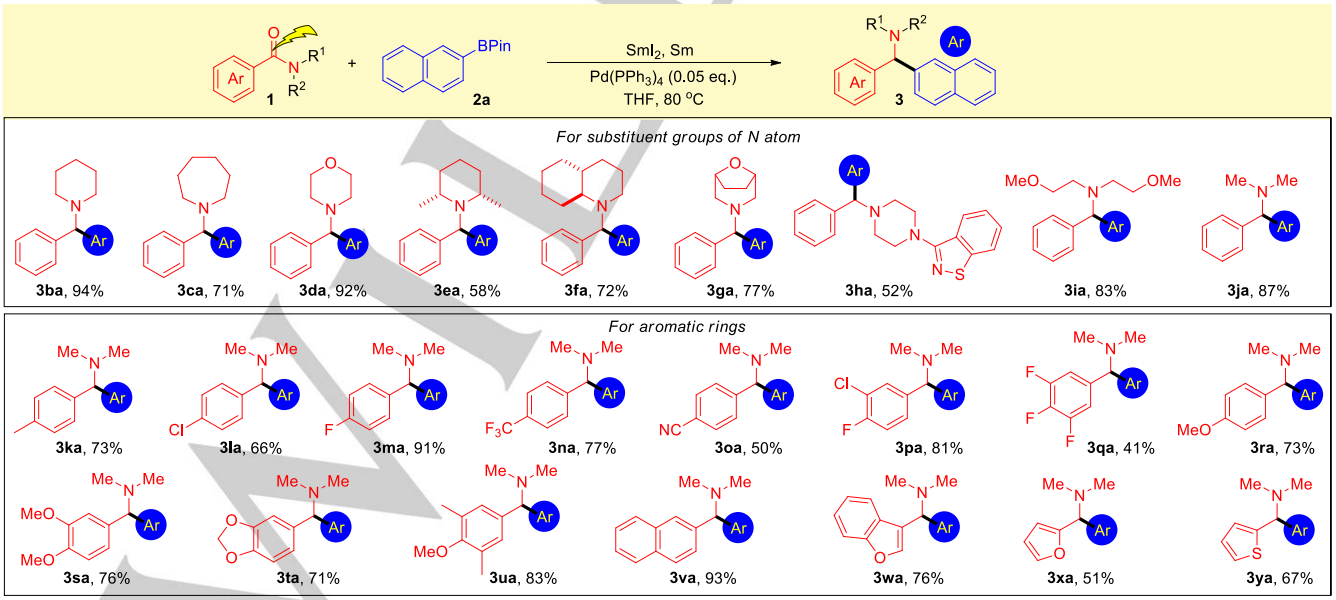
34% yield of **3aa** was obtained (For details, see the Supporting Information). In addition, no by-product from pinacol-type coupling of **1a** was detected during this optimization.

The substrate scope of the arylboron reagents in the deoxygenative cross-coupling reactions of the amide **1a** was examined. As shown in Scheme 2, with the β-naphthyl boron reagent replaced by a phenyl boron reagent, the reaction proceeded in good yield (**3ab**, 84%). Arylboron reagents bearing electron-withdrawing substituents such as Cl- or CF_3- on the arene subunit were converted smoothly to the corresponding products **3ac** (88%) or **3ad** (65%). Electron-rich arylboron reagents with methyl-, TMS-, MeO- and Ph_2N- at the *para* position of the arene produced the corresponding arylation products (**3ae**-**3ai**) in yields of 66-80%. Synthetically versatile vinyl and cyanomethyl groups were well tolerated in these reaction conditions, giving moderate yields of the products **3aj** and **3ak**. The reaction also proceeded smoothly with *meta*-substituted arylboron reagents, affording products **3al** and **3am** in 91% and 59% yield, respectively. Arylpinacolboronates with a disubstituted aryl group are also effective substrates, as exemplified by the reactions of diversely disubstituted boronates **2n**, **2o** and **2p**, which gave the corresponding densely substituted products **3an**, **3ao** and **3ap** respectively, with yields of 67-77%. The reaction is compatible with heteroaryl boronate esters, affording **3aq** (91%) and **3ar** (83%) in good yields. Several boronate esters (**2s**-**2w**) with a highly conjugated arene unit were also investigated in this reaction, and gave the products (**3as**-**3aw**), possibly valuable in material science, in yields of 68-89%. However, the using of n-butyl boron reagent (^{n}Bu-BPin) in the reaction with **1a** failed to afford any of the desired product.

We next sought to explore the scope of various carboxamides in the deoxygenative arylation reactions with 2-naphthylpinacolboronate ester **2a**, obtaining the results in Scheme 3. The reactions of amides derived from different secondary cyclic amines (**1b**-**1g**) proceeded well under the standard conditions, affording the products (**3ba**-**3ga**) with yields of 58-94%. Remarkably, the sterically congested diarylmethylamine **3ea** was isolated in 58% yield. An amine product with a strained ring **3ga** can also be obtained in good yield (77%), and an amide bearing a benzo[d]isothiazole unit can be tolerated in the reaction, giving the product **3ha** with the intact heterocyclic structure, in 52% yield. For amides **1ia** and **1ja**, derived from bis(2-methoxyethyl)amine and dimethylamine respectively, the reactions gave the corresponding products in 83% and 87% yield, respectively. These results indicate that the reaction proceeds well with aryl amides derived from either cyclic or acyclic amines. Aryl amides (**1ka**-**1ua**) with either electron withdrawing groups (such as Cl-, F-, CF_3-, and NC-) or electron-donating groups (MeO-, 3,4-dimethoxy-) on the phenyl ring are good substrates for the reaction, affording the corresponding benzhydryl amines (**3ka**-**3ua**) in moderate to good yields. The cross-coupling product **3la** was obtained with a yield of 66%, indicating that this protocol can tolerate an aryl chloride subunit on the amide. The synthetically versatile cyano group is well tolerated in this reaction conditions, as demonstrated by the 50% yield of the cyano substituted benzhydryl amine **3oa**. Amides bearing a 2-naphthoyl, 3-benzofuroyl, 2-furoyl or 2-thiophene-carbonyl moiety undergo the transformation smoothly, giving the corresponding products (**3va**-**3ya**) in 51-93% yields. For the amide derived from hexanoic acid and pyrrolidine, no desired product was detected in the reaction with **2a**.



Scheme 3. The scope of aryl amides.

Alkylamine motifs are ubiquitous structural motifs found in a wide range of small-molecule drugs and preclinical drug candidates. Late-stage functionalization of such molecules (Scheme 4) is a compelling demonstration of the utility of this reaction and may be a unique way to access new pools of functionalized alkylamine analogues. To demonstrate the applicability of the protocol, amide **4**, derived from norquetiapine and **6**, from desloratadine, were subjected to the reaction with **2n** and **2a**, respectively, under optimized conditions. Both deoxygenative arylation reactions proceeded smoothly affording **5** and **7** in 62% and 90% yield, respectively. In these reactions, functional groups such as amidine, thioether and pyridine are tolerated better than in typical metal- mediated reactions. The present protocol therefore represents a practical alternative method for the conversion of structurally complex dialkylamines to their biologically important benzhydryl amine derivatives. Similarly, several drug molecules containing aryl amide motifs, including CX-546 **8**, Trocimine **9** and Trimetozine **10** were also

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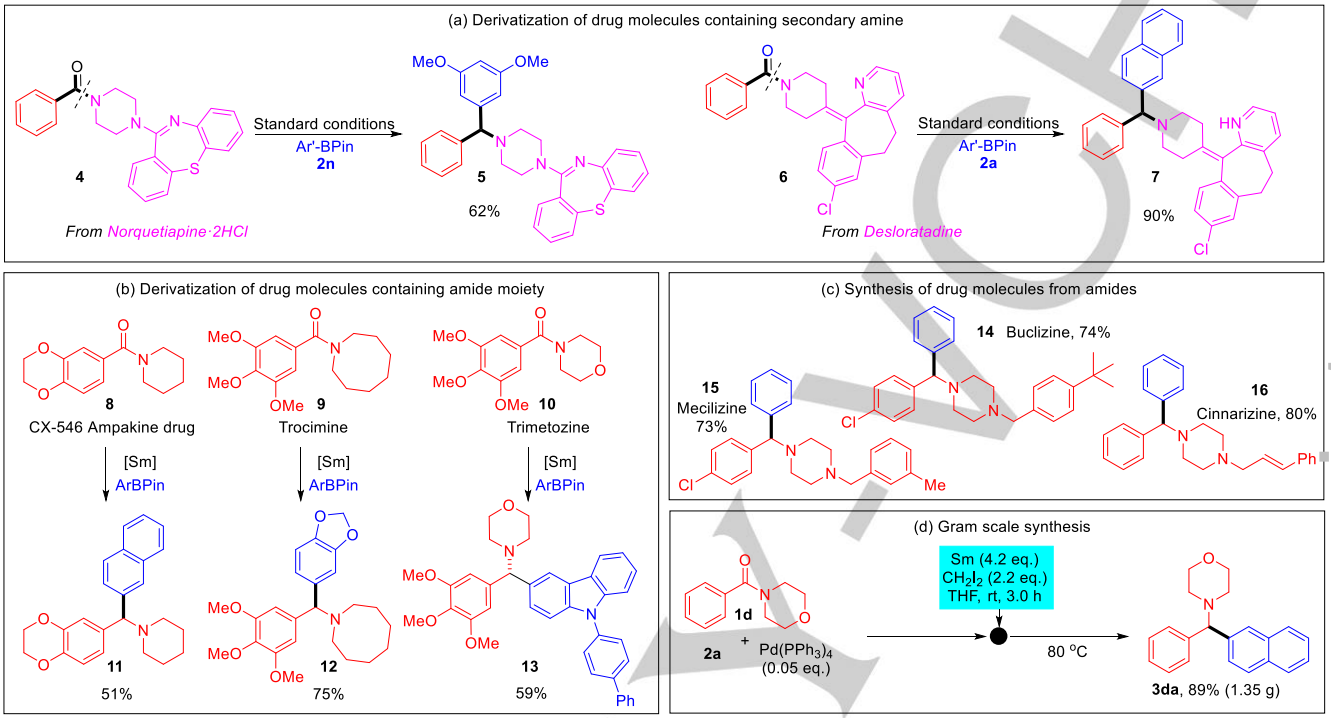
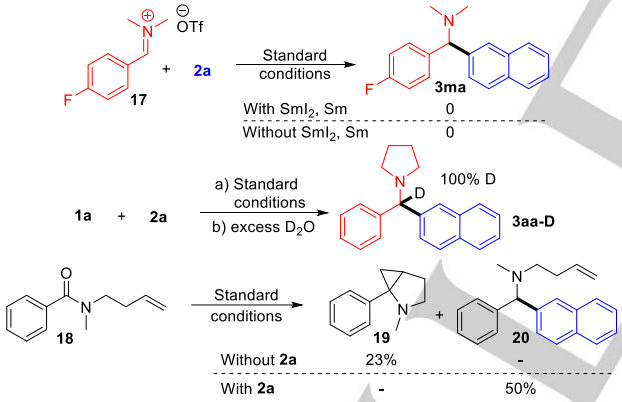


Scheme 4. Late-stage functionalization, the synthesis of drug molecules and gram scale synthesis.



Scheme 5. Preliminary mechanistic studies.

submitted to this late-stage modification and were efficiently transformed into the corresponding benzhydryl amines (**11**-**13**) in 51-75% yields. This methodology was successfully applied to the synthesis from the corresponding amides of some drug molecules containing a diarylmethylamine unit. Buclizine **14**, Meclizine **15** and Cinnarizine **16** were obtained in good yields with this deoxygenative arylation procedure, providing a valuable alternative route to these small drug molecules. The late-stage functionalization of drug molecules, including secondary amines and aryl amides, together with the synthesis of drug molecules demonstrates the wide synthetic utility of this reaction. Finally, the reaction of **1d** and **2a** was performed directly using the *in situ* generation of Sm/SmI_2 mixture from Sm (4.2 eq.) and CH_2I_2 (2.2 eq.) in THF, and **3da** was successfully achieved in 89% isolated yield (1.35 g) using this operationally simple protocol (Scheme 4d).

Preliminary mechanistic studies were conducted in an effort to understand the mechanism of the reaction (Scheme 5). The reaction of preformed iminium triflate **17** with **2a** was explored in the presence or absence of Sm/SmI_2 under otherwise identical conditions. Neither of these reactions gave the desired product **3ma**, suggesting that the iminium intermediate is unlikely to be responsible for the formation of the deoxygenative cross-coupling product of the reaction.[23c] Addition of D_2O to quench the reaction of **1a** and **2a** led to 100% deuteration at the benzhydryl position in the isolated product **3aa-D**, suggesting protonation should be involved in the formation of the final deoxygenative product. In the absence of the boronic ester **2a**, the reaction of the amide **18** under standard conditions gave the deoxygenative cyclopropanation product **19** in 23% yield, suggesting the involvement of an α-aminocarbene species.[16,17] Under the standard conditions, the reaction of amide **18** with **2a** afforded the desired product **20** in 50% yield without any detectable cyclopropanation product **19**, indicating that the boronic ester may intercept the α-aminocarbenoid equivalent **II** prior to the generation of the α-aminocarbene. The possible involvement of a free α-aminocarbene or metal α-aminocarbenoid species in the reaction cannot be totally ruled out and the details regarding the significantly enhanced reactivity for metal additive in this reaction system are unclear at present.[24] Considering that the reaction can proceed smoothly without any co-metal additive (albeit giving a lower yield of the product), it was tempting to tentatively propose that a conceivable role of co-metal might be to increase the reactivity of SmI_2, e.g., *via* facilitating the single electron transfer process from the SmI_2/Sm mixed system to organic species.[24,25]

Conclusion

In summary, we have developed a direct deoxygenative arylation of amides using SmI_2/Sm mixed system. The reactions are operationally simple and proceed under mild conditions, affording a series of biologically important diarylmethylamines in moderate to good yields. The key to this success is the merging of ET induced activation of amide with boron 1,2-metalate rearrangement. The utility of the present methodology was demonstrated in the late-stage diversification of some marketed drugs, and in the synthesis of drugs from corresponding amides. This transformation is an extremely simple way to carry out the challenging deoxygenative transformation of amides, a long-standing goal for organic chemists.

Acknowledgements

This work was generously supported by the National Natural Science Foundation of China (21821002) and Shanghai Pujiang Program (19PJ1411500). We thank X.-L. Hou, G.-S. Liu, Z. Wang (all SIOC) and J. Pei (Peking University) for valuable discussions during the course.

Keywords: Amides • Electron transfer • 1,2-Metalate Rearrangement • Deoxygenative Arylation • SmI_2

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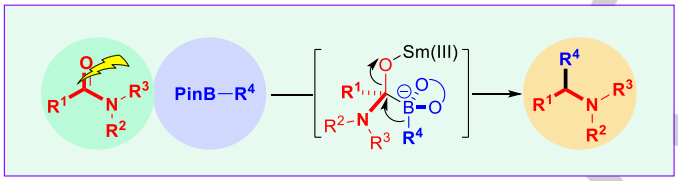

A mild and efficient protocol for deoxygenative C-C bond cross coupling of aromatic amides with air- and moisture-stable arylboronic esters is achieved, affording a series of biologically important diarylmethylamines in moderate to good yields. The key to this success is proposed to be the merging of electron transfer induced activation of amide with boron 1,2-metalate rearrangement.