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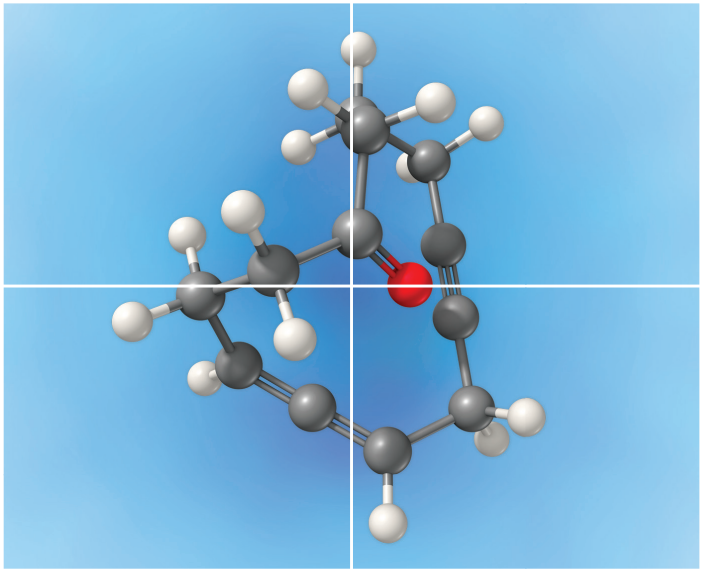

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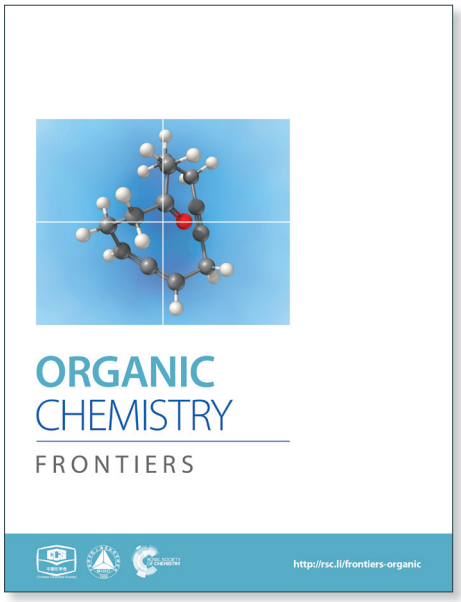

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COMMUNICATION

Palladium-Catalyzed Methylene C(sp3)–H Arylation of Adamantyl Scaffold

Yexing Lao,[ab] Jiaqiang Wu,[a] Yunyun Chen,[a] Shangshi Zhang,[a] Qingjiang Li,[a] Honggen Wang*

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Adamantyl group is prevalent as key pharmacore element in drugs. We describe herein a palladium-catalyzed C-H functionalization logic for the methylene C(sp^3)–H arylation of adamantyl scaffold under the assistance of an amide group. The resulting arylated adamantyl amide was smoothly converted to amine, providing a facile access to memantine analog.

Introduction

Since the discovery of amantadine (1-adamantanamine) as a potent anti-influenza agent as early as in 1964,[1] the polycyclic adamantane motif has been recognized as the key structural elements in numerous drugs, as displayed by anti-alzheimer's disease agent memantine,[2] anti-virus agents rimantadine [3] and tromantodine,[4] anti-diabetic drugs vildagliptin[5] and saxagliptin,[6] and anti-acne agent adapalene[7] (Figure 1).[8] It is well accepted that the incorporation of adamantyl group will increase the lipophilicity and metabolic stability of drugs, thereby improving their pharmacokinetics properties. In addition, as a bulky motif, the adamantyl group frequently occurs in ligands and catalysts in organic synthesis.[9] Synthetically, the parent adamantane has become easily available since the seminal synthesis from Schleyer.[10] Thereafter, the synthetic modifications of this cage hydrocarbon have yielded a number of adamantane derivatives. However, while the modification at the adamantyl methine positions are fruitful due to the intrinsic weaker tertiral C-H bonds therein,[11] the direct functionalization at the methylene positions poses a greater challenge and thus meets with far less success.[12]

The transition metal-catalyzed direct functionalization of inert C-H bonds has matured as a powerful tool for the facile

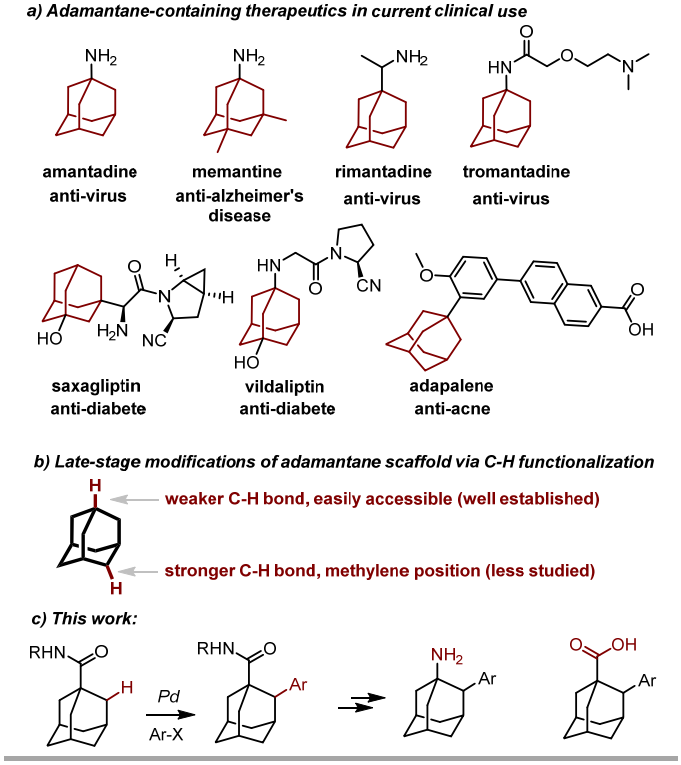

Figure 1 Adamantane-containing therapeutics and strategies for adamantane C-H functionalization.

assembly of a variety of C-C and C-heteroatom bonds in recent years.[13] In this regard, the palladium-catalyzed C(sp^3)-H activation reactions are particularly useful and well suited for the functionalization of aliphatic hydrocarbons.[14] For instance, it has been demonstrated that the catalytic C-H functionalization of aliphatic amines[15] or carboxylic acid[16] derivatives are feasible under the catalysis of palladium. Considering the lack of transformable functional groups at the methylene positions of adamantane and our precedent experience on the direct C-H functionalization of 3-pinanamine,[17] we thus envisioned that a palladium-catalyzed

[a] School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China.
Email: wanghg3@mail.sysu.edu.cn.
[b] The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510230, China.

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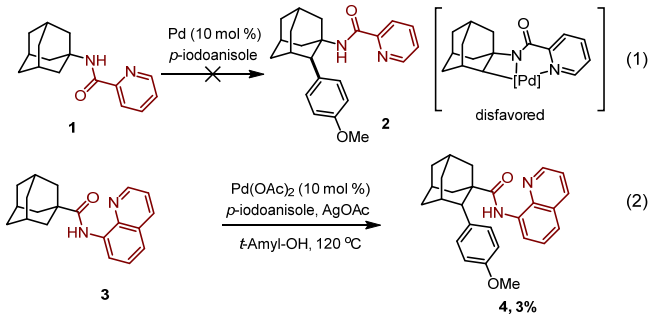
C(sp^3)-H activation strategy might be suitable for a late-stage modification[18] of adamantane. 1-Adamantanamine and 1-adamantanecarboxylic acid are easily available and useful adamantane-containing compounds. We reasoned the amino or the carboxylic acid functional group could serve as a directing group which would therefore facilitate the C-H activation event. Herein we report our realization of a Pd(0)-catalyzed direct arylation of methylene C-H bond of adamantane directed by an amide group. It should be noted the Pd(0)-catalyzed arylation reactions, especially intermolecular examples are rarely developed.[19,20] By simple functional group manipulations, the resulting benzamides can be converted to the memantine analog. (Figure 1).

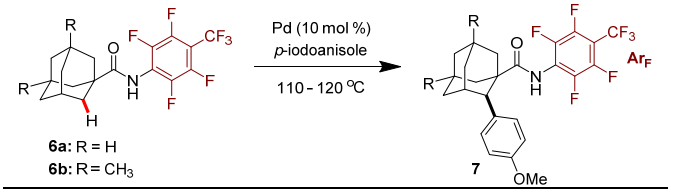
Results and discussion

At the outset of our studies, we investigated the C-H activation of 1-adamantanamine by installing a picoloyl functionality as the directing group. We anticipated this synthetic logic would directly give the amantadine or memantine analogs after removal of the auxiliary. To our disappointment, no desired product **2** was observed after extensive screening of the reaction conditions. We suspected that this might be attributed to the difficulty of forming of a disfavored four-membered-ring cyclometalated intermediate after the C-H activation event. Realizing this, we then turned our attention to the C-H activation of 1-adamantanecarboxylic acid derivative **3**, bearing an 8-aminoquinoline bidentate directing group. To our delight, the reaction of **3** with 4-iodoanisole in the presence of $Pd(OAc)_2$ as catalyst and AgOAc as base indeed gave the desired arylation product **4** in 3% yield. Unfortunately, attempt to further improve the yield failed in our hand.



Even though, encouraged by this promising result, we then investigated the reaction effected by a monodentate *N*-arylamide ($CONHAr_F$) auxiliary devised by Yu.[19d] Some representative results are summarized in Table 1. The arylation of **6a** gave **7a** in 14% isolated yield under the reaction conditions of $Pd(OAc)_2$ (10 mol %), $PCy_3{\cdot}HBF_4$ (10 mol %) and CsF (3.0 equiv) in toluene at 110 °C for 20 h. (Table 1, entry 1). Further optimization including the screening of different palladium sources, solvents, ligands, and bases were conducted, and it was turned out these parameters have trivial effects on the yield (entries 2-10). However, by increasing the loading of ligand PPh_3 to 50 mol % and the amount of 4-iodoanisole to 5.0 equivalents, the yield was doubled (35%, entry 11). It was found

Table 1 Optimization of the reaction conditions[a]



entry	R	ligand	solvent	additive	yield
1	H	$PCy_3{\cdot}HBF_4$	toluene	CsF	14%[b]
2	H	$PCy_3{\cdot}HBF_4$	*o*-xylene	CsF	21%[b]
3	H	$PCy_3{\cdot}HBF_4$	DCE	CsF	14%[b]
4	H	$PCy_3{\cdot}HBF_4$	CH_3CN	CsF	9%[b]
5	H	PPh_3	o-xylene	CsF	21%[b]
6	H	PPh_3	o-xylene	Cs_2CO_3	19%[b]
7	H	PPh_3	o-xylene	K_2CO_3	9%[b]
8	H	$P^tBu_3{\cdot}HBF_4$	o-xylene	CsF	8%[b]
9	H	IPr·HCl	o-xylene	CsF	17%[b]
10	H	-	o-xylene	CsF	16%[b]
11	H	PPh_3	o-xylene	CsF	35%[b]
12	H	PPh_3	*n*-hexane	CsF	53%[c,d]
13	**CH_3**	**PPh_3**	***n*-hexane**	**CsF**	**54%[c]**
14	CH_3	PPh_3	*n*-hexane	PivOH	0[c]

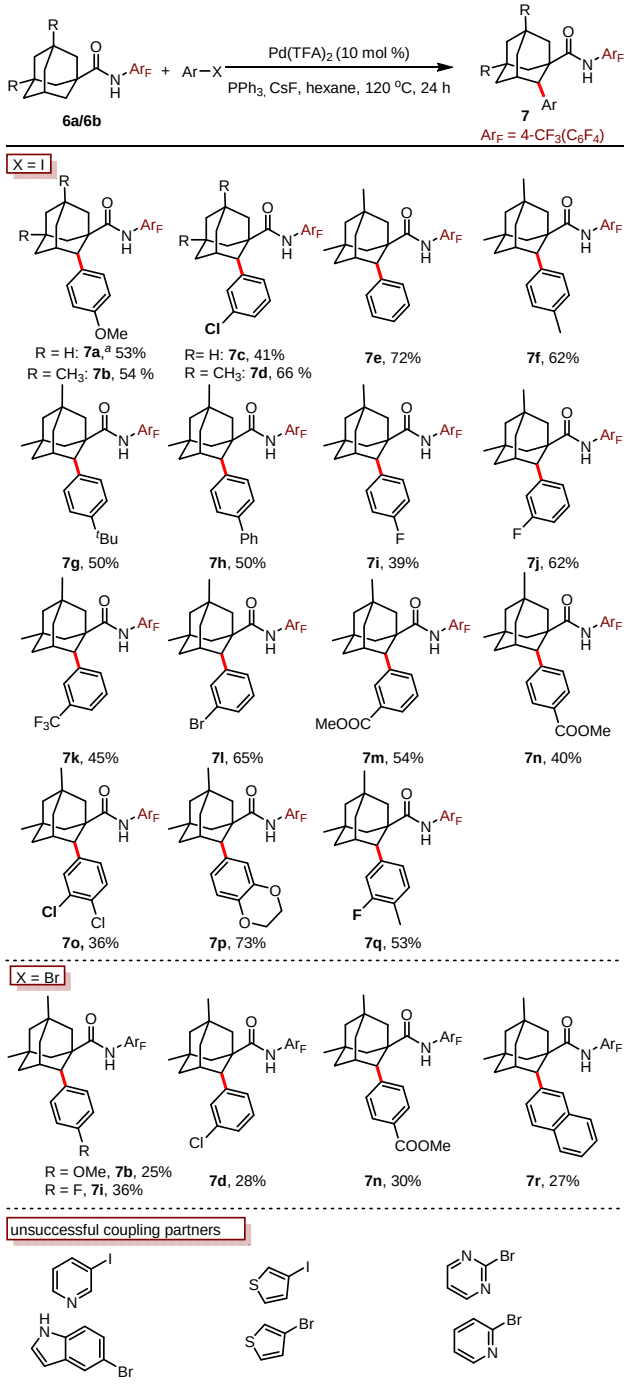
Conditions: entries 1-9: 3.0 equiv of *p*-iodoanisole, 10 mol % ligand, 3.0 equiv of base, 0.2 M. entries 11-13: 5.0 equiv of *p*-iodoanisole, 50 mol % ligand. [b] The yield was determined by ^1H NMR analysis of the crude product using dimethyl terephthalate as the internal standard. [c] 0.5 M, isolated yield. [d] 16% diarylation product was found.

that the transformation is sensitive to the reaction concentration. When the reaction was performed at 0.5 M rather than 0.2 M, the yield was significantly improved to 53% (entry 12). As one might have predicted, the diarylation reaction (around 16% diarylation product) was also observed, which causes the separation difficult. Therefore, **6b** bearing two methyl groups at the methine position was chosen as the model substrate to evaluate the substrate scope of this reaction. The methyl groups were anticipated to impact sufficient steric hindrance to the adjacent methylene position, thereby making mono-arylation exclusive. Indeed, when **6b** was subjected to the standard reaction conditions, the mono-arylation products 7b was obtained in 54% yield, with no di-arylation product found (entry 13). The use of PivOH as additive shut down the reactivity (entry 14).

With the optimized conditions in hand (entry 13, table 1), we next explore the scope of this reaction. As shown in Table 2, this arylation protocol permits the direct C-H arylation of adamantyl amides **6** with a wide range of aryl idodides. Functional groups regardless of their electronic nature, such as alkoxy (**7a**, **7b**, **7p**), chloro (**7c**, **7d**, **7o**), bromo (**7l**), fluoro (**7i**, **7j**, **7q**), aryl (**7e**, **7h**), alkyl (**7f**, **7g**, **7q**), ester (**7m**, **7n**) and trifluoromethyl (**7k**) groups were well tolerated, affording the corresponding monoarylation products in moderate to good yields. The structure of **7d** was unambiguously determined by X-ray crystallographic analysis (Figure 2).[21]

Not only aryl iodides but also aryl bromides were applicable in this transformation, albeit in lower yields. Disappointingly, the

Table 2 Substrate scope of methylene C-H functionalization



Reaction conditions: 0.1 mmol of substrate, 5.0 equiv of Ar-X, 10 mol % $Pd(TFA)_2$, 3.0 equiv of CsF, 0.2 mL hexane, 120 °C, 24 h. All yields are based on the isolated products unless otherwise specified. [a]t-AmylOH was used as solvent.

use of nitrogen or sulfur containing heterocyclic halides shut down the reactivity completely, probably due to the deleterious coordination of the nitrogen or sulfur atoms to the palladium catalyst.

To evaluate the reaction efficacy on preparative scale, a gram scale reaction was performed. The reaction of **6b** with 1-chloro-3-iodobenzene give 1.34 g arylation product **7d** in 50% yield, demonstrating that the reaction is practical (scheme 1a).

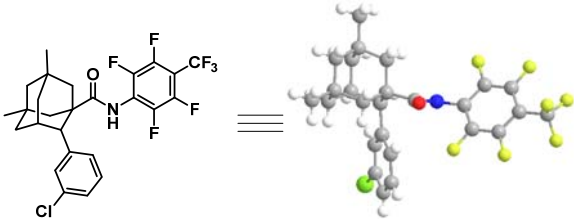
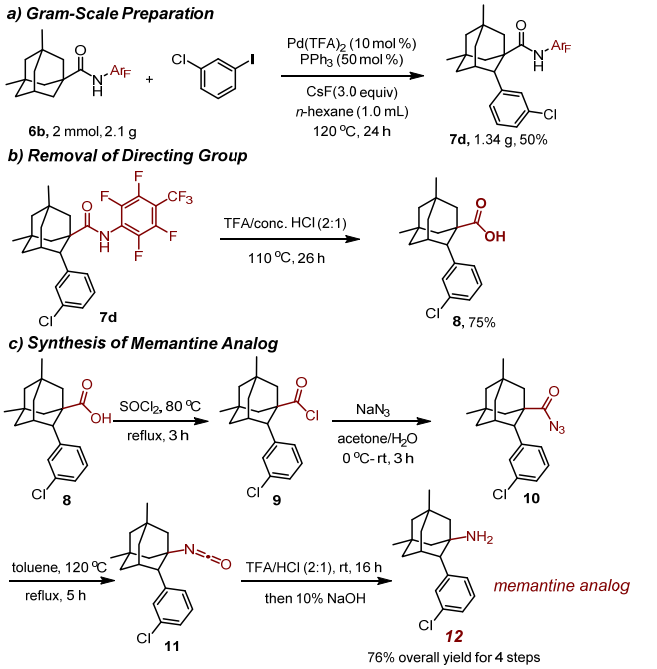


Figure 2. Absolute configuration of **7d**.

The directing group *N*-arylamide ($CONHAr_F$) moiety could be conveniently removed upon the treatment with TFA/conc. HCl (2:1) at 110 °C, giving the corresponding carboxylic acid **8** in 75% yield (scheme 1b). Thereafter, by a Curtius rearrangement, the carboxylic acid could be converted to an amino group, thus providing a memantine analog **12** in 76% overall yield (scheme 1c).[22] The synthesis of the arylated analogs of memantine using this protocol and their biological evaluation are underway in our laboratories and will be reported in due course.



Scheme 1 Gram-scale preparation, removal of the directing group and product derivatization.

Conclusions

In summary, we have realized a palladium-catalyzed direct arylation of methylene C(sp^3)-H of 1-adamantane carboxylic acid derivative. A variety of aromatic iodides and bromides containing different functional groups were well tolerated in this process, giving the arylated products in moderate to good yields. A gram scale reaction was conducted to showcase the efficacy of this reaction. The utility of this method was further demonstrated by the successful synthesis of a memantine analog. Giving the importance of adamatane scaffold in biologically active compounds and in organic synthesis, we anticipate the methodology developed herein will find applications.

Acknowledgements

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