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Synthetic Methods

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Selective Ortho Functionalization of Adamantylarenes enabled by Dispersion and an Air-Stable Pd(I) Dimer

*Indrek Kalvet, Kristina Deckers, Ignacio Funes-Ardoiz, Guillaume Magnin, Theresa Sperger, Marius Kremer and Franziska Schoenebeck**

In memory of Professor Dieter Enders

***Abstract**: Contrary to the general belief that Pd-catalyzed cross-couplings at sites of severe steric hindrance are disfavored, we herein show that the oxidative addition to C-Br ortho to an adamantyl group is as favored as the corresponding adamantyl-free system due to attractive dispersion forces. This enabled the development of a fully selective arylation and alkylation of C-Br in ortho position to an adamantyl group, even if challenged with competing non-hindered C-OTf or C-Cl sites. The method makes use of an air-stable Pd(I) dimer and allows for a straightforward access to diversely substituted therapeutically important adamantylarenes in 5-30 min.*

Owing to its exceptional liphophilicity and stability enhancing properties, the adamantyl group has found widespread applications in materials science,[1] medicinal chemistry and drug development.[2] In fact, the only other hydrocarbon moiety that was similarly successful in generating active therapeutics is the methyl group.[2] Adamantane derivatives are used in the fighting of viral infections, such as Influenza, Herpes, Hepatitis C, HIV, of Malaria or Parkinson's disease and as retinoid antibiotics (see Figure 1).[2-3] Yet, the synthetic access to densely functionalized adamantyl containing molecules is still challenging,[4] especially the diversification *via* arylation or alkylation *ortho* to the adamantyl group is currently out of reach. However, the future discovery of superior therapeutics or antibiotics would vastly benefit from synthetic methodology that allows access to a larger chemical space of diversely substituted adamantyl derivatives. Ideally, this is achieved in a modular and rapid fashion that allows to introduce various potential arene substituents late in the synthesis and with complete site-control, as the nature of the substituents and their relative positioning will ultimately control the function of the final target molecule. While the introduction of the 1-adamantyl group to an arene has significantly advanced in recent years, particularly due to successes in devising radical-based or organometallic methodology,[4c,4e-h,5] these approaches predominantly deliver the adamantyl in *meta* or *para*-position relative to an alternative substituent in the arene, but not *ortho*. Similarly, although electrophilic adamantylations (Friedel-Crafts) could in principle deliver an *ortho* substitution pattern (along with alternative regioisomers),[6] the process requires harsh conditions (concentrated/strong acids, elevated temperature) and will strongly depend on the electronic bias of the particular substrate, precluding late-stage applications.[7]

We therefore set out to address the *ortho*-functionalization challenge and focused on *ortho*-bromo adamantylarenes as coupling motif. More specifically, to maximize the potential for downstream diversification, we initially targeted a poly(pseudo)halogenated adamantyl-arene as modular platform. The selective manipulation of *e.g.* C-Br *vs.* C-OTf would ultimately deliver a library of diversely substituted adamantyl-derivatives with an *ortho*/*meta* relationship that is not yet accessible in a general manner. The key requirements for success of this strategy are (i) that selective C-Br *vs.* C-OTf functionalization can be realized and (ii) that coupling *ortho* to the large adamantyl group is possible.

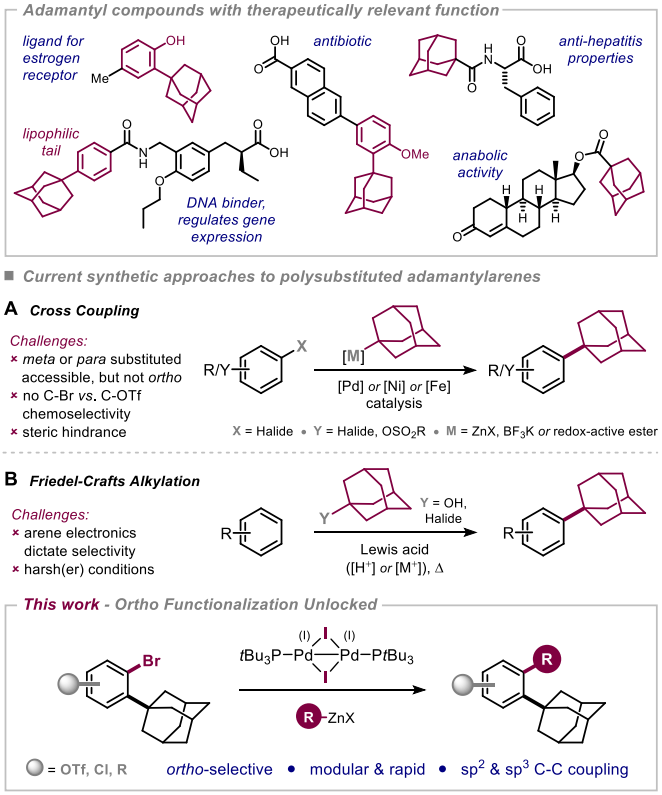

Figure 1. Medicinally relevant adamantyl compounds (top), current synthetic approaches to adamantylarenes and this work (bottom).

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The adverse impact of steric hindrance on the efficiency of Pd-catalyzed cross coupling has been widely documented.[8] For example, although 4-bromoaryl triflate can be selectively coupled at C-Br with a [$PdCl_2${P(*o*-tol)$_3$}$_2$]-catalyzed Kumada reaction, the introduction of two relatively small methyl substituents *ortho* to the C-Br (in 3- and 5-positions) resulted in erosion of selectivity and mixtures of products.[9] The vast majority of literature concludes that the oxidative addition step controls the site-selectivity[10] and that this step is most likely inhibited by steric hindrance.[11]

In this context, we wondered about the feasibility of oxidative addition *ortho* to the adamantyl group. Although the adamantyl group is large, it has also been ascribed to be a privileged dispersion donor.[12] Attractive dispersion forces have previously been found to outweigh steric effects, counterintuitively stabilizing more crowded molecules over their less crowded counterparts.[13]

We focused on compound **1** (see Scheme 1), which bears a C-Br *ortho* to adamantyl and allows for further *meta*-derivatization *via* C-OTf coupling. The methoxy group is representative of a potential linkage to biomolecules.[14]

As a theoretical exercise, we computationally assessed the impact of the adamantyl group on oxidative addition step, utilizing $Pd^{(0)}(PtBu_3)_2$ as a model system, which should be particularly prone to engage in attractive C-H•••H-C dispersion attraction with the adamantyl group.[15] To this end, we calculated the activation free energy barrier for the oxidative addition of 2-adamantyl-6-methoxybromoarene (Figure 2, C) *vs.* the corresponding adamantyl-free systems (Figure 2, A and B). The lowest energy pathway of oxidative addition involves an initial ligand loss, followed by oxidative addition to C-Br by the monophosphine $Pd^{(0)}(PtBu_3)$ complex.[15,17b,c,30] The barriers for oxidative addition to Ar-Br were compared using DFT methods[16] with and without dispersion-corrections. The results are illustrated in Figure 2.

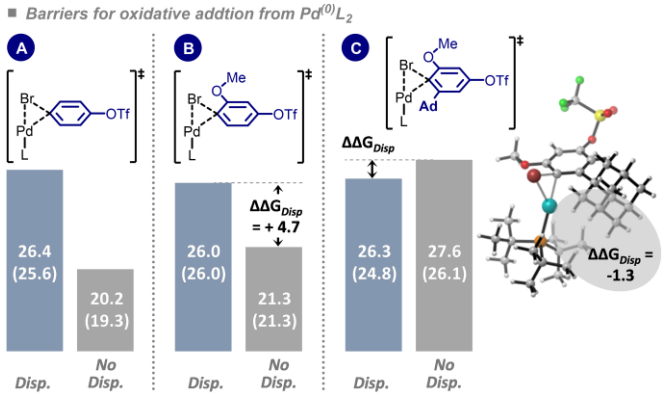
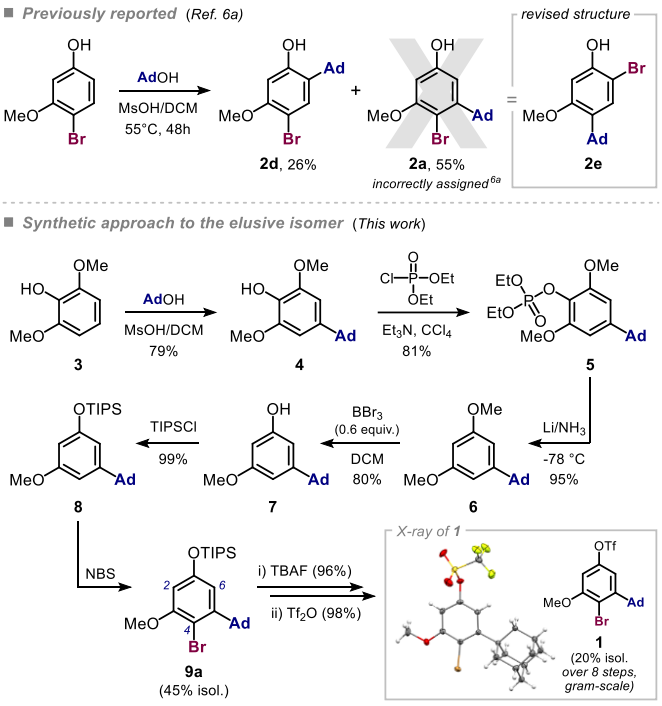


Figure 2. Computational study of activation free energies and enthalpies (in parentheses) for C-Br oxidative addition relative to $Pd(PtBu_3)_2$ in kcal/mol; calculated at CPCM (THF) B3LYPD3/Def2TZVP// B3LYP-D3/6-31G(d)/ LanL2DZ level of theory. See SI for additional computational data with alternative methods on this trend, including D4 dispersion results.[17,30]

Interestingly, while the classical DFT methods (that do not account for dispersion) predict activation barriers in accord with expected steric effects, *i.e.* with barriers A < B < C, inclusion of dispersion in turn predicts roughly the same activation free energy barriers for A, B and C of approximately 26 kcal/mol,[17] suggesting that attractive dispersion between the adamantyl and *tert*-butyl substituent of the Pd-catalyst outweigh steric clashes. As such, although computational challenges exist in unambiguously capturing this phenomenon relative to solute-solvent dispersive interactions,[12a,15,18] these calculations suggest that - as opposed to the general belief of steric effects on the oxidative addition step - the adamantyl substituent should not impede oxidative addition.

We therefore next set out to experimentally target compound **1**. The required substitution pattern has so far been synthetically inaccessible. There is one patent that claims the synthesis of 3-(adamantan-1-yl)-4-bromo-5-methoxyphenol (**2a**) in a single step (see Scheme 1).[6a] However, our follow up investigation revealed that these claims are incorrect and the alternative isomer, 4-(adamantan-1-yl)-2-bromo-5-methoxyphenol (**2e**) was instead generated. As such, previous C-Br coupling attempts of starting materials prepared by this method instead yielded derivatives of **2e**.[9b,26b,19] [We hence embarked on developing a synthetic route to **1** which would establish the 3-(adamantan-1-yl)-2-bromo-phenol substitution pattern for the first time.



Scheme 1. Structural revision of previously claimed *ortho*-bromo-adamantylarene (**2a**) and synthesis of 4-Br-5-methoxy-3-adamantyl-phenyl triflate (**1**) from 1,3-dimethoxyphenol **3**. See SI for detailed reaction conditions.

Scheme 1 presents our successful synthesis. The 1-adamantyl group was introduced to 1,3-dimethoxyphenol **3** *via* Friedel-Crafts alkylation with 1-adamantanol.[20] The free OH group of **4** was then protected as a diethyl phosphate ester (**5**) and subsequently reduced under Li/NH_3 conditions to 5-adamantylresorcinol dimethyl ether **6**. Selective removal of one of the methyl groups was accomplished with BBr_3, followed by the introduction of a TIPS protecting group. This allowed for predominant reaction at the 6-position in the electrophilic bromination with NBS.[21] The structure of **1** was unambiguously confirmed through single crystal X-ray diffraction analysis (Scheme 1),[22] and 2D NMR analyses were conducted on all intermediates and the target compound **1**.[23]

We subsequently set out to study the functionalization of **1**. In the context of $Pd^{(0)}/Pd^{(II)}$ catalysis, the relative reactivity of aryl triflates and bromides is frequently referred to be roughly the same,[24] and the selectivities therefore have historically been a result of a subtle interplay of reaction conditions, catalyst, coupling partner and the steric and electronic effects imposed by the substrate.[9a,10e,10f,24-25]

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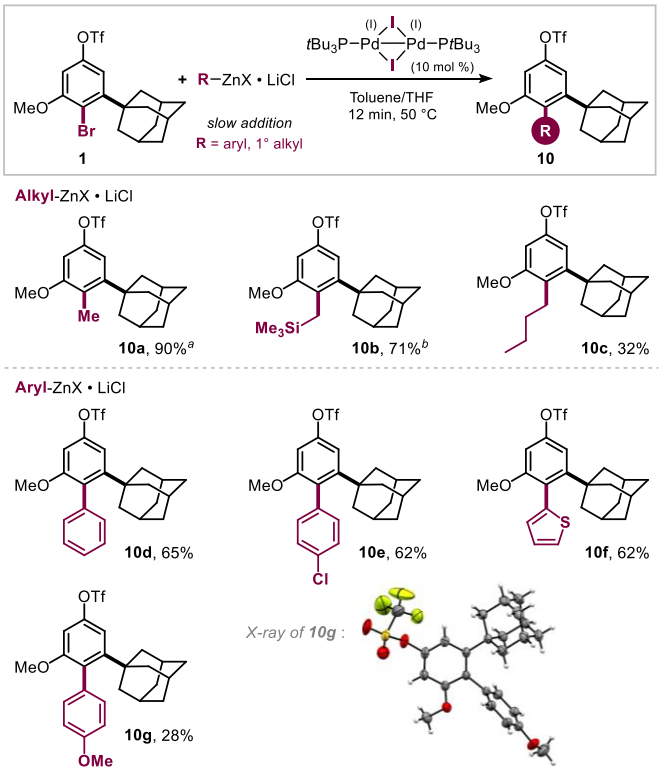
By contrast, we recently established a substrate independent and *a priori* predictable C_{sp2}-C_{sp2} and C_{sp2}-C_{sp3} functionalization exclusively at C-Br in competition with C-OTf and C-Cl sites.[9b, 26] Key to this exquisite selectivity was the employment of an air- and moisture stable Pd(I) dimer that facilitated the couplings in ≤ 5min at room temperature.[27] As such, we envisioned that if the privileged reactivity for C-Br also applies to the adamantyl motif **1**, we would then be in a position to diversify C-Br at will, leaving possibilities for functionalization at the remaining C-OTf with any type of methodology.

Table 1. Pd(I) I-dimer catalyzed Br-selective cross-coupling reactions with **1**.[28]

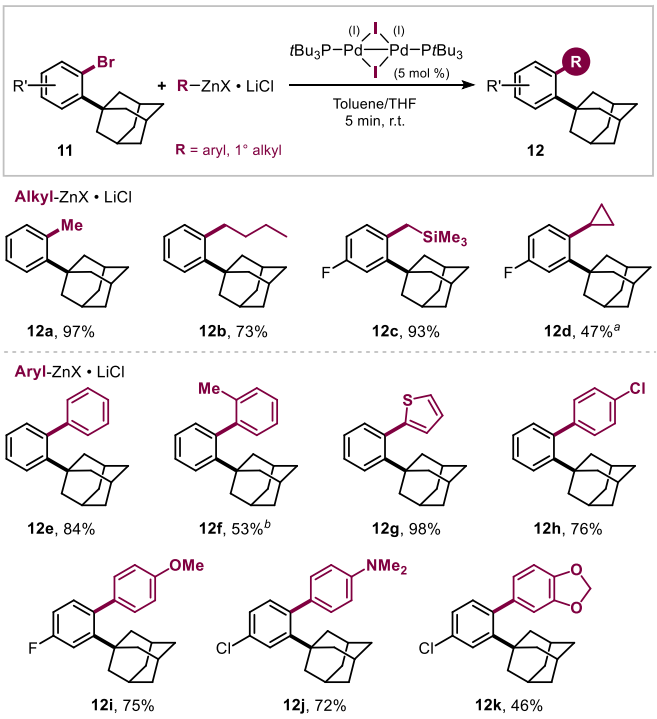


Reaction conditions: **1** (0.1 mmol), organometallic reagent (0.7 mmol in THF),[29] Pd(I) iodo dimer (0.01 mmol), toluene (0.6 mL), 50 °C, slow addition of organometallic reagent over 12 minutes. [a] **1** (0.05 mmol), organometallic reagent (0.15 mmol in THF), Pd(I) iodo dimer (0.0013 mmol), toluene (0.3 mL), r.t., slow addition of organometallic reagent over 4 minutes. [b] As in [a], with 0.25 mmol of organometallic reagent.

When we explored the functionalization of **1** with the methyl- or TMS-CH_2-organozinc reagents in toluene with the air-stable Pd(I) dimer (5 mol%), we saw efficient conversion to the corresponding coupling products arising from exclusive C-Br coupling (**10a** and **10b**) within ≤ 5min reaction time at r.t. (see Table 1). Similarly, arylation and *n*-butylation were equally selective for C-Br and left C-OTf untouched despite the need for slightly elevated temperatures (50 °C), slower addition rates (12 min) and increased organozinc (5-7 equiv.) as well as catalyst (10 mol%) loadings to reach high yields. Under these conditions we were able to introduce phenyl (**10d**, Table 1), 2-thienyl (**10f**), *n*-butyl (**10c**), 4-chlorophenyl (**10e**) as well as 4-methoxyphenyl groups (**10g**) under exclusive coupling at the C-Br site, as unambiguously confirmed also through Xray crystallographic analysis of **10g** (see Table 1).

As such, both arylation and alkylation could be accomplished selectively *ortho* to the adamantyl group, even in the presence of the additional and deactivating methoxy substituent. With this stern test passed, we next investigated the wider scope of functionalization of a range of 2-bromo adamantylarenes (**11**, see Table 2). We were able to couple the C-Br within 5 min at room temperature, and successfully introduced the alkyl substituents methyl, butyl, cyclopropyl and CH_2TMS (**12a-d**, Table 2). Arylations were similarly effective, and electron-rich (**12i**,**j**) as well as -deficient (**12h**) groups coupled equally efficiently. Even the introduction of the more hindered 2-methyl phenyl (**12f**) and the heterocyclic thiophene substituents (**12g**) proceeded smoothly.

Table 2. Pd(I) I-dimer catalyzed Br-selective cross-coupling reactions with **11**.



Reaction conditions: **11** (0.2 mmol), organometallic reagent (0.3 mmol in THF),[29] Pd(I) iodo dimer (0.01 mmol), toluene (0.8 mL), r.t. [a] Organomagnesium was used. [b] Yield obtained by quantitative ^{1}H NMR analysis of the crude.

In summary, we showcased the C-Br selective *ortho*-functionalization in adamantylarenes, while leaving the less sterically encumbered C-OTf or C-Cl sites fully untouched. Our computational studies indicated that oxidative addition to C-Br *ortho* to the adamantyl group is just as facile as to the corresponding adamantyl-free arene, suggesting that attractive P*t*Bu$_3$•••adamantyl dispersion forces override steric repulsion and stabilize the transition state for oxidative addition, which is at odds with current expectations in metal catalyzed cross-coupling chemistry. Given the pronounced therapeutic potential of adamantyl containing motifs, we anticipate a widespread interest in the herein reported unlocked *ortho* diversification method in adamantylarenes.

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[29] Organometallic coupling partner was prepared from R-MgCl (1 equiv.), LiCl (1 equiv.) and $ZnCl_2$ (1.1 equiv.).

[30] $\Delta\Delta G^{\ddagger}$ for C-Br *vs.* C-OTf oxidative addition to substrate **C** is 3.6 kcal/mol in favor of C-Br addition at the level of theory mentioned in Figure 2. For a rationalization why $Pd^{(0)}PtBu_3$ selects for C-halogen over C-OTf addition, see: a) F. Schoenebeck, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 2496; b) A. F. Littke, C. Y. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020.

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Synthetic Methods

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Selective Ortho Functionalization of Adamantylarenes enabled by Dispersion and an Air-Stable Pd(I) Dimer