

Palladium-Catalyzed Alkylation–Hydride Reduction Sequence: Synthesis of Meta-Substituted Arenes

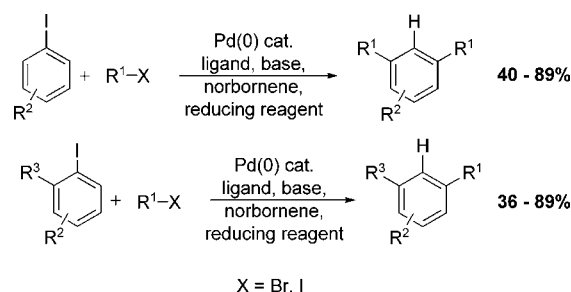
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ABSTRACT



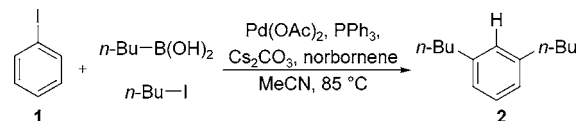
A new three-component, palladium-catalyzed domino reaction which gives access to meta-substituted arenes using aryl iodides and primary alkyl halides is reported. Various functional groups are tolerated on both the aryl iodide and alkyl halide. In addition, isotopic labeling studies provide insight into the mechanism of this Catellani-type reaction.

Multicomponent reactions have proven to be a powerful method for the synthesis of complex molecules from simple building blocks.¹ In particular, great attention has been given to sequential palladium-catalyzed processes.² We recently reported a sequential palladium-catalyzed reaction based on modified Catellani conditions,^{3,4} whereby up to three new C–C bonds are formed in one pot from aryl iodides, alkyl halides, and a Heck acceptor.⁵

In addition to the Heck reaction as the final coupling step in the catalytic cycle, Catellani has also reported the use of

Sonogashira– and Suzuki–Miyaura couplings using terminal alkynes or arylboronic acids, respectively.⁶ Our efforts to expand the scope of this reaction via Suzuki coupling with alkylboronic acids led to C–H bond formation following the initial ortho-alkylation, giving access to meta-substituted arene **2** (Scheme 1).⁷

Scheme 1. Discovery of Reduced Product



We noted this methodology could be useful for preparing polyfunctionalized meta-substituted arenes. Other methods for the alkylation of arenes (Friedel–Crafts alkylation⁸ or the Kumada coupling⁹) may lead to mixtures of regioisomers due to directing effects and rearrangements or be intolerant

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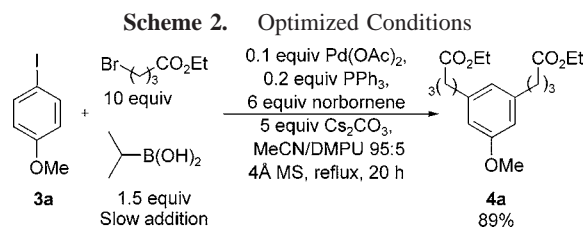
(2) (a) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, 56, 5959–5989. (b) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, 38, 413–422.

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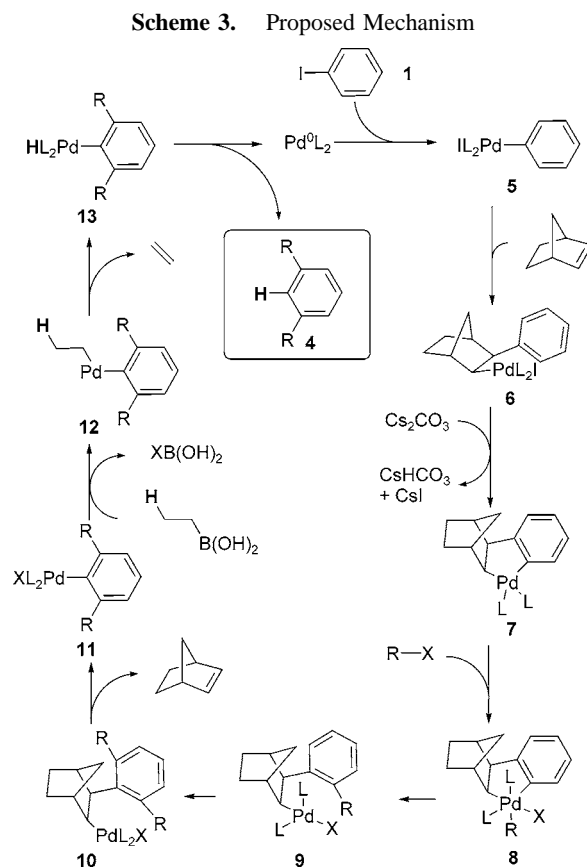
of some functional groups. Hence, a method to efficiently prepare functionalized meta-substituted arenes would be synthetically useful since many physiologically active compounds contain this structural moiety.¹⁰

We optimized the reaction conditions by varying the alkylboronic acid, solvent, equivalents of alkyl halide, base, and norbornene, as well as the effect of different additives and the method of boronic acid addition.¹¹ Scheme 2



illustrates our optimized conditions employing slow addition of isopropylboronic acid,¹² resulting in trisubstituted arene **4a** in 89% yield.¹³

The proposed mechanism for this transformation is based on that described by Catellani (Scheme 3).¹⁴ The first step involves oxidative addition of the iodoarene with Pd(0), followed by carbopalladation onto norbornene forming **6**. Subsequent C–H activation and elimination of HI by the base forms palladacycle **7**.



A second oxidative addition of the alkyl halide to palladium is proposed to form Pd(IV) species **8**. Reductive elimination of intermediate **8** leads to the ortho-alkylated arene **9**. This sequence can be reiterated in the second ortho position leading to **10**. Decarbopalladation with concomitant expulsion of norbornene gives intermediate **11**, which can then undergo a palladium-catalyzed C–H bond formation to regenerate Pd(0) and complete the catalytic cycle. We supposed the final C–H bond formation occurs via transmetalation of **11** with the alkylboronic acid giving **12**, followed by a β -hydride elimination to generate palladium hydride **13** and a reductive elimination to the meta-substituted arene **4**.

Control experiments to elucidate the mechanism indicated that reduced product was also formed in the absence of alkylboronic acid, though in much lower yield. This suggests a second pathway may also be occurring (Scheme 4, eq 1). Using deuterated iodoethane, we observed only deuterated product, implying that the alkyl halide was acting as an alternative hydride source (Scheme 4, eq 2).¹⁵ The detailed reaction pathway for C–H bond formation using alkyl halides as a hydride source is still under investigation. This reduction of iodoarenes appears to be a general reaction that is not limited to our norbornene-containing conditions (Scheme 4, eq 3).

(15) Experiments with deuterated solvents (CD₃CN), other solvents (DME), and without additives (MS and DMPU) using C₂H₅I always gave the nondeuterated product in similar yields thereby excluding other hydride sources (additives or solvent).

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(7) Product **2** was identified by ¹H NMR but not isolated due to the difficult separation. Catellani reported NaO₂CH gave the reduced product **2** (ref 4) but the only examples were with iodobenzene and unfunctionalized alkyl halides.

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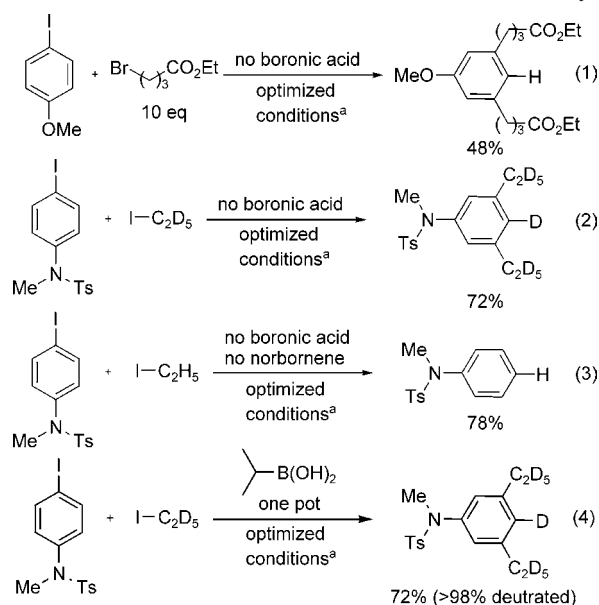
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(11) Optimization was carried out using HPLC yields.

(12) In a one-pot version the yield of compound **4a** is 78%.

(13) **General procedure for the multicomponent reaction:** Pd(OAc)₂ (4.5 mg, 0.02 mmol, 0.1 equiv), PPh₃ (10.5 mg, 0.04 mmol, 0.2 equiv), and molecular sieves (powder, 4 Å, 50 mg) were dissolved in absolute acetonitrile (0.5 mL) under nitrogen and stirred for 15 min. The iodoarene (0.2 mmol, 1 equiv), Cs₂CO₃ (325 mg, 1.0 mmol, 5 equiv), norbornene (113 mg, 1.2 mmol, 6 equiv), alkyl halide (2.0 mmol, 10 equiv), 0.1 mL of DMPU, and 0.5 mL of acetonitrile were added and the mixture was heated to reflux. Isopropylboronic acid (26.4 mg, 0.3 mmol, 1.5 equiv) dissolved in 1.0 mL of acetonitrile was then added at a rate of 0.08 mL/h via syringe pump. After 20 h, the mixture was cooled to room temperature, diluted with pentane, hydrolyzed with H₂O, and extracted with pentane or ether. After drying with MgSO₄ the crude product was purified by chromatography (silica, hexane/EtOAc).

(14) Proposed mechanism is based on mechanistic studies published by Catellani, Pregosin, and co-workers (see refs 3b and 3c).

Scheme 4. Evidence for a Second Mechanistic Pathway^a See ref 16.

The relative contribution of each mechanistic pathway is dependent upon the number of available β -hydrides. If the alkyl halide contains three β -hydrides, as in d_5 -iodoethane, the C–H(D) formation using the alkyl halide pathway is much faster than the alkylboronic acid pathway, resulting in the deuterated product (Scheme 4, eq 4). In contrast, an alkyl halide such as ethyl 4-bromobutyrate bearing two β -hydrides gave a 48% yield in the absence of boronic acid (Scheme 4, eq 1) versus 89% using isopropylboronic acid (Scheme 2). The important reductive role of isopropylboronic acid in the presence of alkyl halides other than iodoethane is clear.¹⁶ Further studies with deuterated boronic acids or alkyl halides are required to determine the contribution of each pathway.

We next investigated the scope of the reaction, beginning with para-substituted iodoarenes.¹⁷ The alkylation–reduction reaction is quite general, with the exception of substrates with base-sensitive groups (Table 1, entry 10). Electron-rich arenes (Table 1, entries 1,2) gave the highest yield whereas electron-poor arenes gave lower yields and required longer reaction times (Table 1, entries 8 and 9). The yields with meta-substituted iodoarenes are generally lower (Table 1, entries 11 and 12). In the case of meta-substituted iodoarenes bearing noncomplexing substituents such as methyl or trifluoromethyl, or bulky substituents such as tosylated amine, no desired product is obtained.

(16) Conditions for one pot-reactions: Amounts are the same as the general reaction. $\text{Pd}(\text{OAc})_2$, PPh_3 , and molecular sieves were dissolved in 1 mL of absolute acetonitrile under nitrogen and the mixture was stirred for 15 min. Afterwards, the iodoarene, Cs_2CO_3 , norbornene, alkyl halide, boronic acid, and DMPU (0.9 mL) were added and the mixture was heated to reflux for 20 h.

(17) Aryl bromides and triflates never lead to the desired product. This is consistent with the results of former investigations of the Lautens group (ref 3b).

Table 1. Scope of Para- and Meta-Substituted Iodoarenes

entry	R	product	yield [%] ^b
1	<i>p</i> -OMe	4a	89
2	<i>p</i> -NMeTs	4b	77
3	<i>p</i> -Me	4c	60
4	H	4d	64
5	<i>p</i> -Cl	4e	68
6	<i>p</i> -F	4f	64
7	<i>p</i> -CO ₂ Et	4g	58
8	<i>p</i> -CF ₃	4h	53 ^c
9	<i>p</i> -NO ₂	4i	51 ^{c,d}
10	<i>p</i> -OAc	4j	40 ^e
11	<i>m</i> -OMe	4k	59
12	<i>m</i> -Cl/ <i>p</i> -Cl	4l	40

^a See ref 13. ^b Isolated yield. ^c Reaction time: 48 h. ^d NMR yield. ^e Lower yield due to deacetylation.

Ortho-substituted iodoarenes as starting material gave rise to unsymmetrical, meta-substituted arenes (Table 2).¹⁸ Also, a variety of electron-donating and -withdrawing substituents are tolerated, but there is no correlation between electronic effects and yield.

Table 2. Scope of Ortho-Substituted Iodoarenes

entry	R	product	yield [%] ^b
1	OMe	15a	36
2	NMeTs	15b	71
3	Me	15c	84 ^c
4	<i>o</i> -Me/ <i>m</i> -Me	15d	75 ^c
5	naphtyl	15e	68
6	CF ₃	15f	82
7	CH ₂ OTBS	15g	89

^a See refs 13 and 17. ^b Isolated yield. ^c NMR yield.

For example, in contrast to the para-substituted arenes, electron-rich 2-iodoanisole gave the lowest yields (Table 2, entry 1), while electron-poor trifluoromethyl-substituted arene gave an excellent yield (Table 2, entry 6). The origin of these effects is not yet understood.

(18) In the case of the ortho-substituted iodoarenes 5 equiv of the alkyl halide was used since one ortho position is blocked.

The range of the primary alkyl halides that participate is quite broad, including both alkyl iodides and bromides with comparable reactivity (Table 3). Secondary alkyl halides are

Table 3. Scope of Alkyl Halides

entry	RI	product	yield [%] ^b
1	1-iodobutane	16a	84
2	1-iodo-2-methylpropane	16b	59
3	1-iodo-3-methylbutane	16c	78
4	<i>O</i> -TBS-3-iodo-1-propanol	16d	77
5	1-iodo-3-phenylpropane	16e	77
6	iodoethane	16f	75

^a See ref 13. ^b Isolated yield.

not reactive due to reduced rates in the ortho-alkylation step.¹⁹ Moreover, functionalized alkyl halides containing esters, alkanes, silyl ethers, and arenes are compatible with the reaction conditions. One noted limitation is the necessity of

at least three methylene units between the halide and the functional group.

In summary, we have shown that ortho-alkylation of iodoarenes followed by a C–H bond formation using a Catellani-type reaction is a viable method of synthesizing meta-substituted arenes containing diverse functionalities. We also demonstrated that alkyl halides can be used as hydride donors in palladium-catalyzed C–H bond formation. Utilization of this reaction in the preparation of bicyclic compounds is in progress.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(19) There are a few example using secondary alkyl halides by Catellani (ref 3b and 6a). However, under our conditions we never observed yields higher than 15%.