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A Rapid Approach to the Synthesis of Highly Functionalized Tetrahydroisoquinolines

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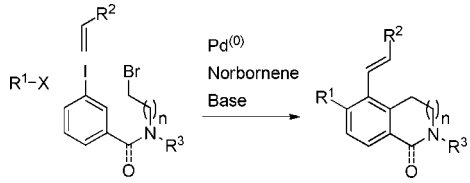
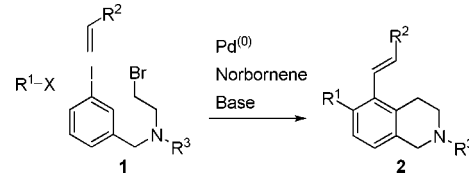


A palladium-catalyzed domino *ortho*-alkylation/alkenylation forming up to three new C−C bonds furnishes functionalized tetrahydroisoquinolines in up to 87% yield. Extension to the formation of tetrahydrobenzoazepines and tetrahydroisoquinolinones is presented.

Tetrahydroisoquinoline natural products[1] have been shown to exhibit biological activity, rendering them potential pharmaceutical agents.[2] Common routes to these compounds include cyclizations such as the Pictet−Spengler and the Bischler−Napieralski reactions.[3] Although metal-mediated and metal-catalyzed syntheses of these heterocycles are known,[4] very few methods allow for easy variation of the substituents present in the benzenoid ring of these compounds.[5] Due to our interest in developing novel routes to common heterocycles, we targeted the synthesis of variably substituted tetrahydroisoquinolines by a Pd-catalyzed, norbornene-mediated domino process which can form up to three carbon−carbon bonds in one synthetic sequence. In this manner, tetrahydroisoquinoline **2** could be formed from aryl derivative **1** by an intramolecular *ortho*-alkylation with a tethered alkyl halide, an intermolecular *ortho*-alkylation with an external alkyl halide, and a Heck reaction with an alkene (Scheme 1). Variants of **1** can be obtained through a short synthesis and all other reaction components are readily available.

SCHEME 1. Proposed Synthesis of Tetrahydroisoquinoline 2



In our previous studies, we have found that substrates with all-carbon tethers inhibit Pd-catalyzed intramolecular *ortho*-alkylations.[6] However, using an oxygen tether is feasible and leads to rapid syntheses of benzofurans, dibenzofurans, and dihydrochromenes[7] (Figure 1).

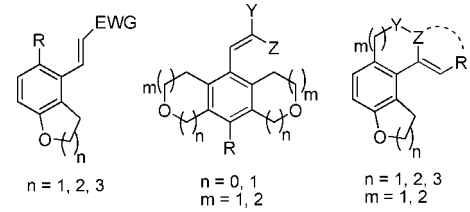


FIGURE 1. Synthesis of benzofurans, dibenzofurans, and dihydrochromenes.

Although benzylic ether substrates are successful, to the best of our knowledge, Pd-catalyzed *ortho*-alkylations with benzylic amine tethers have not been reported. Switching from a benzylic ether to a benzylic amine appeared to be a straightforward change, but obtaining appreciable yields of tetrahydroisoquinoline **2** proved to be challenging. The substituent on nitrogen was crucial, and the *N*-Ts-protected **1** proved most reliable. Other groups that were tested (Bn, PMB, Cbz, and CO_2Et) resulted in substrate decomposition. This may be due to the lone pairs on nitrogen displacing the halide and the resulting aziridinium ion failing to cyclize. Performing the reaction under microwave irradiation using standard conditions[7a,8] or with other ligand and catalyst combinations[9] resulted in no product. Optimizing using *N*-Ts-**1** from these standard conditions (Table 1, entry 1), independently lowering the amounts of Cs_2CO_3, *n*-butyl iodide, DME and *t*ert-butyl acrylate increased or had

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(8) Microwave irradiation was attempted using the conditions listed in Table 1, entry 1, at 190 °C for 5 min and 170 °C for 10 min, both of which gave messy reactions with unidentifiable products.

(9) Only $Pd(OAc)_2$ and $PdCl_2$ have been successful catalysts for our palladium-catalyzed, norbornene-mediated domino reactions, and the latter catalyst yielded no product. Only tri-2-furylphosphine and triphenylphosphine have been successful ligands, and the former yielded only traces of product.

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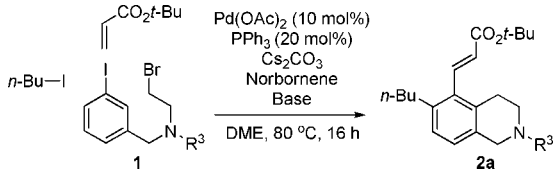
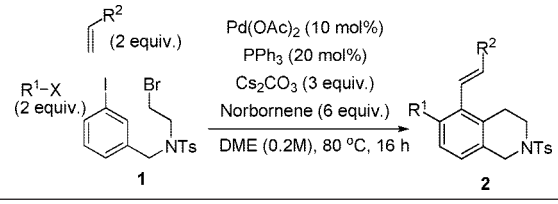
TABLE 1. Optimization[a] for Tetrahydroisoquinoline Product 2a



entry	Cs_2CO_3 (equiv)	DME (M)	*n*-BuI (equiv)	*tert*-butyl acrylate (equiv)	norbornene (equiv)	yield[b] (%)
1	5	0.1	10	5	11	–
2	3	0.1	10	5	5	10
3	5	0.1	10	2	5	17
4	5	0.2	10	5	5	19
5	5	0.1	10	5	6	37
6	5	0.1	2	5	5	44
7	3	0.2	2	2	6	46[c]

[a] All reactions conducted with $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Cs_2CO_3, *n*-BuI, *tert*-butyl acrylate, and norbornene in DME (amounts indicated) at 80 °C for 16 h. [b] ^1H NMR yields using mesitylene as an internal standard. [c] Isolated yield.

TABLE 2. Scope for Tetrahydroisoquinolines 2



entry	R^1X	R^2	product	yield[a] (%)
1	*n*-BuI	CO_2t-Bu	**2a**	46
2	*n*-BuI	C(O)NH*t*-Bu	**2b**	28
3	*n*-BuI	CN	**2c**	15[b]
4	methyl 4-bromobutyrate	CO_2t-Bu	**2d**	31
5	1-chloro-3-iodopropane	CO_2t-Bu	**2e**	38
6	2-methyl-1-iodopropane	CO_2t-Bu	**2f**	34

[a] Isolated yields. [b] Isolated with minor impurities.

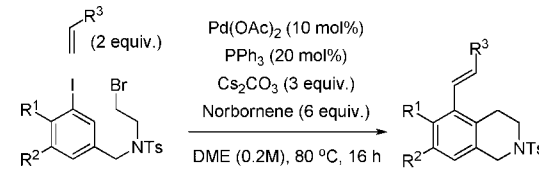
no effect on the yield of **2a** (entries 2, 3, 4 and 6). For an efficient reaction with minimal waste, we maintained the use of these lower amounts. However, a larger number of equivalents of norbornene was necessary (entry 5). Combining these independent variations gave us only 46% isolated yield (entry 7).[10] We tested the scope using our best conditions to determine how other substrates would behave (Table 2).

Methyl 4-bromobutyrate, 1-chloro-3-iodopropane, and 2-methyl-1-iodopropane are all successful *ortho*-alkylators, giving **2d**, **2e**, and **2f** in 31%, 38%, and 34% yields, respectively. Varying the Heck acceptor to *tert*-butyl acrylamide and acrylonitrile gave **2b** and **2c** in lower yields. While the overall yields are not ideal, the ease of introducing variations at two positions offers some appeal for parallel synthesis.

Since having two sites for *ortho*-alkylation can lead to selectivity issues, we speculated that eliminating the intermolecular *ortho*-alkylation would simplify the process and produce a cleaner reaction. Thus, we synthesized *ortho*-blocked substrate **4** and subjected it to our optimal conditions.[11]

We were pleased to observe the formation of tetrahydroisoquinoline **5a** in 70% yield (Table 3, entry 1). The Heck acceptor

TABLE 3. Scope for *Ortho*-Blocked Tetrahydroisoquinolines 5

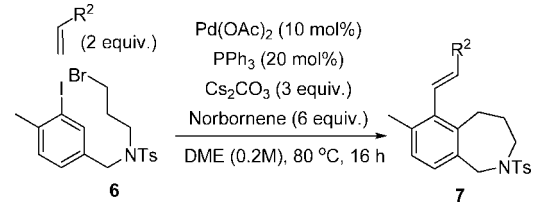


4a (R^1 = Me, R^2 = H)
4b (R^1 = OMe, R^2 = H)
4c (R^1 = OMe, R^2 = OMe)
4d (R^1 = Cl, R^2 = H)

entry	substrate	R^3	product	yield[a] (%)
1	**4a**	CO_2-*t*-Bu	**5a**	70
2	**4a**	CO_2Et	**5b**	73
3	**4a**	CO_2Me	**5c**	74
4	**4a**	CN	**5d**	30
5	**4a**	C(O)NH-*t*-Bu	**5e**	87
6	**4a**	2-pyridine	**5f**	45
7	**4a**	C(O)Me	**5g**	63
8	**4a**	phenyl	**5h**	–
9	**4a**	*p*-MeO-phenyl	**5i**	–
10	**4b**	CO_2-*t*-Bu	**5j**	75
11	**4c**	CO_2-*t*-Bu	**5k**	50
12	**4d**	CO_2-*t*-Bu	**5l**	30

[a] Isolated yields.

TABLE 4. Scope for *Ortho*-Blocked Tetrahydrobenzoazepines 7



entry	R^2	product	yield[a] (%)
1	CO-$_2t$-Bu	**7a**	47
2	C(O)NH-*t*-Bu	**7b**	38
3	C(O)Me	**7c**	59

[a] Isolated yields.

could be varied from *tert*-butyl acrylate to ethyl and methyl acrylate giving greater than 70% yields (entries 2 and 3). Use of acrylonitrile resulted in modest yield (entry 4), while *N*-*t*-Bu-acrylamide gave an excellent 87% yield (entry 5). The presence of an electron-withdrawing group on the alkene appears crucial since styrene and *p*-methoxystyrene failed to give the desired products (entries 8 and 9). Other groups such as methoxy and chloro can serve as *ortho*-position blockers. Products **5j** and **5k** are formed in good yields, though **5l**, containing an *o*-chloro group, was lower yielding.

To expand the scope of this methodology we have shown that larger ring sizes can also be formed (Table 4). The yields for these reactions are reduced compared to those of the corresponding tetrahydroisoquinolines, perhaps because the intramolecular *ortho*-alkylation requires the formation of a seven-membered ring. Nevertheless, this approach rapidly forms substituted tetrahydrobenzoazepines, another important pharmaceutical scaffold.[12]

(10) A major byproduct is the *ortho*-alkylation/halogen reduction product that presumably forms from palladium oxidatively inserting into the alkyl halide followed by β-hydride elimination. For more on this reaction, see ref 17.

(11) Compound **1** was not tried under these conditions.

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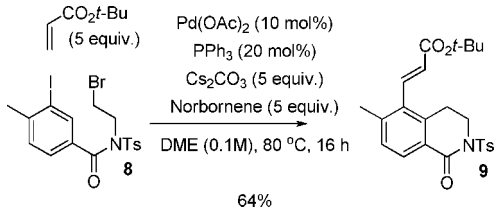
SCHEME 2. Extension to Tetrahydroisoquinolinones



Tetrahydroisoquinolinones are also common motifs among pharmaceuticals.[13] Functionalized derivatives of these heterocycles are usually synthesized through stepwise sequences, though palladium-catalyzed domino processes involving aldol-type condensations or carbonylations yielding ring-fused or substituted isoquinolinones were recently reported by Alper[14] and Daïch.[15] Using the present methodology, substituted tetrahydroisoquinolinone **9** can be synthesized from precursor **8** in 64% yield (Scheme 2). Compared to the tetrahydroisoquinolines, a lower concentration and amount of norbornene but a higher amount of base and Heck acceptor are required for a higher yield.

A proposed mechanism is presented in Figure 2.[16] Pd(0) inserts into the C−I bond of **1**, followed by carbopalladation with norbornene to give **10a**. C−H activation of an *ortho* C−H bond forms **10b**. Oxidative addition of the tethered alkyl bromide chain leads to the Pd(IV) species **10c**, and reductive elimination generates **10d**. This process then occurs for the other *ortho* C−H bond with an external alkyl halide to give complex **10e**. Alternatively, intermolecular *ortho*-alkylation can happen before intramolecular *ortho*-alkylation; at this time, we do not know which process occurs first. Extrusion of norbornene, presumably due to unfavorable steric interactions with the neighboring *ortho* groups, gives the 2,4-dialkylated Pd(II) complex **10f**. The reduced form of **10f**, resulting from an intramolecular *ortho*-alkylation followed by a reduction to a C−H bond, has been observed as a byproduct of these reactions.[17] Finally, a Heck termination with **10f** yields product **2**. We believe an excess of norbornene is needed to compete with the direct Heck pathway.

In conclusion, we present a new and concise route to substituted tetrahydroisoquinolines by a palladium-catalyzed, norbornene-mediated domino reaction. Though up to three C−C bonds can be formed in one pot, the reaction proceeds in higher yields by the presence of an *ortho*-blocking group. The methodology was successfully extended to the formation of tetrahydrobenzoazepines and tetrahydroisoquinolones, two other pharmaceutically important motifs.

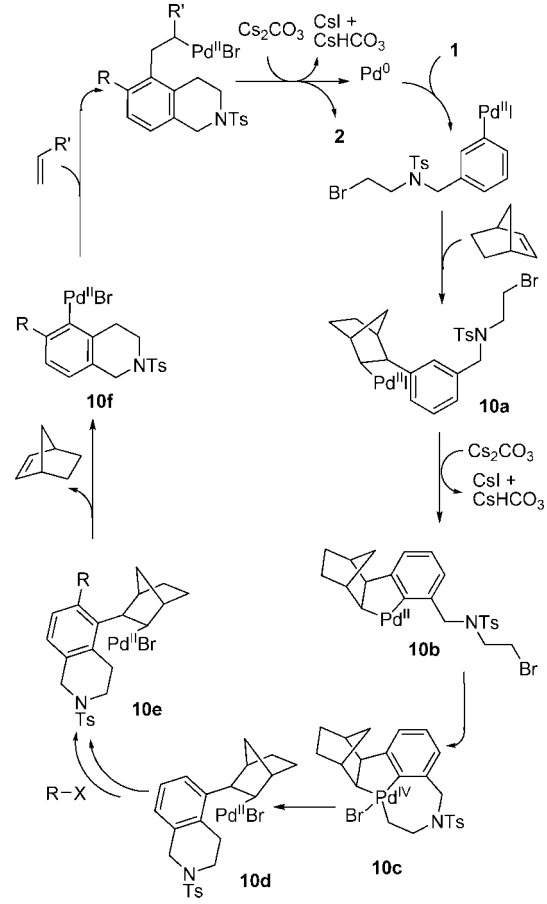


FIGURE 2. Proposed mechanism for the formation of **2**.

Experimental Section

General Procedure for the Synthesis of Tetrahydroisoquinolines. To a 5 mL microwave vessel with a magnetic stir bar were added **1** (99 mg, 0.2 mmol), Cs_2CO_3 (195.5 mg, 0.6 mmol), PPh_3 (10.5 mg, 0.04 mmol), norbornene (113 mg, 1.2 mmol), $Pd(OAc)_2$ (4.50 mg, 0.02 mmol), alkyl iodide (0.4 mmol), and alkene (0.4 mmol). The tube was sealed and flushed with argon, and dry, degassed DME (1 mL) was added. The reaction was stirred at 80 °C for 16 h and then cooled to room temperature, diluted with ether (1 mL), quenched with water (1 mL), and extracted with ether (3×) and brine. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude material. Purification by column chromatography (pentanes/ethyl acetate) gave the pure compounds.

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

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