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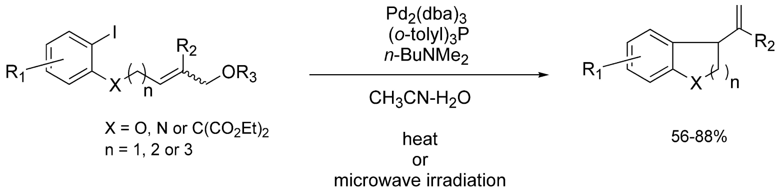

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Palladium-Catalyzed Intramolecular Coupling between Aryl Iodides and Allyl Moieties via Thermal and Microwave-Assisted Conditions

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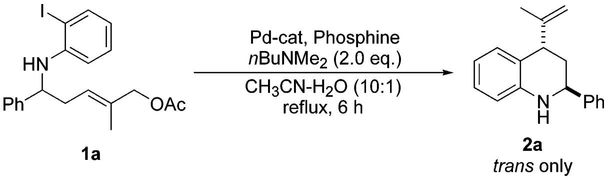
Palladium-catalyzed cross-coupling reactions are valuable processes in organic synthesis. Many reactions have been developed and applied to natural products syntheses, including Heck, Stille, and Suzuki coupling processes and nucleophilic addition to π-allyl palladium intermediates.[1] Despite immense progress, coupling between an aryl halide and an allyl moiety has not been well developed. Until now, this coupling reaction has needed stoichiometric amounts or excess of metal reagents such as hexa-*n*-butylditin,[2] (tri-*n*-butylstannyl)diethylalane,[3] zinc metal,[4] or indium metal[5] to generate an organometallic reagent *in situ* as a nucleophile, which reacts with a palladium(II) intermediate. More recently, cobalt-catalyzed cross-coupling reactions between an aryl halide and an allyl ester have been reported; however, these methods required a large excess of metal reagents[6a] or use of electrochemical reactions.[6b] Herein, we report on palladium-catalyzed intramolecular cross-coupling reactions between an aryl iodide and an allyl moiety, leading to 2,4-disubstituted 1,2,3,4-tetrahydroquinoline[7,8] **2** under conventional thermal conditions as well as to various carbo- and heterocycles **6** under microwave irradiation. This is a rare example of a palladium-catalyzed direct cross-coupling reaction between an aryl halide and an allyl acetate or carbonate.[9]

Preparation of allyl acetates **1a**−**h** was easily achieved in three steps by our recently reported method[10] (direct vinylogous Mannich-type reaction) in excellent yields.

Following optimization studies, we determined that a mixture of **1a**, $Pd_2(dba)_3 \cdot HCCl_3$, tri-*o*-tolylphosphine, and *N*,*N*-dimethylbutylamine in $CH_3CN{-}H_2O$ at reflux promotes coupling to yield the cyclization product **2a** in 76% yield as the *trans* isomer[11] (Table 1, entry 1).

Changing the palladium catalysts and phosphine ligands to Pd(OAc)$_2$-(*o*-tolyl)$_3$P or PdCl$_2$[(*o*-tolyl)$_3$P]$_2$ gave similar results (entries 2 and 3). The use of Pd(PPh$_3$)$_4$ and Pd$_2$(dba)$_3$−PPh$_3$ resulted in almost no reaction (entries 4 and 5). Only (*o*-tolyl)$_3$P gave good yields among the common phosphine ligands; for example, a bidentate ligand, 1,2-bis(diphenylphosphino)ethane (dppe), gave only 19% yield (entry 6). In the absence of H_2O, the reaction yield was ca. 30% with the formation of Pd-black and recovery of starting material. A tertiary alkylamine was used to regenerate the palladium(0) catalyst; *N*,*N*-dimethylbutylamine gave the best result among the common organic bases.[12] Inorganic bases resulted in very low yields. Cyclization of an aryl bromide or aryl triflate with allyl acetate did not give the product.

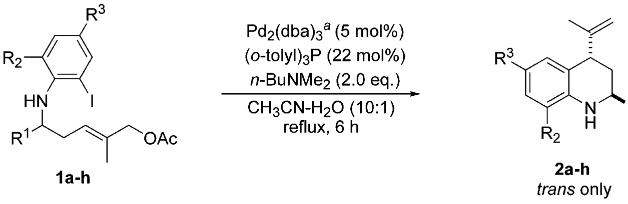
Table 1. Effects of Palladium Catalysts and Phosphine Ligands in Palladium-Catalyzed Intramolecular Cyclization



entry	Pd catalyst (mol %)	phosphine (mol %)	yield[a] (%)
1	Pd$_2$(dba)$_3$[b] (5)	(*o*-tolyl)$_3$P (22)	76
2	Pd(OAc)$_2$ (10)	(*o*-tolyl)$_3$P (22)	69
3	PdCl$_2$[(*o*-tolyl)$_3$P]$_2$ (10)		75
4	Pd(PPh$_3$)$_4$ (10)		<1[c]
5	Pd$_2$(dba)$_3$[b] (5)	Ph$_3$P (22)	2
6	Pd$_2$(dba)$_3$[b] (5)	dppe (11)	19

[a] Isolated yields. [b] $CHCl_3$ adduct was used. [c] **1a** was recovered in 58% yield.

Table 2. Intramolecular Palladium Catalyzed Cross-Coupling Reactions between an Aryl Iodide and Allyl Acetate



entry	R^1	R^2	R^3		yield[b] (%)
1	Ph	H	H	**a**	76
2	4-Me-Ph	H	H	**b**	80
3	4-Cl-Ph	H	H	**c**	81
4	4-Br-Ph	H	H	**d**	73
5	Ph	Me	Me	**e**	79
6	Ph	H	Cl	**f**	88
7	Ph	OMe	H	**g**	77
8	COO-*c*-Hex	Me	Me	**h**	84[c]

[a] $CHCl_3$ adduct was used. [b] Isolated yields. [c] Cis isomer was isolated in 2% yield.

This palladium-catalyzed cyclization is general for a range of substrates (Table 2). At the R^1 position, 4-methylphenyl and 4-chlorophenyl (entries 2 and 3) gave the corresponding 2,4-disubstituted 1,2,3,4-tetrahydroquinolines in good yields, and 4-bromophenyl (entry 4) reacted selectively at the C−I bond. At the R^2 and R^3 positions, dimethyl (entry 5), chloro (entry 6), and methoxy (entry 7) substituents can be introduced on the quinoline. Regardless of the electronic characteristic of the substrate, 2,4-disubstituted 1,2,3,4-tetrahydroquinolines **2e**−**g** were obtained in approximately 80% yields. We further applied the intramolecular cross-coupling reaction to the construction of a 2-quinolinic acid ester. Indeed, **1h** cyclized to give the 1,2,3,4-tetrahydro-2-quinolinic acid ester **2h** in 84% yield (entry 8) with a trace of the *cis* isomer (2% yield).

We decided to study the effect of the ring size as well as the nature of the atom connecting the aryl and allyl moieties (X = O, N, and C, Table 3) on the reactivity of the cross-coupling process. Preparation of five-membered-ring precursors **3a**−**e** was achieved in one step by the reaction of the corresponding iodinated derivatives[13] with (*Z*)-$BrCH_2CH{=}CHCH_2OCO_2Et$.[14] The six- and seven-membered ring precursors **4a**−**d** were easily prepared in four

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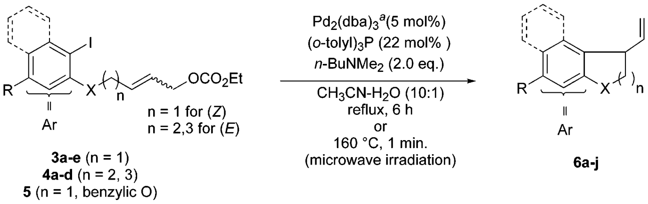
Table 3. Effects of Microwave Irradiation and Ring Size on the Formation of Various Carbo- and Heterocycles via Palladium-Catalyzed Intramolecular Cyclization



3a-e (n = 1)
4a-d (n = 2, 3)
5 (n = 1, benzylic O)

6a-j

						yield^b (%)	
entry	*n*	X	R	Ar		mw^c	ct^d
1	1	O	H	Naph	**a**	56	33
2	1	O	CF$_3$	Ph	**b**	61	20
3	1	O	CO$_2$Me	Ph	**c**	66	36
4	1	NTs	H	Ph	**d**	74	74
5	1	C(CO$_2$Et)$_2$	H	Ph	**e**	67	
6	2	O	H	Naph	**f**	62	46
7	3	O	H	Naph	**g**	72	49
8	3	NTs	H	Ph	**h**	65	
9	3	C(CO$_2$Et)$_2$	H	Ph	**i**	73	
10	1	CH$_2$O	H	Ph	**j**		45

[a] CHCl$_3$ adduct was used. [b] Isolated yields. [c] Microwave-assisted conditions. [d] Conventional thermal conditions. Ph = phenyl, Naph = Naphthyl.

steps from the same iodinated aromatic derivatives.[15] The benzylic oxygen-containing substrate **5** was prepared from the 2-iodobenzylic alcohol following a procedure similar to the one used for the preparation of five-membered-ring precursors.[15]

Oxygen-containing substrates **3a**−**c** gave the cyclized products **6a**−**c** in poor yields (Table 3, entries 1−3), probably due to the competitive formation of the π-allyl complex that generates the corresponding phenol. In an effort to improve these yields, we subjected the reaction to microwave irradiation, which is known to accelerate transition-metal-catalyzed homogeneous reactions.[16] Carrying out the reaction in the microwave at 160 °C for 1 min was found to improve the yield in each case (entries 1−3) by as much as 41% for **6b** (entry 2). According to this procedure, five-membered rings **6a**−**e** (entries 1−5) as well as six- and seven-membered rings **6f**−**j** (entries 6−10) were efficiently formed. Variation of the X group did not affect the cross-coupling process since nitrogen- and carbon-containing cycles, **6d**,**h** and **6e**,**i**, respectively (entries 4, 8 and 5, 9), were obtained in good yields. The cyclization also proceeded with a benzylic oxygen-containing substrate to form the six-membered heterocycle **6j** (entry 10). We found that the yields increased as the ring size increased from five to seven (**6a**,**f**,**g**, entries 1, 6, and 7).

In conclusion, palladium-catalyzed intramolecular cross-coupling reactions between aryl iodides and allyl moieties were successfully demonstrated. We describe a new rapid synthetic approach to a variety of *trans*-2,4-disubstituted 1,2,3,4-tetrahydroquinolines **2** with excellent diastereoselectivities as well as to various five- to seven-membered carbo- and heterocycles **6** *via* conventional thermal and microwave-assisted conditions. We are currently investigating the mechanism of the reaction but believe the role of the amine base is to reduce Pd(II) back to Pd(0) after each catalytic cycle.

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Supporting Information Available: Experimental procedures, spectroscopic characterization of substrates and products, and determination of configuration. This material is available free of charge via the Internet at http://pubs.acs.org.

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