A New Route to Fused Aromatic Compounds by Using a Palladium-Catalyzed Alkylation–Alkenylation Sequence[**]

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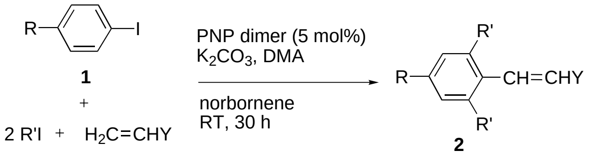
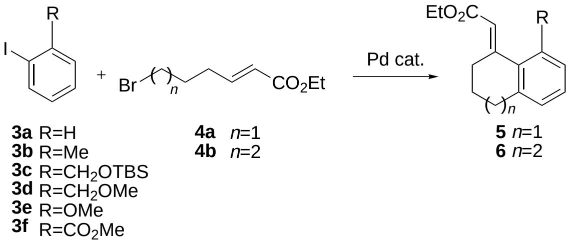
Selective aromatic substitution is a long-standing goal in organic chemistry.[1] Recently, a new method involving a palladium-catalyzed process based on a sequential double aromatic substitution and an intermolecular Heck reaction leading to *o*,*o*′-disubstituted vinylarenes **2** was described (Scheme 1).[2] The potential of this strategy is truly remarkable since it allows the formation of three new carbon–carbon bonds in a one-pot process.



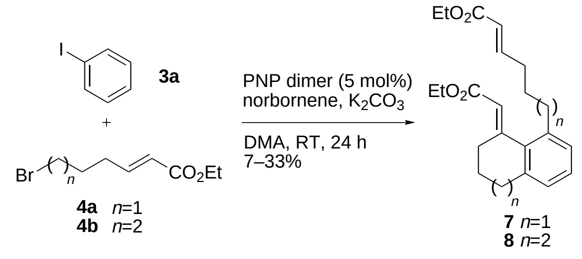
Scheme 1. Palladium-catalyzed synthesis of *O*,*O*′-dialkylvinylarenes. DMA = *N*,*N*-dimethylacetamide; PNP dimer = *cis*,*exo*-2-phenylnorbornylpalladium chloride.[3]

With the goal of synthesizing various fused carbocycles, we sought to extend and modify this domino sequence by using a difunctional acceptor so that an intramolecular Heck reaction can follow the *o*-alkylation, resulting in a new route to fused aromatic compounds starting from iodoaryl compounds (Scheme 2).[4] Herein, we report our first results for the synthesis of benzocarbocycles with six- and seven-membered rings.



Scheme 2. Palladium-catalyzed synthesis of various carbocycles. TBS = *tert*-butyldimethylsilyl.

In our initial studies we used iodobenzene (**3a**) and ethyl (*E*)-6-bromohex-2-enoate (**4a**) as starting materials.[5] By using the procedure described by Catellani and co-workers,[2] the six-membered-ring compound **7** was isolated in a yield ranging from 7 to 33% as a single stereoisomer. This palladium-catalyzed process involved the formation of three new carbon–carbon bonds in one pot through a double aromatic substitution in the *ortho*- and *ortho*′-positions followed by an intramolecular Heck reaction (Scheme 3). However, poor yields and irreproducible results were obtained largely because of variability in the activity of the catalyst.



Scheme 3. Synthesis of carbocycles with six- and seven-membered rings from iodobenzene (**3a**).

It was necessary to find improved conditions, and toward this end ligand effects as well as different palladium sources and solvents were examined. The reaction of iodobenzene (**3a**) with ethyl (*E*)-6-bromohex-2-enoate (**4a**) served as a model for these studies. Among the different phosphanes and palladium sources we tried, tri-2-furylphosphane and $Pd(OAc)_2$ afforded the most encouraging results; the bicyclic compound **7** was obtained in 24% yield as a single stereoisomer and in reproducible yield (Scheme 3).[6] Other catalysts such as $[Pd(PPh_3)_4]$, $[Pd(dppf)Cl_2]$/HgCl (dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, $[Pd_2(dba)_3]$ (dba = *trans*,*trans*-dibenzylideneacetone, $Pd(OAc)_2/PPh_3$, $Pd(OAc)_2/PnBu_3$, $Pd(OAc)_2$/tri-*o*-tolylphosphane, and $Pd(OAc)_2/P(OMe)_3$ either promoted no reaction or gave only traces of the expected compound.[7] An investigation of different solvents revealed that acetonitrile was the solvent of choice. Under the same conditions, the yield increased from 24% in DMA to 43% in refluxing MeCN whereas, in other solvents (CH_2Cl_2, THF, toluene) only traces of **7** were isolated.

We next investigated the scope of the reaction using *ortho*-substituted aryl iodides since the resulting products are of much broader interest. Under the optimized conditions ($Pd(OAc)_2$ (10 mol%), tri-2-furylphosphane (20 mol%), norbornene (2 equiv), K_2CO_3 (2 equiv), MeCN, reflux), we could effect the palladium-catalyzed reaction of a wide array of *ortho*-substituted aryl iodides with **4a** ($n = 1$) and ethyl (*E*)-7-bromohept-2-enoate (**4b**; $n = 2$) leading to carbocycles with six- and seven-membered rings, respectively, in moderate to excellent yields (Scheme 2, Table 1).[8] The overall sequence with *ortho*-substituted aryl iodides involves one aromatic substitution in the *ortho*′-position followed by an intramolecular Heck reaction. Therefore, two new carbon–carbon bonds were formed in a one-pot reaction and the bicyclic compounds were isolated as single *E*-configured stereoisomers as determined by NOE experiments.

The yield of the reaction is strongly influenced by the *ortho*-alkyl substituent R. In fact, when R = alkyl, the reaction is very efficient and the six- and seven-membered rings were isolated in 85 and 62% yield, respectively (entry 1, Table 1).

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Table 1. Effects of *ortho*-substitution and bases on the yield of the reaction shown in Scheme 2.[a]

Entry	R	*n*	K_2CO_3 Yield [%][b]	Cs_2CO_3 Yield [%][b]
1	Me	1	85	90
		2	62	83
2	CH_2OTBS	1	41	60
		2	33	47
3	CH_2OMe	1	20	35
		2	6	25
4	OMe	1	29	26
		2	41	93
5	CO_2Me	1	–[c]	–[c]
		2	–[c]	–[c]

[a] Conditions (optimized): $Pd(OAc)_2$ (10 mol%), tri-2-furylphosphane (20 mol%), norbornene (2 equiv), K_2CO_3 (2 equiv), MeCN, reflux, 12 h. [b] Yield of isolated product. [c] No reaction.

With an electron-withdrawing group (entry 5), no reaction occurred and with an electron-donating group (entry 4), the yield was moderate. When R = CH_2OTBS, the yields were moderate, however, when the silyl group was replaced by a methyl group, the yield was even lower (entries 2 and 3). This lack of reactivity might be explained by a complexation between the oxygen atom and the palladium center, which renders the palladium catalyst unavailable for further reaction. We suppose that this phenomenon is minimized in the case of R = CH_2OTBS because of the steric bulk of the silyl group.

It is also known that some other parameters (such as bases or additives) might influence the yield.[9, 10] Therefore, we surveyed a few bases to optimize the reaction. The same transformation could now be achieved in higher yields by using Cs_2CO_3 instead of K_2CO_3 (Table 1). In both cases ($n = 1$, 2), excellent yields were obtained when R = alkyl (entry 1). Although the yield was still low when R = CH_2OMe, it was improved from 20 to 35% for the six-membered-ring carbocycle and from 6 to 25% for the seven-membered-ring carbocycle (entry 3). This poor yield was due to dimerization of the iodo compound, a pathway we had not previously observed.[11, 12] When R = OMe, the yield increased to 93% for the formation of the seven-membered-ring carbocycle. As before, no reaction occurred when there was an electron-withdrawing substituent on the iodoaryl compound. The difference in reactivity between Cs_2CO_3 and K_2CO_3 might be explained by the better solubility of Cs_2CO_3.

Finally, under our best conditions ($Pd(OAc)_2$ (10 mol%), tri-2-furylphosphane (20 mol%), norbornene (2 equiv), Cs_2CO_3 (2 equiv), MeCN, reflux), the sequence of double aromatic substitution and intramolecular Heck reaction was carried out with iodobenzene (**3a**) and **4a** or **4b** and provided compounds **7** and **8** as single stereoisomers in 59 ($n = 1$) and 64% ($n = 2$) yield, respectively (Scheme 3).

We have developed a new approach for the synthesis of carbocycles, which proceeds by a palladium-catalyzed process based on a sequential aromatic substitution and intramolecular Heck reaction of iodoaryl compounds and involves the formation of at least two new carbon–carbon bonds. Under optimized conditions we can accomplish the sequence with a variety of iodoaryl substrates that have different chain lengths of the alkenyl group, leading to six- and seven-membered-ring carbocycles as single stereoisomers. Application of these methods to the synthesis of five-membered rings and heterocyclic compounds is currently in progress in our laboratory.

Experimental Section

The general procedure is described for the case of 2-iodotoluene and ethyl (*E*)-6-bromohex-2-enoate. Under argon, a flame-dried round-bottom flask equipped with a condenser was charged with 2-iodotoluene (20 μL, 0.157 mmol), ethyl (*E*)-6-bromohex-2-enoate (138 mg, 0.624 mmol), Cs_2CO_3 (105 mg, 0.322 mmol), norbornene (30.2 mg, 0.32 mmol), tri-2-furylphosphane (7.5 mg, 0.032 mmol), $Pd(OAc)_2$ (4 mg, 0.017 mmol), and acetonitrile (1.5 mL). The reaction mixture was heated under reflux for 12 h and then quenched with a saturated aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent and flash chromatography on silica gel of the residue with 1–3% diethyl ether in hexanes afforded the six-membered-ring compound **5b** (32.6 mg, 90%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.1$ (m, 2H; =CH(Ar)), 6.9 (m, 1H; =CH(Ar)), 5.9 (t, $^3J = 2$ Hz, 1H; $=CHCO_2Et$), 4.2 (q, $^2J = 7.2$ Hz, 2H; OCH_2), 3.1 (td, $^2J = 7$ Hz, $^3J = 2$ Hz, 2H; CH_2), 2.6 (br t, $^2J = 6.1$ Hz, 2H; CH_2), 2.47 (s, 3H; CH_3), 1.7 (m, 2H; CH_2), 1.31 (t, $^2J = 7.2$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 166.9$, 154.7, 141.8, 136.3, 134.9, 129.5, 127.8, 125.2, 118.2, 59.7, 30.2, 28.2, 21.7, 21.6, 14.3; MS (EI, 70 eV): *m*/*z* (%): 185 (100) $[M^+ - EtO]$. HR-MS: calcd for $C_{15}H_{18}O_2$ $[M]^+$: 230.1311; found: 230.1306.

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[6] The reaction was run with tri-2-furylphosphane (20 mol%) and $Pd(OAc)_2$ (10 mol%) in the presence of norbornene (2 equiv) and K_2CO_3 (2 equiv) in DMA at room temperature.

[7] No by-products were isolated.

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[11] The dimerization of the iodo compound affords the six-membered-ring carbocycle in 50% yield and the seven-membered-ring carbocycle in 60% yield..

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