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Highly Selective Palladium-Catalyzed Heck Reactions of Aryl Bromides with Cycloalkenes

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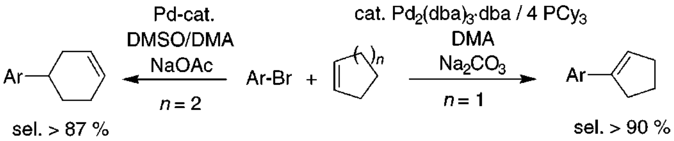
ABSTRACT



The influence of palladium catalysts and reaction conditions on the selectivity of Heck reactions of aryl bromides with cyclohexene and cyclopentene has been investigated. It is shown that the addition of DMSO as a cosolvent leads to improved selectivities of nonconjugated aryl olefins. On the other hand, high selectivities for conjugated arylcyclopentenes have been obtained with the catalytic system DMA/Na_2CO_3/$Pd_2(dba)_3$·dba/PCy_3.

The palladium-catalyzed arylation and vinylation of alkenes (Heck reaction) has become one of the most important and powerful transition-metal-catalyzed transformations in organic synthesis for generating new carbon−carbon bonds.[1] Nevertheless, the control of selectivity in Heck reactions still causes problems; e.g., the coupling of aliphatic (e.g. 1-hexene), 1,1-disubstituted, or cyclic olefins often generates a mixture of double-bond regioisomers. As an example, the intermolecular Heck reaction of cyclic alkenes with aryl bromides does not yield one specific double-bond regioisomer by using standard reaction conditions (125 °C, polar aprotic solvent, NaOAc or NR_3, PdX_2/PAr_3).[2] In addition, in most cases the Heck reaction of aryl halides and cycloalkenes proceeds extremely slowly, and thus only low yields of product are obtained.[1c,3] Although aryl iodides or triflates and aryl diazonium salts can be coupled with cycloalkenes more efficiently,[3,4] the reactions of economically more attractive aryl bromides with cycloalkenes require elevated temperatures (>80 °C) and give isomeric mixtures. In this paper a new procedure for the selective coupling of

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Table 1. Heck Reaction of Cyclohexene with Aryl Bromides[8]

entry	R	solvent[a]	base	catalyst	n-Bu$_4$NBr (mol %)[b]	conversn (%)[c]	yield (%)[c]	**4**:**5**:**6**[d]
1	4-COCH$_3$	DMA	NaOAc	Pd(OAc)$_2$/2 PPh$_3$[e]		96	78	4:17:79
2	4-COCH$_3$	DMA	NaOAc	palladacycle **3**[e]		>99	89	7:15:78
3	4-COCH$_3$	DMA	NaOAc	Pd$_2$(dba)$_3$·dba/4 PCy$_3$[e]		94	75	6:16:78
4	4-COCH$_3$	DMA	Na$_2$CO$_3$	Pd$_2$(dba)$_3$·dba/4 PCy$_3$[e]		15	12	7:24:69
5[f]	4-COCH$_3$	TMSO[g]	NaOAc	Pd(OAc)$_2$/2 PPh$_3$[e]		39	31	2:9:89
6	4-COCH$_3$	DMSO	NaOAc	Pd(OAc)$_2$/2 PPh$_3$[e]		48	36	2:11:87
7	4-COCH$_3$	DMSO/DMA	NaOAc	Pd(OAc)$_2$/2 PPh$_3$[e]		59	49	2:8:90
8	4-COCH$_3$	DMSO/DMA	NaOAc	Pd(OAc)$_2$/2 PPh$_3$[e]	50	98	82	3:9:88
9	4-COCH$_3$	DMA	EtN(^{i}Pr)$_2$[h]	Pd(OAc)$_2$/2 PPh$_3$[e]		63[i]	48	1:33:66
10[j]	3-CF$_3$	DMA	NaOAc	Pd(OAc)$_2$/2 PPh$_3$[e]		67	59	15:16:69
11[j]	3-CF$_3$	DMSO/DMA	NaOAc	Pd(OAc)$_2$/2 PPh$_3$[e]	30	56	48	1:9:90
12[j]	H	DMA	NaOAc	palladacycle **3**[e]		64	54	6:18:76
13[j]	H	DMSO/DMA	NaOAc	palladacycle **3**[k]	30	73	67	1:12:87
14[j]	4-OCH$_3$	DMA	NaOAc	palladacycle **3**[e]		30	27	2:20:78
15[j]	4-OCH$_3$	DMSO/DMA	NaOAc	palladacycle **3**[k]	30	48	46	1:12:87

[a] DMSO/DMA = 1:4. [b] mol % n-Bu$_4$NBr refers to aryl bromide. [c] Conversions and yields were determined by GC with internal standard (diethylene glycol di-n-butyl ether). [d] Selectivities were determined by GC on the basis of area percentage. [e] 0.1 mol % Pd. [f] 130 °C. [g] Tetramethylene sulfoxide. [h] 2 equiv of base. [i] Side product: 7% acetophenone. [j] 150 °C. [k] 1 mol % Pd.

aryl bromides with cyclic olefins via the Heck reaction is presented. The coupling reaction of 4-bromoacetophenone with cyclohexene **2** (known to be a "difficult" substrate for Heck reactions) served as a model reaction to develop improved catalysts. Under standard conditions (DMA (*N*,*N*-dimethylacetamide), NaOAc, 0.1 mol % Pd(OAc)$_2$/2 PPh$_3$, 140 °C, 20 h) only a mixture of double-bond isomers **4**−**6** (4:17:79)[5] was obtained with a conversion of 96% and a yield of aryl olefins of 78%.[6] The difference between the conversion and yield is mainly due to the formation of double-arylated products. In addition, 4,4'-diacetylbiphenyl and acetophenone were observed as side products.

We assumed that the selectivity of the coupling reaction, leading to **4**−**6**, might be influenced by the added base.[7] Indeed, experiments with isolated Heck products (mixture of isomers **4**−**6**) showed that double-bond migration is catalyzed slowly by base and not by a HPdX complex. To improve the selectivity of the arylation of cyclohexene, various palladium catalysts as well as different bases and solvents were applied to this reaction.[8] As shown in Table 1, the choice of solvent and base has an important influence on the extent of C−C double-bond migration; in contrast, different catalysts showed no significant changes in selectivity (Table 1, entries 1−3). Predominantly, by using inorganic bases (e.g. NaOAc) the 4-(aryl)cyclohexene derivative **6** was produced in high yields. By using dimethyl sulfoxide or tetramethylene sulfoxide as solvents, product **6** could be obtained with increased selectivity up to **4**:**5**:**6** = 2:9:89 (entries 5 and 6). Unfortunately, the coordination of the sulfoxide to the metal resulted in a lower reaction rate compared to DMA as the solvent. However, the use of DMSO as cosolvent in combination with DMA in the presence of n-Bu$_4$NBr leads to both high conversion and high selectivity (entry 8). Due to the limited ability to solubilize inorganic bases, nonpolar solvents such as toluene gave very low yields of products. When soluble amines were used as the bases, relatively high amounts of product **5** were observed (entry 9). This observation is explained by a faster HX elimination in the presence of amines.[7] To investigate the scope of the DMSO/DMA system, different aryl bromides were reacted with cyclohexene (Scheme 1, Table 1). In all cases, even for nonactivated or deactivated aryl bromides, improved selectivities for the 4-(aryl)cyclohexene were observed using a mixture of DMSO and DMA. Although electron-donating substituents on the aryl bromide cause a

Scheme 1

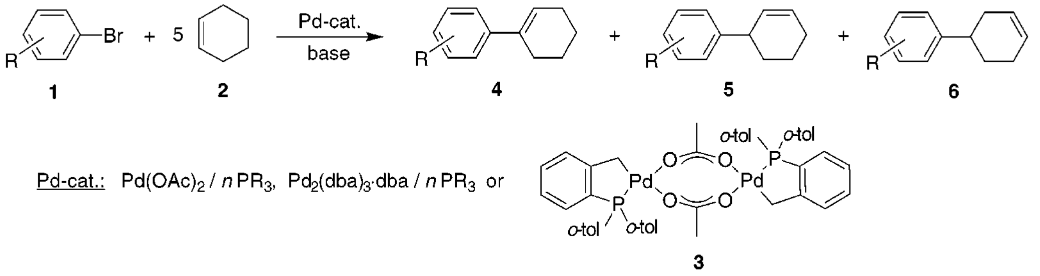


Table 2. Heck Reaction of Cyclopentene with Aryl Bromides[8]

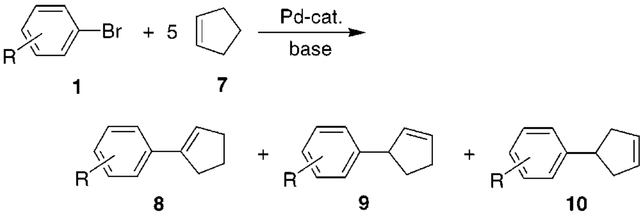
entry	R	base	catalyst[a]	conversn (%)[b]	yield (%)[b]	**8**:**9**:**10**[c]
1[d]	4-$COCH_3$	NaOAc	$Pd(OAc)_2$/2 PPh_3	>99	94	17:72:11
2[e]	4-$COCH_3$	NaOAc	$Pd(OAc)_2$/2 PPh_3	>99	95	11:78:11
3[d]	4-$COCH_3$	NaOAc	$Pd_2(dba)_3$·dba/4 PCy_3	>99	98	39:45:16
4[d]	4-$COCH_3$	Na_2CO_3	$Pd(OAc)_2$/2 PPh_3	>99	98	83:13:4
5[d]	4-$COCH_3$	Na_2CO_3	$Pd_2(dba)_3$·dba/4 PCy_3	>99	>99	91:7:2
6[d]	3-CF_3	NaOAc	$Pd(OAc)_2$/2 PPh_3	98	92	7:82:11
7[d]	3-CF_3	Na_2CO_3	$Pd_2(dba)_3$·dba/4 PCy_3	>99	99	90:9:1
8[d]	H	NaOAc	$Pd(OAc)_2$/2 PPh_3	92	90	7:83:10
9[d]	H	Na_2CO_3	$Pd_2(dba)_3$·dba/4 PCy_3	>99	>99	92:7:1
10[d]	4-OCH_3	NaOAc	$Pd(OAc)_2$/2 PPh_3	39	36	7:80:13
11[d]	4-OCH_3	Na_2CO_3	$Pd_2(dba)_3$·dba/4 PCy_3	93	92	92:7:1

[a] 0.1 mol % Pd refers to the aryl bromide. [b] Conversions and yields were determined by GC with internal standard (diethylene glycol di-*n*-butyl ether). [c] Selectivities were determined by GC on the basis of area percentage. [d] DMA was used as the solvent. [e] 4:1 DMA/DMSO was used as the solvent.

decrease in reactivity, yields of 67% and 46% were obtained using bromobenzene and 4-bromoanisole, respectively.

Next, we studied the reactions of aryl bromides with cyclopentene **7** (Scheme 2). As demonstrated in Table 2, 1-(aryl)cyclopentenes **8** and 3-(aryl)cyclopentenes **9** were produced as the major products. When the standard system DMA/NaOAc/$Pd(OAc)_2$/2 PPh_3 was applied at 140 °C, **9** was obtained with 68% overall selectivity. Again using a mixture of DMA and DMSO (4:1) the selectivity increased (74%); however, the effect is not as pronounced compared to that of cyclohexene. Interestingly, under more basic conditions double-bond isomerization takes place easily to yield 1-(aryl)cyclopentene **8** as the major isomer. After some optimization the catalyst system $Pd_2(dba)_3$·dba/4 PCy_3/Na_2CO_3 turned out to be very useful for the preparation of conjugated arylcyclopentenes **8**. In all cases here yields and product selectivities >90% were observed in the presence of only 0.1 mol % of palladium!

Scheme 2



The different behavior of arylcyclohexenes and arylcyclopentenes toward isomerization is explained to some extent by molecular mechanics calculations, which indicate that in the case of arylcyclohexenes the 4-(aryl)cyclohexene is the most stable isomer. Regarding arylcyclopentenes, the three isomeric products do have approximately the same thermodynamic stability.

In summary, we have shown for the first time that Heck reactions of aryl bromides with cyclohexene and cyclopentene can be performed in an efficient manner. The addition of DMSO as a cosolvent enhances the selectivity for the nonconjugated Heck products. When cyclopentene was applied as the olefinic substrate, both 1-(aryl)- and 3-(aryl)-cyclopentenes were obtained selectively. Worthy of note are the low quantities of catalyst required (0.1 mol %) and the possibility of determining the double-bond selectivity by simply changing the nature of the catalyst system.

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(5) Selectivities were determined by GC on the basis of area percentage.

(6) Conversions and yields were determined by GC with internal standard (diethylene glycol di-*n*-butyl ether).

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(8) **General procedure:** 5 mmol of aryl bromide, 25 mmol of cycloalkene, 6 mmol of base, 0.005 mmol of Pd catalyst, and 0.01 mmol of phosphine were dissolved in 5 mL of DMA/DMSO (4:1), and the mixture was stirred under argon at 140 °C for 20 h in a pressure tube. (*CAUTION*! The reactions were done under pressure. Take the necessary safety measures against explosion.) After it was cooled, the reaction mixture was washed with a mixture of dichloromethane and 5% aqueous HCl (three times). The phases were separated and the combined organic phases neutralized with 10% aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent the desired products were isolated as colorless oils by distillation in vacuo. All products were identified by ^1H and ^{13}C NMR and mass spectroscopy and by comparison with authentic samples by GC.