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First Efficient Palladium-Catalyzed Heck Reactions of Aryl Bromides with Alkyl Methacrylate[1)]

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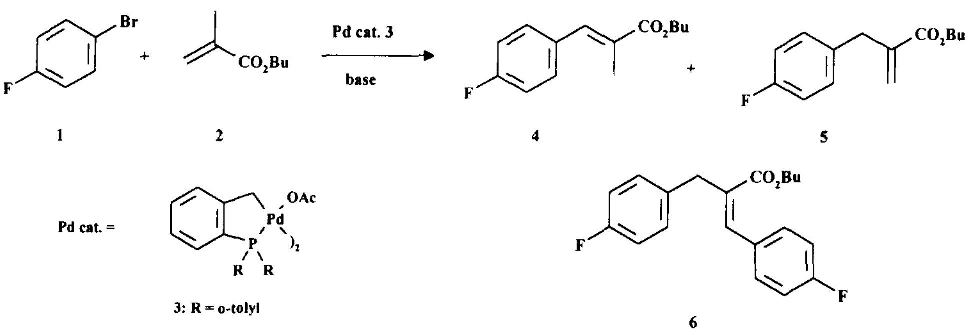
Abstract: *An efficient palladium-catalyzed coupling reaction of aryl bromides with butyl methacrylate has been developed. Depending on the reaction conditions various amounts of butyl 3-aryl-2-methylpropenoate and butyl 3-aryl-2-methyliden-propenoate as well as double arylated products were produced. Superior turn over numbers up to 8300 and turn over frequencies up to 1000 h^{-1} for Heck reactions of aryl bromides with methacrylic acid ester have been obtained for the first time.* Copyright © 1996 Elsevier Science Ltd

The Heck reaction[2)] is arguably one of the most powerful methods for the synthesis of substituted aryl olefins. Nevertheless industrial applications have been rare due to low turn over numbers and low turn over frequencies of known catalyst systems.[3)] This is especially true for Heck reactions with di- or tri-substituted olefins. Because of the versatility of α-methyl-substituted cinnamic acid derivatives as building blocks in organic synthesis, e.g. for the preparation of indanones, we were interested in more efficient coupling reactions with alkyl methacrylates, which have been rarely studied to our surprise.[4)] Recently, we developed cyclometallated palladium complexes as new efficient catalysts for Heck[5)] and related reactions[6)], which also fulfill technical requirements. We studied the coupling reaction of 4-bromofluorobenzene **1** with butyl methacrylate **2** as model reaction to test the utility of palladacycles as catalysts for the synthesis of α-methyl cinnamic acid derivatives (Scheme 1). Following standard conditions (dimethylacetamide, NaOAc, 0.1 mol% **3**; 135-140 °C; 4 h) only a non-selective[7)] mixture of the double bond isomers **4** and **5** as well as the double arylated product **6** (1 : 0.9 : 0.6) was obtained with a conversion[8)] of 65 %.

Clearly, the selectivity of the coupling reaction of **4** and **5** will be influenced either during the catalytic cycle by elimination of the corresponding HPdX complex or by base- or palladium-catalyzed double bond isomerization. We anticipated that in both double bond-selectivity determining processes the role of base is crucial. Indeed, in the presence of 1.2 eq. of more basic tributylamine and 0.1 mol% of **3** the selectivity of **4** : **5** : **6** was improved to 9 : 1 : 1.5 after 24 h (92 % conversion).



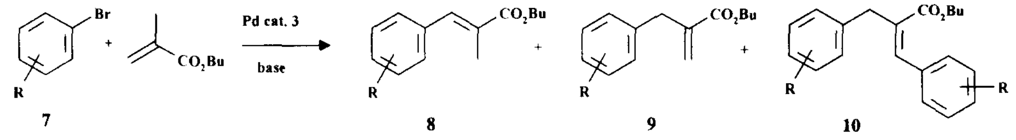
Scheme 1

Further improvement of the selectivity was obtained by using the sterically more hindered base diisopropylethylamine (**4** : **5** : **6** = 17 : 1 : 2.7, 90 % conversion). To our knowledge such influence of different bases on the regioselectivity of disubstituted olefins in Heck reactions has not been reported before. In order to gain more information about the influence of the base 1.0 eq. Bu_3N and 0.1 mol% **3** was added to a 1 : 1-mixture of **4** and **5** in dimethylacetamide. After 22 h at 135°C only little isomerization towards the more stable olefine **4** was detected (**4** : **5** = 1.2 : 1). Therefore, we assume that the amine changes the selectivity via coordination to palladium during the catalytic cycle.

Interestingly, the coordination of the amine to the metal results in a lower conversion rate compared to NaOAc as base. A kinetic study using NaOAc as base demonstrates that in the beginning of the reaction **4** and **5** are produced in equal amounts. After a sufficient amount of **5** is present in solution consecutive reaction to **6** becomes important. Contrary using Bu_3N as base the selectivity towards **4** during the overall reaction is high enough to supress major production of **6**.

Next, we were interested to compare the palladacycle catalyst **3** with conventional in situ palladium phosphane catalysts such as $Pd(OAc)_2/PPh_3$ (1 : 2) and $Pd(OAc)_2/P\text{-}(o\text{-tolyl})_3$ (1 : 1). The reaction of 4-bromofluorobenzene with butyl methacrylate in the presence of tributylamine (dimethylacetamide, 135-140 °C, 4 h) show significantly lower conversion in the presence of 0.1 mol% of both catalyst systems (16 % and < 5 %, respectively) compared to the run with **3**. Despite the better results in the presence of **3** as catalyst, so far it is uncertain whether **3** is the "real" catalyst precursor or if reduction to a palladium-tri-*o*-tolyl-phosphane complex is occurring prior to catalysis. Presumably the palladacycle acts as a stable precursor for the real "$Pd\text{-}P(o\text{-tolyl})_3$" complex. But so far we have no proof for either Pd^0/Pd^{II} or Pd^{II}/Pd^{IV} catalysis.

In contrast using **3** it was even possible to lower the amount of catalyst down to 0.01 mol% while still getting reasonable conversions (83 % with NaOAc, 36 % with Bu_3N, 24 h). *This corresponds to the best* *turn over numbers (TON = 8300) and turn over frequencies (TOF = 1000/h[9]) yet reported in the literature for Heck reactions of α-disubstituted olefins.* To investigate the scope of the reaction, a series of various aryl bromides was subjected to the optimized reaction conditions[10] and the results are listed in Table 1.



Scheme 2

Table 1. Heck Reaction of Butyl Methacrylate with Aryl Bromides

Run	Aryl Halide	R	Base	mol % 3	Time	Conversion of 7[8] (%)	TON	8 : 9 : 10[7]	Yield 8 + 9 (%)
1	7a	4-F	NaOAc	0.1	4 h	65	650	1.1 : 1 : 0.6	27[a]
2	7a	4-F	Bu$_3$N	0.1	24 h	92	920	9.3 : 1 : 1.5	60[b]
3	7a	4-F	NaOAc	0.01	24 h	83	8300	1.4 : 1 : 1.2	31[a]
4	7a	4-F	Bu$_3$N	0.01	24 h	36	3600	3.9 : 1 : 0.2	12[a]
5	7b	4-COCH$_3$	Bu$_3$N	0.1	4 h	> 98	>980	11.5 : 1 : 2.1	74[b]
6	7c	4-OCH$_3$	Bu$_3$N	0.1	4 h	25	250	4.9 : 1 : <0.1	20[b]
7	7d	4-NO$_2$	Bu$_3$N	0.1	8 h	79	790	8.1 : 1 : 0.7	75[b]
8	7e	4-Cl	Bu$_3$N	0.1	4 h	> 98	>980	9.8 : 1 : 2.1	55[a]

a) Isolated yield by distillation.

b) Isolated yield by column chromatography.

As expected, the electronic nature of the aryl bromide has a dominating effect on the reaction. Activated aryl bromides react nearly quantitative (runs 5 and 8). An exception is 4-bromonitrobenzene (run 7). Interestingly, best results for 4-bromonitrobenzene (79 % conversion) were obtained if only 0.6 eq. tributylamine were used. Also the reactions of 4-bromochlorobenzene and 4-bromoacetophenone in the presence of 0.6 eq. of tributylamine results in a similar good conversion (80%). This shows the possibility of performing efficient Heck reactions in the presence of understoichiometric amounts of base, although it is traditionally believed to use at least stoichiometric amounts.

In summary, we have developed the most efficient Heck reaction of aryl bromides with methacrylic acid derivatives to date. Remarkable are the high turnover numbers and the possibility of determining double bond selectivity by the nature of the base.

References and Notes

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7. Selectivities have been determined by GC on the basis of area percentage.
8. Conversions have been determined by GC with internal standard (diethyleneglycoldibutyl ether).
9. Determined by a kinetic study of the reaction of 4-bromofluorobenzene and butyl methacrylate with 0.01 mol% **3** and sodium acetate as base (5 h).
10. Typical reaction: 8.75 g 4-bromofluorobenzene **1**, 10.67 g butyl methacrylate **2**, 7 ml tributylamine, 23 mg **3** and 0.1 mg 2,6-di-tert.butyl-4-methylphenol were dissolved in 50 ml *N,N*-dimethylacetamide and stirred at 135-140 °C for 24 hours. After cooling the reaction mixture was extracted with diethyl ether and 5 % aqueous HCl for three times. The combined organic phases were neutralized with 10 % aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent the desired products were isolated as a colourless oil (7.12 g, 60 %) by distillation in vacuo (b.p.: 95-100 °C / 1 mbar).
    The reaction has been upscaled to 100 g scale for the synthesis of substituted indanones. M. Beller, T. H. Riermeier, S. Klein, K. Kühlein, unpublished results.

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