A Phosphane-Free Catalyst System for the Heck Arylation of Disubstituted Alkenes: Application to the Synthesis of Trisubstituted Olefins

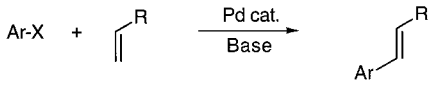
Christoph Gürtler and Stephen L. Buchwald* [a]

Abstract: A new general procedure for the Heck arylation of disubstituted olefins is described. This procedure allows, in many instances, the stereoselective synthesis of trisubstituted olefins. Trisubstituted olefins are easily accessible under mild reaction conditions using a new catalyst system consisting of dicyclohexylamine or methyl(dicyclohexyl)amine and a phase-transfer catalyst. The choice of base was found to be crucial for the rate and stereoselectivity of the Heck arylation reactions. This method is applicable to the coupling of both electron-deficient and electron-rich aryl halides and displays good stereoselectivity and a high degree of functional group compatibility. Labeling studies indicate that the source of this selectivity is thermodynamic in nature.

Keywords: alkenes · base effects · Heck reaction · palladium · phase-transfer catalysis

Introduction

The palladium-catalyzed reaction of organic halides with alkenes (the Heck reaction, Scheme 1)[1] has become a well-established synthetic method for carbon–carbon bond formation.[2] However, to date only a few examples of its use for the stereoselective synthesis of trisubstituted olefins[3] have been reported.[4] The development of an efficient process for the stereoselective Heck arylation of disubstituted olefins would be of significant utility.



Scheme 1. General Heck reaction.

Herein we describe general, phosphane-free, reaction conditions for the Heck type coupling of aryl iodides and aryl bromides with 1,1-and 1,2-disubstituted olefins. Under relatively mild reaction conditions (95–100 °C), trisubstituted olefins could be prepared with high *E* selectivity starting from 1,2-disubstituted alkenes.[5] That this transformation is efficient under these conditions indicates that this system possesses a high level of catalytic activity.

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Since the factors that influence the rate of Heck reactions remain obscure, we sought to reexamine these processes with the goal of developing a simple, relatively general protocol for the Heck arylation reaction, which we hoped to apply to the synthesis of trisubstituted olefins. In initial experiments we investigated the influence of different bases[3b, 6] on the reaction rates and selectivities of Heck reactions using a standard catalyst system developed by Heck (tri-*o*-tolylphosphane, $Pd(OAc)_2$). We began by studying the effect of different bases on the relative rates of the reaction of 4-fluorobromobenzene with butyl methacrylate (see Table 1, entry 1) using triethylamine, tri-*n*-butylamine, pentamethylpiperidine (PMP), diisopropylethylamine, dicyclohexylamine, and methyl(dicyclohexyl)amine. The reaction procedures that employed dicyclohexylamine or methyl(dicyclohexyl)amine were considerably faster (about one order of magnitude) than those that utilized the other amines. In addition, these procedures gave the olefin product with a high level of *E*/*Z* stereoselectivity. The *E*/*Z* selectivity could be improved by using methyldicyclohexylamine as the base in combination with tetraethylammonium chloride, as introduced in the pioneering work of Jeffery.[7] A phosphane ligand was not necessary, and, in fact, led to a loss of selectivity. This finding was important because a phosphane-free system is desirable, particularly for industrial applications. The current phosphane-free protocol is effective for both aryl iodides and bromides, in reactions with both 1,1-and 1,2-disubstituted olefins (Scheme 2). We note that Beletskaya et al.,[8a,b] Jeffery,[7b] Reetz et al.,[8c] and Moreno–Mañas et al.[3a] have previously described phosphane-free Heck procedures for Heck arylations. However, only Moreno–Mañas et al. reported Heck arylations of disubstituted olefins and those were with aryl iodides.

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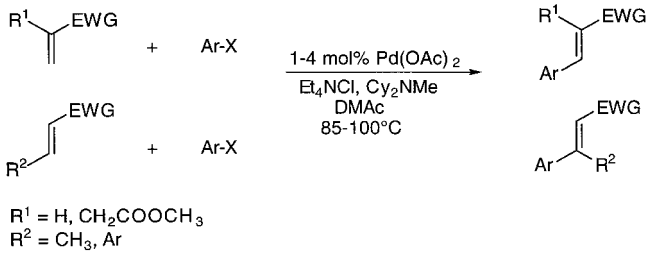


Scheme 2. Modified Heck reaction using bulky amine bases and a phase-transfer catalyst.

Results and Discussion

As shown in Table 1, a procedure employing the $Pd(OAc)_2$/Cy_2NMe/tetraethylammonium chloride[9] system was very effective in coupling activated olefins with both electron-rich and electron-poor aryl halide substrates. Even *ortho*-substituted aryl halides, whose transformations are problematic under typical reaction conditions, were efficiently converted into the desired trisubstituted olefins. However, in these cases a greater quantity of catalyst was required. In most instances, procedures which employed a stoichiometric quantity of tetraethylammonium chloride proceeded with the shortest reaction times and manifested the best *E*/*Z* selectivities. In the case of methacrylate substrates[10] (entries 1 and 2) however, the use of a modified ammonium salt ($Cy_2(Me_2)NBr$) in combination with methyl(dicyclohexyl)amine gave the best results.

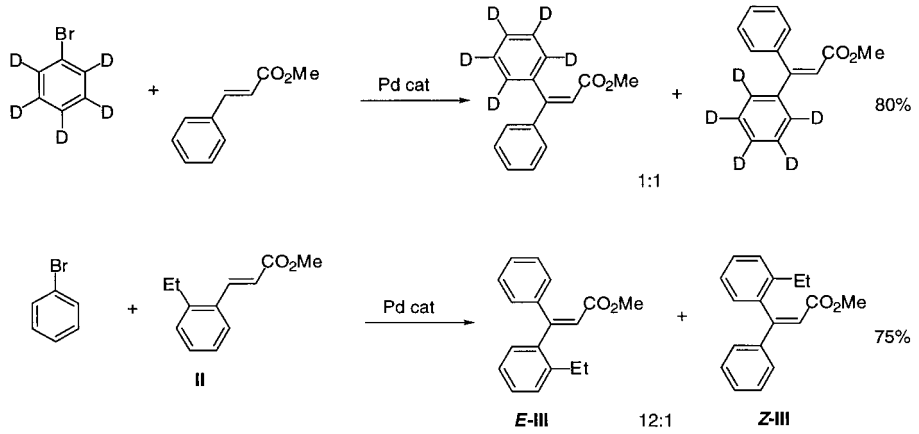
A common side product in reactions with methacrylates results from a second Heck arylation of the initial olefin product.[6,20] Using our modified catalyst system we were able to suppress this side reaction while still achieving a high *E*/*Z* ratio even for an *ortho*-substituted aryl halide (entry 2), if the reaction was stopped after 75% conversion. The Heck coupling of electron-poor vinylic substrates or electron-poor arenes is often inefficient.[11] Using the conditions described herein, in dimethylacetamide, we were able to overcome these problems; the reaction of dimethyl itaconate[12] with 2-iodocyanobenzene afforded the product in 74% yield (entry 4) with essentially complete stereoselectivity.

Heck reactions of β-substituted, α,β-unsaturated esters usually require relatively harsh reaction conditions.[13] In contrast, we were able to couple a variety of substrates including 3-bromothiophene and 2-ethylbromobenzene with cinnamic acid esters at or below 100 °C. Reactions of methyl cinnamate, however, with electron-poor aryl halide substrates (e.g., methyl 4-bromobenzoate or 4-bromobenzonitrile) did not proceed in satisfactory yields.[14] Electron-rich substrates such as *N*,*N*-dimethyl-4-bromobenzene could be coupled with *trans*-methyl cinnamate to afford vinylogous urethanes in high yield (entry 7). The *E*/*Z* ratio in this case reflects the equilibrium ratio at 85 °C.[15]

This methodology was also used to couple aryl bromides or iodides with methyl crotonate.[16] As in the reactions of *trans*-methycinnamate (with the exception of entry 7) only the *E* isomer was obtained. Whereas the coupling of *ortho*-substituted aryl bromides was inefficient, the reaction of *ortho*-substituted aryl iodides proceeded satisfactorily. For example, while 2-bromoanisole was not a suitable coupling partner for methyl crotonate, the use of the corresponding iodide gave a moderate yield of the desired trisubstituted olefin product (entry 11). Bulky ortho substituents had a significant effect on the outcome of the reaction as evidenced by our inability to couple 2-ethyliodobenzene with methyl crotonate.[17] Using a higher catalyst loading (4 mol%) it was possible to couple an electron-poor olefin and an electron-poor aryl bromide (entry 13), albeit in modest yield.

A comparison of the structure of dicyclohexylamine and methyl(dicyclohexyl)amine to phosphanes led us to hypothesize that the similarly shaped amine bases function in the same role as the phosphane ligands often employed in Heck reactions. Dicyclohexylamine and methyl(dicyclohexyl)amine are closer in shape to triphenylphosphane and tri-*o*-tolylphosphane than the usual bases in Heck reactions, triethyl- or tributylamine, which have a more spherical shape. The rate enhancement observed in protocols which use dicyclohexylamine and methyl(dicyclohexyl)amine as base might be due to a more rapid conversion of an intermediate $[L_2Pd(HX)]$ (**I**)[18] complex (L = e.g., methyl(dicyclohexyl)amine) since the base which is needed to remove HX is already bound to the palladium. Bis-phosphane complexes analogous to **I** are intermediates in the regeneration of the Pd^0 catalysts in the Heck reaction and are known to be relatively stable.[19] The slow decomposition of **I** would thus substantially reduce the quantity of catalytically active palladium catalyst. A related proposal for the influence of phase-transfer catalysts has been put forward by Jeffery.[7]

In order to probe the source of the stereoselectivity of the Heck arylation of cinnamate esters, the two experiments shown in Scheme 3 were performed. First, using the reaction protocol described above, $[D_5]$bromobenzene was coupled with (*E*)-methyl cinnamate to give $[D_5]$diphenylmethylacrylate as a 1:1 mixture of geometric isomers in 80% yield. In a



Scheme 3. Heck reactions revealing the thermodynamic origin of selectivity.

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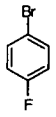
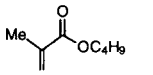
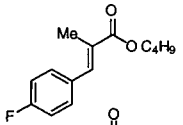
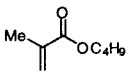
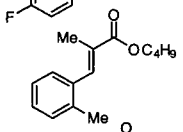
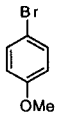
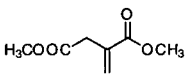
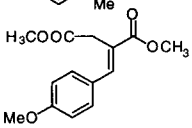
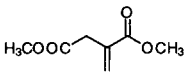
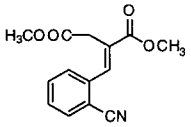
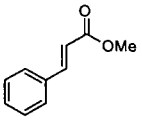
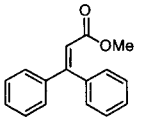
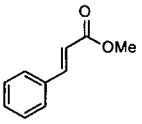
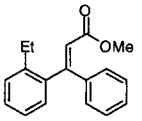
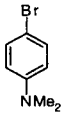
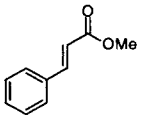
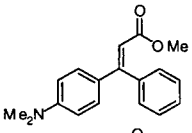
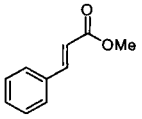
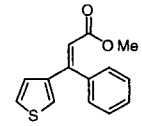
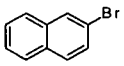
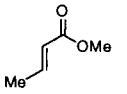
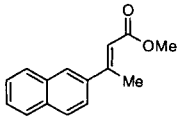
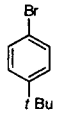
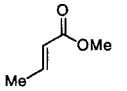
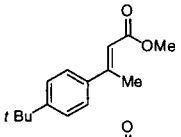
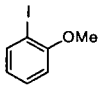
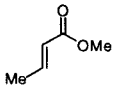
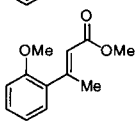
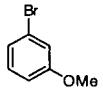
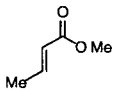
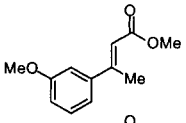
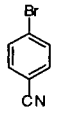
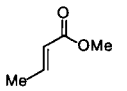
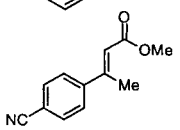
Table 1. Palladium-catalyzed synthesis of trisubstituted olefins.

Entry	Arene	Olefin	Product	Ratio E/Z[a]	Procedure[b]	Time [h]	Yield [%][c]
1				10.3:1:1.7	A	24	84
2				17:2.4:1	D	24	60
3				11:1	A	16	72
4				1 isomer	A	16	74
5				1 isomer	A	16	80
6				25:1	C	60	75
7				2:1	B	45	80
8				1 isomer	A	60	76
9				16:1	A	16	87
10				18:1	A	20	81
11				20:1	A	20	65
12				20:1	A	20	81
13				19:1	A	16	51

[a] E/Z isomer and product of a second Heck reaction. [b] All reactions were carried out in dimethylacetamide using 1.0 equiv of Et_4NCl, and 1.5 equiv of $Me(Cy_2)N$. Conditions A: 95–100 °C, ratio arene/olefin 1.1:1, 2 mol% $Pd(OAc)_2$ (with the exception of entry 9 (1 mol% of Pd) and entries 8 and 13 (4 mol% of Pd). Conditions B: 85 °C, ratio arene/double bond 1.1:1, 3 mol% $Pd(OAc)_2$. Conditions C: 85 °C, ratio arene/double bond 1.5:1, two portions of 2 mol% $Pd(OAc)_2$ added. Conditions D: 110 °C, ratio arene/double bond 1.1:1, 3 mol% $Pd(OAc)_2$ added. The run time is stated at each entry. [c] Yields refer to the average of at least two yields of isolated product >95% purity as determined by GC. The stereochemistry of all new compounds were secured by NOE experiments.

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similar fashion, bromobenzene was coupled with **II** to give **III** $E/Z =$ 12:1. This result should be compared with that described in Table 1, entry 6, in which 2-ethylbromobenzene was coupled with with (*E*)-methyl cinnamate to give a 25:1 ratio of **III** *E*/*Z*. Taken together these results indicate that the stereoselectivity is thermodynamic in origin. This finding is of considerable interest since the generally accepted mechanism for the Heck arylation of a disubstituted alkene predicts that the trisubstituted alkene should be formed in a stereospecific manner. In the case of reactions of cinnamate esters equilibration likely occurs subsequent to the Heck arylation.

In summary, we have developed a general procedure for Heck arylation of disubstituted olefins which allows, in many instances, the stereoselective synthesis of trisubstituted olefins. This method is applicable to the coupling of both electron-deficient and electron-rich substrates and displays good stereoselectivity and a high degree of functional group compatibility. Labeling studies indicate that the source of this selectivity is thermodynamic in nature.

Experimental Section

General considerations: All reactions were performed under an inert atmosphere of argon in oven- or flame-dried glassware. Dimethylacetamide (99.5%) was purchased from Lancaster and used without further purification. Unless otherwise noted, all reagents were purchased from commercial sources and were used without further purification.

Preparative flash chromatography was performed using ICN flash silica gel, 230–400 mesh. Yields refer to the average of two yields of isolated product of 95% or higher purity as determined by GC, ^{1}H NMR, and elemental analysis. All products were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, and elemental analysis from E & R Microanalytical Laboratories, 96–34 Corona Ave, Corona, NY 11368. NMR spectra were recorded on a Bruker AC-250 and a Varian Unity 300 MHz spectrometer. Yields indicated in this section refer to a single experiment, while those reported in the tables are an average of two or more runs, so the numbers may differ slightly. All ^{1}H NMR spectra are reported in δ units ppm downfield from tetramethylsilane internal standard. All ^{13}C spectra are reported in δ units relative to the central line of the triplet for $CDCl_3$ at $\delta =$ 77 ppm, with the exception of entry 6 where the central line of the quintet of CD_2Cl_2 at $\delta = 54$ ppm was employed. IR spectra were recorded on a ASI ReactIR 1000 spectrometer using the ATR technique. Gas chromatography analyses were performed on a Hewlett–Packard 5890 gas chromatograph, with an FID, a 25 meter capillary column with a dimethylpolysiloxane stationary phase, and a 3392A integrator. Melting points were determined using a Haake Buchler melting point apparatus and are uncorrected.

Pd-Catalyzed coupling of bromo-/iodoarene with olefins:

General procedure A: The aryl halide (1.1 mmol), the olefinic substrate (1.0 mmol), Et_4NCl (1.0 mmol), $Cy_2(Me)N$ (1.5 mmol), $Pd(OAc)_2$ (0.02 mmol), (with the exception of entry 9 where 0.01 mol $Pd(OAc)_2$ was employed and entries 8 and 13 where 0.04 mol was used), and dimethylacetamide (4.0 mL) were added to an oven-dried Schlenk tube, which was then sealed with a septum, purged with argon, and heated to 100 °C under argon. When the aryl halide was consumed as determined by GC analysis, the reaction mixture was allowed to cool to room temperature, diluted with Et_2O, and washed three times with water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product. Purification by flash column chromatography afforded the analytically pure product.

General procedure B: The aryl halide (1.1 mmol), the olefinic substrate (1.0 mmol), Et_4NCl (1.0 mmol), $Cy_2(Me)N$ (1.5 mmol), $Pd(OAc)_2$ (0.03 mmol), and dimethylacetamide (4.0 mL) were added to an oven-dried Schleck tube, which was then sealed with a septum, purged with argon, and heated to 85 °C under argon until the aryl halide was consumed as determined by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O, and washed three times with water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product. Purification by flash column chromatography afforded the analytically pure product.

General procedure C: The aryl halide (1.5 mmol), the olefinic substrate (1.0 mmol), Et_4NCl (1.0 mmol), $Cy_2(Me)N$ (1.5 mmol), $Pd(OAc)_2$ (two portions of 0.02 mmol added at the start of the reaction and after 12 h), and dimethylacetamide (4.0 mL) were added to an oven-dried Schlenk tube, which was then sealed with a septum, purged with argon, and heated to 85 °C under argon until the aryl halide was consumed as determined by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O, and washed three times with water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product. Purification by flash column chromatography afforded the analytically pure product.

General procedure D: The aryl halide (1.1 mmol), the olefinic substrate (1.0 mmol), Et_4NCl (1.0 mmol), Cy_2MeN (1.5 mmol), $Pd(OAc)_2$ (0.03 mmol), and dimethylacetamide (4.0 mL) were added to an oven-dried test tube, which was then sealed with a septum, purged with argon, and heated to 110 °C under argon until 75% conversion was achieved as determined by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O, and washed three times with water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel afforded the analytically pure product.

(*E*)-3-(4-Fluorophenyl)-2-methyl-*n*-butyl acrylate (entry 1):[6a] Procedure A was used to convert 4-fluorobromobenzene and *n*-butyl methacrylate to the title product in 24 h. Instead of Et_4NCl (1.0 mmol), Cy(Me)NBr (1.0 mmol) was used. Purification by flash column chromatography (5% EtOAc/pentane) gave the analytically pure product as a clear oil (205 mg, 87% yield). ^{1}H NMR (250 MHz, [D]$CHCl_3$, 20 °C): $\delta = 7.63$ (s, 1H; CH), 7.39 (d, ^3J(H,H) = 8.0 Hz, 1H; CH), 7.36 (d, ^3J(H,H) = 8.0 Hz, 1H; CH), 7.09 (d, ^3J(H,H) = 8.0 Hz, 1H; CH), 7.05 (d, ^3J(H,H) = 8.0 Hz, 1H; CH), 4.21 ('t', ^2J(H,H) = 5.5 Hz, 2H; CH_2), 2.09 (s, 3H; CH_3), 1.67 (m, 2H; CH_2), 1.44 (m, 2H; CH_2), 0.97 (t, ^2J(H,H) = 5.5 Hz, 3H; CH_3); ^{13}C NMR (62.5 MHz, [D]$CHCl_3$, 20 °C): $\delta = 168.6$, 162.3, 137.4, 131.3, 128.5, 115.5, 115.2, 64.7, 30.8, 19.9, 13.3, 13.7; IR (ATR): $\tilde{\nu} = 2960$, 2937, 2875, 1706, 1601, 1509, 1254, 1227, 1200, 1115, 833, 748 cm^{-1}. $C_{14}H_{17}O_2F$ (236.29): calcd C 71.17, H 7.25; found C 71.35, H 7.44.

(*E*)-3-(2-Methylphenyl)-2-methyl-*n*-butyl acrylate (entry 2): Procedure D was used to convert 2-bromotoluene and *n*-butyl-methacrylate to the title product in 24 h. Instead of Et_4NCl (1.0 mmol), Cy(Me)NBr (1.0 mmol) was used. Purification by flash column chromatography (1% EtOAc/pentane) gave the analytically pure product as a clear oil (144 mg, 62% yield). ^{1}H NMR (250 MHz, [D]$CHCl_3$, 20 °C): $\delta = 7.76$ (s, 1H; CH), 7.22 (d, ^3J(H,H) = 7.0 Hz, 1H; CH), 7.20 (dd, ^3J(H,H) = 7.0 Hz, ^3J(H,H) = 7.0 Hz, 1H; CH), 7.18 (dd, ^3J(H,H) = 7.0 Hz, ^3J(H,H) = 7.0 Hz, 1H; CH), 7.15 (d, ^3J(H,H) = 7.0 Hz, 1H; CH), 4.22 ('t', ^2J(H,H) = 5.5 Hz, 2H; CH_2), 2.28 (s, 3H; CH_3), 1.96 (s, 3H; CH_3), 1.71 (m, 2H; CH_2), 1.47 (m, 2H; CH_2), 0.96 (dd, ^2J(H,H) = 5.5 Hz, ^2J(H,H) = 5.5 Hz, 3H; CH_3); ^{13}C NMR (62.5 MHz, [D]$CHCl_3$, 20 °C): $\delta = 168.4$, 138.0, 136.7, 135.1, 130.2, 129.9, 128.7, 128.0, 125.4, 64.6, 30.7, 19.7, 19.2, 13.8, 13.7; IR (ATR): $\tilde{\nu} = 2960$, 2933, 2875, 1710, 1459, 1250, 1219, 1119, 741 cm^{-1}; $C_{15}H_{20}O_2$ (232.33): calcd C 77.55, H 8.68; found C 77.25, H 8.82.

(*E*)-3-(4-Anisyl)-2-methylenemethylcarboxylate-methyl acrylate (entry 3):[12] Procedure A was used to convert dimethyl itaconate and 4-bromoanisole to the title product in 16 h. Purification by flash column chromatography (33% diethyl ether/pentane gave the analytically pure product as a clear oil (180 mg, 74% yield). ^{1}H NMR (250 MHz, [D]$CHCl_3$, 20 °C): $\delta = 7.83$ (s, 1H; CH), 7.30 (d, ^3J(H,H) = 8.0 Hz, 2H; 2CH), 6.89 (d, ^3J(H,H) = 8.0 Hz, 2H; 2CH), 3.81 (s, 3H; CH_3), 3.79 (s, 3H; CH_3), 3.55 (s, 2H; CH_2); ^{13}C NMR (62.5 MHz, [D]$CHCl_3$, 20 °C): $\delta = 171.6$, 168.0, 160.2, 141.8, 130.9 (2C), 127.3, 123.7, 114.1 (2C), 55.2, 52.1, 52.0, 33.5; IR (ATR): $\tilde{\nu} = 3003$, 2952, 2844, 1737, 1706, 1636, 1605, 1513, 1435, 1254, 1204, 1173, 1092, 1030, 837, 764 cm^{-1}; $C_{14}H_{16}O_5$ (264.28): calcd C 63.63, H 6.10; found C 63.82, H 6.30.

0947-6539/99/0511-3110 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 11

(*E*)-3-(2-Cyanophenyl)-2-methylenemethylcarboxylate-methyl acrylate (entry 4): Procedure A was used to convert dimethyl itaconate and 2-cyanoiodobenzene to the title product in 16 h. Purification by flash column chromatography (25% EtOAc/hexane) gave the analytically pure product as a colorless solid (194 mg, 75% yield). M.p. 64 °C; ^{1}H NMR (250 MHz, [D]CHCl$_3$, 20 °C): $\delta = 7.98$ (s, 1H; CH), 7.70 (d, ^3J(H,H) = 7.5 Hz, 1H; CH), 7.60 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 7.5 Hz, 1H; CH), 7.46 (d, ^3J(H,H) = 7.5 Hz, 1H; CH), 7.44 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 7.5 Hz, 1H; CH), 3.82 (s, 3H; CH$_3$), 3.69 (s, 3H; CH$_3$), 3.40 (s, 3H; CH$_3$); ^{13}C NMR (62.5 MHz, [D]CHCl$_3$, 20 °C): $\delta = 171.1$, 166.6, 138.3, 137.4, 133.1, 132.8, 130.1, 129.1, 129.0, 112.5, 81.7, 52.4, 52.2, 33.6; IR (ATR): $\tilde{\nu} = 2960$, 2227, 1717, 1432, 1339, 1269, 1231, 1204, 1092, 775 cm^{-1}; $C_{14}H_{13}NO_4$: (259.26): calcd C 64.86, H 5.05; found C 64.86, H 5.10.

(*E*)-3,3-Diphenylmethyl acrylate (entry 5):[13] Procedure A was used to convert bromobenzene and *trans*-methyl cinnamate to the title product in 16 h. Purification by flash column chromatography (1% Et$_2$O/pentane) gave the analytically pure product as a clear oil (196 mg, 82% yield). ^{1}H NMR (250 MHz, [D$_2$]CH$_2$Cl$_2$, 20 °C): $\delta = 7.43 - 7.40$ (m, 6H; 6CH), 7.35 – 7.32 (m, 4H; 4CH), 6.39 (s, 1H; CH), 3.62 (s, 3H; CH$_3$); ^{13}C NMR (62.5 MHz, [D]CHCl$_3$, 20 °C): $\delta = 166.4$, 157.2, 141.5, 139.5, 130.8, 130.6, 129.5 (2C), 129.2 (2C), 128.1 (2C), 127.5 (2C), 117.6, 51.5; IR (ATR): $\tilde{\nu} =$ 2945, 2856, 1725, 1702, 1617, 1447, 1266, 1188, 1161, 772, 694 cm^{-1}; $C_{16}H_{14}O_2$ (238.29): calcd C 80.65, H 5.92; found C 80.58, H 6.11.

(*E*)-3-(2-Ethylphenyl)-3-phenylmethyl acrylate (entry 6): Procedure C was used to convert 2-ethylbromobenzene and *trans*-methyl cinnamate to the title product in 60 h. Purification by flash column chromatography (5% EtOAc/hexane) gave the analytically pure product as a clear oil (237 mg, 89% yield). ^{1}H NMR (250 MHz, [D]CHCl$_3$, 20 °C): $\delta = 7.30 - 7.22$ (m, 8H; 8CH), 7.06 (d, ^3J(H,H) = 7.5 Hz, 1H; CH), 6.51 (s, 1H; CH), 3.56 (s, 3H; CH$_3$), 2.37 (m, 2H; CH$_2$), 0.99 ('t', ^2J(H,H) = 5.5 Hz, 3H; CH$_3$); ^{13}C NMR (62.5 MHz, [D]CHCl$_3$, 20 °C): $\delta = 166.1$, 129.7, 129.5, 129.2, 129.1, 128.7, 128.5 (2C), 128.2, 128.1, 127.7, 127.5 (2C), 125.7, 125.4, 51.2, 26.1, 14.6; IR (ATR): $\tilde{\nu} = 2968$, 1725, 1617, 1447, 1358, 1262, 1188, 1161, 1015, 760, 694 cm^{-1}; $C_{18}H_{18}O_2$: (266.34): Calcd C 81.17, H 6.81; found C 80.98, H 6.62.

(*E*)-3-(4-Dimethylaminophenyl)-3-phenylmethyl acrylate (entry 7): Procedure B was used to convert 4-*N*,*N*-dimethylaminobromobenzene and *trans*-methyl cinnamate to the title product in 45 h. Purification by flash column chromatography (5% EtOAc/pentane) gave the analytically pure product as a slightly yellow solid (225 mg, 80% yield). M.p. 124 °C; ^{1}H NMR (250 MHz, [D]CHCl$_3$, 20 °C): $\delta = 7.38$ (m, 3H; 3CH), 7.22 (m, 2H; 2CH), 7.20 (d, ^3J(H,H) = 8.0 Hz, 2H; 2CH), 6.62 (d, ^3J(H,H) = 8.0 Hz, 2H; 2CH), 6.30 (s, 1H; CH), 3.58 (s, 3H; CH$_3$), 3.00 (s, 6H; 2CH$_3$); ^{13}C NMR (62.5 MHz, [D]CHCl$_3$, 20 °C): $\delta = 166.8$, 157.5, 151.3, 139.5, 131.2, 129.5 (2C), 129.0 (2C), 128.3, 128.2, 127.7 (2C), 112.0, 111.6 (2C), 50.9, 40.2; IR (ATR): $\tilde{\nu} = 2914$, 2856, 1710, 1605, 1582, 1439, 1370, 1146, 814, 779, 702 cm^{-1}; $C_{18}H_{19}O_2N$ (281.36): calcd C 76.84, H 6.81; found C 76.91, H 6.99.

(*Z*)-3-(4-Dimethylaminophenyl)-3-phenylmethyl acrylate (entry 7): Slightly yellow oil. ^{1}H NMR (250 MHz, [D]CHCl$_3$, 20 °C): $\delta = 8.07$ (d, ^3J(H,H) = 8.0 Hz, 2H; 2CH), 7.96 (d, $^3J = 8.0$ Hz, 2H; 2CH), 7.38 – 7.25 (m, 4H; 4CH), 7.19 (m, 1H; CH), 6.40 (s, 1H; CH), 3.90 (s, 6H; 2CH$_3$), 3.60 (s, 3H; CH$_3$); ^{13}C NMR (62.5 MHz, [D]CHCl$_3$, 20 °C): $\delta = 166.0$, 138.1, 130.8, 129.5 (2C), 129.0 (2C), 128.4, 128.2 (2C), 128.0, 127.2, 118.5 (2C), 117.4, 52.1, 51.3 (2C); IR (ATR): $\tilde{\nu} = 2952$, 2254, 1721, 1609, 1435, 1273, 1165, 1111, 1015, 849, 733, 698 cm^{-1}; MS (GCMS): *m*/*z* (%): 296 (90) [*M*$^+$].

(*E*)-3-(3-Thiophenyl)-3-phenylmethyl acrylate (entry 8): Procedure A was used to convert 3-bromothiophene and *trans*-methyl cinnamate to the title product in 60 h. Purification by flash column chromatography (5% EtOAc/pentane) gave the analytically pure product as a clear oil (190 mg, 78% yield). ^{1}H NMR (250 MHz, [D]CHCl$_3$, 20 °C): $\delta = 7.42$ (m, 3H; 3CH), 7.32 (m, 2H; 2CH), 7.30 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.5 Hz, 1H; 1CH), 7.27 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.5 Hz, 1H; CH), 7.02 (dd, ^4J(H,H) = 1.5 Hz, ^4J(H,H) = 1.5 Hz, 1H; CH), 6.41 (s, 1H; CH), 3.59 (s, 3H; CH$_3$); ^{13}C NMR (62.5 MHz, [D]CHCl$_3$, 20 °C): $\delta = 166.4$, 151.2, 142.7, 129.3, 128.4 (2C), 128.0 (2C), 126.3, 125.7, 124.4, 117.3, 115.1, 51.2; IR (ATR): $\tilde{\nu} = 3107$, 2949, 1721, 1613, 1432, 1262, 1158, 795, 772, 698 cm^{-1}; $C_{14}H_{12}O_2S$ (244.31): calcd C 68.83, H 4.95; found C 68.71, H 5.13.

(*E*)-(2-Naphthyl)-3-methylmethyl acrylate (entry 9):[16c] Procedure A was used to convert 2-bromonaphthalene and methyl crotonate to the title product in 16 h. Purification by flash column chromatography (6.6% EtOAc/pentane) gave the analytically pure product as a colorless solid (197 mg, 87% yield). M.p. 49 °C; ^{1}H NMR (250 MHz, [D]CHCl$_3$, 20 °C): $\delta = 7.96$ (s, 1H; CH), 7.87 (dd, ^3J(H,H) = 7.0 Hz, ^3J(H,H) = 7.0 Hz, 1H; CH), 7.83 (d, ^3J(H,H) = 8.5 Hz, 1H; CH), 7.82 (dd, ^3J(H,H) = 7.0 Hz, ^3J(H,H) = 7.0 Hz, 1H; CH), 7.62 (dd, ^3J(H,H) = 8.5 Hz, ^4J(H,H) = 1.5 Hz, 1H; CH), 7.51 (d, ^3J(H,H) = 7.0 Hz, 1H; CH), 7.49 (d, ^3J(H,H) = 7.0 Hz, 1H; CH), 6.31 (d, ^4J(H,H) = 1.5 Hz, 1H; CH), 3.80 (s, 3H; CH$_3$), 2.71 (s, 3H; CH$_3$); ^{13}C NMR (62.5 MHz, [D]CHCl$_3$, 20 °C): $\delta = 167.1$, 155.0, 139.2, 133.5, 133.1, 128.4, 128.1, 127.5, 126.6, 126.4, 125.9, 123.9, 117.0, 51.0, 19.1; IR (ATR): $\tilde{\nu} = 2949$, 1710, 1621, 1435, 1235, 1192, 1161, 1131, 1042, 856, 818, 756 cm^{-1}; $C_{15}H_{14}O_2$ (226.28): calcd C 79.62, H 6.24; found C 79.78, H 6.46.

(*E*)-3-(4-*tert*-Butylphenyl)-3-methylmethyl acrylate (entry 10):[22] Procedure A was used to convert 4-*tert*-butylbromobenzene and methyl crotonate to the title product in 20 h. Purification by flash column chromatography (6.6% EtOAC/pentane) gave the analytically pure product as a colorless solid (193 mg, 83% yield). ^{1}H NMR (250 MHz, [D]CHCl$_3$, 20 °C): $\delta = 7.42$ (d, ^3J(H,H) = 7.0 Hz, 4H; 4CH), 6.15 (s, 1H; CH), 3.75 (s, 3H; CH), 2.58 (s, 3H; CH$_3$), 1.34 (s, 9H; 3CH$_3$); ^{13}C NMR (62.5 MHz, [D]CHCl$_3$, 20 °C): $\delta = 167.6$, 152.4, 139.1, 126.1, (2C), 125.4 (2C), 115.9, 51.0, 34.7, 31.2 (3C), 17.8; IR (ATR): $\tilde{\nu} = 2964$, 2906, 2871, 1717, 1628, 1435, 1269, 1165, 1115, 1038, 833 cm^{-1}; $C_{15}H_{20}O_2$ (232.33): calcd C 77.55, H 8.86; found C 77.64, H 8.86.

(*E*)-3-(2-Methoxyphenyl)-3-methylmethyl acrylate (entry 11): Procedure A was used to convert 2-iodoanisole and methyl crotonate to the title product in 20 h. Purification by flash column chromatography (6.6% EtOAc/pentane) gave the analytically pure product as a colorless oil (142 mg, 69% yield). ^{1}H NMR (250 MHz, [D]CHCl$_3$, 20 °C): $\delta = 7.27$ (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 7.5 Hz, 1H; CH), 7.10 (d, ^3J(H,H) = 7.5 Hz, 1H; CH), 6.92 (d, ^3J(H,H) = 7.5 Hz, 1H; CH), 6.90 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 7.5 Hz, 1H; CH), 5.89 (s, 1H; CH), 3.80 (s, 3H; CH$_3$), 3.71 (s, 3H; CH$_3$), 2.48 (s, 3H; CH$_3$); ^{13}C NMR (62.5 MHz, [D]CHCl$_3$, 20 °C): $\delta =$ 167.1, 156.9, 156.2, 132.8, 129.4, 128.8, 120.5, 118.6, 110.9, 56.3, 54.3, 20.8; IR (ATR): $\tilde{\nu} = 2999$, 2949, 2841, 1717, 1632, 1490, 1462, 1435, 1262, 1235, 1161, 1026, 876, 752 cm^{-1}; $C_{12}H_{14}O_3$ (206.24): calcd C 69.89, H 6.84; found C 69.94, H 7.03.

(*E*)-3-(3-Methoxyphenyl)-3-methylmethyl acrylate (entry 12): Procedure A was used to convert 3-bromoanisole and methyl crotonate to the title product in 20 h. Purification by flash column chromatography (6.6% EtOAc/hexane) gave the analytically pure product as a clear oil (173 mg, 84% yield). ^{1}H NMR (250 MHz, [D]CHCl$_3$, 20 °C): $\delta = 7.25$ (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 7.5 Hz, 1H; CH), 7.10 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.5 Hz, 1H; CH), 6.96 (dd, ^4J(H,H) = 1.5 Hz, ^4J(H,H) = 1.5 Hz, 1H; CH), 6.88 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.5 Hz, 1H; CH), 6.11 (s, 1H; CH), 3.79 (s, 3H; CH$_3$), 3.72 (s, 3H; CH$_3$), 2.54 (s, 3H; CH$_3$); ^{13}C NMR (62.5 MHz, [D]CHCl$_3$, 20 °C): $\delta = 167.5$, 159.6, 155.1, 143.6, 129.4, 118.7, 116.8, 114.3, 112.0, 55.2, 51.0, 18.5; IR (ATR): $\tilde{\nu} = 2952$, 2918, 2837, 1713, 1632, 1578, 1435, 1219, 1161, 1038, 856, 783 cm^{-1}; $C_{12}H_{14}O_3$ (206.24): calcd C 69.89, H 6.84; found C 69.80, H 7.04.

(*E*)-3-(4-Cyanophenyl)-3-methylmethyl acrylate (entry 13): Procedure A was used to convert 4-bromobenzonitrile and methylcrotonate to the title product in 16 h. Purification by flash column chromatography (6.6% EtOAc/pentane) gave the analytically pure product as a colorless solid (107 mg, 53% yield). M.p. 66 °C; ^{1}H NMR (250 MHz, [D]CHCl$_3$, 20 °C): $\delta = 7.68$ (d, ^3J(H,H) = 7.0 Hz, 2H; 2CH), 7.56 (d, ^3J(H,H) = 7.0 Hz, 2H; 2CH), 6.14 (s, 1H; CH), 3.76 (s, 3H; CH$_3$), 2.56 (s, 3H; CH$_3$); ^{13}C NMR (62.5 MHz, [D]CHCl$_3$, 20 °C): $\delta = 166.5$. 153.4, 146.4, 132.5, 132.1, 127.1, 126.9, 126.7, 118.4, 112.4, 52.4, 18.7; IR (ATR): $\tilde{\nu} = 2952$, 2227, 1713, 1625, 1439, 1351, 1169, 1034, 841 cm^{-1}; $C_{12}H_{11}NO_2$ (201.23): calcd C 71.63, H 5.51; found C 71.54, H 5.26.

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[11] See, for example: A. Spencer, *J. Organomet. Chem.* **1983**, *258*,102.
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[14] Yields for the reaction with 4-bromomethyl carboxylate and 4-bromobenzonitrile were 30% and 35%, respectively. Yields are based on GC yields using an internal standard (dodecane) and are corrected to the GC response factor of the product. Although the use of sodium bicarbonate has been suggested in the literature,[4b] this was found to give considerably slower reactions and lower yields.
[15] Because of the enamide nature of this product, isomerization takes place. This was checked by the isomerization of the pure *E* isomer under the reaction conditions.
[16] a) J. B. Melpolder, R. F. Heck, *J. Org. Chem.* **1976**, *41*, 265; b)R. F. Heck, *Org. React.* **1982**, *27*, 345, and references therein; c)S. Kagabo, Y. Shimizu, I. Chinatsu, K. Moriya, *Synthesis* **1992**, *9*, 830; R. Sarges, J. R. Tretter, *J. Org. Chem.* **1974**, *39*, 1710.
[17] The coupling of 2-ethyliodobenzene and 4-ethyliodobenzene led to the formation of the (*o*-ethylphenyl)-3-methylmethyl acrylate in low yields (30% and 40% and a *E*/*Z* ratio of 4:1 and 2:1 respectively).
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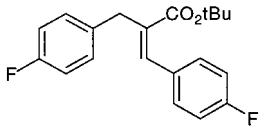
[20] The structure of the product of the double Heck reaction is as follows:



[21] The reaction of 4-bromotoluene with *trans*-cinnamonitrile gives a 2.7:1 isomeric ratio and the reaction of bromobenzene with *trans*-4-methylcinnamonitrile gives a 2.4:1 ratio of isomers with the opposite isomer predominating in the different cases (which isomer predominates in which reaction has not been determined). These results are in constrast to those realized by M. Moreno–Mañas et al. and presumably reflects differences in the catalyst systems used.[3a]
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