A Molten *n*-Bu_4NOAc/*n*-Bu_4NBr Mixture as an Efficient Medium for the Stereoselective Synthesis of (*E*)- and (*Z*)-3,3-Diarylacrylates

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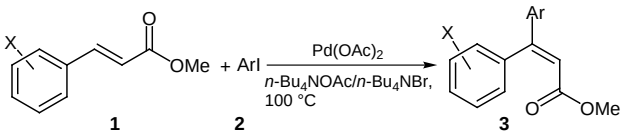
Abstract: The palladium-catalyzed reaction of neutral, slightly electron-rich and slightly electron-poor aryl iodides with methyl cinnamate in a molten *n*-Bu_4NOAc/*n*-Bu_4NBr 2:1.5 mixture provides a highly stereoselective route to (*E*)-3,3-diarylacrylates. Phosphine-free $Pd(OAc)_2$ is employed as precursor of Pd(0) species. The reaction of a variety of methyl 3-arylacrylates with phenyl iodide under the same reaction conditions affords stereoselectively the corresponding (*Z*)-isomers. The catalyst system can be recycled several times.

Key words: Heck reaction, stereoselectivity, molten salts, palladium, aryl halides

During our studies on the Heck reaction of disubstituted olefins,[1] α-substituted[2] and β-substituted α,β-unsaturated carbonyl compounds[3] we have found that many variables may influence the reaction outcome and that the presence of acetate anions[2d,3e–h] may have a beneficial effect on the rate, yield and stereoselectivity of the vinylic substitution reaction. As to the latter, evidence was attained that the presence of acetate anions in the Heck reaction of β-substituted α,β-unsaturated carbonyl compounds may favor the formation of vinylic substitution products with the original β-substituent on the same side of the carbonyl group. This was the basis of our domino Heck arylation/cyclization processes leading to the synthesis of quinolines,[3h] coumarins[3h] and cardenolides[3g] by using phosphine-free $Pd(OAc)_2$.

Our continuing interest in this olefin chemistry prompted us to explore the possibility of taking advantage of this acetate effect to develop a simple and stereoselective synthesis of 3,3-diarylacrylates from cinnamate esters. 3,3-Diaryl acrylates have been employed as intermediates in the preparation of a variety of pharmacologically active compounds such as angiotensin II antagonists,[4] platelet activating factor (PAF) antagonists,[5] and slow-reacting substance of anaphylaxis (SRS-A) antagonists.[6] This has provided the stimulus to the employment of the Heck arylation of cinnamate esters in the preparation of this class of compounds, with the stereoselectivity being the major task (the usually employed Wadsworth–Emmons reaction[4] affords a 1:1 stereoisomeric ratio). A variety of reaction conditions have been used[7–10]and, as far as stereochemistry is concerned, interesting results have been in some cases obtained. However, DMF or DMA are required as solvents,[8–10] hindered tertiary amines are needed as bases,[9] or *ortho* substituents are necessary on the aryl units (either on the aryl acrylate ester or the aryl iodide)[10] and the development of a general, simple and highly stereoselective process is still an important synthetic target.

We now report our preliminary results on the reaction of aryl iodides with 3-arylacrylates **1** in a molten *n*-Bu_4NOAc/*n*-Bu_4NBr mixture (Scheme). The reaction is carried out in the presence of $Pd(OAc)_2$ (no phosphine ligands are required) and a variety of 3,3-diarylacrylates **3** can be prepared, usually in good to high yield, with high stereoselectivity.



Scheme

In initial experiments the influence on the reaction course of solvents and bases was briefly investigated using methyl cinnamate and *p*-iodoanisole as the model system. Some of our results are summarized in Table 1.

As expected, with Et_3N as the base low stereoselectivity was achieved (Table 1, entries 1–3). Employment of an Et_3N/HOAc mixture increased the yield as well as the stereoselectivity (Table 1, entry 4). Switching to KOAc in DMF resulted in a further increase of the stereoselectivity (Table 1, entry 5), that reached a satisfactory 94:6 *E*:*Z* ratio[11] by using *n*-Bu_4NOAc in DMF (Table 1, entry 6). In the latter case, however, a significant decrease of the reaction rate was observed. Using *n*-Bu_4NOAc melt both as solvent and as base provided excellent stereoselectivity (*E*/*Z* = 99:1), but the vinylic substitution product was isolated in moderate yield (Table 1, entry 7), most probably because of its instability in the reaction medium. This view is supported by the observation that the vinylic substitution product and methyl cinnamate were recovered in only 55 and 35% yield when they were treated with *n*-Bu_4NOAc in the presence of iodoanisole at 100 °C for 7 hours, omitting palladium acetate.[12]

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Table 1 Bases and Solvents in the Palladium-catalyzed Reaction of *p*-Iodoanisole with Methyl Cinnamate[a,b]

Entry	Solvent	Base	Time (h)	Vinylic Substitution Product Yield %[c,d]	*E*:*Z* Ratio[e]
1	DMF	Et_3N	84[f]	40 (58)	65:35
2	MeCN	Et_3N	84[f]	27 (72)	60:40
3	–	Et_3N	84[f]	25 (75)	64:36
4	–	Et_3N/HOAc	48[f]	87 (9)	75:25
5	DMF	KOAc	72[f]	97 (2)	85:15
6	DMF	*n*-Bu_4NOAc	168[f]	84 (15)	94:6
7	*n*-Bu_4NOAc (3 equiv)		7[g]	63 (8)	99:1
8	*n*-Bu_4NOAc/*n*-Bu_4NBr (3 equiv:1.5 equiv)		4[g]	61 (4)	99:1
9	*n*-Bu_4NOAc/*n*-Bu_4NBr (3 equiv:1.5 equiv)		6.5[g]	50 (3)	99:1
10	*n*-Bu_4NOAc/*n*-Bu_4NBr (2 equiv:1.5 equiv)		3.5[g]	80 (3.5)	>99:1
11	*n*-Bu_4NOAc/*n*-Bu_4NBr (1.5 equiv:1.5 equiv)		7[g]	87 (10)	97:3

[a] Reactions in molecular solvents were conducted with 0.2 g of methyl cinnamate in 2 mL of solvent, under argon, using the following molar ratios: methyl cinnamate:*p*-iodoanisole:$Pd(OAc)_2$ = 1:1.5:0.02.
[b] Reactions in molten salts were conducted, under argon, with 0.1 g of methyl cinnamate using the following molar ratios: cinnamate:*p*-iodoanisole:$Pd(OAc)_2$ = 1:1.5:0.05.
[c] Yields refer to single runs and are given for isolated products.
[d] Figures in parentheses refer to the recovered methyl cinnamate.
[e] *E*/*Z* ratios were calculated by NMR analyses in C_6D_6.
[f] At 80 °C.
[g] At 100 °C.

Adding *n*-Bu_4NBr to *n*-Bu_4NOAc we were able to limit this side reaction, still achieving a high *E*/*Z* ratio. A 2:1.5 *n*-Bu_4NOAc/*n*-Bu_4NBr mixture provided a reasonable compromise between stereoselectivity and yield (Table 1, entry 10) and this ratio was employed when other aryl iodides were treated with methyl cinnamate[13] (Table 2) and phenyl iodide was treated with a variety of methyl 3-arylacrylates (Table 3). The latter were readily prepared via vinylic substitution of methyl acrylate with aryl iodides.[14]

The reaction produces good results with a variety of neutral, slightly electron-rich and slightly electron-poor aryl iodides. With aryl iodides bearing strongly electron-withdrawing substituents the reaction is inefficient (Table 1, entry 1; the reaction of *p*-nitrophenyl iodide with methyl cinnamate gave the Heck product in only 10% yield). However, these substituents (Table 3, entries 1 and 7) – along with other important functionalities – are well tolerated in the aromatic ring of the starting 3-arylacrylates. Formation of small amounts of biaryl derivatives has been observed in some cases.

Table 2 The Palladium-catalyzed Reaction of Aryl Iodides with Methyl Cinnamate in a Molten *n*-Bu_4NOAc/*n*-Bu_4NBr Mixture[a]

Entry	Aryl iodide **2**	Time (h)	Vinylic Substitution Product **3** Yield %[b]	*E*/*Z* Ratio[c]
1	*p*-EtOOC-C_6H_4-I	9	38	98:2
2	*p*-Cl-C_6H_4-I	6	50	>99:1
3	*p*-MeO-C_6H_4-I	3	80	>99:1
4	*p*-Me-C_6H_4-I	3.5	82	99:1
5	*m*-Me-C_6H_4-I	7	80	99:1
6	*p*-MeCONH-C_6H_4-I	3	91	>99:1
7	*m*-MeO-C_6H_4-I	9	70	>99:1
8	*p*-F-C_6H_4-I	5.5	60	99:1

[a] Reactions were conducted at 100 °C, under argon, in a *n*-Bu_4NOAc/*n*-Bu_4NBr mixture with 0.1 g of methyl cinnamate using the following molar ratios: methyl cinnamate:aryl iodide:$Pd(OAc)_2$ = 1:1.5:0.05.
[b] Yields refer to single runs and are given for isolated products.
[c] *E*/*Z* ratios were calculated by NMR analyses in C_6D_6.

Interestingly, no precipitation of palladium was usually observed. Since this could provide access to recycling procedures, we decided to assess this possibility and found that the catalyst system can be recycled several times without significant loss of activity. For example, the same catalyst system was used to carry out three preparations of the Heck product from *p*-iodoanisole and methyl cinnamate (80, 82 and 84% yield maintaining in each run an *E*:*Z* > 99:1 ratio) and no precipitation of palladium was observed.[15]

As for the stereochemical outcome, equilibration subsequent to Heck arylation has been suggested to occur in the case of reactions of cinnamate esters[7–9] and this has been invoked to account for the observed lack of selectivity.[7] Under our conditions, however, it seems that the stereoselectivity is originated during the vinylic substitution reaction. This view is supported by the fact that highly stereoselective preparation of both (*E*) and (*Z*) stereoisomers was achieved by selecting proper aryl iodides and aryl acrylates and by the following experiment. A pure sample of methyl (*E*)-3-(*p*-methoxyphenyl)-3-phenylacrylate was subjected to reaction conditions producing vinylic substitution products in the presence of methyl cinnamate and *p*-acetamidophenyl iodide. Methyl (*E*)-3-(*p*-methoxyphenyl)-3-phenylacrylate was recovered in quantitative yield and its stereochemistry was maintained, even under prolonged heating. The 3,3-diarylacrylate product formed through the reaction of *p*-acetamidophenyl iodide with methyl cinnamate was isolated in 90% yield.

In effect, stereoisomers might form during the Heck reaction through the well-known elimination–readdition–elimination of hydridopalladium species involving σ-

Table 3 The Palladium-catalyzed Reaction of Phenyl Iodide with Methyl 3-Arylacrylates in a molten *n*-Bu_4NOAc/*n*-Bu_4NBr mixture[a]

Entry	Methyl 3-Arylacrylate **1** X	Time (h)	Vinylic Substitution Product **3** Yield %[b]	E/Z Ratio[c]
1	*p*-COOEt	3.5	84	4:96
2	*p*-Cl	3	73	>1:99
3	*p*-OMe	4	78	2:98
4	*p*-Me	3.5	72	>1:99
5	*m*-Me	6	70	1:99
6	*p*-NHCOMe	5	70	1:99
7	*p*-NO_2	3	70	1:99
8	*m*-OMe	5	76	>1:99
9	*p*-F	6	72	>1:99

[a] Reactions were conducted at 100 °C, under argon, in a *n*-Bu_4NOAc/*n*-Bu_4NBr mixture with 0.1 g of methyl cinnamate using the following molar ratios: methyl cinnamate:aryl iodide:$Pd(OAc)_2$ = 1:1.5:0.05.
[b] Yields refer to single runs and are given for isolated products.
[c] *E*/*Z* ratios were calculated by NMR analyses in C_6D_6.

alkylpalladium adducts. An alternative working hypothesis considers isomerization through equilibration between α-palladated esters and palladium *O*-enolates. The presence of palladium *O*-enolates have been invoked in several cases to account for experimental data[16] (they have also been prepared via the reaction of ArPdBr(bidentate phosphine ligand) with the enolate of isobutyrophenone)[17] and may be responsible for the lack of stereoselectivity in this type of reaction.

Under our conditions, however, acetate anions might play a key role in controlling the stereoselectivity. Their presence might favor the irreversible displacement of palladium from σ-alkylpalladium adducts (possibly through basic intramolecular attack of the acetate moiety of the putative σ-alkylpalladium acetate intermediates on the β-hydrogen),[3e] thus suppressing both the possible isomerization mechanisms.

Several other details of the mechanism of the present reaction are likely to be affected by the nature of the reaction medium. For example, large ammonium cation have been shown to stabilize palladium-nanoparticles[18] and halide and acetate anions have been reported to stabilize palladium(0) through the formation of anion associated anionic palladium(0) species.[19,20] These effects might play a role in our procedure, but we have not investigated this point.

To sum up, we have developed a simple, highly efficient procedure for the stereoselective preparation of both (*E*)- and (*Z*)-isomers of 3,3-diarylacrylates. Recycling of the catalyst system represents an interesting promising future of our protocol. Further work is under way to evaluate the scope of the present procedure and get a better understanding of the catalytic cycle.

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(11) The stereochemistry of vinylic substitution products obtained via our model reaction was established by NOE experiments on pure isomers. That of the other vinylic substitution derivatives has been assigned based on these data.
(12) Interestingly, methyl 3-(*p*-methoxyphenyl)-3-phenylacrylate and methyl cinnamate were recovered in only 30 and 20% yield, respectively, when they were separately subjected to *n*-Bu_4NOAc at 100 °C for 7 h omitting all the other reactants. The corresponding acids were isolated in 70 and 67% yield.

(13) A typical procedure for the preparation of **3** is as follows: to a stirred solution of methyl cinnamate (0.104 g, 0.641 mmol), *p*-iodoanisole (0.225 g, 0.962 mmol), tetrabutylammonium acetate (0.387 g, 1.284 mmol) and tetrabutylammonium bromide (0.310 g, 0.962 mmol) at 100 °C under argon, palladium diacetate (0.007 g, 0.032 mmol) was added. The mixture was stirred at the same temperature for 3 h. Then it was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated under vacuum. The residue was chromatographed on silica gel eluting with *n*-hexane/ethyl acetate (92/8 v/v) to afford 0.134 g (78%) of methyl 3-(*p*-methoxyphenyl)-3-phenylacrylate (*E*:*Z* > 99:1). A sample was further purified through preparative HPLC to give pure methyl (*E*)-3-(*p*-methoxyphenyl)-3-phenylacrylate: Mp 70–71 °C; IR (KBr): 1724 cm^{-1}; ^1H NMR: δ = 7.43–7.38 (m, 3 H), 7.30–7.20 (m, 4 H), 6.89–6.82 (m, 2 H), 6.35 (s, 1 H), 3.82 (s, 3 H), 3.62 (s, 3 H); ^{13}C NMR: δ = 166.6, 160.9, 156.9, 139.1, 133.1, 129.8, 129.1, 128.1, 127.9, 114.7, 113.8, 55.4, 51.2; MS: *m/z* (relative intensity) = 268(100) [M^+], 237(81), 165(47), 135(36). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.12; H, 6.01. Found: C, 76.01; H, 6.12.
Selected NMR and MS data for (*Z*)-3-(*p*-methoxyphenyl)-3-phenylacrylate: ^1H NMR: δ = 7.36–7.29 (m, 5 H), 7.20–7.15 (m, 2 H), 6.94–6.89 (m, 2 H), 6.29 (s, 1 H), 3.85 (s, 3 H), 3.65 (s, 3 H); ^{13}C NMR: δ = 166.6, 159.8, 157.1, 141.5, 130.9, 130.8, 129.4, 128.6, 128.3, 116.2, 113.2, 55.2, 51.2; Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.15; H, 6.02. MS: *m/z* (relative intensity)= 268(100) [M^+], 237(77), 165(53), 135(30).

(14) A typical procedure for the preparation of cinnamate esters is as follows: to a solution of methyl acrylate (422 μL, 4.68 mmol), *p*-iodoanisole (365 mg, 1.56 mmol), and Et_3N (653 μL, 4.68 mmol) in DMF (2 mL) $Pd(OAc)_2$ (7 mg, 0.03 mmol) was added. The solution was stirred at 80 °C for 24 h under argon. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated under vacuum. The residue was chromatographed on silica gel eluting with *n*-hexane/ethyl acetate (90/10 v/v) to afford 279 mg (93% yield) of methyl 3-(*p*-methoxyphenyl)acrylate: Mp 87–88 °C; IR (KBr): 1717 cm^{-1}; ^1H NMR: δ = 7.64 (d, 1 H, *J* = 15.94 Hz), 7.50–7.43 (m, 2 H), 6.92–6.86 (m, 2 H), 6.30 (d, 1 H, *J* = 16 Hz), 3.83 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR: δ = 167.8, 161.4, 144.5, 129.7, 127.1, 115.3, 114.3, 55.4, 51.6; MS: *m/z* (relative intensity) = 192(73) [M^+], 161(100), 133(27). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.60; H, 6.37.

(15) Recycles were carried out by extracting the reaction mixture with diethyl ether and adding *n*-Bu_4OAc to the mixture of the remaining ammonium salts to restore the proper amount of acetate anions (during the vinylic substitution reaction acetate anions are converted into acetic acid, which is lost in the extraction).

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