Stereospecific Preparation of (*E*) and (*Z*)-3,3-Diarylacrylonitriles by Heck Reaction

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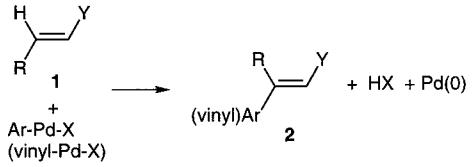
Abstract: Both isomers **5** and **8** of 3,3-diarylacrylonitrile constitution are obtained in highly diastereoselective Pd-catalyzed Heck reactions under Jeffery conditions between (*E*)-cinnamonitriles and aryl iodides.

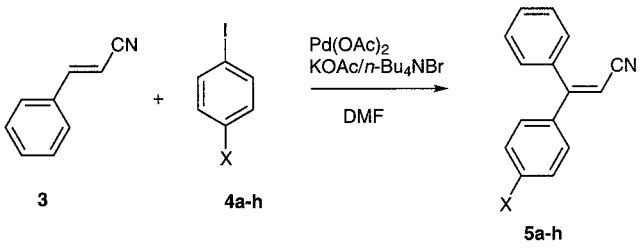
The palladium-catalyzed arylation and vinylation of alkenes (the Heck reaction)[1] is a versatile method of carbon-carbon coupling and several reviews have been recently published,[1c,2] some of them covering intramolecular applications.[3] Although the Heck reaction gives in general excellent results for the preparation of disubstituted ethylenes, less applications to the preparation of trisubstituted olefins have been reported. The mechanistic features of the Heck reaction are well known and they include *syn* addition of the organopalladium (e.g. Ar-Pd-X) to olefin **1** followed by *syn* elimination of H-Pd-X to afford stereospecifically the final olefin **2** (Scheme 1).



Scheme 1

Experimental improvements including the introduction of phase transfer catalysts have broaden the scope of this palladium-catalyzed arylation and vinylation of olefins.[4] Therefore, the Heck reaction is perfectly suitable for the stereospecific preparation of trisubstituted olefins. Previous work by other groups include vinylation or arylation of olefins featuring Y = CHO, CO-Me, or COOMe.[5-9] Since stereospecific preparation of 3,3-diarylacrylates is an important target,[10,11] we studied the Heck reaction of cinnamates with aryl iodides (Y = COOEt, R = Ar^1, and Ar = Ar^2 in Scheme 1).[11] Although the research was successful the severe experimental conditions required produced some *E-Z* equilibration on the resulting 3,3-diarylacrylates. For this reason we looked for a functional group less sterically demanding which could permit milder experimental conditions. The nitrile group was our choice.

Now we present our results on the stereospecific Heck reaction on cinnamonitriles leading to stereochemically pure 3,3-diarylacrylonitriles. These compounds have been non stereoselectively prepared from benzophenones either by aldol[10,12] or Wittig-type reactions.[12] The reactions of cinnamonitrile (**3**) with several *para*-substituted aryl iodides (**4a-h**) give (*E*)-3,3-diarylacrylonitriles **5a-h** with high stereoselectivity since in most cases isomers *Z* could not be detected (Scheme 2 and Table 1). After some optimization Jeffery conditions[4] under phase transfer catalysis gave the best results. Longer reaction times and higher temperatures were required when electron-withdrawing substituents were present in **4** (entries 6 to 10 in Table 1). In these cases reductive self-coupling of iodides **4** to give biphenyls was a side reaction. Under these circumstances a variation of the Jeffery conditions using $NaHCO_3$ and *n*-Bu_4NCl instead of KOAc and *n*-Bu_4NBr gave better results. The stereochemical identities of **5b** and **8h** were verified by NOE experiments, all other compounds are supposed to belong to the same stereochemical families.



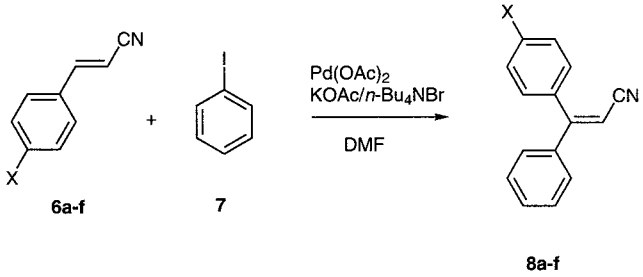
Scheme 2

Table 1. (*E*)-Diarylacrylonitriles (**5**) by Heck reaction of cinnamonitrile (**3**) with aryl iodides (**4**)

Entry	X	*t*(°C)/days	5[a] %[b]	5 mp (°C)
1	NH_2	80/2	**5a** 78	138-140
2	MeO	80/1	**5b** 84	70-71
3	AcNH	80/3	**5c** 86	182-184
4	Me	80/2	**5d** 80 (91)c	74-75
5	H	80/3	**5e** 74 (88)c	oild
6	Cl	80/7	**5f** 55 (71)c	oile
7	Cl	100/2 + 120/8	**5f** 73 (81)c,f	oile
8	Cl	100/6 + 120/2	**5f** 69 (75)c,g,h	oile
9	MeCO	80/2+ 100/6	**5g** 28 (51)g,i	91-93
10	CF_3	100/6 + 120/2	**5h** 28 (58)c,g	82-84

[a] All compounds **5** showed spectroscopic behavior as expected and correct elemental analysis; [b] yields of pure isolated products, in parentheses yields with respect to non recovered **3**; [c] yield calculated by ^1H NMR integration of mixtures of **3** and **5**; [d] bp 190-200 °C (bulb-to-bulb)/0.1 mmHg (Lit.[13] bp 128-131 °C/0.2 mmHg); [e] bp 230-235 °C(bulb-to-bulb)/0.1 mmHg; [f] reaction carried out in the presence of 20% molar of tri-*o*-tolylphosphine, 5% of *Z* isomer was obtained; [g] *n*-Bu_4NCl and $NaHCO_3$ were used instead of *n*-Bu_4NBr and KOAc; [h] 6% of *Z* isomer was obtained; [i] 4% of *Z* isomer was obtained.

In order to prepare isomers (*Z*)-3,3-diarylacrylonitriles **8a-f** (Scheme 3) *para*-substituted cinnamonitriles **6** were required. They were prepared by KOH catalyzed condensation of acetonitrile with *para*-substituted benzaldehydes according to the literature.[13] Pure isomers (***E*)-6** were isolated by recrystallization.[14] Cinnamonitriles **6** reacted with excess of iodobenzene (**7**) under the already defined Jeffery conditions to afford (*Z*)-3,3-diarylacrylonitriles **8a-f** in completely stereoselective reactions (Scheme 3 and Table 2).



Scheme 3

Table 2. (Z)-3,3-Diarylacrylonitriles (**8**) by Heck reaction of cinnamonitriles (**6**) with iodobenzene (**7**)

Entry	X	*t*(°C)/days	**8**[a] %[b]	**8** mp (°C)
1	NH_2	80/3	**8a** 60 (79)	103-105
2	MeO	80/3	**8b** 76	oil[c]
3	AcNH	80/3	**8c** 73 (88)	153-155
4	Me	80/4	**8d** 75 (87)	73-75
5	Cl	80/3	**8f** 80	84-86
6	CF_3	80/2	**8h** 74 (86)	105-106

[a] All compounds **8** showed spectroscopic behavior as expected and correct elemental analysis; [b] yields of pure isolated products, in parentheses yields with respect to non recovered **6**; [c] bp 240-245 °C (bulb-to-bulb)/0.1 mmHg.

In summary, both stereoisomers of 3,3-diarylacrylonitrile constitution can be obtained by separate Pd-catalyzed arylation of cinnamonitriles with stereoselectivities higher than those observed in similar reactions with cinnamic esters.[11]

Typical experimental procedure:

*(E)-3-(4-Methoxyphenyl)-3-phenyl-2-propenenitrile (**5b**)* Cinnamonitrile (**3**) (0.28 mL, 0.29 g, 2.24 mmol) was added to a mixture of 4-methoxyphenyl iodide (**4b**) (1.00 g, 4.27 mmol), potassium acetate (0.55 g, 5.60 mmol), tetrabutylammonium bromide (0.79 g, 2.45 mmol), palladium acetate (25 mg, 0.11 mmol) and DMF (8 mL) kept under nitrogen atmosphere and at room temperature. The mixture was heated at 80 °C under magnetic stirring for 1 day (GC monitoring), and cooled at room temperature. Then water (75 mL) was added and the mixture partitioned with diethyl ether (3 x 60 mL). The organic layer was sequentially washed with brine (2 x 100 mL) and with water (100 mL), dried with sodium sulfate, and the solvent was evaporated. The residue was chromatographed on silica gel eluting with *n*-hexane-ethyl acetate (95/5) to afford **5b** as a white solid (0.44 g, 84%), mp 70-71 °C; IR(KBr) 2934, 2215, 1602, 1587, 1512, 1354, 1253, 1185, 1030, 817 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.84 (s, 3H), 5.67 (s, 1H), 6.87 (AA' part of the AA'BB' system, *J* = 8.8 Hz, 2H), 7.24 (BB' part of the AA'BB' system, *J* = 8.8 Hz, 2H), 7.42-7.46 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.3, 92.7, 114.0, 118.2, 128.4, 129.5, 129.8, 129.9, 131.0, 137.2, 161.5, 162.5; MS (*m/z*) 235 (M^+, 100), 220 (14), 204 (12), 195 (13), 165 (16); Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N. 5.95. Found: C, 81.46; H, 5.59; N, 5.81.

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References and Notes

(1) a) Heck, R.F. *Acc. Chem. Res.* **1979**, *12*,146.
b) Heck, R.F. *Org. React. (N.Y.)* **1982**, *27*, 345.
c) Heck, R.F. Vinyl Substitutions with Organopalladium Intermediates. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4.3

(2) a) De Meijere, A.; Meyer, F.E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.
b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

(3) a) Negishi, E.; Coperet, C.; Ma, S.; Liou, S-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.
b) Gibson, S.E.; Middleton, R.J. *Contemp. Org. Synth.* **1996**, *3*, 447.

(4) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(5) Harnisch, W.; Morera, E.; Ortar, G. *J. Org. Chem.* **1985**, *50*, 1990.

(6) Amorese, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerrini, S.; Fedeli, W.; Ortar, G. *Tetrahedron* **1989**, *45*, 813.

(7) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Tetrahedron* **1996**, *52*, 6983.

(8) Cacchi, S.; Ciattini, P.G.; Morera, E.; Pace, P. *Synlett* **1996**, 545.

(9) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F., Pace, P. *Synlett* **1996**, 568.

(10) Almansa, C.; Gómez, L.A.; Cavalcanti, F.L.; de Arriba, A.F.; Rodríguez, R.; Carceller, E.; García-Rafanell, J.; Forn, J. *J. Med. Chem.* **1996**, *39*, 2197.

(11) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *Tetrahedron Lett.* **1996**, *37*, 7449.

(12) Blank, B.; Zuccarello, W.A.; Cohen, S.R.; Frishmuth, G.J.; Scariacaciottoli, D. *J. Med. Chem.* **1969**, *12*, 271.

(13) DiBiase, S.A.; Lipisko, B.A.; Haag, A.; Wolak, R.A.; Gokel, G.W. *J. Org. Chem.* **1979**, *44*, 4640.

(14) Physical constants of compounds **6**: **6a**: mp 109-111 °C (Lit.[15] mp 109-110 °C); **6b**: mp 62-63 °C (Lit.[13] mp 62-63 °C); **6c**: mp 200-202 °C; **6d**: mp 70-71°C (Lit.[13] mp 71-72 °C); **6f**: mp 84-86 °C (Lit.[13] mp 84-86 °C); **6h**: mp 98-99 °C (Lit.[16] mp 97.5-98.5 °C). Compounds **6a** and **6c** were obtained in the same reaction from *p*-acetylaminobenzaldehyde, partial hydrolysis affording **6a**.

(15) Dolter, R.J.; Curran, C. *J. Am. Chem. Soc.* **1960**, *82*, 4153.

(16) Claisse, J.A.; Gregory, G.I.; Warburton, W.K. *US Patent* 4012377 (**1977**); *Chem. Abstr.* **1978**, *87*, 39491.