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Facile route to dihydroindacene type ligands using multiple Heck reactions on aryl polybromides

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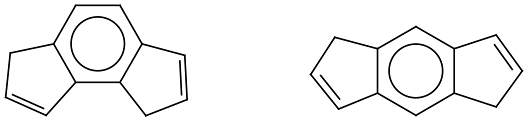
Abstract—The Heck reaction of aryl dibromides and *n*-butyl acrylate catalyzed by $Pd(OAc)_2/P(t\text{-}Bu)_3$ is a high yielding method to produce intermediates for dihydroindacene type ligands. The same synthetic strategy, extended to tribromides, represents a simple route also to tridentate ligands potentially useful in the stabilization of trimeric metal complexes and clusters. © 2002 Elsevier Science Ltd. All rights reserved.

The Heck reaction represents a powerful method to create new C–C σ bonds by reaction of an aryl or vinyl halide and an olefin.[1,2] The reaction, which is catalyzed by palladium complexes through a catalytic cycle presumably involving a Pd^0/Pd^{II} mechanism, leads to the arylation or vinylation of the olefin, with a regiochemistry dependent on the nature of the olefin as well as on the catalyst and on the reaction conditions. The generality and versatility of the Heck reaction has powered its successful application in numerous synthetic routes leading to molecules of practical interest, some of which have reached commercialization.[3] Most of these routes involve the simple Heck reaction of an aryl monohalide with an olefin; however, there are still relatively few accounts of synthetic strategies for the preparation of useful molecules involving multiple Heck reactions on aryl polyhalides.[4]

We have been working for some years on bimetallic complexes having the tricyclic indacenediide ligand as a spacer.[5] The *s*- and *as*-indacenediide systems represent very interesting bridging ligands for two metal model complexes in order to evaluate cooperative electronic effects between the metals which may determine remarkable changes in the physical and chemical properties of one or both metal centers. It is to note, however, that a limiting factor to the synthesis and the study of this type of complexes is the availability of the ligand precursors, the *s*- and *as*-dihydroindacenes (Fig. 1; only one isomer for the two parent structures is displayed for simplicity). In fact, most of the synthetic procedures used up to date require complicated multistep reaction sequences with unsatisfactory overall yields.[6,7]

Functionalized benzene substrates having preformed C–C bonds are in some cases precursors for the tricyclic systems.[7] As an example, in the synthesis of 2,7-dimethyl-1,6-*as*-dihydroindacene, a sequence of complex and tedious reactions (overall yield lower than 20%) is necessary to prepare from *m*-xylene the intermediate *meta*-di-(2-carboxy-*iso*-propyl)benzene **1** which upon double cyclization with polyphosphoric acid



1,6-*as*-dihydro-indacene

1,5-*s*-dihydro-indacene

Figure 1. Isomers of *as*- and *s*-dihydroindacenes.

Keywords: Heck reaction; palladium; catalysis; functionalized benzenes; ligand molecules.

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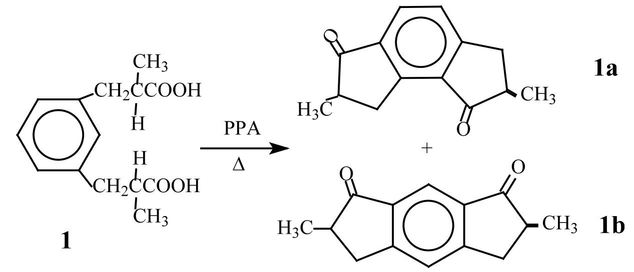
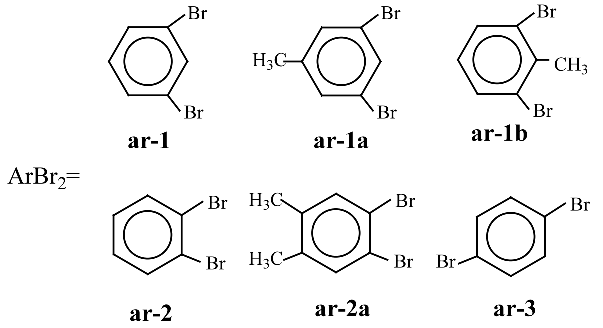


Scheme 1. Products of the double cyclization of **1**.

(PPA) produces the indacenediones **1a** and **1b** in molar ratio n_{1a}/n_{1b} 7:1 (Scheme 1), subsequently transformed into the corresponding dihydroolefins.[7a]

We have been thinking of a more effective synthetic route to difunctionalized benzene derivatives like **1** by introducing a reaction sequence involving a multiple Heck reaction on aryl dihalides as the first step. In this paper, we wish to report our preliminary results on this subject.

We have chosen the following aryl dibromides, $ArBr_2$, *m*-dibromobenzene, **ar-1**, 3,5-dibromotoluene, **ar-1a**, 2,6-dibromotoluene, **ar-1b**, *o*-dibromobenzene, **ar-2**, 3,4-dibromo-*o*-xylene, **ar-2a**, *p*-dibromobenzene, **ar-3**, which are commercially available and differ for the relative position of the bromine atoms or for the presence of methyl groups, and we have tested them in the Heck reaction with *n*-butyl acrylate (1.36 equiv.) in the presence of sodium acetate as the base (Eq. (1)):[8] the catalytic system was made out of palladium acetate (0.01 equiv.) and tris-*t*-butylphosphine (0.02 equiv.), according to the procedure developed by Fu.[9]



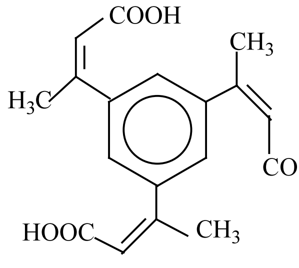
The yields, reported in Table 1, fluctuate between 50 and 75%: the higher yield obtained for the *p*-dibromo substrate **ar-3** seems to be accounted for by a more simple and effective way of purification of the product which was collected as a white powder from methanol, while the *ortho* and *meta* derivatives were obtained as colorless oil by column chromatography on silica gel eluting with petroleum ether. The presence of the methyl group on the ring causes a slight decrease in the yield of the reaction. This is in accordance with the fact that the electron donor properties of methyl substituents make the aryl dibromide less reactive towards oxidative addition to the intermediate Pd(0) complex.[1]

Some elucidation on the reaction mechanism can be drawn out from the analysis of the byproducts: in fact the product obtained by the substitution of just one bromine with an acrylic ester was always present, in particular in more remarkable amount for **ar-1b**, **ar-2**, and **ar-2a**. Such a result suggests that the formation of the C–C bonds occurs in two successive steps and that steric effects due to the presence of a substituent in *ortho* position, which may be another bromine like in **ar-2** and **ar-2a** or a methyl group like **ar-1b**, can negatively affect the reaction yield as well.

All the products have been characterized by NMR spectroscopy (Table 1): Heck arylation at the β carbon atom of the acrylic ester with *trans* stereoselectivity is observed in all cases. The *trans*,*trans* isomer can be easily identified from the value of the vicinal coupling constant of the vinyl protons [$^3J(H,H) = 16$ Hz].

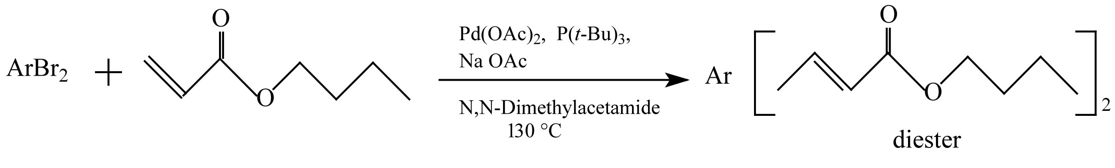
Standard palladium-catalyzed hydrogenation of the double bonds of the diesters and subsequent basic hydrolysis of the ester groups quantitatively yielded dicarboxylic acids similar in structure to **1**. In this way, such dicarboxylic acids become accessible from commercial precursors in only three steps and with a superior overall yield in comparison to the previously reported routes.

The same synthetic strategy[10] was utilized to develop a simple route to the tricarboxylic acid **aci-1**, a tridentate ligand potentially useful in the stabilization of trimeric metal complexes and clusters such as those derived from the $Pd(OAc)_2$ trimer.[11]



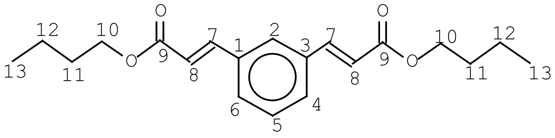
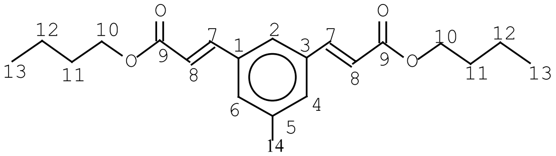
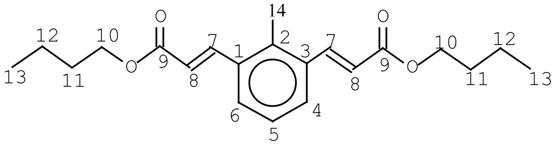
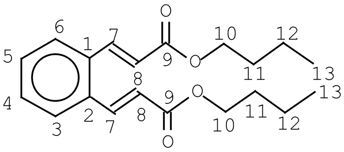
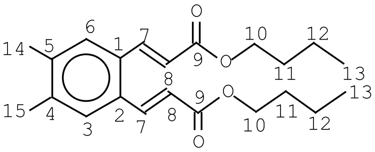
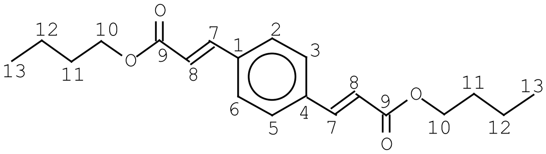
aci-1

In this case, an *all-cis* stereochemistry of the substituents in the reaction product is needed, hence the *trans* position in the starting acrylic ester has to be blocked by substitution. However, care should be taken in doing this since substitution decreases the reactivity of the alkene and can favor competitive Heck arylation at the α carbon atom. Nevertheless, upon reaction of 1,3,5-tribromobenzene with methyl crotonate under the



(1)

Table 1. The diesters obtained from the double Heck reaction with *n*-butyl acrylate, related yields and NMR data

Diester (yield)	NMR data (400 MHz, $CDCl_3$, ppm)
 1,3-di(2-*n*-butoxycarbonyl-*trans*-vinyl)-benzene **es-1** (70%)	**^{1}H-NMR** : 0.97 (t, J = 7.4 Hz, 6H, H13), 1.44 (m, 4H, H12), 1.70 (m, 4H, H11), 4.22 (t, J = 6.6 Hz, 4H. H10), 6.47 (J_{AB} = 16.0 Hz, 2H, H7), 7.41 (t, J = 7.7 Hz, 1H, H5), 7.52 (d, J = 7.7 Hz, 2H, H4, H6), 7.65 (m, 1H, H2), 7.67 (J_{AB} = 16.0 Hz, 2H, H8). **^{13}C-NMR** : 13.73 (2C, C13), 19.19 (2C, C12), 30.75 (2C, C11), 64.56 (2C, C10), 119.33 (2C, C7), 129.36 (2C, C4, C6), 127.20 (1C, C2), 129.41 (1C, C5), 134.80 (2C, C1, C3), 143.60 (2C, C8), 166.81 (2C, C9).
 3,5-di(2-*n*-butoxycarbonyl-*trans*-vinyl)-toluene **es-1a** (50%)	**^{1}H-NMR** : 0.97 (t, J = 7.4 Hz, 6H, H13), 1.45 (m, 4H, H12), 1.70 (m, 4H, H11), 2.39, (s, 3H, H14), 4.22 (t, J = 6.6 Hz, 4H. H10), 6.46 (J_{AB} = 16.0 Hz, 2H, H7), 7.35 (m, 2H, H4, H6), 7.47 (m,1H, H2), 7.64 (J_{AB} = 16.0 Hz, 2H, H8). **^{13}C-NMR**: 13.73 (2C, C13), 19.19 (2C, C12), 21.22 (1C, C14), 30.75 (2C, C11), 64.50 (2C, C10), 119.06 (2C, C7), 124.92 (1C, C2), 130.24 (2C, C4, C6), 135.09 (2C, C1, C3), 139.19 (1C, C5), 143.78 (2C, C8), 166.87 (2C, C9).
 2,6-di(2-*n*-butoxycarbonyl-*trans*-vinyl)-toluene **es-1b** (50%)	**^{1}H-NMR**: 0.97 (t, J = 7.4 Hz, 6H, H13), 1.43 (m, 4H, H12), 1.68 (m, 4H, H11), 2.46 (s, 3H, H14), 4.22 (t, J = 6.7 Hz, 4H, H10), 6.32 (J_{AB} = 15.1 Hz, 2H, H7), 7.23 (t, J = 7.8 Hz, 1H. H5), 7.53 (d, J = 7.8 Hz, 2H, H4, H6), 8.03 (J_{AB} = 15.1 Hz, 2H, H8). **^{13}C-NMR**: 13.73 (2C, C13), 15.61 (1C, C14), 19.19 (2C, C12), 30.75 (2C, C11), 64.53 (2C, C10), 120.88 (2C, C7), 126.33 (1C, C5), 128.21 (2C, C4, C6), 137.12, 134.86, (3C, C1, C2, C3), 143.78 (2C, C8), 166.85 (2C, C9).
 1,2-di(2-*n*-butoxycarbonyl-*trans*-vinyl)-benzene **es-2** (60%)	**^{1}H-NMR**: 0.96 (t, J = 7.3 Hz, 6H, H13), 1.43 (m, 4H, H12), 1.69 (m, 4H, H11), 4.21 (t, J = 6.6 Hz, 4H, H10), 6.34 (J_{AB} = 15.8 Hz, 2H, H7), 7.38 (m, 2H, H4, H5), 7.56 (m, 2H, H3, H6), 8.02 (J_{AB} = 15.8 Hz, 2H, H8). **^{13}C-NMR**: 14.16 (2C, C13), 19.60 (2C, C12), 32.22 (2C, C11), 65.02 (2C, C10), 122.34 (2C, C7), 128.04 (2C, C3, C6), 130.38 (2C, C4, C5), 134.71 (2C, C1, C2), 141.65 (2C, C8), 166.89 (2C, C9).
 4,5-di(2-*n*-butoxycarbonyl-*trans*-vinyl)-*o*-xylene **es-2a** (50%)	**^{1}H-NMR**: 0.97 (t, J = 7.4 Hz, 6H, H13), 1.44 (m, 4H, H12), 1.69 (m, 4H, H11), 2.29 (s, 6H, H14, H15) 4.22 (t, J = 6.7 Hz, 4H, H10), 6.32 (J_{AB} = 15.9 Hz, 2H, H7), 7.36 (s, 2H, H3, H6), 8.00 (J_{AB} = 15.9 Hz, 2H, H8). **^{13}C-NMR**: 13.74 (2C, C13), 19.19 (2C, C12), 19.71 (2C, C14, C15), 30.75 (2C, C11), 64.49 (2C, C10), 120.65 (2C, C7), 128.62 (2C, C3, C6), 131.87 (2C, C1, C2), 139.13 (2C, C4, C5), 141.15 (2C, C8), 166.73 (2C, C9).
 1,4-di(2-*n*-butoxycarbonyl-*trans*-vinyl)-benzene **es-3** (75%)	**^{1}H-NMR**: 0.97 (t, J = 7.3 Hz, 6H, H13), 1.43 (m, 4H, H12), 1.69 (m, 4H, H11), 4.21 (t, J = 6.6 Hz, 4H, H10), 6.34 (J_{AB} = 16.1 Hz, 2H, H7), 7.54 (s, 4H, H2, H3, H5, H6), 7.66 (J_{AB} = 16.1 Hz, 2H, H8). **^{13}C-NMR**: 13.74 (2C, C13), 19.20 (2C, C12), 30.76 (2C, C11), 64.58 (2C, C10), 128.51 (4C, C2, C3, C5, C6), 136.18 (2C, C1, C4), 143.40 (2C, C8), 166.87 (2C, C9).

same conditions listed above, the *all-cis* trisubstituted ester product was obtained, which was subsequently hydrolyzed to yield **aci-1** in 40% yield. The *all-cis* geometry is maintained in the final product as proved by its ^{1}H NMR spectrum:[10] just one signal is observed for the aromatic protons, as well as for the methyl and vinyl protons, whose *cis* geometry was clearly established upon considering their very small coupling constant (1.3 Hz).

Acknowledgements

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References

1. For a comprehensive review, see: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
2. Biffis, A.; Zecca, M.; Basato, M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 249.
3. De Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086.
4. For some examples, see: de Meijere, A.; Meier, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.
5. (a) Santi, S.; Ceccon, A.; Bisello, A; Crociani, L.; Gambaro, A.; Tiso, M.; Venzo, A. *Organometallics* **2002**, *21*, 2679; (b) Ceccon, A.; Bisello, A; Crociani, L.; Gambaro, A.; Ganis, P.; Manoli, F.; Santi, S.; Venzo, A. *J. Organomet. Chem.* **2000**, *600*, 94; (c) Ceccon, A.; Bisello, A; Gambaro, A.; Ganis, P.; Manoli, F.; Santi, S.; Venzo, A. *J. Organomet. Chem.* **2000**, *594*, 315.
6. (a) Wightman, H.; Wain, R. J.; Lake, D. H. *Can. J. Chem.* **1971**, 1360; (b) Corruthers, W.; Stewart, H. N. M.; Hansell, P. G.; Kelly, K. M. *J. Chem. Soc.* **1967**, 2607; (c) Stapler, J. T.; Bornstein, J. *J. Heterocyclic Chem.* **1973**, *10*, 983.
7. (a) Bell, W. L.; Curtis, C. J.; Eigenbrot, C. W., Jr.; Pierpont, C. G.; Robbins, J. L.; Smart, J. C. *Organometallics* **1987**, *6*, 266; (b) Trogen, L.; Edlund, U. *Acta Chem. Scand.* **1979**, *B33*, 109; (c) Dabrouch, M. R.; Jara, P.; Mendez, L.; Portilla, Y.; Abril, D.; Alfonso, G.; Chavez, I.; Manriquez, J. M. *Organometallics* **2001**, *20*, 5591.
8. *Typical procedure*: To a solution of aryl dibromide (21 mmol), NaOAc (3.50 g, 84 mmol), *N*,*N*-dimethylacetamide (40 mL) and butyl acrylate (8.16 mL, 57 mmol), heated at 130°C, was added a solution of $Pd(OAc)_2$ (0.047 g, 0.21 mmol) and $P(t\text{-Bu})_3$ (0.084 g, 0.42 mmol) in *N*,*N*-dimethylacetamide (10 mL), preheated at 80°C. After stirring at 130°C for one day the mixture was allowed to reach room temperature. A 5% solution of potassium bicarbonate in H_2O (50 mL) and toluene (30 mL) were then added, the phases were separated and the aqueous layer was extracted again twice with additional toluene (2×30 mL). The combined organic extracts were washed with brine (3×50 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The oily residue was chromatographed over silica gel (eluent petroleum ether) to afford the diester as a white oil. In the case of the dibromide **ar-3** the residue was a solid from which the diester was recovered pure as a white solid by washing the residue with methanol. All the yields are reported in Table 1.
9. Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10.
10. *Preparation of **aci-1***. To a mixture of 1,3,5-tribromobenzene (2.00 g, 6.35 mmol), NaOAc (1.60 g, 19.1 mmol), $Pd(OAc)_2$ (44 mg, 0.38 mmol) and *N*,*N*-dimethylacetamide (40 mL) was added under dinitrogen a 1.24 M solution of $P(t\text{-Bu})_3$ (240 μL, 1.14 mmol) in *N*,*N*-dimethylacetamide. After heating at 120°C, methyl crotonate (10 mL) was added to the system. After stirring at 120°C overnight, the reaction mixture was allowed to reach room temperature. Water (10 mL) and toluene (30 mL) were then added, the phases were separated and the aqueous layer was extracted with additional toluene (10 mL). The combined organic extracts were washed with water (2×10 mL), filtered over Celite and dried over $MgSO_4$. The solvent was removed under reduced pressure and the oily residue was chromatographed over silica gel (eluent: *n*-hexane:ethyl acetate 5:1, $R_f = 0.50$) to afford the triester product of the triple Heck reaction as a white solid. Yield 0.95 g (40%). ^1H NMR (400 MHz, $CDCl_3$, ppm): 2.60 (s, 9H, $-CH_3$), 3.77 (s, 9H, $-OCH_3$), 6.15 (s, 3H, vinyl-H's), 7.50 (s, 3H, aromatic-CH). The triester was subsequently quantitatively hydrolyzed as described above to yield the desired product **aci-1** as a white, hygroscopic powder. ^1H NMR (400 MHz, acetone-d_6, ppm): 2.62 (d, $J = 1.3$ Hz, 9H, allyl CH_3's), 6.25 (q, $J = 1.3$ Hz, 3H, vinyl H's), 7.71 (s, 3H, aromatic H's). ^{13}C NMR (400 MHz, acetone-d_6, ppm): 17.20 (CH_3), 118.90 (vinyl-CH), 124.66 (aromatic-CH), 143.14 (aromatic quaternary C's), 153.64 (vinyl quaternary C's), 167.56 (CO). Anal. calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.21; H, 5.20%.
11. Basato, M.; Grassi, A.; Valle, G. *Organometallics* **1995**, *14*, 4439.