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Symmetrical and unsymmetrical 2,6-dialkyl-1,1′-biaryls by combined catalysis of aromatic alkylation *via* palladacycles and Suzuki-type coupling

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The title compounds are made readily accessible by a catalytic procedure, occurring under mild conditions, based on palladium-mediated *ortho* alkylation of aromatic iodides with alkyl bromides followed by reaction with arylboronic acids.

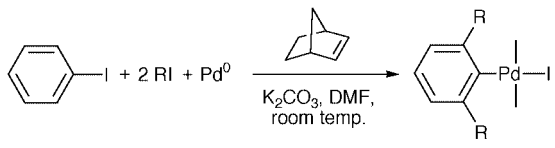
Biaryls are ubiquitous compounds, their unit being present in a variety of natural products and bioactive molecules as well as in many functional advanced materials, and there is wide interest in the development of new synthetic methodologies in spite of the many methods already available.[1] We recently described a new methodology for aromatic *ortho* alkylation based on the formation of palladium(II) and palladium(IV) metallacycles (Scheme 1).[2]

Combining this new alkylation procedure with the Heck reaction enabled us to achieve the catalytic synthesis of vinylarenes selectively substituted in both *ortho* positions with equal or different alkyl groups in a one-pot procedure.[3]

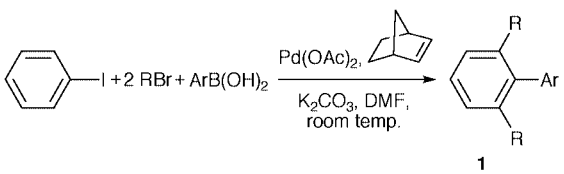
We have now found that a Suzuki-type coupling reaction[1k,l] can be caused to occur directly in the reaction mixture with selective formation of *ortho* substituted biaryls.

To this end we added an arylboronic acid to a reaction mixture containing an iodoarene, norbornene, an alkyl bromide (in two-fold excess), palladium acetate as catalyst and potassium carbonate in DMF. In spite of the possibility that the Suzuki coupling could occur with the initially formed arylpalladium iodide[1k,l] and with other intermediates involved in the aromatic alkylation, as described in the literature,[4] the desired 2,6-dialkylated 1,1′-biaryls were obtained in satisfactory to excellent yields at room temperature.

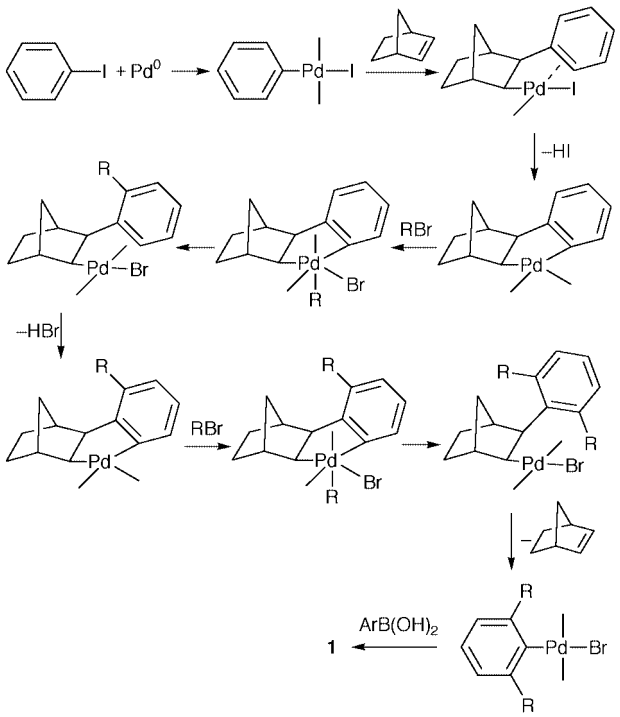
The overall reaction leading to the synthesis of symmetrically *ortho*-dialkylated biaryls is shown in Scheme 2 for iodobenzene. Thus the reaction of iodobenzene (82 mg, 0.4 mmol), 1-bromopropane (220 mg, 1.6 mmol), 2-norbornene (38 mg, 0.4 mmol) and phenylboronic acid (59 mg, 0.48 mmol) with $Pd(OAc)_2$ (9.0 mg, 0.04 mmol) as the catalyst and K_2CO_3 (332 mg, 2.4 mmol) as the base, in DMF (5 mL) at room temperature for 72 h afforded 2,6-di-*n*-propyl-1,1′-biphenyl in 95% yield.† Higher substrate-to-catalyst ratios can be used but so far no optimisation work has been carried out. The course of the reaction can be concisely represented as shown in Scheme 3.



Scheme 1



Scheme 2



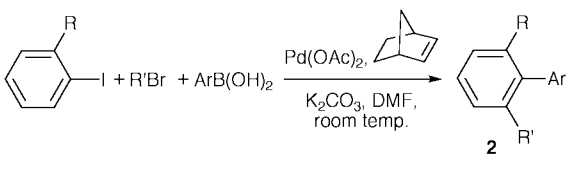
Scheme 3

The reaction was also extended to *ortho*-substituted aromatic iodides. This offers the possibility of obtaining biaryls **2** with two different *ortho* alkyl groups, as shown in Scheme 4.

The scope of the reaction is currently being studied. As shown in Table 1, however, the procedure appears to be tolerant of substituents both in the iodoarene and in the phenylboronic acid, and it can be carried out with different alkyl bromides. Thus it offers a simple and direct tool to gain access to 2,6-dialkyl substituted 1,1′-biaryls. *ortho*-Substituted arylboronic acid gave very poor results both in terms of yield and selectivity, and are not reported.

The reaction is sensitive to the bulkiness of the reagents. Although the reaction becomes slow and longer reaction times are required, selectivity remains high (runs 9–11).

Small amounts (1–4%) of by-products are also obtained, corresponding to *o*,*o*′-disubstituted biaryls, formed as a consequence of aryl exchange between arylpalladium bromide and arylboronic acid,[5] or to *o*,*o*′-disubstituted norbornylbenzenes which result from hydrogenolysis of the palladium complex



Scheme 4

Table 1 Reaction of aryl iodides, alkyl bromides and arylboronic acids in the presence of norbornene, $Pd(OAc)_2$ and K_2CO_3[a]

Run	Aryl iodide	Alkyl bromide R or R′	Boronic acid Ar	Biaryl yield (%)[b]	Aryl iodide conversion (%)[b]
1	PhI	Pr	Ph	95 (90)	98
2	PhI	Bu	Ph	83 (81)	86
3	4-$MeO_2CC_6H_4I$	Bu	Ph	89	97
4	4-MeC_6H_4I	Bu	Ph	74 (63)	93
5	4-MeC_6H_4I	Bu	4-MeC_6H_4	86 (84)	98
6	PhI	Bu	4-MeC_6H_4	71 (66)	77
7	PhI	Bu	4-FC_6H_4	62 (59)	72
8	2-MeC_6H_4I	Bu	Ph	89	96
9	2-BuC_6H_4I	Pr	Ph	70[c]	91[c]
10	2-$Pr^iC_6H_4I$	Bu	Ph	82[c]	84[c]
11	2-$Pr^iC_6H_4I$	Pr^i	Ph	71[c]	74[c]

[a] Molar ratio of the reagents 1 : 4 : 1.2 : 1 : 0.1 : 6; room temperature, 72 h, DMF as solvent, under nitrogen. [b] GC yield on the charged amount of the aryl iodide; isolated yields in brackets. [c] 144 h.

before norbornene deinsertion (Scheme 3), while biaryls resulting from homocoupling[6] of the arylboronic acids are not formed.

In conclusion the present reaction allows the selective preparation of symmetrical and unsymmetrical *o*,*o*′-dialkylated biaryls, an important class of not easily accessible compounds, in a one-pot procedure under mild conditions.

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Notes and references

† All isolated products gave satisfactory elemental analyses. *Selected data* for 2,6-di-*n*-propyl-1,1′-biphenyl: δ_H(300.13 MHz, $CDCl_3$, TMS, 20 °C) 7.40 (2H, m, H3′, H5′), 7.33 (1H, m, H4'), 7.23, 7.11 (3H, AB_2 system, *J* 7.3, H4, H3, H5), 7.15 (2H, m, H2′, H6′), 2.27 (4H, m, 2CH_2Ar), 1.41 (4H, m, 2C$H_2$$CH_3$), 0.75 (6H, t, *J* 7.3 Hz, 2CH_3); δ_C(75.4 MHz, $CDCl_3$, TMS, 20 °C) 141.1, 140.7, 140.4 (q), 129.6 (C2′, C6′), 127.9 (C3′, C5′), 127.0 (C4), 126.5 (C4′), 126.3 (C3, C5), 35.8 (*C*H_2Ar), 24.4 (*C*$H_2$$CH_3$), 14.1 ($CH_3$); *m*/*z* (EI, 70 eV) 238 (M^+, 25%) 209 (20), 178 (23), 167 (100), 165 (50).

1 (*a*) H. Weissman and D. Milstein, *Chem. Commun.*, 1999, 1901; (*b*) J. P. Wolfe and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 1999, **38**, 2413; (*c*) D. S. McGuinness, K. J. Cavell, B. W. Skelton and A. H. White, *Organometallics*, 1999, **18**, 1596; (*d*) W. A. Herrmann, C.-P. Reisinger and M. Spiegler, *J. Organomet. Chem.*, 1998, **557**, 93; (*e*) A. F. Indolese, *Tetrahedron Lett.*, 1997, **38**, 3513; (*f*) S. Darses, T. Jeffery, J.-P. Genet, J.-L. Brayer and J.-P. Demoute, *Tetrahedron Lett.*, 1996, **37**, 3857; (*g*) M. Beller, H. Fischer, W. A. Herrmann, K. Öfele and C. Brossmer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1848; (*h*) J. Clayden and M. Julia, *J. Chem. Soc., Chem. Commun.*, 1993, 1682; (*i*) S. P. Stanforth, *Tetrahedron*, 1998, **54**, 263; (*j*) I. P. Beletskaya, *Pure Appl. Chem.*, 1997, **69**, 471; (*k*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*l*) A. Suzuki, *Pure Appl. Chem.*, 1994, **66**, 213.

2 M. Catellani and M. C. Fagnola, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2421; for a recent review on metallacycles: G. Dyker, *Chem. Ber.*, 1997, **130**, 1567.

3 M. Catellani, F. Frignani and A. Rangoni, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 119; M. Catellani and F. Cugini, *Tetrahedron*, 1999, **55**, 6595.

4 M. Catellani, G.P. Chiusoli and S. Concari, *Tetrahedron*, 1989, **45**, 5263.

5 M. Moreno-Mañas, M. Pérez and R. Pleixats, *J. Org. Chem.*, 1996, **61**, 2346.

6 K.-C. Kong and C.-H. Cheng, *J. Am. Chem. Soc.*, 1991, **113**, 6313; R. van Asselt and C. J. Elsevier, *Organometallics*, 1994, **13**, 1972.

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