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Synthesis of Fluoren-9-ones via Palladium-Catalyzed Cyclocarbonylation of *o*-Halobiaryls

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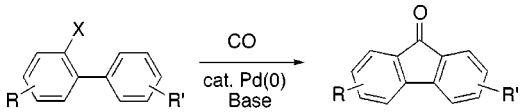
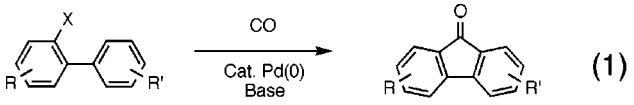
ABSTRACT



The synthesis of various substituted fluoren-9-ones has been accomplished by a novel palladium-catalyzed cyclocarbonylation of *o*-halobiaryls. The cyclocarbonylation of 4′-substituted-2-iodobiphenyls produces very high yields of 2-substituted fluoren-9-ones bearing either electron-donating or electron-withdrawing substituents. 3′-Substituted 2-iodobiphenyls afford in excellent yields with good regioselectivity 3-substituted fluoren-9-ones. This chemistry has been successfully extended to polycyclic and heterocyclic fluorenones.

Fluorenones are an interesting class of compounds because of their important biomedical applications.[1] The most useful syntheses of fluoren-9-ones include Friedel−Crafts closures of biarylcarboxylic acids and derivatives,[2] intramolecular [4 + 2] cycloaddition reactions of conjugated enynes,[3] oxidation of fluorenes,[4] and remote metalation of 2-biphenylcarboxamides or 2-biphenyloxazolines.[5] Fluoren-9-ones have been recently synthesized by the palladium-catalyzed cyclization of *o*-iodobenzophenones.[6] We wish to report at this time a novel palladium-catalyzed cyclocarbonylation of *o*-halobiaryls which offers a highly efficient, direct route to the fluoren-9-one skeleton, as well as other related cyclic aromatic ketones (eq 1).



(1)

Our initial studies focused on developing an optimum set of reaction conditions for the palladium-catalyzed cyclocarbonylation reaction. All the optimization reactions were carried out using commercially available 2-iodobiphenyl under 1 atm of carbon monoxide and DMF as the solvent. The yield of fluoren-9-one (**2**) was strongly dependent on the nature of the palladium ligands. The presence of chelating ligands, such as 1,10-phenanthroline and bis(diphenylphosphino)ethane, drastically reduced the yield of fluoren-9-one. Similarly, electron-deficient phosphine ligands, such as tri(*p*-chlorophenyl)phosphine and tri(*p*-fluorophenyl)phosphine, gave lower yields than triphenylphosphine. On the other hand, the bulky, electron-rich ligand tricyclohexylphosphine was by far the most effective ligand. We have also explored the effect on the reaction yield of other variables, such as the temperature, the palladium catalyst, and the use of various bases. The optimum reaction conditions thus far developed employ 1 atm of carbon monoxide, 1 equiv of the aryl halide (0.25 mmol), 5 mol % of commercially available $Pd(PCy_3)_2$, and 2 equiv of anhydrous cesium pivalate in DMF (6 mL) at 110 °C for 7 h; this procedure provided a yield of 100%. Replacing the unusual

(1) (a) Han, Y.; Bisello, A.; Nakamoto, C.; Rosenblatt, M.; Chorev, M. *J. Pept. Res.* **2000**, *55*, 230. (b) Greenlee, M. L.; Laub, J. B.; Rouen, G. P.; DiNinno, F.; Hammond, M. L.; Huber, J. L.; Sundelof, J. G.; Hammond, G. G. *Biorg. Med. Chem. Lett.* **1999**, *9*, 3225. (c) Perry, P. J.; Read, M. A.; Davies, R. T.; Gowan, S. M.; Reszka, A. P.; Wood, A. A.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **1999**, *42*, 2679.

(2) (a) Olah, G. A.; Mathew, T.; Farnia, M.; Prakash, S. *Synlett* **1999**, 1067. (b) Yu, Z.; Velasco, D. *Tetrahedron Lett.* **1999**, *40*, 3229.

(3) (a) Danheiser, R. L.; Gould, A. E.; Pradilla, R. F.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514.

(4) (a) Hashemi, M.; Beni, Y. *J. Chem. Res., Synop.* **1999**, 434. (b) Nikalje, M.; Sudalai, A. *Tetrahedron* **1999**, *55*, 5903.

(5) (a) Ciske, F.; Jones, W. D., Jr. *Synthesis* **1998**, 1195. (b) Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424.

(6) (a) Qabaja, G.; Jones, G. B. *Tetrahedron Lett.* **2000**, *41*, 5317.

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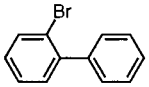
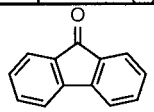
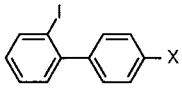
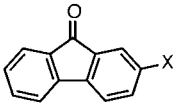
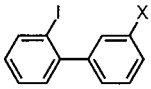
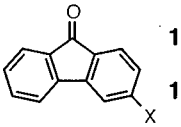
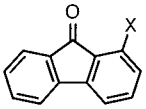
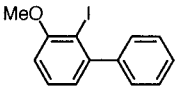
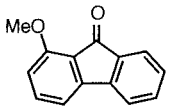
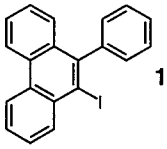
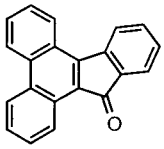
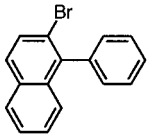
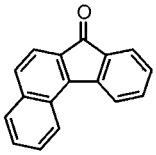
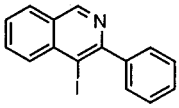
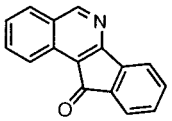
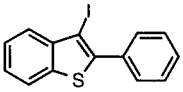
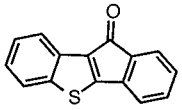
Table 1. Synthesis of Fluorenones by the Pd-Catalyzed Cyclocarbonylation of *o*-Halobiaryls[a]

entry	substrate	product(s)	% isolated yield
1	 **1**	 **2**	100
2	X = H (**3**)	**2**	100
3	 X = Me (**4**)	 **5**	97
4	X = OMe (**6**)	**7**	100
5	X = CHO (**8**)	**9**	100
6	 X = Me (**10**)	 **11** +  **12**	90 + 10
7	X = CHO (**13**)	**14** **15**	94 (9:1)[b]
8	 **16**	 **17**	99
9	 **18**	 **19**	98
10	 **20**	 **21**	96
11	 **22**	 **23**	95
12	 **24**	 **25**	67

[a] All reactions were carried out under the previously specified optimal conditions. [b] The product ratio was determined by ^{1}H NMR spectroscopic analysis.

cesium pivalate base with cesium carbonate or sodium acetate was detrimental to the reaction, with the yield dropping from 100% to 82% and 92%, respectively.

By employing this protocol, 2-bromo- and 2-iodobiphenyl afford fluoren-9-one (**2**) in a quantitative yield (Table 1, entries 1 and 2). However, biphenyl-2-yl trifluoromethanesulfonate failed to afford the desired product under the standard reaction conditions.

The utility of this reaction for the synthesis of 2-substituted fluoren-9-ones was assessed by studying the cyclocarbonylation of readily prepared[7] 4′-substituted 2-iodobiphenyls (entries 2−5). As indicated, the reaction works well, tolerating both electron-donating and electron-withdrawing substituents.

We have also addressed the question of regiochemistry in the cyclocarbonylation of 3′-substituted 2-iodobiphenyls[7] (entries 6 and 7). The cyclocarbonylation of the electron-rich 2-iodo-3′-methylbiphenyl (**10**) and the electron-poor 3-(2-iodophenyl)benzaldehyde (**13**) afforded similar 9:1 regiochemical mixtures in excellent yields. In both cases the predominant isomer arises from ring closure distal to the substituent. These experimental results seem to indicate that there is only a weak electronic effect during the cyclization process and that a more important steric effect favors the less hindered isomers **11** and **14**.

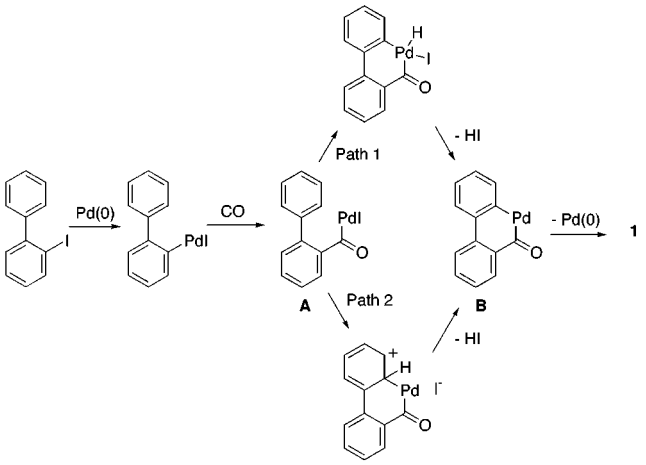
This cyclocarbonylation does not appear to be significantly affected by the presence of substituents *ortho* to the halo group. For example, the palladium-catalyzed reaction of 2-iodo-3-methoxybiphenyl[8] (**16**) produced 1-methoxyfluoren-9-one (**17**) in 99% yield (entry 8).

(7) These starting materials were prepared using the procedure of Hart, H.; Harada, K.; Du, C. J. F. *J. Org. Chem.* **1985**, *50*, 3104.

Interestingly, this palladium-catalyzed transformation is not limited to biphenyl systems. As illustrated by entries 9−12, we have been able to apply this chemistry to polycyclic and heterocyclic systems. Thus, treatment of 9-iodo-10-phenylphenanthrene[9] (**18**) with carbon monoxide under our standard reaction conditions produced indeno[1,2-*l*]phenanthren-13-one[10] (**19**) in 98% yield. Similarly, 2-bromo-1-phenylnaphthalene[11] (**20**) produced a 96% yield of benzo-[*c*]flouren-7-one[12] (**21**) (entry 10). Furthermore, cyclocarbonylation of the heterocycle 4-iodo-3-phenylisoquinoline[13] (**22**) yields 11-oxoindeno[1,2-*c*]isoquinoline[14] (**23**) in 95% yield (entry 11). Finally, the metal-catalyzed transformation of 3-iodo-2-phenylbenzothiophene[15] (**24**) produced a 67% yield of 10-oxo-10*H*-benz[*b*]indeno[1,2-*d*]thiophene[16] (**25**) (entry 12).

The fact that the cyclocarbonylative ring closure occurs equally well onto both electron-rich and electron-deficient aryl systems with no apparent change in the yields (compare entries 2−5 in Table 1) raises an interesting mechanistic question. Scheme 1 provides a possible mechanism for this process. The first step involves oxidative addition of the aryl halide to Pd(0), followed by CO insertion to produce the acylpalladium intermediate **A**. There are two mechanistic possibilities for the cyclization of intermediate **A**, either insertion into an aromatic carbon hydrogen bond (path 1) or electrophilic aromatic substitution (path 2). After elimination of a molecule of HI, both of the reaction pathways converge again to intermediate **B**, which subsequently undergoes reductive elimination of the ketone with simultaneous regeneration of the Pd(0) catalyst. Unfortunately, the experimental results do not provide conclusive evidence favoring either one of these mechanistic paths.

Scheme 1



This novel palladium-catalyzed reaction provides a short, straightforward route to a variety of substituted fluoren-9-ones under mild reaction conditions and short reaction times. Our success in extending this reaction to other biaryl systems indicates its potential for the synthesis of a wide variety of aromatic ketones

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Supporting Information Available: Experimental procedures and characterization data for all compounds in Table 1. This material is free of charge via the Internet at http://pubs.acs.org.

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(8) This starting material was prepared using the procedure of Huisgen, R.; Rist, H. *Justus Liebigs Ann. Chem.* **1955**, *594*, 137.

(9) This aromatic iodide was prepared from 9-phenyl-10-(trimethysilyl)-phenanthrene (Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536) by the iodination procedure of Miller, R. B.; McGarvey, G. *Synth. Commun.* **1978**, *8*, 291.

(10) (a) Sprinzak, Y. *J. Am. Chem. Soc.* **1958**, *80*, 5449. (b) Horspool, W. M. *J. Chem. Soc. C* **1971**, 400. (c) Pandey, B.; Mahajan, M. P.; Tikare, R. K.; Muneer, M.; Rath, N. P.; Kamat, P. V.; George, M. V. *Res. Chem. Intermed.* **1991**, *15*, 271.

(11) Wittig, G.; Hellwinkel, D. *Chem. Ber.* **1964**, *97*, 769.

(12) (a) Fu, J.; Zhao, B.; Sharp, M. J.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 1683. (b) Harvey, R. G.; Abu-shqara, E.; Yang, C. *J. Org. Chem.* **1992**, *57*, 6313.

(13) This aryl iodide was prepared by the procedure of Larock, R. C.; Hunter, J.; Roesch, K.; Huang, Q., work in progress.

(14) (a) Wawzonec, S.; Stowell, J. K.; Karll, R. E. *J. Org. Chem.* **1966**, *31*, 1004. (b) Dusemund, J.; Kroeger, E. *Arch. Pharm.* **1987**, *320*, 617.

(15) This starting material was prepared using the procedure of Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218.

(16) Sauter, F.; Dzerovicz, A. *Monatsh. Chem.* **1969**, *100*, 913.