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PALLADIUM-MEDIATED 2,6-DIALKYLATION OF N-BENZILIDINE IMINES: PREPARATION OF 2,6-DIALKYLBENZALDEHYDES

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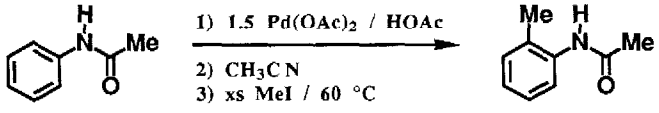
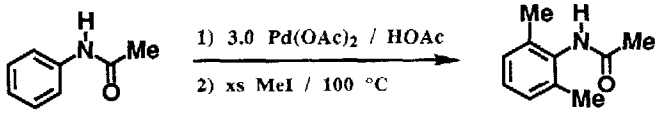
Summary: Treatment of di-μ-trifluoroacetatobis[o-(N-phenylbenzimidoyl)]dipalladium with two equivalents of primary alkyl iodides and subsequent hydrolysis provides an efficient route to 2,6-disubstituted benzaldehydes.

Hetero-atom directed ortho-metallation reactions of aromatic compounds have been the basis of a large number of methods for regio-controlled introduction of substituents.[2,3] Palladium displays a particularly rich variety of ortho-metallated species that undergo useful organic transformations,[4] and of specific relevance to the chemistry described herein, several workers have reported the reaction of such species with alkyl lithiums[5] or acyl halides.[6] Tremont and Rahman reported that *in-situ* generated cyclopalladates of acetanilide reacted with alkyl halides to provide mono or di-orthoalkylated derivatives, depending upon the reaction conditions[7] (eqn **1** and **2**). The authors ruled out the intermediacy of Pd^0 species and suggested that Pd^{IV} species may be involved.

Eqn. 1

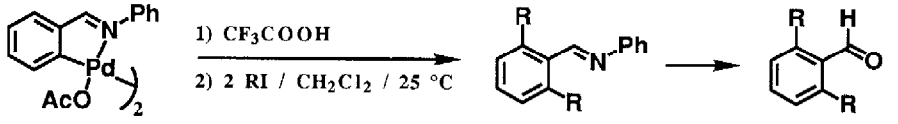


Eqn. 2



We wish to report semicatalytic reactions of *preformed* ortho-palladated benzilidineaniline complexes with alkyl iodides that provide near-exclusive production of di-orthoalkylated imines. Hydrolysis of the intermediate, dialkylated imines provides the corresponding dialkylated benzaldehydes (eqn **3**).

Eqn. 3

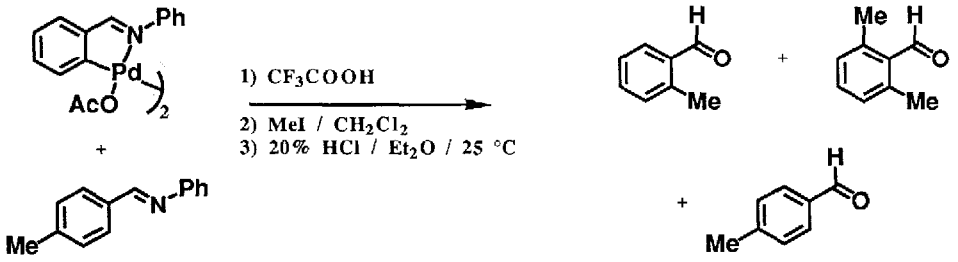


R	*di:mono*	*yield,%*
Me	18:1	72
Et	16:1	74
n-Bu	18:1	66
n-$C_{16}H_{33}$	15:1	84

Optimum conditions for preparation of the dialkylated derivatives involve *in-situ* conversion of the known di-μ-acetatobis[o-(N-phenylbenzimidoyl)]dipalladium[8] to a suspension of the corresponding trifluoroacetate species by treatment with trifluoroacetic acid. The alkyl iodide is then slowly added over *ca* 90 minutes as a methylene chloride solution at room temperature, causing immediate production of a black precipitate.[9] After separation from the solids and removal of trifluoroacetic acid, hydrolysis of the crude reaction mixture with 20% HCl provides a mixture typically consisting of dialkylated, monoalkylated and unalkylated benzaldeyde in the ratio of *ca* 20:1:1. Dialkylated benzaldehydes are isolated in yields of 70-75% after chromatography.[10] Reactions of primary alkyl bromides are much more sluggish and do not proceed to completion. Secondary alkyl iodides or bromides produce visually identical reactions, producing the black palladium precipitate, but no alkylated products. The reaction displays no sensitivity to oxygen.

Trifluoroacetic acid is required for the alkylation reaction to occur; preformed trifluoroacetate complex does not react with methyl iodide when methylene chloride is employed as a solvent, while the coresponding acetate complex is unreactive in acetic acid medium, in contrast to the acetanilide system of Tremont and Rahman. The ratio of mono- to dialkylation is strongly dependent upon reaction conditions: the presence of an *excess* of alkyl iodide promotes higher yields of monoalkylated products at the expense of dialkylated products. The dependence upon alkyl iodide concentration suggests that a palladium species is intercepted by excess alkyl iodide and precipitated out as PdI_2 before remetallation of the aromatic ring can occur. Running the methylation reaction in the presence of N-phenyl-p-tolualdimine produced no detectable crossover products (eqn **4**),[11] suggesting that the palladium remains coordinated to the same imine nitrogen during the dialkylation process.

Eqn. 4



Attempts to metallate N-phenyltolualdimine in trifluroacetic acid with palladium trifluoroacetate or palladium acetate failed, suggesting that intermolecular orthopalladation is probably impossible under the reaction conditions.[12] The failure to orthopalladate in an intermolecular fashion under these conditions, while precluding true catalytic turnover for this particular system, provides strong evidence that the Pd-N bond is maintained throughout the dialkylation process.

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1 Camille and Henry Dreyfus Foundation Teacher-Scholar, 1986–1991.

2 Recent reviews and leading references include: Beak, P.; Meyers, A. I. Acct. Chem. Res. **1986**, *19*, 356; Sibi, M. P.; Chattopadhyay, S.; Dankwardt, J. W.; Snieckus, V. J. Am. Chem. Soc. **1985**, *107*, 6312; Gschwend, H. W.; Rodriguez, H. R. "Heteroatom-Facilitated Lithiations", Organic Reactions **1984**, *26*, 1.

3 A ruthenium catalyzed ortho-ethylation of arylphosphites has been reported: Lewis, L. N.; Smith, J. F. J. Am. Chem. Soc. **1986**, *108*, 2728. Meyers has reported multistep preparations of 2,6-dialkylated benzaldehyde derivatives via sequential alkylation of isoxazoline derivatives: Meyers, A. I.; Himmelsbach, R. J.; Reuman, M. J. Org. Chem. **1983**, *48*, 4053; Meyers, A. I.; Williams, B. E. Tetrahedron Lett. **1978**, 223.

4 For a review of the application of cyclopalladated complexes in organic synthesis see: Ryabov, A. D. Synthesis **1985**, 233. More recently, the insertion of alkynes into the Pd–C carbon has been extensively developed. Dupont, J.; Pfeffer, M.; Daran, J-C.; Gouteron, J. J. Chem. Soc., Dalton Trans. **1988**, 2421 and references contained within.

5 Murahashi, S. H.; Tamba, Y.; Yamamura, M.; Yoshimura, N. *J. Org. Chem.* **1978**, *21* ,4099.

6 Holton, R. A.; Natalie, K. J. *Tett. Lett.* **1981**, *22*, 267.

7 Tremont, S. J.; Rahman, H. R. *J. Amer. Chem. Soc.* **1984**,*106*, 5759.

8 Onoue, H. and Moritani, I. *J. Organomet. Chem.* **1972**, *213*, 431

9 Typical Experimental Procedure: The alkyl halide (2.5 equivalents as a 0.25M solution in methylene chloride) was slowly added using a syringe pump over a period of 90–100 min to a 0.1M suspension of di-μ-trifluoroacetatobis[o-(N-phenylbenzimidoyl)]dipalladium (formed *in-situ* by stirring the corresponding acetate complex in trifluoroacetic acid for 5–10 min). During the course of the addition, the color changed from bright yellow to a black suspension). After addition of the alkyl halide was complete, the mixture was stirred for an additional 4–8 hr. After dilution with diethyl ether, the reaction mixture was centrifuged, the supernatant collected, and the residue resuspended in ether and centrifuged again. The original supernatant and those from three washings of the residue were combined, then the solvents were removed by rotary evaporation followed by evacuation to 0.3 torr. The crude product was dissolved in diethyl ether, approximately one-half volume of 20% aqueous hydrochloric acid was added, and the mixture was stirred for 2–5 h until hydrolysis of the imines was complete by GC monitoring. Hexane was added to force phase separation, the phases were separated, and the organic layer was washed with saturated potassium bicarbonate, then dried over magnesium sulfate. The solvent was removed by rotary evaporation, followed by brief exposure to a vacuum of 0.3 torr to provide a pale yellow oil. The crude product was passed through a short plug of silica gel as an ether solution, and the solvent was removed by rotary evaporation followed by brief exposure to a vacuum of 0.3 torr. Preparative radial chromatography (silica, 5-10% ethyl acetate / hexane) allowed isolation of the dialkylated benzaldehydes. All new compounds exhibited satisfactory ^{1}H NMR, ^{13}C NMR and IR spectra and elemental analyses. Non-crystalline aldehydes were analysed as the semicarbazone derivative.

10 Removal of the last traces of the monoalkylated side product was difficult for the methylation and ethylation products; 1-4% monoalkylated benzaldehyde remained.

11 Analysis by capillary GC and comparison with authentic 2,4,6-trimethylbenzaldehyde prepared by dimethylation of di-μ-acetobis[o-(N-phenyltoluimidoyl)]dipalladium demonstrated the complete absence of crossover products as well as the expected ability of the N-phenyltolualdimine complex to successfully dialkylate under the reaction conditions.

12 Ryabov *et al* report that similar orthopalladated complexes undergo exchange with ligands in the less acidic acetic acid which is often employed as a solvent for their preparation. Ryabov, A. D.; *Koord. Khim* **1985** *11*, 1532; Ryabov, A. D.; Kanzankov, G. M.; *Koord. Khim.* **1986** *12*, 540; Ryabov, A.D. *Zh. Obshch Khim* **1987** *57*, 249.

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