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ipso-Nitration of Arenes**

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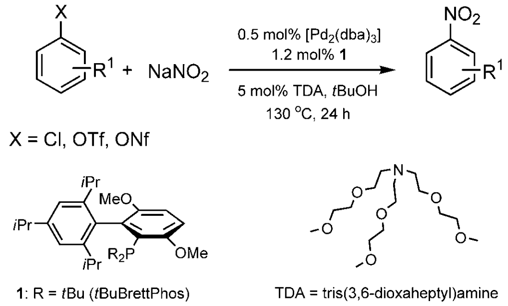
Aromatic nitro compounds are key synthons in the preparation of many dyes, plastics, perfumes, explosives, and pharmaceuticals.[1,2] The electrophilic nitration of arenes, one of the most extensively studied organic reactions, results in mixtures of isomeric nitrated products.[3] Since nitrating agents are also good oxidants, the nitrated compounds are often accompanied by oxidation products. Therefore, the development of mild and regioselective nitration methods is of substantial practical interest.

Recently, Buchwald and Fors have developed an elegant method for the regioselective *ipso*-nitration of aryl chlorides, triflates, and nonaflates to give the corresponding nitroarenes (Scheme 1).[4] The method is similar to that reported for the regioselective fluorination of aryl triflates.[5]



Scheme 1. Palladium-catalyzed regioselective conversion of aryl chlorides, triflates, and nonaflates into nitroarenes. dba = *trans,trans*-dibenzylideneacetone, Nf = nonafluorobutanesulfonyl, Tf = trifluoromethanesulfonyl.

Apart from mixed-acid systems (H_2SO_4/HNO_3), nitronium salts and nitration by means of metalation (mercuration, palladation, thallation etc.) have been developed as efficient nitration methods.[3] The electrophilic nitration of substituted arenes results in low selectivity owing to the formation of various isomers. Ingold's mechanistic studies on the nitration of aromatic compounds[6] and Olah's nitration studies with nitronium salts revealed the significance of *ipso*-nitration and subsequent intramolecular migration processes.[3] Nitration of *ortho*-cymene and *para*-diisopropylbenzene with HNO_3/H_2SO_4 yielded substantial amounts of *ipso*-nitration products.[7] Aromatic substitution of this kind was first referred to as *ipso* substitution by Perrin and Skinner in 1971.[8] During the nitration of alkylbenzenes with $NO_2^+BF_4^-$ in sulfolane, Olah et al.[9] and Myhre et al.[10] found varying degrees of dealkylative nitration along with regular *ortho*- and *para*-nitration products. Other reactions involving *ipso* attack are nitrodehalogenations, nitrodeacylations, nitrodecarboxylations, and nitrodesilylations.[1,11,12] The formation of long-lived nitroarenium ions as a result of *ipso* attack was experimentally shown by Olah et al. by the reaction of pentamethylhalobenzenes with $NO_2^+BF_4^-$ in superacidic medium at low temperatures.[13] Further transformation of such *ipso*-nitroarenium species can occur by intramolecular isomerization pathways (rarely involving migration of nitro groups) leading to a variety of products.[14,15] Evidence of *ipso* attack by the nitrating species has been studied in the gas phase by pulse radiolytic methods.[16] Nitration can also be carried out without acid catalysis under homolytic (radical) nitration conditions.[3,17]

Electron-deficient haloarenes undergo nucleophilic halogen replacement (*ipso* attack involving Meisenheimer intermediates) upon reaction with nitrite salts to give the corresponding nitro derivatives. 1,2,4-Trinitrobenzene has been prepared from 4-iodo-1,2-dinitrobenzene by this method.[18] Nesmeyanov, McEwen, and Olah et al. independently reported the nucleophilic nitrolysis of diaryl halonium ions with sodium nitrite.[19–21] Nitroarenes can also be prepared in good yields by nitro-dediazoniation of arenediazonium salts in the presence of Cu^I in neutral or alkaline solution.[22] Rozen and Carmeli have oxidized aromatic azides to the corresponding nitro compounds in moderate yields using an HOF/CH_3CN complex.[23] However, this conversion does not constitute an *ipso* substitution reaction.

Arylboronic acids have been used extensively as versatile synthons in Suzuki couplings, Petasis reactions, and halogenations.[24] Prakash et al. have carried out the *ipso*-nitration of arylboronic acid using Crivello's reagent.[25] Further modifications to the *ipso*-nitration protocol included the use of chlorotrimethylsilane–nitrate salt, which acts as a selective and efficient *ipso*-nitrating agent.[26] Another *ipso*-nitration protocol developed by Saito and Koizumi involves the transformation of aryl iodides/bromides to nitroarenes catalyzed by Cu bronze in the presence of *N,N*-dimethylethyle-

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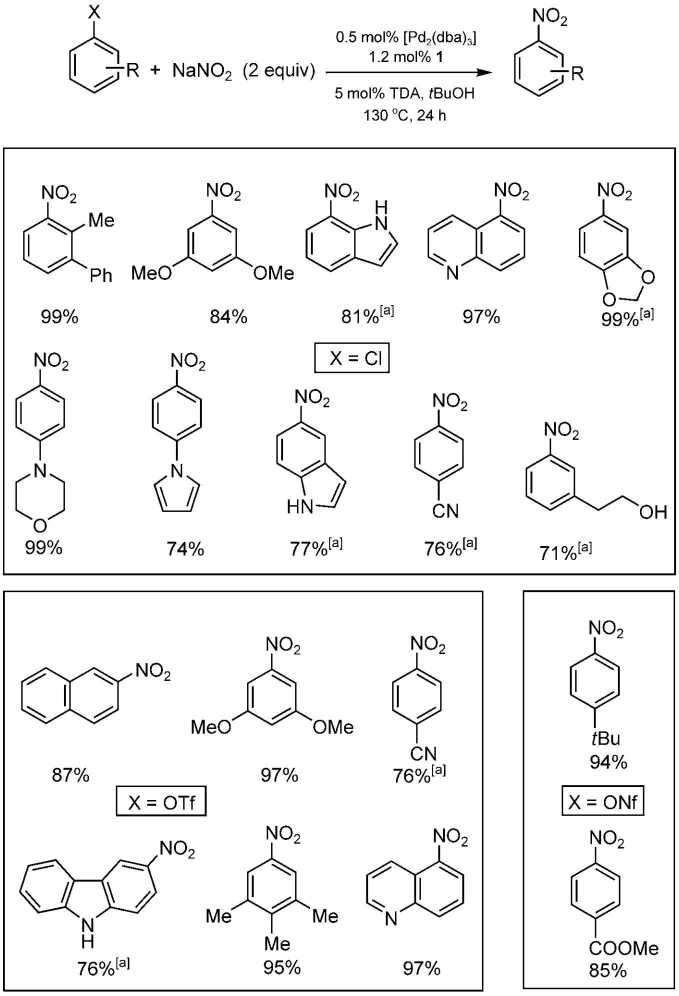
nediamine.[27] However, the general application of this method is limited.

The new *ipso*-nitration method devised by Buchwald et al. is a very efficient palladation–nitration protocol widely applicable to many aromatic compounds such as chlorides, triflates, and nonaflates.[4] Excellent regioselectivity and functional-group compatibility were found. Many nitroarenes, including nitrated heteroarenes, were prepared under mild basic conditions in high yields and purity. Substrates such as 5- and 7-chloroindoles did not require protection of the NH function. Substitutents in the *ortho* position and acid-sensitive functional groups such as acetal, pyrrole, nitrile, and free alcohol are well tolerated. The presence of electron-withdrawing as well as electron-donating groups at various positions did not alter the course of the reaction. The highly efficient methodology was optimized by systematic modification of the Pd^0 catalyst, ligand, solvent, and the phase-transfer catalyst (PTC).

The reaction of 4-chloro-*n*-butylbenzene with 0.5 mol% $[Pd_2(dba)_3]$, 1.2 mol% biarylphosphine ligand **1**, and sodium nitrite in *t*BuOH provided 4-nitro-*n*-butylbenzene in 26% yield. The efficacy of the phosphine ligand **1** has been previously probed for the cross-coupling of amides and aryl chlorides.[28] Addition of the phase-transfer catalyst, tris(3,6-dioxaheptyl)amine (TDA, 5 mol%) increased the solubility of sodium nitrite in *t*BuOH and doubled the yield (52%). In further screening with other PTCs and ligands, the best results were obtained with TDA as the PTC of choice. The presence of both the *tert*-butylphosphino group and the methoxy group (*ortho* to the phosphine group) in the ligand is critical for the reaction. Studies with chloro-, bromo-, and iodoarenes showed that the chloro derivatives are the best substrates since they undergo transmetalation with more facility than the other halo compounds (Cl > Br > I) and have lower rates of oxidative addition with the catalyst.



Scheme 2. Conversion of selected aryl chlorides, triflates and nonaflates to nitroarenes. [a] Reaction conditions: 2.5 mol% $[Pd_2(dba)_3]$ and 6 mol% **1**.

Prior studies using aryl triflates in Pd-catalyzed amidation reactions[29] led the Buchwald team to use triflates and nonaflates as suitable substrates; they found that the transmetalation reaction occurs with an accelerated rate, as anticipated. A variety of conversions were explored; aryl and heteroaryl triflates/nonaflates bearing ester and nitrile groups were converted efficiently to the corresponding *ipso*-nitro derivatives in high yields (Scheme 2).

In summary, the *ipso*-nitration strategy devised by the Buchwald group is the most adaptable and convenient synthetic protocol for the nitration of aromatic and heteroaromatic substrates and can be considered as the best general *ipso*-nitration method reported to date.

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