J|A|C|S COMMUNICATIONS

Published on Web 03/03/2010

Iridium-Catalyzed, Silyl-Directed Borylation of Nitrogen-Containing Heterocycles

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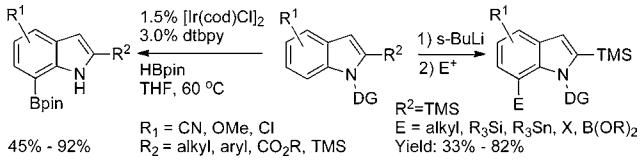
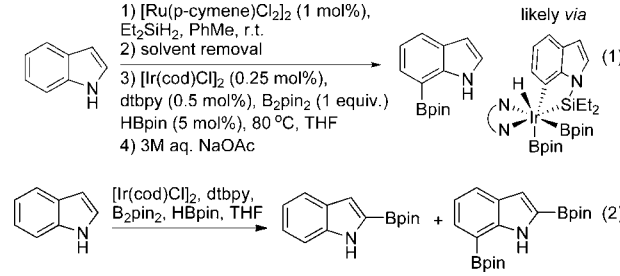
Selective methods for the direct functionalization of nitrogen heterocycles could lead to rapid access to materials that are cumbersome to prepare by classical methods. Although progress has been made,[1−3] few systems selectively functionalize the benzo-fused aromatic ring of indoles and related heterocycles because of the greater reactivity of the azole ring,[4] and the selective functionalization of other biologically important nitrogen-containing heterocycles, such as carbazoles and tetrahydroquinolines,[5−7] has been less studied. Some chloroperoxidases form 7-chloroindoles, but these reactions have not been reported on a synthetic scale or with a scope beyond tryptophan[8,9] or the parent indole.[10]

Scheme 1. Previous Functionalization of the 7-Position of Indoles



Selective functionalization of the 7-position of an indole by chemical methods typically requires a substituent at the 2-position to block reactivity at this site (Scheme 1). The borylation of indoles at the 7-position would create a method for preparing a variety of 7-indole derivatives by exploiting the reactivity of the heteroarylboronate products. Because the 2-position of indole is inherently the most reactive site for metalation,[11] the existing direct borylations of indoles at the 7-position[12] or indirect borylations by initial 7-lithiation of *N*-carbamoyl indoles have been conducted with 2-substituted derivatives.[13] Here we report the application of our recently disclosed hydrosilyl directing group for C−H borylation[14] to alter the inherent selectivity for the reactions of nitrogen heterocycles. This change in selectivity leads to the 7-borylation of indoles lacking any substituent at the 2-position, as well as the borylation of the analogous sites of benzo-fused nitrogen heterocycles containing an N−H bond.

To assess the ability of a hydrosilyl group to affect the selectivity of the borylation of nitrogen heterocycles, we evaluated the borylation of 1-diethylsilylindole with bis(pinacolato)diboron (B_2pin_2) in the presence of the combination of $[Ir(cod)Cl]_2$ and 4,4′-di-*tert*-butylbipyridine (dtbpy).[15] The borylation of this indole derivative occurred in good yield with complete selectivity for borylation at the 7-position (eq 1). In contrast, the undirected borylation of indole gives 2- or 2,7-functionalized products, depending on the amount of boron reagent (eq 2). Thus, the hydrosilyl group completely overrides the inherent site selectivity for the borylation of indole at the 2-position. We envision that this directing effect results from temporary docking of the catalyst on the silyl group (eq 1, right) by reversible reaction of $[Ir(dtbpy)(Bpin)_3]$ with the Si−H bond to release HBpin and form an intermediate silyl complex. The selectivity for borylation at the 7-position would then result from formation of a five-membered metallacycle through C−H bond cleavage at the 7-position, as shown in eq 1, versus formation of a four-membered metalacycle through C−H bond cleavage at the 2-position.



With this result in hand, we sought to develop a one-pot protocol for indole borylations by installation of the silyl group, directed borylation, and desilylation. To do so, we first sought conditions for the generation of *N*-hydrosilylindoles from indole and dihydrosilanes by dehydrogenative coupling under neutral conditions. Studies of several potential catalysts for this reaction showed that $[Ru(p\text{-cymene})Cl_2]_2$ formed the *N*-hydrosilylindole from diethylsilane and indole at room temperature. Indole derivatives that could not be silylated in this fashion were silylated with dimethylchlorosilane and triethylamine as the base.

After evaporation of the solvent, the combination of $[Ir(cod)Cl]_2$ and dtbpy catalyzed the subsequent borylation of the resulting hydrosilylindole at the 7-position without interference from the residual ruthenium. Full conversion of the silyl indole occurred after 4 h at 80 °C in the presence of just 0.25% $[Ir(cod)Cl]_2$.[16] Workup with 3 M aqueous NaOAc released the silyl group to give the free 7-borylindole.

Studies of the scope of the silyl-directed borylation of substituted indoles are summarized in Figure 1. The directed borylation reaction tolerates a variety of substituents at the 3-, 4-, and 5-positions of the indole framework. Reactions of indoles containing halogens, cyano groups, and alkoxy and benzyloxy groups all occurred to exclusively form the corresponding 7-borylindoles, as determined by GC−MS analysis. The isolated yields shown correspond to those for the full reaction sequence starting from the N−H indole.

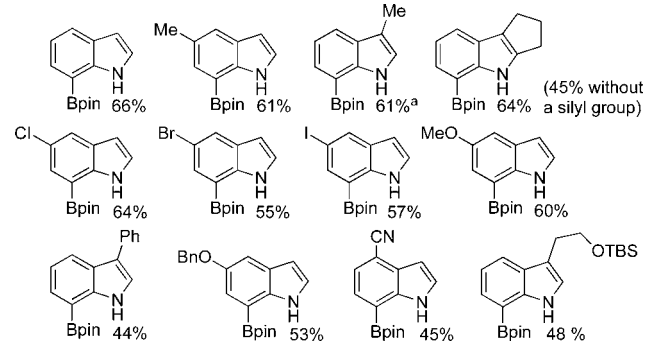


Figure 1. Scope of Ir-catalyzed, silyl-directed indole borylation. Conditions: $[Ir(cod)Cl]_2$ (0.25%), dtbpy (0.5%), B_2pin_2 (1 equiv), HBpin (5%), THF, 80 °C. For the case marked with a superscript "a", the yield of the two-step process run without a drybox was 56%.

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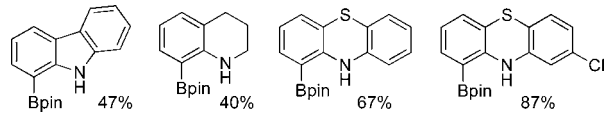
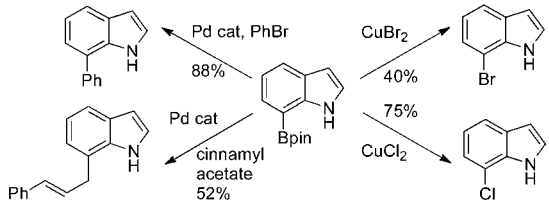


Figure 2. Ir-catalyzed, silyl-directed borylation of other N-heterocycles.

Scheme 2. Functionalization of 7-Borylindoles



The borylation of 3-methylindole reveals the striking effect of the *N*-silyl group. Most iridium-catalyzed borylations of arenes with B_2pin_2 are strongly disfavored at positions ortho to substituents, but borylations of 3-substituted indoles give 2-borylindoles in the absence of a directing group. For example, the borylation of 3-methylindole with B_2pin_2 catalyzed by $[Ir(cod)Cl]_2$ and dtbpy gave a ~2:1 mixture of 2-boryl- and 2,7-diboryl-3-methylindole, whereas the borylation of 3-methyl-*N*-diethylhydrosilylindole occurred exclusively at the 7-position in good yield.

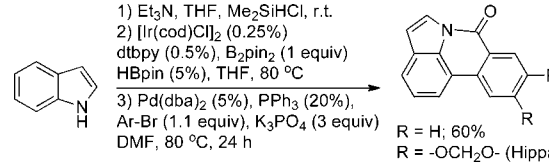
The silyl group also directs borylation exclusively to the indole 7-position in the presence of other aryl C−H bonds. The borylation of 3-phenylindole forms a mixture of at least three products, whereas the borylation of 3-phenyl-*N*-diethylsilylindole formed 7-boryl-3-phenylindole without borylation of the phenyl substituent. Moreover, the borylation of *N*-silylindole in a THF solution containing 6 equiv of added benzene led to exclusive borylation of the indole, as assayed by GC−MS. Conversely, the borylation of indole in the presence of 6 equiv of benzene gave a mixture of 2-borylindole, 2,7-diborylindole and Ph-Bpin.

The hydrosilyl group accelerated not only the rates of the borylation of indoles lacking a 2-substituent but also the rates and yields of the borylations of 2-substituted indoles. The silyl-directed borylation of 1,2,3,4-tetrahydrocyclopentindole occurred at the 7-position in 64% yield for the two-step silylation−borylation process after 8 h, whereas this reaction of indole lacking the silyl group occurred in only 45% yield after a longer time of 36 h.[12]

The results of silyl-directed, Ir-catalyzed borylations of other nitrogen heterocycles containing N−H bonds are shown in Figure 2. The borylation of carbazole, phenothiazines, and tetrahydroquinoline occurred to full conversion and in moderate to good yield in the presence of 1 mol % $[Ir(cod)OMe]_2$ and 2 mol % dtbpy. The lower yields observed in some cases were due to protodeborylation during cleavage of the silyl group. 2-Chlorophenothiazine underwent selective borylation at the less hindered ortho C−H bond. Phenothiazine is the core of a number of neuroleptic antipsychotic drugs, including chlorpromazine, fluphenazine, and prochlorperazine, and is contained within components of organic solar cells and photovoltaics.[17]

The conversion of 7-borylindole to further-functionalized materials is shown in Scheme 2. Suzuki−Miyaura coupling with bromobenzene in the presence of catalytic $Pd(dba)_2$ and PPh_3 with K_3PO_4 as the base in DMF at 80 °C gave 7-phenylindole. Palladium-catalyzed allylation with $PdCl_2$, tri-2-furylphosphine, cinnamyl acetate, and KF in MeOH gave 7-cinnamylindole.[18] Halogenation using the protocol developed for the conversion of arylboronates gave 7-bromo- and 7-chloroindole.[19]

To further illustrate the potential of the silyl-directed, Ir-catalyzed borylation of indoles to facilitate the synthesis of biologically active compounds, we prepared the core of the pyrrolophenanthridone natural products that have shown promising antitumor and other biological activity. Previous syntheses of this class of natural products have utilized prefunctionalized starting materials,[20] such as 7-bromoindole,[21] and relied on blocking groups at the C2 position,[13] and typically required several steps or harsh reaction conditions. In contrast, the Ir-catalyzed, silyl-directed 7-borylation of indole, followed by Suzuki−Miyaura coupling of the desired *o*-bromobenzoate and lactamization in situ, gave the pyrrolophenanthridone alkaloid core and the natural product Hippadine in a single, one-pot sequence in good yield (eq 3). Because this approach begins with an indole and a benzoate, this method should allow the modular introduction of groups on both the indole and arene units.



(3)

In conclusion, a highly selective method for the Ir-catalyzed, silyl-directed C−H borylation of nitrogen heterocycles, including a general borylation of indole at the 7-position, has been developed. This transformation occurs with a low catalyst loading in short reaction times under mild conditions. Furthermore, this reaction possess good functional group tolerance, can be extended to the directed borylation of other nitrogen-containing heterocycles, and creates a versatile intermediate for further functionalization. Studies of the origin of the regioselectivity and application of this approach to additional directed functionalizations are in progress.

Acknowledgment. We thank the NSF (CHE-0910641) for support, Johnson-Matthey for iridium, and Eastman Chemicals for a summer fellowship to D.W.R.

Supporting Information Available: Experimental procedures and characterization of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA1006405