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Direct introduction of a naphthalene-1,8-diamino boryl [B(dan)] group by a Pd-catalysed selective boryl transfer reaction†

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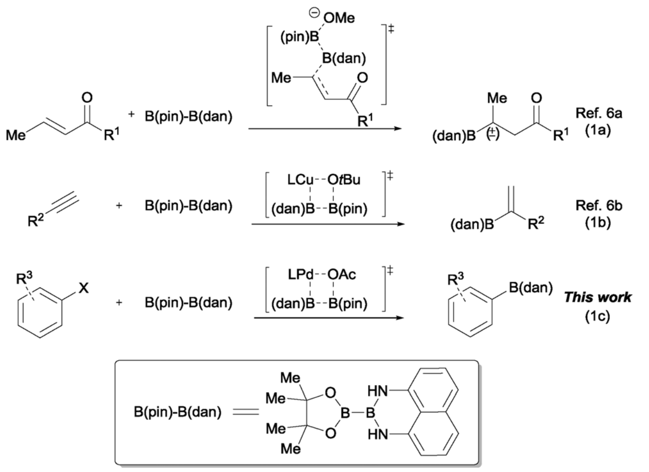
A non-symmetrical diboron reagent, B(pin)-B(dan), has been utilised in the Pd-catalysed borylation of aryl bromides and chlorides. Remarkably selective formation of aryl-B(dan) bonds is established. This represents a direct and efficient way to introduce masked boronic acids. The synthetic usefulness of this reaction is demonstrated in the preparation of boron-differentiated di- and polyboron compounds.

Organoboronic acids have gained broad research interest in synthetic chemistry, drug discovery and materials science. As synthetic building blocks, they can react with various functional groups to construct new carbon–carbon or carbon–heteroatom bonds.[1] On the other hand, their high reactivity complicates the chemical selectivity in complex molecule synthesis. Consequently, practical and readily removable masking groups which render boryl groups temporarily inert have undergone great development in the last decade,[2] especially in the fields of iterative cross-coupling[3] and functionalised polyboron compounds.[4]

The masked boronic acids are commonly synthesized from the corresponding free boronic acids by condensation with masking molecules such as 1,8-diaminonaphthalene (dan) and *N*-methyliminodiacetic acid (MIDA). Although proven successful in many cases, this approach can be troublesome when the starting organoboronic acids are not readily available or unstable. Therefore a direct way to introduce the masked boryl group into simple molecules is more desirable. Suginome and co-workers reported the direct synthesis of alkenyl-B(dan) *via* C–H borylation[5] or hydroboration of alkynes[3e] with 1,8-naphthalenediaminatoborane ((dan)BH). The diboration of alkynes using a non-symmetrical diboron reagent, B(pin)-B(dan), was disclosed by the same group in 2010.[4d] More recently, alkyl and alkenyl 1,8-diaminonaphthalene boronates have been synthesized by hydroboration of alkenes or alkynes using B(pin)-B(dan) with the less Lewis acidic B(dan) moiety being transferred selectively.[6] In contrast, the direct synthesis of aryl B(dan) from commercially available compounds has been rarely studied. The only example of this type was realized *via* C–H borylation using (dan)BH.[7] However, the reaction efficiency remained low. Moreover, the regioselectivity of the C–H borylation was governed by steric effects; some regioisomers were not accessible by the method. Consequently, we wanted to explore for a direct and general approach to the masked aryl boronic acid derivatives.

Recently, differentially protected diboron reagents have been applied in chemoselective transfer of the two boryl groups to various unsaturated bonds. For example, Santos and co-workers have demonstrated that sp^2-hybridized boron of the sp^2–sp^3 hybridized diboron reagents is selectively transferred in the copper-catalyzed β-boration of α,β-unsaturated carbonyl compounds.[8] The sp^2–sp^2 hybridized non-symmetrical diboron reagent B(pin)-B(dan) has recently been applied in the addition reactions of alkenes and alkynes, with the B(dan) moiety transferred selectively (1a and 1b, Scheme 1) as mentioned above.[6] Mechanistically, in both cases, the cause of such selectivity was proposed to be the preferred



Scheme 1 Selective boryl transfer of a non-symmetrical diboron reagent.

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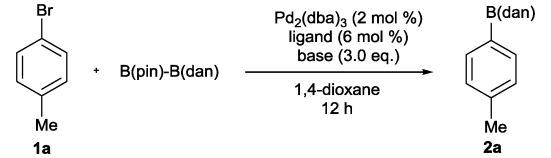
interaction between the more Lewis acidic B(pin) moiety with basic promoting reagents or catalysts. During our study on preparation of functionalised polyboron reagents, we wondered whether a similar chemoselective borylation might be used for direct introduction of B(dan) into arenes by Miyaura-type borylation reaction.[9] In classical Miyaura borylation of aryl halides, [LPd(Ar)OAc] is considered as the key intermediate which then undergoes a transmetalation process with diboron reagents. We envisioned that under Miyaura-type conditions, B(pin)-B(dan) may undergo a selective transmetalation process with [LPd(Ar)OAc] because of the stronger interaction between the Lewis basic-OAc and the more Lewis acidic B(pin) moiety, generating the [LPd(Ar)B(dan)] intermediate preferentially (1c, Scheme 1). The following reductive elimination would then selectively form the final borylation product ArB(dan). This might provide a straightforward method to synthesise aryl-B(dan) from readily available aryl (pseudo)halides.

With this in mind, we initiated our studies by examining the reaction between B(pin)-B(dan) and 4-bromotoluene under Pd-catalysed conditions. In a preliminary experiment, using a catalytic combination of $Pd_2(dba)_3$ (2 mol%) and PPh_3 (6 mol%) (entry 1, Table 1), to our delight, the desired aryl-B(dan) product **2a** could be obtained in 19% yield based on ^{1}H NMR analysis of the crude product. Further screening of phosphine ligands afforded more efficient conditions. Thus, when the reaction was conducted at 100 °C for 12 hours using XPhos, a bulky monophosphine ligand,[9c,10] as the supporting ligand, the desired product could be obtained quantitatively (entry 5). Similar to the classical Miyaura borylation reaction, KOAc was found to be the best base for this system. The reaction temperature could be decreased to 60 °C without loss of yield (entry 9). However, further decreasing the temperature led to dramatically lower yields (entries 7 and 8). Omitting the Pd catalyst and the ligand, no desired product could be observed (entry 11), and therefore a metal-free borylation pathway was not working for this system.

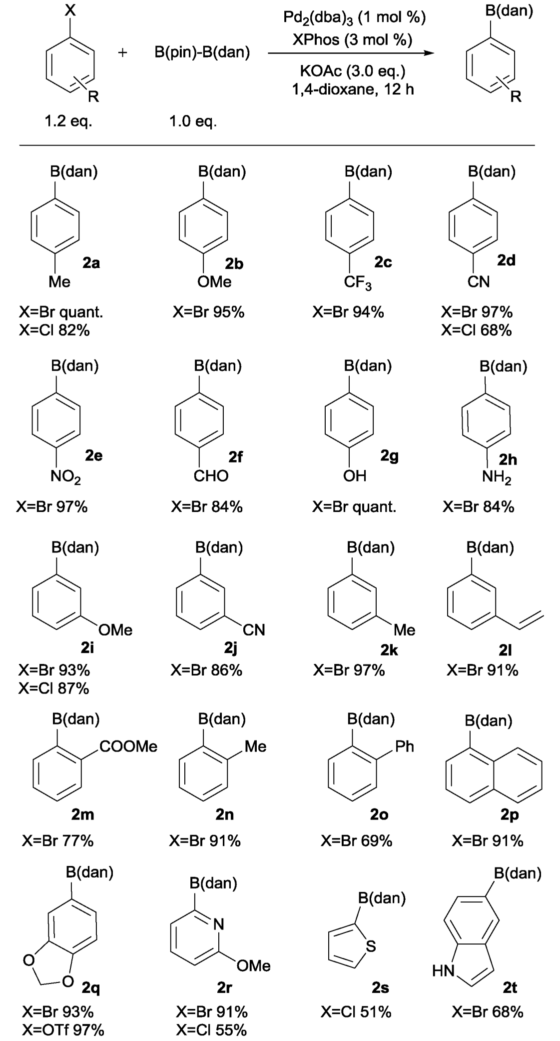
Table 1 Optimization of reaction parameters[a]



Entry	Ligand	Base	T (°C)	Yields[b] (%)
1	PPh_3	KOAc	80	19
2	*t*Bu-XPhos	KOAc	100	20
3	SPhos	KOAc	100	95
4	XantPhos	KOAc	100	29
5	XPhos	KOAc	100	99
6	XPhos	KO*t*Bu	100	Trace
7	XPhos	KOAc	r.t.	18
8	XPhos	KOAc	50	76
9	**XPhos**	**KOAc**	**60**	**99(98)**[e]
10[c]	XPhos	KOAc	60	64
11[d]	—	KOAc	60	N.R.

[a] Reaction conditions: 4-bromotoluene (0.12 mmol), B(pin)-B(dan) (0.10 mmol), 1,4-dioxane (0.5 ml) under a N_2 atomosphere. [b] Yields based on ^{1}H NMR analysis of the crude products with 1,3,5-trimethoxybenzene added as an internal standard. [c] 4 mol% $Pd(OAc)_2$ was used as a catalyst. [d] The catalyst and the ligand were not added. [e] Isolated yield shown in parenthesis.

With the optimized reaction conditions in hand, we next explored the substrate scope of this selective boryl transfer reaction. As shown in Scheme 2, various aryl bromides bearing electron-withdrawing and -donating groups at the *para*- or *meta*-positions were borylated in good to excellent yields (for **2a–2l**). It should be mentioned that free phenolic hydroxyl groups (for **2g**) and amino groups (for **2h**) were well tolerated in the reaction system, while the corresponding free aryl boronic acids bearing these two groups were usually prepared only in moderate yields. Therefore the current method, involving the direct formation of C–B(dan) bonds from C–X bonds, is more practical and efficient than the previous condensation route. This borylation reaction was found to be sensitive to the steric hindrance; elevated reaction temperature (100 °C) was necessary to give satisfactory yields for *ortho*-substituted aryl bromides (for **2m–2o**). Aryl triflate (for **2q**) could also be converted into aryl-B(dan) directly. In addition,

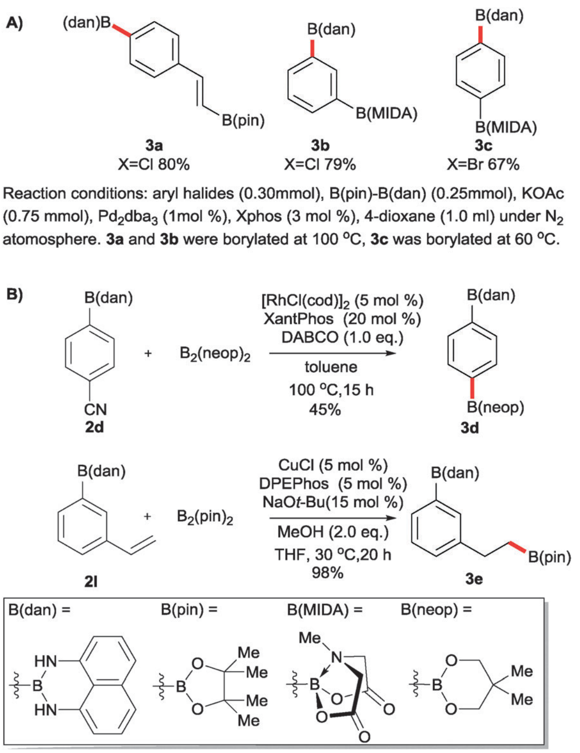


Scheme 2 Substrate scope of Pd-catalysed selective boryl transfer. [a] Reaction conditions: aryl halide (0.30 mmol), B(pin)-B(dan) (0.25 mmol), 1,4-dioxane (1.0 ml) under a N_2 atomosphere. [b] Isolated yields based on the amount of B(pin)-B(dan) used. [c] The aryl chlorides and *ortho*-substituted aryl bromides were borylated at 100 °C. Other cases mentioned were all borylated at 60 °C.

aryl chlorides were also utilized in this reaction, although they generally needed a higher reaction temperature (100 °C) than their bromide analogues (for **2a**, **2d**, **2i** and **2s**).

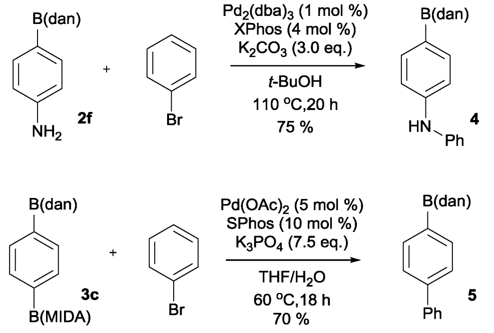
Following our previous work on the synthesis and applications of differentiated polyboron reagents, we applied the present reaction in facile preparation of polyboron compounds containing the B(dan) group.[4i,j] Two routes were utilized toward the synthesis of these compounds. The first one was starting from monoboron aryl halides using selective naphthalene-1,8-diamino borylation to introduce the B(dan) group. Thus, diboron compounds **3a**–**3c** were conveniently prepared in good yields (Scheme 3A). To the best of our knowledge, there has been no literature precedence on compounds containing both B(dan) and B(MIDA) groups. The second route was using functionalised aryl B(dan) compounds as the starting materials and various known borylation methods to introduce a different type of boronyl group (Scheme 3B). For example, Rh-catalyzed borylation of **2d** *via* C–C bond cleavage under the literature conditions produced **3d** containing a neopentanediolato boronyl group B(neop).[11] A Cu-catalysed hydroboration of an alkene moiety also quantitatively furnished diboron reagent **3e** incorporating an alkyl B(pin) group.

Making use of the relative inertness of the B(dan) group, we then assessed the possible utility of the above-prepared functionalised aryl B(dan) compounds.[12] The *para*-naphthalene-1,8-diamino boryl aniline **2f** was subjected to a chemoselective Pd-catalysed Buchwald–Hartwig coupling[13] with bromobenzene and amination product **4** could be obtained in 75% yield without interference from Suzuki–Miyaura type reaction. Much as anticipated, the reactivities of B(MIDA) and B(dan), the two effective protecting groups for boronic acids on **3c**, could also be differentiated in Suzuki–Miyaura coupling under aqueous basic conditions, affording **5** in good yield (Scheme 4).

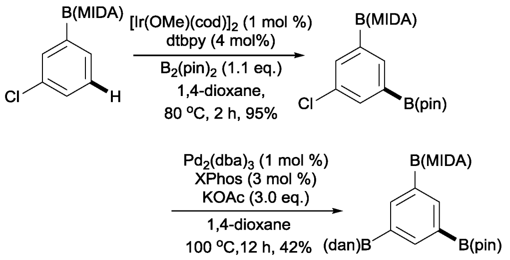


Reaction conditions: aryl halides (0.30mmol), B(pin)-B(dan) (0.25mmol), KOAc (0.75 mmol), Pd_2dba_3 (1mol %), Xphos (3 mol %), 4-dioxane (1.0 ml) under N_2 atomosphere. **3a** and **3b** were borylated at 100 °C, **3c** was borylated at 60 °C.

Scheme 3 The applications of Pd-catalysed selective boryl transfer in preparing boron-differentiated diboron compounds.



Scheme 4 Chemoselective transformations of functionalised aryl B(dan) compounds.



Scheme 5 The synthesis of trisboronylbenzene.

At last, taking advantage of the Ir-catalysed C–H borylation process developed by our group and the methodology reported herein, a 1,3,5-trisboronyl benzene was synthesized in three steps from commercially available 3-chlorophenylboronic acid, with these boronyl groups different from each other (Scheme 5). As far as we know, this represents the first example of assembling three different boronyl groups onto the same molecule. This new type of organoboron reagents should be useful building blocks in modular synthesis of multi-functionalised arene compounds.

In conclusion, by employing the non-symmetrical diboron compound, B(pin)-B(dan), as the borylating reagent in Pd-catalysed Miyaura-type reaction, we have realized the chemoselective B(dan) moiety transfer to various aryl rings, yielding masked boronic acids directly from abundant and cheap aryl halides. We have also demonstrated the usefulness of this naphthalene-1,8-diamino borylation in the facile preparation of boron-differentiated di- and polyboron compounds and other functionalised aryl boron compounds.

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