

Weak Base-Promoted Direct Cross-Coupling of Naphthalene-1,8-diaminato-substituted Arylboron Compounds

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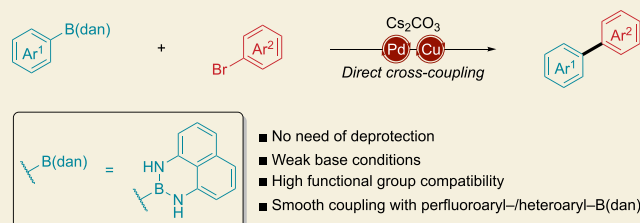
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ABSTRACT: The indispensability of a base in Suzuki–Miyaura coupling (SMC) employing organoboronic acids/esters is well recognized, which occasionally induces competitive protodeborylation in organoboron reagents. This phenomenon is particularly pronounced in fluorine-substituted aryl and heteroaryl boron compounds. Here, we show that direct SMC of naphthalene-1,8-diaminato (dan)-substituted aryl boron compounds, Ar–B(dan), characterized by its remarkable stability toward protodeborylation due to their diminished boron-Lewis acidity, occurs utilizing a weak base in conjunction with a palladium/copper cooperative catalyst system. The approach delineated in this study enables the efficient incorporation of various perfluoroaryl- and heteroaryl–B(dan) reagents, while maintaining high functional group tolerance. Furthermore, the inherent inertness of the B(dan) moiety allowed sequential cross-coupling, where other metallic moieties chemoselectively undergo the reaction, thus leading to the concise, protection-free synthesis of oligoarenes. Our results provide a potent approach to a delicate dilemma between a protodeborylation-resistant property and SMC activity intimately linked to boron-Lewis acidity.



KEYWORDS: C–C coupling, cross-coupling, direct Suzuki–Miyaura coupling, Lewis acidity-diminished organoboron reagents, weak bases

INTRODUCTION

Biaryl skeletons are key motifs frequently encountered in pharmaceuticals and materials science. Nitrogen-containing heteroaryl groups, including pyridyl, thiazolyl, and pyrazolyl, alongside fluorine-substituted aryl groups, feature prominently in a vast array of valuable molecules that substantially enhance our quality of life.^{1–3} Such molecules span diverse applications, from cancer therapeutics and anti-inflammatory drugs to ligands for organic electroluminescent materials (Figure 1).⁴ Consequently, the development of efficient and reliable synthetic routes to these compounds remains a pivotal focus in chemical synthesis.

Cross-coupling techniques utilizing organometallic reagents have significantly advanced as powerful methods for the efficient and streamlined construction of biaryl structures.^{5–7} The Suzuki–Miyaura coupling (SMC) with organoboron compounds stands out as the most prevalent cross-coupling in both industrial applications and laboratory-scale synthesis. This prominence is due to the exceptional chemoselectivity, functional group compatibility, and practicality afforded by the manageable properties of organoboron compounds.^{2,8–12} However, despite its established status in synthetic organic chemistry, SMC faces persistent challenges. Notably, while most arylboronic acids/esters are relatively stable, nitrogen-containing heteroaryl and fluorine-substituted aryl compounds often undergo rapid protodeborylation under aqueous or basic conditions, leading to inefficient SMC in most cases (Scheme

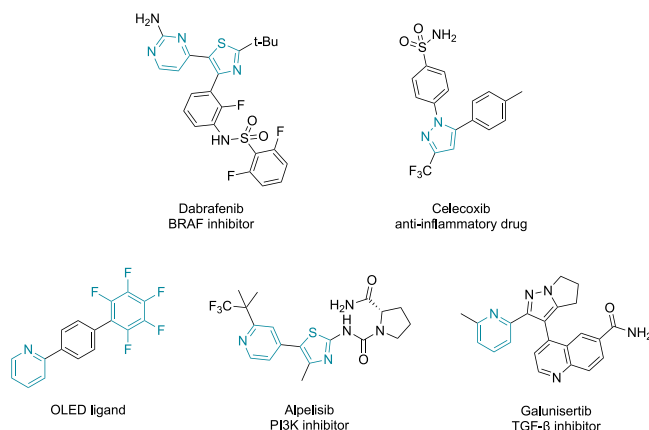


Figure 1. Selected biaryl skeletons encountered in pharmaceuticals and material science.

1a).^{13–31} To address the “protodeborylation problem”, various strategies have been employed, including the use of highly active

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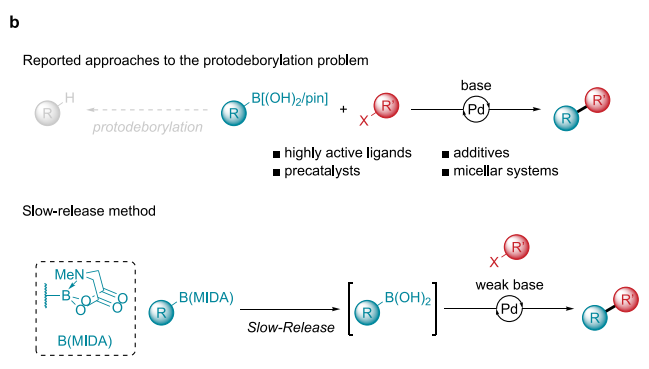
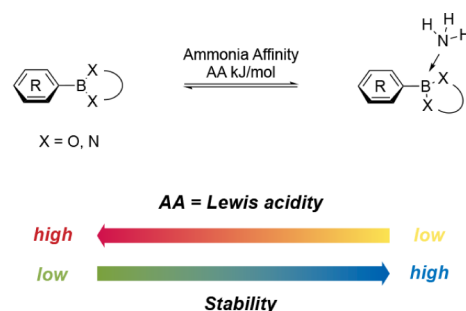
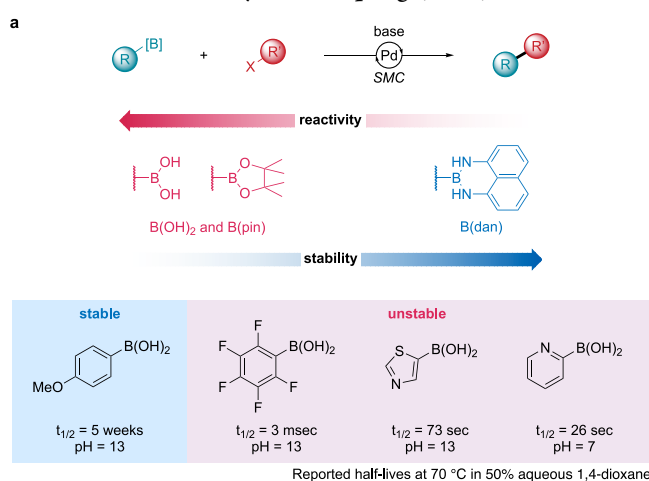
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Scheme 1. Suzuki–Miyaura Coupling (SMC)



ligands,^{32–35} precatalysts,^{27,36–40} and suitable additives^{30,31,41–43} (e.g., silver(I) salt,^{44–49} copper(II) salt,^{50,51} copper(I) salt/phenanthroline⁵² or micellar systems),^{53–57} where the SMC process significantly outpaces protodeborylation. It has also been reported that the protodeborylation can be significantly overcome by using an excess of aryl halides.⁵⁸ Another promising approach, particularly beneficial for heteroaryl compounds, is the boron-masking strategy using stable, SMC-inactive MIDA boronates, which are slowly deprotected in situ to yield boronic acids under SMC conditions.^{29,50,51,59–61} Despite these significant advances in SMC, there remains room for improvement, as all these reactions involve the use of potentially unstable arylboronic acids/esters that are susceptible to protodeborylation (Scheme 1b).

The propensity for protodeborylation in organoboron compounds is closely associated with their boron-Lewis acidity, which can be quantified by computed ammonia affinity (AA) (Figure 2).^{62–64} A reduction in Lewis acidity, achieved by modifying boron substituents, leads to significant stabilization.² In this context, we have focused on 1,8-diaminonaphthalene-substituted boron moieties [B(dan)], characterized by markedly diminished Lewis acidity, for boron-based synthetic chemistry. We observed that various heteroaryl–B(dan) compounds, including 2-pyridyl-, 5-thiazolyl-, and 5-pyrazolyl-, exhibit exceptional resistance to protodeborylation, enabling their isolation even via column chromatography.^{65–69} However, dan-substituted organoboron compounds typically exhibit inactivity toward transmetalation in SMC, as the reduced Lewis acidity impedes interaction between B(dan) moieties and Lewis bases (Scheme 1a). This behavior was highlighted in Sugimoto's

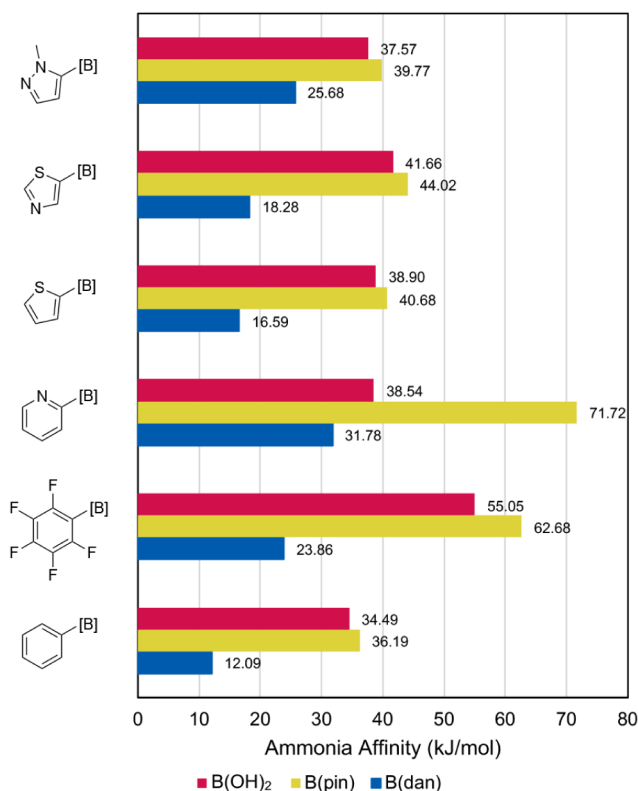
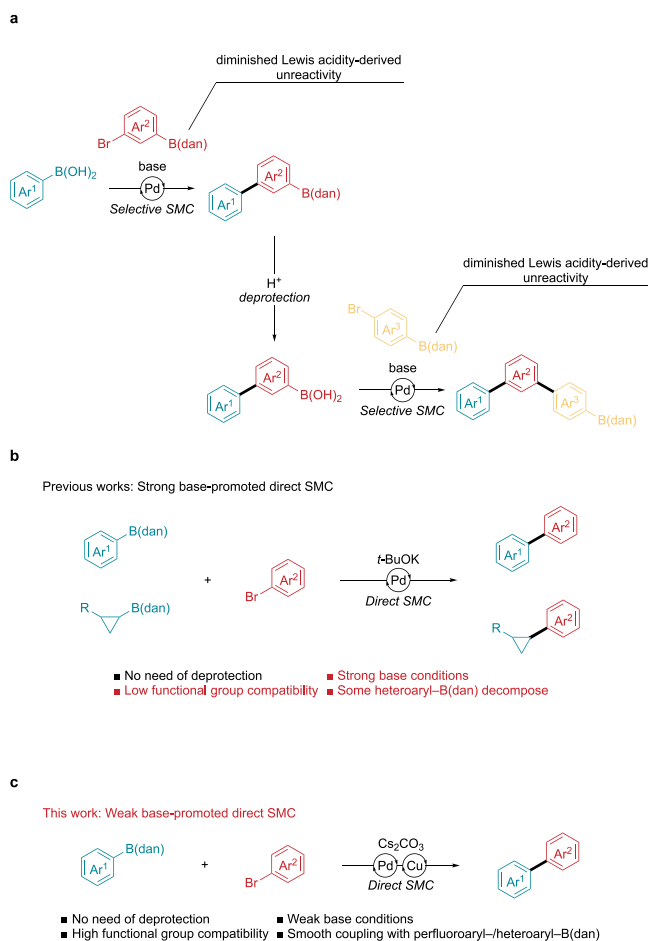


Figure 2. Computed ammonia affinity.

iterative SMC, where “protected” B(dan) moieties remained unreacted (Scheme 2a).^{70,71} In 2020, Saito and our team independently demonstrated that a variety of aryl–B(dan) compounds could be activated by strong bases like *t*-BuOK for efficient SMC.^{72,73} This activation was also found effective for cyclopropyl–B(dan) (Scheme 2b).⁷⁴ This method, wherein protodeborylation-resistant R–B(dan) compounds directly participate in SMC, presents a powerful solution to the aforementioned protodeborylation challenge. Indeed, compounds such as 2-pyridyl- and pentafluorophenyl–B(dan) have been successfully converted into their respective coupling products.⁷⁵ However, this process comes at the expense of reduced tolerance for various functional groups. Another significant drawback of these strongly basic conditions is the rapid decomposition of certain heteroaryl–B(dan) compounds, such as 5-thiazolyl–B(dan) (1i), rendering them unsuitable for direct SMC (*vide infra*). In this study, we report the first successful direct SMC of a diverse range of heteroaryl- and perfluoroaryl–B(dan) under mild base conditions, despite their significantly diminished boron-Lewis acidity. The addition of a copper(I) salt as a cocatalyst is crucial to this transformation.

Scheme 2. SMC with Aryl–B(dan)



This approach offers a reliable and convenient solution to the protodeborylation problem in SMC, utilizing stable, easy-to-handle organoboron reagents (Scheme 2c). In the context of sustainability aspects, the use of protodeborylation-resistant, bench-stable B(dan) compounds is promising; avoidance of contamination by protodeborylation-derived side-products suppresses isolation cost in purifying the cross-coupling products, and storage cost (glovebox, inert gas, refrigerator, etc.) is also significantly reduced. Furthermore, the direct SMC in the organic solvent-only system is preferable in solvent recovery since mixed, aqueous solvent systems, frequently employed for the conventional and slow-release SMC, require costly, higher energy-consuming processes.

RESULTS AND DISCUSSION

Our initial experiment involved the reaction of pentafluorophenyl–B(dan) (**1a**) with 4-bromotoluene (**2a**), using Pd(PPh₃)₄ (5 mol %) and CuTC (10 mol %) as cocatalysts in various solvents in the presence of Cs₂CO₃, a weak base commonly used in conventional SMC.¹⁰ Remarkably, **1a** underwent direct SMC without in situ deprotection of the B(dan) moiety, yielding the coupling product (**3aa**) (*vide infra*). Among the solvents with varied polarities tested, DME proved to be the most effective, achieving an 83% yield (Table 1, Entries 1–9). The use of Cs₂CO₃ was essential for this transformation, as other weak bases, including potassium carbonate (Table 1, Entry 10) and potassium phosphate (Table 1, Entry 11), were ineffective. Optimal results were achieved at a reaction

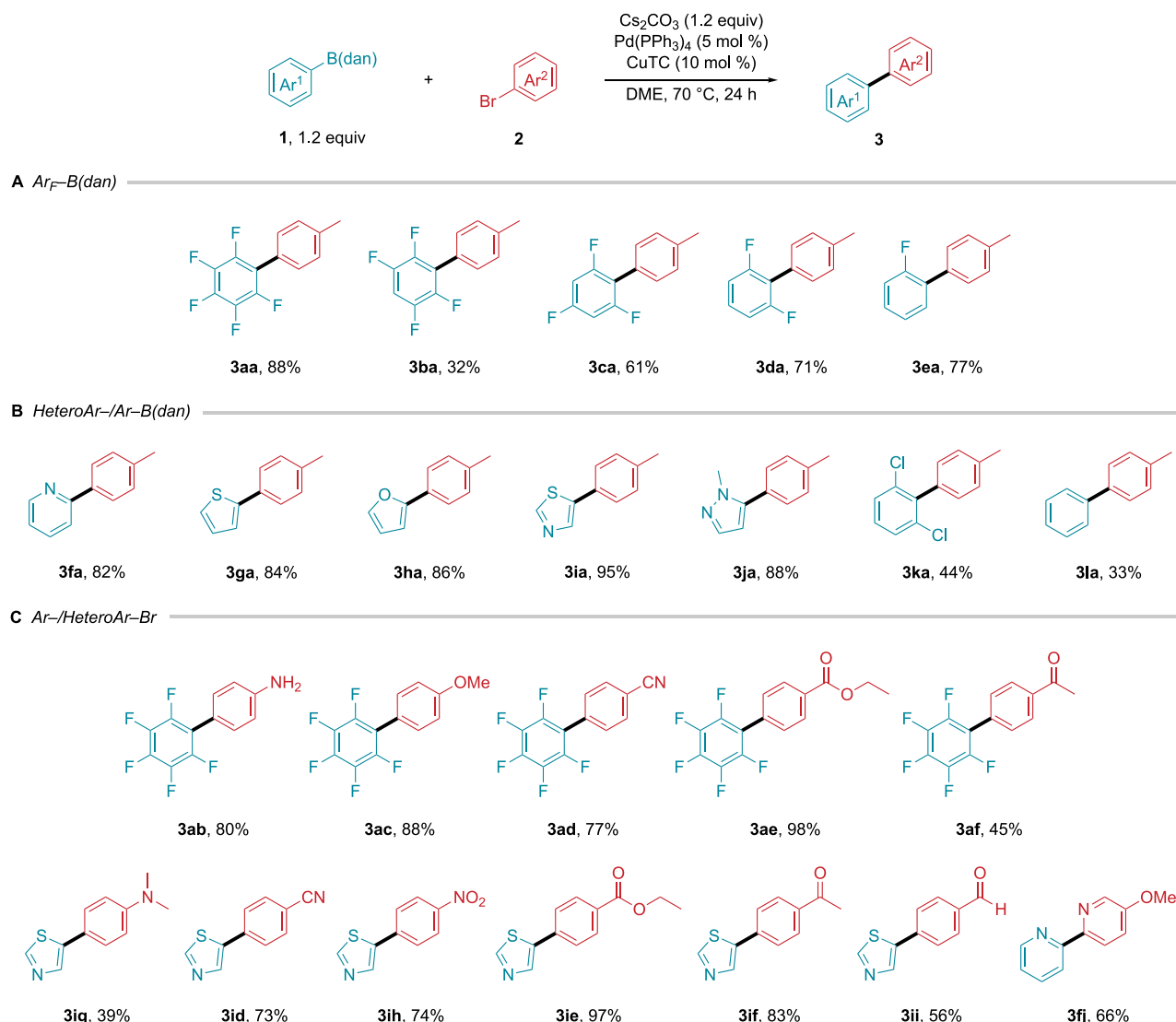
Table 1. Optimization of Reaction Conditions^a

entry	base	solvent	temp/time (°C/h)	3aa (%) ^b
1	Cs ₂ CO ₃	CH ₂ Cl ₂	40/24	18
2	Cs ₂ CO ₃	<i>p</i> -xylene	100/24	20
3	Cs ₂ CO ₃	DMSO	100/24	25
4	Cs ₂ CO ₃	toluene	100/24	33
5	Cs ₂ CO ₃	DMF	100/24	35
6	Cs ₂ CO ₃	THF	60/24	43
7	Cs ₂ CO ₃	CH ₃ CN	80/24	57
8	Cs ₂ CO ₃	DEE	100/24	53
9	Cs ₂ CO ₃	DME	80/24	83
10	K ₂ CO ₃	DME	80/24	28
11	K ₃ PO ₄	DME	80/24	11
12	Cs ₂ CO ₃	DME	60/24	91
13	Cs ₂ CO ₃	DME	70/24	98(88)
14 ^c	Cs ₂ CO ₃	DME	70/24	21
15 ^d	Cs ₂ CO ₃	DME	70/24	0
16 ^e	Cs ₂ CO ₃	DME	70/24	quant(90)
17 ^f	Cs ₂ CO ₃	DME	70/24	70
18 ^g	Cs ₂ CO ₃	DME	70/24	0
19	no base	DME	70/24	10

^aReaction conditions: **1a** (0.18 mmol, 1.2 equiv), **2a** (0.15 mmol, 1.0 equiv), base (0.18 mmol, 1.2 equiv), Pd(PPh₃)₄ (7.5 μmol, 5 mol %), CuTC: copper(I) thiophene-2-carboxylate (15 μmol, 10 mol %) in indicated solvent (1.0 mL). ^bDetermined by GC using bis(2-butoxyethyl) ether as an internal standard. A value in parentheses indicates an isolated yield. ^cWithout CuTC. ^dWithout Pd(PPh₃)₄. ^eCuBr was used instead of CuTC. ^f[Cu(NCMe)₄]PF₆ was used instead of CuTC. ^gNaTC; Sodium thiophene-2-carboxylate was used instead of CuTC.

temperature of 70 °C, with a 98% yield (Table 1, Entry 13). Significantly lower yields were observed under conditions using only palladium or copper, underscoring the importance of Pd/Cu cocatalysis in this SMC (Table 1, Entries 14 and 15). While the use of CuBr (Table 1, Entry 16) or [Cu(NCMe)₄]PF₆ (Table 1, Entry 17) instead of CuTC also promoted the SMC efficiently,⁷⁶ the reaction in the presence of 2-thiophenecarboxylic acid sodium salt (NaTC) was sluggish (Table 1, Entry 18), showing that counteranions of Cu(I) salts including thiophene carboxylate were not important factors in promoting the reaction. Notably, omitting Cs₂CO₃ resulted in only a 10% yield of **3aa** (Table 1, Entry 19), corresponding to the amount of CuTC used, highlighting the base's role in regenerating a transmetalation-active Cu(I) salt (*vide infra*). The critical role of the diminished Lewis acidity in the success of the SMC was further demonstrated by using pentafluorophenyl–B(OH)₂ (**1a'**); the reaction primarily led to protodeborylation, without yielding the desired coupling product (**3aa**).⁷⁷

We examined the direct SMC of a range of aryl–B(dan) compounds under optimal conditions (Scheme 3). Various fluorine-containing aryl–B(dan) compounds, typically prone to protodeborylation in their boronic acid forms,^{15,17–20,26} smoothly produced high yields of their respective coupling products (**3aa**, **3ca–3ea**). An exception was observed with 2,3,5,6-tetrafluorophenyl–B(dan) (**1b**), where concurrent C–H arylation⁷⁸ at the reactive 4-position led to a *p*-teraryl side-

Scheme 3. Substrate Scope^a

^aReaction conditions: aryl-B(*dan*) (**1**) (0.18 mmol, 1.2 equiv), aryl-Br (**2**) (0.15 mmol, 1.0 equiv), Cs₂CO₃ (0.18 mmol, 1.2 equiv), Pd(PPh₃)₄ (7.5 μmol, 5 mol %), CuTC: copper(I) thiophene-2-carboxylate (15 μmol, 10 mol %) in DME: 1,2-dimethoxyethane (1.0 mL) at 70 °C, 24 h. Isolated yields were given in all cases.

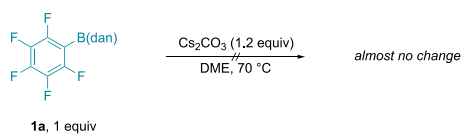
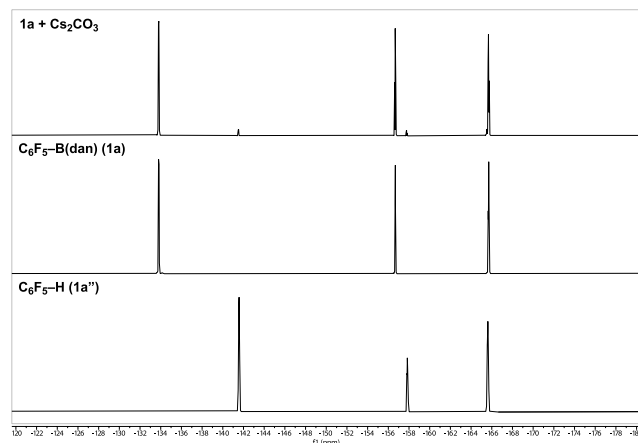
product.⁷⁷ This suggests that in situ protodeborylation of **1a** or **1b**, followed by arylation of the resulting acidic C–H bonds, might be a dominant pathway for generating **3aa** or **3ba**. However, treating **1a** with Cs₂CO₃ in DME at 70 °C scarcely caused protodeborylation (Scheme 4a). Furthermore, the reaction of pentafluorobenzene (**1a**⁷⁷) with **2a** under optimal conditions yielded only a 9% of **3aa** (Scheme 4b), confirming that the reaction proceeds via direct SMC at the B(*dan*) moiety. In reactions involving 2,4,6-trifluorophenyl-B(*dan*) (**1c**), no side-products from C–H arylation were observed, ruling out the protodeborylation–C–H arylation pathway for **1c**–**1e**, which have less acidic C–H bonds. The versatility of this system was exemplified by its application to diverse heteroaryl-B(*dan*) compounds, such as 2-pyridyl (**1f**), 2-thienyl (**1g**), 2-furyl (**1h**), 5-thiazolyl (**1i**), and 5-pyrazolyl (**1j**). These substrates, typically unstable in their Lewis acidic forms, yielded high-yield products (**3fa**–**3ja**) despite being challenging in conventional SMC.^{14, 15–17, 20–29} Notably, our previous strongly basic conditions using *t*-BuOK⁷² were ineffective for 5-thiazolyl–

B(*dan*) (**1i**), leading to its decomposition, which underscores the practicality and reliability of the present weak base conditions (Scheme 4c). However, lower yields were observed with 2,6-dichlorophenyl– (**1k**) and phenyl–B(*dan*) (**1l**), especially with electronically neutral **1l**. This suggests that increased Lewis acidity of the B(*dan*) moiety (AA of **1l** = 12.09 kJ/mol; cf. **1a** = 23.86 kJ/mol; **1b** = 24.07 kJ/mol; **1c** = 19.41 kJ/mol; **1d** = 19.57 kJ/mol; **1e** = 25.12 kJ/mol), induced by electron-deficient aryl groups and directing heteroatoms,^{79, 80} facilitates transmetalation between Ar–B(*dan*) and a Cu(I) salt.

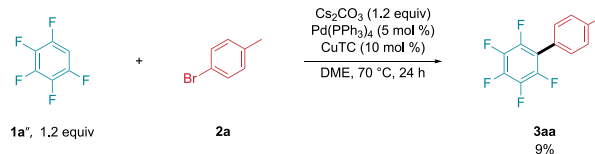
The weak base conditions also preserved various reactive functional groups on aryl bromides during coupling. Pentafluorophenyl– (**1a**) and 5-thiazolyl–B(*dan*) (**1i**) were successfully cross-coupled with aryl bromides featuring acidic protons [NH₂ (**2b**), Ac (**2f**)], electrophilic centers [CN (**2d**), CO₂Et (**2e**), CHO (**2i**)], or other substituents [OMe (**2c**), NMe₂ (**2g**), NO₂ (**2h**)], yielding products (**3ab**–**3af**, **3jg**–**3ji**) in moderate to high yields. Notably, NH₂, Ac, and CO₂Et functionalities, vulnerable under strong base conditions, were successfully

Scheme 4. Additional Experiments^a

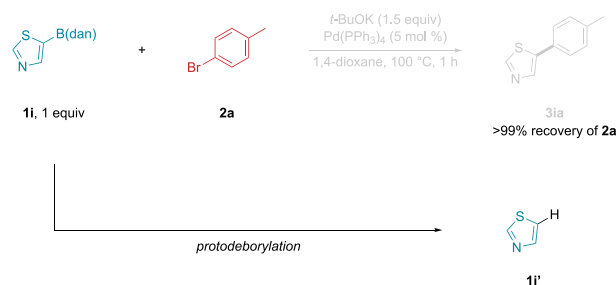
a. Stability of pentafluorophenyl–B(dan) (1a) in the presence of cesium carbonate

¹⁹F NMR (470 MHz, DME)

b. C–H arylation of pentafluorobenzene (1a'') under optimal conditions



c. SMC of 5-thiazolyl–B(dan) (1i) under strong base conditions



protodeborylation of 1i was confirmed by GC analysis

^aReaction conditions: pentafluorophenyl–B(dan) (**1a**) (30 μ mol, 1.0 equiv), Cs₂CO₃ (36 μ mol, 1.2 equiv) in DME: 1,2-dimethoxyethane (0.6 mL) at 70 °C. After the reaction mixture was cooled to room temperature, ¹⁹F NMR was measured. (b) Reaction conditions: pentafluorobenzene (**1a''**) (0.18 mmol, 1.2 equiv), 4-bromotoluene (**2a**) (0.15 mmol, 1.0 equiv), Cs₂CO₃ (0.18 mmol, 1.2 equiv), Pd(PPh₃)₄ (7.5 μ mol, 5 mol %), CuTC: copper(I) thiophene-2-carboxylate (15 μ mol, 10 mol %) in DME: 1,2-dimethoxyethane (1.0 mL) at 70 °C, 24 h. GC yield was given. (c) Reaction conditions: 5-thiazolyl–B(dan) (**1i**) (0.15 mmol, 1.0 equiv), 4-bromotoluene (**2a**) (0.15 mmol, 1.0 equiv), *t*-BuOK (0.23 mmol, 1.5 equiv), Pd(PPh₃)₄ (7.5 μ mol, 5 mol %) in 1,4-dioxane (1.0 mL) at 100 °C, 1 h. GC yield was given.

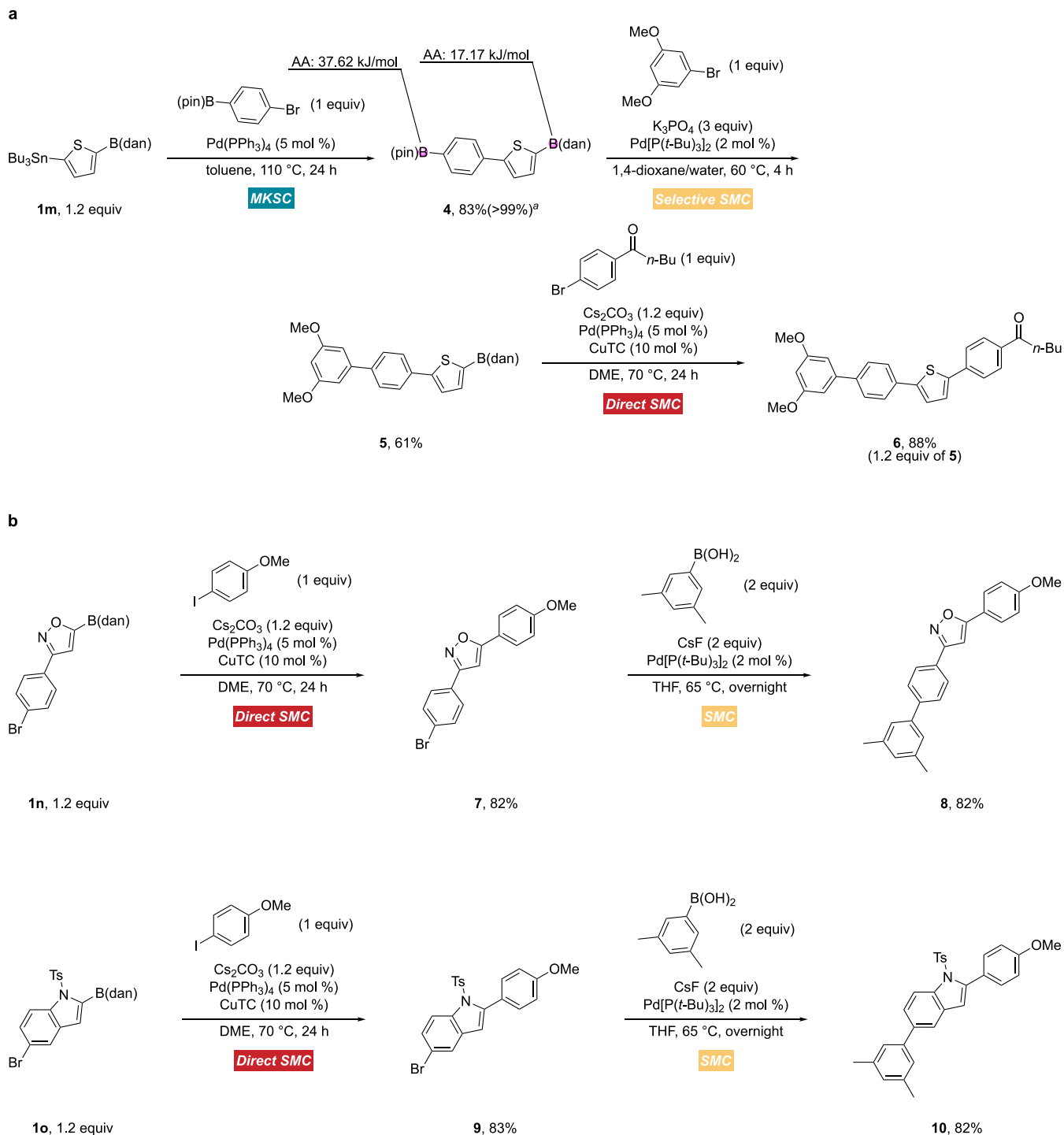
incorporated in the B(dan)-based direct SMC. Additionally, the protodeborylation-resistant nature of heteroaryl–B(dan) facilitated smooth heteroaryl–heteroaryl coupling, often challenging in standard SMC with Lewis acidic heteroarylboron compounds.^{25,33} For instance, treating 2-pyridyl–B(dan) (**1f**) with 2-bromo-5-methoxy pyridine (**2j**) produced a 66% yield of 2,2'-bipyridine (**3fj**).

The inherently “protected” and inert nature of B(dan) moieties, due to their significantly diminished Lewis acidity, can be leveraged for chemoselective cross-coupling sequences, effectively differentiating between various metallic functionalities (Scheme 5a). Initially, 5-(tributylstannyl)-2-thienyl–B(dan) (**1m**), easily synthesized from 2,5-bis(tributylstannyl)-thiophene via a one-pot installation of a B(dan) moiety,⁶⁹ underwent Migita–Kosugi–Stille coupling (MKSC) with 4-B(pin)-substituted phenyl bromide. This process yielded compound **4** in an 83% yield, with both boron moieties remaining intact. Subsequently, the B(pin) moiety of **4** was used for chemoselective cross-coupling under standard SMC conditions,⁷¹ resulting in a B(dan)-containing tetaryl (**5**). The differing reactivities can be attributed to their respective Lewis acidities, as measured by the computed ammonia affinity technique⁶² [37.62 kJ/mol for B(pin) vs. 17.17 kJ/mol for B(dan)]. The direct SMC at the remaining B(dan) moiety, using an aryl bromide with a base-sensitive ketone group, was then conducted under our Pd/Cu cocatalysis conditions, yielding a tetraaryl (**6**) in 88% yield (45% overall yield across three steps). Furthermore, as depicted in Scheme 5b, the direct SMC was successfully applied to 5-isoxazolyl– (**1n**) and 2-indolyl–B(dan) (**1o**), synthesized via our [3 + 2] cycloaddition or Pd-catalyzed heteroannulation using ethynyl–B(dan).⁸¹ This

yielded chemoselectively bromine-substituted coupling products (**7** and **9**) in high yields when treated with 4-iodoanisole. The residual bromine moieties were subsequently utilized in further SMC with 3,5-dimethylphenyl boronic acid, efficiently producing isoxazole- or indole-containing π -extended compounds (**8** and **10**).

A copper(I) cocatalyst has been suggested to facilitate SMC (with organoboronates) through transmetalation with organoboron reagents, yielding more reactive organocopper intermediates.^{82–90} We conducted a stoichiometric reaction of pentafluorophenyl–B(dan) (**1a**) with CuTC in the presence of cesium carbonate. As shown in Scheme 6a-A, the ¹⁹F NMR spectrum revealed the formation of a pentafluorophenylcopper species and its protonated product, pentafluorobenzene (**1a''**), with complete consumption of **1a**. The downfield-shifted signal (ca. –113 pm), characteristic of the pentafluorophenylcopper species,⁹¹ also synthesized by a different method (Scheme 6a-C), which strongly supports that the direct SMC proceeds via transmetalation between aryl–B(dan) and a copper catalyst. The formation of **1a''** as a side-product in the transmetalation between **1a** and CuTC (Scheme 6a-A) may be due to the protonation of C₆F₅–Cu by the N–H moiety of B(dan); treatment of C₆F₅–Cu, generated according to the method of Scheme 6a-C, with **1a** actually resulted in the complete conversion of C₆F₅–Cu to **1a''** via the protonation.⁷⁷ In contrast, without cesium carbonate, transmetalation was significantly hindered, leaving most of **1a** unreacted (Scheme 6a-B), thus highlighting the necessity of a base for efficient transmetalation.⁹² As shown in Scheme 6b, the pentafluorophenylcopper species generated according to Scheme 6a-C was found to be an effective coupling partner with 4-bromotoluene

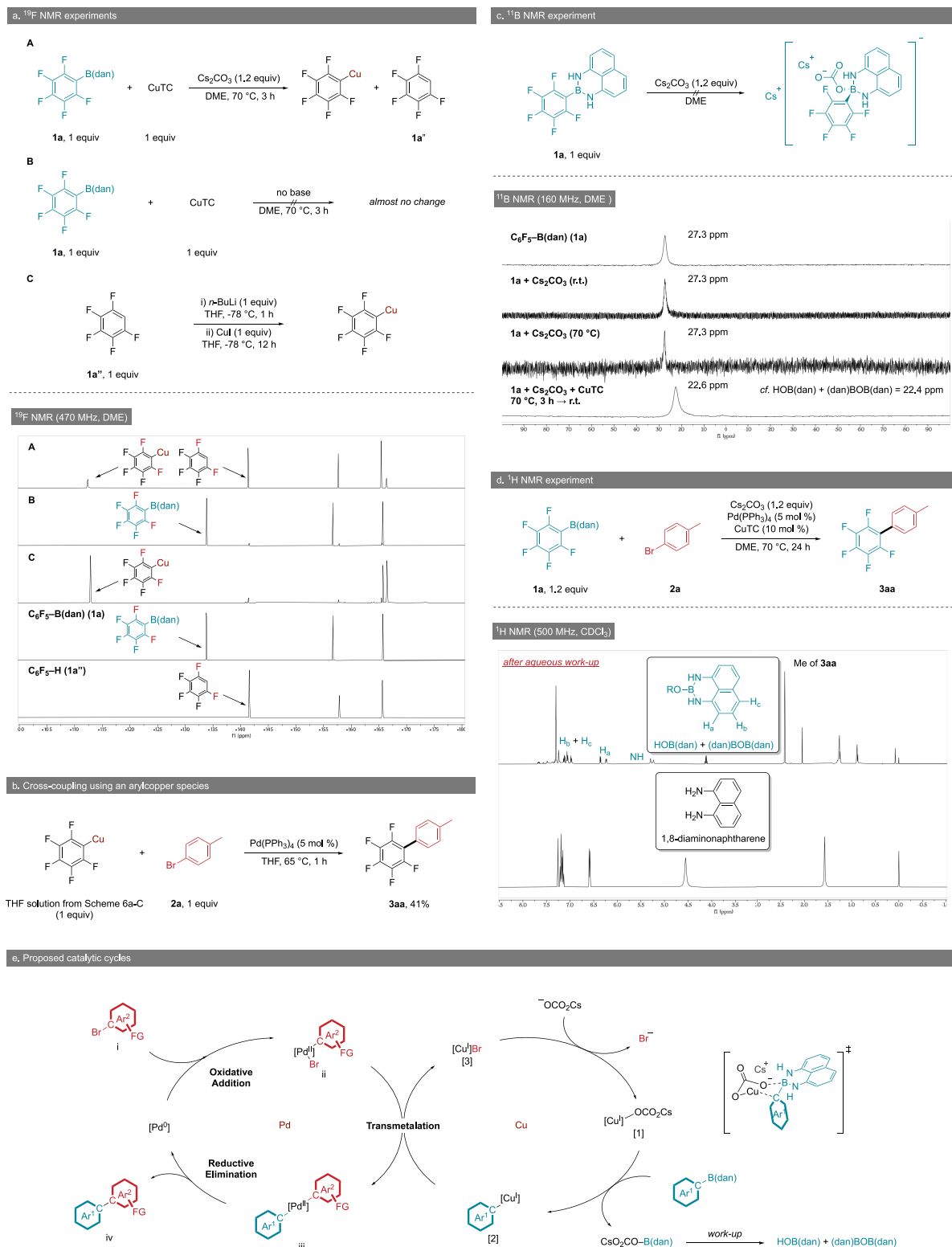
Scheme 5. Applications



(2a) under palladium catalysis to yield 3aa, providing further evidence to suggest that transmetalation from Ar–B(dan) to copper is required for this coupling to occur. To investigate the role of cesium carbonate in enhancing transmetalation, we performed an ^{11}B NMR experiment using 1a. Contrary to expectations, an up-field shifted signal indicative of a tetracoordinate borate species⁷² was not observed when 1a was treated with cesium carbonate, even at a temperature of 70 °C. Instead, the original signal for 1a remained stable at 27.3 ppm (Scheme 6c). These findings suggest that the active species in this transmetalation process is copper carbonate, formed from

CuX (X = Br, TC) and cesium carbonate, which undergoes the transmetalation not with a tetracoordinate borate but rather with a neutral Ar–B(dan), resulting in the formation of an arylcopper species. Moreover, a B(dan)-derived by-product generated in the boron-to-copper transmetalation (Scheme 6a-A) was determined by an ^{11}B NMR experiment: an up-field shifted (4.7 ppm) signal at 22.6 ppm, being in a typical range of O–B(dan) species (cf. 22.4 ppm: HOB(dan) and (dan)BOB(dan), Scheme 6d), was observed. This could be assigned as a B(dan)–carbonate species, which further supports that the

Scheme 6. Mechanistic Studies and Proposed Catalytic Cycles



transmetalation occurs between copper carbonate and $\text{Ar}-\text{B}(\text{dan})$.

Moreover, we confirmed that the SMC directly proceeds without any deprotection of the $\text{B}(\text{dan})$ moieties: ^1H NMR analysis of the crude reaction mixture ($1\text{a} + 2\text{a}$) after aqueous workup showed the presence of $\text{B}(\text{dan})$ -derived byproducts $\text{HOB}(\text{dan})$ and $(\text{dan})\text{BOB}(\text{dan})$ (Scheme 6d),⁷² while 1,8-

diaminonaphthalene, a potential deprotection product, was undetectable via GC, further supporting the direct activation pathway in SMC.

Based on these findings, we propose dual Pd/Cu catalytic cycles for the process (Scheme 6e). Initially, transmetalation-active copper carbonate [1] forms via counteranion exchange between CuX ($X = \text{Br}, \text{TC}$) and cesium carbonate. This is

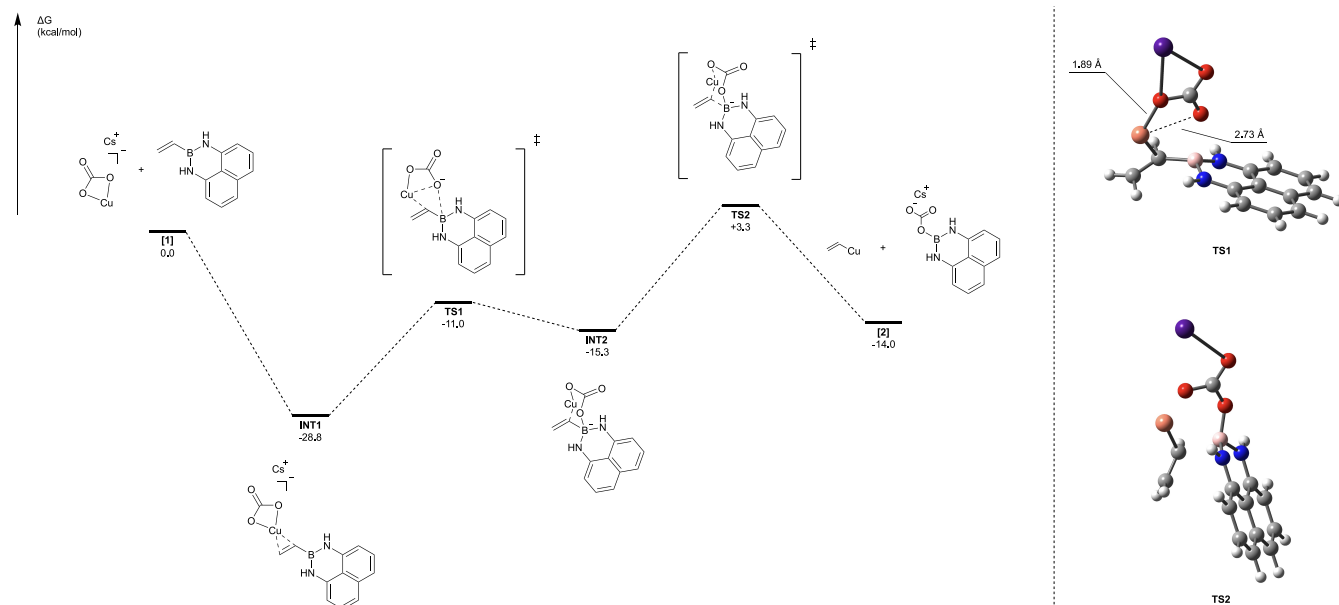


Figure 3. DFT calculation on transmetalation. DFT calculations were performed at the B3LYP/6-311+G(d,p)-SDD(Cu, Cs)/SMD(THF)//B3LYP/6-31+G(d,p)-SDD(Cu, Cs)/SMD(THF) level of theory.

followed by transmetalation from an aryl-B(dan) to copper carbonate [1], yielding an arylcopper species [2] through a six-membered transition state. The enhanced Lewis acidity of B(dan), attributable to electron-deficient aryl groups, and directing heteroatoms aid in the approach of copper carbonate [1] toward aryl-B(dan),^{79,80} thereby facilitating smooth transmetalation. The highly active arylcopper species [2] then undergoes transmetalation with an oxidative adduct (ii), derived from an aryl bromide (i) and a palladium(0) complex. This leads to the formation of iii, culminating in the production of a cross-coupling product (iv) via reductive elimination.

The validity of the key elementary step, transmetalation between an aryl-B(dan) and copper carbonate [1], was evaluated by DFT calculations at the B3LYP/6-311+G(d,p)-SDD(Cu, Cs)/SMD(THF)//B3LYP/6-31+G(d,p)-SDD(Cu, Cs)/SMD(THF) level of theory on Gaussian 16 Rev. A.03 program (Figure 3).⁹³ First, copper carbonate approaches a C–C double bond of a model compound, vinyl-B(dan), to give a π -coordinated vinyl-B(dan)–Cu complex (INT1). One of the carbonate anions then starts to interact with the boron center and the other is connected to the copper (the O–Cu bond length = 1.89 Å) to form TS1, which is converted into a six-membered borate (INT2). Finally, the vinyl group in INT2 transmetalates from B(dan) to Cu through a six-membered transition state (TS2), providing a vinylcopper species; the overall transmetalation process (from copper carbonate to vinylcopper) was calculated to be 14.0 kcal/mol exergonic.

CONCLUSIONS

In summary, we have effectively resolved a challenging balance between protodeborylation resistance and transmetalation activity, both of which are closely related to boron-Lewis acidity. We demonstrated that various protodeborylation-resistant Ar–B(dan) compounds efficiently undergo direct SMC with a weak base under Pd/Cu cocatalysis, despite their significantly diminished Lewis acidity. Notably, this method is particularly effective for perfluoroaryl- and heteroaryl-B(dan), offering a promising solution to the protodeborylation problem

in SMC; their Lewis acidic counterparts, –B(OH)₂ and –B(pin), are typically prone to protodeborylation under conventional SMC conditions. Furthermore, the inherent inertness of the B(dan) moiety, except under the present conditions, can be harnessed for chemoselective cross-coupling sequences, distinguishing between different metal functionalities and yielding heteroaryl-containing π -extended compounds. The success of this SMC approach is largely due to the efficient formation of highly active arylcopper species via transmetalation between neutral Ar–B(dan) and in situ-generated copper carbonate. This process is particularly enhanced by the increased Lewis acidity of B(dan) induced by electron-deficient aryl groups and the presence of directing heteroaryl groups on the B(dan) center.

METHODS

General Procedure for Direct SMC of Ar–B(dan)

A Schlenk tube charged with a magnetic stirring bar and Cs₂CO₃ (1.2 equiv) was heated under vacuum for 5 min using a heating gun, cooled to room temperature, and backfilled with argon. Pd(PPh₃)₄ (5 mol %), CuTC (10 mol %), an aryl-B(dan) (1.2 equiv), an aryl-Br (1.0 equiv), and DME (0.15 M) were then added. After stirring at 70 °C for 24 h, the reaction mixture was quenched with brine, allowing the organic layer to separate. The aqueous layer was extracted with ethyl acetate. The combined organic solution was washed with brine, dried over Na₂SO₄, filtered, and concentrated by rotary evaporation. The crude material was purified by column chromatography on silica gel (hexane/EtOAc as an eluent) to give a cross-coupling product.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacsau.4c00665>.

Experimental procedures, compound characterization data, DFT calculation data for AA and transition state, and copies of NMR spectra (PDF)

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Author Contributions

K.T. and H.Y. conceived the concept and wrote the manuscript. K.T. conducted most of the experiments and data collection. J.L. carried out the cross-coupling using **1n** and **1o**. K.T. performed the theoretical calculations. H.T., M.N., and T.T. gave technical support and conceptual advice. H.Y. directed the project.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

CuTC copper(I) thiophene-2-carboxylate.

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(64) Those with O–B–O angle close to 120° exhibit reduced Lewis acidity due to the energetically unfavorable planar (sp^2)-to-tetrahedral (sp^3) interconversion when forming adducts with Lewis bases. Since the O–B–O angles of Ar–B(OH)₂ are closer to 120° as compared with Ar–B(pin), their AA values would generally become lower than those of Ar–B(pin). For the relationship between the O–B–O angles and the Lewis acidity see: Adamczyk-Wóznia, A.; Jakubczyk, M.; Jankowski, P.; Sporzyński, A.; Urbanski, P. M. *J. Phys. Org. Chem.* **2013**, *26*, 415–419.

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