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Donghuang Chen, Clément Lepori, Régis Guillot, Richard Gil, Sophie Bezzenine, et al.. A Rationally Designed Iron(II) Catalyst for C(sp³)–C(sp²) and C(sp³)–C(sp³) Suzuki–Miyaura Cross-Coupling. *Angewandte Chemie International Edition*, 2024, 63 (32), 10.1002/anie.202408419 . hal-04772950

HAL Id: hal-04772950

<https://hal.science/hal-04772950v1>

Submitted on 8 Nov 2024

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Cross-Coupling

A Rationally Designed Iron(II) Catalyst for C(sp³)–C(sp²) and C(sp³)–C(sp³) Suzuki–Miyaura Cross-Coupling

Donghuang Chen, Clément Lepori, Régis Guillot, Richard Gil, Sophie Bezzenine, and Jérôme Hannedouche*

Abstract: Despite the paramount importance of the Suzuki–Miyaura coupling (SMC) in academia and industry, and the great promise of iron to offer sustainable catalysis, iron-catalyzed SMC involving sp³-hybridized partners is still in its infancy. We herein report the development of a versatile, well-defined electron-deficient anilido-alimine iron(II) catalyst. This catalyst effectively performed C(sp³)–C(sp²) and C(sp³)–C(sp³) SMC of alkyl halide electrophiles and (hetero)aryl boronic ester and alkyl borane nucleophiles respectively, in the presence of a lithium amide base. These couplings operated under mild reaction conditions and displayed wide functional group compatibility including various medicinally relevant *N*-, *O*- and *S*-based heterocycles. They also tolerated primary, secondary and tertiary alkyl halides (Br, Cl, I), electron-neutral, -rich and -poor boronic esters and primary and secondary alkyl boranes. Our methodology could be directly and efficiently applied to synthesize key intermediates relevant to pharmaceuticals and a potential drug candidate. For C(sp³)–C(sp²) couplings, radical probe experiments militated in favor of a carbon-centered radical derived from the electrophile. At the same time, reactions run with a pre-formed activated boron nucleophile coupled to competition experiments supported the involvement of neutral, rather than an anionic, (hetero)aryl boronic ester in the key transmetalation step.

(SMC),^[1] is one of the most commonly applied technology for C–C bond formation in the pharmaceutical, agricultural and fine chemical industries.^[2–4] Notably, around 40 % of C–C bond-forming reactions in small-scale syntheses of drug candidates arose from this coupling, far ahead of couplings with other nucleophiles (<5 %).^[4] The predominance of this coupling stems not only from the mild and broad functional group tolerant reaction conditions but also from the bench stability, easy-to-handle and wide availability of eco-friendly organoboron compounds. These features are not found with other cross-coupling nucleophiles.^[5] Historically, the academic and industrial landscape was dominated by palladium catalysis thanks to the design of efficient bespoke ligands.^[6,7] Nevertheless, although highly efficient, cutting-edge palladium catalysts are mainly restricted to C(sp²)–C(sp²) couplings. This is due to the sluggish oxidative addition of secondary (2°) and tertiary (3°) alkyl halides and the competitive β-H elimination of palladium-alkyl intermediates impeding their widespread applicability to sp³-hybridized coupling partners. This shortfall in palladium catalysis coupled to environmental and economic concerns about this metal have spurred chemists to explore earth-abundant 3d transition metal as potential alternative catalysts for SMC at C(sp³)-centers. Given the current trend in modern medicinal chemistry to enhance sp³ character of drug candidates^[8–10] and the preponderance of sp³-carbons in natural products and related molecules,^[11] the development of efficient C(sp³)–C(sp²) and C(sp³)–C(sp³) SMC methodologies would be highly desirable.

In this vein, cobalt,^[12–15] copper^[16–20] and nickel^[6,21] catalysts have been explored successfully for C(sp³)–C(sp²) couplings. Notable breakthroughs were achieved with nickel for the more challenging alkyl-alkyl coupling of primary (1°) and 2° alkyl halides and 1° alkyl boranes.^[22–26] In contrast, iron catalysts are still in their infancy for sp³-hybridized partners and thus many challenges remain.^[27–40] Iron is a more terrestrial abundant, less toxic and cheaper metal which would hold great promise for greener and more sustainable SMC methods amenable to industrial-scale applications. Initial works on iron-catalyzed SMC with C(sp³)-derived partners required the use of lithium or magnesium-activated boron nucleophiles (in conjunction with MgBr₂ co-catalyst) to promote the key transmetalation step as neutral boron nucleophiles were not effective (Scheme 1, A.1).^[27–33,39] Thus, these couplings are more akin to Kumada-type coupling, lacking the functional group compatibility and ease of handling of neutral boron nucleophiles. They also suffer from limitations in terms of

Introduction

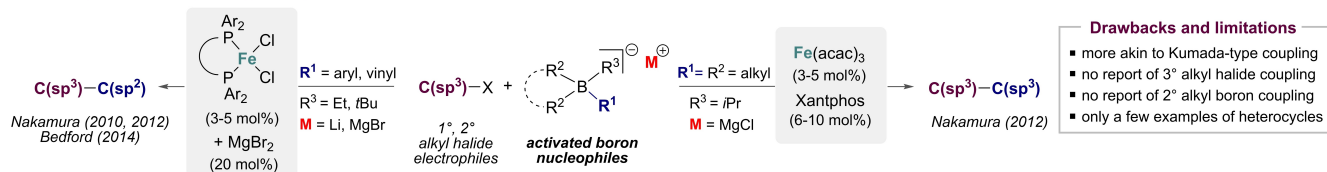
The transition metal-catalyzed cross-coupling of an organohalide (or pseudo-halide) electrophile and an organoboron nucleophile, known as the Suzuki–Miyaura coupling

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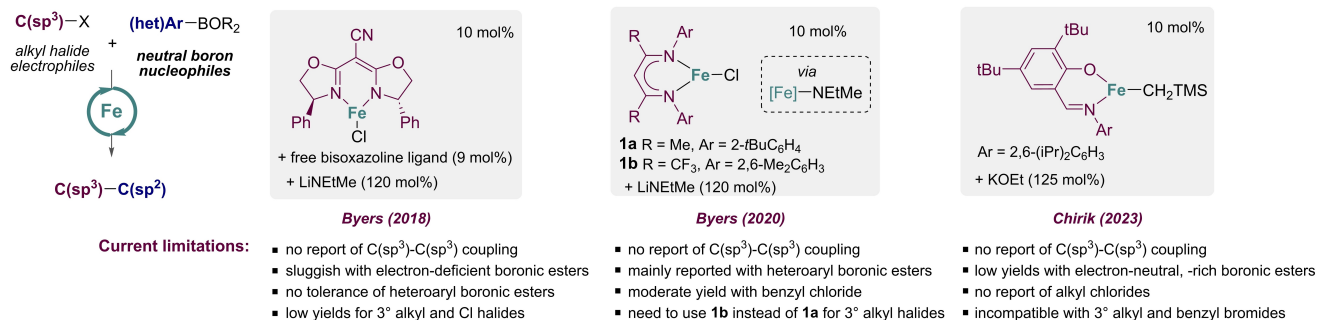
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A. Prior art in Fe-catalyzed C(sp³)-C(sp²/sp³) Suzuki-Miyaura Cross-coupling (SMC)

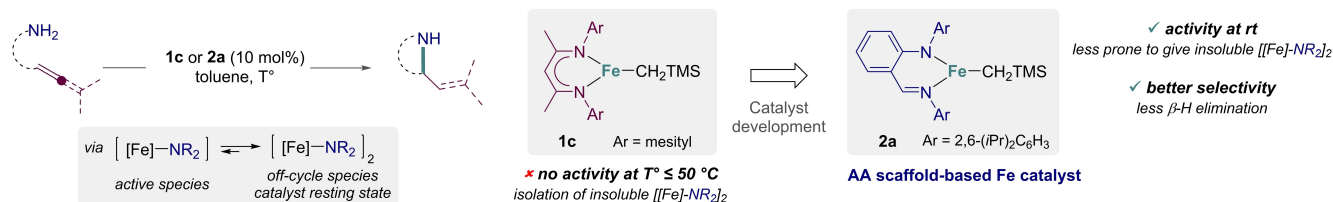
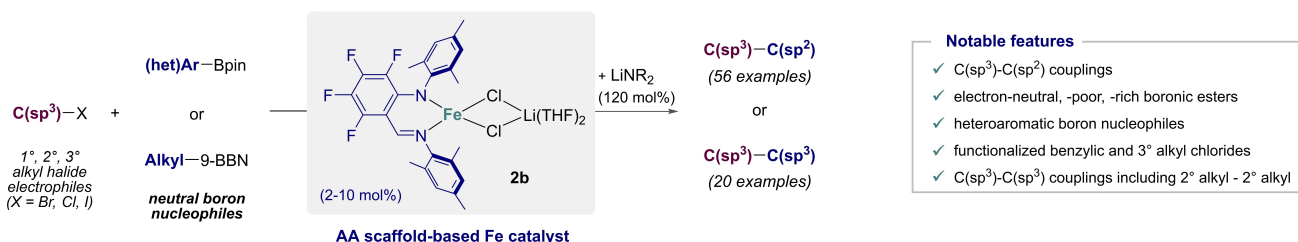
A.1 with activated boron nucleophiles:



A.2 with neutral boron nucleophiles:



B. Our previous works on well-defined β-diketiminato and anilido-aldimine (AA) scaffold-based Fe(II) complexes for catalytic alkene hydroamination

C. C(sp³)-C(sp²) and C(sp³)-C(sp³) Suzuki-Miyaura Cross-coupling catalyzed by a well-defined anilido-aldimine (AA) Fe(II) complex (this work)

Scheme 1. Prior art in iron-catalyzed C(sp³)-C(sp²/sp³) Suzuki-Miyaura cross-coupling (A), our previous works on iron-catalyzed alkene hydroamination (B) and this work (C). pin = pinacolato, 9-BBN = 9-borabicyclo[3.3.1]nonane.

subsets of the possible electrophiles and nucleophiles (Scheme 1, A.1 for details). More recently, a few sporadic reports have emerged for the C(sp³)-C(sp²) SMC of neutral boron nucleophiles with 1° and 2° alkyl bromides using well-defined Fe(II) chloride or alkyl (pre)catalysts under a substoichiometric addition of lithium amide or potassium alkoxide base. All of these bear their own limitations for a broad synthetic utility (Scheme A.2).^[34-36,38] For example, the cyanobis(oxazoline) Fe(II)-based system afforded sluggish coupling reactions with electron-deficient boronic esters, low yields for 3° alkyl halides and did not tolerate heteroaryl boronic esters.^[34] Meanwhile, the phenoxy(imine) Fe(II)-based system provided low yields for the coupling of electron-neutral and -rich boronic esters and was incompatible with 3° and benzylic halide electrophiles.^[38] In terms of reactivity, a major advance was made by superseding the

cyanobis(oxazoline) ligand by the more electron-donating C₂-symmetric β-diketiminato (BDI) ligand such as in **1a**. This affords productive C(sp³)-C(sp²) couplings for mainly heteroaromatic pinacol boronic esters (Scheme 1, A.2).^[36] Tailoring the electronic and steric properties of the catalyst from **1a** to **1b** was however needed to produce a few examples of 3° alkyl couplings. Key to the success of the BDI-based systems was the formation of a low-coordinate mononuclear iron amido species, likely in equilibrium with its dimer, that facilitates transmetalation from a neutral, rather than an anionic, boron nucleophile.^[41-45] Additionally, none of these three catalytic systems was reported to unveil reactivity for C(sp³)-C(sp³) couplings.^[46] These seminal contributions highlight the impediments that still need to be overcome to offer a general Fe-based SMC methodology, and the challenge associated with the development of a

versatile catalyst efficient to forge both C(sp³)-C(sp²) and C(sp³)-C(sp³) bonds.

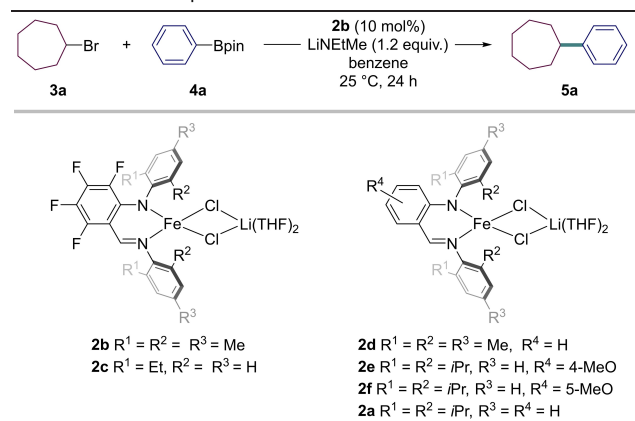
A few years ago, our group reported the first iron-catalyzed hydroamination of unprotected primary amines tethered to unactivated alkenes using well-defined low-coordinate BDI Fe(II) complex **1c** as catalyst (Scheme 1, B.).^[47,48] In-depth mechanistic studies unveiled the active species was a monomeric iron amido species, in equilibrium with its stable, and isolable, dimer that acted as catalyst resting state.^[48] Our further investigations into catalyst development stressed that anilido-aldimine (AA) ligand,^[49] was an attractive platform to build more efficient iron catalysts for hydroamination. Indeed, unlike **1c**, AA-based catalyst **2a** was active at room temperature with improved selectivity, likely due to a slower β-H elimination.^[50,51] We hypothesize that this peculiar behavior of AA-derived metal complexes that we observed, coupled to further attractive features of the AA scaffold moiety^[52-60] should be a strong asset to design innovative iron SMC catalysts for sp³-hybridized partners with wide applications.

In this work, we report the development of a versatile, well-defined and electronically-tuned, anilido-aldimine iron(II) catalyst. This catalyst successfully performed, for the first time, both C(sp³)-C(sp²) and C(sp³)-C(sp³) SMC of alkyl halide electrophiles and (hetero)aryl boronic ester and alkyl borane nucleophiles respectively, in the presence of a lithium amide base (Scheme 1, C.). These couplings operated under mild reaction conditions, were effective for a broad range of 1°, 2° and 3° alkyl halides, electron-neutral, -rich and -poor aryl and heteroaryl boronic esters and 1° and 2° alkyl boranes. They also accommodated a wide diversity of functional groups and *N*-, *O*-, *S*-heterocycles, that can potentially inhibit catalysis. The efficiency of our methodology was illustrated in the high-yield synthesis of key intermediates relevant to pharmaceutically active molecules and a potential drug compound. Preliminary mechanistic investigations were also disclosed for C(sp³)-C(sp²) couplings.

Results and Discussion

Initially, we synthesized a series of well-defined AA iron(II) chloride-ate complexes (**2a-f**) (Scheme S1) with distinctive electronic and steric properties. We next evaluated their performance as catalyst in the prototypical cross-coupling of bromocycloheptane **3a** and phenylboronic acid pinacol ester **4a** under initial reaction conditions inspired by previous works.^[34,36] The “ate” character of these complexes was confirmed by single-crystal X-ray diffraction and ⁷Li NMR analyses.^[61,62] Representative results of our primary investigations disclosed in Table 1 (entries 1–6), showcased not only that both tetrafluorine-substituted AA Fe(II) catalysts **2b** and **2c** (10 mol %) performed highly efficiently, affording the cross-coupled product **5a** in 99 % yield at 25 °C after 24 h (entries 1–2), but also that fluorine substitution on the backbone coupled to adequate steric bulk of the *N*-aryl groups were crucial for productive and selective coupling. For instance, fluorine-free catalyst **2d** bearing similar *N*-aryl

Table 1: Reaction Optimization.



Entry	Variations from optimized conditions ^[a]	Conv. [%] ^[b]	Yield [%] ^[b]
1	none	99	99
2	2c instead of 2b	99	99
3	2d instead of 2b	71	65
4	2e instead of 2b	46	15
5	2f instead of 2b	56	33
6	2a instead of 2b	42	10
7	MTBE, anisole or TAME instead of benzene ^[d]	99 ^[c]	99 ^[c]
8	LiNMe ₂ instead of LiNMeEt	94 ^[c]	94 ^[c]
9	LiNEt ₂ instead of LiNMeEt	99 ^[c]	90 ^[c]
10	LiN <i>i</i> Pr ₂ instead of LiNMeEt	97 ^[c]	18 ^[c]
11	4 h instead of 24 h	99 ^[c]	99 ^[c]
12	1a , 4 h instead of 2b , 24 h	–	64 ^[e]
13	2 mol % instead of 10 mol % ^[f]	99	79
14	In situ generated 2b instead of isolated 2b ^[g]	99 ^[c]	78 ^[c]

[a] Reactions run on a 0.25 mmol scale at 25 °C for 24 h with **3a** (1.0 equiv.), **4a** (2.0 equiv.), LiNMeEt (1.2 equiv.), **2b** (10 mol %) in benzene (0.08 M) unless otherwise stated. [b] Determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard unless otherwise stated. [c] Determined by GC using dodecane as internal standard. [d] Methyl *tert*-butyl ether (MTBE), *tert*-amyl methyl ether (TAME). [e] Value from Ref. [36]. [f] Run on a 2.5 mmol scale for 72 h. [g] **2b** generated in situ from reaction of FeCl₂ and the lithium salt of the tetrafluorine-substituted AA ligand of **2b** and reaction run on a 0.5 mmol scale. pin = pinacolato.

substituents to **2b** showed substantially lower yield of coupling product (entry 3). Furthermore, MeO-substituted **2e-2f** or **2a** catalysts bearing bulkier 2,5-diisopropylphenyl substituents on *N*-atoms than **2b** and **2d** were poorly active and selective for this transformation (entries 4–6). Variation of several reaction parameters was next examined with optimal catalyst **2b** (entries 7–11, 13–14 and Table S1). To our delight, the reaction performed equally well in methyl *tert*-butyl ether (MTBE), anisole or *tert*-amyl methyl ether (TAME) as solvent, providing **5a** in >99 % yield after a 24 h-reaction time (entry 7). These results are in sharp contrast with what was observed with BDI iron catalysts for which low yields were attained in MTBE and anisole.^[36] MTBE and anisole are classified as ICH Q3C class 3 solvents while TAME and anisole are recommended solvents by the CHEM21 solvent guide.^[63,64] These solvents could be valuable and sustainable substitutes to the highly hazardous and toxic benzene for applications in pharma-

ceutical industry. Although benzene was primarily used as solvent for practical reasons, some beneficial effects were noticed with MTBE or TAME as illustrating for some coupling reactions (see below). Unlike a previous study,^[34] the lithium amide base LiNMeEt could be replaced by commercially available bases LiNMe₂ and LiNEt₂ with substantial effect on the reaction outcome, thereby sustaining the practicability and synthetic utility of our methodology (entries 8–9). Nevertheless, LiNiPr₂ (entry 10) and other amide or alkoxide bases (Table S1) were less or not effective for this coupling. Gratifyingly, the kinetic profile of the coupling reaction of **3a** and **4a** at 25 °C catalyzed by **2b** (10 mol %) in the presence of LiNMeEt underlined that only 4 h was needed to reach >99 % yield of **5a** (entry 11). This highlights **2b** was significantly more active than previously reported iron SMC catalysts using neutral boron nucleophiles including **1a** (entry 11 vs 12).^[34,36,38]

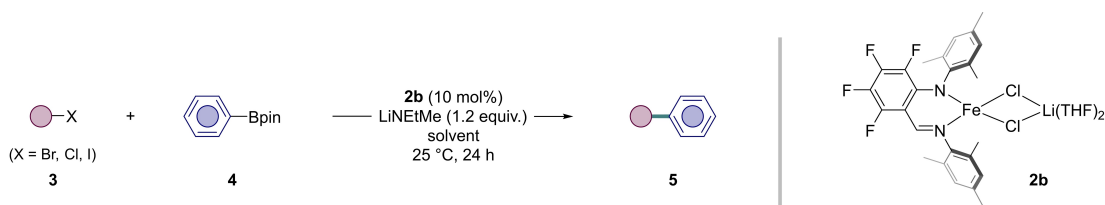
To our delight, the coupling could also be conducted at lower nucleophile **4a** loading (1.5 equiv. relative to **3a**) without any detrimental effect on the reaction efficiency (Table S1). Reducing the catalyst loading to 2 mol % of **2b** on a 2.5 mmol scale reaction still afforded excellent conversion (>99 %) but only 79 % yield in **5a** (Table 1, entry 13). Of note, albeit slightly less selective, catalyst **2b** did not need to be synthesized prior to coupling as in situ combination of FeCl₂ and the lithium salt of the corresponding tetrafluorine-substituted AA ligand provided >99 % conversion and a synthetically useful yield of **5a** of 78 % (Table 1, entry 14). Finally, control experiments demonstrated that all components were crucial for optimal cross-coupling (Table S1).

With the competency of catalyst **2b** for SMC established and the optimized conditions in hand, we next sought to assess the generality and limitations of our coupling methodology (Scheme 2). Regarding the coupling of electrophilic partners with **4a**, various secondary cyclic and acyclic alkyl bromides containing hydrocarbons (**3a**, **3b**, **3c**, **3d**, **3i**, **3ah**), carbamates (**3e**, **3f**), an ether (**3g**) or *N,N*-diphenylamide (**3h**) were tolerated, affording the coupling products in excellent yields (>99 %) for most of the cases (**5a**, **5b**, **5c**, **5e**, **5f**, **5h**, **5i**, **5ah**) at 25 °C. Only moderate yields were obtained for **5d** (45 %) and 3-phenyloxetane **5g** (69 %). *N,N*-diphenylamides are valuable synthetic handles for downstream functionalization,^[23] while aliphatic six-, four- and three-membered rings such as piperidine (**5e**) azetidine (**5f**), oxetane (**5g**) or cyclopropane (**5d**) are highly relevant scaffolds in medicinal chemistry.^[65,66] To our knowledge, our catalytic system leads to the highest reported yield for **5e** and the first syntheses of **5f** and **5g** by a Fe-catalyzed SMC. In contrast to previous reports,^[27,34,38,39] the methodology was not limited to alkyl bromides as chlorocyclopentane and iodocyclopentane were also efficient partners albeit a slight diminished yield in **5b** was noticed with the latter. Similarly, high-yielding couplings (>99 %) were achieved with 1° alkyl bromides containing linear hydrocarbons (**5j**, **5k**) or a TBS-protected alcohol (**5l**) at 25 °C. The reaction of benzyl halide derivatives and **4a** gave significant higher yields with chloride than bromide and when catalyst **2c** was used instead of **2b**. Indeed, cross-coupling of benzyl chloride, *p*-F

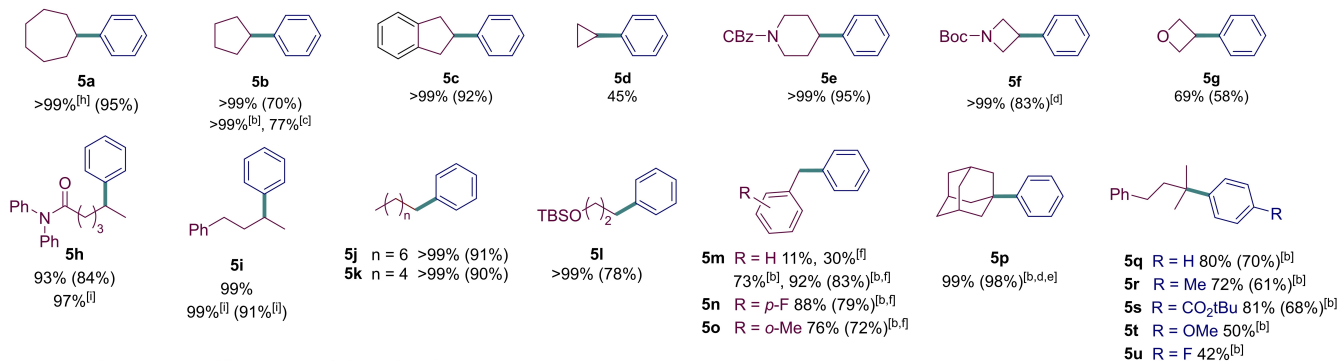
benzyl chloride, *o*-Me benzyl chloride and **4a** catalyzed by **2c** afforded **5m**, **5n** and **5o** in 92 %, 88 %, 76 % yield respectively. These coupling values are the highest values described by a Fe-catalyzed SMC using neutral boron nucleophiles.^[34,36] Finally, the SMC catalyzed by **2b** was also effective for the rarely reported coupling of adamantylchloride and challenging 3° alkyl chlorides (which could potentially undergo β-hydride elimination) as adamantylbenzene (**5p**) and **5q** were synthesized in 99 % and 80 % yield respectively. Such tertiary alkylative SMC could also be conducted to access electron-neutral (**5r**), electron-withdrawing (**5s**, **5u**) or electron-donating (**5t**) products in good-to-moderate yields.

With respect to the aryl boronic pinacol esters, various phenyl boronic esters (**4**) with either electron-neutral (**4aa**, **4ab**, **4ac**, **4ai**), electron-donating (**4ad**, **4ae**, **4af**, **4ag**, **4aj**) or electron-withdrawing (**4ak**, **4al**, **4am**, **4an**) substituents at the *ortho*-, *meta*- or *para*-position of the ring furnished very high yields of coupling products (**5aa**, **5ab**, **5ac**, **5ad**, **5ae**, **5af**, **5ag**, **5ai**, **5aj**, **5ak**, **5al**, **5am**, **5an**) (Scheme 2). This demonstrates the high functional group and substitution pattern tolerance of our protocol. However, *p*-chloro- and *p*-nitro-phenyl substituents resulted in lower product yields (**5ao**, **5ap**) ascribed to catalyst deactivation as confirmed by control experiments.^[62] Optimal reaction also proceeded with 2-naphthyl substituent (**5aq**). We next explored the coupling of heteroaryl boronic pinacol esters featuring heterocyclic skeletons of interest for the pharmaceutical industry.^[65,66] Benzofuran, furan and thiophene were efficiently alkylated at the α- or β-position of the heteroatom producing the desired products (**5ar**, **5as**, **5at**, **5au**, **5av**) in good yields (78–>99 %). *N*-heterocycles such as indoles masked by a Ts- or a BOC- group, quinolines and 2-functionalized pyridine were also competent boronic esters partners, delivering the coupling products **5aw**, **5ax**, **5ay**, **5az** and **5ba** in good-to-excellent yields at 80 °C or 25 °C. *N*-methylpyrrolazole-containing substrate gave low yield of 2-alkylated product **5bb**. The methodology described herein is a prominent step forward in addressing some of the limitations of the previously reported iron catalytic systems for C(sp³)–C(sp²) SMC in terms of reactivity and compatible subsets of electrophiles and nucleophiles. These include 1°, 2°, 3° alkyl and benzylic halides (Br, Cl), electron-neutral, -rich and -poor aryl and heteroaryl boronic esters (Scheme S2 for comparison).^[62]

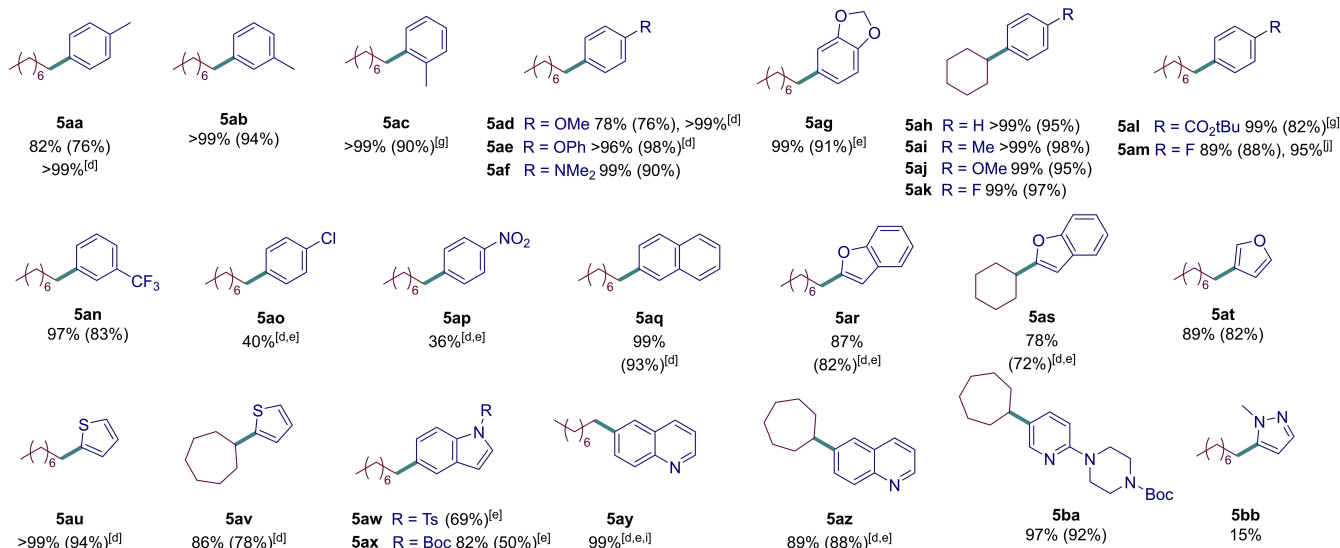
To further exhibit the applicability and underlying potential of our methodology for the synthesis of key intermediates relevant to the pharmaceutical sector, we synthesized **5bc** (98 % yield in TAME) and **5bd** (>99 % yield in TAME), key building blocks in the synthesis of APD334^[67] and an active compound^[68] against CNS-disorders (Scheme 2). Both of them were previously prepared by Fe-catalyzed Kumada coupling in 57 % and 61 % yield respectively. Furthermore, the anticancer and antiviral drug candidate **5be**, industrially prepared by a 100 gram-scale Ni-catalyzed SMC^[69] in 38 % yield, was obtained in 93 % (in TAME) yield by our protocol. It is pertinent to note that the use of TAME as a recommended solvent by the CHEM21 solvent guide for pharmaceutical industry, instead of highly



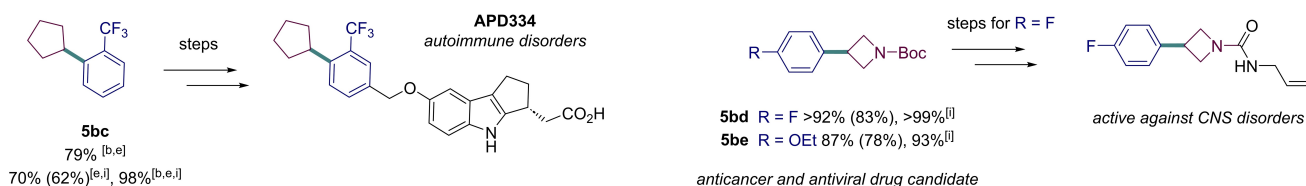
scope in secondary, primary and tertiary alkyl halides



scope in aromatic and heteroaromatic boronic esters



key intermediates to pharmacologically active molecules and a drug candidate

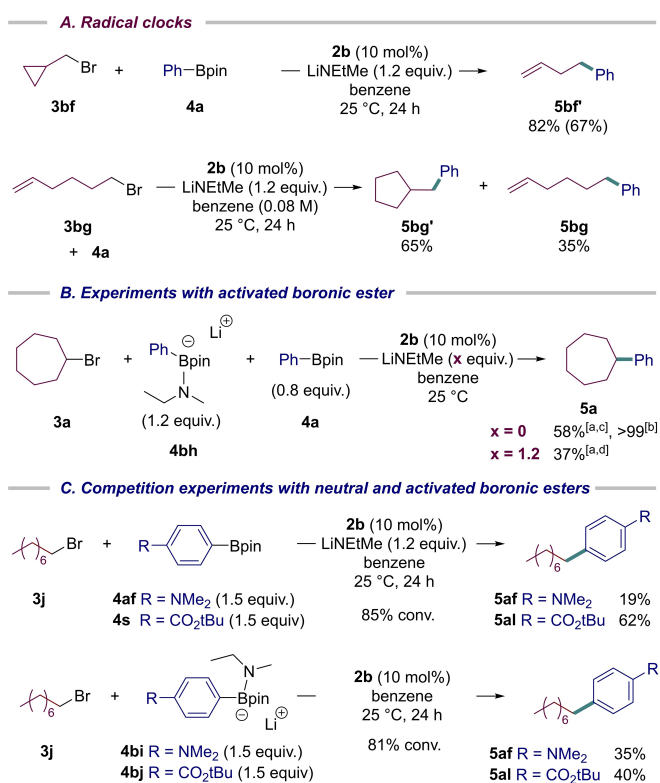


Scheme 2. Scope of the Fe-catalyzed C(sp³)–C(sp²) SMC.^[a] [a] Reactions run on a 0.25 mmol scale at 25 °C for 24 h with alkyl bromide (X = Br) (1.0 equiv.), (hetero)aryl boronic pinacol ester (2.0 equiv.), LiNEtMe (1.2 equiv.), **2b** (10 mol%) in benzene (0.08 M) as solvent unless otherwise stated. Yield determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard and isolated yield in parenthesis. [b] X = Cl. [c] X = I. [d] 48 h. [e] 80 °C. [f] Run with **2c**. [g] 40 °C. [h] 4 h. [i] *tert*-amyl methyl ether (TAME) as solvent. [j] methyl *tert*-butyl ether (MTBE) as solvent. pin = pinacolato.

hazardous benzene, has a beneficial effect on the yields of synthesis of these 3 compounds and also of products **5h** and **5i**.

To get some preliminary insights into the reaction mechanism, a series of control experiments were conducted

(Scheme 3). As Fe-catalyzed cross-coupling reactions were suggested to proceed by carbon-based radical intermediates derived from the electrophile,^[70–73] catalytic experiments were initially performed with (bromomethyl)cyclopropane (**3bf**) and 6-bromohex-1-ene (**3bg**), two well-established

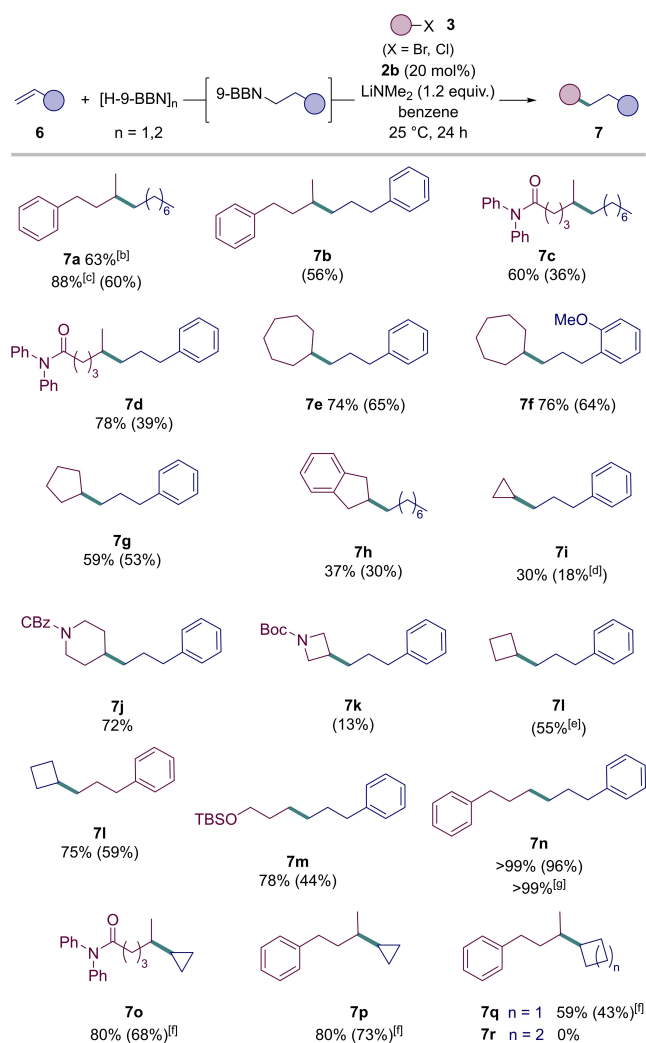


Scheme 3. Mechanistic probe experiments. [a] 4 h. [b] 24 h. [c] 62% conv. [d] 84% conv. pin = pinacolato.

radical clocks,^[74] under the optimized conditions (Scheme 3, A.).^[75] The exclusive formation of the ring-opened product **5bf** (82% yield) was consistent with the intermediacy of carbon-centered radical.^[29,34,38] The observation of a 1.9:1 mixture of ring-closing coupled product **5bg'** (that occurred after 5-*exo-trig* radical cyclization) and direct coupled product **5bg** also supported the involvement of a radical intermediate, with a lifetime of similar order of magnitude as the 5-*exo*-cyclization rate of 5-hexenyl radical ($k \approx 1 \times 10^5 \text{ s}^{-1}$ at 25 °C).^[74] Early works on iron phosphine-catalyzed $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ SMC had shown the use of highly reactive boron nucleophiles was crucial for reactivity, thereby suggesting sluggish transmetalation rates with neutral nucleophiles. Recent studies with iron catalysts stabilized by *N*-containing ligands militated against and in favor of aryl boronates being competent in cross-coupling respectively, suggesting a dissimilar pathway of transmetalation.^[34,36,38] Although the pre-formed activated lithium amide phenyl boronate **4bh** proved competent in this process, it was poorly reactive compared to the combined use of neutral boronic ester and lithium amide base (Scheme 3, B.). Indeed, under the stoichiometry of our catalytic conditions, the coupling of **3a** and **4bh** (1.2 equiv.) and **4a** (0.8 equiv.) afforded **5a** in only 58% yield after 4 h (62% conv.). Even if the reaction went to completion after 24 h, it was significantly slower (but as selective) compared to the one when the lithium amide and the phenyl boronic ester were added to the reaction vessel independently (>99%, 4 h, Table 1, entry 11). Running the same experiment in the

presence of additional LiNEtMe base (1.2 equiv.) led to a substantial drop in coupling product yield and selectivity (84% conv. after 4 h and 37% yield of **5a**). This is likely a result of the extra base driving the putative **4a–4bh** equilibrium towards the less reactive lithium amide phenyl boronate adduct **4bh** and the catalyst undergoing unproductive pathways. Additionally, a competition experiment between the electron-rich boronic ester **4af** (1.5 equiv.) and the electron-deficient boronic ester **4s** (1.5 equiv.), under our optimized catalytic conditions using 1.2 equiv. of LiNEtMe base, led to the preferential formation of **5al** (62% yield) over **5af** (19% yield) thereby suggesting a faster coupling with a more Lewis acidic boronic ester. Notably, if a similar competition reaction was run employing the corresponding pre-formed activated lithium amide aryl boronates **4bi** (1.5 equiv.) and **4bj** (1.5 equiv.) instead of neutral boronic esters **4af** and **4s**, but without additional base, no reversal of the electronic preference was noticed. This is in contrast to what could have been anticipated from the assumption that the activated boronic esters was the more reactive species.^[76] Indeed, only a decrease in yield of the preferred **5al** (40% yield) versus **5af** (35% yield) was witnessed. All these observations advocate in favor of a neutral boron nucleophile being kinetically preferred over an activated boron species in the key transmetalation step, analogously to the oxo-palladium pathway operating in most Pd-catalyzed Suzuki–Miyaura reactions.^[77–80]

Despite prominent advances using nickel catalysis,^[22–25] $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ SMC remains highly challenging and is exceedingly rare in iron catalysis.^[39,40] Seeking to expand the scope of our catalytic SMC method involving $\text{C}(\text{sp}^3)$ -partners, we next examined the challenging coupling of alkyl halide electrophiles and alkyl boron nucleophiles. Although disappointing results were initially obtained for the reaction of (1-octyl)-Bpin and (3-bromobutyl)benzene under the conditions developed for $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ coupling (Table S2), the use of more Lewis-acidic 9-octyl-9-BBN (9-BBN=9-borabicyclo[3.3.1]nonane) and less bulky and commercially available LiNMe₂ base afforded the coupled product **7a** in 63% yield after 24 h at 25 °C (Scheme 4). Gratifyingly, increasing the catalyst loading of **2b** to 20 mol% improved the yield to 88%. Under these conditions (20 mol% **2b**, LiNMe₂ (1.2 equiv.)), secondary acyclic alkyl bromides featuring phenyl groups and synthetic valuable *N,N*-diphenylamides showed good performance in producing the coupled products (**7a**, **7b**, **7c**, **7d**) with either in situ generated 9-octyl-9-BBN or 9-phenylpropyl-9-BBN. In addition, when a series of functionalized secondary cyclic alkyl bromides was coupled with similar alkylborane partners or 9-(2-methoxyphenyl)propyl-9-BBN, products containing cycloheptane (**7e**, **7f**), cyclopentane (**7g**), *N*-CBz-piperidine (**7j**) and cyclobutane (**7l**) rings were successfully obtained in good yields while those including dihydroindenyl (**7h**), cyclopropyl (**7i**) and *N*-Boc-azetidyl (**7k**) groups were isolated in serviceable yields. Worth noting is that the electrophile and nucleophile coupling partners could also be switched with similar efficiency as illustrated by the good-yield synthesis of **7l** from the reaction of B-cyclopropyl-9-BBN and (3-bromopropyl)benzene. Effective couplings



Scheme 4. Scope of the Fe-catalyzed C(sp³)-C(sp³) SMC.^[a] [a] Reactions run on a 0.25 mmol scale at 25 °C for 24 h with alkene **6** (2.1 equiv.), [H-9-BBN]_n (n = 1, 2.0 equiv.; n = 0, 1 equiv.), alkyl bromide (X = Br) (1.0 equiv.), LiNMe₂ (1.2 equiv.), **2b** (20 mol%) in benzene (0.08 M) unless otherwise stated. Yield determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard and isolated yield in parenthesis. [b] 10 mol% **2b**. [c] Determined by GC using dodecane as internal standard. [d] Isolated yield from a 5 mmol scale reaction. [e] Reaction run on a 1 mmol scale. [f] *B*-cyclopropyl-9-BBN and *B*-cyclobutyl-9-BBN were generated ex situ. [g] X = Cl. 9-BBN = 9-borabicyclo[3.3.1]nonane.

were also achieved with a primary alkyl bromide bearing a TBS-protected alcohol functionality (**7m**) or a phenyl ring (**7n**). Alkyl chlorides were also as efficient as bromides as electrophiles for alkyl-alkyl coupling reactions as **7n** was also obtained in >99% yield from (3-chloropropyl)benzene.

Next, we tackled the challenging and poorly reported coupling of 2° alkyl halides and 2° alkyl boranes. To our delight, productive 2° alkyl-2° alkyl couplings were performed between functionalized secondary alkyl bromides (**3h**, **3i**) and either *B*-cyclopropyl-9-BBN or *B*-cyclobutyl-9-BBN affording *N,N*-diphenyl-containing product **7o** and phenyl-containing products **7p** and **7q** in 80%, 80% and 59% yields respectively. However, no coupling was noticed

for **3i** and cyclopentene. It is worth noting that, in contrast to the scarce contributions on C(sp³)-C(sp³) SMC using iron catalysis,^[39,40] the wide scope of our Fe-catalyzed alkyl-alkyl SMC methodology was reached without any electronic or steric alteration of the structure of catalyst **2b**, efficiently applied to alkyl-aryl couplings. This features the high versatility of this AA-based iron catalyst in SMC involving sp³-hybridized partners and represents a step forward to a universal iron catalyst for C(sp³)-C(sp²) and C(sp³)-C(sp³) SMC.

Conclusion

In summary, we disclose herein a versatile, well-defined electron-deficient anilido-alimine iron(II) catalyst with, for the first time, excellent efficiency for both C(sp³)-C(sp²) and C(sp³)-C(sp³) SMC of alkyl halides and unactivated boron nucleophiles, in the presence of a lithium amide base. These couplings performed under mild reaction conditions, were compatible with sustainable solvents, exhibited broad functional group tolerance covering an array of pharmaceutically relevant *N*-, *O*- and *S*-based heterocycles, and tolerated 1°, 2° and 3° alkyl halides (Br, Cl, I), electron-neutral, -rich and -poor boronic esters and 1° and 2° alkyl boranes. Our methodology was productively applied to prepare key intermediates for the construction of pharmaceuticals and a potential drug candidate, in significant higher yields than previously reported, emphasizing its great potential of applicability. This study affords a highly efficient and general route for the SMC at C(sp³)-centers, paving the way for more extensive access to relevant C(sp³)-C(sp²) and C(sp³)-C(sp³) coupling products from underexplored classes of electrophiles and nucleophiles such as 3° alkyl and benzylic chlorides, heterocyclic boronic esters and 2° alkyl boranes. Although deeper investigations are needed, key to the success might likely arise from the propensity of anilido-alimine Fe(II) complex **2b** to favor monomeric over off-cycle dimeric amido species, coupled to unique features specific to the ligand framework, thereby enhancing catalyst reactivity. Initial mechanistic studies conducted on sp³-sp² coupling advocated the intermediacy of a carbon-centered radical emanating from the electrophile, and the preferential involvement of neutral, rather than an anionic, (hetero)aryl boronic ester nucleophile in the key transmetalation step. Future studies will be to gain a deeper understanding of the mechanism of this Fe-catalyzed C(sp³)-C(sp²) and C(sp³)-C(sp³) SMC methodology and underlying the singular role of the anilido-alimine skeleton.

Acknowledgements

The China Scholarship Council is gratefully acknowledged for the Ph.D. scholarship of D.C. Financial support for this work was provided by the MENSUR (Ph.D. grant to C.L.), ANR ("LowFeCoCat" project, ANR-22-CE07-0003-01), the CNRS and Université Paris-Saclay.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: cross-coupling · Suzuki–Miyaura · iron · heteroaromatic boronic esters · alkyl boranes

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Manuscript received: May 3, 2024

Accepted manuscript online: May 22, 2024

Version of record online: June 30, 2024