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Rational Design of an Iron-Based Catalyst for Suzuki-Miyaura Cross-Couplings Involving Heteroaromatic Boronic Esters and Tertiary Alkyl Electrophiles

Michael P. Crockett‡, Alexander S. Wong‡, Bo Li, and Jeffery A. Byers*

Abstract: Suzuki-Miyaura cross-coupling reactions between a variety of alkyl halides and unactivated aryl boronic esters are described using a rationally designed iron-based catalyst supported by β-diketiminate ligands. High catalyst activity resulted in a broad substrate scope that included tertiary alkyl halides and heteroaromatic boronic esters. Mechanistic experiments revealed that the iron-based catalyst benefited from the propensity for β-diketiminate ligands to support low-coordinate and highly reducing iron amide intermediates, which are very efficient for effecting the transmetalation step required for the Suzuki-Miyaura cross-coupling reaction.

Due in part to nearly 40 years of elegant ligand design and logical catalyst development,[1] the Suzuki-Miyaura cross-coupling reaction has become one of the most common methods used in the pharmaceutical industry to construct C–C bonds.[2] Despite its remarkable utility and broad generality,[3] there remain underexplored classes of substrates that require further innovations in catalyst design. One way to identify existing limitations is by surveying the published articles describing Suzuki-Miyaura cross-coupling reactions (Figure 1a). As others have noted,[2] the majority of reported Suzuki-Miyaura reactions involve the cross-coupling of two sp^2-hybridized substrates. This fact likely contributes to the exploration of mostly flat molecules as drug candidates. In order to "escape from flatland," constructing saturated molecules with stereogenic centers is desirable.[4] However, the propensity for elimination reactions has resulted in a smaller number of Suzuki-Miyaura reactions that involve at least one sp^3-hybridized substrate. Fewer still are examples involving heteroaromatic coupling partners, which can inhibit catalysis (Figure 1a).[5] The dearth of these substrates is notable considering that nearly 70% of all pharmaceutical molecules contain at least one heterocycle.[6] Analysis of the literature also reveals that most reported alkyl-aryl Suzuki-Miyaura cross-coupling reactions involve primary alkyl fragments (Figure 1b). Successful reactions with secondary and tertiary alkyl coupling partners are rare, particularly when the alkyl fragment is the electrophilic partner:[7] Only four reports describe using tertiary alkyl halide substrates.[8]

To address these limitations, there have been tremendous advances in the development of cross-coupling reactions using

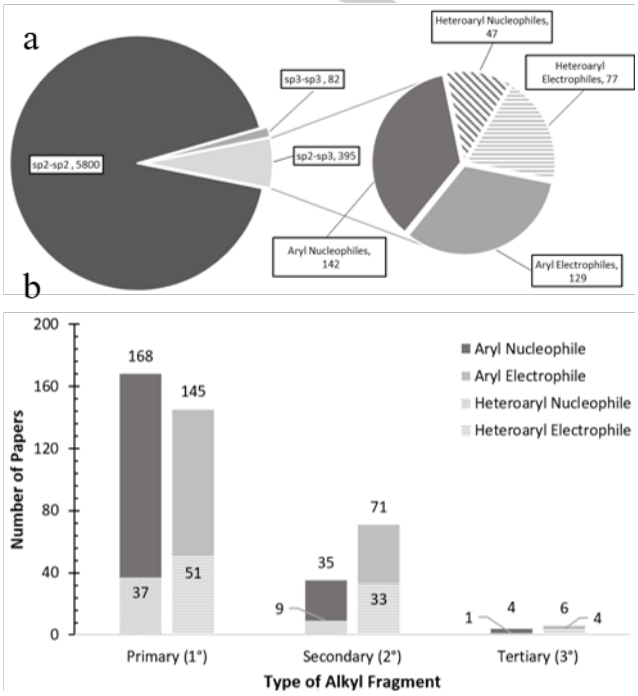

Figure 1. Journal articles* describing Suzuki-Miyaura reactions for: a) hybridization of nucleophiles/electrophiles and types of nucleophiles/electrophiles involved in sp^2-sp^3 cross-coupling reactions (inset), and b) types of nucleophiles/electrophiles used in sp^2-sp^3 cross-coupling reactions for primary, secondary, or tertiary sp^3-hybridized substrates. *Details describing data collection available in the ESI.

catalysts based on group 10 metals,[9] particularly for cross-coupling reactions involving alkyl halide electrophiles.[10] However, group 10 metals have toxicity[11] and long-term viability concerns,[12] which pose economic and safety challenges for the pharmaceutical industry. Remarkably efficient cross-coupling reactions involving abundant and potentially less toxic iron-based catalysts have recently emerged as viable alternatives, but transmetalating reagents in these reactions are generally limited to basic Grignard (i.e. Kumada-type) or difficult-to-handle organozinc (i.e. Negishi-type) reagents.[13] Iron-based catalysts used for the Suzuki-Miyaura reaction are rare[14] with many remaining substrate limitations. The system reported herein addresses some of these limitations through mechanistically-motivated catalyst design that led to alkyl-aryl cross-coupling reactions that tolerate heteroaromatic boronic esters and tertiary alkyl halides as substrates.

Recently, we reported that controlling catalyst aggregation is important for iron-based catalysts to engage in the Suzuki-Miyaura reaction.[14e] These studies resulted in the working mechanistic hypothesis presented in Figure 2. In this mechanism, iron amide intermediate **II** is formed from reaction of an iron(II) chloride precursor **I** with a lithium amide base. This additive inhibited catalyst aggregation and facilitated transmetalation from

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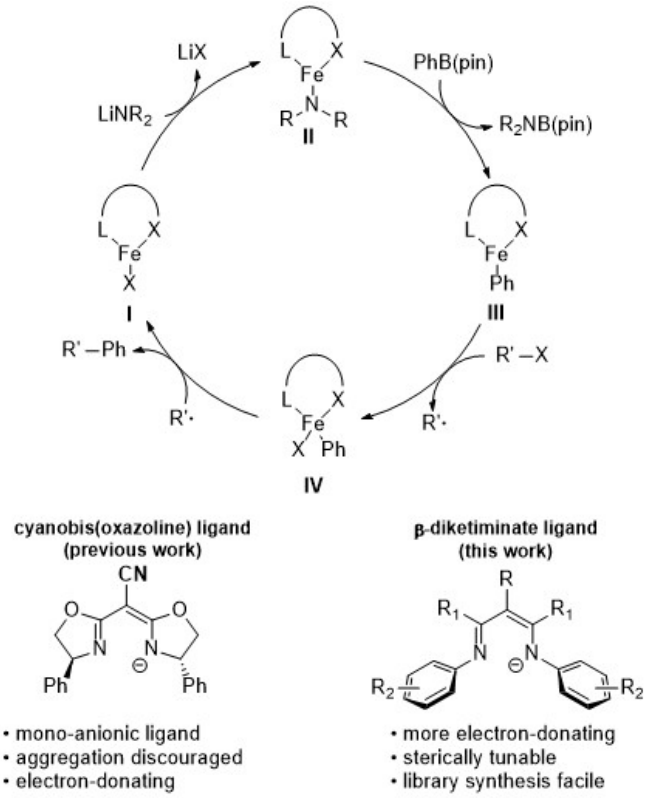
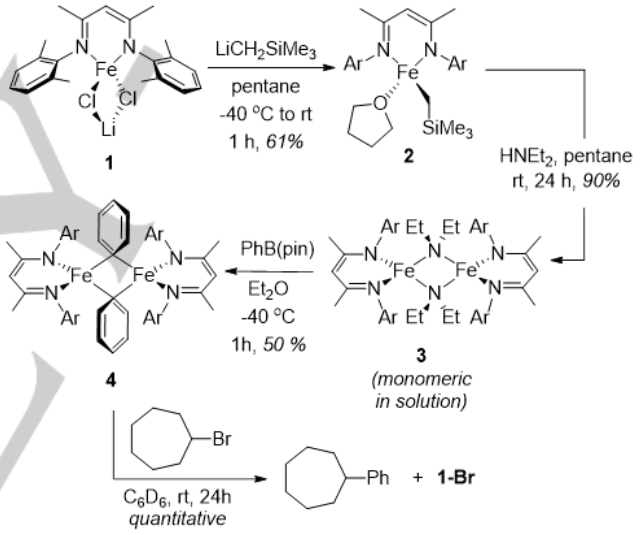
Figure 2. Working mechanistic hypothesis and ligand design features for iron-based catalysts used in Suzuki-Miyaura cross-coupling reactions.



the boronic ester to form iron(II) aryl intermediate **III**. Halogen atom abstraction resulting from reaction between **III** and the alkyl halide formed iron(III) complex **IV** and a carbon-centered radical. We speculated that product formation and catalyst turnover occurred either by radical recombination with **IV** followed by reductive elimination or by radical rebound with **IV**. This working mechanistic hypothesis revealed two ligand design principles that we used for further catalyst development:[14e] 1) bidentate anionic ligands with tunable steric bulk positioned proximal to the metal center were targeted to prevent deleterious iron aggregation; 2) electron-donating ligands that supported low coordination numbers were targeted to accelerate transmetalation.

A class of ligands adhering to both design principles is the β-diketiminate ligands (Figure 2). These ligands are better σ-donors than the less basic cyanobis(oxazoline) ligands previously used.[14e] Moreover, these ligands are exceptional for stabilizing low-coordinate iron species,[15],[16] including 3-coordinate iron alkoxide[15b] and amide[15b] complexes. To test our working mechanistic hypothesis and to evaluate whether iron complexes supported by β-diketiminate ligands would be suitable for cross-coupling reactions, we set out to synthesize discrete iron amide (e.g. **3**) and iron phenyl (e.g. **4**) complexes (Figure 3). Iron amide **3** was accessible through the protonolysis[17] of iron alkyl complex **2** with diethylamine.[18] X-ray crystallographic characterization of **3** confirmed the formation of an iron amide species, which was dimeric by virtue of two μ^2-diethylamide ligands (Figure S1, CCDC #194239).[15b] Contrasting the solid state structure, diffusion-ordered spectroscopy (DOSY) revealed that **3** is predominately mononuclear in solution (Figures S2-S3).[19] This assessment has been further supported by magnetic moments measured in the solid and solution states, which reveal a diamagnetic compound in the solid state and a paramagnetic compound(s) in solution (μ_{eff} = 3.5). The solution state magnetic moment is too small to be a high spin iron(II) complex, and is either best described as an intermediate spin complex or (more likely) represents an equilibrium mixture of the diamagnetic dimeric species and a high spin mononuclear species in solution. Regardless to the precise nature of **3** in solution, combining it with an equivalent of phenylboronic acid pinacol ester (B(pin)) resulted in an immediate color change that coincided with changes in the ^{1}H and ^{11}B NMR spectra consistent with the formation of an iron phenyl complex **4** (Figures S4-S5). This assignment was confirmed by X-ray crystallography, which revealed that **4** was also dimeric in the solid state (Figure S1, CCDC #1942400).[20] Finally, treating complex **4** with bromocycloheptane delivered the cross-coupled product in nearly quantitative yields with the concomitant formation of iron halide complex **1-Br** (Figure 3).

Figure 3. Stoichiometric reactions relevant to Suzuki-Miyaura cross-coupling reactions involving iron complexes supported by β-diketiminate ligands.



The monomer-dimer equilibrium suggested by DOSY and solution state magnetic moment measurements on **3** demonstrated that the β-diketiminate complexes undergo more reversible aggregation events than the cyanobis(oxazoline) complexes. Moreover, the rapid conversion of the iron amide **3** to the iron phenyl **4** highlights the efficient transmetalation reaction afforded by the electron-releasing and sterically accommodating β-diketiminate ligands. Finally, efficient transmetalation occurred even in the absence of a borate intermediate, which is consistent with our working mechanistic hypothesis (Figure 2). Notably, stoichiometric experiments between **1**, a preformed amino borate, and the alkyl halide also produced the cross-coupled product, but these reactions were lower yielding than the reaction between **4** and cycloheptyl bromide (Figures S6-S7). These findings are similar to results reported for metal hydroxide complexes proposed as intermediates in Suzuki-Miyaura reactions catalyzed by palladium-based complexes, which were found to be more efficient transmetalating intermediates compared to borates.[21]

Encouraged by the stoichiometric experiments, iron halide **1** was next explored as a precatalyst for the cross-coupling

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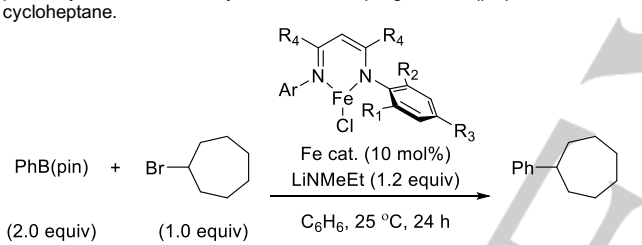
between PhB(pin) and bromocycloheptane (Table 1). Using 10% of complex **1**, the catalytic reaction proceeded efficiently to give >90% of the cross-coupled product (entry 1).[22] Importantly, **1** must be made prior to cross-coupling. Despite similar initial rates, much lower yields were obtained by combining iron dichloride with the ligand (entry 2). The rate of the reaction was sensitive to the identity of the aryl imines installed on the β-diketiminate ligands. Decreasing steric bulk led to increased rates: complexes containing 2-aryl imine ligands (**5-8**, entries 3-6) were superior compared to complexes containing 2,6-dimethyl aryl imine ligands (**1**, **10-12**, entry 1 and entries 8-10). Reactions involving complexes with even bulkier ligands, such as **13**, consumed the starting material efficiently but failed to produce an appreciable amount of the desired cross-coupled product. Despite this trend, the ligands had an optimal size because 2-methylphenyl imine complex **8** (entry 6) was less efficient than 2-ethylphenyl imine complex **7** (entry 5) and unsubstituted phenylimine complex **9** (entry 7) produced cross-coupling products in low yields despite efficient conversion of the alkyl halide. Compared to the notable steric effects, the electronic properties of the ligand minimally impacted the rate of the reaction. For example, complexes **10-12** (entries 8-10) with various electron donating and withdrawing groups installed on the ligand generally led to similar reaction rates as the 2,6-dimethylphenyl imine complex **1** (entry 1).

Table 1. Representative iron(II) β-diketiminate complexes used as precatalysts for Suzuki-Miyaura cross-coupling of PhB(pin) and bromocycloheptane.



(2.0 equiv) (1.0 equiv)

entry	Fe cat.	R_1	R_2	R_3	R_4	Yield (%)[a]	k_{app}[b]	k_{rel}
1	**1**	Me	Me	H	Me	91	2.43	1.0
2	**1**[c]	Me	Me	H	Me	58	2.25	0.9
3	**5**	t-Bu	H	H	Me	97	7.95	3.3
4	**6**	i-Pr	H	H	Me	95	44.0	18.1
5	**7**	Et	H	H	Me	100	45.4	18.7
6	**8**	Me	H	H	Me	85	29.9	12.3
7	**9**	H	H	H	Me	28	17.4	7.2
8	**10**	Me	Me	H	CF_3	92	2.34	1.0
9	**11**	Me	Me	Me	Me	96	3.38	1.4
10	**12**	Me	Me	OMe	Me	95	3.47	1.4
11	**13**	i-Pr	i-Pr	H	Me	<1	2.31	1.0

[a]GC yield relative to an internal standard. [b]k_{app} (x 10^{-5} s^{-1}) based on consumption of bromocycloheptane. [c]formed in situ.

These cross-coupling reactions demonstrated notable advantages compared to our previously reported system.[14e] Reactions were significantly faster due to prolonged catalyst lifetimes, which obviated the need for additional equivalents of ligand required previously (Figures S9-S10). The reaction also does not require an excess of the boronic ester substrate. However, reactions using an excess of boronic ester were faster, slightly more selective, and were void of side reactions so that the excess boronic ester could be recovered nearly quantitatively after the reaction (Figures S11-S12).

The generality of the cross-coupling reaction for a variety of heteroaromatic boronic ester substrates was tested next (Table 2). Catalyst **5** was selected for this purpose because a cursory exploration of boronic ester substrates demonstrated that **5** led to higher yields compared to catalyst precursors that were faster in the reaction between PhB(pin) and bromocycloheptane (e.g., **6-8**).[23] The sterically more encumbered ligand in **5** likely provides the optimal steric environment to overcome irreversible substrate binding while maintaining the accessibility needed for transmetalation. With this precatalyst, several heteroaromatic boronic ester substrates produced the desired products in moderate to excellent yields (Table 2a). 2-thiophenyl-B(pin) and 3-thiophenyl-B(pin) produced the desired cross-coupling products **14-17** involving primary and secondary alkyl halides. These results demonstrate complementary reactivity with electrophilic aromatic substitution of thiophene rings, which selectively functionalize at the 2-position, and are prone to rearrangement when primary alkyl halides are used.[24] In addition to thiophenes, furans were compatible (**18**) as well as several nitrogen-containing heteroaromatic boronic esters (**19-23**). The latter substrates often required the reaction to be carried out at 50 °C or using an excess of boronic ester. Quinolines (**19-20**), sterically encumbered pyridines (**21**) and Boc-protected indoles (**22**) were all tolerated. Such substrates were completely inactive when iron complexes supported by cyanobis(oxazoline) ligands were used as precatalysts. Substrates more likely to bind to iron, such as sterically unencumbered pyridines (**23**) or heterocycles containing multiple nitrogen atoms (**24**), did not undergo efficient cross-coupling using the β-diketiminate ligands.

In addition to the enhanced boronic ester substrate scope, the previously reported alkyl halide substrate scope was maintained to a high degree. Generally faster and cleaner reactions were observed using **5** as the precatalyst compared to cyanobis(oxazoline) complexes (**25-30**, Table 2a). Primary alkyl halides (**25-26**) and secondary alkyl halides (**27-31**) were well tolerated with alkyl bromides being superior to alkyl chlorides and alkyl iodides (Figure S14).[25] One notable exception were benzylic halide substrates (**26**), which gave respectable amounts of product but did not perform as well as with the cyanobis(oxazoline) complexes.[14e] In addition to being tolerant to many heterocycles, the reaction produced useful yields for substrates containing carbamates (**30**) and silyl protected alcohols (**31**).[26] Moreover, the cross coupling reaction proceeds well in other solvents (See Figure S16), and can be carried out on a gram scale as evidenced by the high yields (85%) obtained in a reaction between PhB(pin) and bromocycloheptane.

Finally, tertiary alkyl halides proved to be excellent substrates for the cross-coupling reaction (Table 2, **32**, **33-37**). Previously, the cyanobis(oxazoline) iron complexes led to low yields of cross-coupled product with 1-chloroadamantane,[14e] but the reaction was not general for a variety of tertiary alkyl halides. In contrast, cross-coupling using **5** resulted in a near quantitative yield of **32** when 1-chloroadamantane was used as a substrate (Table 2a). Surveying the precatalysts used in Table 1 revealed that the fluorinated catalyst **10** was more general for cross-coupling of a variety of tertiary alkyl chlorides (Table 2b). Using this catalyst, reactions between *tert*-butyl chloride and a variety of

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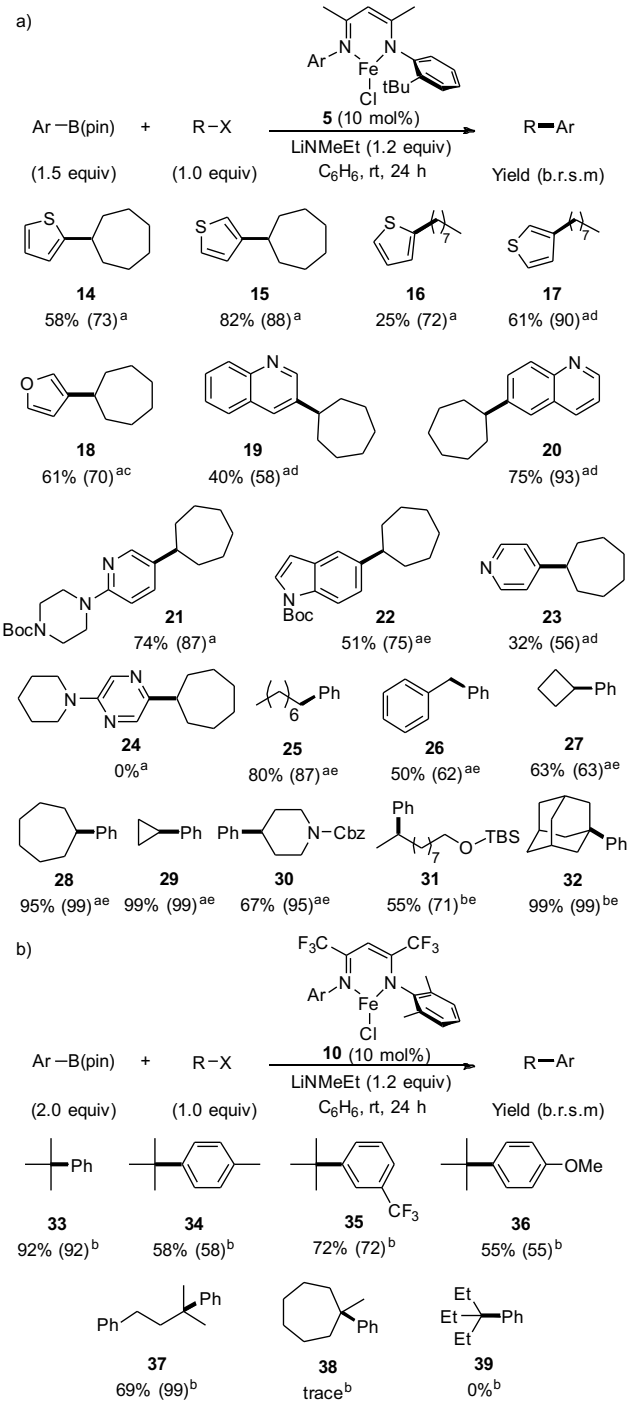
Table 2. Substrate scope for cross-coupling reactions using **5** or **10** as catalyst precursors. Isolated yields are reported with yields based on recovered starting material appearing in parentheses.



[a] X = Br. [b] X = Cl. [c] 0.1 mmol of electrophile. [d] at 50 °C. [e] 2.0 equiv. of B(pin).

electronically diverse boronic esters resulted in moderate to excellent yields of cross-coupled products (**33**-**36**). A bulkier RMe_2Cl substrate also produced cross-coupled product **37** in good yield and without any isomerization due to chain walking. Such isomerization can be problematic for nickel-catalyzed cross electrophile cross-coupling reactions involving tertiary alkyl halides.[27] The limitation of the current system is with tertiary alkyl halides of the general formula R_2MeCl and larger, which were completely unreactive under the reaction conditions (e.g., **38**-**39**). The substrate scope observed complements a nickel-based catalyst developed by Fu and coworkers that has a broader alkyl halide substrate scope but is more sensitive to the electronic nature of the nucleophile.[8a] Moreover, the high reactivity of the iron-based complexes allowed for cross-coupling reactions to occur with boronic esters as opposed to the 9-BBN boranes required in the nickel-catalyzed system.

In conclusion, an iron-based catalyst system was designed for the efficient cross-coupling of unactivated boronic ester nucleophiles and alkyl halide electrophiles. The electron-releasing β-diketiminate ligands used favor reactive intermediates with low coordination numbers that are beneficial for transmetalation. Compared to our previous system involving cyano(bisoxazonline) ligands,[14e] the complexes bearing β-diketiminate ligands are less prone to ligand dissociation and irreversible aggregation. As a result, unproductive iron aggregates are avoided, which led to high catalyst activity that was leveraged for cross-coupling reactions involving underrepresented substrate classes, including heteroaromatic boronic ester nucleophiles and tertiary alkyl halide electrophiles. Future reaction design will be aimed at reducing catalyst loading and extending the method to incorporate broader classes of substrates, including different heteroaromatic nucleophiles, alkyl-alkyl cross-coupling reactions, and enantioselective variants. Finally, methodology development will be coupled with mechanistic studies focused on better understanding the key C–C bond forming step, which remains poorly understood in catalytic cross-coupling reactions involving iron complexes.[28]

Acknowledgements

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Supplementary Materials

All experimental procedures, NMR data, additional conversion versus time plots, and crystallographic data appear in the electronic supplementary information. Deposition Numbers 194239 and 1942400 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service, www.ccdc.cam.ac.uk/structures.

Keywords: Cross-Coupling • Iron • Suzuki-Miyaura • heteroaromatic boronic ester • tertiary alkyl halide

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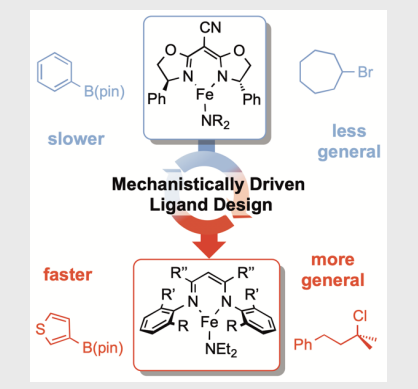
Nacnac! Who's there? A mechanistically driven approach to Suzuki-Miyaura cross-coupling with an iron-based catalyst enables the facile construction of Csp^3–Csp^2 bonds with heteroaromatic boronic esters. Additional advancements allow for the construction of all carbon quaternary centers with no observable isomerization.



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Rational Design of an Iron-Based Catalyst for Suzuki-Miyaura Cross-Couplings Involving Heteroaromatic Boronic Esters and Tertiary Alkyl Electrophiles

Layout 2:

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TOC graphic

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