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COMMUNICATION

Iron-catalysed enantioconvergent Suzuki-Miyaura cross-coupling to afford enantioenriched 1,1-diarylalkanes

Chet C. Tyrol,*[a] Nang S. Yone[a], Connor F. Gallin[a] and Jeffery A. Byers[a]

The first stereoconvergent Suzuki-Miyaura cross-coupling reaction was developed to afford enantioenriched 1,1-diarylalkanes. An iron-based complex containing a chiral cyanobis(oxazoline) ligand framework was best to obtain enantioenriched 1,1-diarylalkanes from cross-coupling reactions between unactivated aryl boronic esters and benzylic chlorides. Enhanced yields were obtained when 1,3,5-trimethoxybenzene was used as an additive, which is hypothesized to extend the lifetime of the iron-based catalyst. Exceptional enantioselectivities were obtained with challenging ortho-substituted benzylic chlorides, a motif common in many pharmaceuticals. In addition to providing access to enantiomerically enriched 1,1-diaryl alkanes, this method further expands the coupling partners available to enantioselective cross-coupling reactions catalysed by iron-based complexes.

Since the renaissance of iron-based catalysts used for cross-coupling reactions were galvanized by the seminal work of Fürstner at the turn of the century,[1] industrial and academic interest in these catalysts have increased due to the high abundance and low toxicity of iron as well as the unique reactivity that these types of catalysts afford.[2a-c] Fast reaction kinetics are often observed with iron-based catalysts, which leads to complementary reactivity compared to many nickel-based catalysts used for similar reactions.[1,3] A particularly prolific area of cross-coupling reactions that has benefited from the development of iron-based catalysts are reactions involving alkyl halide electrophiles with organomagnesium,[4a-c] organozinc,[5a-b] and most recently organoboron-based[6a-e] organometallic nucleophiles. These catalysts have demonstrated remarkable reactivity, especially for cross coupling reactions involving sterically demanding substrates and heteroaromatic boronic esters.[7] Despite these advances, enantioselective cross-coupling reactions that utilize iron-based catalysts are exceedingly rare and have been greatly overshadowed by the tremendous achievements in enantioconvergent systems employing nickel-based catalysts.[8] In fact, only three enantioselective cross coupling reactions that utilize iron-based catalysts have been reported.[9a-c] All of these reactions use α-haloesters as electrophiles and none of them use unactivated boronic esters as nucleophiles. With this report, we expand the nascent scope of enantioselective iron-based cross-coupling reactions and advocate for their value in chemical synthesis with the synthesis of enantioenriched 1,1-diarylalkanes (Figure 1).

Blockbuster pharmaceuticals, such as Zoloft, Detrol and

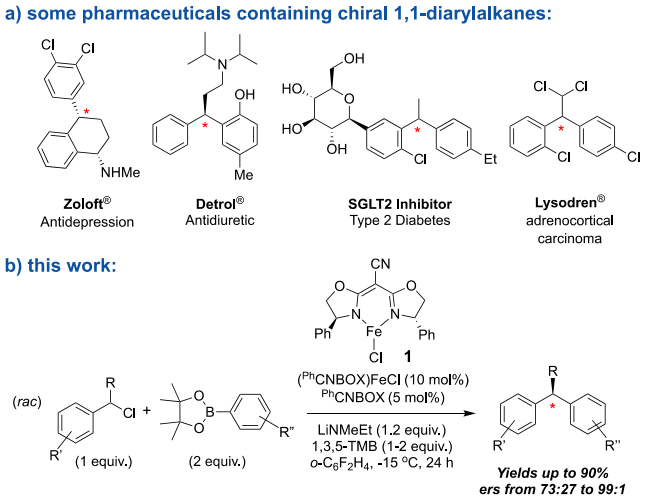


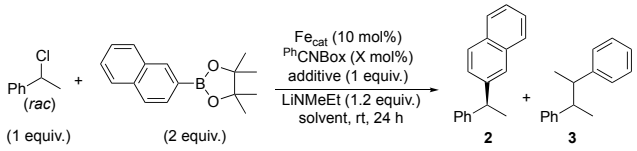
Figure 1 a) Pharmaceuticals containing the 1,1-diarylalkane motif. b) Enantioconvergent Suzuki-Miyaura cross-coupling of benzylic chlorides catalysed by iron complexes supported by cyanobis(oxazoline) ligands.

SGLT2 inhibitors all contain the chiral 1,1-diarylalkane motif while eliciting a range of physiological responses (Figure 1a).[10] Despite the fact that one enantiomer of these drugs is often more potent,[11] they are either sold as racemates, mixtures of diastereomers,[12] or are obtained in enantioenriched form as a result of a late stage resolution.[12,13] These tactics are a likely symptom of synthetic limitations that have prevented access to enantiomerically enriched 1,1-diaryl alkanes. Consequently, the enantioselective synthesis of the 1,1-diarylalkane subunit has become a popular contemporary topic for synthetic organic chemists.[14] Current approaches toward such motifs include asymmetric hydrogenation of 1,1-diarylalkenes,[15] nucleophilic and radical additions to alkenes,[16] and stereospecific[17] as well as stereoconvergent[18a-b] cross coupling reactions. A method that is noticeably absent from this list is a stereoconvergent Suzuki-Miyaura cross coupling reaction. Such a reaction would closely mimic the ubiquitous Suzuki-Miyaura cross coupling reactions used in the pharmaceutical industry for the construction of C–C bonds between two sp^2-hybridized substrates.[19]

[a] Department of Chemistry, Boston College, 2609 Beacon Street, Chestnut Hill, MA 02467 (USA). E-mail: byersja@bc.edu

Herein, we report the first enantioselective Suzuki-Miyaura cross-coupling reaction between benzylic chlorides and unactivated arylboronic-pinacol esters that is made possible by capitalizing on the reactivity of an iron-based catalyst (Figure 1b). Previously it was shown that iron-based complexes supported by chiral cyanobis(oxazoline) ligands (e.g., **1**) are competent catalysts for Suzuki-Miyaura cross coupling reactions between alkyl halides and unactivated aryl boronic esters.[6e] Given that the method utilized a chiral catalyst and tolerated secondary alkyl halides, we hypothesized that it would be suitable for the stereoselective cross-coupling of secondary benzyl halide electrophiles and arylboronic ester nucleophiles to give enantioenriched 1,1-diarylalkanes. Exploratory reactions between (1-chloroethyl)benzene and 2-naphthylboronic acid pinacol ester under previously reported conditions[6e] using cyano(bisoxazoline) iron(II) chloride complex **1** as the catalyst precursor led to 1,1-diaryl alkane **2** in 64% yield and with an enantiomeric ratio (er) of 74:26 (Table 1). A competitive side product was compound **3**, which results from the homodimerization of the benzyl halide starting material. Importantly, using the preformed iron complex was necessary to obtain **2** in high yield, although identical enantioselectivity was observed for a reaction carried out by mixing the cyano(bisoxazoline) ligand with iron dichloride (entry 2).

Table 1. Suzuki-Miyaura cross-coupling reaction between 1-chloroethylbenzene and 2-napthylboronic pinacol ester.



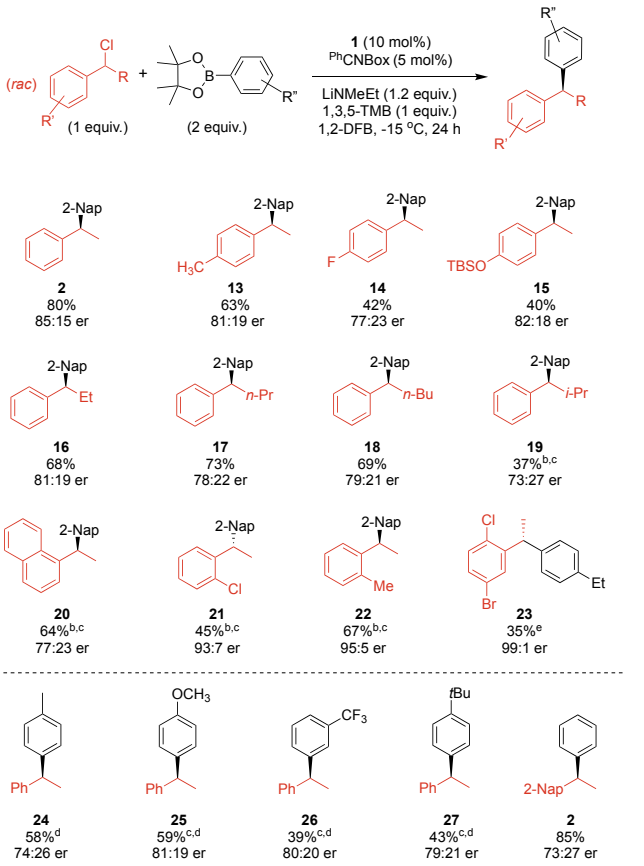
Entry	Fe_{cat}	^{Ph}CNBox (mol%)	solvent	additive	Yield **2** (%)[a]	er of **2**[b]	Yield **3** (%)[a]
1	**1**	10	C_6H_6	none	64	74:26	9
2	$FeCl_2$	20	C_6H_6	none	19	74:26	19
3	**1**	10	1,2-DFB[d]	none	66	76:24	11
4	**1**	10	1,2-DFB[d]	1,3,5-TMB[c]	73	79:21	9
5	**1**	0	1,2-DFB[d]	1,3,5-TMB[c]	90	75:25	10
6	**1**	0	1,2-DFB[d]	none	68	75:25	18
7[e]	**1**	5	1,2-DFB[d]	1,3,5-TMB[c]	90	85:15	0

[a] Yields determined by ^{1}H-NMR spectroscopy relative to 1,3,5-trimethoxybenzene as an internal or external standard. [b] enantiomeric ratios determined by chiral column HPLC. [c] 1,3,5-trimethoxybenzene. [d] 1,2-difluorobenzene. [e] -15 °C.

An evaluation of solvents and stoichiometric additives (see Table S1) revealed similar yield and selectivity for a reaction carried out in 1,2-difluorobenzene (1,2-DFB) as the solvent (entry 3). A modest improvement in yield and selectivity was obtained by using 1,3,5-trimethoxybenzene (1,3,5-TMB) as a stoichiometric additive (entry 4). With these conditions, we carried out a screen of iron precatalysts containing various aromatic and aliphatic substituted cyanobis(oxazoline) ligands (Table S2). Unfortunately, all variants explored demonstrated decreased yields and/or selectivities compared to reactions using iron precatalyst **1**. Therefore, **1** was used for final optimization. Previously, we found that reactions carried out with additional ^{Ph}CNBox ligand improved yields,[6e] but here we found that reactions carried out without extra ligand but in the presence of 1,3,5-TMB led to appreciably higher yields of **2** despite lower selectivity (see entry 5). Control experiments confirmed once again that 1,3,5-TMB had little to no effect on selectivity but was important to obtain high yields, particularly in the absence of additional ligand (c.f., entries 5 and 6). Finally, enantioselectivity was improved for a reaction carried out at -15 °C (e.r. = 85:15). However, at this temperature it was necessary to add 5% ligand to maximize yields of **2**.

The benzyl halide substrate scope of the reaction was evaluated next (Table 2, top). Benzyl halides containing electron-donating and electron-withdrawing functional groups led to lower yields but only modestly affected enantioselectivity (c.f., **2**, **13-15**). Increasing the chain length of the alkyl substituent from methyl to butyl lead to slightly lower yields and similar enantioselectivities (c.f., **2, 16-18**). However, introducing branching acjacent to the alkyl halide led to lower yield and enantioselectivity (e.g., **19**). The reaction demonstrated moderate functional group tolerance with

Table 2. Substrate scope for the cross-coupling of benzylic halides and boronic ester scope catalysed by **1**.[a]



[a] Yields are isolated yields and enantiomeric ratios were determined by chiral column HPLC. [b] 15 mol% [Fe], no extra ligand, 2 equiv. 1,3,5-TMB. [c] $LiNMe_2$ used. [d] 15 mol% Fe_{cat}, 7.5 mol% ligand, 2 equiv. 1,3,5-TMB and -10 °C. [e] 40 mol% [Fe], no extra ligand, 2 equiv. 1,3,5-TMB and -10 °C.

ethers, silyl-protected alcohols, aryl bromides, and aryl chlorides all being tolerated. Of particular note was the high enantioselectivities (er ≥ 93:7) observed for benzylic halides containing ortho-substituted aryl groups (e.g., **21-23**). These substrates are important because ortho substituted 1,1-diaryl alkanes are common motifs in many pharmaceuticals (Figure 1a), and they are challenging to obtain in high enantiopurity using the previous methods reported to synthesize 1,1-diarylalkanes,[18b,20] except for one isolated report.[15] To compensate for the lower reactivity of these demanding substrates, higher loadings of **1** and 1,3,5-TMB were required. Additionally, using $LiNMe_2$ instead of LiNMeEt was beneficial to obtain appreciable yields of **22.** In addition to being a common motif in pharmaceuticals, product **21** is a versatile synthetic intermediate because it can be used futher as the electrophile in cross coupling reactions, converted into a nucleophile for cross-coupling reactions through Miyaura borylation, and undergo protodechlorination.[15] To demonstrate the synthetic utility of the method, we synthesized an intermediate for an SGLT2 inhibitor used to treat type II diabetes (Figure 1a).[21] Using 40 mol% of **1**, product **23** was formed in modest yield but with excellent enantioselectivity (>99:1 er). Elaboration of this intermediate to the SGLT2 inhibitor has previously been reported through glycosylation of the aryl bromide,[22] which remains unreacted in the cross-coupling reaction.

With respect to the boronic ester substrate scope, arylboronic acid pinacol ester coupling partners derived from PhB(pin) were less reactive than 2-naphthylboronic acid pinacol ester (Table 2, bottom). Consequently, reactions involving these nucleophiles required higher temperatures (-10 °C) and higher catalyst loadings (15 mol%) to obtain useful yields of cross-coupled product. Despite these changes, only a small erosion in enantioselectivity was observed (e.g., **24-27**). As was found with the benzyl halides, varying the electronic nature of the boronic ester had minimal effect on enantioselectivity.

A puzzling feature of the reaction was the benefit of using 1,3,5-TMB as an additive. Analysing the reaction over time in the presence and absence of 1,3,5-TMB provided some insight into the role of 1,3,5-TMB (Figure 2). These experiments revealed that addition of 1,3,5-TMB had no effect on the initial rate of the reaction nor did it impact the selectivity of the reaction. The major difference was observed at long reaction times where higher yields were obtained in the presence of 1,3,5-TMB.

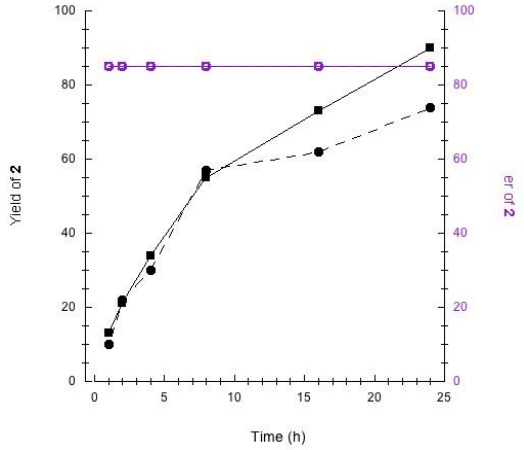


Figure 2. Effects on yield (closed symbols) and er (open symbols) of **2** for the coupling reaction between 1-chloroethylbenzene and 2-napthylboronic pinacol ester catalysed by **1** in the absence (circles) and presence (squares) of 1,3,5-TMB (1 equiv.) at -15 °C. Ultimate yields are 90% and 75% with and without 1,3,5-TMB, respectively.

Several observations provided additional information about the mechanism for stereoinduction in the cross-coupling reaction.[23a-b] Importantly, the enantioselectivity of the reaction remained constant throughout the reaction (Figure 2). Additionally, when stereoenriched **2** was introduced at the onset of a cross-coupling reaction, no loss in its enantiopurity occurred over the course of the reaction (see Figure S2). Both results demonstrate that the basic reaction conditions employed do not lead to product epimerization. In contrast, racemic alkyl halide was recovered from a reaction taken to partial completion (Figure S3), and the homodimerization product **3** was obtained as a near statistical mixture of all three possible stereoisomers (*S*,*S*:*R*,*R*:*R*,*S* ~ 1:1:2) (Figure S4). These findings are most consistent with a stereoconvergent cross-coupling reaction mechanism that proceeds through a free radical intermediate formed without kinetic resolution of the alkyl halide. The mechanism for stereoconvergence is likely through an unselective halogen atom abstraction step.[9a-b,24] To gain information about the nuclearity of the catalyst during the selectivity determining step,[25] stereoselectivity was evaluated as the catalyst enantiopurity was altered. These reactions revealed a linear relationship between product and catalyst enantiopurity (see Figure S5), which suggested that the selectivity-determining step in the cross-coupling reaction likely occurs at a metal centre containing one cyanobis(oxazoline) ligand. Interestingly, reaction of 2-(1-chloroethyl)naphthalene with PhB(pin) produced **2** with a similar yield but lower enantioselectivity as obtained for the complementary reaction between 2-napthylboronic acid pinacol ester and (1-chloroethyl)benzene (Table 2). This observation suggests that the electrophile and the nucleophile are present in the selectivity-determining step.

A possible catalytic cycle is shown in Scheme 1. Precatalyst **I** engages in salt metathesis with the lithium amide to form iron(II) amide **II**. This intermediate competitively undergoes transmetalation with the aryl boronic ester to form iron(II) aryl **IV** and unselective halogen abstraction to form iron(III) amide-halide **III** and a carbon-centred radical**.** The carbon-centred radical reversibly recombines with **IV** to form iron(III) aryl-alkyl species **V**. Complex **V** is poised for reductive elimination to form the formally iron(I) complex **VII** and the cross-coupled product. In order to avoid unstable low coordinate iron species from forming, we suspect that reductive elimination requires prior coordination of solvent or 1,3,5-TMB to form **VI**. Benzene has previously been shown to stabilize iron(I) complexes supported by the structurally similar β-diketiminate ligands.[26] Regardless to the precise nature of the reductive elimination, **III** formed from halogen atom abstraction can re-enter the catalytic cycle by a comproportionation reaction with **VII** to complete the catalytic cycle by regenerating **I** and forming an equivalent of **II**. The selectivity determining step is radical recombination to form **V** and/or reductive elimination.[27] Currently, we cannot rule out either step as the selectivity determining step, but what is clear from our mechanistic experiments is that the enantiodetermining step(s) occurs from a single metal centre.

We favour the mechanism shown in Figure 3 as opposed to other mechanisms that utilize one metal complex throughout the catalytic cycle for several reasons. One possibility is radical recombination occurs after halogen atom abstraction from iron(II) aryl species **IV** (Figure S6). In such a mechanism, an iron(IV) intermediate would be formed, which is unlikely under the reducing

reaction conditions. Another alternative would be C–C bond formation through an outer sphere radical rebound mechanism to form the C–C bond (Figure S7). This mechanism avoids forming an iron(IV) intermediate, but the radical rebound step would be the selectivity determining step of the reaction if this mechanism were operative. We disfavour such a step as the selectivity determining step because it is very similar to the microscopic reverse of halogen atom abstraction, which is an unselective event. Instead, we favour the bimetallic mechanism shown in Figure 3 that resembles similar mechanisms previously proposed for cross coupling reactions catalysed by iron[34a-b] and nickel[24,28] complexes.

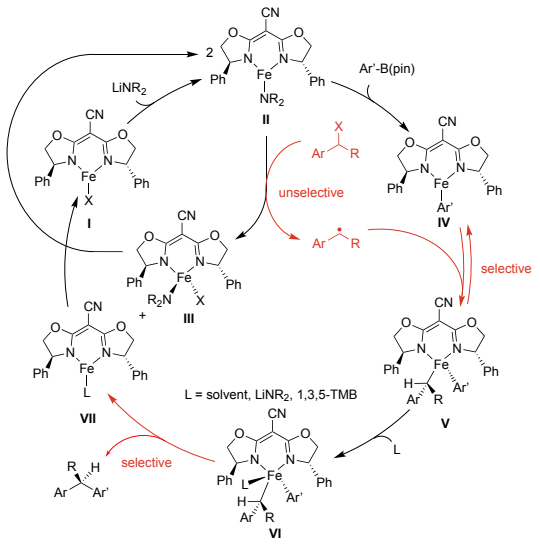


Figure 3. Proposed catalytic cycle for the Suzuki-Miyaura cross-coupling between benzylic halides and arylboronic pinacol esters catalysed by iron-cyanobis(oxazoline) complexes.

Conclusion

The first enantioselective Suzuki-Miyaura reaction used to synthesize enantioenriched 1,1-diarylalkanes was developed. The method relies on an iron-based catalyst that proceeds through a stereoconvergent cross-coupling mechanism between racemic benzylic chlorides and unactivated aryl boronic esters. The anionic cyano(bisoxazoline) ligand and 1,3,5-TMB additive employed were important to extend catalyst lifetime so that high yields could be obtained. In addition to being the first catalyst reported for this transformation, the iron-based catalyst demonstrates reactivity that expands the substrate scope compared to existing nickel-based catalysts that have previously been developed.[18a,18b] Most notably were the high selectivities observed for cross-coupling reactions involving challenging ortho-substituted diarylalkane substrates. Perhaps more importantly, the method expands the classes of electrophiles that can engage in enantioselective cross coupling reactions effected by iron-based cross-coupling catalysts.

Conflicts of interest

There are not conflicts to declare.

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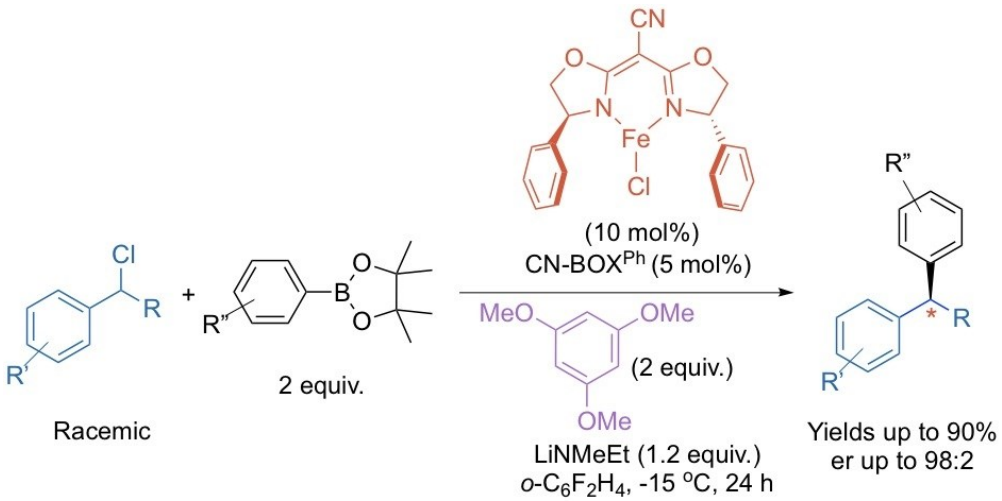

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