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The first iron-catalysed enantioselective Suzuki–Miyaura coupling reaction has been developed. In the presence of catalytic amounts of $FeCl_2$ and (*R,R*)-QuinoxP*, lithium arylborates are cross-coupled with *tert*-butyl α-bromopropionate in an enantioconvergent manner, enabling facile access to various optically active α-arylpropionic acids including several nonsteroidal anti-inflammatory drugs (NSAIDs) of commercial importance. (*R,R*)-QuinoxP* is specifically able to induce chirality when compared to analogous P-chiral ligands that give racemic products, highlighting the critical importance of transmetallation in the present asymmetric cross-coupling system.

Transition-metal-catalysed coupling reactions with organoboron reagents, namely Suzuki–Miyaura coupling reactions, are among the most powerful methods for the construction of carbon–carbon bonds in both academic and industrial chemical syntheses.[1] Intensive studies involving catalysts and ligands have firmly established this synthetic method; however enantioselective versions remain challenging, particularly for the construction of sp^3 carbon centres. Owing to the appreciable significance of such stereogenic centres in current pharmaceutical design,[2] considerable effort has been devoted to developing enantioselective cross couplings involving alkyl reagents.[3]

Enantioconvergent coupling reactions of alkyl halides with boron nucleophiles represent the most sophisticated approaches because they directly synthesise optically active molecules from readily available racemic halides. Fu and co-workers have made significant progress in such transformations through the use of nickel catalysts (Figure 1a).[4] At present, the scope of this type of enantioconvergent reaction has been expanded to various combinations of alkyl halides and nucleophiles,[3a,3e,5] and to other transition-metal catalysts;[6] however, the use of organoboron reagents is still severely limited to nickel catalysis.

Iron has gained considerable attention due to its cost-effectiveness and safe properties, which advantages this metal catalyst in pharmaceutical and agrochemical syntheses.[7] Over the past decade, our group and others have developed iron-catalysed coupling reactions involving organoboron reagents,[8] including those with alkyl halides.[9] However, the application of an organoboron reagent to an enantioselective iron-catalysed coupling reaction has not been achieved so far. Here we report the first examples of iron-catalysed enantioselective couplings of organoboron reagents to produce optically active α-aryl esters from racemic α-haloesters and arylboron reagents (Figure 1b).

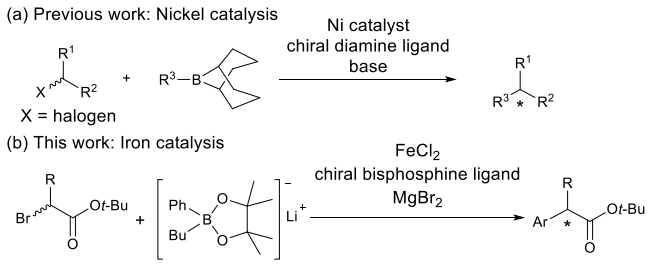

Figure 1. Enantioconvergent couplings of alkyl halides with organoboron reagents.

Our studies began by screening ligands in the coupling of *tert*-butyl α-bromopropionate (**1**) with the lithium phenylborate **2a**, which was easily prepared from the boronic ester and BuLi (Table 1).[9b] In the previously reported enantioselective iron-catalysed coupling of aryl Grignard reagents, P-chiral bisphosphine ligand of (*R,R*)-BenzP* was the most effective among a variety of ligands.[6c] Based on these results, we initially examined several P-chiral bisphosphines[10] and found that the ligand backbone has a remarkable effect on enantioselectivity. As shown in Table 1, to our surprise, the present reaction with (*R,R*)-BenzP* **L1** did not exhibit chiral induction at all. In addition,

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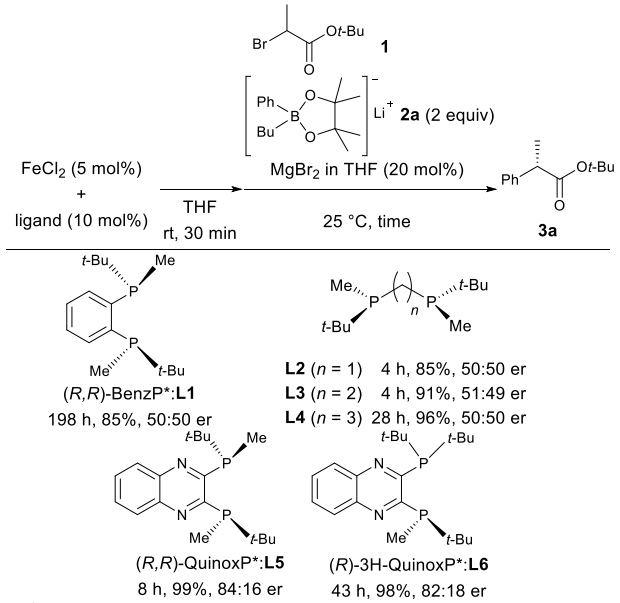
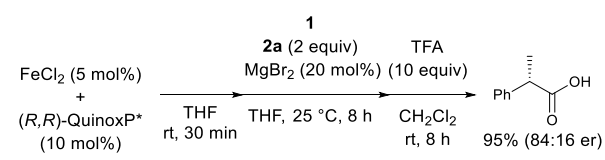
the reaction needed an unexpectedly long reaction time (198 h) for full conversion of the alkyl halide. The use of P-chiral ligands **L2–L4**, which have aliphatic backbones, were also totally ineffective, providing the racemic coupling product. In sharp contrast, chiral ligands bearing quinoxaline backbones were specifically able to induce chirality; (*R,R*)-QuinoxP* **L5** was found to be optimal and gave product **3a** in 94% yield with 84:16 er. *C1*-Symmetric (*R*)-3H-QuinoxP* **L6** also provided **3a** with comparable enantioselectivity, although the reaction proceeded slowly probably due to the steric hindrance of three *t*-Bu groups. Other types of chiral ligand, including nitrogen-based ones, were less effective in this reaction (see ESI). It is noteworthy that the yield is affected by the synthetic procedure; the arylborate, α-haloester, and $MgBr_2$ need to be added in this order to the mixture of $FeCl_2$ and the chiral ligand as depicted in Table 1 (see ESI for experimental details).

Table 1. Chiral-ligand screening



[a] Yields and er values were determined by GC and HPLC, respectively.

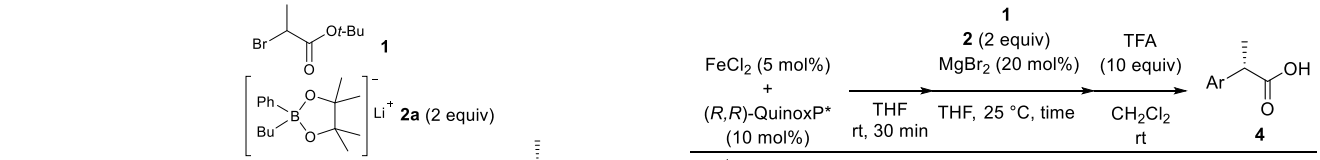
Optically active α-aryl esters are useful intermediates for the synthesis of several bioactive molecules, such as α-arylpropionic acids, which are well known to be nonsteroidal anti-inflammatory drugs (NSAIDs).[11] Indeed, the coupling product was smoothly transformed into α-phenylpropionic acid without any loss of optical purity upon hydrolysis with TFA (Scheme 1). Notably, this sequential method involving coupling and hydrolysis did not require any chromatographic purification, and simple liquid-liquid extraction provided pure *α*-phenylpropionic acid in high yield.

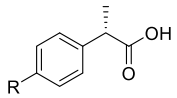
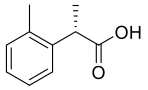
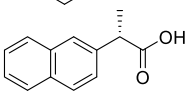
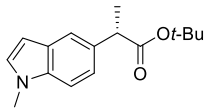
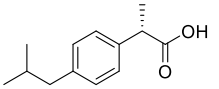
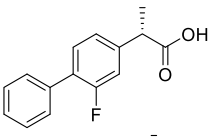
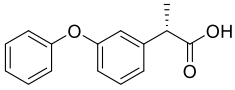
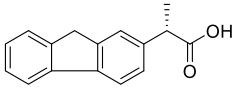
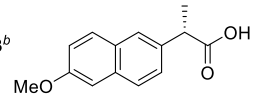


Scheme 1. Synthesis of chiral α-phenylpropionic acid by iron-catalysed enantioconvergent coupling and hydrolysis.

With the optimal procedure in hand, we examined the scope of the arylboron reagent (Table 2). Both electron-rich (entries 1–3) and deficient (entry 4) arylborates provided the coupling products in high yields and with reasonable enantioselectivities. The chloro substituent, which is potentially useful for further synthetic elaborations including cross-couplings, was untouched under the present reaction conditions; the product was obtained in 83% yield with 84:16 er (entry 5). *Ortho*-substituted phenyl- and 2-naphthylborates were also amenable to the reaction (entries 6 and 7). Coupling with the indolylborate also proceeded smoothly and enantioselectively (entry 8); however, hydrolysis of the coupling product failed due to the decomposition of the indolyl unit under acidic condition. Furthermore, the developed synthetic method was applied to the synthesis of a variety of bioactive α-phenylpropionic acids with enantioselectivities in excess of 80:20 (entries 9–13).

Table 2. Arylboron reagent scope



entry	product		time (h)	yield [%] (er)[a]
1		**4b:** R = Me **4c:** R = OMe **4d:** R = NMe_2 **4e:** R = CF_3 **4f:** R = Cl	6 35 3 23 12	90 (81:19) 85 (82:18) 89 (82:18) 81 (76:24) 83 (84:16)
2[b]				
3				
4				
5				
6		**4g**	20	65 (88:12)
7		**4h**	19	91 (77:23)
8[c]		**3i**	15	80 (81:19)
9		(*S*)-Ibuprofen **4j**	5	95 (82:18)
10		(*S*)-Flurbiprofen **4k**	16	51 (84:16)
11		(*S*)-Fenoprofen **4l**	22	52 (82:18)
12		(*S*)-Cicloprofen **4m**	13	49 (81:19)
13[b]		(*S*)-Naproxen **4n**	22	80 (80:20)

[a] Isolated yields; er values determined by HPLC. [b]$FeCl_2$ (1 mol %) and (*R,R*)-QuinoxP* (2 mol %) were used. [c]Hydrolysis failed due to the decomposition of the indolyl group, and yield was determined by ^1H NMR .

We next turned to the specific chiral-inducing ability of (*R,R*)-QuinoxP* compared to other P-chiral bisphosphine ligands. We previously reported that both (*R,R*)-QuinoxP* and (*R,R*)-BenzP* induced comparable enantioselectivities in iron-catalysed couplings involving aryl Grignard reagents, which is in stark contrast to the present system.[6c,12] On the basis of these results, we have tentatively concluded that the observed difference between (*R,R*)-QuinoxP* and (*R,R*)-BenzP* in the present system cannot be attributed to their chiral induction abilities. To examine the difference between the two ligands, we performed stoichiometric reactions of pre-formed complexes, namely $FeCl_2$/(*R,R*)-QuinoxP* **A_1** and $FeCl_2$/(*R,R*)-BenzP* **A_2**, with phenyl borate **2a** in the presence of $MgBr_2$ (Figure 2). The reaction of **A_2** proceeded quite slowly, and more than 60% of the starting iron complex remained even after 62 h. On the other hand, iron complex **A_1** was completely consumed within 2 h under the same conditions. These results indicate that (*R,R*)-QuinoxP* is crucial to facilitate transmetallation, which is most likely the key step for the generation of the active iron species in the enantioselective catalytic cycle (*vide infra*). The electron-withdrawing nature of the quinoxaline backbone renders the iron centre more electrophilic, thereby accelerating transmetalation.[13]

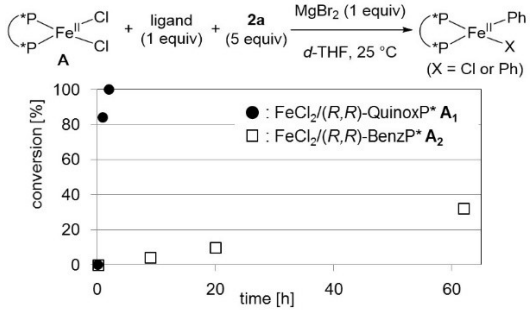


Figure 2. Stoichiometric reactions of $FeCl_2$/bisphosphine with borate **2a** in the presence of $MgBr_2$. Conversions of $FeCl_2$/(*R,R*)-QuinoxP* **A_1** (circles) and $FeCl_2$/(*R,R*)-BenzP* **A_2** (squares) were determined by ^{1}H NMR spectroscopy. The produced iron complex was unable to be characterised by NMR techniques.

Based on our experimental and theoretical studies on the iron-catalysed couplings of alkyl halides, we present a plausible mechanism in Figure 3a.[6c,9b,13a,14] Transmetallation of $FeCl_2$/bisphosphine **A** with the boron reagent[15] and subsequent reductive elimination provides $Fe^{I}X$/bisphosphine **B**, which is the active species during the first C–Br bond-activation step. Complex **B** then abstracts the bromine atom from the alkyl bromide to generate the corresponding alkyl radical; this radical recombines with complex **C**, which is generated by the transmetallation of **A** with the boron reagent,[16] to produce Fe^{III}BrArAlkyl/bisphosphine **D**. Reductive elimination of complex **D** provides the coupling product. In the case of (*R,R*)-BenzP*, transmetallation with the arylborate is quite slow. As a consequence, the racemic background reaction triggered by ligand dissociation from complex **A** dominates (Figure 3a, left).[17] Due to tiny amount of ligand-dissociated iron species in the reaction solution, the coupling with (*R,R*)-BenzP* proceeded quite slowly.

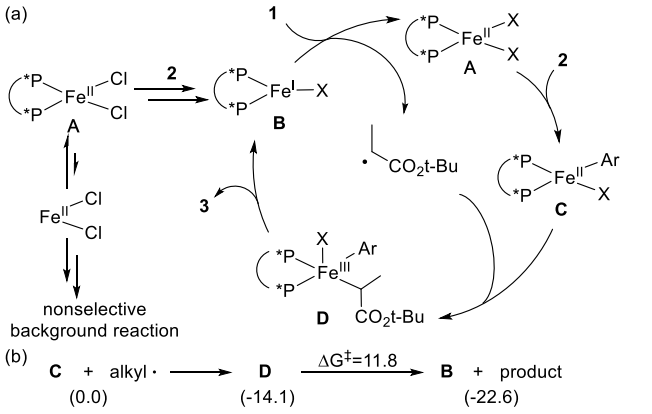


Figure 3. (a) Plausible mechanism for the enantioselective coupling reaction of aryl boron reagents and (b) energy profile of recombination and reductive elimination calculated at the B3LYP/6-311G* with GD3BJ empirical dispersion. Energy values (kcal/mol) relative to sum of **C** and alkyl radical are shown in parentheses. For the detail of complex structures and discussion, see ESI.

DFT calculations reveal that the recombination and the final reductive elimination are exergonic, with Δ*G* values of 14.1 and 22.6 kcal/mol, respectively (Figure 3b). In addition, the energy barrier for reductive elimination is predicted to be 11.8 kcal/mol. Although the transition state for the recombination step was unable to be optimized due to the flatness of the potential energy surface, the calculated energy profile suggests that each step proceeds irreversibly under the reaction conditions; hence, we conclude that recombination is most likely to be the enantiodetermining step.

In summary, we developed the first iron-catalysed enantioselective coupling reactions involving organoboranes, in which the use of a P-chiral ligand containing an electron-deficient quinoxaline backbone is the key to attaining high enantioselectivities. This reaction enables facile access to a variety of optically active α-arylpropionic esters from racemic α-bromoesters, which are readily deprotected to the corresponding α-arylpropionic acids, including several pharmaceutical compounds. Although the enantioselectivity can still be improved, the combination of an iron catalyst with a boron reagent clearly endows this method with practical advantages over other coupling reactions. Efforts to further develop more-selective iron catalysts and expand the scope are underway in our laboratory.[18]

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University and Nippon Chemical Industries) for kindly gifting the P-chiral ligands.

Conflicts of interest

There are no conflicts to declare.

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12. On the basis of our DFT calculations, coupling reactions with either boron- or Grignard reagents proceed through similar mechanisms, in which the nucleophile is not directly involved in the enantiodetermining step; see ref 13a.
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15. When the coupling reaction was performed using $FeCl_2$/(*R,R*)-QuinoxP* (5 mol%) instead of a mixture of $FeCl_2$ (5 mol%) and (*R,R*)-QuinoxP* (10 mol%), the reaction proceeded quantitatively to provide the product with 79:21 er, which is almost identical to that obtained under optimal conditions. Therefore, we concluded that (*R*,*R*)-QuinoxP* is coordinated to iron in 1:1 ratio.
16. Based on our previous mechanistic study, complex **C** is the predominant iron species in the reaction mixture.
17. In the absence of chiral ligands, the background coupling reaction proceeded rapidly, with the racemic product obtained in 98% yield after 1 h.
18. Since we have already reported that alkenyl borates can participate in iron-catalyzed coupling of alkyl halides,[9c] the present method could be applied to the enantioselective installation of alkenyl units.

