Iron-Catalyzed Enantioselective Cross-Coupling Reactions of α-Chloroesters with Aryl Grignard Reagents

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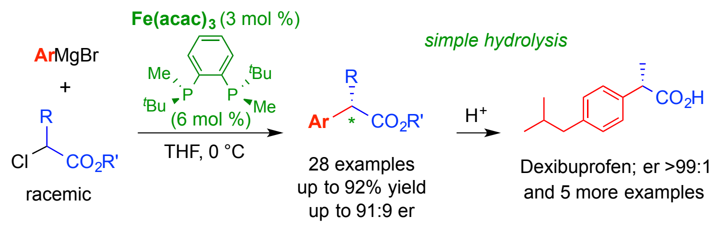
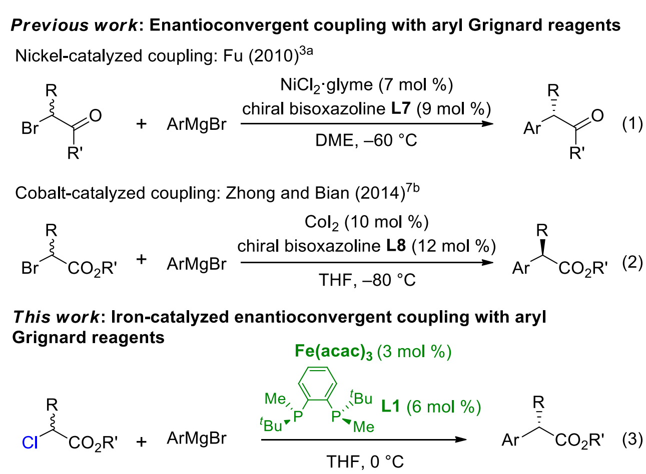
ABSTRACT: The first iron-catalyzed enantioselective cross-coupling reaction between an organometallic compound and an organic electrophile is reported. Synthetically versatile racemic α-chloro and α-bromoalkanoates were coupled with aryl Grignard reagents in the presence of catalytic amounts of an iron salt and a chiral bisphosphine ligand, giving the products in high yields with acceptable and synthetically useful enantioselectivities (er up to 91:9). The produced α-arylalkanoates were readily converted to the corresponding α-arylalkanoic acids with high optical enrichment (er up to >99:1) via simple deprotections/recrystallizations. The results of radical probe experiments are consistent with a mechanism that involves the formation of an alkyl radical intermediate, which undergoes subsequent enantioconvergent arylation. The developed asymmetric coupling offers facile and practical access to various chiral α–arylalkanoic acid derivatives, which are of significant pharmaceutical importance.



INTRODUCTION

Transition-metal-catalyzed enantioselective cross-coupling reactions are powerful tools in the asymmetric synthesis of functional chiral molecules.[1] Recent progress in the cross coupling of various alkyl halides[2] has led to the development of a new class of enantioconvergent cross-coupling reactions, which enable the construction of various molecular frameworks and the catalytic installation of asymmetric carbon centers in one operation from racemic substrates. During the past decade, significant success has been achieved by Fu and coworkers using nickel catalysts (e.g. eq 1).[3] However, despite the rapid and notable development of iron,[4] cobalt,[5] and copper[6] catalysts for the coupling reactions of alkyl halides, the viability of these metal catalysts in the enantioconvergent cross coupling of alkyl halides remains virtually unexplored; only one example of a Co-catalyzed asymmetric cross coupling between α-bromoesters and aryl Grignard reagents has been reported recently (eq 2).[7] In particular, iron has never been used in the catalytic, enantioselective coupling of organometallic compounds,[8] while its toxicologically benign nature and cost-effectiveness present clear practical advantages in the production of optically active fine chemicals, such as pharmaceutical and agricultural compounds.

In line with our research regarding the precise control of iron catalysis in C–C bond formation,[8b,9] we present the first example of iron-catalyzed enantioselective cross coupling facilitated by a commercially available P-chiral bisphosphine ligand, BenzP*.[10] Specifically, synthetically versatile racemic α-chloroalkanoates were cross coupled with aryl Grignard reagents to afford optically active α-arylalkanoates (eq 3)



and the related alkanoic acids, upon simple deprotection, which are of particular pharmaceutical and biological importance as nonsteroidal anti-inflammatory analgesics or cyclooxygenase inhibitors.[11]

RESULTS AND DISCUSSION

Asymmetric Cross-Coupling Reactions of α-Haloalkanoates with Grignard Reagents. We began our study by exploring effective chiral ligands and conditions for the coupling of *tert*-butyl α-bromopropionate **1a** with PhMgBr **2a** in the presence of catalytic amounts of $Fe(acac)_3$ and a ligand (scheme in Table 1). Based on our previous success in controlling iron-catalyzed cross-coupling reactions using the SciOPP ligand,[9e] we examined various chiral bisphosphine ligands, and observed a certain level of chiral induction when using (*R*,*R*)-QuinoxP* **L2** (up to 84:16 er, Table 1, entries 1–9). The coupling reaction proceeded in the temperature range −40 to 40 °C, to give the desired product; the optimal selectivity (83:17 er) was observed at both 0 and −40 °C (entries 2 and 3). The choice of the solvent was critical in this reaction: ethereal solvents and toluene generally afforded the coupling products with good selectivities (74:26–84:16 er; entries 2 and 4–7); however, the use of *N*,*N*′-dimethylpropyleneurea (DMPU) and *N*-methylpyrrolidinone (NMP) as solvents resulted in low yields with low er, suggesting that these strongly coordinating solvents displace the chiral ligands from iron centers, facilitating the formation of ferrate species[4d] (entries 8 and 9).

Chart 1. α-Haloalkanoates

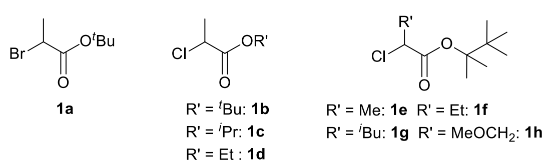


Chart 2. SciOPP and Examined Chiral Ligands

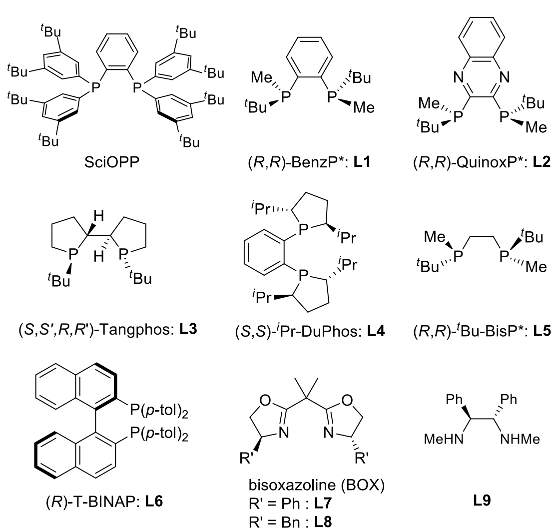
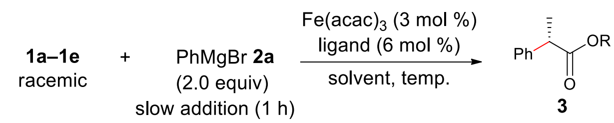


Table 1. Screening of Reaction Conditions for Iron-Catalyzed Enantioselective Cross Coupling of 1a–1e with PhMgBr (2a) [a]



entry	1	ligand	solvent	temp (°C)	%yield[b]	er[c] (config.)
1	**1a**	**L2**	THF	40	39	78:22 (*S*)
2	**1a**	**L2**	THF	0	66	83:17 (*S*)
3	**1a**	**L2**	THF	−40	63	83:17 (*S*)
4	**1a**	**L2**	toluene	0	33	74:26 (*S*)
5	**1a**	**L2**	MTBE	0	50	81:19 (*S*)
6	**1a**	**L2**	DME	0	42	84:16 (*S*)
7	**1a**	**L2**	1,4-dioxane	0	61	80:20 (*S*)
8	**1a**	**L2**	DMPU	0	2	60:40 (*S*)
9	**1a**	**L2**	NMP	0	11	59:41 (*S*)
10	**1a**	**L1**	THF	0	91	85:15 (*S*)
11	**1a**	**L3**	THF	0	69	79:21 (*S*)
12	**1a**	**L4**	THF	0	75	62:38 (*R*)
13	**1a**	**L5**	THF	0	51	52:48 (*S*)
14	**1a**	**L6**	THF	0	39	50:50
15	**1a**	**L7**	THF	0	80	76:24 (*R*)
16	**1a**	**L8**	THF	0	78	77:23 (*R*)
17	**1a**	**L9**	THF	0	10	50:50
18	**1a**	none	THF	0	32	50:50
19	**1b**	none	THF	0	0	NA
20	**1b**	**L1**	THF	0	91	87:13 (*S*)
21	**1c**	**L1**	THF	0	75	83:17 (*S*)
22	**1d**	**L1**	THF	0	40	82:18 (*S*)
23	**1e**	**L1**	THF	0	82	90:10 (*S*)
24[d]	**1e**	**L1**	THF	0	14	58:42 (*S*)
25	**1b**	**L1**	THF	−20	62	87:13 (*S*)
26	**1b**	**L1**	THF	−40	31	78:22 (*S*)

[a]Reactions were carried out on a 0.50 mmol scale using 3 mol % $Fe(acac)_3$, 6 mol % ligand, and 2.0 equiv of PhMgBr at 0 °C. PhMgBr was slowly added over 1.0 h, using a syringe pump, unless otherwise noted. [b]GC yields obtained using undecane as an internal standard. [c]The er values were determined via chiral HPLC analysis. The absolute configurations are shown in parentheses. [d]PhMgBr was added in one portion.

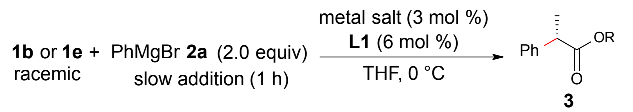
We next examined various chiral ligands, shown in Chart 2, and eventually found that the cross coupling of **1a** with **2a** proceeded in the presence of $Fe(acac)_3$/(*R*,*R*)-BenzP* (**L1**) to give the product in 91% yield, with a higher enantioselectivity of 85:15 er (entry 10).[12] The use of (*S*,*S*′,*R*,*R*′)-Tangphos (**L3**), which has a rigid aliphatic backbone and P-chirality, provided the product with comparable selectivity (79:21 er, entry 11). However, the use of (*R*,*R*)-^{t}Bu-BisP* (**L5**), which contains a flexible ethylene backbone, and (*S,S*)-^{i}Pr-DuPHOS (**L4**), a non-P-chiral ligand, afforded the products with substantially lower enantioselectivities (entries 12 and 13), suggesting that the *o*-phenylene moiety or a rigid backbone connecting the P-stereogenic centers is important. Axially chiral ligands such as (*R*)-T-BINAP (**L6**), which was effective in iron-catalyzed enantioselective carbometalation reactions,[8b] gave the racemic product (entry 14, and the Supporting Information). Nitrogen-containing ligands such as **L7**, **L8**, and **L9** showed moderate or no chiral induction in the iron-catalyzed coupling, although these ligands are reported to achieve high enantioselectivities in nickel-[3a,k] or cobalt-catalyzed[7b] cross-coupling reactions (entries 15–17). Background, non-stereoselective arylation of **1a** was observed in the absence of chiral ligands (entry 18).[9d]

When chloropropionate **1b** was used instead of **1a**, a slightly higher enantioselectivity was observed under the same reaction conditions (87:13 er, entry 20) because of the lack of the racemic background arylation (entry 19). Furthermore, 2,3,3-trimethylbut-2-yl 2-chloropropionate (Theptyl 2-chloropropionate; **1e**) was arylated with optimal enantioselectivity (90:10 er) in 82% yield (entry 23), but lower er and yields were observed in the coupling of the sterically less demanding isopropyl ester **1c** or ethyl ester **1d** (entries 21 and 22). As shown in entry 24, slow addition of the Grignard reagent[4f,9a,9h] was essential to achieve a high yield and enantioselectivity, and to avoid over-reduction of iron species or detachment of the formed aryl ferrate species from the chiral ligand (see the discussion regarding the time-course study described below). Again, the best er was obtained at 0 °C and no cryogenic conditions were required (entries 25 and 26).

Table 2 shows the effects of the catalyst loading and other metal salts on the enantioselective cross-coupling reaction.[12] A 1:1 ratio of iron:ligand also achieved substantial chiral induction to give the corresponding product in 80:20 er, while slightly higher yields and er were observed by using excess amounts of ligand to iron (entries 1–3). We propose that an iron species possessing one chiral ligand is capable of inducing enantioselectivity (see also non-linear effect in mechanistic considerations). The catalyst loading affected the chemical yield, but not the enantioselectivity, in the presence of a 1:2 ratio of iron:ligand (entries 1, 4, and 5). Full conversion of **1e** and a high yield with good enantioselectivity was obtained using 3 mol% of $Fe(acac)_3$ and 6 mol% of (*R,R*)-BenzP* (entry 6). $Co(acac)_3$ gave a low yield and er (entry 7), and other transition-metal acetylacetonates did not afford the desired products under the present conditions (entries 8–10).

The data presented in Table 3 show the scope of the developed coupling reaction in the synthesis of a range of optically active α-arylalkanoic acid derivatives. The reactions of **1e** with various aryl Grignard reagents are shown in entries 1–22. Electron-rich and neutral aryl Grignard

Table 2. Effects of Catalyst Amount and Metal Salts on Enantioselective Cross Coupling[a]

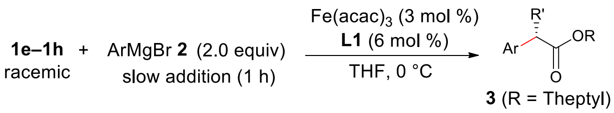


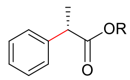
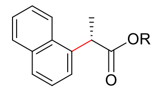
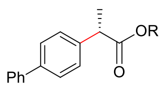
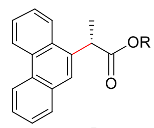
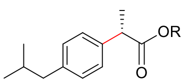
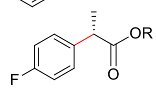
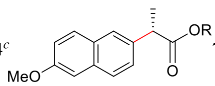
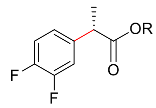
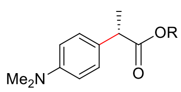
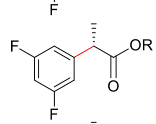
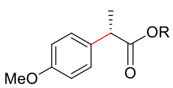
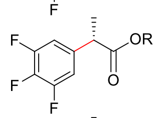
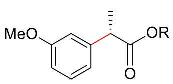
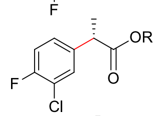
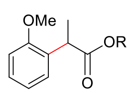
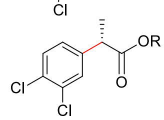
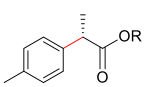
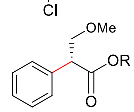
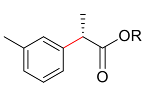
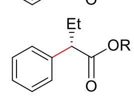
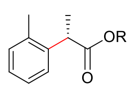
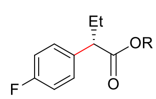
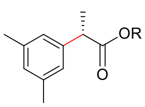
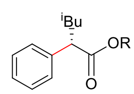
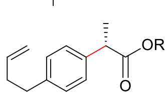
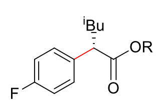
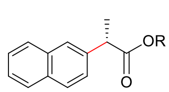
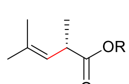
entry	1	metal salt (mol %)	L1 (mol %)	%yield[b]	er[c] (config.)
1	**1b**	$Fe(acac)_3$ (3)	6	91	87:13 (*S*)
2	**1b**	$Fe(acac)_3$ (3)	3	36	80:20 (*S*)
3	**1b**	$Fe(acac)_3$ (3)	9	85	87:13 (*S*)
4	**1b**	$Fe(acac)_3$ (1)	2	65	87:13 (*S*)
5	**1b**	$Fe(acac)_3$ (5)	10	89	87:13 (*S*)
6	**1e**	$Fe(acac)_3$ (3)	6	82	90:10 (*S*)
7	**1e**	$Co(acac)_3$ (3)	6	49	68:32 (*S*)
8	**1e**	$Ni(acac)_2$ (3)	6	0	NA
9	**1e**	$Cu(acac)_2$ (3)	6	0	NA
10	**1e**	$Pd(acac)_2$ (3)	6	0	NA

[a]Reactions were carried out on a 0.50 mmol scale using 3 mol % metal salt, 6 mol % ligand, and 2.0 equiv of PhMgBr at 0 °C. PhMgBr was slowly added over 1.0 h, using a syringe pump. [b]GC yields obtained using undecane as an internal standard. [c]The er values were determined via chiral HPLC analysis. The absolute configurations are shown in parentheses.

reagents reacted to give the desired products in high yields with adequate enantioselectivities (entries 1–7, and 9–14). A terminal olefin moiety, which often undergoes isomerization to an internal olefin under transition-metal catalysis,[13] remained intact under the present conditions (entry 13). *Ortho*-substituted aryl Grignard reagents reacted slowly (entries 8, 11, and 15), while the use of 9-phenanthryl Grignard reagent resulted in a good yield and reasonable selectivity (entry 16). As in entries 17–22, electron-deficient aryl Grignard reagents reacted to give coupling products in relatively high er of ca. 9:1 and mostly in good yield with the exception of 3,4,5-trifluorophenyl Grignard reagent (25 % yield). Although chloroarenes are known to react with Grignard reagents via iron catalysis, a chlorinated aryl group was installed with the chloro group remaining intact (entries 21 and 22).[4c, 14] Theptyl 2-chlorobutyrate and 4-methyl-2-chloropentanoate (**1f** and **1g**) were cross-coupled to afford the products in good yields and with adequate er, especially when a 4-fluorophenyl Grignard reagent was employed (entries 24–27). The use of heteroaromatic Grignard reagents such as 2-thienyl- and 3-pyridylmagnesium bromide did not result in the formation of cross-coupled products under the present conditions. The use of an alkenyl Grignard reagent furnished the corresponding α-chiral β,γ-unsaturated ester in 52% yield with 91:9 er (entry 28).

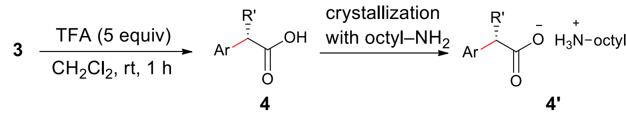
Table 3. Scope of Iron-Catalyzed Enantioselective Coupling of α-Chloroalkanoates[a]

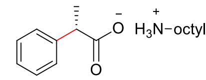
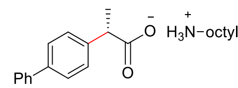
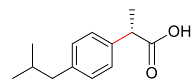
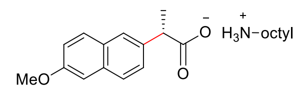
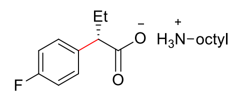
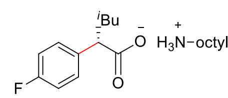


entry	product	% yield (er)[b]	entry	product	% yield (er)[b]
1		82 (90:10)	15		31 (58:42)
2[c]		90 (86:14)	16		81 (74:26)
3[c]		75 (87:13)	17		87 (91:9)
4[c]		79 (87:13)	18		83 (91:9)
5		78 (88:12)	19		89 (90:10)
6		78 (88:12)	20		25 (90:10)
7		70 (89:11)	21		83 (91:9)
8		0 (NA)	22		88 (90:10)
9		89 (87:13)	23		31 (77:23)
10		84 (88:12)	24		68 (88:12)
11		38 (84:16)	25		69 (90:10)
12		74 (89:11)	26		38 (74:26)
13		92 (86:14)	27		72 (91:9)
14		90 (88:12)	28		52 (91:9)

[a]Reactions were carried out on a 0.50–1.0 mmol scale using 3 mol % $Fe(acac)_3$ and 6 mol % ligand **L1** unless otherwise noted. ArMgBr was slowly added over 1.0 h. [b]The er values were determined via chiral HPLC analysis. Absolute configurations were inferred from the optical rotation by comparison with the know compounds (see the Supporting Information). [c]3.0 mmol scale.

Table 4. Enantioenrichment of Cross-Coupling Product after Hydrolysis[a]



entry	product (major enantiomer)	% yield (er)[b]
1		72 (>99:1)
2		72 (>99:1)
3		65 (>99:1)
4		74 (93:7)
5		46 (97:3)
6		75 (94:6)

[a]Reactions were carried out on a 2 mmol scale. [b]The er values were determined via chiral HPLC analysis.

As shown in Table 4, the obtained cross-coupling products were readily deprotected under acidic conditions without any concomitant decrease in optical purity. Furthermore, the resulting 2-arylpropionic acids were enantioenriched by co-crystallization with octylamine; (*S*)-2-arylpropionic acids, including dexibuprofen and naproxen,[15] were obtained in optically pure or highly enriched forms (entries 1–4). 2-Arylbutyric acid and 2-aryl-4-methylpentanoic acid were also obtained in optically active forms using this method (entries 5 and 6).

Mechanistic Considerations. In order to gain insights into the nature of the present cross-coupling reaction, we conducted a set of elementary mechanistic studies. Results of the time-course analysis of the cross-coupling reaction of **1e** and PhMgBr (**2a**) under the standard conditions are shown in Figure 1. No reaction of **1e** was observed during addition of the first 0.12 equivalents [i.e., 4 equivalents with respect to $Fe(acac)_3$] of PhMgBr, and biphenyl was obtained in 1% yield as the sole product, corresponding to the partial reduction of $Fe(acac)_3$ to an iron(II) species[16,17] prior to the commencement of the cross-coupling reaction. Following the addition of more PhMgBr, the coupling reaction initiated and the conversion of the substrate to the corresponding coupling product, **3**, was observed. The steric hindrance caused by the BenzP* ligand (**L1**), along with the limited

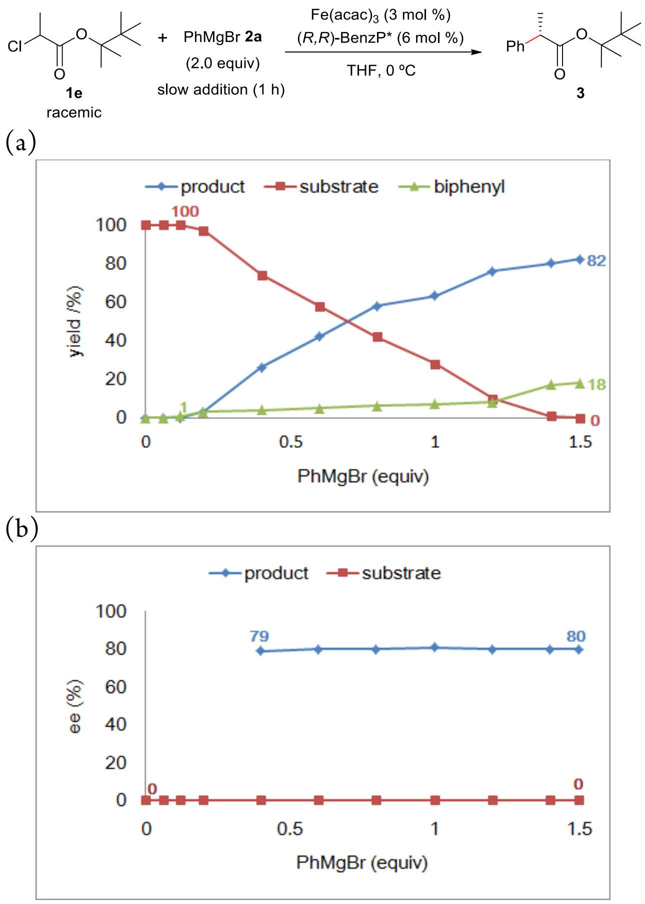


Figure 1. GC and HPLC traces of cross-coupling reaction of ***1e*** **with PhMgBr (*2a*): (a) red, blue, and green lines show recovery of substrate 1e, yield of product** ***3*****, and yield of biphenyl, respectively. (b) Red and blue lines show enantiomeric excesses of 1e and product** ***3*****, respectively.**

concentration of the slowly added Grignard reagent possibly suppressed the further reduction of the iron(II) species to iron(I) or iron(0).[18, 19] During the course of the cross-coupling reaction, no kinetic resolution of racemic **1e** was detected and the enantioselectivity of product **3** remained constant, suggesting the selectivity determining step is the C–C bond forming reaction (Figure 1, b).

The enantioselectivity of product **3** was found to be directly proportional to the enantiomeric excess of the chiral ligand and non-linear effects (NLEs)[20] in the chiral induction were not observed (Figure 2). This result supports the conclusion that the enantioselectiviy is determined under the influence of a chiral phosphine ligand that coordinates to an iron center, which was also suggested by the effective chiral induction observed in the presence of a 1:1 ratio of **L1** and $Fe(acac)_3$ (Table 2, entry 2).

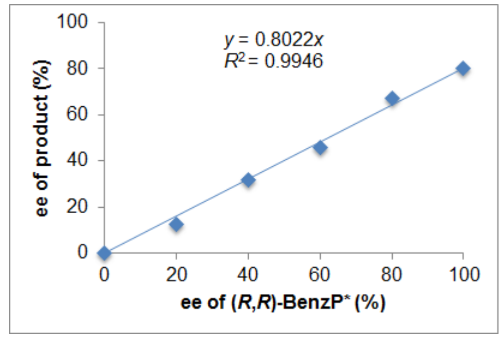
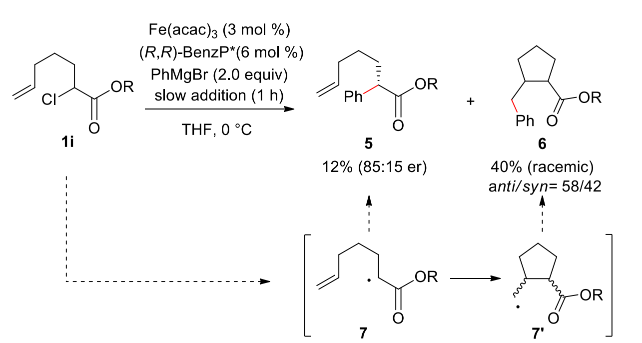


Figure 2. Dependence of enantiomeric excess of product ***3*** **on that of (*R*,*R*)-BenzP*.**

The use of radical probes provided more detailed mechanistic insights into the developed coupling reaction. As shown in Scheme 1, an α-chloroalkanoate with a terminal alkenic moiety, **1i**, reacted with PhMgBr to afford a mixture of direct arylation (uncyclized) product **5** and diastereomers of cyclized product **6**, consistent with the formation of alkyl radical intermediate from **1i** as previously proposed for racemic iron-catalyzed cross-coupling reactions.[9a–e] The radical probe reaction with various catalyst loadings of $Fe(acac)_3$ and **L1** (Figure 3) resulted in the observation of a first order relationship between the ratio of **5**/**6** and the catalyst loading. This supports the possibility that once formed, the alkyl radical intermediate escapes from the solvent cage and undergoes the sequential cyclization/arylation or direct arylation with an aryliron species which is different from the one that reacts to generate the alkyl radical intermediate.[3h,21]

It should be noted that product **5** was obtained enantioselectively (85:15 er), whereas **6** was obtained as a racemic mixture of diastereomers. This observation indicates that the cyclization reaction (**7** to **7'**) proceeded in the outer-sphere of the chiral environment created by **L1**, supporting the *out-of-cage* mechanism.[22] This result is consistent with the enantioconvergent arylation proceeding via an alkyl radical intermediate as reported for Ni-catalyzed enantioconvergent cross-coupling reactions of α-halo sulfonamides and sulfones.[3h,j]

Scheme 1. Cross-Coupling Reaction Using Radical Probe Substrate (1i; R = Theptyl)



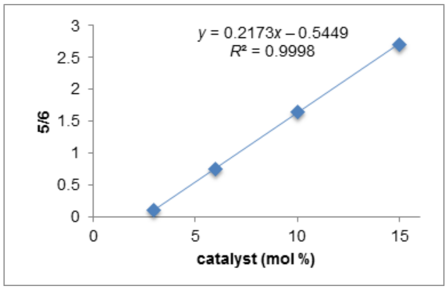


Figure 3. Dependence of ratio of uncyclized product 5 to cyclized product 6 on iron catalyst loading.

Figure 4 shows a plausible mechanism that is in good agreement with the present and previous experimental observations. The catalytic cycle starts from divalent iron species **A**, which is generated from the partial reduction of $Fe(acac)_3$ in the presence of **L1,** the limited concentration of the Grignard reagent and an excess amount of the α-haloester substrate**.** This species **A** abstracts a halogen from the substrate to generate alkyl radical intermediate **C** and iron species **B**. We proposed previously the mechanism depicted in Cycle 1, where arylation of alkyl radical **C** takes place with the aryl group of **B** in the solvent cage to give the arylation product and an iron complex **D**, which undergoes transmetalation with ArMgBr to regenerate **A** (in-cage mechanism).[9b,c,e] However, the observation of the first order relationship between the ratio of **5**/**6** and the catalyst loading is not consistent with this cycle. We therefore favor an alternative process based on a bimetallic mechanism.[19d,21] Cycle 2 shows the favorable out-of-cage mechanism, in which alkyl radical intermediate **C** escapes from the solvent cage to react with another divalent iron(II) species **A** to form the coupling product, possibly by forming iron(I) species **E**, which has one bulky **L1** ligand.[18a,b] Comproportionation of complexes **B** and **E** forms iron(II) species **A** and **D** or halogen abstraction of **E** from the α-haloester forms **D** and radical intermediate **C**, which may participate in a chain reaction process.[21c] Although we cannot identify the predominant pathway of the generation of alkyl radical intermediate **C**, the arylation of the radical intermediate takes place with iron(II) species **A** possessing chiral ligand **L1**, and hence, in an enantioselective manner.

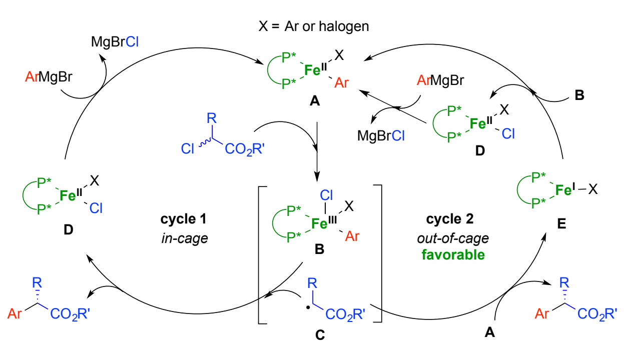


Figure 4. Possible catalytic cycles.

CONCLUSION

In summary, we developed the first iron-catalyzed enantioselective cross-coupling reaction, which provides facile access to optically active α-arylalkanoic acid derivatives from racemic α-haloesters and a range of aryl Grignard reagents. The use of rigid P-chiral bisphosphine ligands, such as BenzP*, was critical to achieve high reactivity and substantial chiral induction. Moreover, the developed protocol can be considered expedient and practical; a simple mixture of the commercially available BenzP* and easy-to-handle $Fe(acac)_3$ catalyzed the arylation reaction under mild conditions. Although there is still room for improvement in the enantioselectivity, we hope that the preliminary findings described here will advance the development of enantioselective carbon–carbon bond forming reactions under iron catalysis. Such reactions show promise for the sustainable synthesis and production of chiral functional molecules such as pharmaceuticals and agrochemicals that will continuously support our society.

EXPERIMENTAL SECTION

Typical Procedure for Enantioselective Cross Coupling

ArMgBr (0.50–1.0 M solution in THF, 2.0 equiv) was slowly added over 60 min, using a syringe pump, to a THF solution (1.0 mL) of $Fe(acac)_3$ (5.3 mg, 3 mol %), (*R*,*R*)-BenzP* (8.5 mg, 6 mol %), and 2,3,3-trimethylbut-2-yl 2-chloroalkanoate (0.50 mmol) at 0 °C. After stirring at that temperature for 10 min, the resulting mixture was quenched with a 1.0 M aqueous solution (1.0 mL) of hydrochloric acid and extracted with MTBE (3.0 mL × 3). The organic layer was dried over Na_2SO_4, evaporated in vacuo, and the residue was purified by silica-gel column chromatography and gel-permeation chromatography if necessary.

Representative Procedure for Deprotection and Crystallization: Enantioenrichment of Dexibuprofen

TFA (0.69 mL, 5.0 equiv) was added dropwise to a CH_2Cl_2 solution (5.5 mL) of 2,3,3-trimethylbut-2-yl (*S*)-2-[4-(2-methylpropyl)phenyl]propionate (550 mg, 1.8 mmol) at room temperature, and the mixture was stirred at that temperature for 1 h. A crude white solid (398 mg, quantitative) was obtained after removing the volatile solvents under reduced pressure. CH_3CN (27.5 mL) and octylamine (299 μL, 1.0 equiv) were added to the crude solid, and the mixture was heated to 60 °C to dissolve the solid entirely. The mixture was allowed to cool to room temperature, with stirring, and white crystals formed. After stirring for 1 h, the white crystals were collected by filtration, washed with CH_3CN (1.7 mL), and dried under reduced pressure (454 mg, 75%, 92:8 er). Recrystallization from

CH_3CN (27.5 mL) furnished optically pure crystals (394 mg, 65%, >99:1 er).

ASSOCIATED CONTENT

Supporting Information

Experimental details, procedures, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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