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Communication

A Cobalt-Catalyzed Enantioconvergent Radical Negishi C(sp^3)–C(sp^2) Cross-Coupling with Chiral Multidentate *N,N,P*-Ligand

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Cite This: *Organometallics* 2021, 40, 2215–2219

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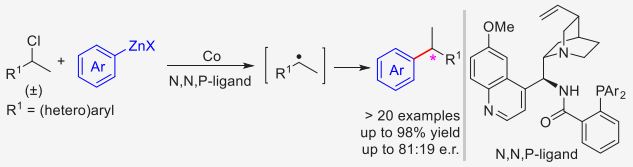
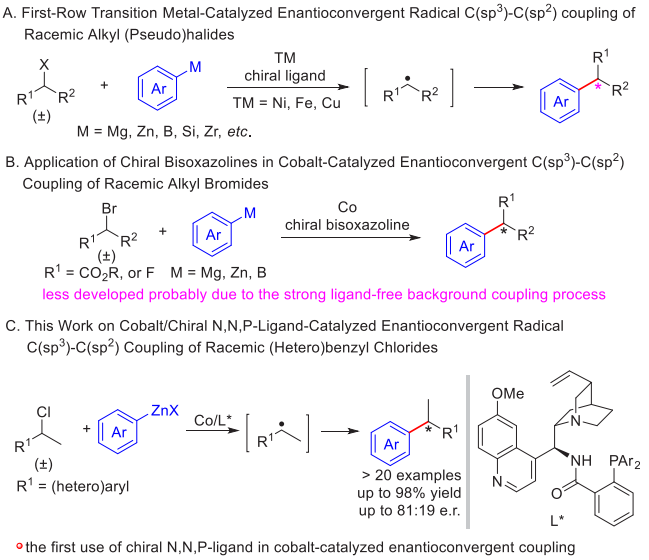
ABSTRACT: A cobalt-catalyzed enantioconvergent radical Negishi C(sp^3)–C(sp^2) cross-coupling of racemic benzyl chlorides with arylzinc reagents has been developed in good yield with moderate enantioselectivities. This strategy provides an expedient access toward a range of enantioenriched 1,1-diarylmethanes. Key to this discovery is the utilization of a chiral multidentate anionic *N,N,P*-ligand to strongly coordinate with the cobalt catalyst and tune its chiral environment, thus achieving the enantiocontrol over the highly reactive prochiral alkyl radical species.



Transition metal catalyzed enantioconvergent C(sp^3)–C(sp^2) cross-coupling of racemic alkyl electrophiles and organometallic reagents represents a powerful tool in the synthesis of enantioenriched three-dimensional molecules.[1] Recent emphasis on sustainability and economy has led to the use of an earth-abundant transition metal catalyst as a new horizon in the cross-coupling reactions.[2] In this context, the first-row transition metals (Ni, Co, Fe, and Cu) have high-spin electronic configurations and easily convert racemic alkyl electrophiles to the prochiral alkyl radical species via a single-electron transfer process, thus providing a general mechanism for enantioconvergence.[2] As such, tremendous progress has been made by Fu and others in developing chiral nickel catalysis to realize the enantioconvergent C(sp^3)–C(sp^2) cross-coupling of racemic alkyl electrophiles in the past two decades (Scheme 1).[3,4] Very recently, the chiral iron and copper catalysis have been designed for such transformations.[5−7] Owing to the earth-abundant, low-cost, and nontoxic nature of cobalt catalyst, it has been widely used in the cross-coupling of alkyl electrophiles with organometallic reagents in the past three decades.[8,9] However, the enantioconvergent cross-coupling has been much less developed. The main reason might be that the cobalt-catalyzed C(sp^3)–C cross-coupling occurs easily even in the absence of any ligand, and this background reaction would thwart the development of a chiral ligand-induced enantioconvergent process.[8b,10] It is thus a challenging task to design suitable chiral ligands to promote the enantioconvergent cross-coupling. Until now, only limited examples have been demonstrated by using chiral bisoxazoline ligands in the enantioconvergent C(sp^3)–C(sp^2) cross-coupling of racemic α-bromo esters or fluorinated benzyl bromides since the seminal work of Zhong and Bian.[11] Therefore, the development of new chiral ligands to tune the chiral environment of cobalt catalyst and realize the enantioconvergent cross-coupling of more alkyl halides is highly desirable.

Scheme 1. Design of Chiral Ligand in Cobalt-Catalyzed Enantioconvergent C(sp^3)–C(sp^2) Cross-Coupling



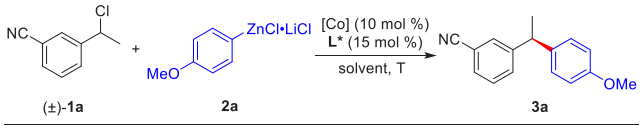
Special Issue: Organometallic Solutions to Challenges in Cross-Coupling

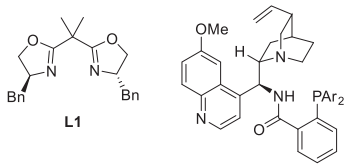
Received: March 29, 2021
Published: May 14, 2021

Our group has focused on designing new chiral anionic ligands to develop the first-row transition metal catalyzed enantioconvergent C(sp^3)−C cross-coupling of racemic alkyl halides with diverse nucleophiles.[6] During this course, we found that a chiral multidentate anionic *N,N,P*-ligand could tune the chiral environment of the copper catalyst to realize the enantiocontrol over the in situ generated prochiral alkyl radical species.[6] We speculated that such a multidentate anionic ligand might coordinate strongly with the cobalt catalyst to realize the enantioconvergent C(sp^3)−C cross-coupling of racemic alkyl halides. The success of this strategy would open new vistas for the development of cobalt-catalyzed enantioconvergent cross-coupling. Given the importance of chiral 1,1-diarylalkanes in drug discovery,[12] we herein report the first application of quinine-derived *N,N,P*-ligand in the cobalt-catalyzed enantioconvergent Negishi C(sp^3)−C(sp^2) cross-coupling of racemic benzyl chlorides with arylzinc reagents. Notably, this is also the first time that the more stable alkyl chlorides rather than bromides,[11] are used in the cobalt-catalyzed enantioconvergent C(sp^3)−C(sp^2) cross-coupling.

In order to verify our hypothesis, we first investigated the cross-coupling between racemic 3-(1-chloroethyl)benzonitrile **1a** and 4-methoxyarylzinc reagent **2a** in the presence of catalytic amount of $CoBr_2$. The initial attempts showed that the reaction proceeded smoothly to afford coupling product **3a** without the addition of any ligand in THF even at 0 °C, which supported the background Negishi cross-coupling (Table 1, entry 1). We then lowered down the reaction temperature to −20 °C and found that the background reaction could be inhibited (Table 1, entry 2). As such, we examined chiral bisoxazoline ligand **L1** which was previously utilized in cobalt-catalyzed asymmetric cross-coupling[11] and found that **L1** was not effective for the reaction of benzyl chlorides **1a**. We then investigated the effect of our developed multidentate electron-rich *N,N,P*-ligand **L2**,[6b] and found that it not only greatly promoted the reaction but also afforded the coupling product **3a** in 50% yield with an enantiomeric ratio (e.r.) of 77:23 (Table 1, entry 4). Encouraged by this result, we systematically screened the reaction parameters. We first modified the structure of ligands with different steric and electronic properties at different positions of the *P*-aryl ring (Table 1, entries 5−11). The screening results indicated that the electron-withdrawing substituents on 3,5-position of the *P*-aryl ring (**L3**) provided **3a** with a lower e.r. than the electron-donating groups (**L4**), albeit with a similar yield (Table 1, entries 5 and 6). While the reaction with phenyl-substituted ligand **L5** provided **3a** with a comparable enantioselectivity, it provided the product in a much lower yield than that of **L4** (Table 1, entry 7). The electron-donating substituents on the *para* position of the *P*-aryl ring (**L6**) gave **3a** in 65% yield with a 79:21 e.r. (Table 1, entry 8). Although the *para* phenyl-substituted ligand **L7** gave a similar yield with **L6**, the enantiomeric ratio is lower (Table 1, entry 9). The *ortho*-substituent of the *P*-aryl ring (**L8**) has a deleterious effect on the reaction efficiency, suggesting that the steric environment on the cobalt is crucial to the cross-coupling reaction (Table 1, entry 10). The reaction with a naphthyl-substituted ligand **L9** gave a poor result as well (Table 1, entry 11). Considering the reaction efficiency and the enantioselectivity, we chose **L6** as the best ligand for the subsequent reaction optimization. The results showed that **3a** was generated in 90% yield with a 77:23 e.r. at 0 °C, and this retention of e.r. revealed that the chiral

Table 1. Screening of Reaction Conditions[a]





L2, Ar = Ph
L3, Ar = 3,5-$(CF_3)_2C_6H_3$
L4, Ar = 3,5-$(MeO)_2C_6H_3$
L5, Ar = 3,5-$Ph_2C_6H_3$
L6, Ar = 4-$MeOC_6H_4$
L7, Ar = 4-PhC_6H_4
L8, Ar = 2,4,6-$Me_3C_6H_4$
L9, Ar = 2-naphthyl

entry	[Co]	L*	solvent	*T*/°C	yield[b]	e.r.[c]
1	$CoBr_2$		THF	0	75%	
2	$CoBr_2$		THF	−20	0%	
3	$CoBr_2$	**L1**	THF	−20	15%	50:50
4	$CoBr_2$	**L2**	THF	−20	50%	77:23
5	$CoBr_2$	**L3**	THF	−20	41%	54:46
6	$CoBr_2$	**L4**	THF	−20	35%	82:18
7	$CoBr_2$	**L5**	THF	−20	19%	80:20
8	$CoBr_2$	**L6**	THF	−20	65%	79:21
9	$CoBr_2$	**L7**	THF	−20	63%	70:30
10	$CoBr_2$	**L8**	THF	−20	trace	
11	$CoBr_2$	**L9**	THF	−20	21%	57:43
12	$CoBr_2$	**L6**	THF	0	90%	77:23
13	$CoBr_2$	**L6**	THF	rt	45%	50:50
14	Co(salen)	**L6**	THF	0	95%	76:24
15	$Co(PPh_3)_2Cl_2$	**L6**	THF	0	93%	75:25
16	**$CoBr_2$**	**L6**	**toluene**	**0**	**99%**	75:25
17	$CoBr_2$	**L6**	DCM	0	76%	74:26
18	$CoBr_2$	**L6**	DMF	0	87%	69:31
19	$CoBr_2$	**L6**	EtOAc	0	98%	74:26

[a]Reaction conditions: (±)-**1a** (0.05 mmol), **2a** (0.15 mmol), [Co] (10 mol %), and **L*** (15 mol %), in solvent (0.50 mL) for 72 h under argon. [b]Yield was based on ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard. [c]The e.r. values were determined by HPLC analysis.

N,N,P-ligand/cobalt catalysis could suppress the background reaction and promote the enantioconvergent process (Table 1, entries 1 and 12). However, the reaction afforded **3a** with no e.r. at room temperature (Table 1, entry 13). Further screening of different cobalt salts and solvents showed that the reaction provided the best yield with a slightly decreased e.r. in toluene (Table 1, entries 14−19). Finally, we identified the optimal reaction conditions as follows: The reaction of **1a** and **2a** in a molar ratio of 1:3 in the presence of 10 mol % of $CoBr_2$ and 15 mol % of **L6** in toluene afforded **3a** in 99% yield, with 75:25 e.r. at 0 °C.

With the optimal reaction conditions established, we then examined the scope of benzylic chlorides (Table 2). The reaction of benzyl chloride without any substituent on the aryl ring provided **3b** in 61% yield with 71.5:28.5 e.r.. The chlorine-substituted substrates both afforded desired products **3c** and **3d** in good yields, and the *meta*-substituted one gave a higher yield and enantioselectivity than the *para*-substituted one. The fluorine-substituted substrates provided **3e** and **3f** in a similar yield and e.r. The substrate with a trifluoromethyl group provided **3g** with the best enantioselectivity (80:20 e.r.). To investigate the functionality tolerance, we studied the cross-coupling reaction of carbonyl-substituted benzyl chloride, the reaction delivered product **3h** as well, albeit with a lower yield (40%). In addition, the substrates with an ester substituent

https://doi.org/10.1021/acs.organomet.1c00190
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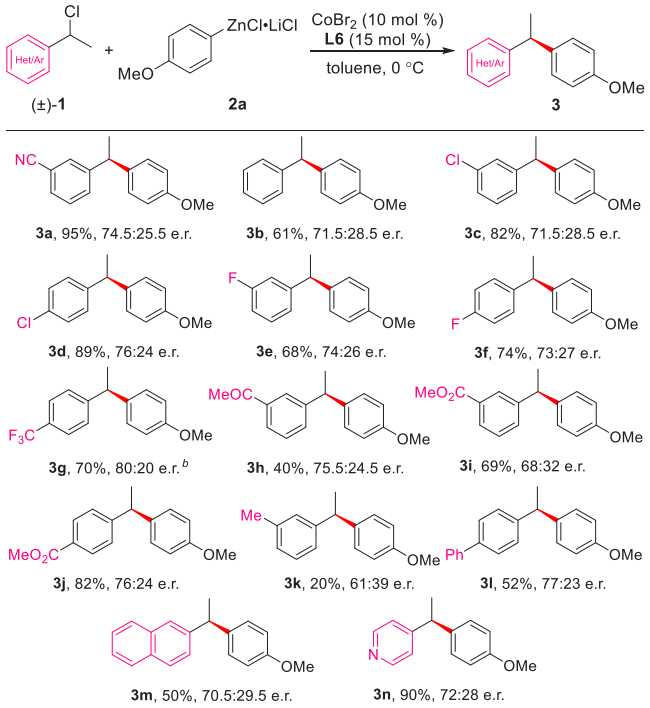
Table 2. Scope of Benzyl Chlorides[a]

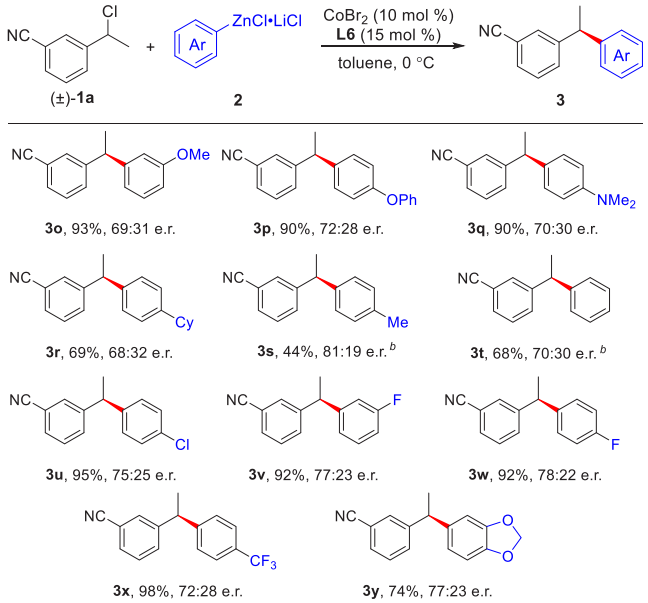


[a]Reaction conditions: (±)-**1** (0.20 mmol), **2a** (0.60 mmol), $CoBr_2$ (10 mol %), and **L6** (15 mol %), in toluene (2.0 mL) for 72 h under argon. Isolated yields were based on **1** and e.r. values were determined by HPLC analysis. [b]THF (2.0 mL) was used as the solvent.

either at *meta* or *para* positions of the aryl ring are also suitable for the reaction to provide **3i** and **3j**. However, the substrates with an electron-donating (Me) and a phenyl group gave products **3k** and **3l** with a poor yield and enantioselectivity. The absolute configuration of **3l** was determined to be *R* by comparing its HPLC spectrum and optical rotation with those reported in literature,[13] and the stereochemistry of other products was determined in reference to **3l**. Moreover, the naphthyl-substituted benzyl chloride was also a viable substrate to furnish desired product **3m** in 50% yield with 70.5:29.5 e.r. In addition, we investigated the possibility of introducing a heterocycle to the 1,1-diarylalkane skeleton and found that the substrate with a pyridyl group was applicable to the current strategy to afford **3n** in 90% yield with 72:28 e.r..

Encouraged by the above results, we next evaluated the scope of arylzinc reagents (Table 3). We first investigated the effect of electron-donating groups on the aryl ring. The methoxyl group at the *meta* position of aryl ring did not affect the reaction efficiency, and the reaction provided **3o** in 93% yield, albeit with a lower e.r. than that of **3a**. Besides, the phenoxyl group was also tolerable in the reaction to generate **3p** in excellent yield with 72:28 e.r.. Furthermore, the amino-substituted arylzinc reagent reacted well to afford **3q** in 90% yield with a moderate enantioselectivity. Further investigation revealed that the alkyl-substituted arylzinc reagents reacted smoothly to provide **3r** and **3s**. In addition to the electron-donating groups, the unfunctionalized arylzinc reagent was also suitable for the reaction to deliver **3t** in 68% yield with 70:30 e.r. We then studied the influence of electron-withdrawing substituents of the arylzinc reagents on the reaction. The halogen (Cl, F) substituents are tolerated to afford **3u**–**3w** under the standard reaction conditions. More significantly, the

Table 3. Scope of Arylzinc Reagents[a]

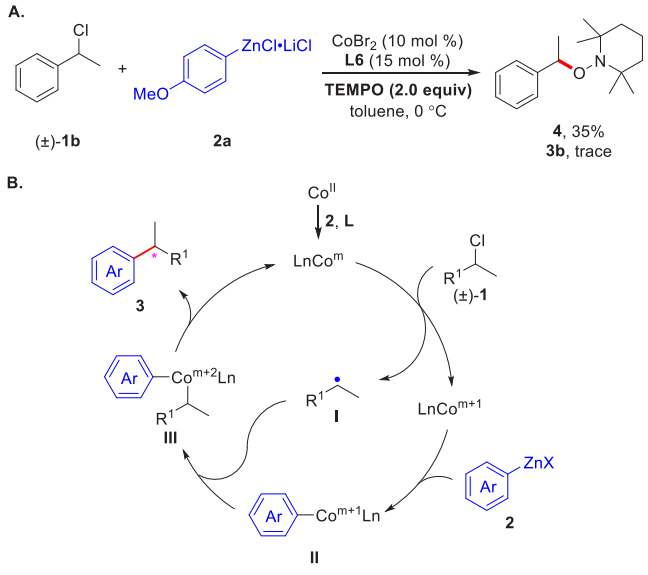


[a]Reaction conditions: (±)-**1a** (0.20 mmol), **2** (0.60 mmol), $CoBr_2$ (10 mol %), and **L6** (15 mol %), in toluene (2.0 mL) for 72 h under argon. Isolated yields were based on **1a** and e.r. values were determined by HPLC analysis. [b]THF (2.0 mL) was used as the solvent.

trifluoromethylated arylzinc reagent was amenable to the reaction to give **3x** in 98% yield with 72:28 e.r. The arylzinc reagent containing the 1,3-benzodioxole group worked as well to give desired product **3y**.

To verify the hypothesis of a radical process, we carried out the radical-inhibiting experiment with TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl). The result showed a complete inhibition of the desired cross-coupling reaction of **1b** and TEMPO-trapped product **4** was obtained in 35% yield, which supported the formation of the alkyl radical species (Scheme 2A). On the basis of the literature reports,[8d,14] we proposed a

Scheme 2. Mechanistic Study and Proposed Reaction Pathway



https://doi.org/10.1021/acs.organomet.1c00190
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plausible mechanism as shown in Scheme 2B. The precatalyst Co^{II} was first be reduced by the arylzinc reagent to the active catalytic species $LnCo^{m}$ for the initiation of the reaction. The low-valent $LnCo^{m}$ species would then undergo a single-electron transfer with the benzyl chloride **1** to generate prochiral benzyl radical **I** and the $LnCo^{m+1}$ species. A transmetalation between the $LnCo^{m+1}$ species and arylzinc reagent **2** would provide complex **II**, which subsequently recombined with prochiral benzyl radical **I** to deliver Co^{m+2} complex **III**. A final reductive elimination of complex **III** furnished coupling product **3** and regenerate the active catalyst for the next catalytic cycle.

In sum, we have developed a cobalt-catalyzed enantioconvergent radical Negishi $C(sp^3)-C(sp^2)$ cross-coupling of racemic benzyl chlorides, providing an access to enantioenriched 1,1-diarylmethanes in good yields with moderate enantioselectivities. Critical to the success was the first utilization of a chiral multidentate anionic *N*,*N*,*P*-ligand to tune the chiral environment of cobalt catalyst to achieve the enantiocontrol over the highly reactive prochiral alkyl radical species. It constitutes an important complement to the developed Co/chiral bisoxazoline catalysis, and we believe that it will open new vistas for cobalt-catalyzed enantioconvergent cross-coupling. Further designing of more robust chiral multidentate anionic ligand is still ongoing in our laboratory to realize the cobalt-catalyzed enantioconvergent cross-coupling in high enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.1c00190.

Experimental procedures and characterization of compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support is from the National Natural Science Foundation of China (21831002, 22025103, 22001109, and 22001111), Guangdong Provincial Key Laboratory of Catalysis (2020B121201002), Guangdong Innovative Program (2019BT02Y335), Guangdong Basic and Applied Basic Research Foundation (2019A1515110822), Shenzhen Special Funds (JCYJ20200109141001789), Shenzhen Key Laboratory of Small Molecule Drug Discovery and Synthesis (ZDSYS20190902093215877), SUSTech Special Fund for the Construction of High-Level Universities (G02216303), and Special Funds for the Cultivation of Guangdong College Students' Scientific and Technological Innovation.("Climbing Program" Special Funds.) (pdjh2020b0524). The authors appreciate the assistance of SUSTech Core Research Facilities.

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https://doi.org/10.1021/acs.organomet.1c00190
Organometallics 2021, 40, 2215–2219