

Palladium-Catalyzed Intramolecular Asymmetric C–H Functionalization/Cyclization Reaction of Metallocenes: An Efficient Approach toward the Synthesis of Planar Chiral Metallocene Compounds

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S Supporting Information

ABSTRACT: A palladium-catalyzed asymmetric synthesis of planar chiral metallocene compounds is reported. The reaction stereoselectively functionalized one of the *ortho* C–H bonds of Cp rings by intramolecular cyclization to form indenone derivatives in high yields with excellent enantioselectivity. The mild set of reaction conditions allowed a wide variety of chiral metallocene compounds to be synthesized with broad functional group tolerance. The influences of preinstalled chiralities on the other Cp-ring were also investigated.

Planar chiral molecules have attracted great attention these past decades since they were first predicted by Cahn, Ingold, and Prelog in 1966.¹ This class of compounds represents the most successful scaffolds for chiral ligands and catalysts for asymmetric catalysis. Examples of such planar chiral ligands and catalysts include Josiphos and Fu's catalysts etc. (Figure 1).² Additionally, applications which incorporate planar

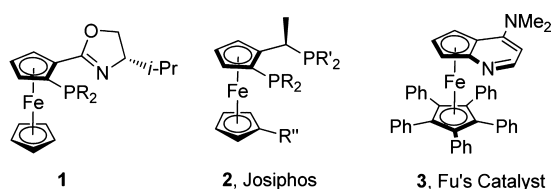


Figure 1. Representative ferrocene-based planar chiral ligands and catalyst.

chiral molecules have also appeared in biochemistry and material sciences.³ Ligands or catalysts that contain planar chiralities, in some cases combining with other chiral moieties, usually showed very unique characters.

Several approaches have been developed to access these types of chiral scaffolds. Diastereoselective synthesis is one of the most frequently used methods for preparation of planar chiral compounds. This preparation includes the use of Ugi's amine⁴ as well as the introduction and use of various of chiral auxiliaries.^{5,6} Additionally, the groups of Snieckus⁷ and Simpkins⁸ have demonstrated that "traceless" enantioselective *ortho*-directed metalation reactions of ferrocene compounds can be accomplished by using a stoichiometric amount of a

(–)-sparteine/lithium complex or chiral lithium amide, respectively.

Catalytic asymmetric approaches to the synthesis of chiral planar molecules are a desirable alternative to using chiral starting materials and/or stoichiometric amounts of chiral reagents or auxiliaries. Currently studies on the catalytic asymmetric construction of planar chiral compounds mostly focus on the desymmetrization of prochiral compounds. The groups of Uemura,⁹ Schmalz,¹⁰ Kündig,¹¹ and Richards¹² have developed palladium-catalyzed desymmetric cross-couplings of prechiral dihalogenated metallocenes with chiral ligands to discriminate between these two halogen atoms with moderate to excellent enantioselectivities. Very recently You and Gu have reported a direct oxidative Pd(II)/amino acid-catalyzed asymmetric C–H functionalization reaction that couples aminomethylferrocenes with organic boronic acids.¹³ Gold(I)-catalyzed desymmetric cyclizations of 1,3-dihydroxymethyl-2-alkynylbenzene chromium complexes have also been demonstrated to generate planar chiral molecules with high enantioselectivities.¹⁴ Additionally the Ogasawara and Takahashi group described a synthesis of planar chiral phosphoferrocenes via chiral molybdenum carbene-catalyzed ring-closing metathesis.¹⁵ However, the development of new efficient methods for the synthesis of scaffold-different planar chiral metallocenes with good functional group tolerance is still challenging and necessary.

Catalytic direct arylation of arenes is a powerful and atom economic method¹⁶ for the construction of biaryl compounds, which has caught significant attention in recent years.^{17,18} Despite tremendous advances and great efforts that have been made for enantioselective C–H activation by the groups of Yu, Cramer, and others,¹⁹ there are still only very limited studies that focused on the Pd(0)-initiated asymmetric arylation of arenes.^{19i–m} The deficit in the area reflects the great challenges in controlling both the reactivity and stereoselectivity for these transformations.

Here we report a palladium(0)-initiated catalytic asymmetric intramolecular C–H functionalization/arylation reaction to synthesize planar chiral metallocenes with high enantioselectivities. We anticipate that during the C–H functionalization step

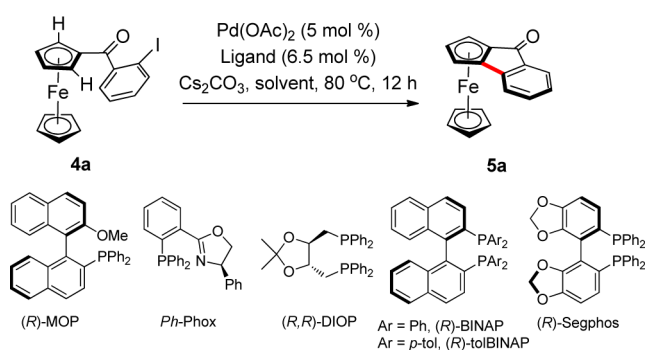
Received: January 22, 2014

Published: March 11, 2014

a chiral palladium(II)/phosphine complex would discriminate between two *ortho* C–H bonds on the Cp ring. This strategy has several advantages: (1) a variety of commercially available or readily prepared phosphine ligands are suitable for screening for Pd(0)-initiated reactions; (2) over-reacted byproducts (double cross-couplings products) could be avoided by the intramolecular cyclization process, and as a result usually high yields could be achieved.

Our initial studies commenced with the reaction of the model compound **4a**, which was readily prepared by a Friedel–Crafts acylation reaction from 2-iodobenzoyl chloride and ferrocene. With monodentate phosphine ligand (*R*)-MOP the reaction did not take place at all and starting material was recovered (Table 1, entry 1).²⁰ By the use of *P,N*-ligand *Ph*-

Table 1. Reaction Condition Optimization^a



entry	ligand	solvent	yield / % ^b	ee / % ^c
1	(<i>R</i>)-MOP	toluene	NR	–
2	<i>Ph</i> -Phox	toluene	10 ^d	<5
3	(<i>R</i>)-BINAP	toluene	74	98
4	(<i>R</i>)-tolBINAP	toluene	74	98
5	(<i>R</i>)-Segphos	toluene	85	80
6	(<i>R,R</i>)-DIOP	toluene	<5	–
7	(<i>R</i>)-BINAP	DMF	NR	–
8	(<i>R</i>)-BINAP	(ClCH_2) ₂	NR	–
9	(<i>R</i>)-BINAP	CH_3CN	NR	–
10 ^e	(<i>R</i>)-BINAP	dioxane	77	93
11 ^e	(<i>R</i>)-BINAP	toluene	85	99

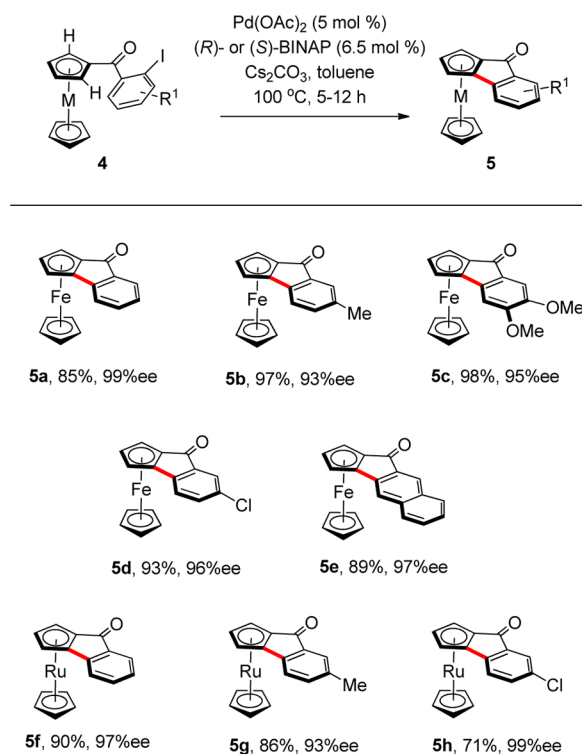
^aThe reaction was conducted with **4a** (0.10 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %), ligand (6.5 mol %) [for (*R*)-MOP, 13 mol %], Cs_2CO_3 (2.0 equiv) at 80 °C. ^bIsolated yields. ^cThe ee was determined by HPLC analysis on chiral columns. The absolute configuration of the product was not determined. ^dThere was 17% of conversion after 12 h at 100 °C. ^eThe reactions were conducted at 100 °C for 10 h.

Phox the reaction afforded 10% of isolated product **5a**, which was essentially racemic (entry 2). Fortunately, in the presence of 5 mol % $\text{Pd}(\text{OAc})_2$ and 6.5 mol % of (*R*)-BINAP full conversion was achieved and product **5a** was isolated in 74% yield with 98% ee (entry 3). Encouraged by these results, other bidentate phosphine ligands were further screened: (*R*)-tolBINAP showed promising results for this transformation in both yield and enantioselectivity (entry 4). The reaction with (*R*)-segphos delivered **5a** in decent enantioselectivity albeit the yield was increased to 85% (entry 5). It is interesting to find that tartaric acid derived bidentate phosphine (*R,R*)-DIOP was not suitable for this cyclization reaction, giving a very poor conversion (entry 6). A brief screening of the solvents revealed that DMF, 1,2-dichloroethane, and CH_3CN were not good solvents for this transformation, while the reaction in 1,4-

dioxane provided **5a** in moderate yield and good enantioselectivity (entries 7–10). Finally considering the cost and easy accessibility, BINAP was chosen as the optimal ligand. The reaction at an elevated reaction temperature (100 °C) with (*R*)-BINAP gave an increased isolated yield (85%) without loss in enantioselectivity (entry 11).²¹

On the basis of these results, the generality of this reaction was tested by the subjection of various substituted acyl metallocene compounds to the optimized reaction conditions. The reactions work well for 5-methyl or 4,5-dimethoxyl substituted iodobenzenes, affording excellent yields and enantioselectivities (Table 2, **5b** and **5c**). The aryl chloride

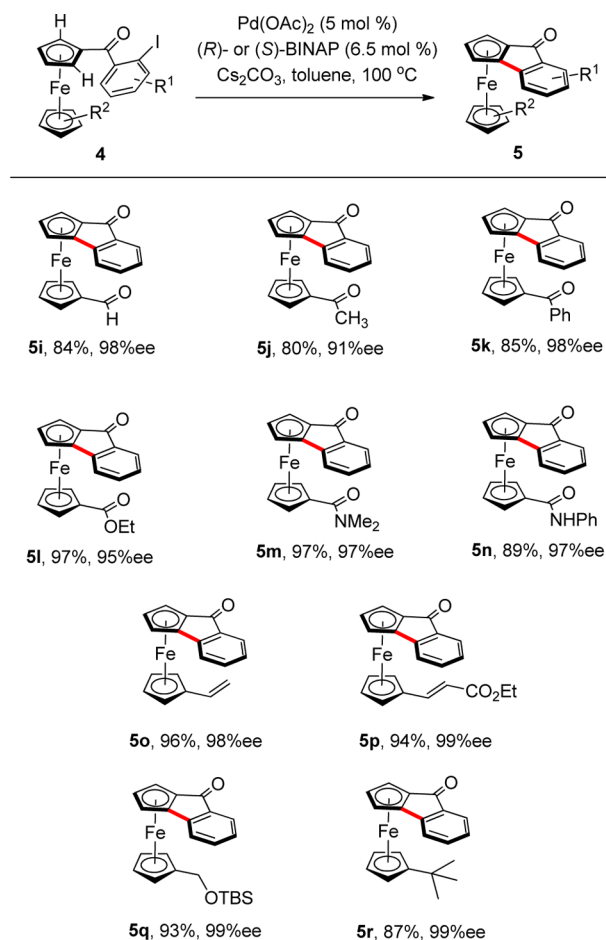
Table 2. Substrate Scope^a



^aThe reaction was conducted with **4** (0.10 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %), (*R*)- or (*S*)-BINAP (6.5 mol %), Cs_2CO_3 (2.0 equiv) at 100 °C for 5–12 h.

bond is well tolerated, which provided opportunities for further functionalization (**5d**). With 2-iodonaphthalene derivatives, the reaction performance was equally efficient, affording the corresponding product in 89% yield with 97% ee (**5e**). Notably, bis(cyclopentadienyl) ruthenium (ruthenocene) derivatives are suitable substrates, and the corresponding cyclization products are yellow or light red solids and stable enough for chromatography. For instance, under standard conditions the reactions with ruthenocenes proceeded uneventfully and gave the products with excellent enantioselectivities, albeit with relatively low yields (**5f–h**).

Compared to the traditional lithium reagent-mediated transformations, the relatively mild conditions of palladium catalysis allow a wide range of functional groups. As depicted in Table 3, substitutions on the second Cp ring could include aldehyde, ketones, carboxyl ester, and amides (Table 3, **5i–m**). Notably, the amide bearing a free N–H bond is tolerant, which did not affect the palladium catalyst by chelation (**5n**). In addition, under the current reaction conditions the terminal

Table 3. Substrate Scope^a

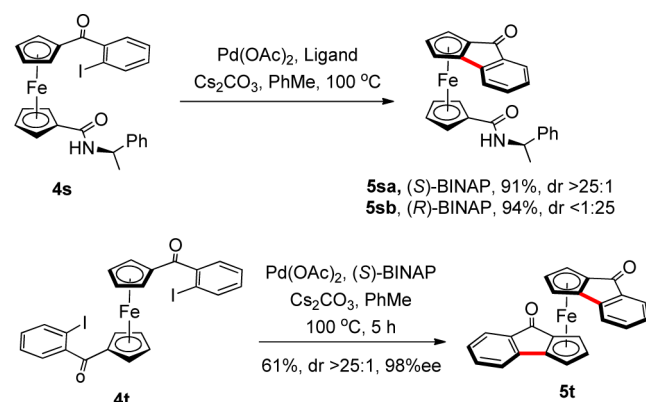
^aThe reaction was conducted with **4** (0.10–0.15 mmol), Pd(OAc)₂ (5 mol %), (R)- or (S)-BINAP (6.5 mol %), Cs₂CO₃ (2.0 equiv) at 100 °C for 5–12 h.

C=C double bond and α,β -unsaturated ester are compatible, which are conventional substrates for Pd-catalyzed Heck reactions. For instance, the reactions afforded **5o** and **5p** in excellent yields and enantiomeric excesses, and no intra- or intermolecular Heck product was detected. Ferrocenes bearing an electron-rich group, such as CH₂OTBS and *tert*-butyl, on the second Cp ring are also good substrates, which could be efficiently advanced to the desired cyclization products in excellent selectivity and yields (**5q** and **5r**).

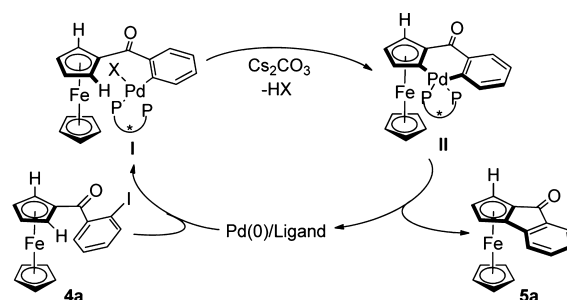
In order to discover the effects of the preinstalled chiral moieties (center and planar chiralities) on this transformation, two additional reactions were conducted (Scheme 1). The chiral amide **4s** derived from (*R*)- α -methylbenzylamine was subjected to the optimized reaction conditions in the presence of (*S*)-BINAP giving **5sa** in 91% yield and >25:1 diastereoselectivity, while with (*R*)-BINAP the reaction favored the formation of the other diastereomer with a *dr* of <1:25. It is worth noting that the double cyclization of **4t** also worked well, delivering the desired product **5t** with excellent diastereo- and enantioselectivity, indicating the “preformed” planar chirality does not affect the second cyclization reaction.

A brief catalytic cycle with **4a** as the representative substrate was proposed in Scheme 2. The oxidative addition of Pd(0) with **4a** gave the anticipated palladium species I, which would undergo C–H palladation to afford II.²² The Pd with a chiral

Scheme 1. Effects of the Preinstalled Chiral Moieties



Scheme 2. Plausible Catalytic Cycle



phosphine ligand could discriminate between two *ortho* C(Cp)–H bonds to selectively form II, which ultimately delivered the cyclization product **5a** via reductive elimination.

In summary, the present results demonstrated an efficient synthesis of planar chiral metallocenes by the strategy of a palladium-catalyzed intramolecular C–H functionalization/cyclization reaction. Generally good to excellent yields with high enantioselectivities could be achieved. This method provided a new and efficient way to synthesize structurally different planar chiral metallocenes with a wide range of functional group tolerance. Studies on the mechanistic aspects and applications of these structurally new metallocene compounds in organic synthesis are underway in our laboratories.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental procedures, characterization data, HPLC traces, ¹H and ¹³C NMR spectra for new compounds. 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 interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (21272221), the Recruitment

Program of Global Experts, the Fundamental Research Funds for Central Universities, and the Cross-disciplinary Collaborative Teams Program for Science, Technology and Innovation (2014-2016) from the Chinese Academy of Sciences. We thank Dr. C. E. Stivala (Stanford University) for his assistance with the manuscript preparation.

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