

Enantioselective Assembly of Ferrocenes with Axial and Planar Chiralities via Palladium/Chiral Norbornene Cooperative Catalysis

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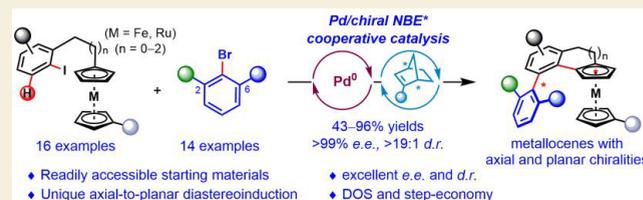
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ABSTRACT: The preparation of ferrocenes with both axial and planar chiralities poses a considerable challenge. Herein, we report a strategy for the construction of both axial and planar chiralities in a ferrocene system via palladium/chiral norbornene (Pd/NBE*) cooperative catalysis. In this domino reaction, the first established axial chirality is dictated by Pd/NBE* cooperative catalysis, while the latter planar chirality is controlled by the preinstalled axial chirality through a unique axial-to-planar diastereinduction process. This method exploits readily available *ortho*-ferrocene-tethered aryl iodides (16 examples) and the bulky 2,6-disubstituted aryl bromides (14 examples) as the starting materials. Five- to seven-membered benzo-fused ferrocenes with both axial and planar chiralities (32 examples) are obtained in one step with constantly high enantioselectivities (>99% *e.e.*) and diastereoselectivities (>19:1 *d.r.*).



KEYWORDS: asymmetric Catellani reaction, multiple chiralities, axial-to-planar diastereinduction, planar chirality, metallocenes

Planar chiral ferrocenes (PCFs)¹ have been extensively studied due to their broad applications in asymmetric catalysis,^{2–5} materials science,^{6,7} and biomedical research.⁸ As a result, substantial efforts have been devoted to the efficient preparation of this valuable chiral scaffold, culminating in the development of several elegant strategies.^{9–11} In addition, growing research efforts have demonstrated that the incorporation of other stereogenic elements into planar chiral ferrocene skeletons can dramatically tune their properties, which leads to the discovery of quite a few elegant ligands and catalysts (Figure 1A).^{12–14} Nevertheless, current methods to access ferrocenes with multiple stereogenic elements have been mainly limited to planar and central chiralities.^{3–5} Methods to access ferrocenes with both planar and axial chiralities have been rarely explored. Until now, only three approaches^{15–17} have been revealed to access these scaffolds, to the best of our knowledge.¹⁸ In 2015, Ogasawara, Takahashi, and Kamikawa reported a simultaneous introduction of axial and planar chirality in arene-chromium complexes by molybdenum-catalyzed enantioselective ring closing metathesis (RCM).¹⁵ In 2019, Jiao reported the preparation of axial and planar chiral ferrocene derivatives from chiral substrates via a multistep protocol.¹⁶ In 2021, Zhang, Li, and Wu developed a unique strategy for the simultaneous construction of axial and planar chiralities via gold-catalyzed asymmetric intramolecular hydroarylation (Figure 1B).¹⁷ Though being effective, these approaches rely on special/complex substrates and are of limited product diversity, which prevents their broad application. Therefore, the development of novel strategies

for the quick assembly of ferrocenes with both axial and planar chiralities from readily available starting materials is a highly desirable yet challenging subject.¹⁷

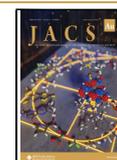
Recently, the research on simultaneous construction of multiple chiralities has been flourishing.^{19–27} For instance, in 2022, Shi and co-workers reported a one-step construction of atropisomers with vicinal C–C and C–N chiral diaxes by cobalt-catalyzed intramolecular atroposelective C–H annulation.²⁶ Recently, our group developed a three-component protocol for the assembly of atropisomeric *o*-terphenyls with 1,2-diaxes²⁷ via palladium/chiral norbornene (Pd/NBE*) cooperative catalysis^{28–33} (namely the asymmetric Catellani reaction^{34–40}) and axial-to-axial diastereinduction. Inspired by these elegant studies, we envisioned a new strategy for quick assembly of the aforementioned unique ferrocenes with both axial and planar chiralities, via palladium/chiral norbornene cooperative catalysis.⁴¹ As depicted in Figure 1C, the reaction of readily available *ortho*-ferrocene-tethered aryl iodide **1** with the bulky 2,6-disubstituted aryl bromide (**2**) under Pd/NBE* cooperative catalysis will form an axially chiral Pd^{II} complex **I**,^{28–33} which may subsequently undergo an intramolecular asymmetric C(sp²)-H activation to form the desired cyclized

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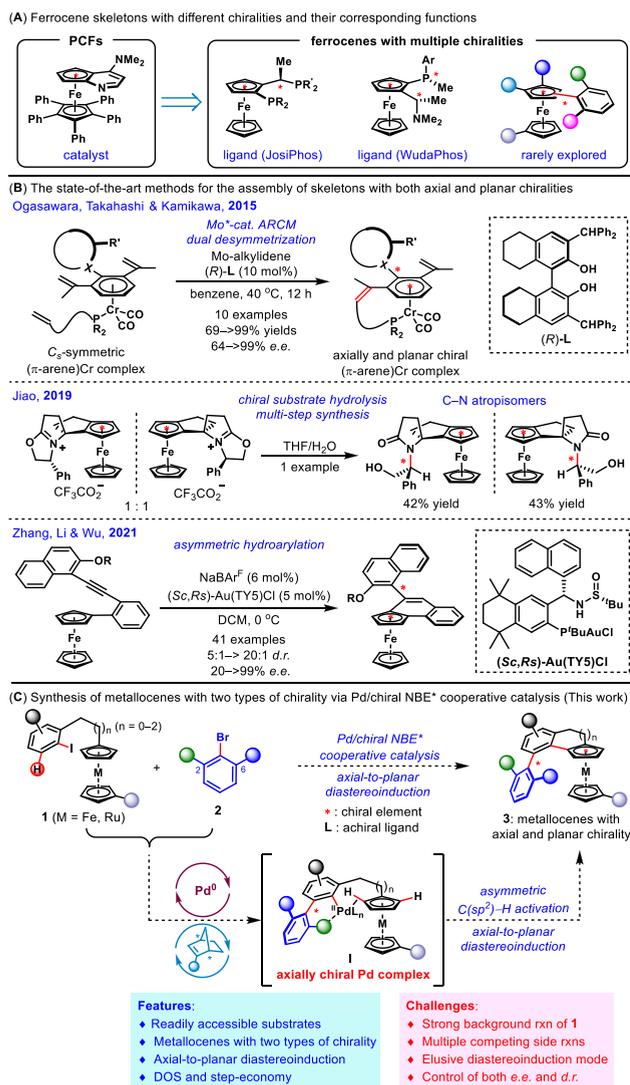


Figure 1. Approaches to access ferrocenes with multiple chiralities.

ferrocene product 3. In this fascinating domino process, the first established axial chirality is dictated by Pd/NBE* cooperative catalysis,^{28–33} while the latter planar chirality will be controlled by the preinstalled axial chirality through an unprecedented axial-to-planar diastereoselection process. Potential features of this strategy include readily accessible starting materials (1 and 2), the unique axial-to-planar diastereoselection mode, diversity-oriented synthesis (DOS) of 3, and good step economy. Nevertheless, multiple challenges are also associated with this protocol, such as (1) as reported by the groups of You,^{42–44} Gu/Kang,^{45,46} and others,^{47–49} the direct cyclization of 1 may constitute a strong background reaction to terminate the cascade process prematurely; (2) the ferrocene moiety of 1 is susceptible to C(sp²)-H activation by a palladium catalyst,^{9–11} which may result in multiple side reactions to compete with the target process; (3) the axial-to-planar diastereoselection process is unprecedented and challenging due to its innate dynamic nature, and the diastereoselection efficiency remains elusive.^{26,27}

To probe this intriguing process, our efforts commenced with a model reaction using 2-iodophenethylferrocene (1a) and the bulky methyl 2-bromo-3-methylbenzoate (2a) as the reactants (Table 1). After an extensive survey of the reaction

Table 1. Optimization of Reaction Conditions^a

1a (1.5 equiv) + 2a (1.0 equiv) → 3a

Pd(OPiv)₂ (5 mol%)
N^{1*} (10 mol%)
MePhos (10 mol%)
pivalic acid (50 mol%)
Cs₂CO₃ (2.5 equiv)
toluene (0.1 M), 120 °C
"Standard Conditions"

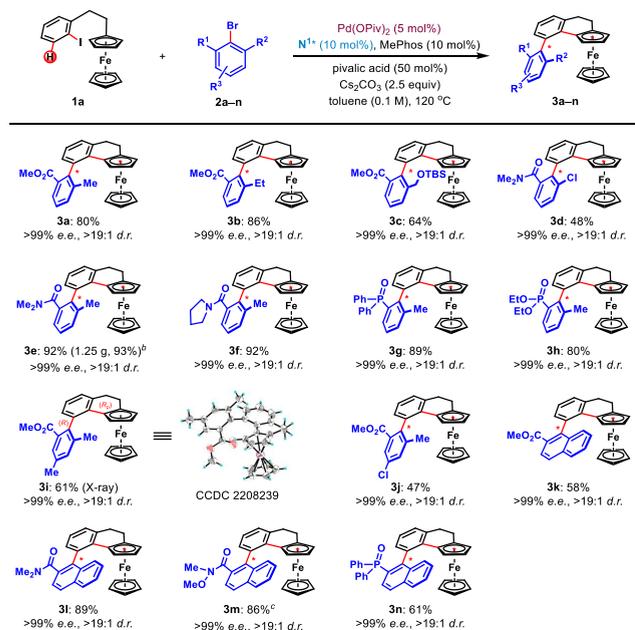
Entry	Change from the standard conditions	Yield (%) ^b	e.e. (%) ^{c,d}
1	none	82(80) ^e	>99
2	without pivalic acid	63	>99
3	Pd(OAc) ₂ instead of Pd(OPiv) ₂	44	>99
4	N ^{2*} instead of N ^{1*}	0	--
5	TFP instead of MePhos	28	>99
6	K ₂ CO ₃ instead of Cs ₂ CO ₃	15	>99
7	CH ₃ CN instead of toluene	4	--

N^{1*} (>99% e.e.)
N^{2*} (>99% e.e.)
MePhos

^aAll reactions were performed on a 0.05 mmol scale. ^bGC yield with biphenyl as an internal standard. ^ce.e. was determined by chiral HPLC analysis. ^dThe diastereomeric ratio (d.r.) was determined by crude ¹H NMR analysis, and all the measured d.r.s were >19:1. ^eIsolated yield in parentheses. Piv = pivalic, TFP = tri-2-furanylphosphine, Cy = cyclohexyl.

parameters (see Tables S1–S5 for details), it was identified that the desired product 3a was obtained with the highest yield, enantioselectivity, and diastereoselectivity (82%, >99% e.e., and >19:1 d.r.) under the following optimal reaction conditions: Pd(OPiv)₂ (5 mol%) as the catalyst, MePhos (10 mol%) as the ligand, (1*R*,4*S*)-2-ethyl-ester-substituted norbornene (>99% e.e.) (N^{1*}, 10 mol%) as the cocatalyst, pivalic acid (50 mol%) as the additive, and 2.5 equiv of Cs₂CO₃ as the base in toluene (0.1 M) at 120 °C (the standard conditions, Table 1, entry 1). A set of control experiments were subsequently conducted to understand the role of each component. The pivalate anion proved critical for this reaction,^{50–53} as the yield of 3a decreased dramatically either without pivalic acid or using Pd(OAc)₂ instead of Pd(OPiv)₂ as the catalyst (entries 2–3). Changing the cocatalyst N^{1*} to 2-amide-substituted norbornene N^{2*} led to no 3a formation, with large amounts of starting materials remaining, indicative of the importance of the ester group in N^{1*} (entry 4). Either a ligand change to TFP or a base change to K₂CO₃ or a solvent change to CH₃CN all resulted in a much lower yield of 3a (entries 5–7). Notably, in all cases, the desired product 3a was obtained with excellent enantioselectivity (>99% e.e.) and diastereoselectivity (>19:1 d.r.). In addition, it is striking to see only 10 mol% of N^{1*} is enough to secure the desired domino reaction to surpass the direct cyclization of 1 and other competing side reaction pathways. To the best of our knowledge, 10 mol% is the lowest NBE cocatalyst loading in Catellani-type reactions.^{30,35–40,54}

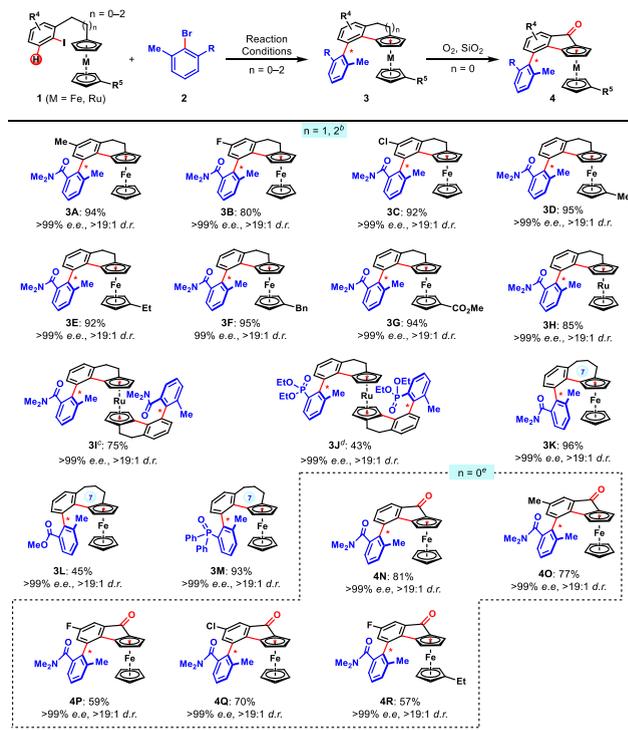
With the above-optimized reaction conditions identified, we first examined the scope of the bulky arylating reagent (2), with 1a as the reaction partner (Table 2). Gratifyingly, aryl bromides containing an *ortho*-electron-withdrawing group including ester (3a–c, 3i–k), amide (3d–f, 3l–m), and phosphoryl (3g–h and 3n) all proved to be competent substrates, providing the desired products in 47–92% yields with >99% e.e. and >19:1 d.r.. The other *ortho*-substituent of 2 could be methyl (3a, 3e–j), ethyl (3b), TBS-protected hydroxymethyl (3c), and chloro (3d) groups. In addition,

Table 2. Reaction Scope with Respect to Aryl Bromide^a

^aAll reactions were performed on a 0.1 mmol scale. Reported yields are for the isolated products. ^bThe reaction was performed on a 3.0 mmol scale, and the reaction time was 8 h. ^c10 mol % Pd(OPiv)₂, 20 mol % MePhos, and 30 mol % N^{1*} were applied.

polysubstituted and bicyclic bulky aryl bromides were also suitable arylating reagents to afford the desired products (3i–n) in 47–89% yields. The scalability of this protocol was demonstrated by a 3.0 mmol scale experiment, which provided 1.25 g of 3e (93% yield), alongside 95% recovery of N^{1*}. Finally, the absolute configurations of these enantiopure products are assumed to be (R_a, R_p) based on X-ray crystallographic analysis of the representative product 3i (see Part 7 in the Supporting Information for details).⁵⁵

We next explored the scope of aryl iodide 1. As shown in Table 3, aryl iodides with an electron-donating substituent (Me) or electron-withdrawing substituent (F and Cl) on the phenyl moiety all proved to be competent substrates, affording the desired products 3A–C in 80–94% yields with >99% e.e. and >19:1 d.r.. In addition, modification (e.g., an alkyl or ester substitution) on the other Cp ring of the ferrocene moiety of 1 was also well tolerated, giving the corresponding products 3D–G in 92–95% yields with excellent stereoselectivities. Moreover, even ruthenocenes were suitable substrates under the standard conditions, providing the corresponding product 3H in 85% yield with >99% e.e. and >19:1 d.r.. Notably, an intriguing dual cascade process was achieved by using 1,1'-di(2-iodophenylethyl)ruthenocene (1j) as the substrate, which generated single enantiomers 3I and 3J⁵⁶ featuring two sets of axial and planar chiralities in 75 and 43% yield, respectively, both with excellent enantioselectivity (>99% e.e.) and diastereoselectivity (>19:1 d.r.). Moreover, the aryl iodide with a longer tether was also amenable to this protocol, delivering the corresponding seven-membered benzo-fused ferrocenes 3K–M in 45–96% yields with equally excellent enantioselectivity and diastereoselectivity. Encouraged by the successful construction of six- and seven-membered benzo-fused ferrocene products, we then set out to synthesize the five-membered ones, whose substrates are more challenging,

Table 3. Reaction Scope with Respect to the Aryl Iodide^a

^aAll reactions were performed on a 0.1 mmol scale. Reported yields are for the isolated products. ^bStandard conditions: Pd(OPiv)₂ (5 mol %), MePhos (10 mol %), N^{1*} (10 mol %), pivalic acid (50 mol %), Cs₂CO₃ (2.5 equiv), toluene (0.1 M), 120 °C. ^c1j (0.1 mmol), 2e (0.2 mmol), Pd(OPiv)₂ (10 mol %), MePhos (20 mol %), N^{1*} (20 mol %), pivalic acid (100 mol %), and Cs₂CO₃ (5.0 equiv) were applied. ^d1j (0.1 mmol), 2h (0.25 mmol), Pd(OPiv)₂ (15 mol %), MePhos (30 mol %), N^{1*} (30 mol %), pivalic acid (100 mol %), and Cs₂CO₃ (5.0 equiv) were applied. ^eThe reaction conditions were slightly modified as follows: Pd(OPiv)₂ (10 mol %), TFP (20 mol %), N^{1*} (30 mol %), Cs₂CO₃ (2.0 equiv), toluene (0.1 M), 120 °C.

since they are susceptible to undergo intramolecular C(sp²)–H arylation directly according to previous studies.^{42–49} To our delight, through minor modifications of the standard conditions including increasing the loading of N^{1*} to 30 mol % (see Table S6 for details), we found a series of 2-iodobenzylferrocenes (1i–p) reacted with 2-bromo-N,N,3-trimethylbenzamide 2e smoothly to afford the corresponding products 3N–R in good yields. However, these products are unstable during the purification procedure and can be readily oxidized to the corresponding ketones in the presence of O₂ and silica gel.⁵⁷ Thus, the stable ketone products 4N–R were isolated in 57–81% yields with equally excellent enantioselectivity and diastereoselectivity (>99% e.e. and >19:1 d.r.).

According to the mechanistic hypothesis in Figure 1C and the above results, a postulated axial-to-planar diastereoselection model is proposed in Figure 2A. The 2-R_a-configured axially chiral palladium complex I-1a, formed from 1a, 2i, and pivalic acid via palladium/N^{1*} cooperative catalysis,³⁰ undergoes an intramolecular C(sp²)–H activation followed by a reductive elimination to afford diastereomer (R_a, R_p)-3i (via transition state (R_a, R_p)-TS) or (R_a, S_p)-3i (via transition state (R_a, S_p)-TS). Due to the larger steric repulsions caused by the proximal placement of the pivalic group and the ferrocene ring in (R_a, S_p)-TS as compared to (R_a, R_p)-TS, the

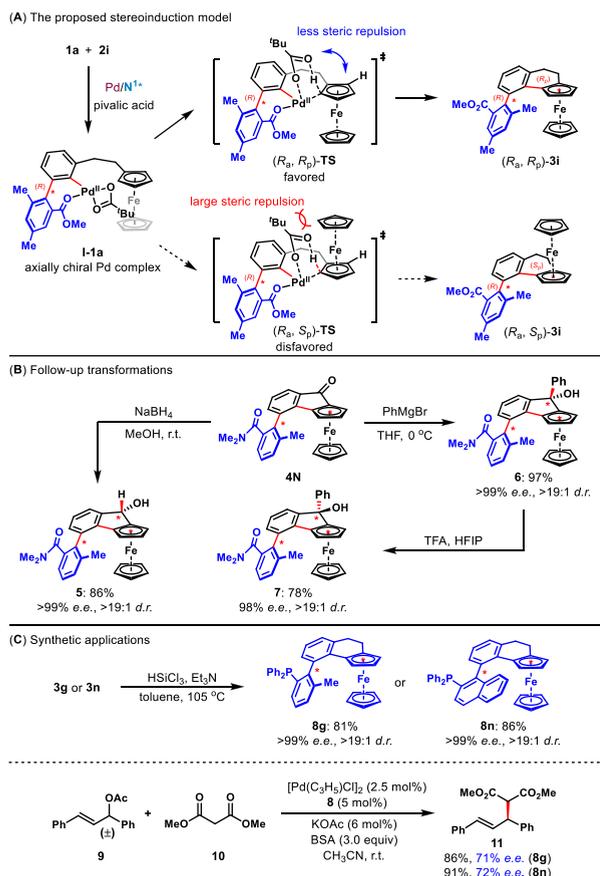


Figure 2. Proposed stereinduction model and synthetic applications.

formation of diastereomer (R_a, R_p) -**3i** is more favorable. These predicted results were consistent with the corresponding X-ray crystallographic analysis (**3i**) (see Part 7 in the [Supporting Information](#) for details).

As the obtained ferrocenes with both axial and planar chiralities are very useful intermediates, their synthetic value was demonstrated by follow-up transformations. First, the reduction or nucleophilic addition of ketones **4N–R** can be performed in a highly stereoselective manner to generate the corresponding products with three different kind of stereogenic elements: axial, planar, and central chirality. The absolute configuration of newly generated chiral center is fully dictated by the planar chirality.^{58,59} For instance, the reduction of **4N** with NaBH_4 gave **5** as a single diastereomer in 86% yield. In addition, the reaction of **4N** with a phenyl Grignard reagent also proceeded smoothly to afford the single diastereomer **6** in 97% yield, which was further converted into **7** in 78% yield through an acid-mediated stereospecific stereoinversion of the tertiary alcohol moiety^{58–60} (Figure 2B). Moreover, **3g** and **3n** of Table 2 were readily reduced to deliver novel phosphines **8g** and **8n**, which are preliminarily proved as chiral ligands for the palladium-catalyzed asymmetric allylic alkylation reaction⁶¹ (Figure 2C).

In summary, we have developed a modular strategy for the assembly of ferrocenes with both axial and planar chiralities via palladium/chiral norbornene (Pd/NBE^*) cooperative catalysis. In this fascinating domino reaction, the first established axial chirality is dictated by Pd/NBE^* cooperative catalysis, while the latter planar chirality is controlled by the preinstalled axial chirality through a unique axial-to-planar diastereoinduc-

tion process. It is noteworthy that only 10 mol % of cocatalyst N^{1*} is required to secure the desired domino reaction with good synthetic efficiency. This method exploits readily available *ortho*-ferrocene-tethered aryl iodides and the bulky 2,6-disubstituted aryl bromides as the starting materials. Five- to seven-membered benzo-fused ferrocenes with both axial and planar chiralities are obtained in one step with constantly excellent enantioselectivities and diastereoselectivities. This chemoselective and scalable protocol is compatible with a wide range of functional groups, providing a versatile platform for further structural modifications. Further investigation on the cause of excellent stereocontrol of this unique axial-to-planar diastereoinduction process is currently ongoing in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacsau.2c00630>.

Experimental details, spectra, and X-ray crystallography (PDF)

X-ray data (CIF)

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J.Y. and L.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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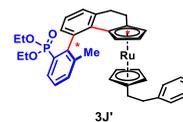
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