Asymmetric Synthesis of Chiral-at-Iridium Complexes through Pd-Catalyzed Kinetic Resolution

Yun-Peng Chu, Xue-Lin Yue, De-Hai Liu, and Jiajia Ma*

[1]Frontiers Science Center for Transformative Molecules, Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, P. R. China

[2]Zhang jiang Institute for Advanced Study, Shanghai Jiao Tong University, Shanghai 200240, P. R. China

*Corresponding author: majj@sjtu.edu.cn

Abstract: Metal-centered chirality has been recognized for over a century, and chiral-at-metal complexes have been widely applied across various natural science fields. However, the synthesis of these molecules remains constrained. Notably, while asymmetric catalysis has played a crucial role in the production of optically active organic molecules, its application to chiral-at-metal complexes is less straightforward. In this study, we introduce a kinetic resolution strategy employing a Pd-catalyzed asymmetric Suzuki-Miyaura cross-coupling reaction that efficiently produces optically active chiral-at-iridium complexes from racemic mixtures with high selectivity (achieving an *s*-factor of up to 133). This method enables further synthesis of complexes relevant to metallodrugs and chiral photosensitizers, underscoring the practical utility of our approach. Mechanistic studies suggest that reductive elimination is the turnover-limiting step over the Suzuki-Miyaura cross-coupling.

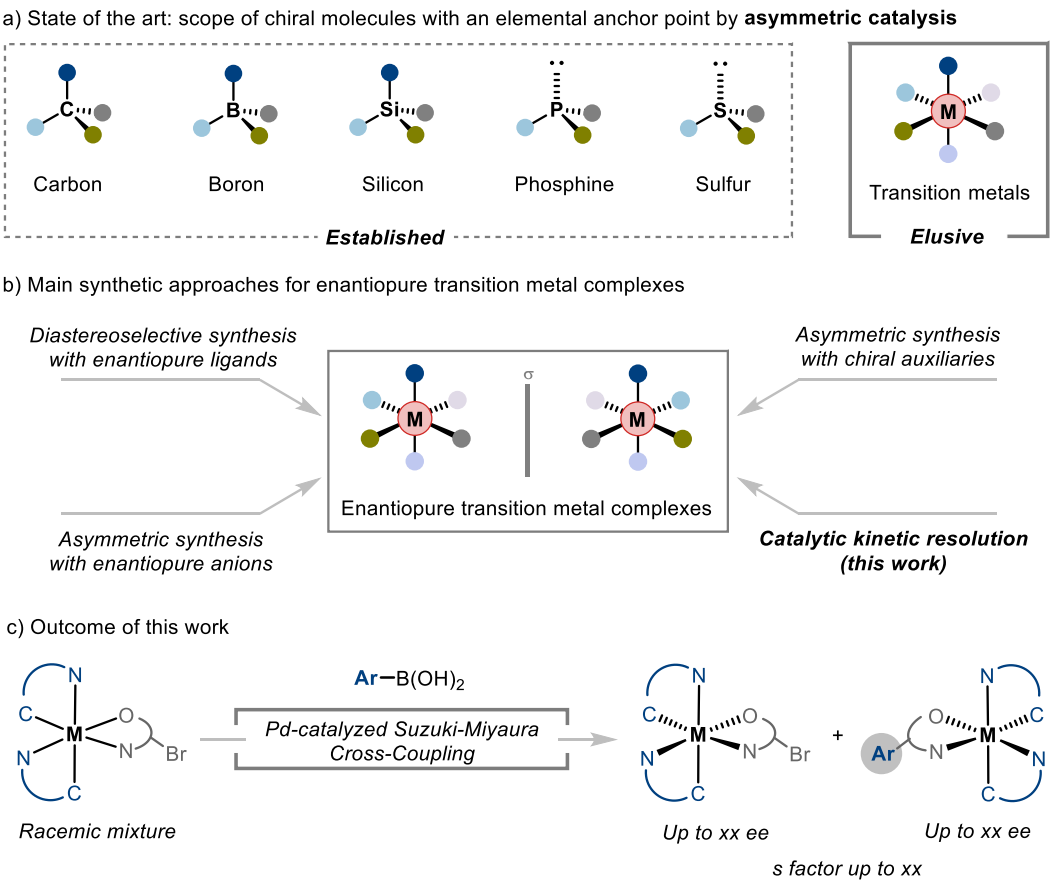


Figure 1. a) Molecular chirality; b) Current approaches to chiral-at-metal complexes; c) This work: asymmetric synthesis of chiral-at-metal complexes through Pd-catalyzed kinetic resolution.

Optically active molecules constitute pivotal components in various realms of natural science. Over the past century, significant strides have been made in the development of synthetic methodologies for their acquisition. The pioneering work of synthetic chemists has culminated in the emergence of asymmetric catalysis as a sophisticated and indispensable tool for accessing enantiomerically pure molecules. While the synthetic access to those with chiral main group elements, including carbon, boron, silicon, phosphine, sulfur, and others via asymmetric catalysis, has been successfully established, the pursuit of chiral-at-metal complexes in a catalytic fashion remains a formidable challenge (Figure 1a).

Optically active transition metal complexes endowed with metal-centered chirality have found numerous applications spanning catalysis,[1-3] medicinal chemistry,[4-7] and material science.[8-10] Despite the elaborated exploration for their preparation since the recognition of metal-centered chirality by Werner in 1900s,[11,12] progress has been slow and gradual. The current state-of-the-art synthetic methods can be classified into three main types, as described below:

1) *Diastereoselective synthesis utilizing enantiomerically pure ligands*.[13-15] In 1920, Smirnoff

reported the pioneering example of a diastereoselective synthesis strategy, where the metal-centered chirality of platinum(IV) complexes was induced by an enantiomerically pure diamine ligand.[16] This work initiated the broad use of diastereoselective synthesis strategy, whilst there're associated with two main concerns that the employed chiral ligands generally need tailored design and the stereochemical outcome of central metal is often unpredictable.

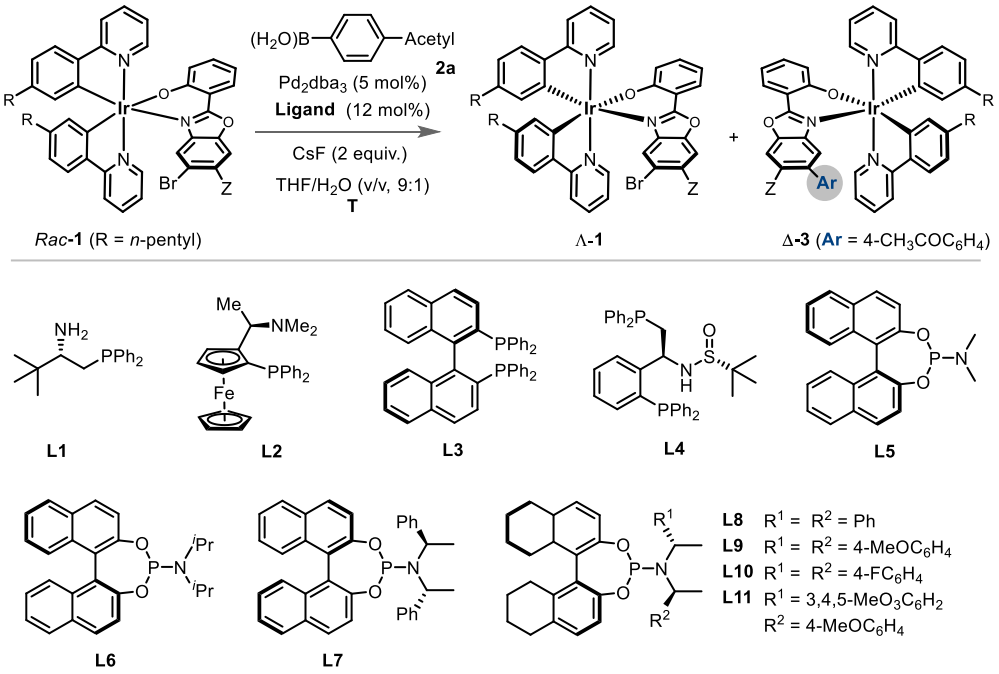
2) *Asymmetric synthesis employing enantiomerically pure anions*.[17] For instance, Lacour and colleagues revealed that the chiral phosphate(V) anion TRISPHAT exhibited asymmetric induction in the synthesis of ionic iron(II) complexes.[18,19] Fontecave and coworkers later reported that this strategy was applicable for synthesizing enantiomerically pure ruthenium(II) complexes.[20] However, owing to its reliance on the formation of chiral ion pairs, this strategy is not applicable for obtaining neutral metal complexes.

3) *Asymmetric synthesis incorporating enantiomerically pure auxiliaries*.[21,22] Meggers group has pioneered the chiral auxiliary-mediated asymmetric coordination chemistry[23] and this strategy has found practical applications in synthetic chemistry. For example, enantiopure homogeneous catalysts,[24,25] metallodrugs[26] and building blocks of supermolecules[27] can be readily prepared using this strategy.

While these notable advancements, the pursuit of an economical and sustainable synthetic approach, ideally in a catalytic fashion, holds paramount significance. As a seminal contribution in 2010, Meggers and coworkers presented an elegant paradigm wherein enantiopure $[Ru(bpy)_3]^{2+}$ was obtained under catalytic conditions.[28] To the best of our knowledge, this represents the singular instance of utilizing asymmetric catalysis for synthesizing enantiopure transition metal complexes, thus serving as a proof of concept, albeit with a single example exhibiting 78% ee. Encouraged by this groundbreaking work, we are prompted to explore the potential introduction of alternative catalytic strategies to enrich the synthetic toolbox for enantiopure transition metal complexes.

Pleasingly, we herein report the catalytic kinetic resolution is applicable, wherein racemic brominated octahedral chiral-at-iridium complexes undergo efficient kinetic resolution through Pd-catalyzed asymmetric Suzuki-Miyaura cross-coupling. Both enantiomers of the chiral-at-iridium complexes were obtained with favorable enantioselectivities, thus underscoring the feasibility and utility of this catalytic strategy.

Table 1. Reaction optimization. [a]



Entry	Z	T (°C)	Ligand	t	ee of Λ-**1**[b]	ee of Δ-**3**[b]	*C* (%)[c]	s[d]
1	H (**1a**)	50	L1-L6	24 h	-	-	NR	-
2	H (**1a**)	50	L7	12 h	40	59 (**3a**)	40	5.7
3	H (**1a**)	50	L8	12 h	23	65 (**3a**)	26	5.9
4	H (**1a**)	50	L9	12 h	16	69 (**3a**)	19	6.4
5	H (**1a**)	50	L10	12 h	37	17 (**3a**)	69	1.9
6	H (**1a**)	50	L11	12 h	8	59 (**3a**)	12	4.2
7	Me (**1b**)	30	L9	12 h	9	87 (**3b**)	9	15.7
8	MeO (**1c**)	30	L9	12 h	9	96 (**3c**)	9	54
9	^{i}PrO (**1d**)	30	L9	12 h	44	87 (**3d**)	34	22
10[e]	MeO (**1c**)	30	L9	3.5 d	90	90 (**3c**)	50	58

[a]Conditions: *Rac*-**1** (0.01 mmol), **2** (0.02 mmol), $Pd_2(dba)_3$ (5 mol%, 0.0005 mmol), Ligand (12 mol%, 0.0012 mmol) and CsF (0.02 mmol) in THF/H_2O (v/v=9/1, 0.1 mL) stirred at designated temperatures under N_2. [b]Determined by HPLC analysis on a chiral stationary phase and the absolute values are displayed. [c]Conversion (C) = $ee_s/(ee_s+ee_p)$. [d]s = $\ln[(1-C)(1-ee_s)]/\ln[(1-C)(1+ee_s)]$. [e]Reactions were performed on 0.05 mmol scale. (for more details, see Supplementary Information)

Results and discussions

Reaction development. Iridium(III) complexes with two identical cyclometalating ligands and a second complementary one are the versatile scaffold as photocatalyst[24,29-33], metallodrug[6,26,34], organic-light-emitting-diode (OLED) emitter[35-38] etc. As such, given their significance in these fields, cyclometalated iridium(III) complexes were chosen as the objective in this study. Experimentally, inspired by the seminal asymmetric Suzuki-Miyaura cross-coupling works by Buchwald,[39] Cammidge[40] and many others,[41-49] we commenced the study by examining the reaction of racemic brominated iridium(III) complex *rac*-**1a** and a boronic acid **2a** under palladium-catalyzed conditions. Despite an initial screening of chiral phosphine ligands L1-6 failed (entry 1), the Feringa's phosphonamidite L7 was found to be applicable for the kinetic resolution of *rac*-**1a**, thus giving the desired cross-coupling product Δ-**3a** with 59% ee (entry 2). The partially saturated Feringa's ligand L8 led to an increased enantioselectivity for Δ-**3a** (entry 3). Tuning electronic property of the chiral benzylic amines sphere revealed that the electron-rich derivative (L9) was superior over the electron-deficient one (L10) in terms of the kinetic resolution selectivity (entries 4 versus 5). However, introducing more electron-donating methoxys (L11 versus L9) led to inferior result (entry 6). Next, we moved to adjust the substrate by introducing substituents to ortho position of the bromo in *rac*-**1a**. To our delight, with a methyl (Z= Me), this Pd-catalyzed Suzuki-Miyaura reaction turned to be operative under decreased temperature (50 → 30 °C), which has been recognized as a key parameter for obtaining high selectivity,[42] thus giving an increased *s*-factor of 15.7 (entry 7). Further, a methoxy (Z= MeO) was found to be optimal with the highest *s*-factor whilst a bulkier ^{i}PrO led to inferior results (entries 8 versus 9). A scale-up reaction with prolonged reaction time furnished the cross-coupling product Δ-**3c** with 90% ee under the recovery of Λ-**1c** with 90% ee, thus corresponding to a conversion of 50% and an *s*-factor of 58 (entry 10).

Scope and generality evaluation. With the optimal kinetic resolution conditions in hand, we next evaluated the scope of racemic iridium(III) complexes and the cross coupling partners. As outlined in Figure 2, placing a methyl or phenyl group at the 5-position of pyridyl, upon kinetic resolution, led to the cross-coupling products Δ-**5** and Δ-**7** in 85-86% ee under the recovery of Λ-**4** and Λ-**6** in 90-96% ee. Even though 4-methyl pyridyl gave the cross-coupling product Δ-**9** in 66% ee, the remained Λ-**8** was obtained with excellent enantioselectivity of 97%. Interestingly, an extended ring

system of isoquinoline led to product Δ-**11** in 94% ee under the recovery of Λ-**10** in 92% ee, corresponding to a conversion of 49% and an excellent *s*-factor of 106. Next, we evaluated the substituent effect on cyclometalating phenyl ring. A bulkier *i*Pr (Δ-**13**), an electron-deficient CF_3 (Δ-**15**), an electron-donating MeO (Δ-**17**), and a phenyl (Δ-**19**) are compatible under this kinetic resolution protocol, thus giving the *s*-factor of 21-57. Further, bis-trifluoromethylated racemic iridium(III) complexes **20** and **22**, which often serves as photocatalyst scaffolds, can also undergo the Pd-catalyzed kinetic resolution to give optically active chiral-at-iridium complexes with up to 99% ee. It's noteworthy that while replacing the Ir with Rh (**24**), the kinetic resolution became not operative in which both the cross-coupling product **25** and the remained **24** were found to be racemic at a conversion of 50%. Kinetic study of the rhodium complexes by ^{1}H NMR analysis suggested a rapid exchange kinetic of the aryl bromide ligand, which indicates that the Suzuki-Miyaura cross-coupling might take place when aryl bromide dissociated from the rhodium center (for more details, see Supplementary Information). Therefore, chiral recognition between substrate **24** and catalyst [Pd/L9] turned to be unfeasible. Scope of the coupling partners was further evaluated (Figure 3). Accordingly, aryl boronic acid, the corresponding pinacol ester (Bpin) and trifluoroborate potassium salt led to comparable results while the trifluoroborate potassium salt required an elevated reaction temperature of 40 °C for obtaining high conversion. The acetyl substituent at both *meta* (Δ-**28**) and *ortho* (Δ-**29**) positions of phenyl were compatible. Due to the exist of two substituents at the biaryl of Δ-**29**, rotational isomerization was observed as suggested by HPLC analysis and room/high temperature ^{1}H NMR analysis (see Supplementary Information). Besides these, other electron-withdrawing groups such as ester and sulfonyl led to cross-coupling products in excellent ee of 95% (Δ-**30**) and 92% (Δ-**31**), respectively. Meanwhile, electron-rich phenyl boronic acid derivatives are also suitable coupling partners thus giving Δ-**32-34** in 91-93% ee. Interestingly, heteroaromatic and olefinic boronic acids (products Δ-**35-37**) are suitable coupling partners in this Pd-catalyzed kinetic resolution protocol.

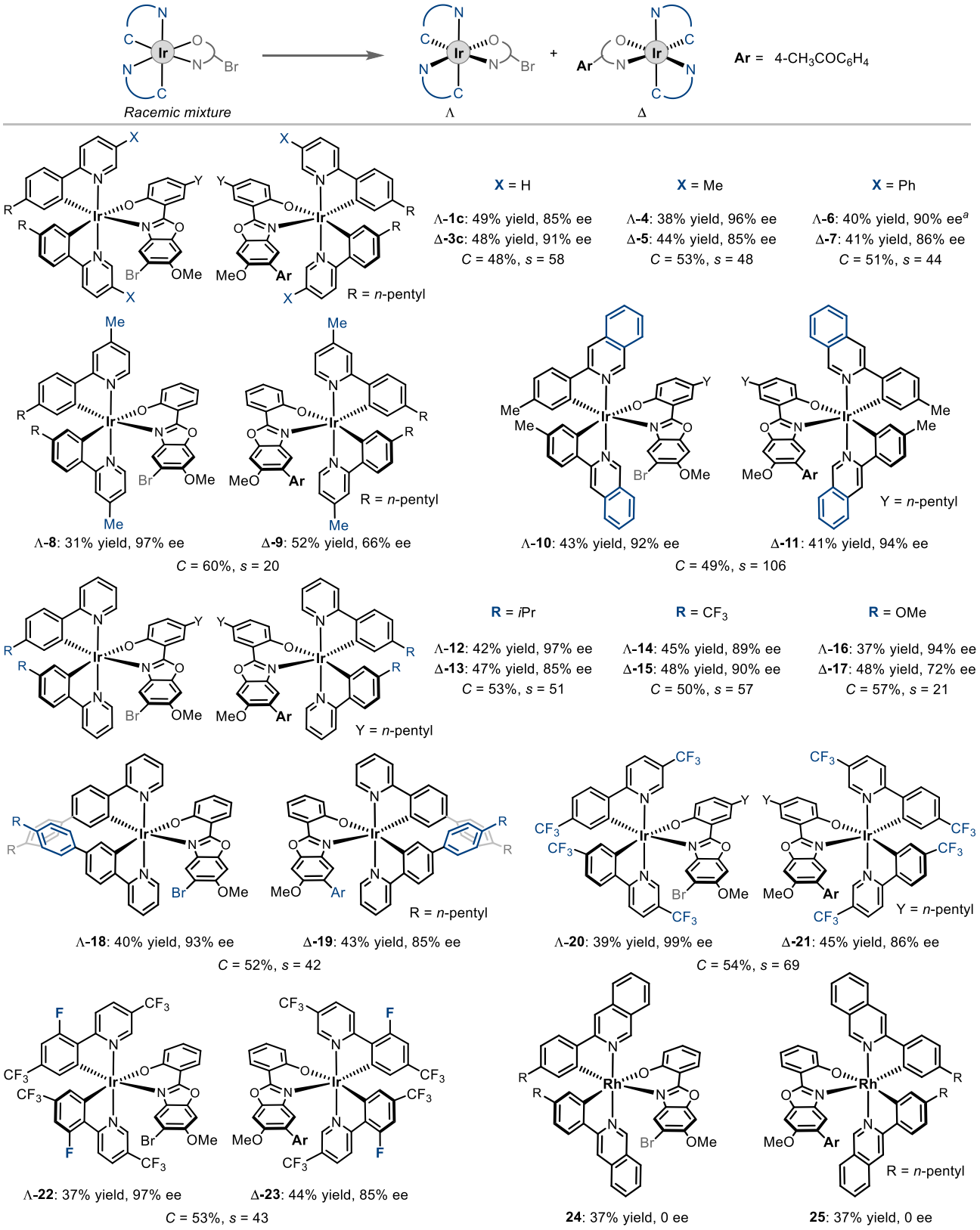


Figure 2. Scope of iridium(III) complexes.

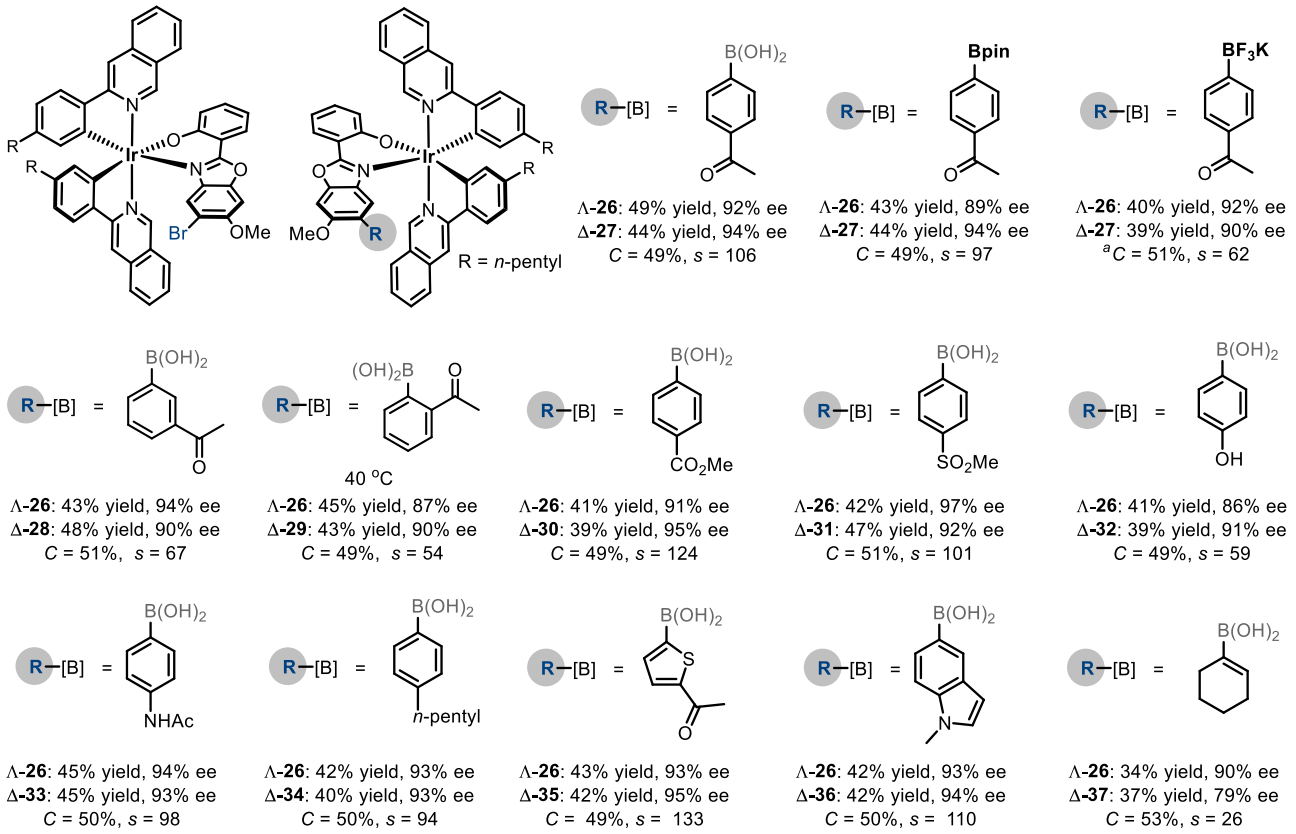


Figure 3. Scope of cross-coupling partners. [a]Reaction was conducted at 40 °C.

Synthetic application. An acid-induced ligand exchange reaction of Δ-**11** was conducted in the presence of 2,2'-bipyridine, thus providing complex **38**, which is suitable for crystallization (Figure 4a). X-ray crystallographic analysis of **38** ambiguously showcased the Δ configuration of complex **11**. Circular dichroism (CD) analysis showcased the opposite configuration of complexes **10** and **11**, therefore the former one was assigned as Λ (Figure 4b). Configuration of other complex pairs such as **12** vs **13**, **14** vs **15** etc. were further assigned accordingly by CD analysis (see Supplementary Information). Next, the brominated iridium complex Λ-**1c** can undergo diverse synthetic transformations (Figure 4c). Under achiral $Pd(PPh_3)_4$-catalyzed cross-coupling or hydrodehalogenation conditions, Λ-**1c** was smoothly converted into complexes **39** and **40**, respectively, in excellent enantioselectivities of >99% and 99%. Meanwhile, acid-induced ligand exchange reactions with acetylacetone or a phenanthroline derivative were performed to furnish complexes **41** and **42**, respectively, which are related scaffolds of OLED emitter[35] and metallodrug[26]. Notably, the chiral photosensitizer **43** as demonstrated by Yoon and coworkers[50], was obtained in 90% yield by ligand exchange of Λ-**20** with 2-(1*H*-pyrazol-3-yl)pyridine.

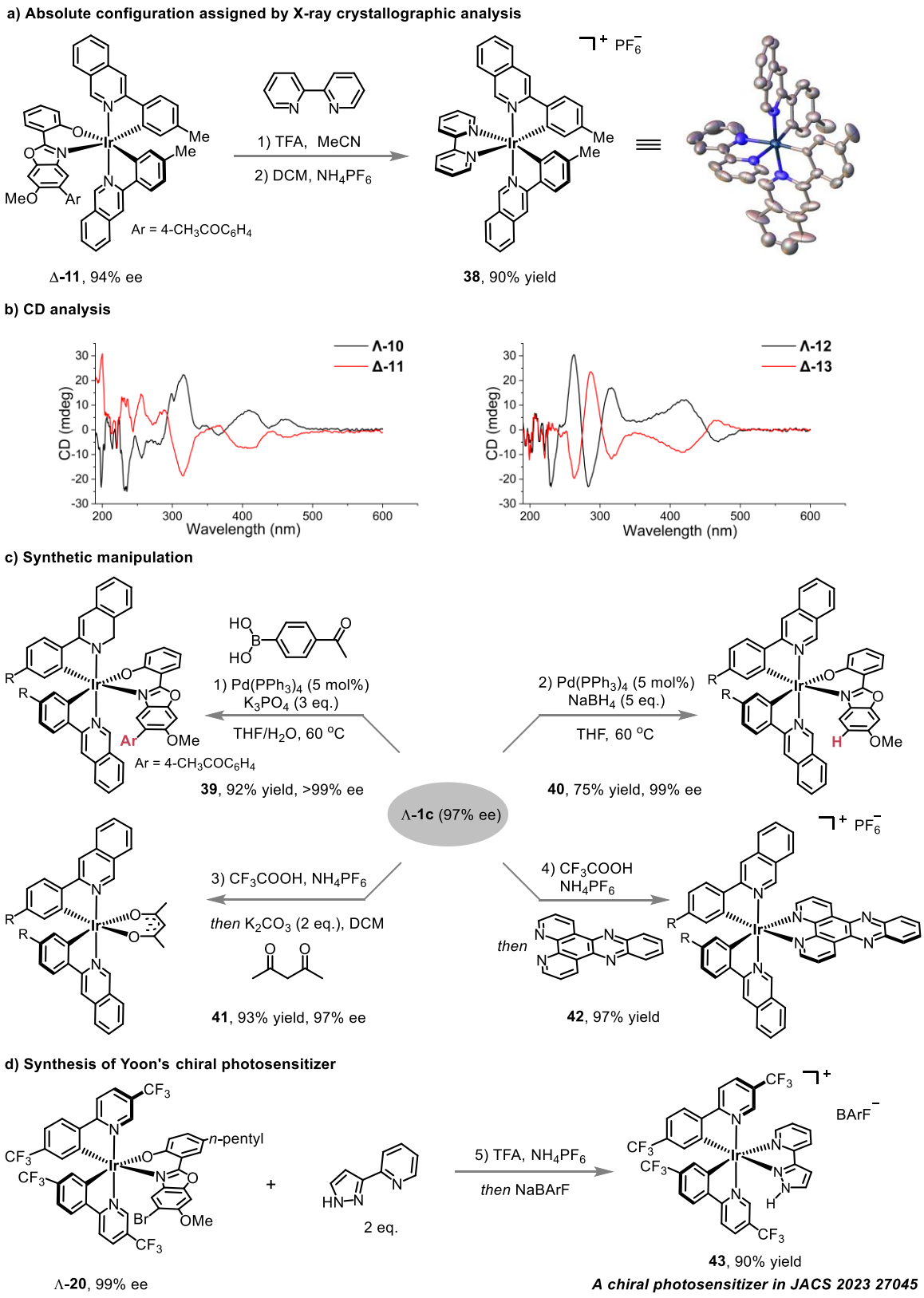


Figure 4. Synthetic application.

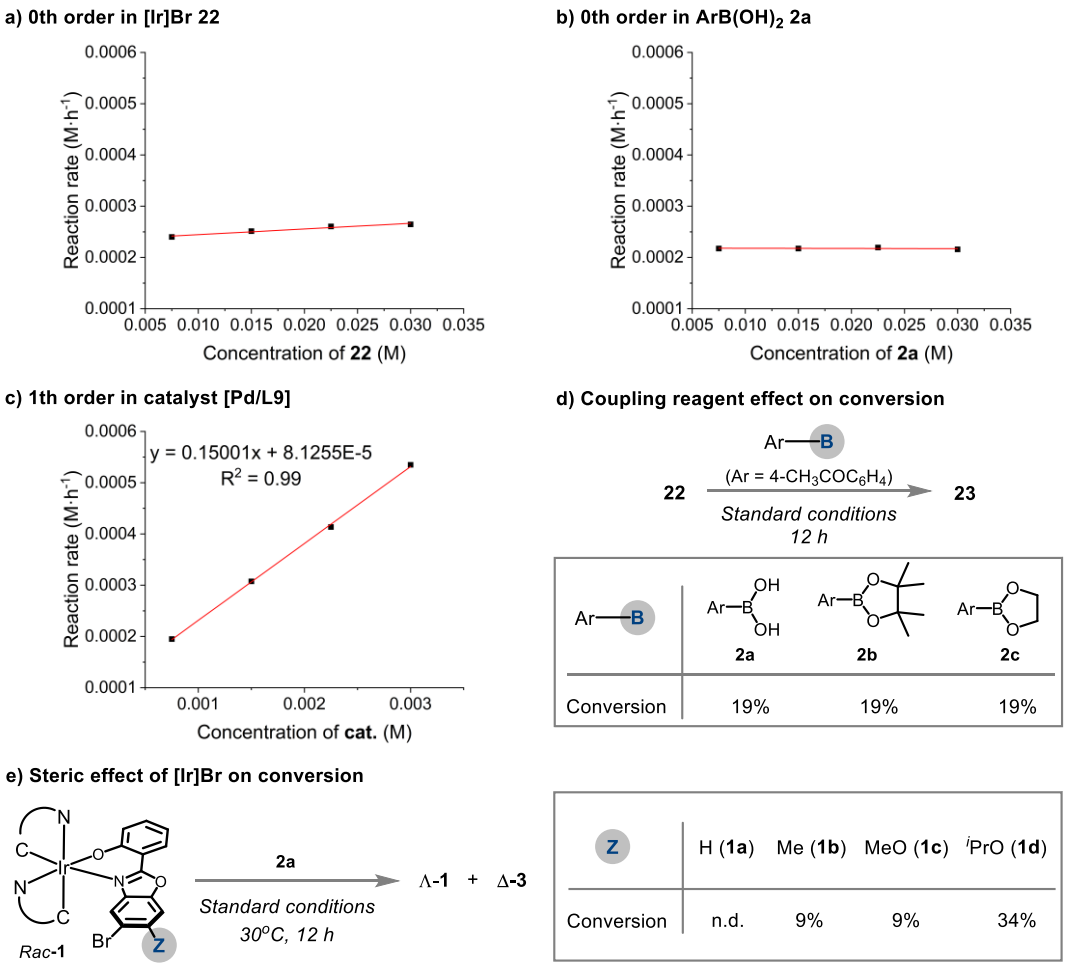


Figure 5. Mechanistic investigation.

Mechanistic investigation. To probe the turnover-limiting step in the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction, kinetic investigations were performed (Figure 5). Initial reaction rates were measured under an array of concentrations regarding racemic brominated iridium complex **22**, boronic acid **2a** and the precatalyst [Pd/L9], respectively. As a result, increasing the concentration of **22** or **2a** didn't affect the initial reaction rates which is consistent with a zeroth-order dependence (Figure 5a-b). Therefore, neither the oxidative addition nor transmetalation is likely turnover-limiting. Meanwhile, this cross-coupling reaction was found as a first-order independence on the precatalyst [Pd/L9], thus suggesting a monomeric Pd complex engaging in the turnover-limiting step (Figure 5c). Next, identical conversions of 19% were observed while subjecting boronic acid (**2a**) and borates (**2b** and **2c**) to the standard reaction conditions, respectively (Figure 5d). This observation further excludes out that transmetalation is the turnover-limiting step. Last, the steric effect at the ortho position of Br was evaluated (Figure 5e). Accordingly, the cross-coupling product was not detected at 30 °C with **1a** (Z = H) while placing a methyl (**1b**, Z = Me) or methoxy group (**1c**, Z = MeO) led to a remarkable conversion of 9%. A bulkier ^{i}PrO was

capable of accelerating the reaction significantly with a high conversion of 34%. Therefore, the reaction rate correlates with the size of substituents at ortho position of Br. Collectively, these kinetic studies indicate the reductive elimination might serve as the turnover-limiting step.

Conclusion

We herein demonstrate optically active chiral-at-iridium complexes can be obtained by kinetic resolution under a Pd-catalyzed asymmetric Suzuki-Miyaura cross-coupling reaction. Excellent enantioselectivities of up to 99% ee and high kinetic resolution performance with *s*-factor of up to 133 were obtained. This work remarkably complements the current synthetic toolbox for chiral-at-metal complexes and we anticipate that it'll spur more advancements for accessing chiral-at-metal complexes with asymmetric catalysis.

Data availability

Materials and methods, experimental procedures, mechanistic studies, NMR spectra and HPLC traces are available in the Supplementary Information or from the corresponding author upon reasonable request. Crystallographic data for compounds **38** (CCDC 2349911) is available free of charge from the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge via https://www.ccdc.cam. ac.uk/structures/.

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Author contributions

J.M. conceived and supervised the project. Y.-P.C., X.-L.Y. and D.-H.L. performed the synthetic experiments. J.M. wrote the manuscript with contributions from all authors.

Competing interests

The authors declare no competing interest.

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