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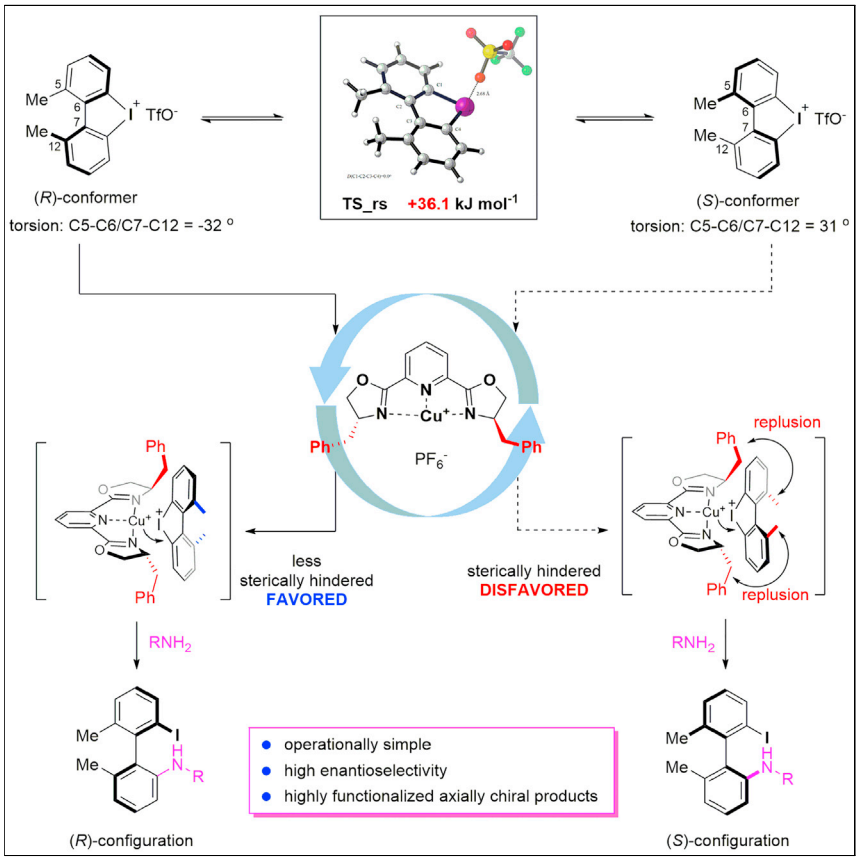
Enhanced Reactivity by Torsional Strain of Cyclic Diaryliodonium in Cu-Catalyzed Enantioselective Ring-Opening Reaction



An efficient method is developed for preparing functionalized axially chiral compounds via the ring-opening reaction of cyclic diaryliodonium salts. Two conformers of the cyclic diaryliodonium salt observed in the crystal structure underwent quick equilibration. The distortion of the diaryliodonium salts significantly increased reactivity toward the chiral copper catalyst, which enabled the reaction to take place in mild conditions to furnish the products in enantioselectivities up to 99.5:0.5 (*R*:*S*).

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HIGHLIGHTS

Significant reactivity improvement by torsional strain of cyclic diaryliodoniums

Rapid access to optically active amino aryliodide atropisomers

Highly atom-economic synthesis of aryliodide atropisomers via ring-opening reaction

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Enhanced Reactivity by Torsional Strain of Cyclic Diaryliodonium in Cu-Catalyzed Enantioselective Ring-Opening Reaction

Kun Zhao,[1,2] Longhui Duan,[1,2] Shibo Xu,[1] Julong Jiang,[1] Yao Fu,[1,*] and Zhenhua Gu[1,3,*]

SUMMARY

Atropisomers are stereoisomers arising from the restricted rotation around a single bond. In particular, biaryl atropisomers represent an important class of compounds, as they are widely present in natural products, ligands and pharmaceutical molecules. However, the preparation of structurally diverse biaryl atropisomers under mild conditions is a significant challenge. Here, we describe a Cu-bis(oxazolinyl)pyridine-catalyzed asymmetric ring-opening amination reaction of cyclic diaryliodoniums. Increasing the torsional strain of these cyclic compounds significantly improved the reactivity of cyclic diaryliodoniums. Computational investigation indicated that the two conformers of the cyclic diaryliodoniums had a low rotational barrier, and generally the reaction achieved high yields and high enantioselectivity (up to >99% ee). Furthermore, this ring-opening amination reaction also featured high atom economy in comparison with traditional reactions involving diaryliodonium. Finally, we propose a catalytic cycle and a mechanistic model that accounts for the observed enantioselectivity.

INTRODUCTION

Atropisomerism is a type of stereoisomerism where rotation via a single bond is restricted. Atropisomers are frequently seen in amides, biaryls, and diaryl ethers.[1,2] In some cases, the atropisomeric architecture is the key feature in bioactive natural products, pharmaceuticals (i.e., vancomycin) (Scheme 1B), and privileged ligands or catalysts (i.e., [1,1′-binaphthalene]-2,2′-diol [BINOL] and KenPhos) (Scheme 1C).[3–6] In contrast to stereogenic sp^3 carbons bearing four distinct substituents, biaryl atropisomerism requires two conditions: (1) a restricted rotation around a stable axis, typically a bond, and (2) different substituents on both sides of the axis (A ≠ B and C ≠ D; Scheme 1A). Thus, the axis of a stable biaryl atropisomer is usually sterically congested, and its construction is challenging. Because of their importance and widespread applications in both medicinal and synthetic chemistry, a number of strategies for the construction of biaryl atropisomers have been developed, including metal-catalyzed asymmetric cross-coupling,[7–11] asymmetric "aromatic substitution,"[12] and *de novo* aromatic ring formation (such as asymmetric [2 + 2 + 2] cycloaddition).[13–15] In addition, modification of the existing biaryl structures enables access to enantio-enriched atropisomers via either a desymmetrization reaction or (dynamic) kinetic resolution (Scheme 1D).[16–25] Furthermore, the construction of benzylic center chirality, followed by center-to-axial chirality transfer aromatization is also an effective approach to access enantio-enriched biaryl atropisomers.[26,27] Recently, there have been a number of reports on organocatalyzed asymmetric atropisomer synthesis.[28–36] Ring opening of strained biaryl compounds

The Bigger Picture

Axially chiral biaryls represent an important class of stereoisomers that arise from restricted rotation around a single bond. They can be found among natural products, ligands, and pharmaceutical molecules. Divergent and atom-economic synthetic approaches toward optically active biaryl atropisomers, in particular ones generating little to no waste, constitute a significant challenge. Here, we describe a highly enantioselective copper-catalyzed ring-opening reaction of cyclic diaryliodoniums where increasing the torsional strain of the diaryliodonium salts improved the relative poor reactivity of the cyclic diaryliodoniums. This method enabled us to access enantio-enriched amino aryliodides with higher atom economy than traditional reactions involving diaryliodonium. These axially chiral molecules are important precursors for divergent synthesis of axially chiral compounds, which are potentially useful catalysts or ligands in industry.

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is a powerful method for the construction of functionalized biaryl atropisomers. Bringmann and co-workers reported the asymmetric reduction of biaryl lactones to form a series of axially chiral 2′-(hydroxymethyl)-[1,1′-biphenyl]-2-ol analogs, and a number of atropisomeric natural products have been efficiently synthesized by this protocol.[3,4] Nickel-catalyzed ring opening of dinaphthothiophene to afford axially chiral 1,1′-binaphthyls was described by Hayashi and colleagues.[37] In addition, the same group reported an elegant palladium-catalyzed asymmetric carbonylation reaction of dinaphthaleneiodonium, albeit with low enantioselectivity.[38] It is of significance to develop synthetic methods to access atropisomers that can serve as ''platform molecules'', i.e., compounds that can be readily converted to structurally diverse atropisomers. Recently, copper-catalyzed aminations of diaryliodonium have emerged as important methods for the synthesis of aniline derivatives.[39–45] Diaryliodoniums act as powerful reagents for arylation of nucleophiles in both asymmetric and non-asymmetric reactions, most notably in contributions from the Gaunt group.[46–53] We reasoned that the ring-opening reaction of cyclic diaryl iodoniums would give atropisomeric aryl iodides, which represent an ideal class of precursors for the divergent synthesis of biaryl atropisomers (Scheme 1E).[54–59] The key challenges, however, are (1) how to increase the reactivity, because cyclic diaryliodoniums showed significantly lower activity than noncyclic reagents,[57] and (2) how to avoid the formation of diamination products or carbazoles. These requirements prompted us to establish proper reaction conditions that are mild enough to keep the aryl-iodine bonds in the products intact. Here, we report on the realization of this ring-opening amination process that directly converts cyclic iodonium salts to valuable atropisomeric products with very high enantiocontrol. The merits of this transformation include (1) a very high level of enantiocontrol, (2) high atom economy, and (3) high synthetic utility. The resulting aryl iodides are not only precursors for further diverse elaboration but also possible catalysts in hypervalent iodine oxidation reactions.[59]

RESULTS AND DISCUSSION

As a result of the extreme importance of the C–N bond formation reaction in chemistry,[60] our initial trials started with the ring-opening reaction between cyclic diaryliodonium **1a** (Figures S9–S13) and *p*-methylaniline with a copper salt as catalyst. X-ray single-crystal analysis found that iodonium **1a** has two atropisomeric conformers (Figure 1; also see Data S1). Computational calculations indicated that the two conformers have a very low rotation barrier ($\Delta_r^{\neq} G_m^{\theta}$ = 36.1 kJ mol^{-1}) and are thus configurationally dynamic with a half-life around 1.2 × 10^{-7} s under ambient conditions (Figures S2–S4). The ring-opening product **2a** bearing four *ortho* substituents exhibits a much higher rotation barrier and should be configurationally stable. Our preliminary survey focused on identifying a class of suitable chiral ligands for asymmetric induction. The reactions with picolinamide derivative **L1**, PHOX (**L2**), and (*R*)-BINAP (**L3**) as ligands gave no atropselectivity, albeit virtually quantitative yields of **2a** were obtained (Scheme 2, entries 1–3). The reaction with bis(oxazoline) **L4** as ligand gave a complex mixture (entry 4). The Cu(OAc)$_2$/(ligand **L5**) combination delivered **2a** in only 10% yield with 37% enantiomeric excess (ee) (entry 5). Displacing bis(oxazoline) ligand with tri-dentated bis(oxazolinyl)pyridine **L6** boosted the yield, and the enantioselectivity was also increased to 54% (entry 6). Phenyl-substituted ligand **L7** further improved the enantiomeric excess (entry 7). The use of a cationic copper source Cu(OTf)$_2$ or CuOTf·0.5PhH boosted the enantioselectivity to 85%, but the valence of the copper pre-catalysts had no influence on either reactivity or selectivity (entries 8 and 9). A decrease in loading of the ligand **L7** (Cu(OTf)$_2$/**L7** = 1:1) did not result in deterioration of the yield, whereas the

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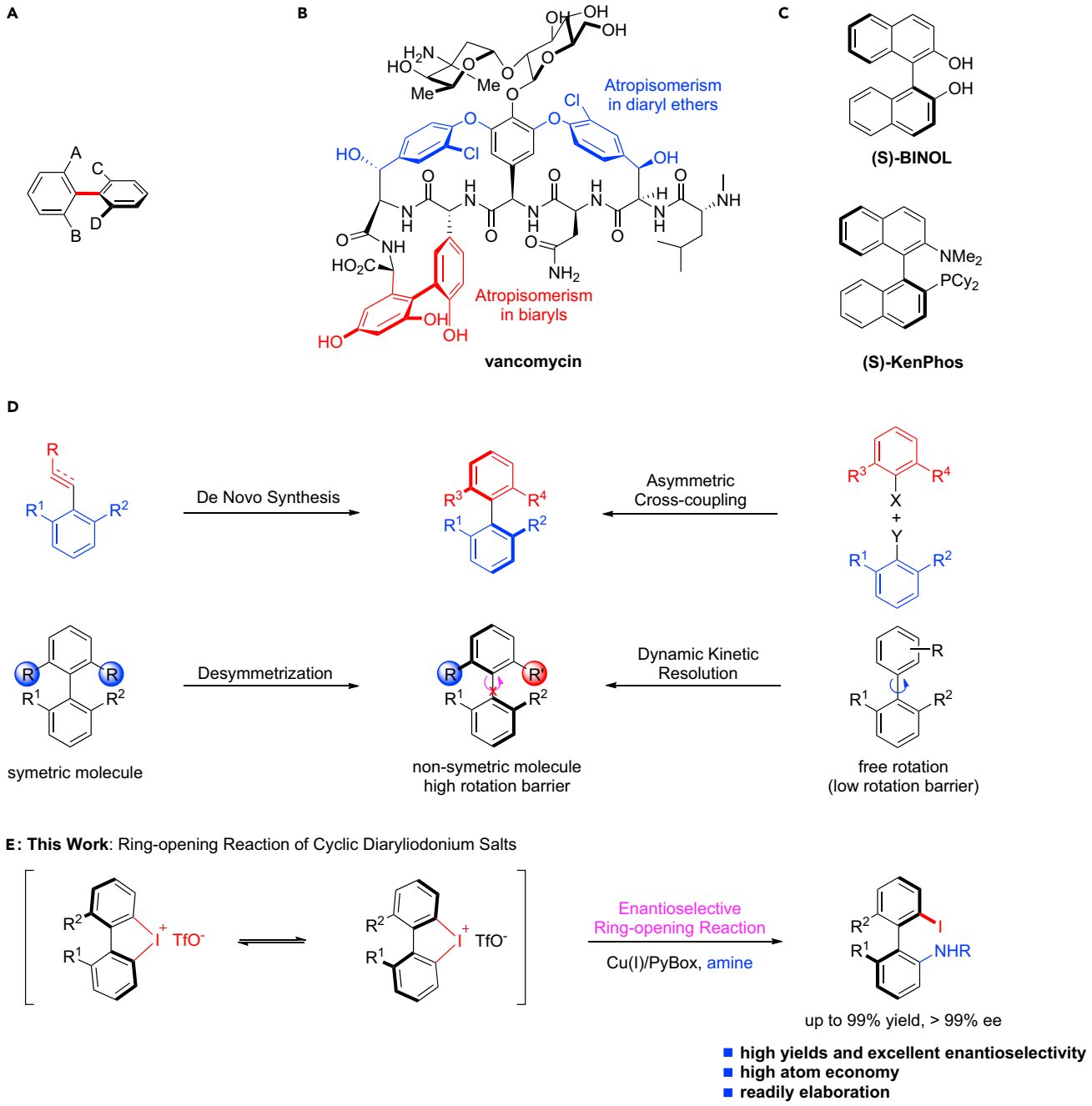

Scheme 1. Strategies in Biaryl Atropisomer Synthesis

(A) Model structure of biaryl atropisomers.

(B) Structure of vancomycin.

(C) Ligands with a biaryl atropisomeric skeleton.

(D) Strategies for the synthesis of asymmetric biaryl atropisomers.

(E) This work.

enantioselectivity was significantly reduced (entry 10). Further screening of the ligands revealed that benzyl- or 2,3-dihydro-1*H*-indene-derived ligands **L8** and **L9** improved the enantiomeric excess to 99% with almost quantitative yields (entries 11 and 12). Copper(I) complexes **A1** or **A2** with a composition of Cu:ligand = 1:2

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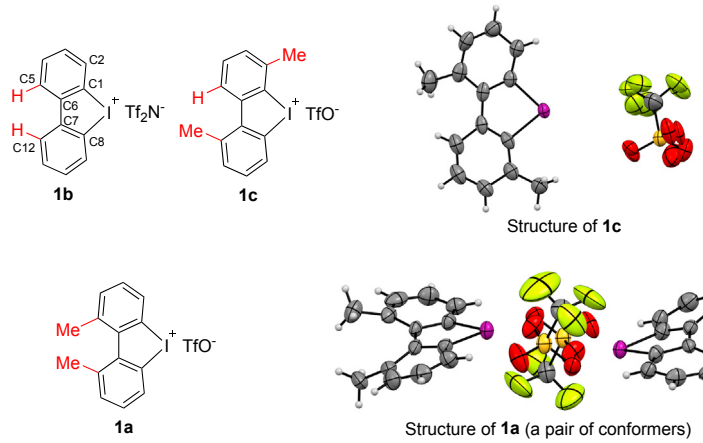

	1b	1c	1a
Angle			
∠C5-C6-C7	125.0 °	128.0 °	127.9 °
∠C6-C7-C12	125.9 °	128.3 °	129.7 °
Distortion C5-C6/C7-C12	0.3 °	3.6 °	31.0 °
Reactivity	0°C, 24 hr: 5% 40°C, 5 hr: 97%	40°C, 5 hr: 30%	0°C, 24 hr: 98%

Figure 1. Structure and Reactivity Properties of Cyclic Diaryliodoniums

Reaction conditions: the reaction was catalyzed by $Cu(Bn\text{-}PyBox)_2PF_6$ (**A1**) in the presence of $BnNH_2$ and Na_2CO_3 in dichloromethane.

prepared independently according to the literature[61] gave more consistent results for the reactions wherein (sub)milligrams of catalyst was used. In addition, the loading of the catalyst **A1** or **A2** could be decreased to 5 mol % without compromising the yield or enantioselectivity of **2a** (entries 13 and 14) (Figures S98, S99, and S188–S189).

A single crystal of **1a** was obtained by slow evaporation of the solvent (methanol/H_2O = 10:1) at room temperature. The crystal structure of **1a** revealed that the distortion of C5-C6/C7-C12 was over 30°, and both (*S*) and (*R*) conformers were found in the crystal packing (Figure 1; also see Data S1). However, the corresponding structures without *ortho* methyl (**1b**)[62] or with one *ortho* methyl group (**1c**) barely have distortion (0.3° and 3.6°, respectively) (Figure 1; also see Data S2), and all the atoms of the biaryl moiety are in approximately the same plane (Figures S14–S18). In sharp contrast to compound **1a**, there are no stereoisomers ((*R*) or (*S*) conformers) in the crystal structures of **1b** or **1c** (Figure 1). Furthermore, the angles of C5–C6–C7 and C6–C7–C12 of **1a** were slightly larger than those of **1b**. It was reported that the five-membered cyclic diaryliodonium showed much lower reactivity than noncyclic $[Ar_2I]^+$ for aromatic nucleophilic substitution reactions.[57,63] Our studies found that the reactivity of these cyclic diaryliodonium depended significantly on their structural properties. Substrates with more distorted structure exhibited higher reactivity (Figure 1). Specifically, under the optimized catalytic system, the reaction of compound **1b** and benzylamine gave 5% yield of the corresponding product at 0°C after 24 hr and 97% yield at 40°C after 5 hr. However,

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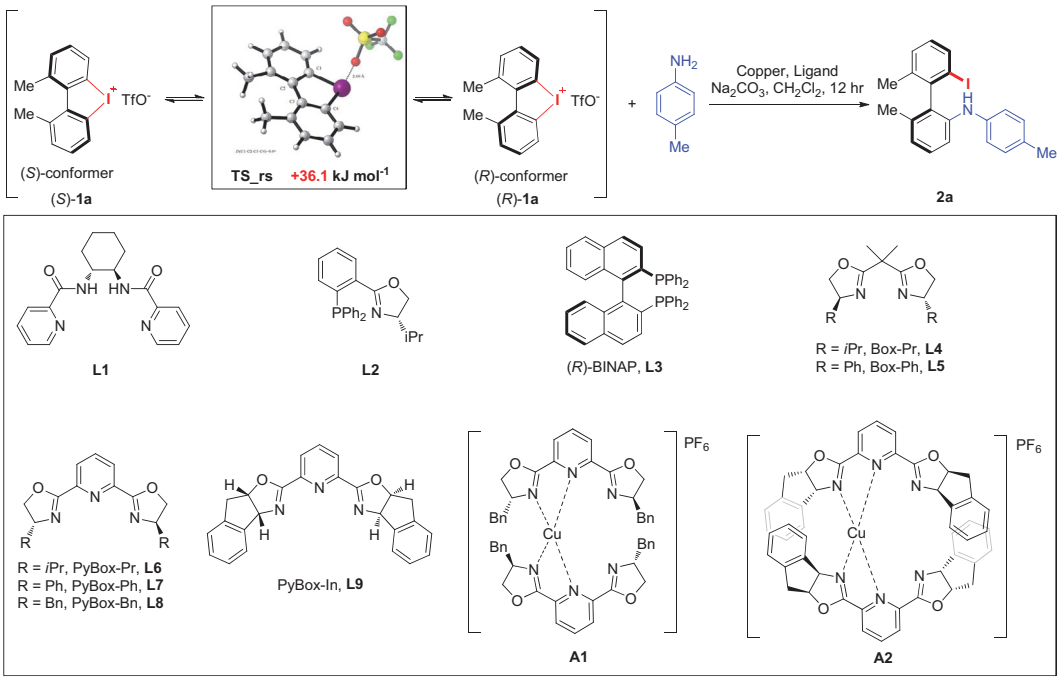

Entry	Cu source	Ligand/mol%	Temp./°C	Yield/%	ee%
1	$Cu(OAc)_2$, 20 mol%	**L1**, 40 mol%	40	99	0
2	$Cu(OAc)_2$, 20 mol%	**L2**, 40 mol%	40	99	0
3	$Cu(OAc)_2$, 20 mol%	**L3**, 40 mol%	40	99	0
4	$Cu(OAc)_2$, 20 mol%	**L4**, 40 mol%	40	complex	-
5	$Cu(OAc)_2$, 20 mol%	**L5**, 40 mol%	40	10	37
6	$Cu(OAc)_2$, 20 mol%	**L6**, 40 mol%	40	99	54
7	$Cu(OAc)_2$, 20 mol%	**L7**, 40 mol%	40	99	60
8	$Cu(OTf)_2$, 20 mol%	**L7**, 40 mol%	40	99	85
9	CuOTf·0.5PhH, 20 mol%	**L7**, 40 mol%	40	99	85
10	$Cu(OTf)_2$, 20 mol%	**L7**, 20 mol%	40	99	26
11	$Cu(OTf)_2$, 20 mol%	**L8**, 40 mol%	0	99	99
12	$Cu(OTf)_2$, 20 mol%	**L9**, 40 mol%	0	99	99
13	**A1**, 5 mol%	-	0	99	98
14	**A2**, 5 mol%	-	0	99	98

Scheme 2. Optimization of the Reaction Conditions

The enantiomeric excess (ee) was determined by chiral high-performance liquid chromatography analysis.

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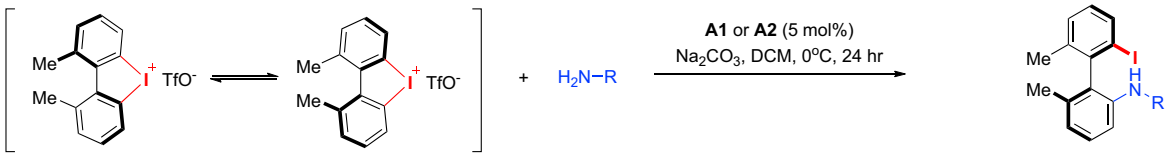
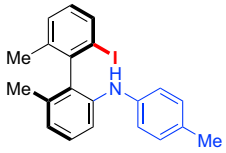
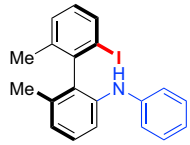
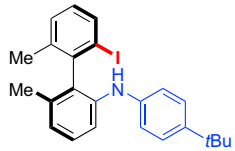




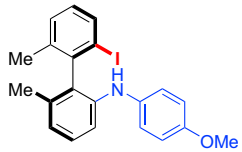
2a, 99%, 98% ee (99%, 98% ee at 1.14 g, 2.50 mmol)



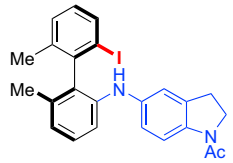
2b, 99%, >99% ee



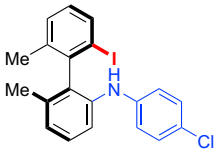
2c, 99%, 98% ee



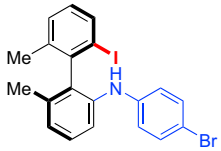
2d, 99%, 97% ee



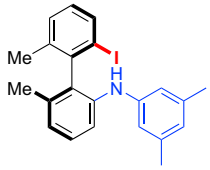
2e, 96%, 98% ee



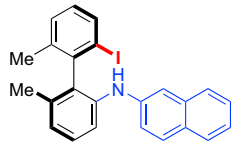
2f, 72% (75% conv.), 99% ee (48 hr)



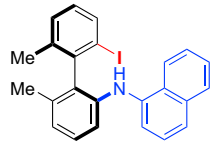
2g, 69%, 99% ee (48 hr)



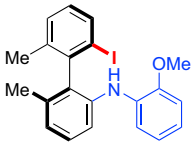
2h, 97%, 99% ee



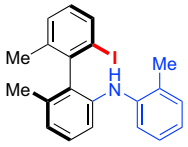
2i, 72% (80% con.), 95% ee (48 hr)



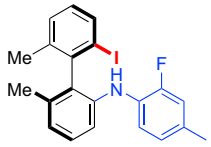
2j, 70% (77% conv.), >99% ee (60 hr)†



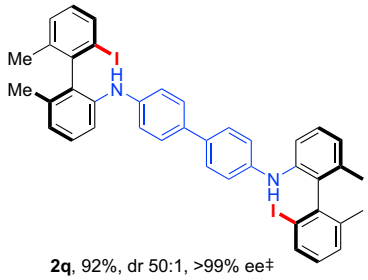
2k, 98%, 99% ee



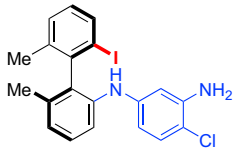
2l, 90%, 96% ee (at 35 °C, 24 hr)



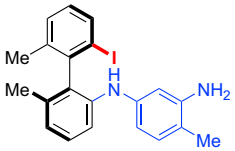
2m, 79% (88% con.), >99% ee (48 hr)



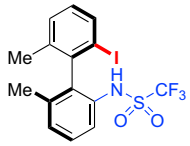
2q, 92%, dr 50:1, >99% ee‡



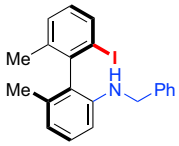
2n, 95%, 98% ee (48 hr)



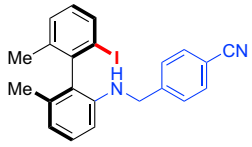
2o, 96%, 96% ee



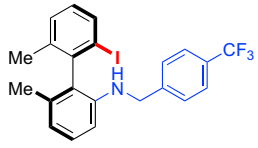
2p, 55% (89% brsm), 90% ee (-20 °C, 48 hr)



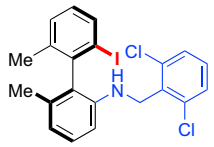
2r, 99%, 95% ee (-5°C)# (24 hr)



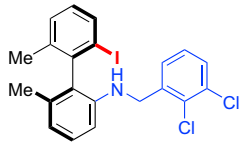
2s, 63% 90% ee (-5°C) (72 hr)



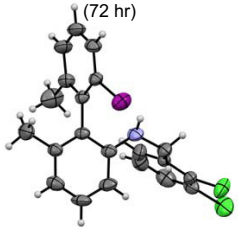
2t, 99% 95% ee (0°C) (24 hr)



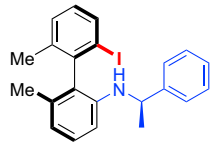
2u, 99% 97% ee (-5°C)



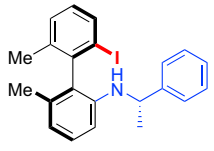
2v, 96% 90% ee (-5 °C) (36 hr)



Structure of (R)-**2v**



2w, 86%, dr 20:1 (-5 °C) (48 hr)



2x, 93%, dr 1:13 (-5 °C) (48 hr)

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Scheme 3. Substrate Scope with Various Amines

Reaction conditions: cyclic diaryliodonium **1a** (1.0 equiv), amine (1.2 equiv), copper catalyst (5.0 mol %) (**A1** for anilines, **A2** for benzylamines), and Na_2CO_3 (3.0 equiv) in dichloromethane (0.050 mol L^{-1}) at 0°C or indicated otherwise. [†]*ent*-**A1** was used; [‡]benzidine (0.5 equiv) was used; [#]benzylamine was used as a limiting reagent.

the reaction of **1c** only produced the desired product in 30% yield after 5 hr at 40°C, possibly as a result of enhanced steric hindrance. Pleasingly, the ring-opening reaction of the more torsionally strained substrate **1a** proceeded uneventfully at 0°C and afforded the corresponding product in 98% yield after 24 hr.

With the optimal conditions for asymmetric ring-opening reaction in hand, we examined the scope for the substrate (Scheme 3). First, a panel of substituted aniline derivatives were tested (**2a–2x**) (Figures S98–S148 and S188–S231). Alkyl substituents had a negligible effect on either the yield or enantioselectivity (**2a–2c**, **2h**). Electron-donating groups on the aniline ring diminished the enantioselectivity slightly (**2d** and **2e**). Electron-withdrawing groups significantly decreased the reactivity of this ring-opening reaction, although almost perfect enantioselectivity could still be achieved (**2f**, **2g**, and **2m**). The bulkiness of *ortho* substituents on the aniline had significant effects on the reactivity (**2j–2m**). For instance, with naphthalen-1-amine and 2-methylaniline as the substrates, the reaction became sluggish and either increased reaction temperature or prolonged reaction time was necessary to get satisfactory conversion (**2l** and **2j**). Taking advantage of this *ortho*-substituent effect, the catalyst was able to differentiate two amino groups with different steric environments. Compounds **2n** and **2o** were formed as the key products with attractive yields and enantioselectivity. In addition, trifluoromethanesulfonamide was also amenable to the copper-catalyzed ring-opening reaction, and a lower reaction temperature was applied to get satisfactory enantioselectivity (**2p**). Starting from benzidine, double ring-opening product **2q** was formed with 50:1 dr and fantastic selectivity. Benzylamines displayed higher reactivity than anilines, and the reactions of benzylamines were conducted at a slightly lower reaction temperature to gain satisfactory ee values (**2r–2x**). The structure of the products was confirmed by single-crystal X-ray diffraction analysis of **2v**, and the absolute configuration of the major enantiomer was determined to be *R* (Data S3). The extant chirality in 1-phenylethanamine imparted negligible effects on the yield or selectivity. With optically pure (*R*)- and (*S*)-1-phenylethanamine as the amination reagents, compounds **2w** and **2x** were formed with excellent diastereoselectivities regardless of the existed center chirality, underlining the high catalyst-directed stereocontrol. Finally, to demonstrate the practicability, the copper-catalyzed asymmetric ring-opening reaction was facilely performed on a gram scale of **1a** (1.14 g, 2.50 mmol) with *p*-methylaniline, and product **2a** was obtained in 99% yield with 98% ee (see Scheme 3, **2a**).

Subsequently, a study was initiated to further explore the substrate scope regarding the diaryliodonium salts (Scheme 4; Figures S19–S97). The reaction smoothly delivered the corresponding products with enantiomeric excesses ranging from 95% to 97% when additional methyl groups were introduced to the *meta* or *para* positions (**2y–2cc**) (Figures S149–S158 and S232–S241). Pleasingly, the asymmetric ring-opening reaction was applicable to the 2,2′-diethyl-1,1′-biphenyl-derived cyclic iodonium salt, and the reaction proceeded uneventfully with minimal reduction in stereocontrol (**2dd** and **2ee**) (Figures S159–S162 and S242–S245). For non-symmetric cyclic diaryliodoniums, a group adjacent to the iodine atom was introduced to accomplish exclusive regioselectivity (**2ff–2nn**) (Figures S163–S181 and S246–S263). Furthermore, the reaction was not limited to 1,1′-biphenyl substrates, and compound **2jj**

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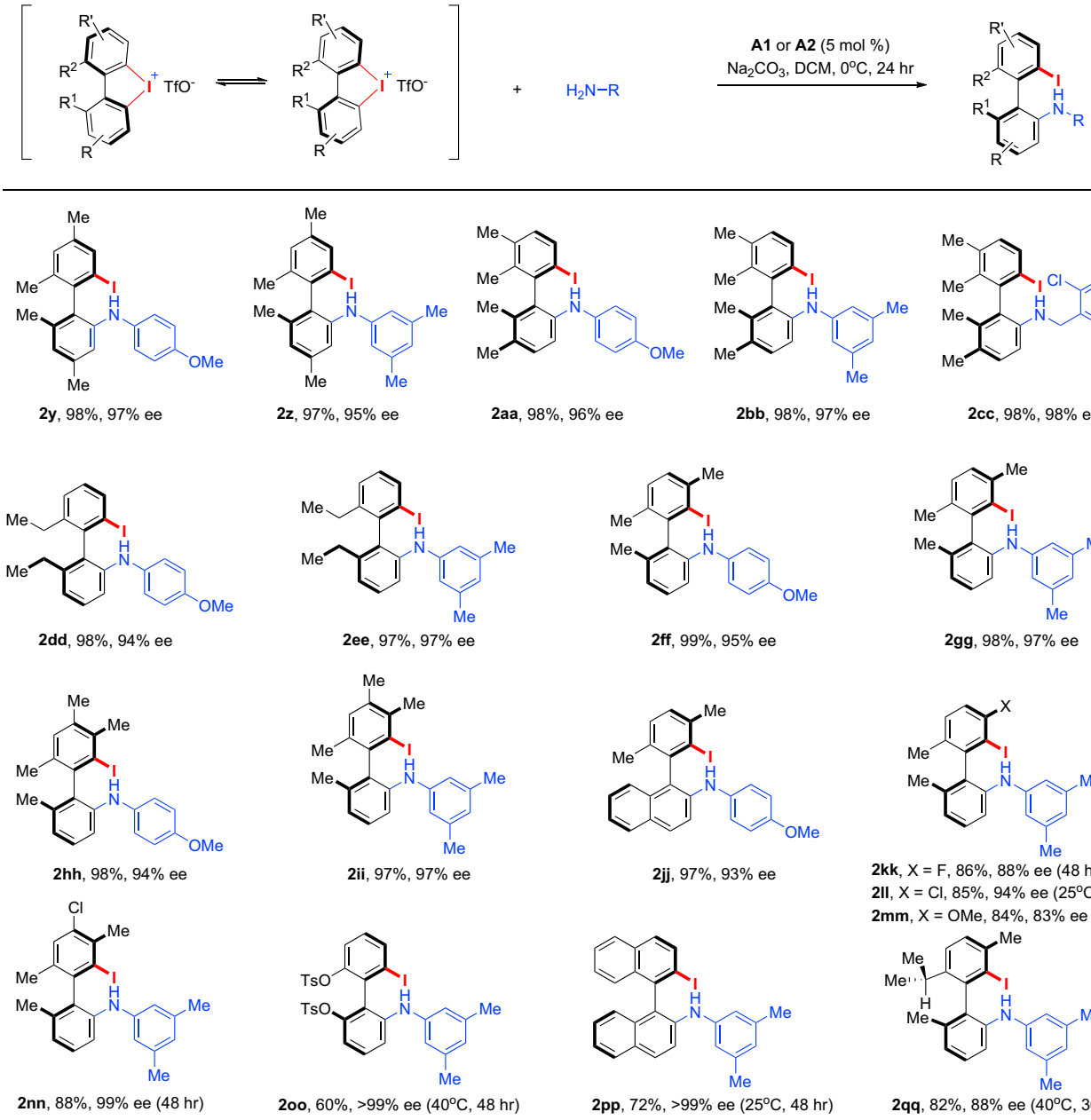

Scheme 4. Substrate Scope with Cyclic Diaryliodoniums

Reaction conditions: cyclic diaryliodonium **1a** (1.0 equiv), amine (1.2 equiv), copper catalyst (5.0 mol %) (**A1** for anilines and **A2** for benzylamines), and Na_2CO_3 (3.0 equiv) in dichloromethane (0.05 mol L^{-1}) at 0°C or indicated otherwise.

bearing a naphthyl-phenyl skeleton was isolated in 97% yield with excellent stereoinduction. Incorporation of a fluorine or chlorine atom, or a methoxyl group adjacent to the iodine atom resulted in a decrease of enantioselectivity, and the corresponding products **2kk–2mm** were delivered in 84%–86% yields and synthetically valuable enantioselectivity. High enantiocontrol could still be achieved when the substrate had an electron-withdrawing group at the *meta* position of the iodine atom (compare **2nn** with **2gg**). Notwithstanding the sluggish reaction rate of the 2,2-biphenol derivative, the high ee value of **2oo** still showcased the high potential of this reaction to apply in *ortho* oxygenated biaryls (Figures S182–S183 and

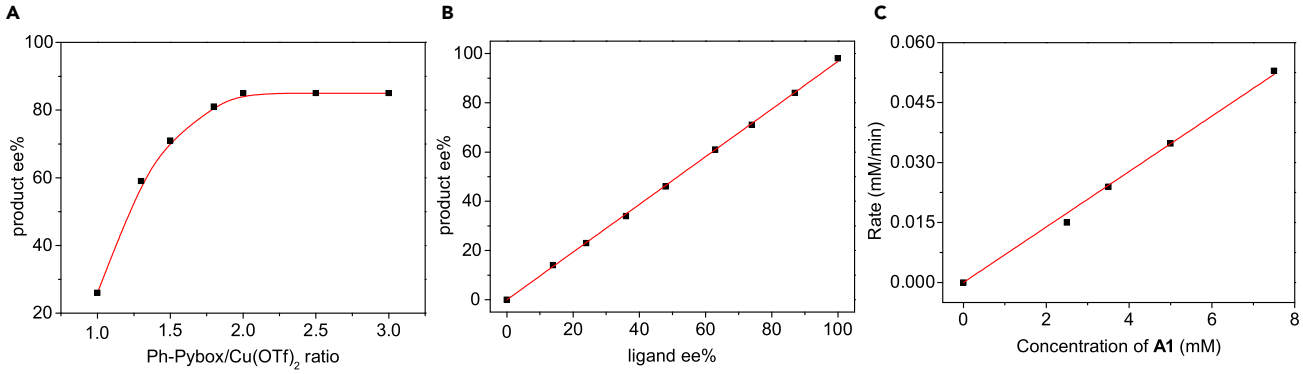

Figure 2. Mechanistic Studies

(A) Enantiomeric excess of **2a** versus the ratio of Ph-PyBox/Cu(OTf)2.

(B) Correlation between the enantiomeric excesses of **2a** and the ee values of Bn-PyBox.

(C) Plot of the initial rate versus the concentration of **A1**.

S264–S265). The reaction of diaryliodonium with the 1,1′-binaphthalene skeleton also proceeded uneventfully to afford high enantioselectivity (**2pp**) (Figures S184–S185 and S266–S267). However, introducing an *iso*-propyl group at the 6-position resulted in a decrease in enantioselectivity (88% ee) of the corresponding aminoiodide (**2qq**) (Figures S186–S187 and S268–S269).

To get preliminary mechanistic insights of this copper-catalyzed ring-opening reaction, we examined the effect of the ratio of **L7**/Cu(OTf)$_2$ on the enantioselectivity. The enantiomeric excess gradually increased when the ratio of **L7**/Cu(OTf)$_2$ was increased before reaching the highest value when **L7**/Cu(OTf)$_2$ was 2:1 (Figure 2A). Further increasing the loading of ligand **L7** did not improve the ee values. Analysis of the ee values of the product **2a** produced by Pybox-Bn ligand **L8** with various degrees of reduced enantiomeric excess revealed a linear correlation between the ee values of the product and the ligand (Figure 2B), suggesting that monomeric CuL* (L* = Pybox-Bn) might be the active species. Catalysts containing one copper bearing two bis(oxazolinyl)pyridine ligands (i.e., complex **A1**), dimeric forms, or higher-order aggregates were not supposed to be active species. These results corroborate the requirement of excess ligand for high enantiocontrol, which allows effective suppression of the dissociation of bis(oxazolinyl)pyridine ligand from the metal center.

Although a precise understanding of the catalytic rationale is beyond reach at this point, a plausible reaction pathway was proposed on the basis of the above studies (Scheme 5). Disproportionation of copper species occurred in a solution of pre-catalyst **A1** and amine in dichloromethane. The catalyst **A1** is an inactive species, which would quickly dissociate to give **A3**. Species **A3** was postulated as the real catalytically active species in this reaction. On the basis of the results presented in Figure 2B, the dissociation of **A1** to **A3** was much faster than the rate of the **A3**-catalyzed ring-opening reaction. The fast dissociation of **A1** to **A3** was further confirmed by the first-order dependence of the reaction rate on the concentration of catalyst **A1**, which was measured by monitoring the initial reaction rates at various catalyst loadings (Figure 2C) (Tables S1–S4; Figure S1). In addition, in the presence of amines, the copper complex **A3** undergoes ligand displacement to form an amino-copper complex, which, because of the lack of chiral ligand, catalyzes the reaction to give products with no stereoinduction. The independent reactions of Cu(OTf)$_2$ or CuOTf·0.5PhH in the absence of bis(oxazolinyl)pyridine

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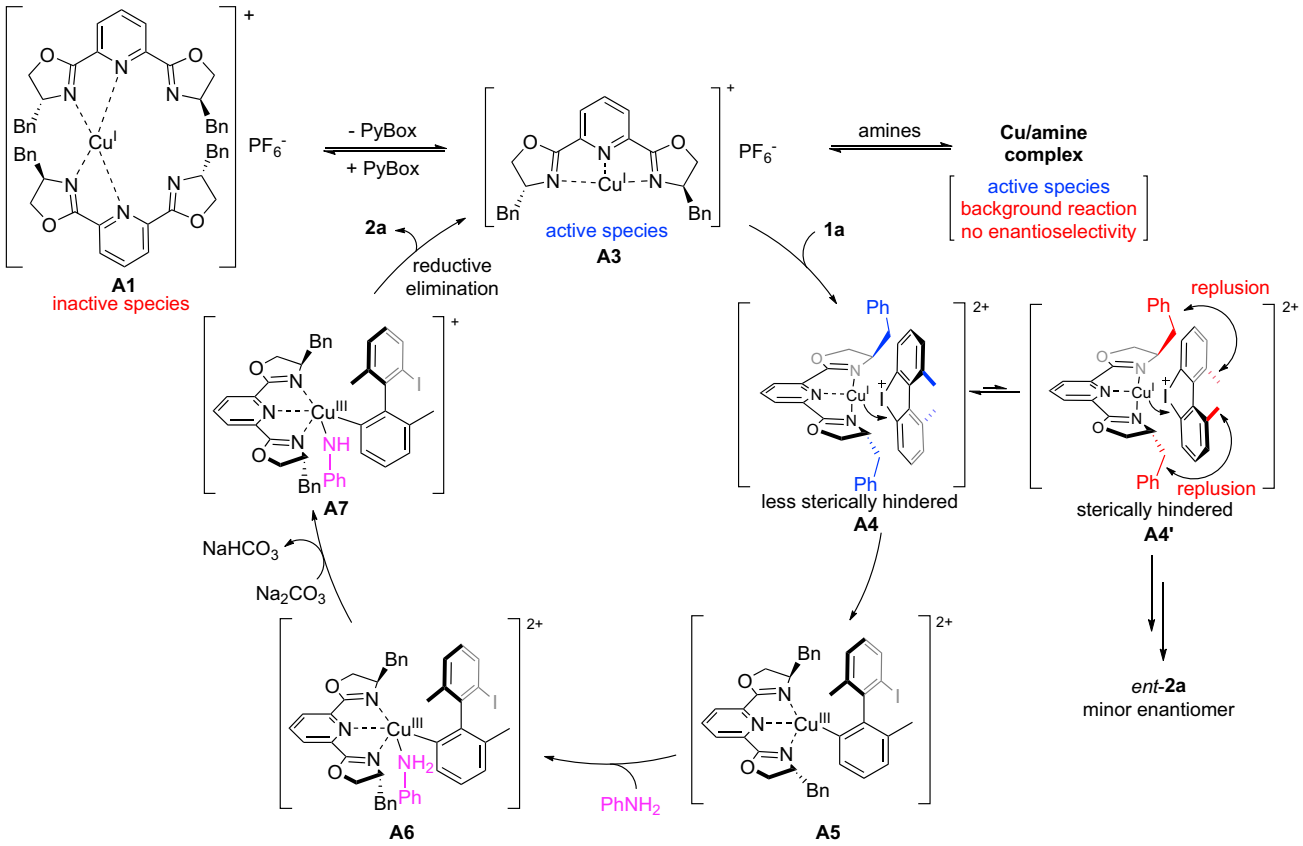

Scheme 5. The Rationale of the Copper-Catalyzed Ring-Opening Reaction

ligand proceeded faster than the reactions with ligands. The amount of amino-copper complex may decrease significantly via coordination-dissociation equilibrium upon increasing the loading of bis(oxazolinyl)pyridine. The interaction between **A3** and cyclic iodonium would give **A4** and **A4′**, where the two conformers of iodonium moieties should rapidly interconvert. However, **A4′** is sterically disfavored because of steric repulsion between the benzyl group of bis(oxazolinyl)pyridine and the methyl in cyclic diaryliodonium, which would quickly invert to **A4** and undergo a ring-opening reaction to give **A5** to establish axial chirality. Subsequently, the coordination of aniline to the Cu(III) center would give intermediate **A6**. Deprotonation of the amine moiety of **A6** followed by reductive elimination delivers the major enantiomer (*R*)-**2a** and regenerates the catalyst **A3** to complete the catalytic cycle.

Computational calculations on the ring-opening step with **A3** as the catalyst were performed (Figures S4–S8). It was found that (1) the two diastereomers of the ring-opening copper complexes have significant energy differences (30.4 kJ/mol for **1b**-derived complexes and 18.8 kJ/mol for **1a**-derived complexes) (Scheme 6A), and (2) the oxidation addition is a fast step. The reaction of Cu(I)/PyBox with **1a** proceeds much faster than the reaction of Cu(I)/PyBox with **1b** (3.7 kJ/mol versus 19.3 kJ/mol) (Schemes 6B and 6C), but oxidative addition could not be the rate-determining step. The computational activation energies are consistent with the results reported by Canty and Sanford and their co-workers, who found that the oxidative addition of Cu(I) with $[(Mes)PhI]^+$ had a very low activation energy.[64,65]

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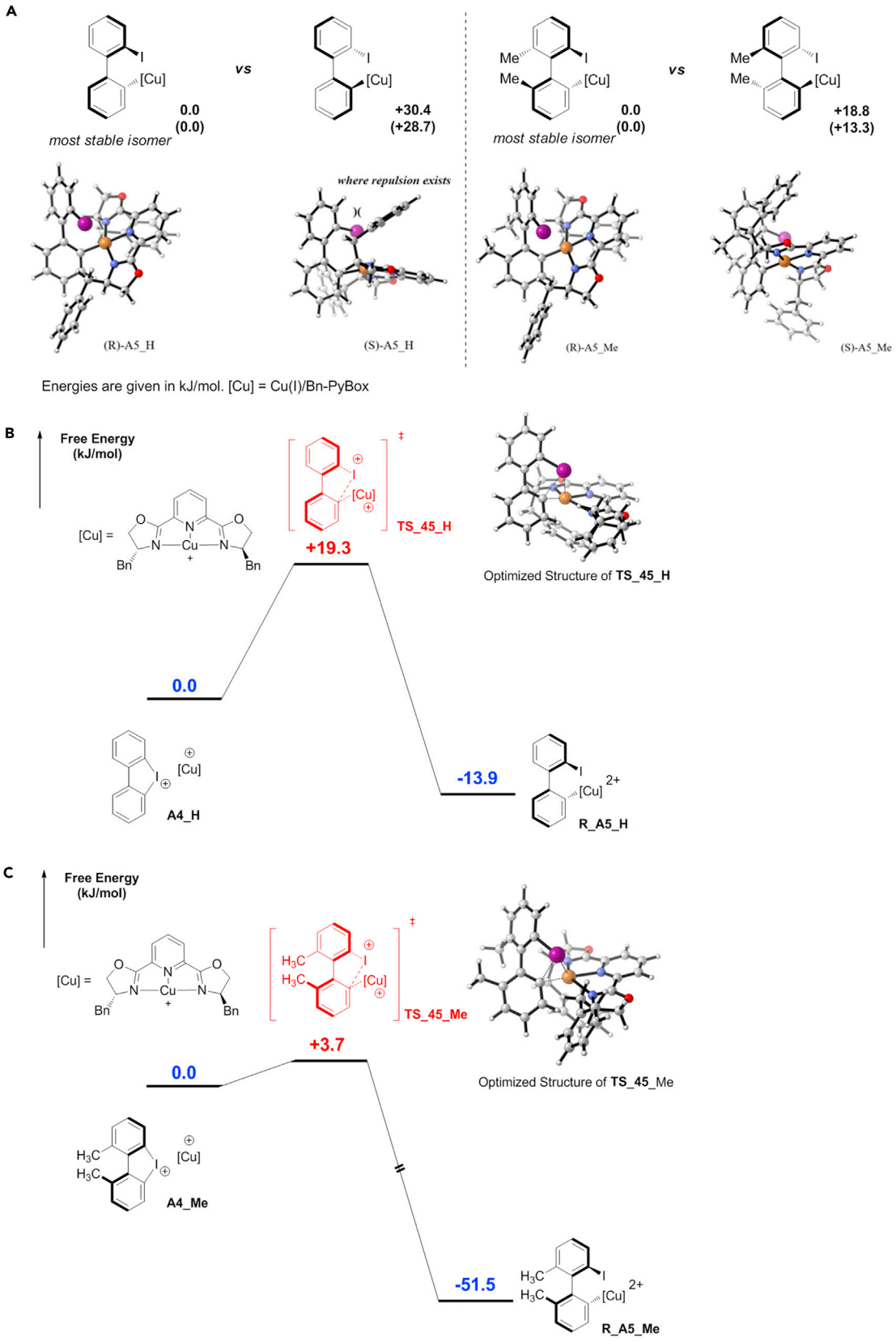

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Scheme 6. Computational Results
(A) Energies for copper complexes.
(B) Energy changes of the oxidative addition step with **1b**.
(C) Energy changes of the oxidative addition step with **1a**.

Conclusion

A catalytic enantioselective synthesis of atropisomeric 2′-iodo-[1,1′-biphenyl]-2-amines by a highly efficient ring-opening amination reaction of cyclic diaryliodoniums was developed. The relatively low reactivity of cyclic diaryliodoniums was overcome by increasing the distortion of the cyclic substrates. In this reaction, the chiral Cu-bis(oxazolinyl)pyridine complex likely discriminated the two conformers of cyclic diaryliodonium salts to give products with very high enantiomeric excess. A linear correlation between ee values of **2a** and the ee values of Pybox-Bn was observed, indicating that monomeric $Cu(Pybox\text{-}Bn)^{+}$ was more likely to be the actual catalyst in this reaction. The protocol offers a general method for the construction of axially chiral biaryliodides under mild conditions, which are expected to be useful precursors for further elaboration to structurally diverse biaryl atropisomers.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

DATA AND SOFTWARE AVAILABILITY

The crystallography data have been deposited at the Cambridge Crystallographic Data Center (CCDC) under accession numbers CCDC: 1565987 (**1a**), CCDC: 1565988 (**1c**), and CCDC: 1565989 (**2v**) and can be obtained free of charge from www.ccdc.cam.ac.uk/getstructures.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, 269 figures, 4 tables, and 3 data files and can be found with this article online at https://doi.org/10.1016/j.chempr.2018.01.017.

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AUTHOR CONTRIBUTIONS

K.Z. initiated this project. K.Z., L.D., and S.X. performed the experiments and analyzed data for all compounds. Z.G. designed and directed the project. Z.G. wrote the manuscript. J.J. and Y.F. performed the computational calculation.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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REFERENCES AND NOTES

1. Kumarasamy, E., Raghunathan, R., Sibi, M.P., and Sivaguru, J. (2015). Nonbiaryl and heterobiaryl atropisomers: molecular templates with promise for atropselective chemical transformations. Chem. Rev. *115*, 11239–11300.
2. Wencel-Delord, J., Panossian, A., Leroux, F.R., and Colobert, F. (2015). Recent advances and new concepts for the synthesis of axially stereoenriched biaryls. Chem. Soc. Rev. *44*, 3418–3430.
3. Bringmann, G., Gulder, T., Gulder, T.A.M., and Breuning, M. (2011). Atroposelective total synthesis of axially chiral biaryl natural products. Chem. Rev. *111*, 563–639.
4. Bringmann, G., Mortimer, A.J.P., Keller, P.A., Gresser, M.J., Garner, J., and Breuning, M. (2005). Atroposelective synthesis of axially chiral biaryl compounds. Angew. Chem. Int. Ed. *44*, 5384–6527.
5. Smyth, J.E., Butler, N.M., and Keller, P.A. (2015). A twist of nature – the significance of atropisomers in biological systems. Nat. Prod. Rep. *32*, 1562–1583.
6. Clayden, J., Moran, W.J., Edwards, P.J., and LaPlante, S.R. (2009). The challenge of atropisomerism in drug discovery. Angew. Chem. Int. Ed. *48*, 6398–6401.
7. Kozlowski, M.C., Morgan, B.J., and Linton, E.C. (2009). Total synthesis of chiral biaryl natural products by asymmetric biaryl coupling. Chem. Soc. Rev. *38*, 3193–3207.
8. Zhang, D., and Wang, Q. (2015). Palladium catalyzed asymmetric Suzuki–Miyaura coupling reactions to axially chiral biaryl compounds: chiral ligands and recent advances. Coord. Chem. Rev. *286*, 1–16.
9. Hayashi, T., Hayashizaki, K., Kiyoi, T., and Ito, Y. (1988). Asymmetric synthesis catalyzed by chiral ferrocenylphosphine-transition-metal complexes. 6. Practical asymmetric synthesis of 1,1′-binaphthyls via asymmetric cross-coupling with a chiral [(alkoxyalkyl)ferrocenyl] monophosphine/nickel catalyst. J. Am. Chem. Soc. *110*, 8153–8156.
10. Shirakawa, D., Wu, X., and Maruoka, K. (2013). Kinetic resolution of axially chiral 2-amino-1,1′-biaryls by phase-transfer-catalyzed N-allylation. Angew. Chem. Int. Ed. *52*, 14200–14203.
11. Shen, X., Jones, G.O., Watson, D.A., Bhayana, B., and Buchwald, S.L. (2012). Enantioselective synthesis of axially chiral biaryls by the Pd-catalyzed Suzuki–Miyaura reaction: substrate scope and quantum mechanical investigations. J. Am. Chem. Soc. *132*, 11278–11287.
12. Meyers, A.I., and Lutomski, K.A. (1982). Enantioselective synthesis of binaphthyls via nucleophilic aromatic substitution on chiral oxazolines. J. Am. Chem. Soc. *104*, 879–881.
13. Tanaka, K., ed. (2013). Transition-Metal-Mediated Aromatic Ring Construction (John Wiley).
14. Tanaka, K., Nishida, G., Wada, A., and Noguchi, K. (2004). Enantioselective synthesis of axially chiral phthalides through cationic [$Rh^{I}(H_8$-binap)]-catalyzed cross alkyne cyclotrimerization. Angew. Chem. Int. Ed. *43*, 6510–6512.
15. Link, A., and Sparr, C. (2014). Organocatalytic atropselective aldol condensation: synthesis of axiallyl chiral biaryls by arene formation. Angew. Chem. Int. Ed. *53*, 5458–5461.
16. Shibata, T., Fujimoto, T., Yokota, K., and Takagi, K. (2004). Iridium complex-catalyzed highly enantio- and diastereoselective [2+2+2] cycloaddition for the synthesis of axially chiral teraryl compounds. J. Am. Chem. Soc. *126*, 8382–8383.
17. Ros, A., Estepa, B., Ramírez-López, P., Álvarez, E., Fernández, R., and Lassaletta, J.M. (2013). Dynamic kinetic cross-coupling strategy for the asymmetric synthesis of axially chiral heterobiaryls. J. Am. Chem. Soc. *135*, 15730–15733.
18. Bhat, V., Wang, S., Stoltz, B.M., and Virgil, S.C. (2013). Asymmetric synthesis of quinap via dynamic kinetic resolution. J. Am. Chem. Soc. *135*, 16829–16832.
19. Zheng, J., and You, S.L. (2014). Construction of axial chirality by rhodium-catalyzed asymmetric dehydrogenative Heck coupling of biaryl compounds with alkenes. Angew. Chem. Int. Ed. *53*, 13244–13247.
20. Wang, J., Chen, M.W., Ji, Y., Hu, S.B., and Zhou, Y.G. (2016). Kinetic resolution of axially chiral 5- or 8-substituted quinilines via asymmetric transfer hydrogenation. J. Am. Chem. Soc. *138*, 10413–10416.
21. Hirai, M., Terada, S., Yoshida, H., Ebine, K., Hirata, T., and Kitagawa, O. (2016). Catalytic enantioselective synthesis of N–C axially chiral mebroqualone and its derivatives through reductive asymmetric desymmetrization. Org. Lett. *18*, 5700–5703.
22. Ma, G., Deng, J., and Sibi, M.P. (2014). Fluxionally chiral DMAP catalysts: kinetic resolution of axially chiral biaryl compounds. Angew. Chem. Int. Ed. *53*, 11818–11821.
23. Hazra, C.K., Dherbassy, Q., Wencel-Delord, J., and Colobert, F. (2014). Synthesis of axially chiral biaryls through sulfoxide-directed asymmetric mild C-H activation and dynamic kinetic resolution. Angew. Chem. Int. Ed. *53*, 13871–13875.
24. Wesch, T., Leroux, F.R., and Colobert, F. (2013). Atropodiastereoselective C-H olefination of biphenyl *p*-tolyl sulfoxides with acrylates. Adv. Synth. Catal. *355*, 2139–2144.
25. Dherbassy, Q., Schwertz, G., Chessé, M., Hazra, C.K., Wencel-Delord, J., and Colobert, F. (2016). 1,1,1,3,3,3-Hexafluoroisopropanol as a remarkable medium for atroposelective sulfoxide directed Fujiwara-Moritani reaction with acrylates and styrenes. Chem. Eur. J. *22*, 1735–1743.
26. Guo, F., Konkol, L.C., and Thomson, R.J. (2011). Enantioselective synthesis of biphenols from 1,4-diketones by traceless central-to-axial chirality exchange. J. Am. Chem. Soc. *133*, 18–20.
27. Raut, V.S., Jean, M., Vanthuyne, N., Roussel, C., Constantieux, T., Bressy, C., Bugaut, X., Bonne, D., and Rodriguez, J. (2017). Enantioselective syntheses of furan atropisomers by an oxidative central-to-axial chirality conversion strategy. J. Am. Chem. Soc. *139*, 2140–2143.
28. Gustafson, J.L., Lim, D., and Miller, S.J. (2010). Dynamic kinetic resolution of biaryl atropisomers via peptide-catalyzed asymmetric bromination. Science *328*, 1251–1255.
29. Miyaji, R., Asano, K., and Matsubara, S. (2015). Bifunctional organocatalysts for the enantioselective synthesis of axially chiral isoquinoline N-oxides. J. Am. Chem. Soc. *137*, 6766–6769.
30. Mori, K., Ichikawa, Y., Kobayashi, M., Shibata, Y., Yamanaka, M., and Akiyama, T. (2013). Enantioselective synthesis of multisubstituted biaryl skeleton by chiral phosphoric acid catalyzed desymmetrization/kinetic resolution sequence. J. Am. Chem. Soc. *135*, 3964–3970.
31. Li, G.Q., Gao, H., Keene, C., Devonas, M., Ess, D.H., and Kürti, L. (2013). Organocatalytic aryl–aryl bond formation: an atroposelective [3,3]-rearrangement approach to binam derivatives. J. Am. Chem. Soc. *135*, 7414–7417.
32. Kanta De, C., Pesciaioli, F., and List, B. (2013). Catalytic asymmetric benzidine rearrangement. Angew. Chem. Int. Ed. *52*, 9293–9295.
33. Gao, H., Xu, Q., Keene, C., Yousufuddin, M., Ess, D.H., and Kürti, L. (2016). Practical organocatalytic synthesis of functionalized non-C2-symmetrical atropisomeric biaryls. Angew. Chem. Int. Ed. *55*, 566–571.
34. Chen, Y.H., Cheng, D.J., Zhang, J., Wang, Y., Liu, X.Y., and Tan, B. (2015). Atropselective synthesis of axially chiral biaryldiols via organocatalytic arylation of 2-naphthols. J. Am. Chem. Soc. *137*, 15062–15065.
35. Zhang, L., Zhang, J., Ma, J., Cheng, D.J., and Tan, B. (2017). Highly atropselective synthesis of arylpyrroles by catalytic asymmetric Paal-Knorr reaction. J. Am. Chem. Soc. *139*, 1714–1717.
36. Jolliffe, J.D., Armstrong, R.J., and Smith, M.D. (2017). Catalytic enantioselective synthesis of atropisomeric biaryls by a cation-directed O-alkylation. Nat. Chem. *9*, 558–562.
37. Shimada, T., Cho, Y.H., and Hayashi, T. (2002). Nickel-catalyzed asymmetric Grignard cross-coupling of dinaphthothiophene giving axially chiral 1,1′-binaphthyls. J. Am. Chem. Soc. *124*, 13396.
38. Kian, A., Miki, H., Cho, Y.H., and Hayashi, T. (2004). Palladium-catalyzed Heck and carbonyl reactions of a dinaphthaleneiodonium salts forming functionalized 2-iodo-1,1′-binaphthyls. Adv. Synth. Catal. *346*, 1728.
39. Zhu, D., Liu, Q., Luo, B., Chen, M., Pi, R., Huang, P., and Wen, S. (2013). Synthesis of carbazoles via one-pot copper-catalyzed amine insertion into cyclic diphenyleneiodoniums as a strategy to generate a drug-like chemical library. Adv. Synth. Catal. *355*, 2172–2178.
40. Kang, S.K., Lee, S.H., and Lee, D. (2000). Copper-catalyzed N-arylation of amines with hypervalent iodonium salts. Synlett *2000*, 1022–1024.

41. Chatterjee, N., and Goswami, A. (2017). Synthesis and application of cyclic diaryliodonium salts: a platform for bifunctionalization in a single step. Eur. J. Org. Chem. *2017*, 3023–3032.

42. Modha, S.G., and Greaney, M.F. (2015). Atom-economical transformation of diaryliodonium salts: tandem C–H and N–H arylation of indoles. J. Am. Chem. Soc. *137*, 1416–1419.

43. Berzina, B., Sokolovs, I., and Suna, E. (2015). Copper-catalyzed para-selective C–H amination of electron-rich arenes. ACS Catal. *5*, 7008–7014.

44. Sokolovs, I., Lubriks, D., and Suna, E. (2014). Copper-catalyzed intermolecular C–H amination of (hetero)arenes via transient unsymmetrical λ^3-iodanes. J. Am. Chem. Soc. *136*, 6920–6928.

45. Li, J., and Liu, L. (2012). Simple and efficient amination of diaryliodonium salts with aqueous ammonia in water without metal-catalyst. RSC Adv. *2*, 10485–10487.

46. Beringer, F.M., Forgione, P.S., and Yudis, M.D. (1960). Diaryliodnium salts-XII: the phenylation of dimedone, dibenzoylmethane and tribenzoylmethane. Tetrahedron *8*, 49–63.

47. Beringer, F.M., Galton, S.A., and Huang, S.J. (1962). Diaryliodonium salts. XVII. the phenylation of 1,3-indandiones. J. Am. Chem. Soc. *84*, 2819–2823.

48. Bigot, A., Williamson, A.E., and Gaunt, M.J. (2011). Enantioselective alpha-arylation of N-acyloxazolidinones with copper(II)-bisoxazoline catalysts and diaryliodonium salts. J. Am. Chem. Soc. *133*, 13778–13781.

49. Cahard, E., Male, H.P., Tissot, M., and Gaunt, M.J. (2015). Enantioselective and regiodivergent copper-catalyzed electrophilic arylation of allylic amides with diaryliodonium salts. J. Am. Chem. Soc. *137*, 7986–7989.

50. Zhu, S., and MacMillan, D.W.C. (2012). Enantioselective copper-catalyzed construction of aryl pyrroloindolines via an arylation-cyclization cascade. J. Am. Chem. Soc. *134*, 10815–10818.

51. Harvey, J.S., Simonovich, S.P., Jamison, C.R., and MacMillan, D.W.C. (2011). Enantioselective α-arylation of carbonyls via Cu(I)-bisoxazoline catalysis. J. Am. Chem. Soc. *133*, 13782–13785.

52. Lukamto, D.H., and Gaunt, M.J. (2017). Enantioselective copper-catalyzed arylation-driven semipinacol rearrangement of tertiary allylic alcohols with diaryliodonium salts. J. Am. Chem. Soc. *139*, 9160–9163.

53. Beaud, R., Phipps, R., and Gaunt, M.J. (2016). Enantioselective Cu-catalyzed arylation of secondary phosphine oxides with diaryliodonium salts toward the synthesis of P-chiral phosphines. J. Am. Chem. Soc. *138*, 13183–13186.

54. Phipps, R.J., Grimster, N.P., and Gaunt, M.J. (2008). Cu(II)-catalyzed direct and site-selective arylation of indoles under mild conditions. J. Am. Chem. Soc. *130*, 8172–8174.

55. Phipps, R.J., and Gaunt, M.J. (2009). A meta-selective copper-catalyzed C–H bond arylation. Science *323*, 1593–1597.

56. Merritt, E.A., and Olofsson, B. (2009). Diaryliodonium salts: a journey from obscurity to fame. Angew. Chem. Int. Ed. *48*, 9052–9070.

57. Grushin, V.V. (2000). Cyclic diaryliodonium ions: old mysteries solved and new applications envisaged. Chem. Soc. Rev. *29*, 315–324.

58. Wu, B., and Yoshikai, N. (2015). Conversion of 2-iodobiaryls into 2,2′-diiodobiaryls via oxidation-iodination sequences: a versatile route to ladder-type heterofluorenes. Angew. Chem. Int. Ed. *54*, 8736–8739.

59. Yoshimura, A., and Zhdankin, V.V. (2016). Advances in synthetic applications of hypervalent iodine compounds. Chem. Rev. *116*, 3328–3435.

60. Mailyan, A.K., Eickhoff, J.A., Minakova, A.S., Gu, Z., Lu, P., and Zakarian, A. (2016). Cutting-edge and time-honored strategies for stereoselective construction of C–N bonds in total synthesis. Chem. Rev. *116*, 4441–4557.

61. Panera, M., Diez, J., Merino, I., Rubio, E., and Gamasa, M.P. (2009). Synthesis of copper(I) complexes containing enantiopure pybox ligands. First assays on enantioselective synthesis of propargylamines catalyzed by isolated copper(I) complexes. Inorg. Chem. *48*, 11147–11160.

62. Postnikov, P.S., Guselnikova, O.A., Yusubov, M.S., Yoshimura, A., Nemykin, V.N., and Zhdankin, V.V. (2015). Preparation of X-ray structural studies of dibenziodolium derivatives. J. Org. Chem. *80*, 5783–5788.

63. Kotali, E., and Varvoglis, A. (1987). Dialkylcarbamoyl(diaryl)iodanes. J. Chem. Soc. Perkin Trans. 1, 2759–2763.

64. Ichiishi, N., Canty, A.J., Yates, B.F., and Sanford, M.S. (2013). Cu-Catalyzed fluorination of diaryliodonium salts with KF. Org. Lett. *15*, 5134–5137.

65. Ichiishi, N., Canty, A.J., Yates, B.F., and Sanford, M.S. (2014). Mechanistic investigations of Cu-catalyzed fluorination of diaryliodonium salts: elaborating the Cu^{I}/Cu^{III} manifold in copper catalysis. Organometallics *33*, 5525–5534.