Enantioselective Access to C-N Axially Chiral Isoquinolones via Dynamic Kinetic Transformation of Carbene Reagents: Unique Chiral Induction Enabled by Dual Role of the Catalyst

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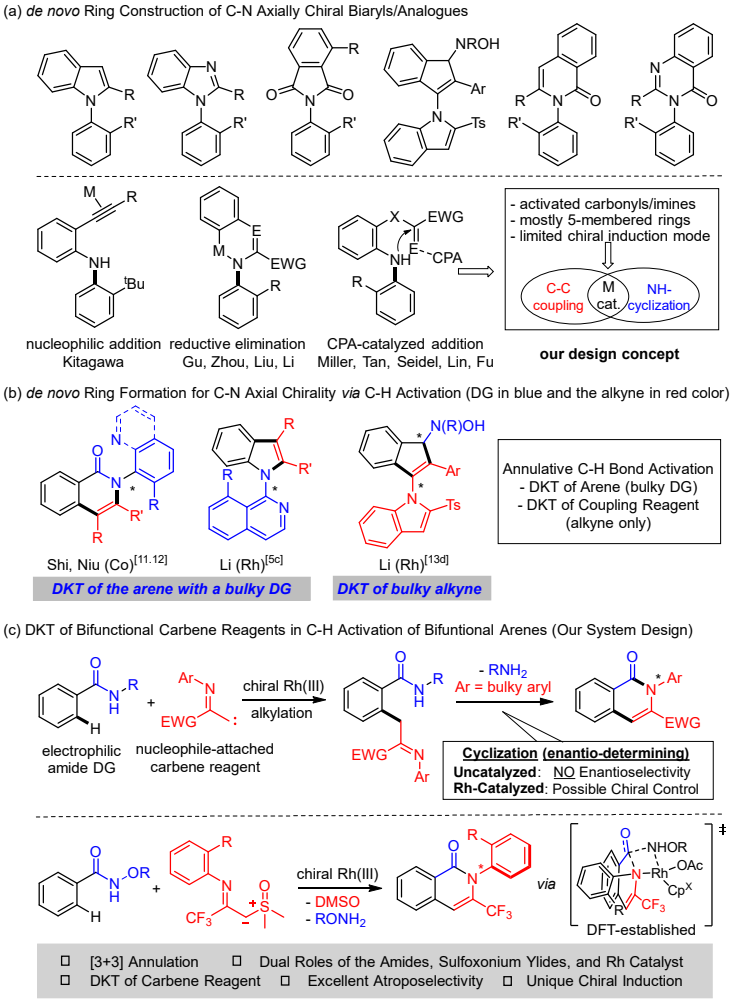
Isoquinolones are important structural motifs in synthetic and medicinal chemistry. Reported herein is highly atroposelective access to C-N axially chiral isoqionolones *via* rhodium-catalyzed C-H activation of *N*-alkoxy benzamides and [3+3] annulation with imidoyl sulfoxonium ylides. The coupling system proceeded efficiently under mild and redox-neutral conditions with excellent functional group tolerance as a result of dynamic kinetic transformation of the ylidic coupling reagent (carbene precursor). Experimental and computational studies revealed a pathway of C-H activation, carbene insertion, and formal nucleophilic substitution-cyclization for this coupling system. In particular, the C-N cyclization is enantio-determining and occurs *via* an unusual rhodium-catalyzed σ-bond metathesis mechanism. The benzamide, the imidoyl sulfoxonium ylide, and the chiral catalyst each played a dual role. The amide functionality acts as a directing group as well as an electrophilic acylating group, and the imidoyl sulfoxonium ylide participated as a nucleophile-functionalized carbene reagent. Applications of representative products as potentially useful chiral ligands have also been demonstrated.

The past decade has witnessed the flourish of chemistry of axially chiral (hetero)biaryls, which have found widespread applications as chiral ligands and organocatalysts.[1-8] Among the axial chirality family, C-N axially chiral heterobiaryls[9-14] remain underexplored possibly due to their synthetic challenges in that the relatively short distance of the C-N bond may cause steric hindrance during proximal bond formation. Two synthetic strategies are typically adopted in construction of C-N axially chiral biaryls. In one category, functionalization of the peripheral groups in existing (hetero)aryl rings allows restriction of the C-N rotation by size-increasing effect.[15-22] Alternatively, *de novo* construction of a new (hetero)aryl ring with incorporatation of the C or N atom into it may also restrict the conformation of the C-N axis.[23-45] The latter strategy is particularly important because new chiral platforms are constructed with modularity, which allows exploitation of diverse chiral structures. In this context, C-N axially chiral indoles,[32-35] benziimidazoles,[36-40] maleimides,[41] and isoqionolones[42-45] have been readily constructed by metal- or organocatalysis (Scheme 1a). The predominant chiral induction modes in these annulation reactions include Pd-catalyzed cyclization of bulky *o*-alkynylanilines,[10,32] C-N reductive elimination,[35,39,41,44,45] and CPA-catalyzed addition of NH nucleophiles to electrophiles (Scheme 1a).[28,29,33,34,37-39] While significant progress has been made in CPA-catalyzed fabrication

of axial chirality, the reaction patterns are restricted to the intrinsic Brønsted acidic properties of the catalyst and are mostly limited to formation of 5-membered heterocycles. Metal catalysis has provided privilidged approaches to cross-coupling reactions. Thus, these concepts of metal- and organocatalysis evolved indepenently. Thereofore, it is imporant to adopt a single metal catalyst in dual role to integrate both cross-coupling and subsequent nucleophilic addition/C-N cyclization for construction of C-N axially chiral biaryls, especially by a C-H activation strategy. Meanwhile, it is well-recognized that introduction of fluorine atoms into organics improved their lipophilicity and bioactivity, with no exception to axially chiral biarlys. However, synthetic examples are limited.[37,40,46,47]



Scheme 1 C-N Axial Chirality and the C-H Activation Approach (DG = directing group, DKT = dynamic kinetic transformation, CPA = chiral phosphoric acid).

Indeed, C-H bond activation has been established as an increasingly important strategy in asymmetric synthesis of axially chiral biaryls,[48-50] including *de novo* construction of rings in C-N axially chiral biaryls (Scheme 1b). Recently, Zhou realized synthesis of isoqionolones via palladium-catalyzed Catellani reactions using bifunational and bulky aryl bromides.[45] In 2022, the Shi[51] group and the Niu[52] group independently reported Co-catalyzed oxidative C-H activation of amides and [4+2] annulation with alkynes, affording isoquinolones via dynamic kinetic transformation (DKT) of the bulkyl directing group, where the C-N axis originates from the directing group. Our group previously applied bulky *N*-isoqinoline as a directing group to assist C-H activation of anilines and [3+2] annulation with internal alkynes, affording C-N axially

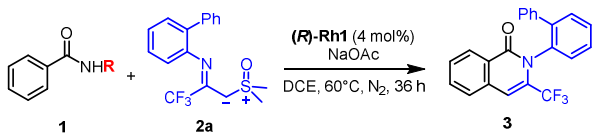
chiral indoles.[35] We have also extended the DKT concept to sterically hindered alkynes[53-56] such as 1-indolylphenylacetylenes which coupled with nitrones via C-H activation-annulative coupling to give C-N axially chiral indoles.[55] Despite the reports, the directing group is limited to bidentate chelation or bulky ones. On the other hand, although DKT of the coupling partner has been employed in C-H activation, it is restricted to alkynes.

Reaction Design. Our design boils down to development of new coupling reagents that are both bulky and reactive. To reconcile these seemingly contradictive criteria, we employed a bifunctional carbene reagent such as CF_3-imidoyl sulfoxonium ylides (TFISYs)[57-65] bearing a proximal nucleophilic imine nitrogen as well as a bulkyl *N*-aryl group (Scheme 1c). Consequently, a secondary amide bearing an electrophilic directing group[66-71] was applied as the C-H substrate. Thus, both the arene and the carbene reagent are bifunctional,[72] and the polarity-matched cyclization affords the chiral isoquinolone. In fact, related [3+3] or [4+2] annulation systems have been extensively explored using sulfoxonium ylide as the carbene reagent in racemic synthesis.[73-88] Regardless of the design, a formidable challenge exist that defies development of the asymmetric catalytic system. Following the C-H alkylation, the C-N cyclization process is enantio-determining, but this key process is generally proposed or assumed to be uncatalyzed or Lewis acid-promoted (Scheme 1c).[89-92] These scenarios inevitably lead to no or poor enantioselectivity. We now report rhodium-catalyzed asymmetric C-H activation of *N*-alkoxy benzamides and [3+3] annulation with imidoyl sulfoxonium ylides, as a result of dynamic kinetic transformation of the ylidic carbene precursor. Most importantly, experimental studies revealed that the formal nucleophilic cyclization process is rhodium-catalyzed, and DFT studies suggest that C-N formation and the C-N cleavage take place in a concerted fashion via a unique σ-bond metathesis mechanism.

Results

Optimization Studies. With the design principle in mind, we applied secondary benzamide as the arene reagent (**1**), and the presence of a CF_3 group in the TFISY (Table 1) activates the carbene species toward migratory insertion and it also serves to reduce the nucleophilicity of the imine nitrogen so that the background C-N cyclization is suppressed. The amide directing group in **1** was initially screened using Cramer's second-generation chiral rhodium catalyst[93-96] (*R*)-**Rh1** in the presence of a base (see Tables 1 and 2). The desired [3+3] annulation product isoquinolone **3** was indeed obtained in good yield at 60 °C when an *N*-alkoxy group was employed, and the *N*-O^{i}Pr group outperformed other secondary alkoxy groups in enantioselectivity (-63% ee). The employment of other *N*-substituents such as *N*-OPiv, -Ts, and -Ac all suppressed the rection, indicating significant electronic and steric effect of the *N*-directing group.

Table 1. Initial Screening of the Amide Directing Group.[a,b,c]



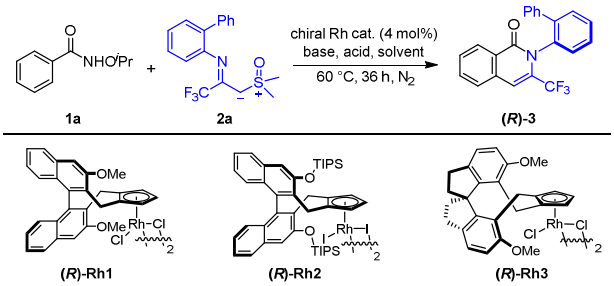
1 2a 3

R	OMe	OEt	O^{i}Pr	O^{c}Pent	OCy	OPiv	Ts/Ac
Yield (%)	77	68	**72**	60	65	< 5%	0
Ee (%)[c]	-26	-1	**-63**	-46	-62	--	--

(a) Reactions were carried out using secondary benzamide (0.1 mmol), **2a** (1.5 equiv), (*R*)-**Rh1** (4 mol%), NaOAc (2.0 equiv) at 60 °C in DCE (2 mL) for 36 h under N_2. (b) Isolated yield. (c) Negative ee refers to the (*S*)-configured product. See Table 2 for the structure of (*R*)-**Rh1** catalyst.

Further screening was conducted using *N*-O^{i}Pr benzamide as the arene reagent (Table 2). It was found that the (*R*)-Rh(III) catalyst played a pivotal role. While no reactivity was found for the (*R*)-**Rh2**, switching to a spirocyclic (*R*)-**Rh3** catalyst,[97] which was originally developed by You, significantly improved the enantioselectivity (80% ee), and the inversed configuration is ascribed to the opposite spatial orientation of the chiral ligand (entries 1-3). Screening of solvent and base additive indicated that DCM and KOAc seemed to be better choices (entries 4-10). Further introduction of a carboxylic acid (1 equiv) slightly boosted the enantioselectivity when the reaction was performed at 50 °C (entries 11 and 12), and AcOH outperformed PivOH. Finally, inclusion of 4Å MS afforded the product **3** in excellent enantioselectivity (93% ee) and good efficiency (entry 13).

Table 2. Further Optimization Studies[a,b]



Entry	Rh cat.	Base/Acid	Solvent	Ee (%)	Yield (%)
1	**Rh1**	NaOAc	DCE	-63	72
2	**Rh2**	NaOAc	DCE	--	0
3	**Rh3**	NaOAc	DCE	80	63
4	**Rh3**	CsOAc	DCE	72	58
5	**Rh3**	AgOAc	DCE	88	45
6	**Rh3**	KOAc	DCE	81	64
7	**Rh3**	KOAc	PhCl	78	25
8	**Rh3**	KOAc	MeOH	66	54
9	**Rh3**	KOAc	DCM	82	68
10[c]	**Rh3**	KOAc	DCM	85	65
11[c]	**Rh3**	KOAc/PivOH	DCM	89	68
12[c]	**Rh3**	KOAc/AcOH	DCM	92	70
13[c,d]	**Rh3**	KOAc/AcOH	DCM	93	74

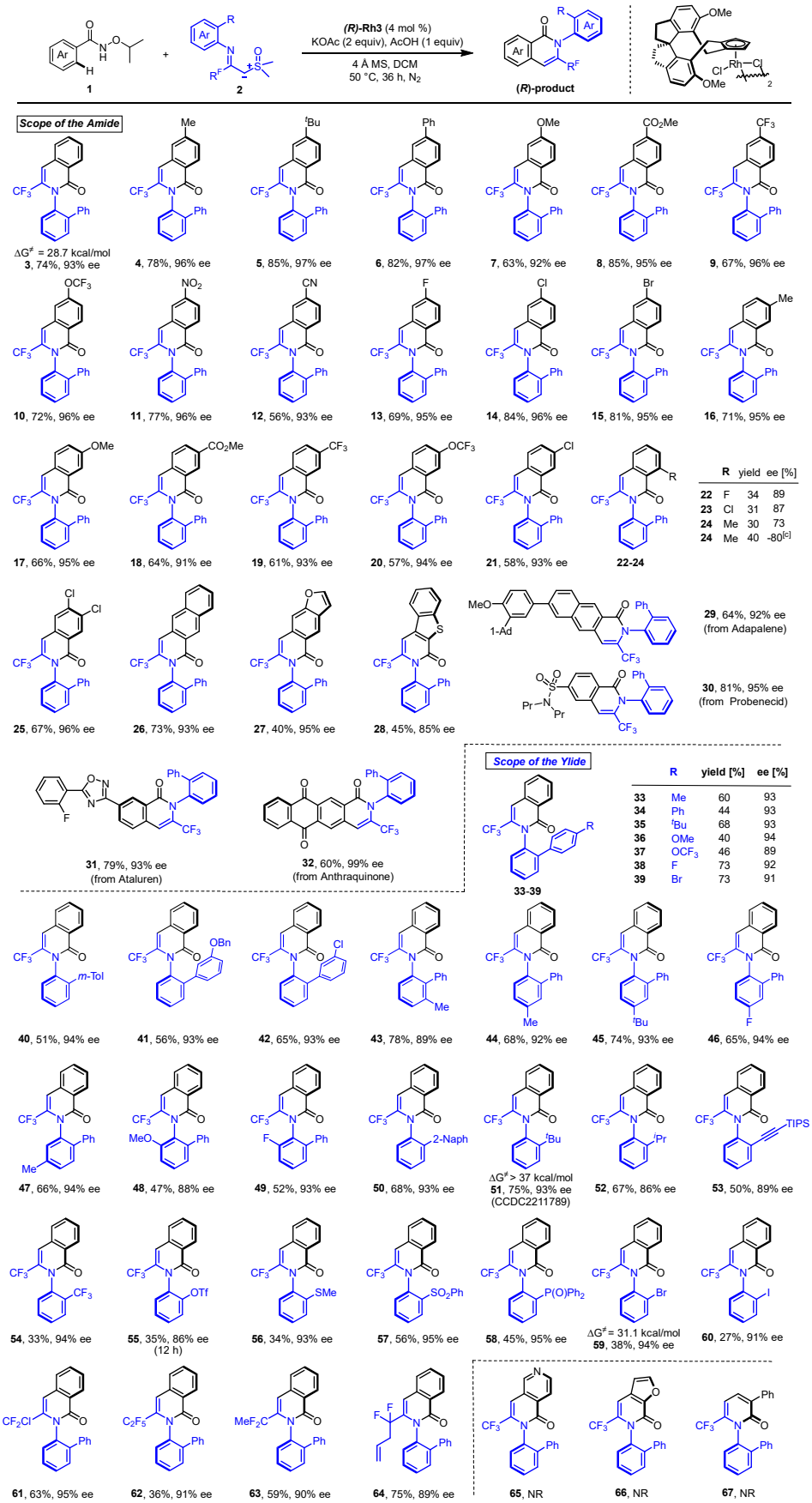
(a) Reactions were carried out using amide **1a** (0.1 mmol), ylide **2a** (1.5 equiv), **(*R*)-Rh3** (4 mol%), base (2.0 equiv) and acid (1.0 equiv, if any) at 60 °C in solvent (2 mL) for 36 h under N_2. (b) Isolated yields. (c) At 50 °C. (d) 4Å MS (50 mg) was added.

Reaction Scope. With the establishment of the optimal reaction conditions, we then extensively explored the scope and limitation of this coupling system under the standard reaction conditions (Scheme 2). The scope of the amide substrate turned out to be very broad when ylide **2a** was employed as a coupling reagent. Thus, introduction of various electron-donating (**4**-**7**), -withdrawing (**8**-**12**), and halogen (**13**-**15**) groups into the para position of the benzamide substrate

was fully tolerated, affording the desire product in good efficiency (56-85% yield), and excellent enantioselectivity was consistently observed within a small range of 93-97% ee. The same functional group compatibility was also observed for different classes of meta-substituted benzamide substrates (**16**-**21**, 91-95% ee). Pronounced steric and electronic effects of the *ortho* substituents were observed. Lower efficiency and slightly lower enantioselectivity was observed when an *ortho*-fluoro or -chloro group was present (**22** and **23**). The introduction of an *ortho*-Me group significantly reduced the enantioselectivity likely due to the steric effect. Fortunately, switching to the (*R*)-**Rh1** catalyst improved the enantioselectivity to -80% ee ((*S*)-**24**). The coupling of disubstituted benzamides or several (hetero)arene-fused benzamides (**25**-**27**, 93-96% ee) proceeded smoothly with excellent enantioselectivity. A heteroarene-derived amide was also applicable as in the isolation of product **28** in attenuated enantioselectivity. Of note, our protocol is applicable to drug-related benzamides, and four functionalized benzamide substrates underwent efficient coupling all in excellent enantioselectivity (**29**-**32**, 92-99% ee), suggesting the potential importance in late-stage functionalization of related functional molecules. An acrylamide and other heteroarene-derived amides failed to undergo any coupling (**65**-**67**).

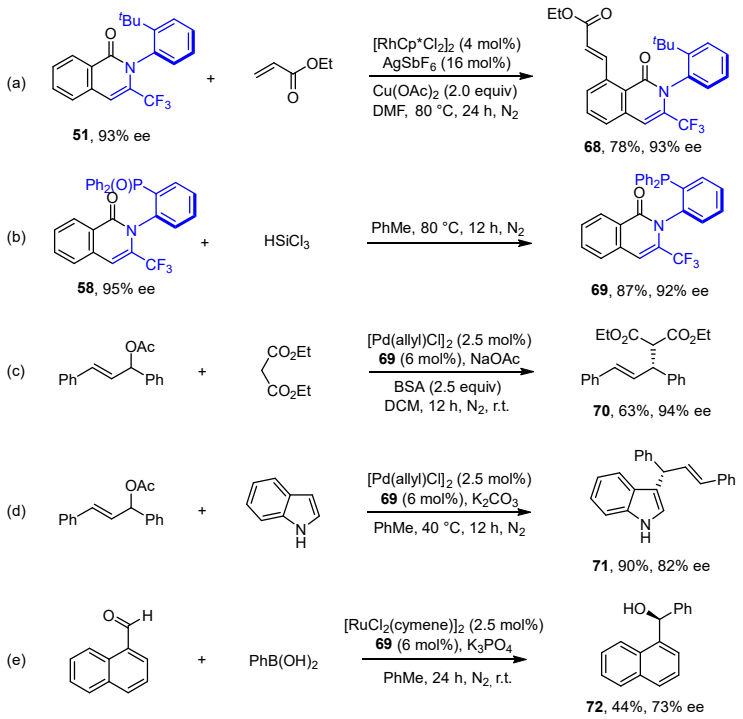
The scope of the ylide reagent was also extensively examined. Introduction of a wide variety of substituents (alkyl, aryl, OMe, halogen, or OCF_3) into the *para* or *meta* position of the *N*-(*o*-phenyl) ring of the imidoyl sulfoxonium ylide was fully tolerated (**33**-**42**, 89-94% ee), and the bulky N-aryl group was also extended to an *N*-(*o*-(2-naphthyl)phenyl) group (**50**, 93% ee). In addition, disubstituted bulky *N*-aryl rings were also compatible (**43**-**49**, 88-94% ee), including several 1,6-disubstitited aryl rings (**48** and **49**). The *ortho* substituent in the *N*-aryl group was not limited to an aryl, and a surprisingly broad scope of *ortho* groups such as alkyl (**51** and **52**), alkynyl (**53**), CF_3 (**54**), triflate (**55**), methylthio (**56**), sulfonyl (**57**), phosphoryl (**58**), and heavy halogen groups (**59** and **60**) were fully amenable to the reaction conditions (86-95% ee). The absolution configuration of product **51** has been confirmed to be (*R*) by X-Ray crystallography (CCDC2211789). The CF_3 group in the imidoyl sulfoxonium ylide was also successfully extended to C_2F_5 and other difluoalkyls (**61**-**64**) with no loss of enantioselectivity (89-94% ee). In contrast, no reaction occurred when the CF_3 was replaced by a Ph group, suggesting necessity of EWG-activation of the carbene reagent. The rotational barrier of representative products (**3**, **51** and **59**) along the C-N axis has been determined, with the $\Delta G^{\neq}$ranging from 28.7 to > 37 kcal/mol and a bulkier *o*-substituent results in higher barrier (Scheme 2).

Synthetic Applications. Synthetic applications of representative products have been demonstrated (Scheme 3). Rh(III)-catalyzed oxidative olefination of product **51** with an arylate ester afforded product **68** with no erosion of the enatiopurity. Standard reduction of phosphine oxide **58** (95% ee) delivered the phosphine **69** in essentially the same optical purity. Phosphine **69** (97% ee) has been extensively examined as a chiral ligand in asymmetric catalysis. Palladium-catalyzed asymmetric allylic alkylation using diethyl malonate afforded **70** in excellent enantioselectivity (94% ee). In contrast, significantly lower enantioselectivity (28-52% ee) was reported for this reaction when the CF_3 in the ligand was replaced by a methyl, highlighting the significance of the electronic/steric effect of CF_3 group.[98] Arylation of the same allyl acetate using an unprotected indole afforded **71** also in high enantioselectivity. Chiral ligand **69** was also applied to Ru-catalyzed nucleophilic addition between a benzaldehyde and phenyl boronic acid, affording diarylmethanol **72** in 73% ee.



Scheme 2. **Reaction Scope of the [3+3] annulation.**[a,b] (a) Reactions were carried out using **1** (0.1 mmol), **2** (1.5 equiv), *(R)*-**Rh3** (4 mol%), KOAc (2.0 equiv), AcOH (1.0 equiv) and 4Å MS (50 mg) at 50 °C in DCM (2 mL)

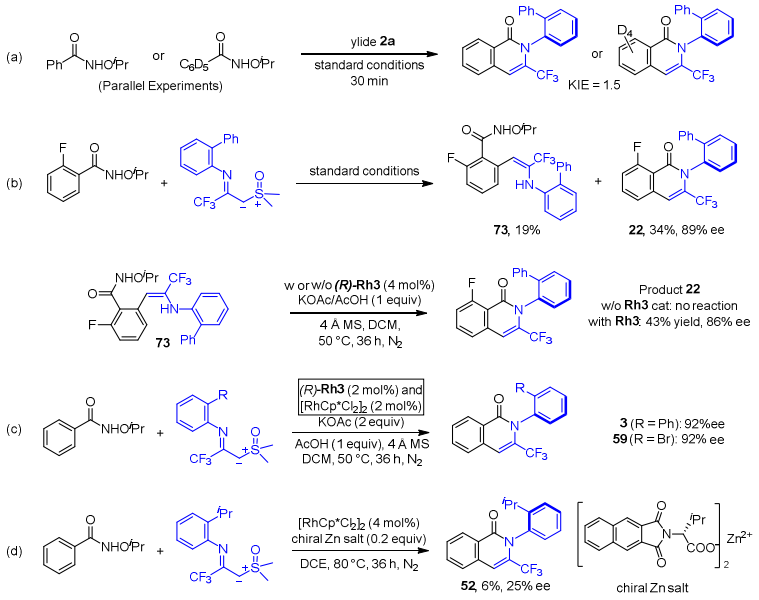
for 36 h under N_2. (b) Isolated yields. (c) The (*R*)-**Rh1** catalyst was used.



Scheme 3. Synthetic Applications of Representative Products.

Experimental Mechanistic Studies. *N*-alkoxybenzamdes[99-116] are typical arene substrates that react via a C-H activation pathway through a concerted-metalation-deprotonation mechanism. The kinetic isotope effect (KIE) of the C-H cleavage was then determined using benzamides **1** and **1**-d_5 in parallel coupling reactions with **2a** (Scheme **4a**). ^{1}H NMR analysis of the isotopomeric products gave k_H/k_D = 1.5 at a low conversion, which indicates that the C-H cleavage may occur prior to the turnover-limiting step and hence is probably not involved in the turnover-limiting step. Based on various reports of catalytic C-H activation using the related sulfoxonium ylides as an acylmethylating reagent,[117-123] the reaction likely proceeds through a closely analogous pathway, followed by C-N bond-forming cyclization. While we failed to isolate the C-H alkylated intermediate after many attempts, the expected intermediate (**73**, achiral) was isolated as a minor product during the synthesis of isoquinolone **22** (Scheme **4b**), where the presence of an *ortho*-F group likely retarded the C-N cyclization that is turnover-limiting in this specific case. As expected, no background cyclization of **73** occurred in the absence of the chiral Rh(III) catalyst, while subjection of **73** into the standard catalytic conditions afforded the product **22** in 86% ee in an acceptable yield. These control experiments highlighted the role of the Rh catalyst during cyclization, and either **73** or its Rh(III) enamido species is an intermediate with reversible N-coordination. To further explore the C-N cyclization process, an equimolar mixture of the achiral ([Cp*RhCl$_2$]$_2$) and the chiral **Rh3** catalysts (2 mol% for each) was applied as the catalyst for the coupling of **1** and a 2-bromophenyl-substitited ylide reagent (Scheme **4c**), from which essentially no change was detected in either the yield or the enantioselectivity (92% ee) of the product **59**. This control experiment manifested that the chiral catalyst **Rh3** overshadowed the achiral [RhCp*Cl$_2$]$_2$ during the cyclization event. To examine the role of the carboxylate during the cyclization, a chiral zinc carboxylate was introduced to replace the KOAc in the standard conditions (Scheme **4d**). A non-negligible enantioselectivity (25%) was detected for

product (*S*)-**52** although the reaction suffered from poor conversion. These observations may suggest that the carboxylate is rhodium-bound during the enantio-determining cyclization.



Scheme 4. Experimental Mechanistic Studies.

Computational Mechanistic Studies. To gain deeper insights into the key C-N bond-forming cyclization step and the origins of the enantioselectivity, density functional theory (DFT) calculations were performed at the ωB97M-D4(SMD)/def2-QZVP//B3LYP-D3BJ/def2-SVP level of theory (see the Supporting Information for the computational details). The racemic system was first explored to establish the detailed mechanism using Cp*Rh(OAc)$_2$ as the active catalyst species. The calculated most favorable pathway of the C-N bond forming cyclization is depicted in Figure 1a. The neutral intermediate **IM1**, which can be generated by the C-H activation followed by the carbene insertion, was selected as the starting point of the computations. The results show that intermediate **IM1** first undergoes an isomerization step to give intermediate **IM2**, which is more stable than **IM1** by 6.8 kcal/mol. Then, the C-N bond forming cyclization was found to proceed through transition state **TS1**, with an energy barrier of 22.5 kcal/mol relative to **IM2**. The optimized geometry implies that transition state **TS1** corresponds to the σ-bond metathesis between the Rh-N and N-C(acyl) bonds (see the Supporting Information for details), with the formation and cleavage of the C-N bonds occurring in a concerted manner. Of particular note, the possible pathway from the cationic analogue formed by the dissociation of OAc was also considered, which was computed to be much higher in energy than that from **IM1** (see the Supporting Information for details), in line with the experiments that the carboxylate is likely rhodium-bound during the C-N bond forming cyclization (Scheme 4d). This proposed mechanism is also in line with our optimization studies in that introduction of a Lewis acid additive (Zn^{II} or Sc^{III}) either had negligible influence or slightly increased the enantioselectivity (Supporting Information, Table S1).

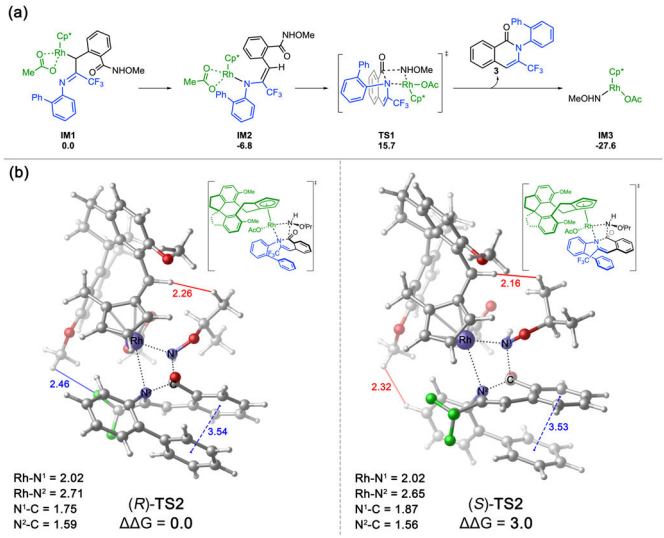


Figure 1. (a) Calculated most favorable pathway of the C-N bond forming cyclization in racemic system; (b) Optimized geometries of (*R*)-TS2 and (*S*)-TS2 in the Rh3-catalyzed system. Free energies and bond distances are given in kcal/mol and Å, respectively.

To further shed light on the origins of the enantioselectivity, the σ-bond metathesis transition states corresponding to the (*R*)-**Rh3** catalyst were evaluated (Figure 1b). It was found that transition state (*R*)-**TS2** is lower in energy than (*S*)-**TS2** by 3.0 kcal/mol, which corresponds to a calculated enantioselectivity of 98% ee at 50 °C, in accordance with the experimentally observed excellent enantioselectivity. The optimized geometries indicate the presence of π-π interactions between the *N*-(*o*-phenyl) ring and benzamide moiety in both (*R*)-**TS2** and (*S*)-**TS2** (3.54 and 3.53 Å). However, in (*S*)-**TS2**, the steric repulsions of the N-aryl ring and OiPr group with the chiral ligand were found (2.32 and 2.16 Å, respectively). While in (*R*)-TS2, only the steric repulsion between the O^{i}Pr group and chiral ligand exists (2.26 Å). Moreover, the attractive H---F interaction was observed in the (*R*)-TS2 (2.46 Å), which is absent in (*S*)-TS2. The combination of the steric repulsions and H-F interaction results in higher energy of (*S*)-TS2 than the (R)-TS2, thus leading to the experimentally observed excellent enantioselectivity. In addition, the activation barrier for the cyclization to give the (*R*)-product was calculated to be 18.1 kcal/mol, which is 4.4 kcal/mol lower than in the RhCp*$(OAc)_2$-catalyzed racemic coupling. These calculation data are consistent with our competitive studies using mixed rhodium catalysts (Scheme 4c).

Conclusions

We have developed a redox-neutral protocol to access to C-N axially chiral isoqionolones *via* rhodium-catalyzed C-H activation of *N*-alkoxy benzamides and [3+3] annulation with imidoyl sulfoxonium ylides that act as unusual carbene reagents. The coupling system proceeded efficiently under mild conditions with excellent functional group tolerance. The C-N chiral axis originates from the ylide reagent and the axial chirality was constructed via dynamic kinetic transformation of the ylide reagent. Experimental and computational studies revealed a pathway of C-H activation, carbene insertion, and formal nucleophilic substitution-cyclization for this coupling system. In particular, DFT studies suggest that this enantio-determining C-N cyclization occurs via an unusual rhodium-catalyzed σ-bond metathesis mechanism. The benzamide, the imidoyl sulfoxonium ylide, and the rhodium catalyst each plays a dual role, where the amide

functionality acts as a directing group as well as an electrophilic acylating group, and the imidoyl sulfoxonium ylide participated as a nucleophile-functionalized carbene reagent. A representative coupled product has been demonstrated as a useful ligand in cross-coupling reactions. Further studies of atroposelective C-H activation *via* other underexplored mechanisms are underway in our lab and will be reported in due course.

Methods

Synthesis of 3-64. A screw-cap vial (8 mL) was charged with *N*-isopropoxybenzamide **1** (0.1 mmol, 1.0 equiv), sulfoxonium ylide **2** (0.15 mmol, 1.5 equiv), *(R)*-**Rh3** (4.4 mg, 4 mol%), KOAc (19.6 mg, 0.2 mmol, 2.0 equiv), AcOH (6.0 mg, 0.1 mmol, 1.0 equiv) and 4Å MS (50 mg) in DCM (2 mL) was stirred in a vial at 50 ^{o}C for 36 h. The reaction mixture was evaporated under vacuum and the residue was purified by preparative TLC (PE/EA 10/1)to give the corresponding product **3-64**.

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Author contributions

X. L. proposed the research direction and guided the project. P. W. designed and performed the experiments. X.-P. Z. and X. L. analyzed and discussed the experimental results and drafted the manuscript. G. H. and H. W. conducted mechanistic studies by DFT calculations. All authors contributed to the writing of the manuscript. The authors declare no competing financial interests.

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