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Rhodium(I)-Catalyzed Asymmetric Hydroarylative Cyclization of 1,6-Diynes to Access Atropisomerically Labile Chiral Dienes

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Abstract: Axially chiral open-chained olefins are an underexplored class of atropisomers, whose enantioselective synthesis represents a daunting challenge due to their relatively low racemization barrier. We herein report rhodium(I)-catalyzed hydroarylative cyclization of 1,6-diynes with three distinct classes of arenes, enabling highly enantioselective synthesis of a broad range of axially chiral 1,3-dienes that are conformationally labile ($\Delta G^{\neq}$(*rac*) = 26.6-28.0 kcal/mol). The coupling reactions in each category proceeded with excellent enantioselectivity, regioselectivity, and Z/E selectivity under mild reaction conditions. Computational studies of the coupling of quinoline *N*-oxide system reveal that the reaction proceeds *via* initial oxidative cyclization of the 1,6-diyne to give a rhodacyclic intermediate, followed by σ-bond metathesis between the arene C-H bond and the Rh-C(vinyl) bond, with subsequent C-C reductive elimination being enantio-determining and turnover-limiting. The DFT-established mechanism is consistent with the experimental studies. The coupled products of quinoline *N*-oxides undergo facile visible light-induced intramolecular oxygen-atom transfer, affording chiral epoxides with complete axial-to-central chirality transfer.

Introduction

Atropisomerism results in chirality associated with hindered rotation along a single bond,[1] and axial chirality has been extensively investigated in the past decades in that axially chiral functional molecules have found extensive applications in synthetic chemistry, material science, and biological studies.[2] Among the large family of atropisomers, axially tetrasubstituted 6,6-biaryls have been heavily explored owing to their conformational stability.[3] The increasing demands for diversified applications call for development of new axially chiral platforms. In this context, the conformational stability of atropisomers becomes a major issue that largely dictates the synthetic methods. Axially chiral platforms with a relatively low racemization barrier such as trisubstituted biaryls,[4] 5,6 or 5,5-biaryls,[5] chiral amides,[6] and diaryl ethers[7] are challenging but important targets. Their asymmetric synthesis requires mild reaction conditons to preserve the axial chirality during the synthesis (Scheme 1a). However, high reaction efficiency is the perpetual goal of asymmetric synthesis, and the mutual exclusion between mild reaction conditions and high synthetic efficiency poses a daunting challenge, which calls for development of efficient coupling systems by manipulating other reaction parameters. Axially chiral open-chained olefins constitute a large family of atropisomers that also fall into this challenging category in that distortion of the four bonds around the C=C unit decreases the racemization barrier (Scheme 1a).[8-16]

Catalytic functionalization of alkynes represents a straightforward approach to access axially chiral olefins. Recently, Zhu and coworkers realized Ni-catalyzed reductive arylation of internal alkynes.[9] The groups of Yan,[10a-c] Tan,[10d-f] Li,[11a] Wang,[11b] and Yao[12] accomplished asymmetric synthesis of diverse trisubstituted styrenes *via* organo- or metal-catalyzed hydrofunctionalization of sterically hindered alkynes (Scheme 1a). The Liu group disclosed Cu(I)-catalyzed difunctionalization of terminal alkynes *via* a radical pathway.[13] Recently, the Song group tackled the limitation of hindered alkynes and realized an atroposelective construction of tetrasubstituted styrenes *via* carboborylation of simple internal alkynes.[14]

Ideally, novel chiral olefin platforms are constructed from readily available substrates with 100% atom-economy and high step-economy such as *via* C-H bond activation (Scheme 1b). Indeed, C-H bond activation using two distinct classes of metal catalysts has been employed to access axially chiral structures (Scheme 1b)[15,16] owing to the availability of arene reagents. The majority of these chiral olefins have been accessed by high-valent metal catalysis such as Pd(II) and Rh(III), where a concerted metalation-deprotonation (CMD) mechanism is typically proposed (Scheme 1b).[15,16] Thus, by resorting to vinyl or aryl C-H bond activation, the Shi group realized Pd(II)-catalyzed highly enantioselective synthesis of tetra-substituted chiral olefins (Scheme 1b).[15a-c] Our group recently addressed atroposelective synthesis of both tri- and tetrasubstituted olefins *via* Rh(III)-catalyzed C-H activation of arenes and coupling with sterically hindered alkynes, which is realized via dynamic kinetic transformation of the alkynes.[16] In these high-valent catalytic systems, the initial reactive M-C species is unanimously generated via the CMD mechanism, and the reaction efficiency was ensured by proper design of specific chiral ligands or by substrate activation. Nevertheless, the limited strategies to creat the initial organometallic species may restrict the applications of broad substrates. Meanwhile, low-valent metal catalysis have been much less studied toward construction of axial chirality via C-H activation,[17] which proceeds via a dictinct mechanism of initial oxidation (such as oxidative addition) of the metal catalyst (Scheme 1b). However, the products are restricted to axially chiral biaryls, and no axially chiral olefins have been

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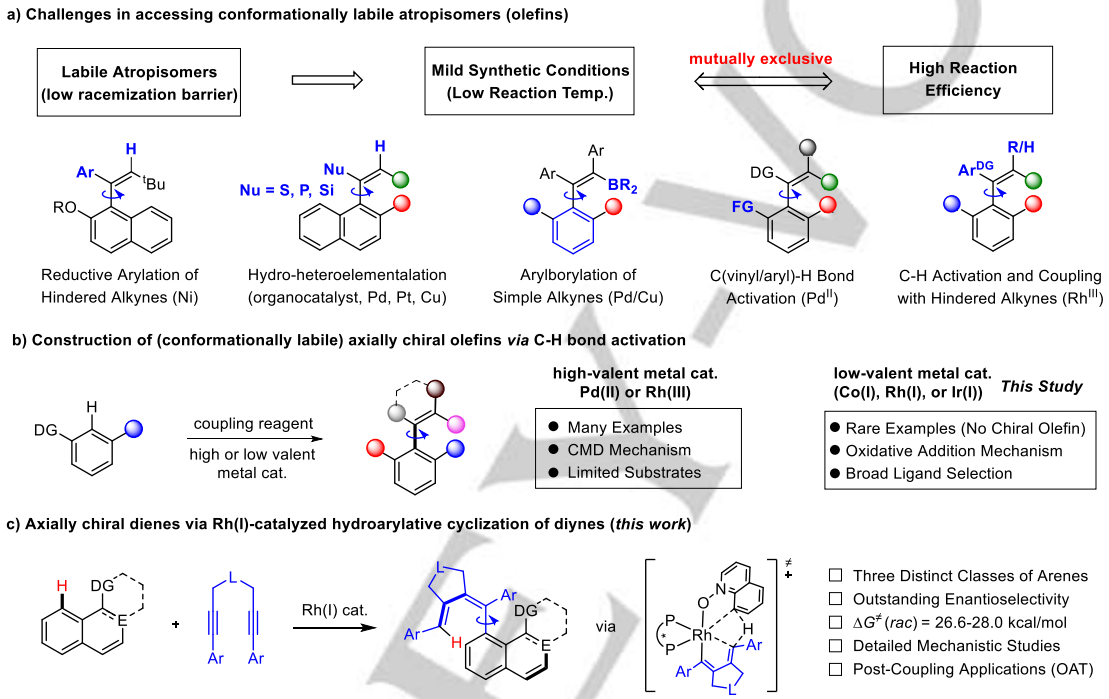
accessed. In addition, such coupling systems are limited to dynamic kinetic transformation (DYKAT) of arenes bearing a pre-existing axis, and the coupling reagent is also restricted to alkenes,[18] alkynes,[19] and aryl halides.[20] While such systems all inevitably involve some M^{n+2} intermediates, the underlying mechanism and the reaction patterns are drastically different. We believe that low-valent metal-catalyzed systems are advantageous owing to the wide selections of chiral phosphine ligands. Thus, both the ligand repertoire and high tendency of oxidative addition of low-valent catalysts will offer complementary strategies to tackle the challenges in construction of axially chiral olefins. Inspired by the reactivity of 1,6-diynes disclosed by the groups of Shibata, Takana, and Matsunaga in achiral couplings,[21] we designed enantioselective hydroarylation of diynes using sterically hindered arenes to create a chiral axis (Scheme 1c). Of note, although 1,6-diynes have been extensively studied in Rh(I)/Ir(I)-catalyzed atroposelective [2+2+2] annulations, the products are limited to conformationally stable axially chiral molecules.[22] We now report Rh(I)-catalyzed C-H activation of diverse arenes en route to hydroarylation of diynes for synthesis of axially chiral 1,3-dienes via *de novo* construction of a chiral axis, which proceeds with excellent atom-economy, enantioselectivity, and *Z*/*E* selectivity. Moreover, important applications of a large family of chiral products have been realized by integration with photochemistry.



Scheme 1. Atroposelective synthesis of chiral olefins via C-H activation. (OAT = oxygen-atom transfer, CMD = concerted metalation-deprotonation)

Results and Discussion

We commenced our studies with optimization of the reaction parameters between quinoline *N*-oxide (**1a**)[23] and a 1,6-diyne (**2a**). A series of chiral diphosphine ligands were initially screened in combination with a cationic Rh(I) catalyst under mild conditions (Table 1). While essentially no reactivity was observed for ligands **L1-L3**, **L11** and **L13-L15**, the desired diene product **3** was isolated in generally high efficiency and enantioselectivity as a result of *peri* C-H activation when electron-rich C_2-symmetric diphosphines (**L4-L10**) were used. Of note, both excellent reactivity and enantioselectivity were obtained when **L9** or **L10** was used. The latter delivered excellent (> 20:1) *Z*/*E* selectivity, and it was retained for further studies.

The ligand **L10** was then employed for further screening (Table 1). It was found that lowering the temperature to 30 ºC resulted in slightly enhanced enantioselectivity (entry 2). However, this temperature seemed inapplicable to some substrate during our scope studies. As expected, elongation of the reaction time led to reduced enantioselectivity (entry 3), likely due to the racemization of the chiral product **3** (*vide infra*). Variation of the anion of the rhodium catalyst verified the superiority of the triflate anion (entries 4-8). THF was identified as the optimal solvent, and lower reactivity or enantioselectivity was realized for other oxygenated solvents (entries 9-14). In contrast to activity of the Rh(I) catalyst, no desired coupling was observed when a typical Ir(I) or Rh(III) catalyst was used (entry 15). Besides, reducing the catalyst loading or extending reaction time was not beneficial to the reactivity and enantioselectivity (entries 16 and 17).

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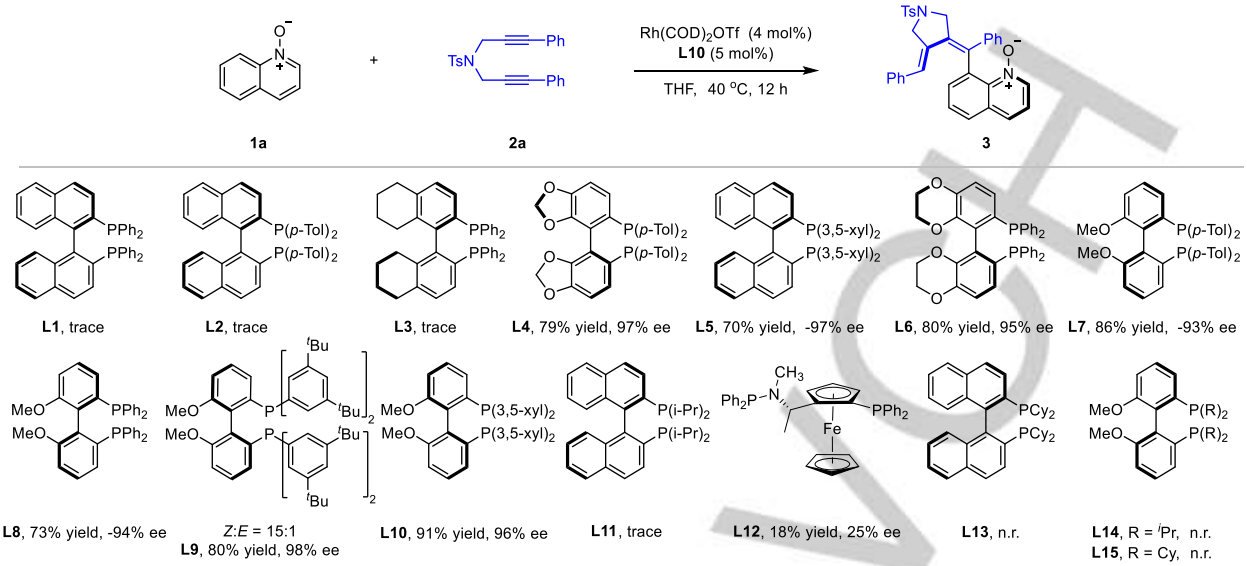
Table 1. Optimization studies on atroposelective synthesis of axially chiral dienes.[a]



entry	variations from standard conditions	yield (%)	ee (%)
1	**none**	**91**	**96**
2	30 °C instead of 40 °C	84	98
3	24 h instead of 12 h	88	94
4	$[Rh(COD)X]_2$ (X = Cl, OH, OMe)	n.r.	-
5	$Rh(COD)_2BF_4$ as a catalyst	83	96
6	$Rh(COD)_2PF_6$ as a catalyst	n.r.	-
7	$Rh(COD)_2SbF_6$ as a catalyst	71	96
8	$Rh(COD)_2NTf_2$ as a catalyst	76	96
9	^{t}BuOMe as a solvent	16	ND
10	2-Me-THF as a solvent	74	96
11	MeOH as a solvent	84	96
12	HFIP as a solvent	n.r.	-
13	DCM as a solvent	81	93
14	DME as a solvent	73	94
15	Ir(I) or Rh(III) catalyst [b]	n.r.	-
16	3 mol% $Rh(COD)_2OTf$	53	96
17	2 mol% $Rh(COD)_2OTf$ [c]	55	90

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), **Rh(I)** (4 mol%), chiral ligand **L** (5 mol%) in a solvent (1 mL) for 12 h, isolated yield. The ee was determined by HPLC using a chiral stationary phase. The ratio of *Z*/*E* was determined by ^{1}H NMR analysis of the crude reaction mixture, unless otherwise noted, *Z*:*E* > 20:1. [b] $[Ir(COD)_2]OTf$ or $[RhCp^*Cl_2]_2/AgSbF_6$/AcOH in various solvents. [c] Reaction time = 24 h.

The scope of the quinoline *N*-oxide was next studied using diyne **2a** as the coupling reagent under the optimal conditions (Conditions A, Scheme 2). Introduction of diversified substituents such as alkyl, aryl, halo, ester, and methoxy group into the 2-, 3-, 4-, 5-, and 6-position of the quinoline *N*-oxide all led to smooth coupling, and the products were obtained in excellent enantioselectivity (**4**-**25**, 94-99% ee). The catalytic activity is only marginally affected by the electronic effect of the substituent, with the lowest reactivity (56% yield) being observed for a 5-methoxy-substituted quinoline *N*-oxide (**15**). The absolute configuration of product **23** has been determined to be (*R*) by X-ray crystallographic analysis (CCDC 2285080).[24] Besides, the *N*-oxide substrate has been extended to a phenanthridine *N*-oxide with excellent enantioselectivity and efficiency (**26**, 97% ee). In contrast, no reactivity was observed for a 7-substituted (OMe or Me) quinoline oxide due to the steric effects. The scope of the diyne was then explored with **1a** as the arene reagent. Symmetric 1,6-diynes bearing diverse electron-donating, -withdrawing, and halogen groups at the *para* position of the benzene ring all reacted with excellent enantioselectivity although lower yields were obtained for products with electron-withdrawing substituents in the *p*-position of the benzene ring (**32** and **33** *versus* **27**-**31**). The similar trend was also found for diynes bearing different *meta* substituents (**34**-**38**), which all reacted with excellent enantioselectivity (95-98% ee). In contrast, lower enantioselectivity was observed when an *ortho* fluoro group was introduced, possibly due to steric effect (**39**, 81% ee). The alkyne terminus has been extended to a 2-thienyl group, and the product **40** was isolated in outstanding enantioselectivity (> 99% ee). A nonsymmetric diyne

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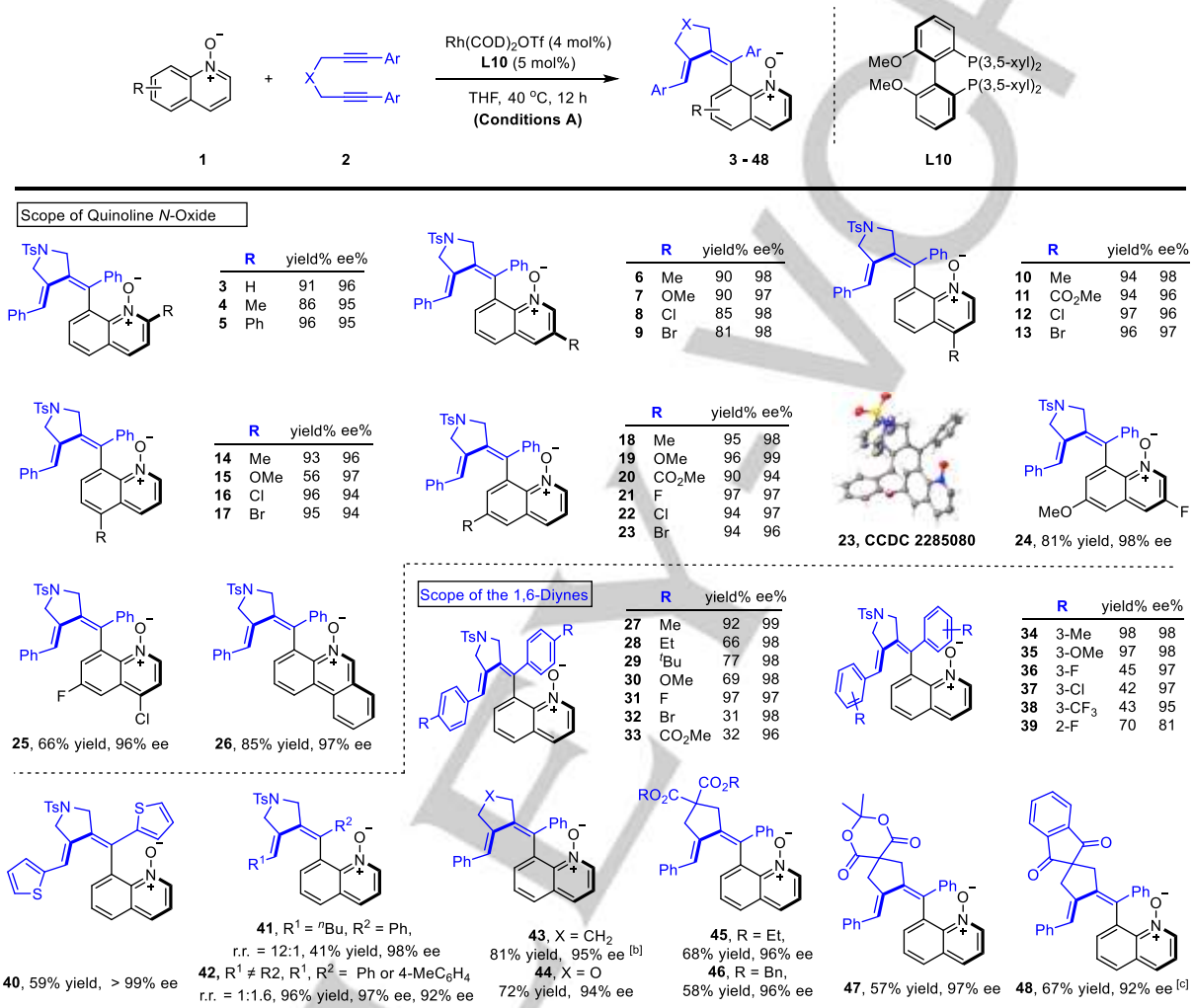
also proved viable under the standard conditions, as in the isolation of product **41** in excellent enantioselectivity and high regioselectivity (12:1 r.r.), favoring the formation of an alkenyl C-H group proximal to the butyl group. When a (phenyl)(4-methylphenyl)diyne was employed transformation, two regioisomers of **42** were afforded in excellent enantioselectivity and reactivity, but with low regioselectivity. The linker in the diyne reagent has been successfully expanded to a simple methylene group (**43**), an oxygen group (**44**), and diverse dicarbonyl-functionalized methylene groups (**45-48**). The *Z*/*E* selectivity in these systems was generally high, except for the product **43**.



Scheme 2. Scope of coupling of quinoline *N*-oxide and diyne. [a] [a] Reaction conditions: **1** (0.10 mmol), **2a** (0.12 mmol), $Rh(COD)_2OTf$ (4 mol%), **L10** (5 mol%) in THF (1 mL), 40 °C 12 h, isolated yield. The ee was determined by HPLC using a chiral stationary phase. The r.r. and the ratio of *Z*/*E* were determined by ^1H NMR analysis of the crude reaction mixture, unless otherwise noted, *Z*:*E* > 20:1. [b] *Z*:*E* = 4:1, [c] *Z*:*E* = 12:1.

Two more classes of arenes have then been identified for this atroposelective hydroarylation system (Scheme 3). Benzo[h]quinoline (**49**) exhibited good reactivity toward coupling with diyne bearing a diester-functionalized methylene linker under modified reaction conditions (**L3** ligand, DME, 40 °C, Conditions B). Introduction of alkyl, aryl, halo, and alkenyl substituent at the 3-, 4-, and 6-position of the benzo[h]quinoline ring all rendered smooth coupling, and the corresponding products were isolated in moderate yield and high enantioselectivity (**50-55,** 88-92% ee). The similar trend also applies for the coupling of symmetrically substituted diynes (**56-64,** 90-94% ee), albeit with moderate to low yields. Extension to other methylene-linked diynes was also successful (**65-68**). The third class of arenes, *N*-ethylisoquinolones (**69**), were next briefly explored in the coupling with diester methylene-linked 1,6-diynes. Generally excellent enantioselectivity was realized when the **L5** ligand was used (Conditions C), regardless of the halogen and methoxy substituents in the isoquinolone ring at the 3-, 4-, 5-, and 6-positons (**70-76**, 88-96% ee). Compatibility of symmetrically substituted diynes has also been demonstrated (**77-83**, 91-94% ee). In this category, the reaction efficiency was moderate due to incomplete conversion of the arene substrate. Increasing the reaction temperature improved the efficiency but caused significant decrease of enantioselectivity as a result of the low racemization barrier of the product (see Scheme 4). In all cases, excellent (> 20:1) *Z*/*E* selectivity was maintained.

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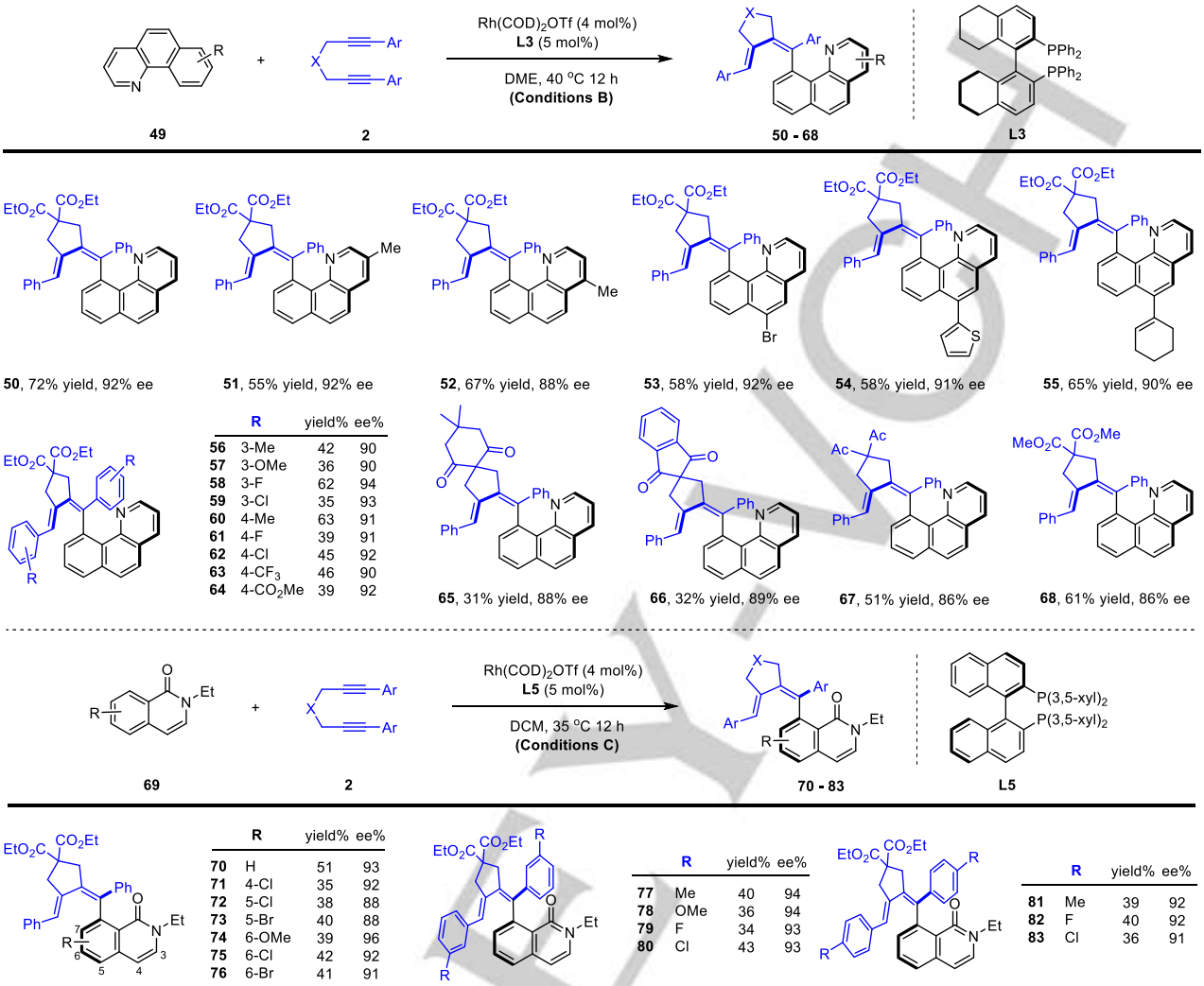


	R	yield%	ee%
56	3-Me	42	90
57	3-OMe	36	90
58	3-F	62	94
59	3-Cl	35	93
60	4-Me	63	91
61	4-F	39	91
62	4-Cl	45	92
63	4-CF_3	46	90
64	4-CO_2Me	39	92

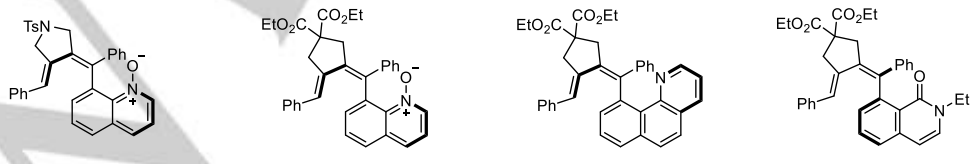
	R	yield%	ee%
70	H	51	93
71	4-Cl	35	92
72	5-Cl	38	88
73	5-Br	40	88
74	6-OMe	39	96
75	6-Cl	42	92
76	6-Br	41	91

	R	yield%	ee%
77	Me	40	94
78	OMe	36	94
79	F	34	93
80	Cl	43	93

	R	yield%	ee%
81	Me	39	92
82	F	40	92
83	Cl	36	91

Scheme 3. Scope of coupling of benzo[h]quinolines and isoquinolin-1(2*H*)-ones with diynes.[a] [a] **Conditions B**: benzo[*h*]quinoline (0.10 mmol), **2** (0.12 mmol), $Rh(COD)_2OTf$ (4 mol%), **L3** (5 mol%) in DME (1 mL), 40 °C 12 h. **Conditions C:** *N*-ethylisoquinolone (0.10 mmol), diyne (0.12 mmol), $Rh(COD)_2OTf$ (4 mol%), **L5** (5 mol%) in DCM (1 mL), 35 °C 12 h, isolated yield. The ee was determined by HPLC using a chiral stationary phase. The ratio of *Z*/*E* was determined by ^1H NMR analysis of the crude reaction mixture, unless otherwise noted, *Z*:*E* >19:1.

The conformational stability of all three classes of the diene products has been experimentally determined by HPLC analysis (Scheme 4). Closely comparable racemization barriers were found for dienes derived from quinoline *N*-oxide and benzo[h]quinoline (**3**, **45**, and **50**, 27.7 to 28.0 kcal/mol), where the nature of the linker has marginal effect. In contrast, a noticeably lower barrier was determined for the diene obtained from the *N*-ethylisoquinolone (**70**, 26.6 kcal/mol), likely due to a shorter C-O bond that has partial double bond character. All these values indicated the atropisomeric instability of the axially chiral dienes, and they fall to the Class-2 atropisomers based on LaPlante and Edwards's atropisomeric stability classification.[25]



3 **45** **50** **70**

$\Delta G^{\neq}(rac) = 28.0\ kcal{\bullet}mol^{-1}$ $\Delta G^{\neq}(rac) = 27.7\ kcal{\bullet}mol^{-1}$ $\Delta G^{\neq}(rac) = 27.7\ kcal{\bullet}mol^{-1}$ $\Delta G^{\neq}(rac) = 26.6\ kcal{\bullet}mol^{-1}$

Scheme 4. Conformational stability of axially chiral dienes (60 °C, DCE).

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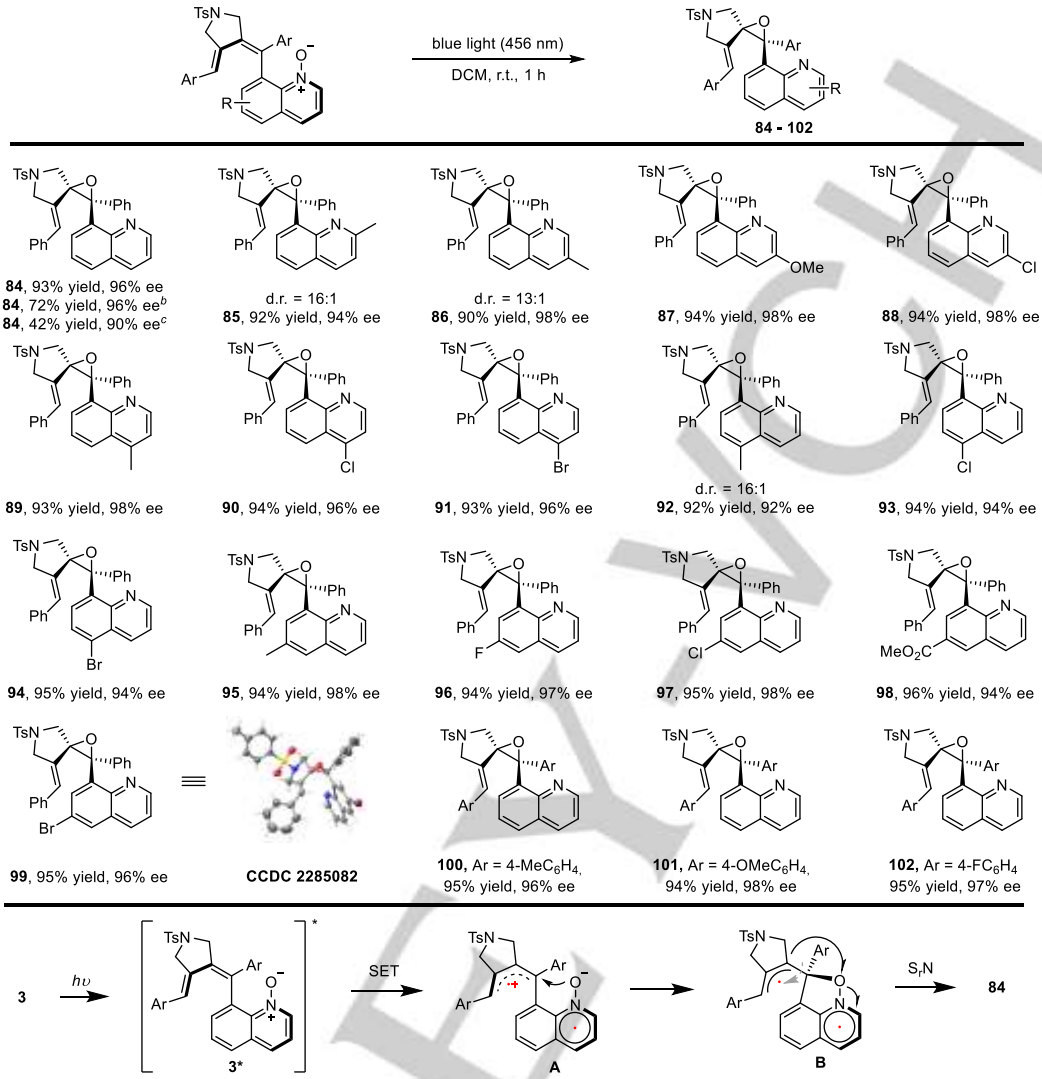

Scheme 5. Oxygen-atom transfer of axially chiral olefins under blue light irradiation. [a] Reaction conditions: axially chiral diene (0.10 mmol) in DCM (1 mL), irradiated with blue LED light (456 nm) at r.t. for 1 h. The ee was determined by HPLC using a chiral stationary phase. The d.r. value was determined by ^{1}H NMR analysis of the crude reaction mixture. The d.r. was > 20:1 unless otherwise noted. [b] Reaction of **1a** and **2a** under Conditions A (0.1 mmol), followed by irradiation with blue LED light (456 nm) at r.t. for 1 h, isolated yield. [c] Reaction of **1a** and **2a** under Conditions A (0.1 mmol) and blue LED light (456 nm) at r.t. for 12 h at the outset, isolated yield.

During the workup and isolation of the product **3**, we found clean formation of a new product under natural light conditions. This conversion was rapidly promoted by blue light irradiation, and the product was identified as an epoxide *via* a highly diastereoselective photoinduced *O*-atom transfer process (OAT).[26] Thus, the scope of this intriguing OAT reaction was explored (Scheme 5). Nearly quantitative formation of the epoxides was achieved with no erosion of enantiopurity, and the central chirality was completely retained *via* axial-to-central chirality transfer. Diverse functional groups in the quinoline ring are tolerated (**84-102**), and in most cases the diastereoselectivity is > 20:1. The absolute configuration of product **99** has been confirmed by X-ray crystallography (CCDC 2285082).[24] This OAT reaction is also telescoped to the alkyne hydroarylation system, and the one-pot, two-stage reaction of **1a** and **2a** afforded product **84** in 72% yield with no variation of the enantioselectivity (Scheme 5). Furthermore, treatment of **1a** and **2a** under both Conditions **A** and blue LED lead to a slight decrease in yield and enantioselectivity. The intramolecularity of this OAT reaction seems crucial, and we failed to realize any epoxidation of the diene unit in **3** with *m*-CPBA after many trials, suggesting poor reactivity of the olefin.

In this light-induced transformation, the diene **3** is likely sensitized to its triplet state **3*** (Scheme 5, bottom), which then induces intramolecular SET, from which the quinolinium moiety is reduced to a delocalized radical and the diene is oxidized to a radical cation (**A**). Intramolecular nucleophilic addition/O-C coupling gives a diradical **B**, followed by radical substitution at the electrophilic oxygen to give the product **84**. We feel that the opposite electron flow pathway with the *N*-oxide oxygen being a single-electron donor seems less likely because of the high oxidation potential of the *N*-oxide (1.55 V for simple quinoline *N*-oxide).[27] In addition, the absence of an EWG in the diene renders it a poor electron acceptor. In this system, excellent diastereoselectivity was observed because of rapid attack of the carbon nucleophile with essentially no rotation along the C-C bond in intermediate **B**. Our control experiments using exogenous $H_2{}^{18}O$ also verified that the OAT is likely

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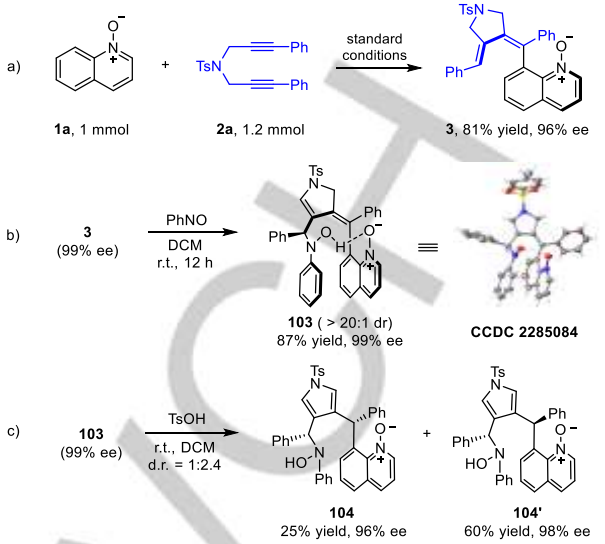
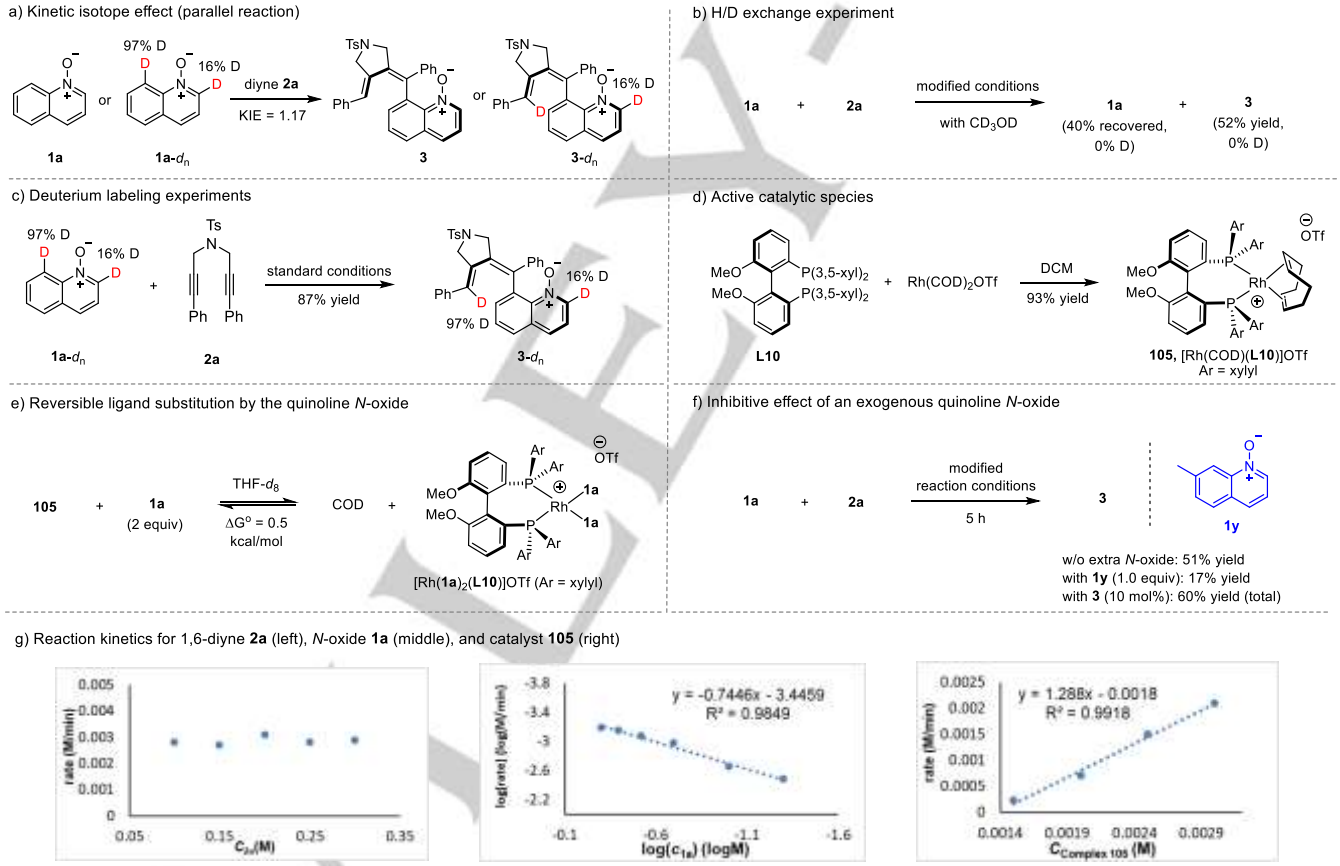
intramolecular. At this stage, we cannot exclude the energy-transfer pathway (see Supporting Information).

Other synthetic applications were also performed (Scheme 6). Synthesis of product **3** at a mmol-scale has been conducted, affording excellent enantioselectivity and high yield. Treatment of **3** with nitrosobenzene at room temperature furnished a formal ene-reaction product **103** as a single diastereomer in excellent enantioselectivity, with complete retention of the enantiopurity. Thus, the axial chirality offers excellent chiral induction during the C-C bond formation. In the X-ray crystal structure of product **103** (CCDC 2285084),[24] both π-π interactions (between the quinoline ring and the nitrosobenzene ring) and hydrogen bonding have been detected, which results in a significantly high epimerization barrier. Indeed, no decay of the d.r. was detected even at a high temperature (120 °C, PhCl). Treatment of this product with an acid led to aromatized products as a mixture of diastereomers **104** (CCDC 2285083)[24] and **104'** in 1:2.4 d.r. (Scheme 6c).



Scheme 6. Synthetic applications of selected products.



Scheme 7. Experimental mechanistic studies on the coupling of quinoline *N*-oxide and diyne.

A series of mechanistic studies have been carried out to explore the mechanistic details of the coupling of *N*-oxide **1a** and the diyne **2a** (Scheme 7). Kinetic isotope effect has been measured from two parallel reactions using quinoline *N*-oxide and its isotopologue (Scheme 7a), and a small KIE = 1.17 was obtained by independent kinetic studies. This indicates that the C-H cleavage is not involved in the turnover-limiting step. We next conducted H/D exchange studies. The coupling of **1a** and **2a** was conducted in CD_3OD solvent, and no deuterium incorporation was detected in either the coupled product or the recovered quinoline *N*-oxide (Scheme 7b). This outcome is also consistent with our D-labeling studies (Scheme 7c), where employment of a C2- and C8-deuterated quinoline *N*-oxide as an arene source afforded the product 3-d_n with the

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C(8)-D fully transposed to the alkenyl position with no scrambling. These data may suggest irrelevancy of acidic cationic Rh(III) hydride species in the catalytic cycle, and the arene ring remains bound following the C−H bond cleavage.

We next explored possible reaction intermediates. The stoichiometric reaction between [Rh(COD)$_2$]OTf and the chiral ligand **L10** rapidly afforded a ligand-substituted complex **105** [(**L10**)Rh(COD)]OTf in high yield (Scheme 7d). Complex **105** proved to be catalytically active for the coupling of **1a** and **2a**, affording product **3** in 98% ee. Treatment of **105** with quinoline *N*-oxide **1a** (2 equiv) gave rise to an equilibrium system *via* reversible substitution of the COD ligand by the quinoline *N*-oxide (Scheme 7e). The free energy of the forward reaction was measured to be ΔG^{o} = 0.5 kcal/mol, indicating a nearly thermoneutral substitution. This thermodynamics may be entangled with the kinetic profile of the quinoline *N*-oxide substrate (*vide infra*). To further probe the coupling mechanism, kinetic studies have been performed for both substrates and the active catalyst species **105** by using the initial rate methods. A 0th order dependence was evoked for the 1,6-diyne **2a** (Scheme 7g, left), which may suggest that the diyne participates to give a resting state. Surprisingly, an unusual inverse fractional order of -0.74 was measured for the quinoline *N*-oxide **1a** (Scheme 7g, middle), and this inhibitive effect of the quinoline *N*-oxide might be correlated to the nearly thermoneutral substitution between complex **105** and quinoline *N*-oxide **1a** (*vide infra*), and the resulting [(**L10**)Rh(**1a**)$_2$]$^+$ species is likely an off-loop species that is catalytically inactive. Besides, our kinetic studies revealed that the reaction was first-order respective to the active catalyst species **105** (Scheme 7g, right). This inhibitive effect was further evidenced by introduction of an exogenous 7-methylquinoline *N*-oxide that is unreactive toward this coupling, where significantly lower yield of product **3** was obtained (Scheme 7f). In contrast, no inhibitive effect of the *N*-oxide product was detected both in our kinetic studies and by introduction of the product **3** at the beginning of the reaction, likely due to enhanced steric effect of the coupled product.

The mechamism of this system has been ambiguous in previous studies because two distinct pathways have been proposed for the same hydroaylation of 1,6-diynes with acetophenone. Tanaka and Matsunaga proposed a pathway of oxidative cyclization of diynes,[21a,c] while Shibata indicated that arene C-H oxidative addition may be operative.[21b] The same ambiguity also exists in C-H activation-hydroarylation reactions of 1,6-enynes.[28] Moreover, previously proposed mechamisms are based on preliminary mechanistic studies. For example, in the previously proposed mechanism featuring diyne oxidative cyclization, the mechanistic details the of subsequent C-H bond cleavge remains unclear. DFT studies have been performed to elucidate the detailed mechanism of the coupling of quinoline *N*-oxide **1a** and diyne **2a**. We thus investigated both oxidative cyclization and chelation-assisted C-H oxidative addition pathways. The cationic Rh(I) species stabilized with the diphosphine ligand (**L10**) and COD has been set to the zero energy. The energy profile of the diyne oxidative cyclization pathway is shown in Figure 1a. The computed transition state (**TS1**) of the oxidative cyclization carries a kinetic barrier of only 12.7 kcal/mol. Subsequently, the resultant Rh(III) alkenyl intermediate (**INT3**) reacts with quinoline *N*-oxide via a σ-bond metathesis[29-30] mechanism through the **TS2** ($\Delta G^{\ddagger}$ = 15.8 kcal/mol), generating a Rh(III) aryl alkenyl species **INT5**. The subsequent C(aryl)–C(alkenyl) reductive elimination (via **TS3** or **TS4**) is turnover-limiting, leading to formation of the hydroarylated product. Alternatively, the reaction might be possibly initiated by C–H oxidative addition of quinoline *N*-oxide (see Supporting Information), as was proposed in a racemic system using acetophenone as an arene reagent.[21b,23b] Although the C–H oxidative addition of Rh(I) and the alkyne insertion into rhodium hydride have accessible kinetic barriers (ca. 20 kcal/mol) when compared to the formation of the **INT1** (Supporting Information), the subsequent alkyne migratory insertion into Rh–C(sp^2) bond is much less favorable, which requires a drastically high overall barrier of 26.4 kcal/mol to reach the common intermediate **INT5**. Thus, the C-H oxidative addition pathway seems unlikely, and our studies resolved the mechanistic ambiguity in this system.

As given in Figure 1b, the axial chirality in this pathway is determined by the irreversible C–C reductive elimination step (**TS3** versus **TS4**). The energy difference ($\Delta\Delta G^{\ddagger}$ = 3.0 kcal/mol) between the **TS3** and **TS4** is in line with the experimentally observed enantioselectivity (Table 1, entry 1). As depicted in Figure 1b, the favored **TS3**, which leads to the major (*R*)-**3** product, is stabilized by stronger π···π interactions between the diyne unit and the chiral ligand. In contrast, relatively weaker non-covalent interactions, mostly composed of C–H···π interactions, are detected in the disfavored **TS4**. The difference in these non-covalent interactions between **TS3** and **TS4** is evidenced by the NCI plots.[31] Our DFT studies are also consistent with the experimental studies in the following aspects. The small KIE of 1.17 is consistent with the DFT-computed free energy profile in which C-H cleavage is not turnover-limiting. In addition, no H/D exchange with an external proton source is expected in this catalytic process because of the well-defined σ-bond metathesis pathway. Kinetically, with the formation of thermodynamically stable intermediates **INT3** through a rather low kinetic barrier (through **TS1**), the diyne **2a** is expected to follow a 0th order kinetics, as was indeed experimentally observed (Scheme 7g). One would also expect 0th order dependence for the quinoline *N*-oxide (**1a**) because the resting state **INT5** was formed with a rather low barrier via a down hill process. However, this conclusion is contingent upon no other lower-energy or interfering pathways. The experimentally observed nearly thermoneutral ligand substitution between complex **105** and two equivalents of quinoline *N*-oxide may account for the observed kinetics for substrate **1a**. An inverse fractional order is consistent with the approximately thermoneutral substitution. This is because a very endergonic substitution reaction will lead to 0th order kinetics, while a very exergonic one should lead to inverse second order kinetics of the quinoline *N*-oxide. Overall, good agreement has been realized between experimental and theoretical studies. Thus, an overall catalytic reaction mechanism that involves an off-loop reversible ligand substitution between quinoline *N*-oxide and the COD is given in Figure 1c. Starting from the intermediate **C**, oxidative cyclization of diyne **2a** generates a rhodacyclic intermediate **D** with dissociation of the COD ligand. Subsequent ligation of the quinoline *N*-oxide (**E**) is followed by σ-bond metathesis of the *peri* C-H bond through a four-membered ring transition state. The resulting Rh(III) aryl species (**F**) undergoes enantio-determining C-C reductive elimination to complete the catalytic cycle.

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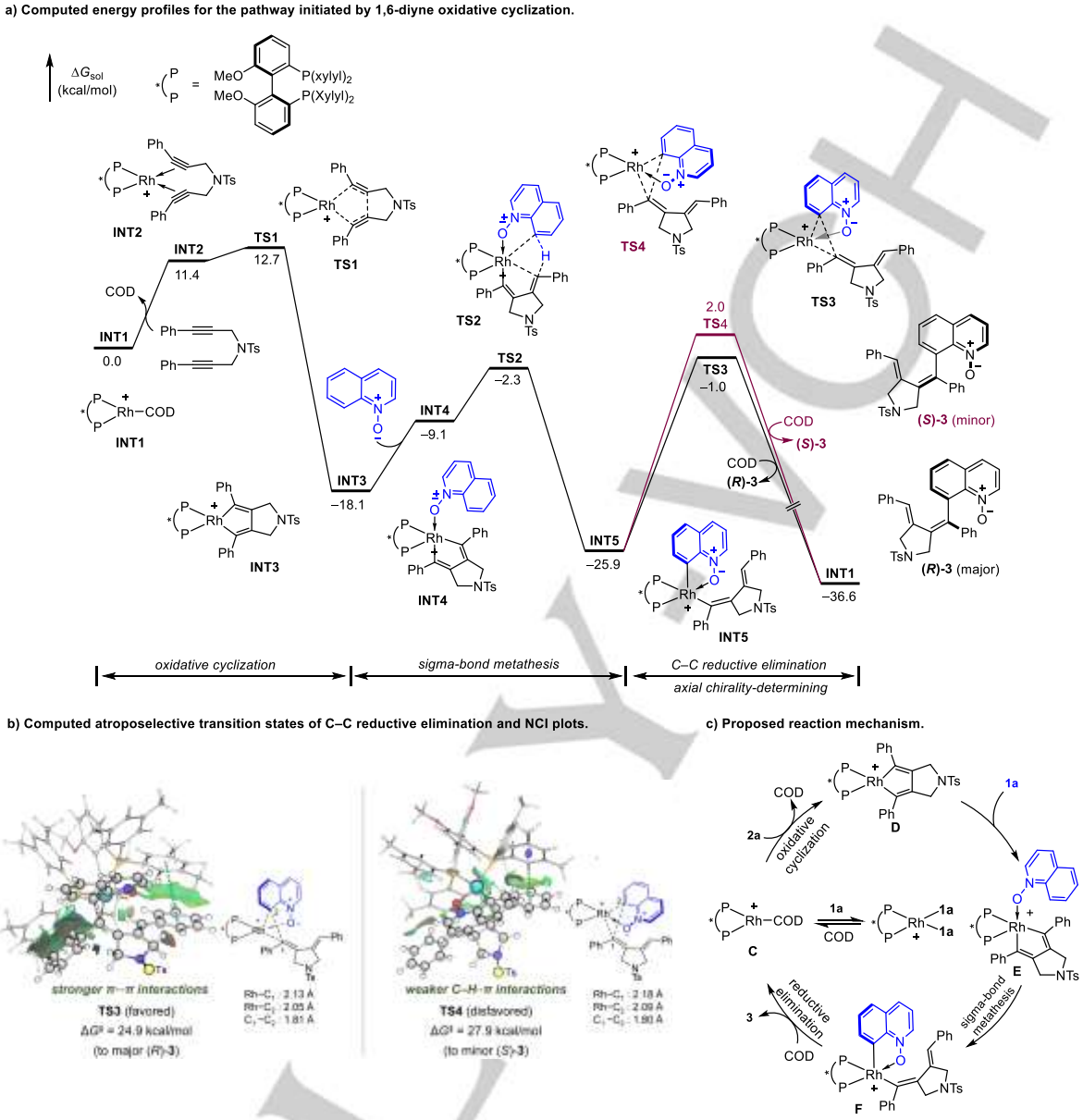

Figure 1. Computational studies and a proposed reaction mechanism.

Conclusion

In conclusion, we have accomplished rhodium(I)-catalyzed hydroarylative cyclization of 1,6-diynes with diverse classes of arenes (quinoline *N*-oxide, *N*-protected isoquonolone, and benzo[*h*]quinoline). The reaction proceeds *via* a C-H bond activation of these arenes at the *peri* positions, enabling highly enantioselective synthesis of a broad range of axially chiral 1,3-dienes that bear a low racemization barrier of $\Delta G^{\neq}(rac)$ = 26.6-28.0 kcal/mol. The coupling reactions in all categories proceeded with excellent enantioselectivity, regioselectivity, and *Z*/*E* selectivity, and the low racemization barrier of the product has been accommodated by the mild reaction conditions and high catalytic reactivity. Experimental and computational studies of the coupling of quinoline *N*-oxide system have been conducted, and the reaction proceeds *via* initial oxidative cyclization of the 1,6-diyne, followed by σ-bond metathesis between the arene C-H bond and one of the Rh-alkenyl groups. The subsequent C-C reductive elimination has been identified as both the enantio-determining and turnover-limiting step. The DFT-established mechanism is consistent with our experimental studies. Synthetic applications of the coupled products have been demonstrated. Significantly, the coupled products of quinoline *N*-oxides undergo photo-induced intramolecular oxygen-atom transfer in the absence of any photosensitizer, affording chiral epoxides with complete axial-to-central chirality transfer in excellent enantio- and diastereoselectivity. The ready availability of low-valent metal catalysts and chiral phosphine ligands may allow development of other challenging atroposelective catalytic systems.

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Keywords: C-H activation • axial chirality • olefin • rhodium • diyne

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RESEARCH ARTICLE

Rhodium(I)-Catalyzed Asymmetric Hydroarylative Cyclization of 1,6-Diynes to Access Atropisomerically Labile Chiral Dienes

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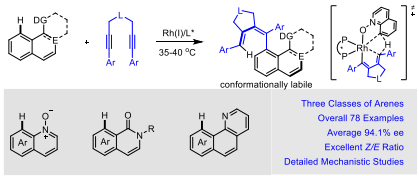

Rhodium(I)-catalyzed hydroarylative cyclization of 1,6-diynes with three distinct classes of arenes has been realized, enabling highly enantioselective synthesis of a broad range of axially chiral 1,3-dienes that are conformationally labile. Detailed mechanistic studies have been explored by experimental and computational methods.

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