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Rhodium-catalyzed enantioselective C–H alkynylation of sulfoxides in diverse patterns: desymmetrization, kinetic resolution, and parallel kinetic resolution†

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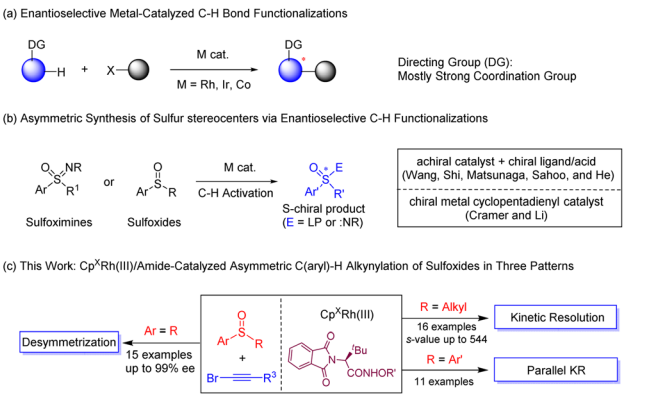
Rhodium-catalyzed enantioselective C–H alkynylation of achiral and racemic sulfoxides is disclosed with alkynyl bromide as the alkynylating reagent. A wide range of chiral sulfoxides have been constructed in good yield and excellent enantioselectivity (up to 99% ee, *s*-factor up to > 500) *via* desymmetrization, kinetic resolution, and parallel kinetic resolution under mild reaction conditions. The high enantioselectivity was rendered by the chiral cyclopentadienyl rhodium(III) catalyst paired with a chiral carboxamide additive. The interactions between the chiral catalyst, the sulfoxide, and the chiral carboxylic amide during the C–H bond cleavage offer the asymmetric induction, which is validated by DFT calculations. The chiral carboxamide functions as a base to promote C–H activation and offers an additional chiral environment during the C–H cleavage.

Introduction

Metal-catalyzed enantioselective C–H functionalization has emerged as a powerful strategy to synthesize complex chiral organic scaffolds owing to the atom- and step-economy of the reaction system and availability of the C–H substrates (arenes).[1] A large array of transition metal catalysts have been successfully employed in enantioselective C–H bond activation. Among the chiral ligands employed, chiral phosphines are predominant, as in palladium, rhodium(I), iridium(I), and nickel(0) catalysts.[2] In addition, great achievements have been made in palladium-catalyzed C–H bond activation using monoprotected amino acids (MPAA) as privileged chiral ligands.[3] Chiral NHC ligands also allowed the development of intriguing C–H activation systems.[4] Recently, with the plethora of racemic/achiral C–H activation systems enabled by trivalent metals *via* a typical concerted-metalation-deprotonation mechanism, group IX complexes stabilized by chiral cyclopentadienyl ligands ($Cp^XM(III)$) have proven as efficient and versatile catalysts in asymmetric C–H activation of diverse arenes,[5] and elegant systems have been reported by the groups of Cramer,[6] Rovis,[7] You,[8] Wang,[9] Li,[10] Waldmann,[11] and others.[12] Chelation-assistance remains a predominant strategy in C–H bond activation, and strong coordination groups such as amide,[6a,d,e,7,8c,e,9,10e,11,12a,c] imine,[6b,10c] pyridyl,[8a,b,8d] pyrimidyl,[10a,f] nitrone,[10b,d] and thioether[10a] in the arene are typically necessary to ensure catalytic reactivity (Scheme 1a). The employment of arenes bearing a weak directing group have been less explored in this context, with the exception of biarylphosphine oxides and sulfoxonium ylides as substrates.[13] Thus, development of asymmetric C–H activation systems with weak and functionalizable chelating groups is under great demand.

Enantioenriched sulfoxides are ubiquitous as pharmaceuticals and bioactive compounds, and they have also been utilized as chiral ligands in asymmetric catalysis.[14] Traditional protocols in synthesis of chiral sulfoxides such as resolution, nucleophilic



Scheme 1 Transition-metal-catalyzed enantioselective C–H activation.

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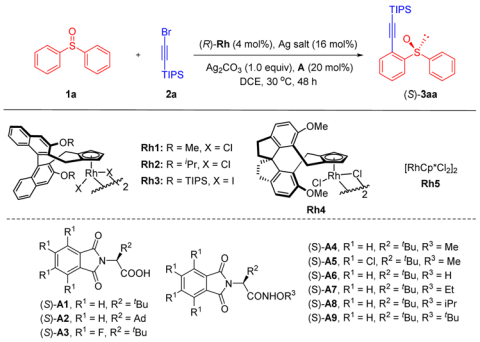
substitution, and biocatalytic reactions generally suffer from stoichiometric amounts of chiral reagents, poor efficiency, and/or limited substrate scope.[15] The C–H activation strategy was not introduced to asymmetric synthesis of chiral sulfoxides until very recently, likely due to inhibitive binding of the sulfur atom.[16] In 2018, Wang and coworkers reported Pd(II)-catalyzed enantioselective C–H olefination of diaryl sulfoxides through parallel kinetic resolution (PKR) and desymmetrization utilizing monoprotected amino acid (Ac-Leu-OH) as the ligand.[17] Recently, the He group reported Cp*Ir(III)-catalyzed enantioselective C–H amidation of dibenzyl sulfoxides through desymmetrization and parallel kinetic resolution also using a MPAA ligand, with the sulfur atom serves being a directing group (Scheme 1b).[18] Shi and coworkers achieved Pd-catalyzed C–H alkynylation-kinetic resolution of a special class of sulfoxides with 2-pyridyl as a directing group.[16b] Despite the progress and the powerful role of chiral $Cp^XRh(III)$ catalysts, no asymmetric catalytic system had been established in $Cp^XRh(III)$-catalyzed C–H activation using sulfoxides as arene substrates. On the other hand, alkynes as reactive organic intermediates have been employed in a wide variety of catalytic transformations, especially annulation reactions. Meanwhile, direct alkynylation of $C(sp^2)$-H bonds in high stereoselectivity and activity is highly desirable owing to the significance of the alkynyl functionality and the chiral platform in the product. Of note, hypervalent iodine-based alkynes and alkynyl bromides have been extensively studied in Rh/Ir-catalyzed C–H activation.[19] Nevertheless, enantioselective C–H alkynylation remains largely limited. Herein, we report rhodium-catalyzed enantioselective sulfoxide-directed C–H alkynylation utilizing both achiral and racemic sulfoxides, delivering chiral sulfoxides in high stereoselectivity *via* diverse patterns such as desymmetrization, kinetic resolution, and parallel kinetic resolution (Scheme 1c).

Results and discussion

We initially investigated the feasibility of the alkynylation of diphenyl sulfoxide (**1a**) with 1-bromo-2-(triisopropylsilyl) acetylene (**2a**) in the presence of a chiral rhodium cyclopentadienyl catalyst ((*R*)-**Rh1**-**Rh4**, Table 1). The desired alkynylated product **3aa** was indeed obtained in 32% yield and 25% ee when catalyzed by (*R*)-**Rh1** (4 mol%)/$AgSbF_6$ (16 mol%) in the presence of LiOAc (20 mol%) and Ag_2CO_3 (1.0 equiv.) in DCE at 30 °C for 48 h (entry 1). Switching the LiOAc additive to a *tert*-butyl-substituted chiral carboxylic acid improved the enantioselectivity to 51% ee (entries 2–4). Catalyst screening revealed that (*R*)-**Rh3** was superior to others (entries 5–7). To our delight, *tert*-Leucine-derived chiral amide[20] **A4** significantly improved the enantioselectivity to 86% ee (entry 8). A brief evaluation of the silver additive indicated that AgOTf performed best, affording **3aa** in 65% yield and 90% ee (entries 9–11). Further investigation of the chiral amides (**A5–A9**) indicated that employment of **A8** bearing an *N*-O^{i}Pr group afforded the product in the highest ee (91%, entries 12–16). The enantioselectivity remained even the temperature was increased to 55 °C (entry 17). Finally, the alkynylated product was obtained in an improved yield (72%) and enantioselectivity (91% ee) when Ag_2O (1.2 equiv.) was used as a base in the presence of 4 Å molecular sieves (entry 19). Lower yield was obtained when the catalyst loading was decreased to 4 mol% (entry 20). The employment of a chiral catalyst was necessary since switching to an achiral catalyst-(*S*)-**A8** only afforded poor enantioselectivity (entry 21).

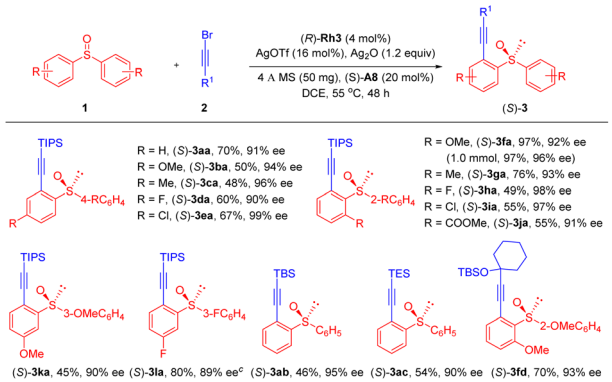
With the optimal conditions in hand (Table 1, entry 19), we next examined the scope of this enantioselective C–H alkynylation-desymmetrization (Scheme 2). Achiral diarylsulfoxides bearing electron-withdrawing (COOMe), donating (Me and OMe), and halogen groups at the *para* or *ortho* position of the benzene ring, all coupled effectively with alkyne **2a**, affording the desired products in 48–97% yield and 91–99% ee (**3aa-3ja**). Compatibility of diverse *ortho* substituents highlighted tolerance of steric effect of the benzene ring. In addition, the reaction could also be carried out on a 1 mmol

Table 1 Optimization of the reaction conditions[a]



Entry	[Rh]	Ag salt	Additive	Yield (%)	ee(%)[b]
1	**Rh1**	$AgSbF_6$	LiOAc	32	25
2	**Rh1**	$AgSbF_6$	(*S*)-**A1**	25	37
3	**Rh1**	$AgSbF_6$	(*S*)-**A2**	30	46
4	**Rh1**	$AgSbF_6$	(*S*)-**A3**	56	51
5	**Rh2**	$AgSbF_6$	(*S*)-**A3**	48	37
6	**Rh3**	$AgSbF_6$	(*S*)-**A3**	51	59
7	**Rh4**	$AgSbF_6$	(*S*)-**A3**	57	−40
8	**Rh3**	$AgSbF_6$	(*S*)-**A4**	60	86
9	**Rh3**	AgOTf	(*S*)-**A4**	65	90
10	**Rh3**	$AgBF_4$	(*S*)-**A4**	62	89
11	**Rh3**	$AgNTf_2$	(*S*)-**A4**	65	89
12	**Rh3**	AgOTf	(*S*)-**A5**	54	79
13	**Rh3**	AgOTf	(*S*)-**A6**	—	—
14	**Rh3**	AgOTf	(*S*)-**A7**	60	90
15	**Rh3**	AgOTf	(*S*)-**A8**	66	91
16	**Rh3**	AgOTf	(*S*)-**A9**	55	56
17[c]	**Rh3**	AgOTf	(*S*)-**A8**	54	90
18[d]	**Rh3**	AgOTf	(*S*)-**A8**	68	92
19[e]	**Rh3**	AgOTf	(*S*)-**A8**	72 (70)[f]	91
20[e,g]	**Rh3**	AgOTf	(*S*)-**A8**	46	94
21	**Rh5**	AgOTf	(*S*)-**A8**	42	5

[a] Reaction conditions: *rac*-**1** (0.05 mmol), **2** (0.06 mmol), (*R*)-**Rh** (4 mol%), Ag salt (16 mol%), additive (20 mol%), and Ag_2CO_3 (1.0 equiv.) in DCE (1.0 mL) at 30 °C for 48 h under N_2 in a sealed reaction tube, isolated yield. [b] The ee value was determined by chiral HPLC. [c] At 55 °C. [d] Ag_2O (1.2 equiv.) at 55 °C. [e] Ag_2O (1.2 equiv.) and 4 Å MS (25 mg) at 55 °C. [f] 0.1 mmol. [g] (*R*)-**Rh** (2 mol%).

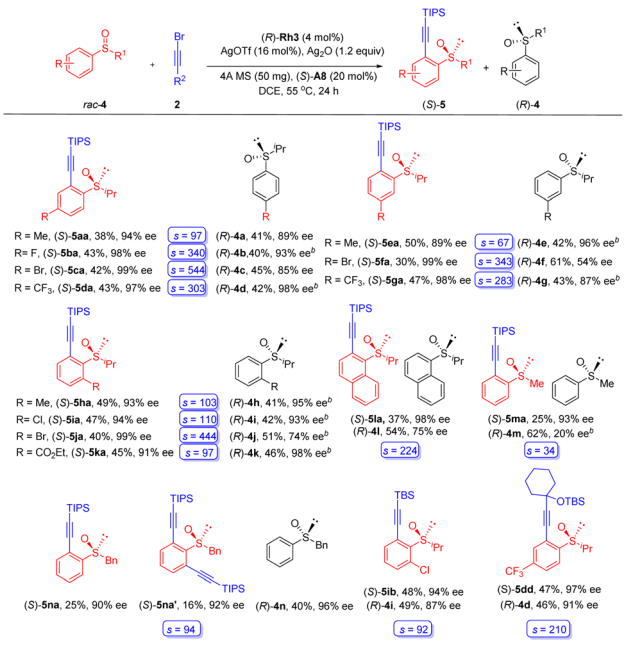


Scheme 2 Substrate scope of desymmetrization reactions. [a] reaction conditions: achiral sulfoxide **1** (0.1 mmol), **2** (0.12 mmol), (*R*)-**Rh3** (4 mol%), AgOTf (16 mol%), (*S*)-**A8** (20 mol%), Ag_2O (1.2 equiv.), 4 Å MS (50 mg) in DCE (2.0 mL) at 55 °C for 48 h under N_2 in a sealed reaction tube, isolated yield. [b]The ee was determined by chiral HPLC. [c]At 45 °C.

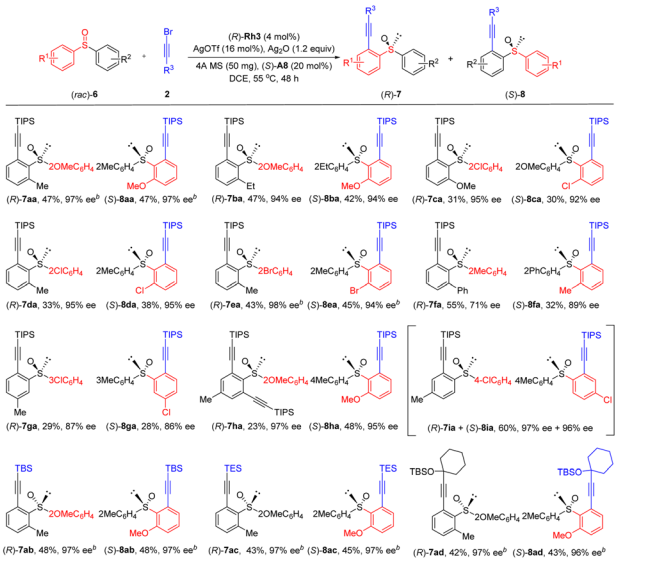
scale, and the product **3fa** was still isolated in 96% ee. Diarylsulfoxides with *meta*-Me and F substituents reacted selectively at the less hindered *ortho* site, and the desired products were obtained in 89–90% ee (**3ka** and **3la**). Replacement of the TIPS group in the alkyne by a TBS, TES, or a siloxyl-based tertiary alkyl group afforded the product in moderate yields and excellent 90–95% ee (**3ab**, **3ac**, and **3fd**).

To better explore the reaction patterns, kinetic resolution of biased racemic sulfoxides was also successfully realized under our standard reaction conditions (Scheme 3). The reaction of (*iso*-propylsulfinyl)benzene was first examined using alkyne **2a** as the coupling partner. Racemic (*iso*-propylsulfinyl)benzenes containing electron-donating groups (Me), withdrawing groups (CF_3), as well as halogen substituents (F and Br) at the *para* and the *meta* position of the benzene ring were well tolerated, furnishing the desired products **5aa**-**5ga** in consistently excellent enantioselectivities (89–99% ee), and the recovered sulfoxide substrate was obtained in 54–98% ee, which corresponds to a *s*-factor ranging from 67 to 544. As expected, the presence of an *ortho* Me, Cl, Br, and CO_2Et group was also well compatible with this protocol, delivering the alkynylation products in high yields and enantioselectivities (**5ha**-**5ka**, 91–99% ee), and the recovered substrates **4h**–**4k** were isolated in 41–51% yields with 74–98% ee. The arene ring has been extended to a fused one, and the alkynylation of 1-naphthoyl sulfoxide (**4l**) afforded the product in 98% ee (s = 224). Extension of the *S*-alkyl group to a methyl led to diminished reactivity, and the product **5ma** was isolated in 93% ee (s = 34). To our delight, mono- and disubstituted products (**5na**, and **5na′**) were obtained in excellent enantioselecttivity when a benzyl-substituted sulfoxide **4n** was used. Excellent yield and enantioselectivity were also realized for a TBS (**5ib**) or a propargyl silyl ether-substituted (**5dd**) alkynyl bromide. The (*R*) configuration of a recovered sulfoxide substrate **4m** was determined based on a previous report.[21]

To further broaden the substrate scope and the asymmetric reaction patterns, biased diaryl sulfoxides were then examined toward dynamic kinetic resolution since both arene rings may undergo competitive alkynylation (Scheme 4). Indeed, the alkynylation occurred at both arene rings under the standard reaction conditions, furnishing products **7** and **8** in a parallel



Scheme 3 Substrate scope of kinetic resolution reactions. [a]Reaction conditions: (*rac*)-**4** (0.2 mmol), **2** (0.3 mmol), (*R*)-**Rh3** (4 mol%), AgOTf (16 mol%), (*S*)-**A8** (20 mol%), Ag_2O (1.2 equiv.), 4 Å MS (50 mg) in DCE (2.0 mL) at 55 °C for 24 h under N_2 in a sealed reaction tube, isolated yield. [b] At 35 °C. [c] Calculated according to $s = \ln[(1 - C)(1 - ee^{2a})]/\ln[(1 - C)(1 + ee^{2a})]$.

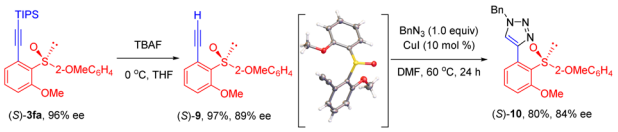


Scheme 4 Substrate scope of parallel kinetic resolution. [a]Reaction conditions: *rac*-**6** (0.1 mmol), **2** (0.15 mmol), (*R*)-**Rh3** (4 mol%), AgOTf (16 mol%), (*S*)-**A1** (20 mol%), Ag_2O (1.2 equiv.), 4 Å MS (50 mg) in DCE (2.0 mL) at 55 °C for 48 h under N_2 in a sealed reaction tube, isolated yield. [b]Ag_2CO_3 (1.0 equiv.) was used at 45 °C.

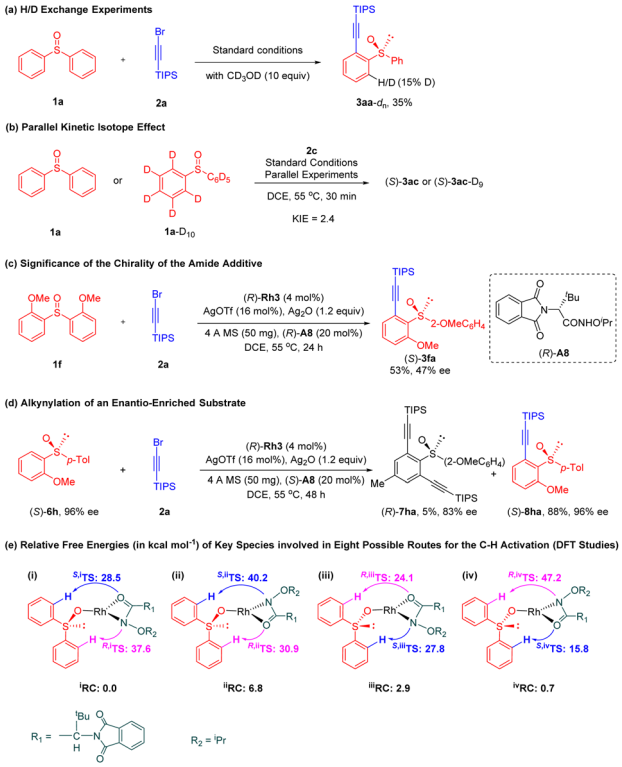
kinetic resolution (PKR) fashion. The scope of this reaction seems broad. Thus, racemic sulfoxides **6** with two different *ortho* substituents in the benzene rings were applicable, giving the two alkynylated products in good yields and high ee values (**7aa-7fa**, **8aa-8fa**, 71–97% ee). Slightly lower enantioselectivity was observed when two different *meta* substituents were introduced (**7ga**, 87% ee; **8ga**, 86% ee), likely because these substituents are distal to the reaction site or the directing group. A dialkynylated product was obtained in 97% ee (**7ha**) and the other single alkynylated product was isolated in 48% yield and 95% ee (**8ha**) when a *para* substituted sulfoxide 1-methoxy-2-(*p*-tolylsulfinyl)benzene was employed. A mixture of products (**7ia** + **8ia**) were isolated using 1-chloro-4-(*p*-tolylsulfinyl)benzene as an arene. For the alkynyl bromide substrates, different alkynyl terminus such as TBS, TES, and propargyl silyl ether were compatible, giving the corresponding products **7ab-7ad** and **8ab-8ad** in high yields and enantioselectivity under slightly modified conditions using a different base (silver carbonate). The absolute configuration of ethynyl sulfoxide derived from product **7aa** was determined to be (*S*) by X-ray crystallography (CCDC 2207905).

To demonstrate the synthetic utility of the chiral products, synthetic applications have been briefly demonstrated (Scheme 5). The triisopropylsilyl (TIPS) group could be readily removed to give the ethynyl sulfoxide **9** in 97% yield and 89% ee. Meanwhile, the (*S*) configuration of product **9** was determined by X-ray crystallography (CCDC 2207903) and was extrapolated to the other products. Chiral ethynyl sulfoxide **9** was further transformed to a triazole **10** in attenuated enantiopurity *via* a cycloaddition reaction.

Several experiments have been conducted to probe the reaction mechanism (Scheme 6). H/D exchange experiments in the presence of **2a** was conducted under the standard conditions and afforded product **3aa**-d_n with deuteration at the *ortho* position (Scheme 6a), indicating reversibility of the C–H activation. Isotope effect was observed in side-by side reaction (KIE = 2.4), thus indicating C–H cleavage is likely involved in the turnover-limiting step (Scheme 6b). Lower yield and enantioselectivity (53% yield and 47% ee) were obtained when the oppositely configured (*R*)-**A8** was designated as additive, indicating that the match between the catalyst and chiral amide was crucial (Scheme 6c), as has been disclosed in other stereodetermining C–H activation processes.[20,22] In another experiment, enantio-enriched sulfoxide substrate (*S*)-**6h** was synthesized and was subjected to the reaction conditions in order to evaluate the parallel kinetic resolution. The (*S*)-**6h** reacted selectively at the *o*-OMe-attached benzene, leading to the corresponding product **8ha** in 96% ee, suggesting that



Scheme 5 Synthetic applications.



Scheme 6 Mechanistic studies.

regiodivergent parallel kinetic resolution (PKR) was involved in this transformation (Scheme 6d).

A series of DFT[23] calculations were then conducted at the B3LYP/Def2TZVPP//Def2SVP level[24,25] to understand the origin of the enantioselectivity. Only the C–H activation event was explored because the turnover-limiting feature has been revealed by the KIE experiment. The reaction follows a concerted metalation-deprotonation pathway, and the chiral amide functions as a base to bridge the rhodium and the reactive C–H proton. Due to prochirality of the diaryl sulfoxide and the two possible binding modes of the chiral amide group, eight possible deprotonation pathways have been investigated for the concerted metalation-deprotonation process (Scheme 6e). Interestingly, the amide oxygen rather than nitrogen is found to serve as the effective proton acceptor. Our preliminary studies revealed that the lowest (*S*)-forming transition state ^{S,iv}**TS** (15.8 kcal mol^{-1}) is 8.3 kcal mol^{-1} lower in energy than the lowest (*R*)- forming transition state ^{R,iii}**TS** (24.1 kcal mol^{-1}) due to the loss of the hydrogen-bonding interaction between amide additive and substrate in the latter case (see Scheme S1†), which is consistent with our experimental studies. By passing this lowest (S)-forming transition state, the cyclometallation process is nearly thermoneutral. Thus, the chiral amide offers additional chiral environment in the second coordination sphere of the catalyst to assist the C–H activation.

Conclusions

In summary, we have developed a rhodium(III)-catalyzed enantioselective C–H alkynylation of sulfoxides with alkynyl

bromides as the alkylating reagent. Diverse asymmetric reaction patterns such as desymmetrization, kinetic resolution, and parallel kinetic resolution have been realized for the sulfoxide substrates. The chiral catalyst and the chiral amide additive collectively played an important role during the C–H bond activation. A broad range of chiral sulfoxides were constructed in good yields and consistently excellent enantioselectivities (up to 99% ee). Further studies on selective and catalytic synthesis of sulfur- or phosphorus-stereogenic products are in progress in our laboratories.

Data availability

Further details of the experimental procedure, ^{1}H, and ^{13}C NMR, HPLC spectra, and X-ray crystallographic data for **7aa** and **9** are available in the ESI.†

Author contributions

X. L. conceived the ideas and directed the project. L. K. and Y. Z. performed the experiments. X.-X. L. and X.-P. Z. conducted the computational studies. X. L. and L. K. wrote the manuscript with feedback from all authors.

Conflicts of interest

The authors declare no competing financial interests.

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