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Selective C(sp^3)−H Bond Insertion in Carbene/Alkyne Metathesis Reactions. Enantioselective Construction of Dihydroindoles

Kuiyong Dong,[†] Chao Pei,[†] Qian Zeng,[†] Hanlin Wei,[†] Michael P. Doyle,*[,§] and Xinfang Xu*[,†,‡]

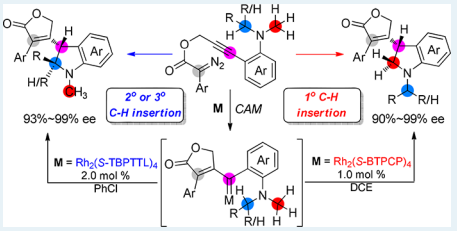
[†]Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China

[‡]School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China

[§]Department of Chemistry, University of Texas at San Antonio, San Antonio, Texas 78249, United States

Supporting Information

ABSTRACT: A general access to chiral dihydroindole derivatives in high yields is achieved by C−H functionalization in a highly site- and enantioselective cascade reaction of propargyl diazoacetates. Highly site-selective intramolecular C(sp^3)−H bond insertions are realized by catalyst control. Sterically demanding dirhodium carboxylates, optimized with Rh_2(*S*-BTPCP)$_4$, favor C−H insertion into 1° C−H bonds with regioselectivities reaching >95:5 (1° > 2° benzylic) and >90% ee. With Rh_2(*S*-TBPTTL)$_4$, preferential 2° and 3° C−H bond insertion occurs due to the configuration of catalyst and electronic effects. The chiral dirhodium catalyst not only promotes carbene/alkyne metathesis (CAM) to generate the donor/donor carbene intermediate, but is also responsible for the observed asymmetric induction in the terminating C−H bond insertion reaction.

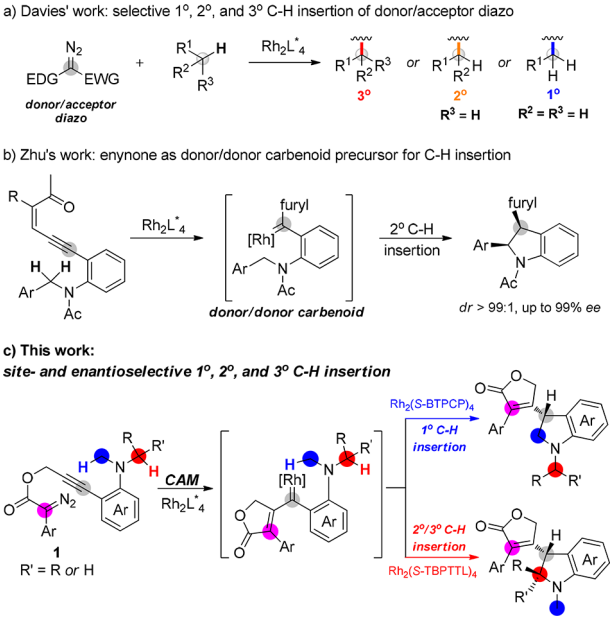


KEYWORDS: *C−H bond insertion, carbene/alkyne metathesis, diazo compound, dirhodium-catalysis, chiral dihydroindole*

INTRODUCTION

Transition-metal catalyzed C−H bond functionalization has provided significant advances in the synthesis of complex natural products and potential pharmaceuticals.[1] A major challenge has been to realize site-selective methods for the C−H bond functionalization, as well as high levels of stereocontrol.[2] In this context, directing groups from the substrate for catalysts are used to achieve selectivity control for the modification of ubiquitous C−H bonds, and significant results have been disclosed by Yu,[3] Gaunt,[4] Glorius,[5] and others.[6] In contrast, direct C−C bond formation via selective C−H insertion with metal carbenes in which the catalyst ligands impart selectivity has emerged as a promising method for enantioselective C−H bond functionalization,[7] especially for inert C(sp^3)−H bonds. Davies and co-workers have reported site- and enantioselective C−H bond functionalization, including 1°,[8a−c] 2°,[8d] and 3°[8e] C(sp^3)−H bond insertion reactions, using chiral dirhodium catalysts with donor−acceptor diazo compounds (Scheme 1a). However, the use of donor−acceptor diazo compounds, although enhancing selectivity, is limiting in applications. Recently, the Zhu group disclosed a catalytic asymmetric intramolecular 2° C−H insertion reaction for the construction of chiral dihydroindoles with excellent enantioselectivity using enynones as efficient nondiazo carbene precursors. The key intermediate in this reaction is a furyl-metal-carbene, which is a donor/donor carbene that would be difficult to obtain from other precursors (Scheme 2b).[9]

Scheme 1. Rh-Catalyzed Site- and Enantioselective C(sp^3)−H Bond Insertion



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Carbene/alkyne metathesis (CAM) cascade reactions have shown extraordinary efficiency for the multibond formations in one operation. Since the pioneering work reported by Padwa[10] and Hoye,[11] the resultant vinyl metal carbene intermediate was reported to be terminated by a variety of metal carbene reactions that include formal [3 + 2]-cycloaddition,[12] cyclopropanation,[13] Buchner reaction,[14] and others,[15] Recently, May's group reported an enantioselective carbene/alkyne cascade reaction terminated with C−H bond insertion to form bridged polyclic molecules.[16] Although versatile catalytic asymmetric carbene transformations have been studied,[17] there have been very few examples of asymmetric carbene/alkyne metathesis (CAM) cascade reactions, presumably because of dissociation of the metal catalyst occurs prior to the asymmetric induction step that terminates the cascade process.[16b,18] Inspired by these advances and in conjunction with our recent studies on carbene/alkyne metathesis (CAM) cascade reactions,[19] we envisioned that the situ generated donor/donor metallocarbene intermediate formed via carbene/alkyne metathesis would have attenuated reactivity compared to acceptor or donor/acceptor substituted carbenes. The attenuated reactivity of donor/donor metallocarbenes would enable high selectivity, including site- and stereoselectivity, to be achieved in the presence of an appropriate ligated catalyst (Figure 1).

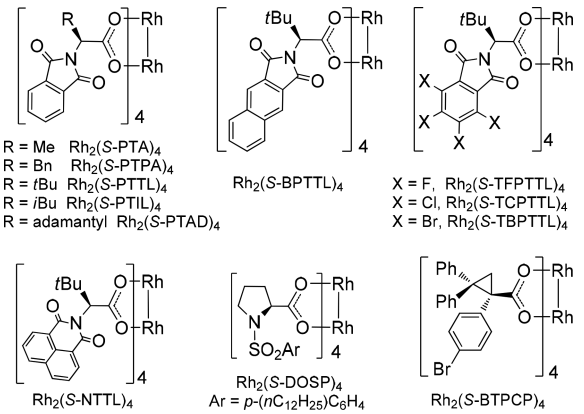


Figure 1. Dirhodium tetracarboxylates catalysts.

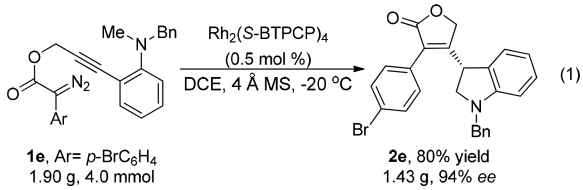
Herein, we report dirhodium-catalyzed carbene/alkyne metathesis reactions of propargyl diazoacetates **1** followed by selective C−H bond functionalization that occurs with high levels of site-selectivity and enantioselectivity (Scheme 1c).[20]

RESULTS AND DISCUSSION

Initially, we employed the propargyl diazoacetate **1a** as the model substrate which contains both electronically activated primary and secondary C−H bonds (Table 1). This reactant was easily synthesized from phenylacetic acid and the corresponding propargyl alcohol via esterfication followed by diazo transfer reaction.[21] When the established catalyst Rh_2(*S*-DOSP)$_4$ and dirhodium carboxylate complexes were used, the reaction resulted in benzylic C−H bond insertion product **3a** predominately with moderate to high diastereoselectivity and enantioselectivity (entries 1−11). Further screening of solvents in the presence of Rh_2(*S*-TBPTTL)$_4$ revealed that both the diastereoselectivity and enantioselectivity were improved when the reaction was performed in chlorobenzene, generating **3a** in 81% isolated yield, 85:15 dr with 94% and 97% ee with 2.0 mol % of catalyst loading (entry 15).[21] In contrast, the triarylcyclopropane carboxylates catalyst Rh_2(*S*-BTPCP)$_4$ switched selectivity toward the primary C−H bond,[8] providing **2a** as the major product in a combined 85% isolated yield with 84:16 site selectivity and 94% ee (entry 16). Additional optimization of the solvent revealed that slow addition of **1a** in 2 h to Rh_2(*S*-BTPCP)$_4$ in DCE at −20 °C gave the highest level of site-selectivity and enantioselectivity, generating **2a** as the only product in 89% yield and 96% ee (entry 22). Notably, the only catalyst involved in this cascade transformation is a chiral dirhodium catalyst, which not only promotes the carbene/alkyne metathesis (CAM) processes but is also responsible for the observed high asymmetric induction in the terminating C−H insertion reaction.

SCOPE

The generality of the reaction was then explored, from which we discovered that the Rh_2(*S*-BTPCP)$_4$-catalyzed reactions of alkyne-tethered diazo compounds **1** selectively provided the primary C−H bond insertion products with routinely excellent levels of enantioselectivity (Scheme 2, 90−99% ee). A series of aryl diazoacetates bearing electron-neutral, -rich, or -deficient substituents on the aromatic ring reacted smoothly to give the corresponding products in high yields (71−85%) with excellent enantioselectivity (**2a**−**2f**). The *para*-, *meta*-, and *ortho*-substitutions on the aryl group had little effect, and all led to the insertion products in high yields with >90% ee (**2g**−**2i**). The substitution pattern on the aryl group of the *N*-benzylic unit was then examined; the electronic-influence showed little effect on both reactivity and selectivity, and high yields with 94%−96% ee were obtained in these reactions (**2j**−**2o**). Notably, when substrates containing potentially reactive sites were applied, such as furyl (**2p**), *n*-butyl (**2q**), isopropyl (**2r**), and cyclopropyl (**2s**), only the products derived from C−H bond insertion into the methyl group were observed with high yields and >90% ee. The phenyl-tethered substrate **1t** was also well tolerated under these conditions, selectively affording the desired product **2t** in 89% yield and 93% ee without observation of any aromatic substitution product.[22] Substituents on the aryl group of the propargylic linkage were accommodated under these conditions, and their corresponding products were formed in >75% yields with 90%−94% ee (**2u**−**2w**). The (*S*)-configuration of the generated chiral center in the dihydroindole **2n** was confirmed by single-crystal X-ray diffraction analysis,[23] and the absolute configurations of the other products were assigned by analogy. In addition, the reaction of bromo-substrate **1e** was conducted on a gram scale with a 0.5 mol % catalyst loading, generating **2e** in 80% isolated yield and 94% ee (eq 1).



Insertion into the secondary benzylic C−H bond of **1** promoted by Rh_2(*S*-TBPTTL)$_4$ in chlorobenzene was then investigated (Scheme 3). This insertion reaction was also insensitive to electronic effects. Substrates bearing electron-neutral, -rich, or -deficient substitutions on the aromatic ring

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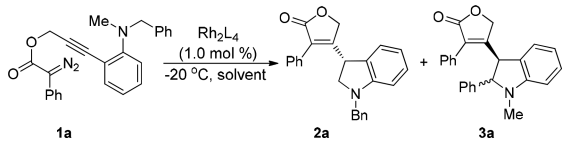
Table 1. Optimization Studies[a]



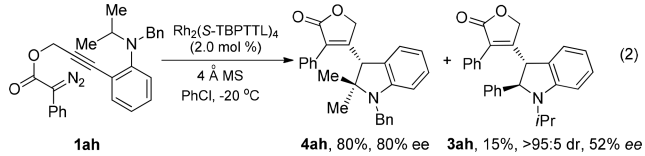
1a 2a 3a

entry	Rh(II)	solvent	yield[b] (%) 2a + 3a	ratio[c] (2a:3a)	dr[c] (3a)	ee[d] (%) 2a/*syn*-3a/*anti*-3a
1	Rh_2(*S*-DOSP)$_4$	DCM	88	<5:95	91:9	−/70/56
2	Rh_2(*S*-PTAD)$_4$	DCM	83	<5:95	83:16	−/73/9
3	Rh_2(*S*-NTTL)$_4$	DCM	85	<5:95	64:36	−/78/53
4	Rh_2(*S*-BPTTL)$_4$	DCM	79	<5:95	80:20	−/56/−5
5	Rh_2(*S*-PTA)$_4$	DCM	88	<5:95	64:36	−/33/37
6	Rh_2(*S*-PTPA)$_4$	DCM	85	<5:95	67:33	−/39/59
7	Rh_2(*S*-PTIL)$_4$	DCM	81	<5:95	68:32	−/63/61
8	Rh_2(*S*-PTTL)$_4$	DCM	74	<5:95	74:26	−/50/58
9	Rh_2(*S*-TFPTTL)$_4$	DCM	80	<5:95	76:24	−/67/−38
10	Rh_2(*S*-TCPTTL)$_4$	DCM	78	<5:95	73:27	−/86/36
11	Rh_2(*S*-TBPTTL)$_4$	DCM	81	<5:95	67:33	−/92/31
12	Rh_2(*S*-TBPTTL)$_4$	DCE	77	<5:95	67:33	−/97/58
13	Rh_2(*S*-TBPTTL)$_4$	$CHCl_3$	78	<5:95	40:60	−/94/71
14	Rh_2(*S*-TBPTTL)$_4$	toluene	80	<5:95	72:28	−/87/74
15[e]	Rh_2(*S*-TBPTTL)$_4$	PhCl	81	<5:95	85:15	−/94/97
16	Rh_2(*S*-BTPCP)$_4$	DCM	85	84:16		94/−/−
17	Rh_2(*S*-BTPCP)$_4$	DCE	82	91:9		95/−/−
18	Rh_2(*S*-BTPCP)$_4$	$CHCl_3$	88	87:13		92/−/−
19	Rh_2(*S*-BTPCP)$_4$	toluene	88	76:24	75:25[d]	84/70/91
20	Rh_2(*S*-BTPCP)$_4$	PhCl	93	78:22	87:13[d]	87/67/93
21	Rh_2(*S*-BTPCP)$_4$	PhF	92	85:15		91/−/−
22[f]	Rh_2(*S*-BTPCP)$_4$	DCE	89	>95:5		96/−/−

[a]The reaction was carried out on a 0.1 mmol scale: to the Rh-catalyst (1.0 mol %), and 4 Å MS (100 mg) in the corresponding solvent (1.0 mL), was added **1a** in the same solvent (1.0 mL) via syringe pump over 1 h under an argon atmosphere. [b]Isolated combined yields of **2a** + **3a**. [c]The ratio and dr were determined by ^{1}H NMR of the crude reaction mixture. [d]Determined by chiral HPLC analysis. [e]With 2.0 mol % of Rh_2(*S*-TBPTTL)$_4$. [f]Compound **1a** in DCE (1.0 mL) was added via syringe pump over 2 h.

all underwent this C−H insertion reaction smoothly, producing the corresponding products in high yields (77−88%), high diastereoselectivity (>80:20), and excellent enantiocontrol for both of the two diastereomers (**3a**−**3e**). Alkyl substituted methylene insertion, instead of benzylic insertion, proceeded cleanly and afforded the 2 °C−H bond insertion products in 81−91% yields as a single diastereomer in most cases with 94%−95% ee (**3f**−**3i**). However, with the corresponding alkyl diazo compound, the reaction gave complex results, and only the *β-H* shift product was identified as the major product according to the proton NMR spectrum of the crude reaction mixture (see Figure S1 in the Supporting Information (SI) for details). It is worth mentioning that the enantiomeric product could be obtained with comparable yield and diastereoselectivity when the reaction was catalyzed by Rh_2(*R*-TBPTTL)$_4$ (note b). The absolute configuration of the major isomer *anti*-**3e** was assigned as 2*R*,3*S* by single crystal X-ray crystallography,[23] and the absolute configurations of the other products were assigned by analogy. Notably, in comparison with Zhu's report for the synthesis of *syn*-product,[9] the current method provides an important complement for the preparation of *anti*-derivatives.

The selectivity for insertion in competition between 1° and 3° C−H bonds was also examined (Scheme 4). High selectivity for insertion into 3° C−H bonds, even with the significant steric advantage of 1° C−H bonds over the 3° C−H bond, gave their corresponding products in 81−92% yield with 93−97% ee when these reactions were catalyzed by Rh_2(*S*-TBPTTL)$_4$ in PhCl (**4a**−**4c**). Further study of selectivity between 2° and 3° C−H bonds was also conducted. With material **1ah** in the presence of Rh_2(*S*-TBPTTL)$_4$ in PhCl, the reaction gave the 3° insertion product **4ah** as the major product in 80% yield with 80% ee, combined with a minor amount of the 2° insertion product **3ah** in 15% yield with moderate enantioselectivity (eq 2).



(2)

1ah **4ah**, 80%, 80% ee **3ah**, 15%, >95:5 dr, 52% *ee*

These studies demonstrate that a small structural change in catalyst ligands can achieve high site-selectivity. Subsequent preliminary DFT calculations at the B3LYP/6-31G* (Rh: LANL2DZ) level were performed on the simplified $Rh_2(O_2CH)_4$ carbene insertion models[24] to provide insights into the catalyst-controlled selectivity, and two optimized transition states **TS-1** and **TS-2** were located for the 1° C(sp^3)−H and 2° C(sp^3)−H bond insertions, respectively (for other possible C−H bond insertion transition states, see Figure S4 and S5 for details).[21] The calculated transition state structures for both the benzylic and methyl C−H bond insertion of in situ generated donor/donor carbenes are shown in Figure 2 along with selected bond lengths. The X-ray crystallographic structure of *tert*-butyl catalyst, Rh_2(*S*-

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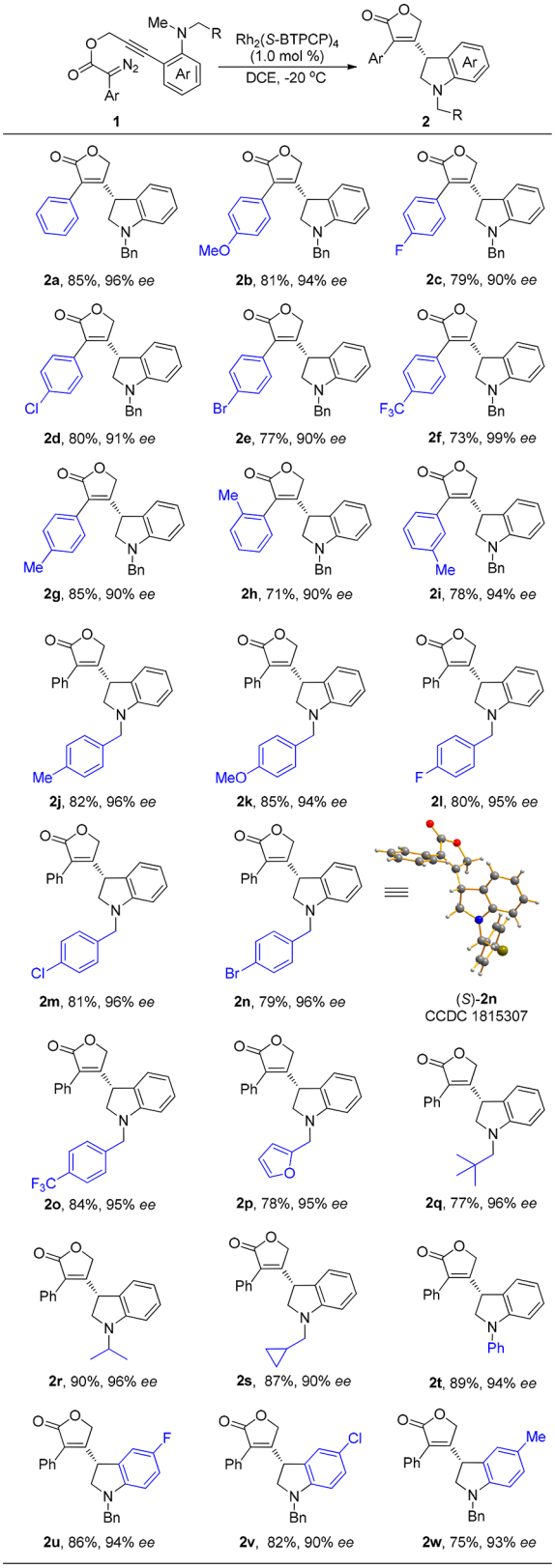
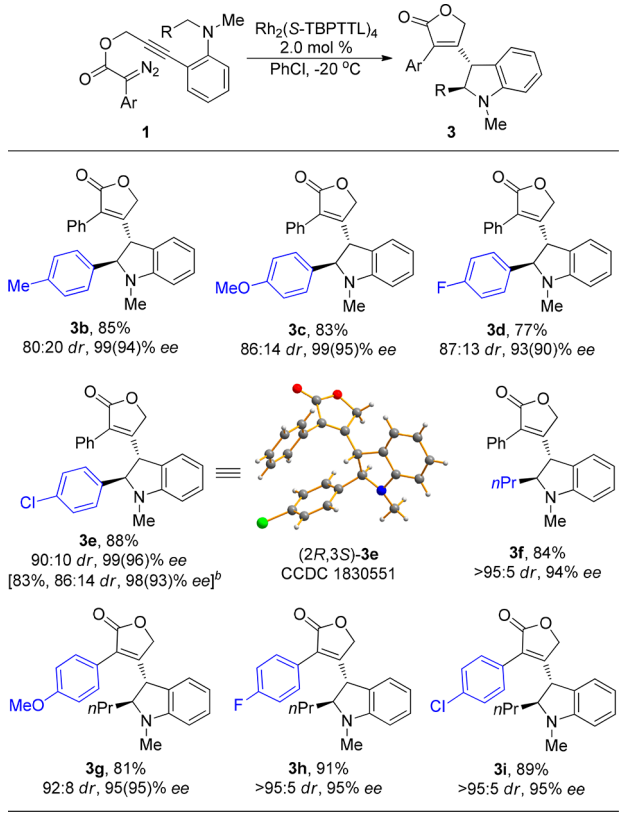
Scheme 2. Scope of the Enantioselective 1° C−H Bond Insertion[a]



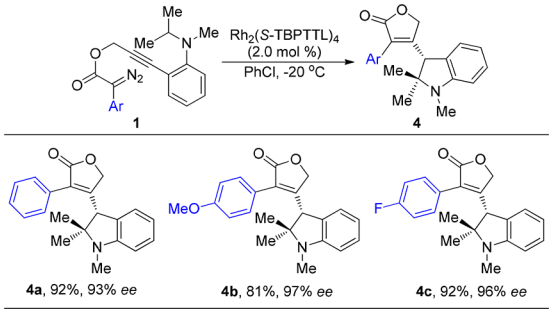
[a]Reaction conditions: to Rh_2(S-BTPCP)$_4$ (1.8 mg, 1.0 mol %) and 4 Å MS (100 mg) in DCE (1.0 mL_) was added **1** (1.0 mmol) in DCE (1.0 mL) via a syringe pump over 2 h under argon atmosphere. The yields are given in isolated yields and the enantiomeric excess was determined by chiral HPLC analysis.

Scheme 3. Scope of the Enantioselective 2° C−H Bond Insertion[a]



[a]Reaction conditions: to Rh_2(S-TBPTTL)$_4$ (5.1 mg, 2.0 mol %), and 4 Å MS (100 mg) in chlorobenzene (1.0 mL_), was added **1** (1.0 mmol) in chlorobenzene (1.0 mL) via syringe pump over 1 h under argon atmosphere. The yields are given in isolated yields, The *dr* was was determined by ^{1}H NMR of the crude reaction mxiture, and the enantiomeric excess was determined by chiral HPLC analysis. Data in parentheses are the *ee* of the minor isomers. [b]Catalyzed by Rh_2(*R*-TBPTTL)$_4$.

Scheme 4. Enantioselective 3° C−H Bond Insertion[a]



[a]Reaction conditions: to Rh_2(S-TBPTTL)$_4$ (5.1 mg, 2.0 mol %), and 4 Å MS (100 mg) in chlorobenzene (1.0 mL), was added **1** (1.0 mmol) in chlorobenzene (1.0 mL) via syringe pump over 1 h under argon atmosphere. The yields are given in isolated yields, and the enantiomeric excess was determined by chiral HPLC analysis.

TBPTTL)$_4$, with all the phthalimido groups on the same side forming a C_4 symmetric structure was reported by Hashimoto,[24b] and the analogous structures were studied by

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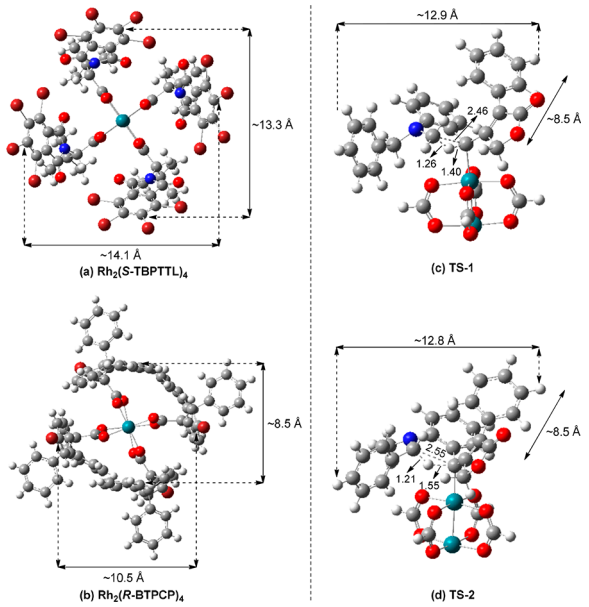

Figure 2. DFT calculated 3-D structures of Rh_2(*S*-TBPTTL)$_4$ (**a**) and catalytically active sites of Rh_2(*R*-BTPCP)$_4$ (X-ray, **b**), and methyl and benzylic C−H bond insertion transition states (**c**, **d**). The bond lengths in the structures at the bottom are given in Å.

Charette,[24c] Müller,[24d] and Fox[24e,f] independently. The calculated rectangular binding cavity with the phthalimido groups for this catalyst on the rhodium face (Figure 2a, 13.3 × 14.1 Å) is significantly larger than the comparable cavity of Rh_2(*R*-BTPCP)$_4$ as reported by Davies (Figure 2b, 8.5 × 10.5 Å).[25] The DFT optimized conformations of corresponding transition states show that both the methyl and benzylic C−H bonds can reach the reactive carbene center (Figure 2c: 12.9 × 8.5 Å, and 2d: 12.8 × 8.5 Å) in the case of Rh_2(*S*-TBPTTL)$_4$ with a bigger cavity (Figure 2a),[21] suggesting that the selectivity in this case is determined mainly by the inherent property of the substrate, and the electronically favored (or electronically activated) 2° or 3° C(sp^3)−H bond insertion occurs preferentially.[7h] For Rh_2(*S*-BTPCP)$_4$, which has the same cavity as Rh_2(*R*-BTPCP)$_4$, due to the limited binding space, only the methyl C−H bond insertion transition state **TS-1** with an easy-to-rotate *N*-benzylic group pointing outside could fit into the tight environment of the distorted cavity of Rh_2(*S*-BTPCP)$_4$, and 1 °C(sp^3)-H bond insertion occurs predominately.[25] Notably, detailed computational studies of rhodium-catalyst controlled selective tertiary (or secondary)-to-primary C−H functionalization were well documented by Sigman, Davies, and Houk.[26] In addition, the computational studies also reveal that the final activated C−H bond insertion step of **1a** might be a nonsynchronous process involving hydride transfer to the carbene center with formation of a zwitterionic intermediate,[21] which is consistent with previous studies.[27]

CONCLUSION

In summary, we have developed a novel catalytic asymmetric cascade reaction of alkynyl diazoacetates, which provides general access to chiral dihydroindole derivatives in high yields with excellent enantiocontrol. Notably, highly site- and enantioselective 1°, 2°, and 3° C(sp^3)−H bond insertion can be realized with a selection of chiral dirhodium catalysts that promote the entire cascade process, including the observed asymmetric induction of the terminating C−H insertion reaction. In addition, the catalytic carbene/alkyne metathesis (CAM) strategy, which provides an effective approach to donor/donor carbene intermediates that is not possible with other precursors, is highly appealing for the synthesis of complex molecules via novel cascade transformations. Investigations on further applications of these catalytic cascade reactions are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b02822.

Experimental procedure, and the ^{1}H and ^{13}C NMR spectra of all the products (PDF)

Crystallographic data for **2n** (CIF)

Crystallographic data for **3e** (CIF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: michael.doyle@utsa.edu.

*E-mail: xinfangxu@suda.edu.cn.

ORCID

Michael P. Doyle: 0000-0003-1386-3780

Xinfang Xu: 0000-0002-8706-5151

Notes

The authors declare no competing financial interest.

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