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Cyclopropanation

Low Coordination State Rh^{I}-Complex as High Performance Catalyst for Asymmetric Intramolecular Cyclopropanation: Construction of *penta*-Substituted Cyclopropanes

*Junyou Zhang, Weici Xu, and Ming-Hua Xu**

In memory of Professor Robert H. Grubbs

Abstract: A simple, broad-scope rhodium(I)/chiral diene catalytic system for challenging asymmetric intramolecular cyclopropanation of various *tri*-substituted allylic diazoacetates was successfully developed. The low coordination state Rh^{I}-complex exhibits an extraordinarily high degree of tolerance to the variation in the extent of substitution of the allyl double bond, thus allowing the efficient construction of a wide range of *penta*-substituted, fused-ring cyclopropanes bearing three contiguous stereogenic centers, including two quaternary carbon stereocenters, in a highly enantioselective manner with ease at catalyst loading as low as 0.1 mol %. The stereoinduction mode of this Rh^{I}-carbene-directed asymmetric intramolecular cyclopropanation was investigated by DFT calculations, indicating that π-π stacking interactions between the aromatic rings of chiral diene ligand and diazo substrate play a key role in the control of the reaction enantioselectivity.

Introduction

Cyclopropane is an appealing structural unit with distinctive properties bearing a rigid and strained three-membered carbocyclic ring.[1] The cyclopropane scaffold is widely present in numerous biologically active natural products,[2] and has been frequently used in drug design to achieve specific therapeutic goals.[3] Moreover, cyclopropanes are attractive building blocks in organic synthesis due to their unique reactivity and versatile transformations.[4] Consequently, extensive efforts were devoted to the efficient synthesis of cyclopropane-containing compounds.[5] Notably, the last few decades have witnessed great achievements in the field of asymmetric preparation of diversely substituted cyclopropanes.[6] However, the stereoselective synthesis of highly (*penta*- or *hexa*-) substituted cyclopropanes with simultaneous control of all three vicinal carbon stereocenters remains a significant challenge, and successful catalytic asymmetric approaches are very few in the literature.[7] To the best of our knowledge, *penta*- or *hexa*-substituted cyclopropane-core structures also occur in many naturally occurring compounds and pharmaceuticals (as exemplified in Figure 1), and are associated with remarkable biological properties.[8] It is therefore highly desirable to develop efficient methodologies for the stereospecific synthesis of highly substituted cyclopropanes.

Catalytic asymmetric cyclopropanation of olefins with diazo compounds via metal carbenoid intermediates represents an attractive and straightforward strategy for the construction of cyclopropane structures.[9–16] Specifically, the seminal work of Doyle,[10] Davies,[11] Che,[12] Iwasa,[13] Zhou,[14] Zhang[15] and others[16] revealed that asymmetric intramolecular cyclopropanation of allylic diazoacetates is applicable for stereoselective synthesis of polysubstituted cyclopranes with the use of chiral rhodium,[7b,10,11,16a] ruthenium,[12,13,16b,d] cobalt,[15,16b,c] copper,[16e] and iron[14,16f] catalysts. However, the reaction is mainly restricted to *α*-

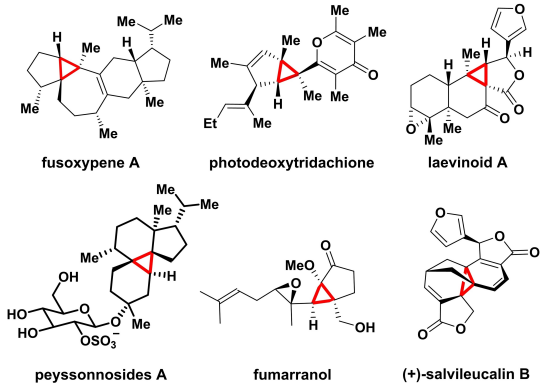

Figure 1. Selected examples of natural products and bioactive compounds containing *penta*-/*hexa*-substituted cyclopropane skeletons.

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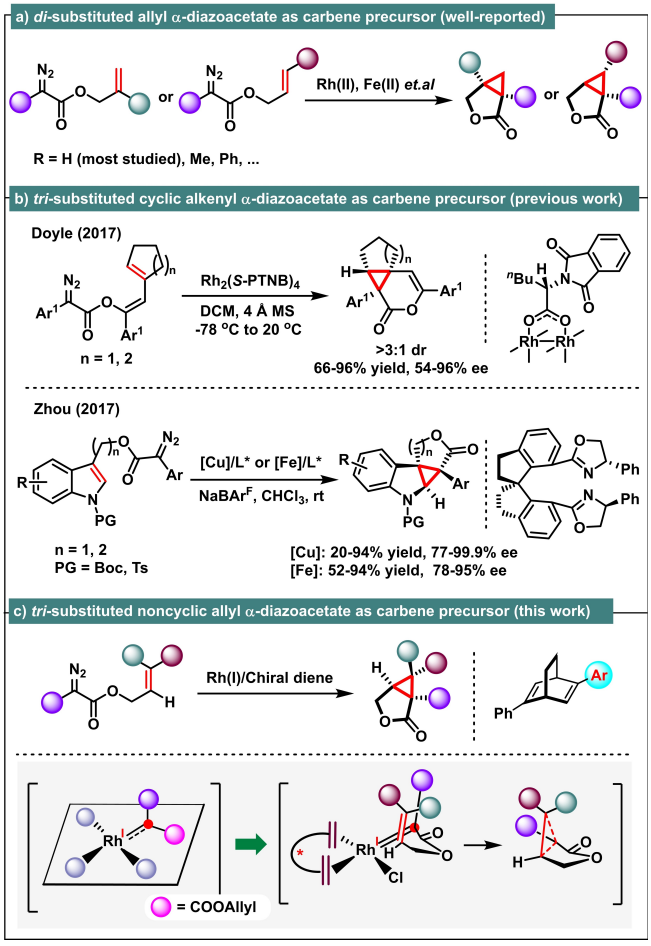
nonsubstituted diazoesters and the enantioselectivity is highly sensitive to the substitution on the allyl double bond (Scheme 1a).[7b,10–14,15b,16] For this reason, access to highly substituted cyclopropanes in a highly enantioselective manner is very challenging, and has only been realized for selected cases. Remarkably, two successful examples were demonstrated by the groups of Doyle[7c] and Zhou/Zhu[7d] by designing unique *tri*-substituted cyclic alkenyl α-diazoacetates as the carbene precursor, allowing the construction of *penta*-substituted cyclopropanes with excellent stereocontrol (Scheme 1b).

Recently, we have been involved in Rh^{I}-carbene chemistry for asymmetric transformations.[17,18] Encouraged by the results that our Rh^{I}/chiral diene complexes are versatile catalysts in various carbene X–H insertion reactions,[17] we wondered if the Rh^{I}/diene catalytic system can be employed to address the above challenge. Compare to the rigid octahedral rhodium(II) complexes, the low-coordination rhodium(I) complex adopts a four-coordinate square planar structure with no ligand coordination to the axial sites. Therefore, the steric hinderance between the ligand and α-substitutent as well as the olefin substituents of the diazo substrate is less, which may facilitate the formation of a favorable transition state geometry for cyclopropanation. The stereofacial selectivity of the reaction might be distinguished by the two oppositely oriented aryl groups substituted on the double bond of the chiral olefin ligand (Scheme 1c). Herein, we report our successful development of a highly efficient asymmetric intramolecular cyclopropanation that enables broad scope synthesis of diverse *penta*-substituted cyclopropanes in a highly enantioselective manner under mild conditions.

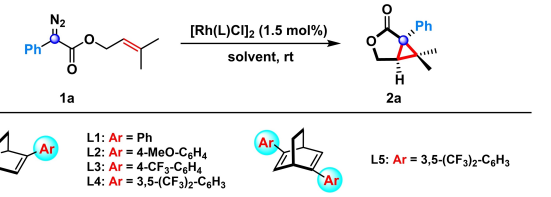


Scheme 1. Transition-metal catalyzed asymmetric intramolecular cyclopropanation.

Results and Discussion

To verify our hypothesis, dimethyl substituted allyl α-phenyldiazoacetate (**1a**) was initially used as the model substrate for the investigation of intramolecular cyclopropanation under rhodium(I) catalysis. At the outset, the feasibility of the reaction was proved by using $[Rh(COD)Cl]_2$ as the catalyst, giving the desired product bicyclo[3,1,0]-lactone **2a** in 82 % yield (entry 1). Very encouragingly, with Hayashi's C_2-symmetric chiral diene **L1** as the ligand, the reaction took place smoothly and gave **2a** in 89 % yield with a promising 88 % ee (Table 1, entry 2). A

Table 1: Evaluation of reaction conditions.[a]



entry	catalyst	solvent	*t* [h]	yield [%][b]	ee [%][c]
1	$[Rh(COD)Cl]_2$	DCM	4	82	–
2	$[Rh(\mathbf{L1})Cl]_2$	DCM	4	89	88
3	$[Rh(\mathbf{L2})Cl]_2$	DCM	4	89	88
4	$[Rh(\mathbf{L3})Cl]_2$	DCM	4	91	93
5	$[Rh(\mathbf{L4})Cl]_2$	DCM	4	96	93
6	$[Rh(\mathbf{L5})Cl]_2$	DCM	4	97	−93
7[d]	$[Rh(\mathbf{L4})Cl]_2$/$NaBAr^F$	DCM	4	73	81
8	$[Rh(\mathbf{L4})Cl]_2$	DCE	4	95	93
9	$[Rh(\mathbf{L4})Cl]_2$	$CHCl_3$	4	99	92
10	$[Rh(\mathbf{L4})Cl]_2$	toluene	4	90	93
11	$[Rh(\mathbf{L4})Cl]_2$	THF	4	82	93
12[e]	$[Rh(\mathbf{L4})Cl]_2$	DCM	8	97	95
13[f]	$[Rh(\mathbf{L4})Cl]_2$	DCM	30	99	96
14[e,g]	$[Rh(\mathbf{L4})Cl]_2$	DCM	12	99	95
15[e,h]	$[Rh(\mathbf{L4})Cl]_2$	DCM	12	98	95
16[e,i]	$[Rh(\mathbf{L4})Cl]_2$	DCM	30	96	95
17[e,i,j]	$[Rh(\mathbf{L4})Cl]_2$	DCM	24	98	95
18[e,i,j]	$Rh_2[(R)\text{-DOSP}]_4$	DCM	12	79	-28
19[10f]	$Rh_2[(S)\text{-MEAZ}]_4$	DCM	3	93	45
20[10f]	$Rh_2[(S)\text{-TBSP}]_4$	DCM	3	76	29
21[14]	Fe^{II}/(*Ra,S,S*)-SpiroBox-Ph/$NaBAr^F$	$CHCl_3$	7	85	−33

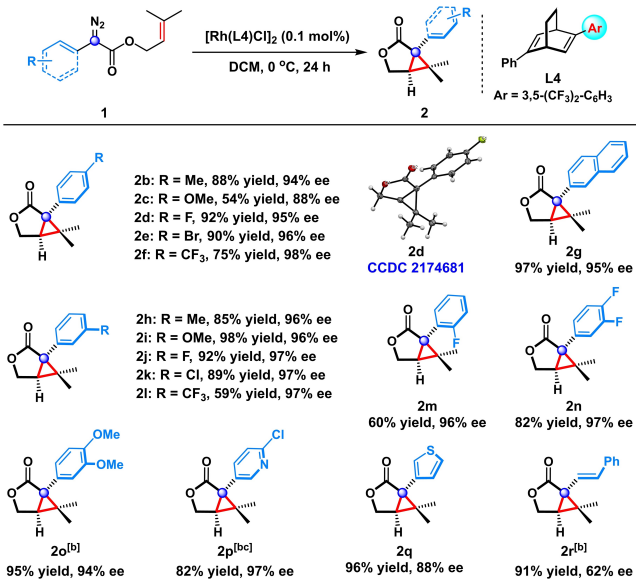
[a] Unless otherwise noted, all reactions were performed with **1a** (0.20 mmol), catalyst (1.5 mol %) in 2 mL of solvent at room temperature; [b] Isolated yield; [c] Determined by HPLC analysis on a chiral stationary phase; [d] $NaBAr^F$ (3.0 mol %); [e] 0 °C; [f] −20 °C; [g] 1.0 mol % of $[Rh(\mathbf{L4})Cl]_2$ used; [h] 0.5 mol % of $[Rh(\mathbf{L4})Cl]_2$ used; [i] **1a** (1.0 mmol), catalyst (0.1 mol %) in 10 mL of DCM; [j] 5 mL of DCM instead.

series of C_1-symmetric chiral diene ligands represented by **L2**–**L4** were then evaluated, and **L4** was found to be the best (entry 5 vs entries 3 and 4). Notably, the corresponding C_2-type ligand **L5** exhibited the same catalytic activity and enantioselectivity as **L4** (entry 6), indicating that only one 3,5-bis(trifluoromethyl)phenyl substituent is needed. When a cationic rhodium complex with **L4** was used, both yield and ee dropped dramatically (entry 7).[19] Next, the solvent effect was examined. Interestingly, besides DCM, other solvents such as $CHCl_3$, toluene, and THF seem also suitable for this reaction (entries 8–11). Lowering the reaction temperature from rt to 0 °C and −20 °C could result in a slight increase of ee to 95–96 % (entries 12–13). Very pleasingly, this rhodium complex with **L4** was found to exhibit excellent catalytic performance (entries 14–16) and the catalyst loading could be decreased to even 0.1 mol % without losing the efficiency (entry 16). Performing the reaction at 0 °C in a higher concentration could lead to an increase in the reaction rate and gave the product **2a** with excellent yield (98 %) and enantioselectivity (95 % ee) (entry 17). In all these reactions, no diazo condensation (dimerization) products were found. *It is worth to note that the previous rhodium(II) catalysis gave only low ee values (19 %–45 %, entries 19 and 20),*[10f,g] *and almost the same level of enantiocontrol (33 % ee) was reported with iron catalysis (entry 21).*[14] We also tested the reaction with $Rh_2[(R)\text{-DOSP}]_4$ as the catalyst, and similarly, the same low ee value was obtained (28 % ee, entry 18).

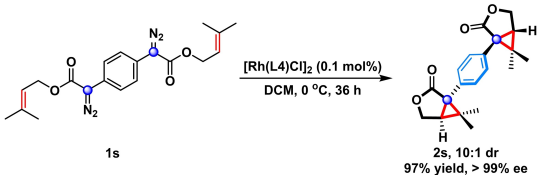
Based on the optimized reaction conditions, a series of dimethyl substituted allyl diazoacetates with different *α*-aryl groups were examined to explore the reaction scope (Scheme 2). Gratifyingly, all reactions of diazoacetates with *para*- and *meta*-substituents on the phenyl ring proceeded smoothly and afforded the expected products (**2b**–**2l**, **2n**, **2o**) mostly in high yields with good to excellent enantioselectivities (88–98 % ee). The absolute configurations of the two newly formed carbon stereocenters of **2d** were assigned by X-ray crystallographic analysis.[20] While substitution of a fluorine at the *ortho*-position is tolerated (**2m**), substrates bearing 1-naphthyl and 2-bromophenyl gave only low yield (13 %) and trace product formation, suggesting that steric hindrance at the *ortho*-position seems to be unfavorable for cyclopropanation. It is noteworthy that heteroaryl substituents such as pyridine and thiophene were compatible with the reaction conditions (**2p**, **2q**). When α-styryldiazoacetate was employed, the corresponding product (**2r**) was obtained in excellent yield (91 %) with an encouraging enantioselectivity (62 %).[11]

Intriguingly, we found that the current catalyst system can also be applied to stereoselective double intramolecular cyclopropanation. Under the standard conditions, the reaction of 1,4-bis(allyl phenyldiazoacetate) **1s** proceeded smoothly to furnish bis-(*penta*-substituted cyclopropane)-containing product **2s** in 97 % yield and >99 % ee with a 10:1 dr ratio (Scheme 3). In this case, the meso isomer was detected as minor products.

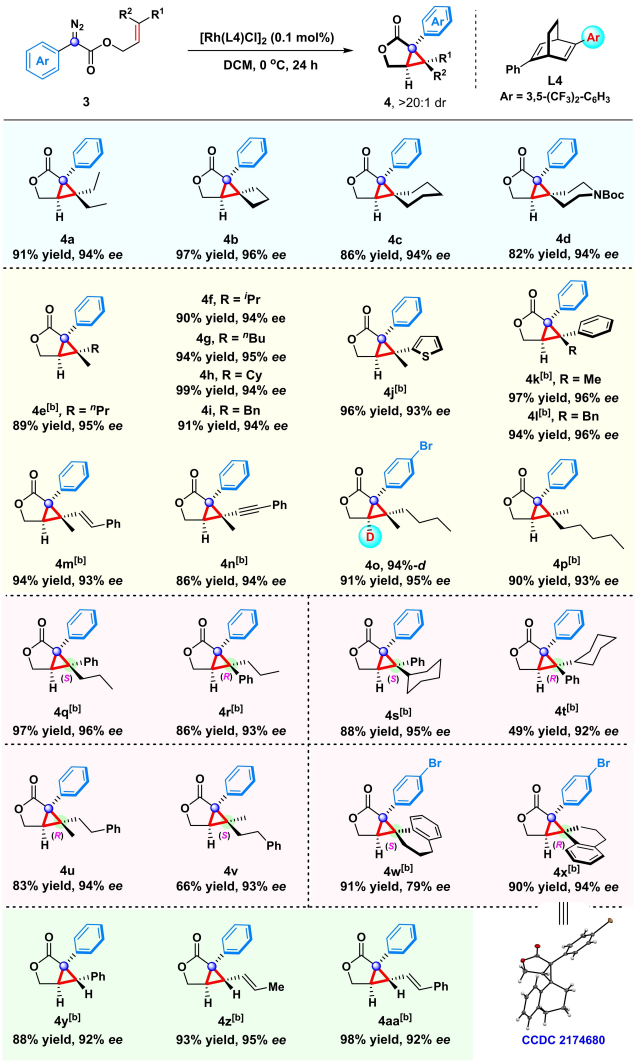
Subsequently, we investigated the generality of this intramolecular cyclopropanation with respect to the substituents around the allyl group. As illustrated in Scheme 4, the scope of this catalytic system proved to be quite general and variation in the extent of substitution of the allyl double bond is very well tolerated. Apart from terminal dimethyl substitution, more sterically hindered diethyl, cyclobutyl, cyclohexyl, piperidinyl substituted substrates also underwent smooth cyclopropanation, giving the expected products (**4a**–**4d**) in identically high yields and excellent enantioselectivities. It is interesting to note that structures of **4b**, **4c** and **4d** contain both a fused- and spiro-ring skeleton. Moreover, the use of diazo substrates possessing unsymmetrical disubstitution on the allyl terminus having different steric hindrance and different electronic nature were thoroughly explored. (*E*)-Allyl phenyldiazoacetates prepared from a variety of simple alkyl/(hetero)aryl methyl ketones could be used as suitable substrates, afforded the corresponding products (**4e**–**4k**, **4p**) uniformly in high yields and highly enantiomerically enriched form. Remarkably, the introduction of an alkenyl or alkynyl group onto the allylic terminus was also successful, allowing easy access to *penta*-substituted chiral cyclopropanes bearing additional alkene and alkyne functionalities (**4m**, **4n**). In some cases, a slow conversion was observed due to very low catalyst loading at 0.1 mol %, thus



Scheme 2. Scope of dimethyl substituted allyl aryldiazoacetate.[a] [a] Unless otherwise specified, all reactions were performed with **1** (1 mmol), [Rh(**L4**)Cl]$_2$ (0.1 mol %) in 5 mL of DCM at 0 °C for 24 h; Isolated yield; Determined by HPLC analysis on a chiral stationary phase; [b] **1** (0.2 mmol), [Rh(**L4**)Cl]$_2$ (1.5 mol %) in 2 mL of DCM at 0 °C for 12 h; [c] 36 h.



Scheme 3. Double intramolecular cyclopropanation.

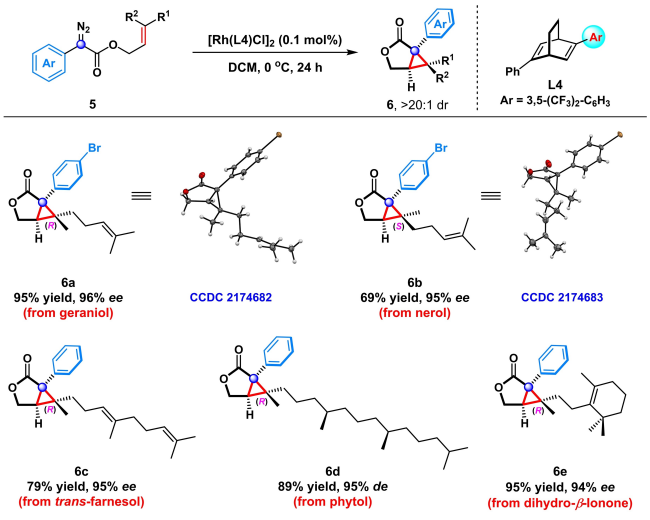


Scheme 4. Scope of *tri*- or *di*-substituted allyl 2-diazo-2-arylacetate.[a] [a] Unless otherwise specified, all reactions were performed with **3** (1 mmol), [Rh(**L4**)Cl]$_2$ (0.1 mol%) in 5 mL of DCM at 0 °C for 24 h; Isolated yield; Determined by HPLC analysis using a chiral stationary; [b] **1** (0.2 mmol), [Rh(**L4**)Cl]$_2$ (1.5 mol%) in 2 mL of DCM at 0 °C for 12 h.

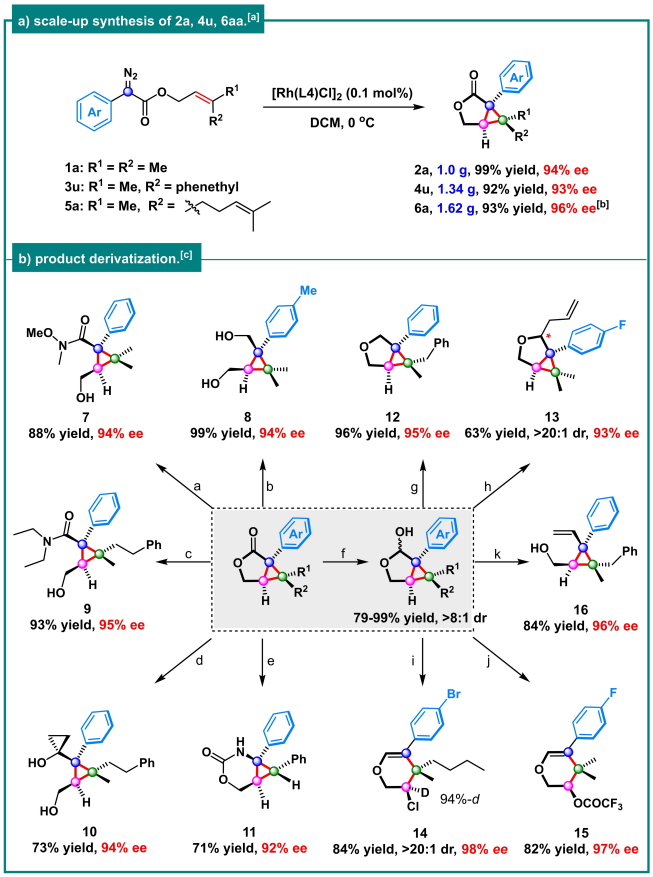
these reactions were carried out at a higher catalyst loading of 1.5 mol%. It should be mentioned that the reaction does not occur if a substitution at the internal position of the allyl double bond is incorporated likely due to severe steric repulsion with chlorine ligand adjacent to the carbenoid in the transition state. Fortunately, pharmaceutically interesting deuterium-containing chiral cyclopropanes could be readily accessed by simply replacing the olefinic hydrogen with deuterium (heavy hydrogen), as represented by **4o**. Furthermore, the variation on stereochemical pattern on the allyl double bond was also examined. To our delight, almost the same high level of stereocontrol was observed in the reactions of a range of substrates with different R^1/R^2 substituents (**4q**–**4x**), including alkyl/alkyl and alkyl/aryl groups. The *cis*/*trans* double bond configuration appears to have no significant influence on the stereoselectivity of the reaction, and by simply reversing the stereochemical pattern of the double bond, the complementary opposite configuration of the R^1/R^2-substituted stereocenter can be exclusively obtained (**4q** vs **4r**, **4s** vs **4t**, **4u** vs **4v**, **4w** vs **4x**). The stereochemistry of **4x** was unambiguously as-signed by X-ray diffraction analysis.[20] To further evaluate the efficiency of this catalytic system, intramolecular cyclopropanation of disubstituted allyl diazo substrates was carried out. Not surprisingly, the results were again very promising and encouraging in terms of both yield and enantioselectivity (**4y**, **4z**, and **4aa**). It is worth noting that the result for **4y** is far better than those reported in the literature.[10g,14] In all cases, no other diastereoisomers were detected. However, we found that the cyclopropanation reaction was unsuccessful when substituents such as strong electron-withdrawing CF_3 and F, and heteroatom-containing OPh and $SiMe_3$ are introduced into the double bond.

Given such a broad scope, we wondered whether this catalytic system is applicable to asymmetric cyclopropanation of more complex drug-like molecules. Thus, a set of structurally interesting allyl diazoacetates was rapidly assembled by a two-step reaction of arylacetic acid with natural alcohols such as geraniol, nerol, *trans*-farnesol, phytol and dihydro-*β*-ionone derivative. Gratifyingly, in the presence of 0.1 mol% of catalyst all reactions proceeded in a highly enantiomeric manner (94–96% ee) and delivered the desired products in good to excellent yields (69–95%) (Scheme 5, **6a**–**6e**).[20]

To illustrate the potential practicability of this methodology, gram scale (5 mmol) cyclopropanation reaction of **1a**, **3u** and **5a** were carried out with only 0.1 mol% of [Rh(**L4**)Cl]$_2$ catalyst. As shown in Scheme 6a, the desired products **2a**, **4u** and **6a** were obtained in comparable yields with the same high level of enantioselectivities. Remarkably, the lactone moiety in product molecules could serve as a



Scheme 5. Applicability of the synthetic protocol to access complex drug-like molecules from natural alcohols.[a] [a] Reactions were performed with **5** (1 mmol), [Rh(**L4**)Cl]$_2$ (0.1 mol%) in 5 mL of DCM at 0 °C for 24 h; Isolated yield; Determined by HPLC analysis using a chiral stationary.



Scheme 6. Application and derivatization of *penta*-substituted cyclopropane compounds. [a] Unless otherwise specified, all reactions were performed with 5 mmol scale, [Rh(**L4**)Cl]$_2$ (0.1 mol%) in 5 mL of DCM at 0 °C for 24 h; [b] 36 h; [c] a) MeNHOMe·HCl, Me_3Al, DCM, 0 °C; b) $LiAlH_4$, THF, 0 °C; c) Et_2NH, ^{n}BuLi, THF, 0 °C; d) $Ti(O^iPr)_4$, EtMgBr, THF, 0 °C; e) (i) $NH_3·H_2O$, MeOH, rt; (ii) $PhI(OAc)_2$, MeCN, 40 °C; f) DIBAL-H, DCM, −78 °C; g) Et_3SiH, $BF_3·Et_2O$, DCM, 0 °C; h) allyltrimethylsilane, $BF_3·Et_2O$, DCM, −78 °C; i) $Et_3N·HCl$, $BF_3·Et_2O$, DCM, 0 °C; j) TFA, DCM, 0 °C; k) $Ph_3P{=}CH_2$, THF, −78 °C.

versatile handle for further synthetic transformations to provide a wide variety of highly functionalized cyclopropanes. As illustrated in Scheme 6b, treatment of **2a** with *N*,*O*-dimethylhydroxylamine hydrochloride under Me_3Al, CH_2Cl_2 conditions afforded the Weinreb amide **7** in 88% yield. Reduction of **2b** with $LiAlH_4$ provided the diol **8** in a quantitative yield. Ammonolysis of **4u** with lithium diethylamide gave the substituted chiral cyclopropanecarboxamide **9**, a potential synthetic precursor of novel Milnacipran analog,[21] in 93% yield. On the other hand, **4u** underwent Kulinkovich reaction[22] smoothly to afford an interesting cyclopropane product **10** bearing a fascinating cyclopropanol substitutent. In another case, **4y** was ammonolyzed in methanol with ammonium hydroxide and then treated with iodobenzene acetate in acetonitrile by Hofmann rearrangement to afford an unique chiral cyclic carbamate **11** possessing fused three/six-membered rings in 71% overall yield and 92% ee. It is worth noting that incomplete reduction of the lactone with DIBAL-H could lead to the stable γ-lactol (>8:1 dr, 79–99% yield), which is also amenable to a diverse set of synthetic transformations. A few representative examples are depicted in Scheme 6b. Simple reduction of hemiacetal functionality with Et_3SiH promoted by Lewis acid $BF_3·OEt_2$, furnished a tetrahydrofuran-fused, highly substituted cyclopropane **12** in excellent yield. Similarly, $BF_3·Et_2O$-induced substitution with allylsilane via a cyclic oxocarbenium ion intermediate afforded allyl-substituted fused-heterocyclic compound **13**.[23] Interestingly, other nucleophilic additions to the corresponding oxocarbenium ions under $Et_3N·HCl$, $BF_3·Et_2O$ or TFA conditions gave the cycloproprane ring-opened 3,4-dihydro-2*H*-pyran products **14** and **15** in good yields. Enantioenriched 3,4-dihydro-2*H*-pyrans are important and versatile intermediates for the synthesis of bioactive molecules and natural products.[24] Wittig olefination of the corresponding γ-lactol obtained from **4i** occurred smoothly to afford *penta*-substituted-vinylcyclopropane alcohol **16** bearing *multi*-functional groups poised for further transformation.

Given that the bis(rhodium(I)/diene) complex was used for the reaction, we were intrigued to understand the kinetic behavior of the dimeric species when dissociated to the active monomeric species under reaction conditions. The asymmetric cyclopropanation of allyl α-phenyldiazoacetate **1a** using **L4** as the ligand was investigated. Interestingly, a moderate negative nonlinear effect was observed when the ee value of the product **2a** was plotted against the ee of **L4** (Figure 2), suggesting that the heterochiral dimer is less stable than the homochiral species and more liable to dissociation.[25]

To gain some insight into the origin of reaction stereocontrol, a preliminary DFT study at M06/def2svp level was then carried out.[26] For simplicity, our calculation was performed with the intramolecular cyclopropanation of **1a** catalyzed by the bis(rhodium/diene) complex of C_2-symmetric **L1**. As showed in Figure 3, when the active monorhodium catalyst [Rh(**L1**)Cl] (**Rh1**) reacts with diazo substrate, two **Rh^I** carbenoid intermediates **CB-1** or **CB-2** are formed. Our DFT results reveal that **CB-1**, in which the phenyl groups of diene ligand **L1** and phenyldiazo substrate **1a** forms π-π stacking interactions, is lower in Gibbs free energy

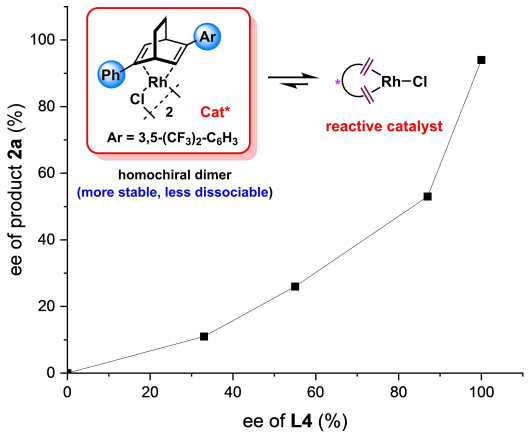


Figure 2. Experimental ee (product **2a**) *vs* ee (**L4**) in the cyclopropanation of allyl α-phenyldiazoacetate **1a**.

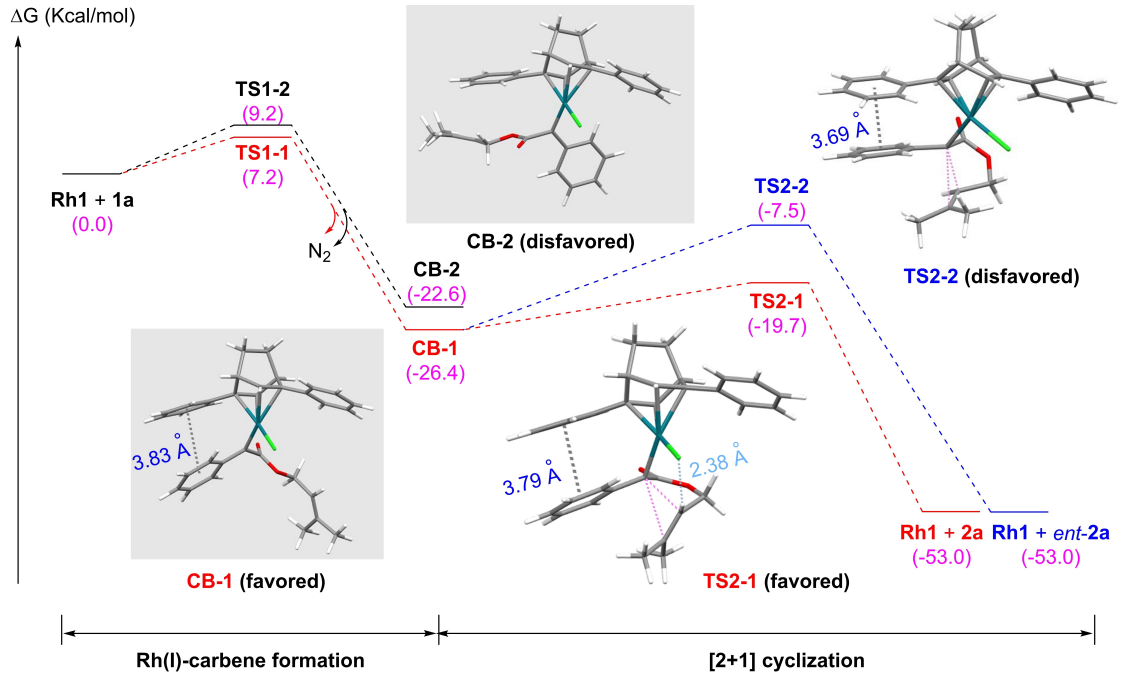


Figure 3. Free energy diagram and the proposed stereochemical pathway (red) of the asymmetric intramolecular cyclopropanation of **1a** catalyzed by the active species [Rh(**L1**)Cl] (at M06/def2svp level).

than that with the opposite orientation of the phenyl-carbenoid part (**CB-2**) by around 3.8 kcal mol^{-1} in solution, indicating that the carbenoid intermediate **CB-1** is more stable. In the intramolecular carbene transfer step to form cyclopropane, the most favorable transition state **TS2-1** to form the desired (*R*,*R*)-product has a much lower free-energy barrier than the counterpart pathway to form the (*S*,*S*)-product (**TS2-2**). Notably, the computed transition state geometry in **TS2-1** reveals that the hydrogen at the internal position of the allyl double bond points to the chlorine atom of rhodium catalyst, and the two atoms are in close proximity with a distance of around 2.38 Å. This observation suggests that incorporation of other groups at the internal double bond would produce strong steric repulsion with chlorine, which agrees with the experimental results. In addition, substitutions on the allyl terminus are oriented away from the catalytic center, which is consistent with the observed broad scope of the reaction. For better understanding, we summarize our calculations and the stereochemical outcome of reactions into a working model that can interpretate the stereochemical control of asymmetric intramolecular cyclopropanation of various *tri*-substituted allylic diazoacetates under rhodium(I) catalysis (Figure 4).

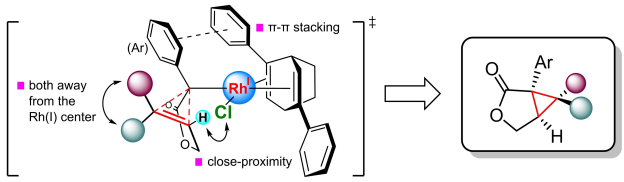


Figure 4. Transition state model for the reaction stereochemical control.

Conclusion

In summary, we have developed an efficient and broad-scope method for challenging asymmetric intramolecular cyclopropanation of various *tri*-substituted allylic diazoacetates for practical synthesis of diverse enantioenriched *penta*-substituted cyclopropanes. The low coordination state Rh^{I}-complex exhibits an extraordinarily high degree of tolerance to the variation in the extent of substitution of the allyl double bond. Notably, this protocol could be implemented under very mild conditions at even 0.1 mol % of catalyst to access a wide variety of interesting *cis*-fused products bearing valuable γ-lactone and cyclopropane rings and three contiguous stereocenters, including two quaternary carbon stereocenters. Moreover, the applicability of this synthetic strategy to access complex drug-like molecules from natural alcohols and the utility of these bicyclic, polysubstituted products as highly versatile building blocks to provide densely functionalized cyclopropanes and other fascinating intermediates were demonstrated. Our preliminary DFT calculations indicate that π-π stacking interactions between the aromatic rings of diene ligand and diazo substrate play a pivotal role in the control of the reaction enantioselectivity. We believe that the methodology disclosed in this report will serve as a useful platform for synthesis of highly substituted chiral cyclopropanes and find its application in drug discovery.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Asymmetric Cyclopropanation · Chiral Diene · Metal Carbene · *penta*-Substituted Cyclopropanes · Rhodium

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