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Asymmetric Rh(I)-Catalyzed Intramolecular [3 + 2] Cycloaddition of 1-Yne-vinylcyclopropanes for Bicyclo[3.3.0] Compounds with a Chiral Quaternary Carbon Stereocenter and Density Functional Theory Study of the Origins of Enantioselectivity

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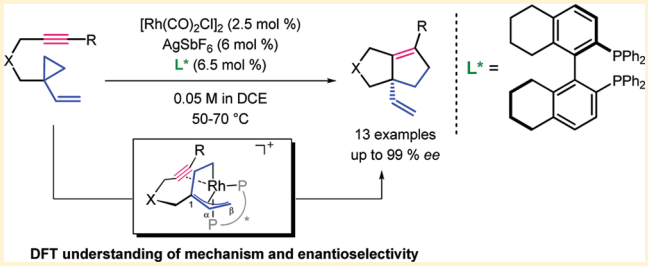
Supporting Information

ABSTRACT: A highly enantioselective Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition of 1-yne-VCPs to bicyclo[3.3.0] compounds with an all-carbon chiral quaternary stereocenter at the bridgehead carbon was developed. DFT calculations of the energy surface of the catalytic cycle (complexation, cyclopropane cleavage, alkyne insertion, and reductive elimination) of the asymmetric [3 + 2] cycloaddition reaction indicated that the rate- and stereo-determining step is the alkyne-insertion step. Analysis of the alkyne-insertion transition states revealed that the serious steric repulsion between the substituents in the alkyne moiety of the substrates and the rigid H_8-BINAP backbone is responsible for not generating the disfavored [3 + 2] cycloadducts.



DFT understanding of mechanism and enantioselectivity

INTRODUCTION

Five-membered carbocyclic rings are ubiquitous in organic molecules. Due to this, developing methods to synthesize five-membered rings is one of the key endeavors in the science of synthesis. Among them, discovering and developing [m + n], [m + n + o] cycloaddition catalyzed by either organocatalysts or transition-metal catalysts is especially attractive since such cycloaddition strategy could provide cyclopentane skeletons with several stereogenic centers built up in one pot.[1] Developing these cycloaddition to their asymmetric variants is of the same importance considering that five-membered carbocycles in natural products and pharmaceutical compounds are usually chiral. Unfortunately, today only a few asymmetric catalytic cycloadditions (for examples, Lu's [3 + 2],[2] Trost's two [3 + 2],[3] and Murakami–Ito's [4 + 1],[4] Pauson–Khand's [2 + 2 + 1][5] cycloadditions and their variants) to reach cyclopentane skeletons have been reported.[6] Therefore, great endeavors are required from the synthetic community to develop more efficient and versatile asymmmetric cycloadditions to construct five-membered carbocycles.

Previously, we reported that a new type of vinylcyclopropane (VCP) derivatives, 1-ene-vinylcyclopropanes and 1-yne-vinylcyclopropanes can undergo a novel Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition, giving cyclopentane- and cyclopentene-embedded 5,5- and 6,5-bicyclic compounds (Scheme 1).[7a] In these [3 + 2] reactions, the VCP moiety serves as a three-carbon unit,[8] rather than the traditional five-carbon unit.[9] These reactions provide very efficient methods for the construction of multisubstituted five-membered rings, especially those with an all-carbon quaternary stereocenter at the bridgehead carbon of the cycloadducts. Thus, we were eager to develop asymmetric versions of these [3 + 2] cycloadditions, which would provide efficient and powerful access to the multifunctional chiral bicyclo[3.3.0] rings. In addition to this, we believed that such efforts are worthy, considering these asymmetric [3 + 2] reactions could access cyclic compounds with chiral all-carbon quaternary stereocenters, which are posing challenges to today's synthetic community.[10] Herein, we report our realization of the asymmetric Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition of 1-yne-VCPs for the construction of bicyclic five-membered rings. This realization represents the first asymmetric transition-metal-catalyzed cycloaddition of unactivated VCP acting as a three-carbon synthon (for the only example of an activated VCP as a three-carbon synthon, see ref 3c). In addition, we have performed density functional theory (DFT) calculations to study the reaction mechanism and identify origins of the stereoinduction in this asymmetric [3 + 2] reaction.

RESULTS AND DISCUSSION

1. Developing the Asymmetric [3 + 2] Cycloaddition Reaction of 1-Yne-VCPs. Our test of the new asymmetric [3 + 2] cycloaddition started with the identification of an effective chiral ligand under the previous Rh(I)-catalyzed [3 + 2] cycloaddition conditions ($[Rh(CO)_2Cl]_2/AgSbF_6$ as the catalyst, 1,2-dichloroethane as the solvent, reaction temperature of 80 °C). The previous [3 + 2] cycloaddition reactions using the diphosphine ligand dppp (1,3-bis(diphenylphosphino)propane)

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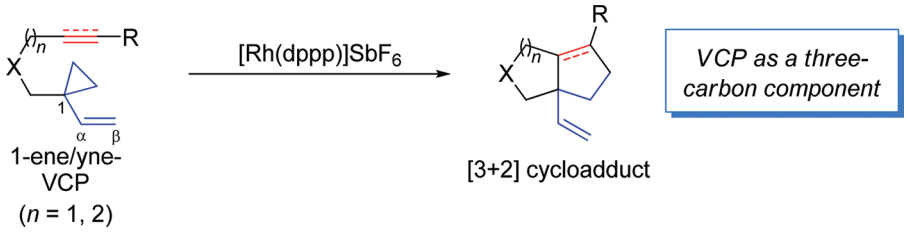
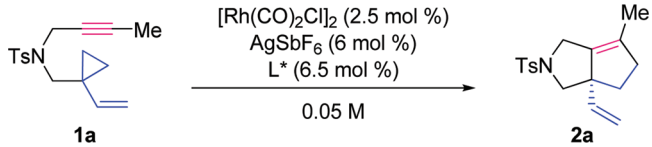
Scheme 1. Rh(I)-Catalyzed Intramolecular [3 + 2] Cycloaddition Reaction



gave high reaction yields of the cycloadducts. This implied that using chiral diphosphines could achieve the asymmetric variant of the [3 + 2] cycloaddition reaction (Table 1). Therefore, we employed 1-yne-VCP **1a** as the substrate to screen various chiral diphosphine ligands. Fortunately, the application of Takasago BINAP ligands **A** and **B** both gave high ee values, and the reaction yield with ligand **B** is higher than that with ligand **A** (entries 1−2). Although the cycloaddition with ligand **C** afforded the cycloadduct **2a** with a high ee value, the yield was even lower. Other diphosphine ligands listed in Table 1 were less effective for the enantioselectivities in our reactions compared with ligands **A** and **B** (entries 4−9). We then studied how solvent affected the asymmetric [3 + 2] cycloaddition, finding that high ee value can be obtained in 1,2-dichloroethane (DCE) rather than in toluene or 1,2-dimethoxyethane (DME) (entries 2 and 10−11). A brief screening of various temperatures indicated that lower temperature could improve the ee value, although this improvement was not significant (entries 2 and 12−14). We also examined the catalytic reaction of 1-yne-VCP **1a** using lower catalyst loading. To our delight, when the loading of $[Rh(CO)_2Cl]_2$ was reduced to 1 mol %, high yield and excellent enantioselectivity were obtained as well (entry 15). Further studies revealed that concentration of the reactant in this reaction had no obvious influence on the reaction yield and ee value (entry 16).

Various 1-yne-VCP substrates were submitted to the optimal reaction conditions (2.5 mol % $[Rh(CO)_2Cl]_2$, 6 mol % $AgSbF_6$, 6.5 mol % (*R*)-ligand **B** ((*R*)-2,2′-bis(diphenylphosphino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl, (*R*)-H_8-BINAP) as the catalyst system, DCE as solvent, 0.05 M concentration) to explore the substrate scope of the asymmetric Rh(I)-catalyzed [3 + 2] cycloaddition reactions (Table 2). It was found that the yields of the asymmetric [3 + 2] cycloaddition were generally moderate to high. Significantly, excellent enantioselectivities were obtained from 1-yne-VCPs with both internal and terminal alkynes. Also increasing the length of the substituent at the internal alkyne gave high ee values (entries 1−5, 11, and 13). Nitrogen-,oxygen-, *gem*-diester-tethered substrates could afford hetero- and carbobicyclic compounds. A chloroalkyl substituent on the 1-yne-VCP substrate could achieve a moderate yield and high ee value, producing a bicyclic product with a chlorine-substituted alkyl chain, which could help further elaboration of the cycloadduct (entry 4). The present asymmetric [3 + 2] cycloaddition reactions also tolerated different protecting groups, such as silyl, benzyl hydroxyl (entries 5 and 11), tosyl, and nosyl N-protecting groups (entries 1−10). Interestingly, the asymmetric [3 + 2] cycloaddition reactions of substrates with an electron-withdrawing group at the terminal position of 1-yne-VCPs gave α,β-unsaturated bicyclo[3.3.0] compounds in moderate yields and excellent ee values up to 99% (entries 6−7 and 12). Single-crystal X-ray diffraction analysis confirmed the absolute configuration of **2b** (Figure 1). Unfortunately, an aryl substituent on the 1-yne-VCP

Table 1. Optimization Studies of the Asymmetric [3 + 2] Cycloaddition[a]



1a **2a**

entry	L*	solvent	temperature [°C]	*t* [h]	yield [%][a]	ee [%][b]
1	**A**	DCE	80	1	61	93
2	**B**	DCE	80	1	83	92
3	**C**	DCE	80	3.5	26	86
4	**D**	DCE	80	45	77	23
5	**E**	DCE	80	144	42	0
6	**F**	DCE	80	144	46	39
7	**G**	DCE	80	3.5	74	15
8	**H**	DCE	80	72	64	−29
9	**I**	DCE	80	4.5	83	25
10	**B**	toluene	80	3.5	69	79
11	**B**	DME	80	40	79	14
12	**B**	DCE	70	1	90	97
13	**B**	DCE	60	1	86	96
14	**B**	DCE	50	4	78	96
15[c]	**B**	DCE	70	2.5	71	96
16[d]	**B**	DCE	70	1	83	97

[a]Isolated yield after column chromatography. [b]Determined by chiral HPLC. [c]1 mol % $[Rh(CO)_2Cl]_2$, 2.4 mol % $AgSbF_6$, and 2.6 mol % L* were used. [d]Substrate concentration: 0.03 M.

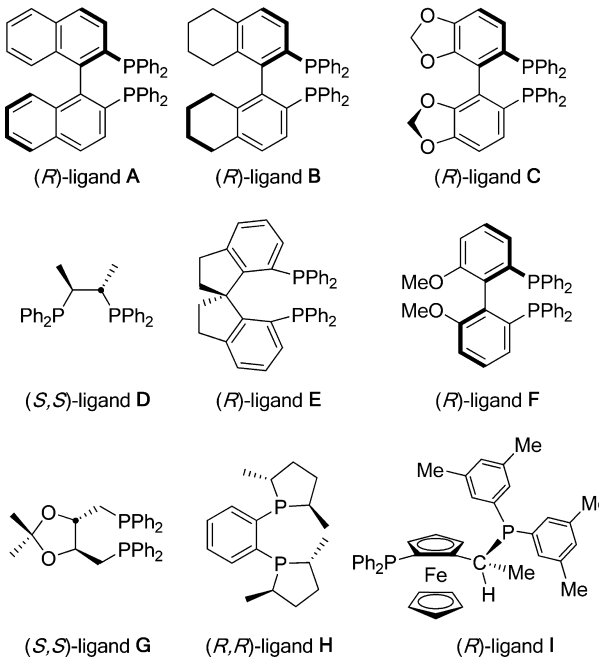


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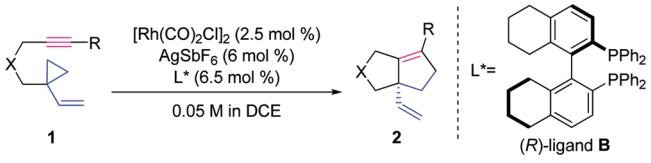
Table 2. Rh(I)-Catalyzed Asymmetric [3 + 2] Cycloaddition Reactions[a]



entry	substrate	cycloadduct	temperature [°C]	*t* [h]	yield [%][b]	*ee* [%][c]
1	**1a** R = Me	**2a**	70	1	90	97
2	**1b** R = H	**2b**	50	3	90	87
3	**1c** R = Et	**2c**	70	2.5	90	93
4	**1d** R = $(CH_2)_3Cl$	**2d**	60	10	74	94
5	**1e** R = $(CH_2)_3OTBS$	**2e**	70	4	63	95
6	**1f** R = COMe	**2f**	70	1	70	98
7	**1g** R = CO_2Me	**2g**	70	1	62	99
8	**1h** R = Ph	**2h**	60	7	69	48
9[d]	**1i** R = TMS	**2i**	70	120	60 (brsm)	61
10	**1j**	**2j**	70	1	87	96
11	**1k** R = $(CH_2)_3OBn$	**2k**	70	5	61	93
12	**1l** R = CO_2Me	**2l**	70	2	40	97
13	**1m**	**2m**	50	1	41 (brsm)[e]	90

[a]Ts = *p*-toluenesulfonyl, Ns = 4-nitrobenzenesulfonyl, Bn = benzyl, E = CO_2Bn. The stereochemistry of all other compounds is derived from **2b** by analogy. [b]Isolated yield after column chromatography. [c]Determined by chiral HPLC. [d]Recovered 28% of **1i**, brsm = based on the recovered starting material. When the temperature was up to 110 °C, the results are below: 24 h of reaction time, recovered 15% of **1i**, 52% of yield, 61% of yield (brsm), and 9% of ee value. [e]Recovered 36% of **1m**.

substrate gave moderate ee value (entry 8). When a bulky TMS group was introduced to the substrate's alkyne moiety, the reaction of the corresponding substrate **1i** was sluggish (70 °C, 120 h) and gave moderate ee value (entry 9).

In our previous study, we found that yne-VCPs could not undergo [3 + 2] cycloaddition to give 6/5 bicyclic cycloadducts using dppp as ligand.[7a] To test whether using chiral ligand **B** could overcome this shortcoming encountered in the racemic [3 + 2] cycloaddition, we subjected substrates **1n** and **1o** to the standard asymmetric [3 + 2] cycloaddition conditions (Scheme 2). Unfortunately, no reactions occurred and only the starting materials were recovered. We also tested whether 1-ene-VCPs could give the bicyclic 5/5 or 6/5 cycloadducts. However, both reactions of **1p** and **1q** under the standard asymmetric [3 + 2] cycloaddition conditions afforded inseparable complex mixtures of high polarity, and no corresponding products were isolated (Scheme 3). The reasons why these reactions in Schemes 2 and 3 failed are not known at this stage and will be the subjects of further mechanistic studies.

2. DFT Investigation of the Asymmetric [3 + 2] Cycloaddition Reactions. *Overview of the Catalytic Cycle.* We applied DFT calculations using M06//B3LYP functional to study the mechanism of the asymmetric [3 + 2] cycloaddition reactions using the chiral ligand **B**, and the origins of its enantioselectivity.[11] Previous DFT mechanistic investigation of the racemic [3 + 2] cycloaddition of yne-VCPs using dppp as the ligand revealed that the reaction occurs through substrate-catalyst complex formation, cyclopropane cleavage, alkyne insertion, and reductive elimination.[7b] When a chiral ligand is used, the catalytic cycle is the same, except that all steps involve generation of chiral intermediates (Figure 2).

Therefore, identifying the first stereo-generating step and the stereo-determining step, which could be the same step or not, is critical to understanding the enantioselectivity of the present asymmetric [3 + 2] cycloaddition. The DFT computed whole potential energy surface of the asymmetric [3 + 2] reaction that gives the experimentally observed (*S*)-product is shown in Figure 3.[12] The competing pathway of generating the minor (*R*)-product is not given in Figure 3, but this will be discussed in the next section, aiming to identify the origins of enantioselectivity of the present asymmetric [3 + 2] reaction.

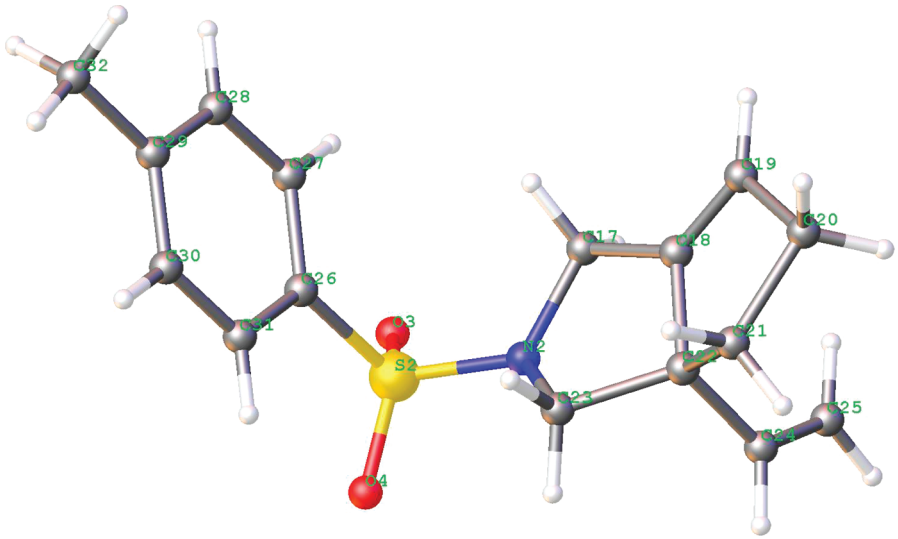


Figure 1. X-ray structure of **2b**.

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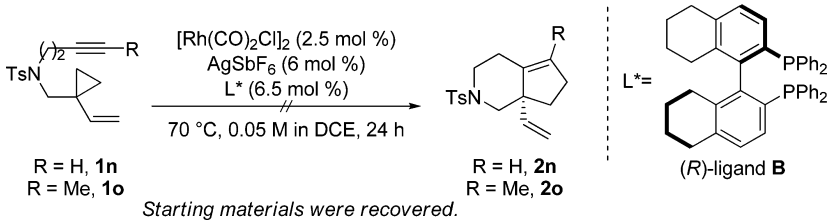
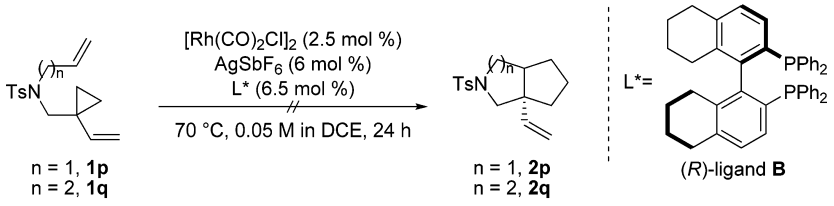
Scheme 2. Attempts for Asymmetric [3 + 2] Cycloaddition of 1-Yne-VCPs with an Elongated Tether to Give Bicyclo[4.3.0] Compounds



Starting materials were recovered.

Scheme 3. Attempts for Asymmetric [3 + 2] Cycloaddition of 1-Ene-VCPs



Inseparable mixtures of high polarity were obtained.

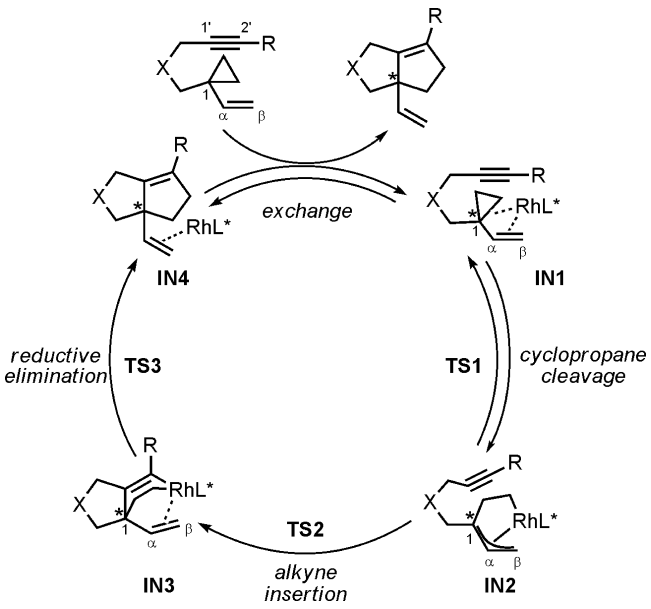


Figure 2. [3 + 2] catalytic cycle.

The asymmetric [3 + 2] catalytic cycle starts with the ligand exchange between the product−Rh(I) complex (*S*)-**IN4**, which is generated in the previous catalytic cycle, and the substrate 1-yne-VCP **S**. The ligand exchange reaction is a neutral process, giving a 16-electron Rh(I) complex (*S*)-**IN1**, in which the VCP moiety binds to the rhodium center by both the vinyl group and the cyclopropane unit. The complexation step is the first stereogenerating step since coordination of the catalyst to the opposite face of VCP moiety of the substrate will give (*R*)-**IN1** (see this in Figure 4). The chirality in complex (*S*)-**IN1** can be transferred to the final (*S*)-product, the same as (*R*)-**IN1** to the (*R*)-product through the followed steps shown in Figure 2.

The CP ring-opening reaction from (*S*)-**IN1** to (*S*)-**IN2**, via the transition state (*S*)-**TS1**, is facile with an activation free energy of 12.5 kcal/mol in DCE. The followed step is the alkyne complexation to the Rh center, transforming the 16-e complex (*S*)-**IN2** to the 18-e complex (*S*)-**IN2′**. Subsequent alkyne insertion into the Rh−C bond via (*S*)-**TS2** generates (*S*)-**IN3**, and this whole step from (*S*)-**IN2** to (*S*)-**TS2** requires an activation free energy of 15.7 kcal/mol. The final step of this asymmetric [3 + 2] catalytic cycle is an easy reductive elimination reaction with an activation free energy of 6.5 kcal/mol, converting intermediate (*S*)-**IN3** to the product−catalyst complex (*S*)-**IN4** via transition state (*S*)-**TS3**.

The rate-determining step of the asymmetric [3 + 2] cycloaddition is the alkyne-insertion step. DFT calculations found that the alkyne-insertion step is irreversible, suggesting that the alkyne-insertion step (via **TS2**) is the rate- and stereochemistry-determining step of this asymmetric [3 + 2] reaction.

Origins of Enantioselectivity. The above DFT study showed that the first stereogeneration step is the substrate complexation step, where both (*S*)-**IN1** and (*R*)-**IN1** can be generated. The followed alkyne-insertion step is irreversible and this step is the stereodetermining step. Therefore, analyzing energetic and structural features of two competing alkyne-insertion transition states of (*R*)-**TS2** and (*S*)-**TS2** (Figure 4) can unveil the origins of enantioselectivity of the asymmetric [3 + 2] cycloaddition. Experiments have shown that the substituents in the alkyne part of yne-VCPs have influence on the enantioselectivity of the asymmetric [3 + 2] reaction, finding that bigger substituents in the alkyne moiety of the substrates usually give higher enantioselectivity. Therefore, we computed (*R*)-**TS2** and (*S*)-**TS2** with different R groups (H or Me) in the alkyne part of the substrates to model how different substituents affect the enantioselectivity and to understand the origins of this selectivity.

Comparison of the alkyne-insertion transition states unveils that the steric repulsion between the substituents in the alkyne of the substrates and the chiral ligand is responsible for the enantioselectivity of the [3 + 2] reaction. In (*S*)-**TS2**, the R group points to the diphosphine moiety, while in (*R*)-**TS2**, the R group points to the H_8-BINAP backbone. The diphosphine moiety is flexible and can easily adjust its position when the R group is pointed to it. However, the H_8-BINAP backbone in the ligand is very rigid, implying that the ligand in the transition state (*R*)-**TS2** is difficult and requires more energy to adjust its

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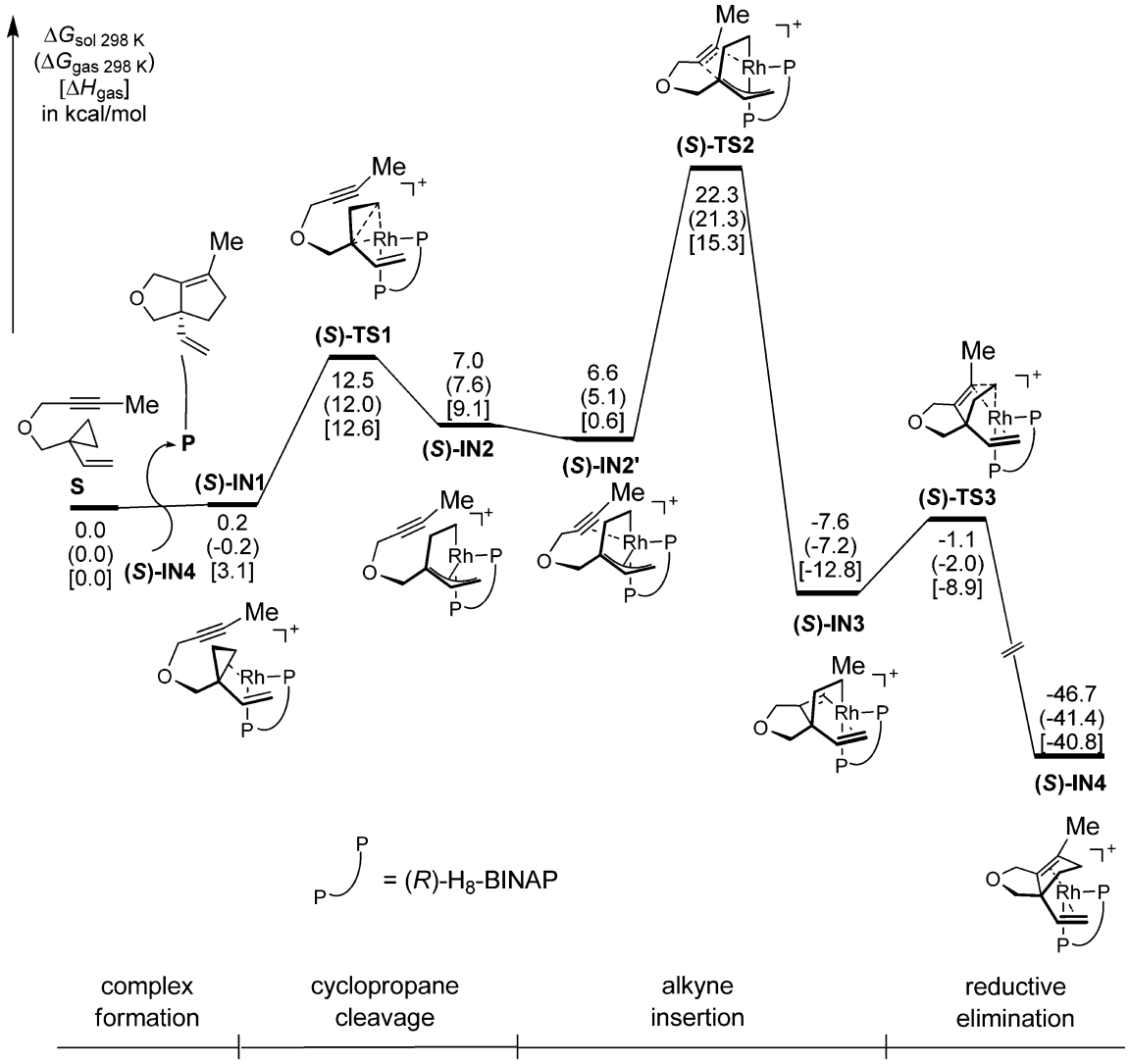

Figure 3. M06//B3LYP computed energy surface of the asymmetric [3 + 2] reaction leading to the (*S*)-product.

geometry when the R group points to it. Consequently, (***R***)-**TS2** has to suffer from the both steric repulsion between the H_8-BINAP backbone and the R group in the alkyne moiety of the substrate, and the distortion energy due to the ligand backbone conformation change compared with that in (***S***)-**TS2**. This is why, in DCE solution, (***R***)-**TS2** is 1.3 kcal/mol higher than (***S***)-**TS2** in terms of free energy (this difference is 2.3 kcal/mol in terms of enthalpy in the gas phase) when R is hydrogen, in preference to generating the *S*-product (a predicted ee of 80% at 298 K). This agrees with experimental results.

From the model we can predict that, when the R group in the alkyne moiety of the substrate is bigger, the alkyne insertion transition state (***S***)-**TS2** should become more disfavored due to increased steric repulsion between the H_8-BINAP backbone and the R group, and the distortion energy associated with the ligand backbone conformation change. In other words, for substrate 1-yne-VCPs with big R group in the alkyne moiety, the asymmetric [3 + 2] cycloaddition should give higher enantioselectivity compared to substrates with small R groups. Our DFT calculations supported this, showing that the free energy difference between (***R***)-**TS2** and (***S***)-**TS2** for R = Me is 2.9 kcal/mol in the DCE solution (3.7 kcal/mol in terms of enthalpy in the gas phase) with a preference of generating the *S* product (a predicted ee of 98% at 298 K) with higher enantioselectivity than that for reactant with R = H. These computational results are consistent with experimental findings, where usually substrates with substituents in the alkyne moieties have ee values of more than 90%. DFT studies of the asymmetric [3 + 2] cycloaddition reactions of nitrogen- and *gem*-dimethyl-tethered substrates gave the same conclusion as the oxygen-tethered substrate, indicating that *S* configuration of [3 + 2] cycloadducts is favored (parts a and b of Figure 5, respectively).

On the basis of our explanation of the chirality induction model, when the R substituent in the alkyne moiety of the substrate is as big as a TMS group, high ee value should be obtained for the [3 + 2] reaction of **1i** (see entry 9, Table 2). However, only a moderate ee value of 61% was obtained experimentally. We did calculations to check whether introducing a TMS group will give a lower ee value. But to our surprise, calculations found that high ee value should also be obtained with R = TMS because (***S***)-**TS2** is still favored than (***R***)-**TS2** by 5.3 kcal/mol, suggesting that 100% ee of the (*S*)-product will be generated (see ref. 13 and the Supporting Information). We attributed the failure of obtaining high ee value for the reaction of **1i** to the fact that this reaction is very slow. Experimentally, the asymmetric [3 + 2] reaction of **1i** with R = TMS needed a reaction time of 120 h at 70 °C, while the other asymmetric [3 + 2] reactions usually finished within 1−2 h. We hypothesized

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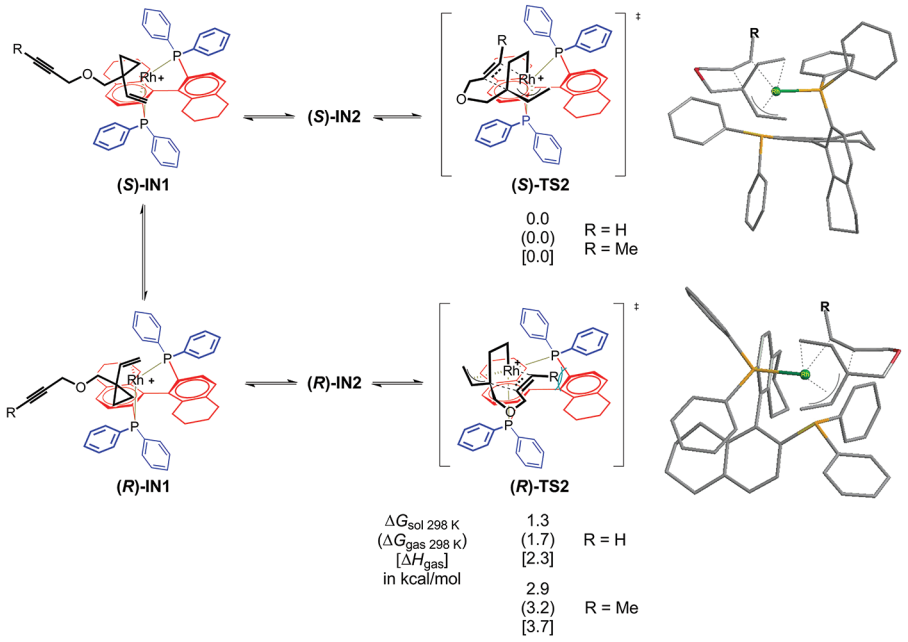

Figure 4. Computational model for explaining the rate- and stereoselectivity-determining step and their transition states.

that for a very slow [3 + 2] reaction such as the reaction of **1i**, some catalyst could decompose to other catalytic species, which could catalyze the background racemic [3 + 2] reaction either without the involvement of chiral ligand, or with very low chiral induction even the chiral ligand is still coordinated to the catalytic specie. Due to the presence of some background reaction without enantioselectivities, the reaction of **1i** gave lower ee value than that expected from DFT calculations. A direct experimental support for this is that, when the [3 + 2] reaction of **1i** was conducted at high temperature (110 °C) to accelerate the reaction rate, we found that the reaction yield can be increased, but unfortunately, the ee value is almost negligible (see the footnote [d] in Table 2). This experiment supports our hypothesis.

On the basis of the calculations and the experimental results, we proposed that a trade-off of reaction rate and enantioselectivity should be taken into consideration for achieving high enantioselectivity. Increasing the R group in the alkyne moiety of the substrate can increase the enantioselectivity, with a precondition that the reaction rate is not very slow (for examples, reactions of **1b**−**1e**). If the R group is too bulky and the [3 + 2] reaction becomes extremely slow, low enantioselectivity could be obtained (this is the case of reaction of **1i**).[13]

CONCLUSION

In summary, we have developed a highly enantioselective Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition of 1-yne-VCPs. The experimental findings represent the first time that unactivated VCP serves as a three-carbon component in asymmetric transition-metal-catalyzed cycloaddition. The present methodology provides an efficient and versatile approach to carbo- and heterobicyclo[3.3.0] compounds with an all-carbon chiral quaternary stereocenter at the bridgehead carbon. Furthermore, DFT calculations have been carried out to understand the reaction mechanism and stereochemistry, revealing that the serious steric repulsion between the substituents in the alkyne moiety of the substrates and the rigid H_8-BINAP backbone in the alkyne-insertion step is responsible for suppressing the formation of the less favored [3 + 2] cycloadducts.

COMPUTATIONAL DETAILS

All calculations were performed with the *Gaussian 09* program. Density functional theory calculations using the B3LYP method[14] were used to locate all the stationary points involved. The 6-31G(d) basis set was applied for all elements except for Rh, for which the LANL2DZ[15] basis set and pseudopotential were used. Single-point energies based on the structures obtained at the B3LYP level using the same basic set were obtained by M06 calculations in order to take the dispersion energies into consideration.[16] We found that both B3LYP and M06 gave very similar potential energy surfaces and the reaction mechanisms about the rate-determining and stereo-determining steps are the same for the two calculations methods. However, M06 calculations gave the ee values that are much closer to the experimentally observed ones than those from the B3LYP method (see Supporting Information for discussions).[17,18] Frequency calculations at the B3LYP level at 298 K were performed to confirm each stationary point to be either a minimum or a transition structure. The computed zero-point energies, thermal corrections, and entropies were used for computing enthalpies and free energies at 298 K. Solvation energies were evaluated by a self-consistent reaction field (SCRF) using the CPCM model, where UFF radii were used. Solvation calculations were carried out on the gas-phase optimized structures. The reported energies are zero-point energy-corrected enthalpies (ΔH_{gas}), Gibbs free energies ($\Delta G_{gas\ 298K}$), and Gibbs free energies in 1,2-dichloroethane (DCE) solution ($\Delta G_{sol\ 298K}$, where the entropies in solution were approximated by the computed gas phase entropies at 298 K). Unless specifically mentioned, all discussed relative energies in this paper are referred to $\Delta G_{sol\ 298K}$.

EXPERIMENTAL SECTION

Preparation of the cationic Rh(I) catalyst. Anhydrous DCE (5.0 mL) was added to a mixture of $[Rh(CO)_2Cl]_2$ (9.9 mg, 25.4 μmol) and $AgSbF_6$ (21.0 mg, 61.1 μmol, 1.2 equiv to Rh) under argon. The mixture was stirred at room temperature for 10 min. The resulting yellow suspension was left to stand until the formed AgCl precipitated. The supernatant was used in the [3 + 2] cycloaddition reactions as the catalyst precursor ($[Rh(I)^+]$ = 10.2 μmol/mL).

Standard Asymmetric [3 + 2] Reaction Procedure. Under argon, the above $[Rh(I)^+]$ solution (5 mL per mmol substrate, 5 mol %) was added to flame-dried reaction tube containing (*R*)-ligand **B** (*R*)-(+)-2,2′-bis(diphenylphosphino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl ((*R*)-H_8-BINAP) (42 mg per mmol substrate, 6.5 mol %). The resulting light-yellow solution was stirred at room temperature for

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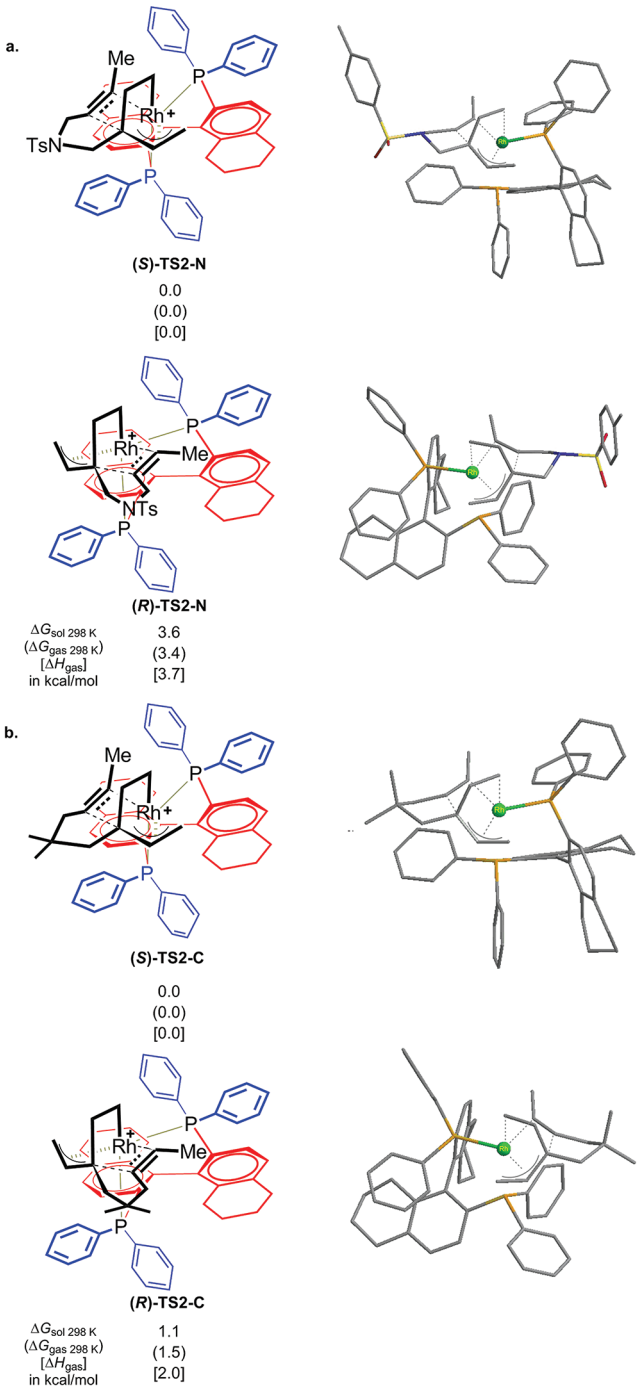

Figure 5. Alkyne-insertion transition states in the asymmetric [3 + 2] cycloaddition of nitrogen- and *gem*-dimethyl-tethered substrates.

10 min, and then a solution of the 1-yne-VCP substrate in DCE (~15 mL per mmol substrate) was added. The reaction tube was immersed into the oil bath and heated at the indicated temperature. When TLC indicated the disappearance of the starting material, the reaction mixture was cooled to room temperature and filtered through a thin pad of silica gel. The filter cake was washed with PE/EA, and the combined filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel to afford the corresponding [3 + 2] cycloadduct.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, computational details, Cartesian coordinates for all stationary points, and full citation for ref 14. This material is available free of charge via the Internet at http://pubs.acs.org.

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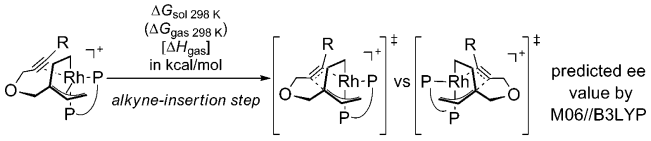
(12) The labeling of *R* and *S* here in the intermediates and transition states is not based on the traditional nomenclature of chirality for chiral compounds but is used to specify that the (*R*)-intermediates and (*R*)-transition states are connected to the (*R*)-product, while the (*S*)-intermediates and (*S*)-transition states are connected to the (*S*)-product.

(13) The M06//B3LYP predicted ee values of substrates with different R substituents in solution are given below. The electronic effect introduced by the R group in the substrate can influence the reaction rate, but not the enantioselectivity, since both (*R*)- and (*S*)-transition states have almost the same electronic effects. Therefore, origin of enantioselectivity is still due to steric effect of the R group (Figure 4).



0.0 (0.0) [0.0]	R = H	15.9 (16.4) [16.0]	17.2 (18.1) [18.3]	80%
0.0 (0.0) [0.0]	R = Me	15.7 (16.2) [14.7]	18.6 (19.4) [18.4]	98%
0.0 (0.0) [0.0]	R = TMS	16.7 (16.9) [14.8]	22.0 (22.4) [21.1]	~100%
0.0 (0.0) [0.0]	R = CO_2Me	11.7 (12.4) [11.0]	15.4 (16.8) [16.8]	99.6%
0.0 (0.0) [0.0]	R = Ph	14.0 (14.1) [12.5]	17.4 (17.7) [17.1]	99.3%

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