

■ Methods and Reactions

Co-Catalyzed Asymmetric Intramolecular [3+2] Cycloaddition of Yne-Alkylidenecyclopropanes and its Reaction Mechanism

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Abstract: Developing new transition metal-catalyzed asymmetric cycloadditions for the synthesis of five-membered carbocycles (FMCs) is a research frontier in reaction development due to the ubiquitous presence of chiral FMCs in various functional molecules. Reported here is our discovery of a highly enantioselective intramolecular [3+2] cycloaddition of yne-alkylidenecyclopropanes (yne-ACPs) to bicyclo[3.3.0]octadiene and bicyclo[4.3.0]nonadiene molecules using a cheap Co catalyst and commercially available chiral ligand (S)-Xyl-BINAP. This reaction avoids the use of precious

Pd and Rh catalysts, which are usually the choices for [3+2] reactions with ACPs. The enantiomeric excess in the present reaction can be up to 92 %. Cationic cobalt(II) species was suggested by experiments as the catalytic species. DFT calculations showed that this [3+2] reaction starts with oxidative cyclometallation of alkyne and ACP, followed by ring opening of the cyclopropyl (CP) group and reductive elimination to form the cycloadduct. This mechanism is different from previous [3+2] reactions of ACPs, which usually start from CP cleavage, not from oxidative cyclization.

Introduction

Five-membered carbocycles (FMCs) are ubiquitously found in biologically active molecules including pharmaceuticals, natural products, and non-natural products. Due to this, great efforts have been made to discover and develop general reactions accessing FMCs in high efficiencies.^[1] Among them, transition metal-catalyzed [3+2] cycloadditions of various 3C synthons with 2C synthons (which are usually alkenes, alkynes or allenes) have evolved as powerful tools for chemists to synthesize various FMC-embedded functional molecules.^[2] The intramolecular [3+2] reactions are very useful for the synthesis of 5/5 and 6/5 skeletons and have attracted efforts from many leading chemists. Unfortunately, only a limited number of these intramolecular [3+2] cycloadditions have their asymmetric versions,^[3] whereas the asymmetric intermolecular [3+2] reactions can be widely found.^[1m,2b-d,4] Therefore, there is a high demand for discovering and developing new intramolecular asymmetric [3+2] reactions.

We have been inspired by many leading discoveries of the intramolecular cycloaddition reactions of alkylidenecyclopropanes (ACPs) or methylenecyclopropanes (MCPs) with 2C syn-

thons (Scheme 1 a).^[5] Among them, to our surprise, there is only one asymmetric reaction, the Pd-catalyzed asymmetric [3+2] cycloaddition between an ACP and an alkene (Scheme 1 b), which was elegantly elaborated by Mascareñas and co-workers.^[3a] In this reaction, R¹ and R² can be changed and this reaction had good scope to synthesize 5/5 bicycles (even though the 2 π component in this [3+2] reaction required the use activated alkenes, this group could be further converted to various groups, as demonstrated by the authors). With these encouraging results, we wondered whether the 2 π component of the asymmetric intramolecular [3+2] reactions can be alkynes, which was not reported in literature. We speculated that all previously developed intramolecular [3+2] reactions of ACPs and MCPs with alkynes either had not been tested for their asymmetric versions or that it was difficult to achieve high enantiomeric excess (ee).^[6] Based on this, we wondered whether, if a new metal catalyzed [3+2] cycloaddition of ACPs with alkynes could be developed, in this new scenario asymmetric version could be realized by choosing appropriate chiral ligands. Here we report our efforts to this aim that led to the development of a Co-catalyzed asymmetric intramolecular [3+2] reaction of yne-ACPs. In addition, DFT calculations and experimental investigations of the reaction mechanism are also described here.

Results and Discussion

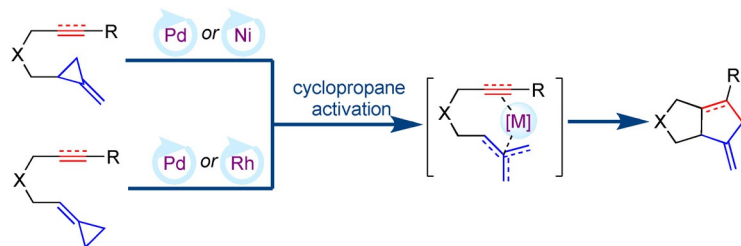
Developing the asymmetric intramolecular [3+2] cycloaddition reaction of yne-ACPs

Recently, cobalt-catalyzed transformations have attracted a lot of attention with the consideration of its high natural abundance, low cost, limited toxicity, and unique catalytic proper-

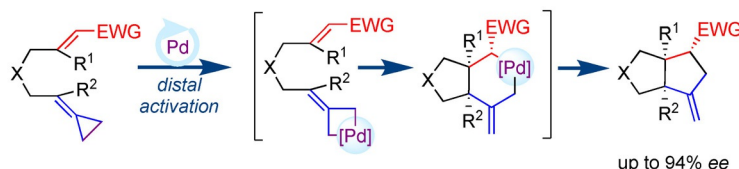
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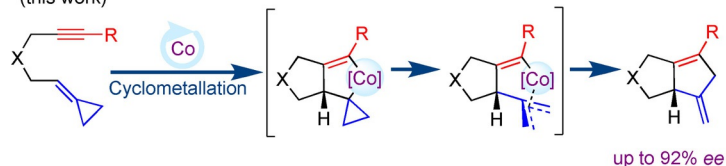
a) Transition-metal catalyzed intramolecular [3+2] cycloadditions of MCPs and ACPs



b) Enantioselective Pd-catalyzed intramolecular [3+2] cycloaddition of ene-ACPs



c) Enantioselective Co-catalyzed intramolecular [3+2] cycloaddition of yne-ACPs (this work)



Scheme 1. Transition-metal catalyzed intramolecular [3+2] cycloadditions of MCPs and ACPs with alkenes/alkynes. EWG = electron-withdrawing group.

ty.^[7] We wondered if we could circumvent using precious metal catalysts of Pd and Rh in the ACPs-participated cycloadditions, by exploiting a $\text{Co}^0/\text{Co}^{\text{II}}$ or $\text{Co}^{\text{I}}/\text{Co}^{\text{III}}$ redox cycle to achieve [3+2] cycloadditions of ACPs with alkynes or alkenes (the other reason for this, as mentioned in the introduction part, was to find a new catalytic system having great potential to be advanced to its asymmetric version). With this goal in mind, we started our experimental study of the intramolecular [3+2] cycloaddition reaction of yne-ACPs using **1a** as the substrate and $\text{Co}(\text{dppf})\text{Cl}_2$ ($\text{dppf} = (1,1'\text{-bis(diphenylphosphino)ferrocene})$), Zn/ZnI_2 as the catalyst. This catalytic system has been widely used to promote cycloaddition reactions.^[7a,8] To our delight, the designed cycloadduct **2a** was obtained in 15% yield along with 74% recovery of the starting material (Table 1, entry 1). Using Et_2Zn as the reductant, an increased yield (32%) was obtained (entry 2). In some reported cobalt-catalyzed reactions, compared with other reductants, alkyl aluminum reagents have shown their special properties and advantages.^[9] So, we systematically screened various alkyl aluminum reagents, different quantities of the used reductant, various solvents (for more details, see the Supporting Information), finding that carrying out the cycloaddition of **1a** in dichloroethane (DCE) (0.1 M) at 60 °C in the presence of Me_2AlCl (0.5 equiv) gave cycloadduct **2a** in 93% yield. Therefore, conditions in entry 7 were chosen as the optimal conditions for the racemic [3+2] reaction. We then spent our efforts on advancing this reaction to an asymmetric version by screening several chiral ligands. Using (*S*)- H_8 -BINAP led to high yield of **2a**, but the ee

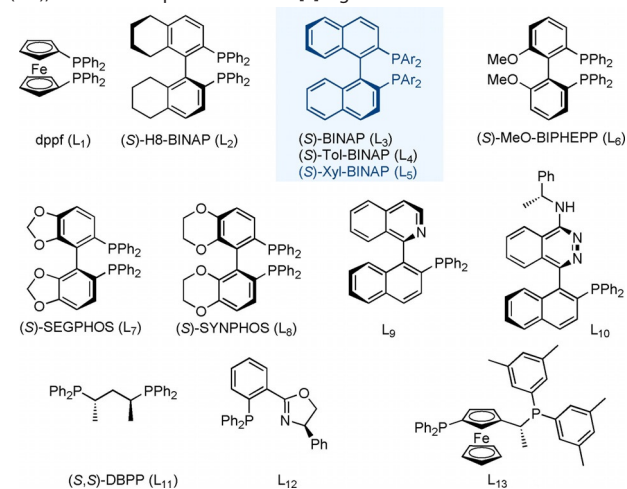
value was just 6% (entry 8). To our delight, other BINAP ligands (L_3 , L_4 , L_5) were found to give good yields with high ee values. For example, using sterically hindered bisphosphine ligand (*S*)-Xyl-BINAP (L_5) provided the desired product **2a** in 85% yield and 89% ee (entry 11). It was interesting to observe that using axial chiral ligands (L_6 – L_{10} ; entries 12–16) and other types of ligands (L_{11} – L_{13} ; entries 17–19) can all realize the reaction. However, poorer enantioselectivities were obtained compared to the L_5 ligand. Based on these results, we chose L_5 as the chiral ligand for further optimization of other parameters of the reaction conditions. After a brief study of solvent, temperature, concentration (for more detail, see the Supporting Information), we found that under these optimal reaction conditions (using Me_2AlCl (0.5 equiv) as the activator, $\text{Co}(\text{L}_5)\text{Cl}_2$ (0.1 equiv) as the catalyst, DCE/*n*-heptane (1:1) as the solvent, substrate in 0.1 M, reaction temperature at 30 °C), the reaction was completed in 1.5 h and provided the desired **2a** in 96% yield and 91% ee (entry 22).

Having the optimal reaction conditions in hand, the scope of intramolecular [3+2] cycloaddition of various yne-ACP substrates were examined next (Table 2). First, substrates with a variety of aryl groups were tested, finding that electron-donating (OMe) (**1b/1e**) or electron-withdrawing groups (CF_3 , Br) (**1c/1d/1f**) at *para* or more steric hindered *ortho* position in the aryl rings were tolerated and all [3+2] cycloadditions gave good yields (77–96%) with high enantioselectivities (88–92% ee; **2a–f**). Single-crystal X-ray diffraction analysis confirmed the absolute configuration of **2c**, which has an *S* configuration.^[10] To our delight, the aryl bromide atom can be tolerated in the reaction and this success makes it possible to further functionalize the [3+2] cycloadducts of **2d** and **2f** by coupling reactions. Moreover, heterocycle-substituted substrates (**1g**, **1h**) also underwent cycloadditions to form the corresponding **2g** (76%, 81% ee) and **2h** (92%, 92% ee), respectively. The different enyne-ACP substrates (**1i**, **1j**, **1k**) can also generate the cycloadducts (**2i**, **2j**, **2k**) in excellent yields (from 87% to 96%) with high ee values (from 81% to 91%). In addition, substrates with substituted alkynes, which are aliphatic groups such as methyl (**1l**), cyclopropyl (**1m**), and functionalized alkyl group bearing a OTBS substituent (**1n**), generated the desired products (**2l**, **2m**, **2n**) in good yields (72–90%) and enantioselectivities (71–87% ee). It should be pointed out that, in some cases, more equivalents of AlMe_2Cl (1.0 equiv) and a higher reaction temperature (60 °C) were needed to accelerate the transformations and ensure efficient conversions (entries 7–18). Interestingly, the protocol we developed can not only afford the fused 5,5-bicyclic ring systems but also generate the bicyclo[4.3.0]nonadiene derivatives **2o** (83%, 74% ee), **2p** (68%, 55% ee), and **2q** (95%, 59% ee). For the substrate bearing a methyl at the internal position of the ACP alkene (**1r**), low yield and no asymmetric induction was obtained. In addition, we also tried some substrates with a Lewis acid-sensitive functional group (**1s**, **1t**, **1u**), lower reac-

Table 1. Reaction optimization.^[a]

Entry	Ligand ^[e]	Reductant [equiv]	Time [h]	Yield [%]	ee [%]
1	L ₁	Zn (0.5), ZnCl ₂ (0.1)	24	15	–
2	L ₁	Et ₂ Zn (0.5)	1	32	–
3	L ₁	Me ₃ Al (1.0)	16	5	–
4	L ₁	Et ₂ Al (1.0)	16	6	–
5	L ₁	Et ₂ AlCl (1.0)	16	6	–
6	L ₁	Me ₂ AlCl (1.0)	10	94	–
7	L ₁	Me ₂ AlCl (0.5)	16	93	–
8	L ₂	Me ₂ AlCl (0.5)	18	90	6
9	L ₃	Me ₂ AlCl (0.5)	18	94	87
10	L ₄	Me ₂ AlCl (0.5)	18	86	85
11	L ₅	Me ₂ AlCl (0.5)	18	85	89
12	L ₆	Me ₂ AlCl (0.5)	18	12	60
13	L ₇	Me ₂ AlCl (0.5)	18	82	33
14	L ₈	Me ₂ AlCl (0.5)	18	73	54
15	L ₉	Me ₂ AlCl (0.5)	18	17	22
16	L ₁₀	Me ₂ AlCl (0.5)	18	76	–39
17	L ₁₁	Me ₂ AlCl (0.5)	18	85	–16
18	L ₁₂	Me ₂ AlCl (0.5)	18	82	25
19	L ₁₃	Me ₂ AlCl (0.5)	18	83	21
20 ^[b]	L ₅	Me ₂ AlCl (0.5)	18	98	90
21 ^[c]	L ₅	Me ₂ AlCl (0.5)	18	99	90
22 ^[d]	L ₅	Me ₂ AlCl (0.5)	1.5	96	91

[a] General reaction conditions: DCE as solvent and 60 °C as temperature; isolated yields and enantiomeric excess (ee) values were determined by high-performance liquid chromatography (HPLC). [c] Reaction temperature: 30 °C. [c] Reaction temperature: 0 °C. [d] Solvent: DCE/*n*-heptane (1:1), reaction temperature: 30 °C. [e] Ligands used herein:



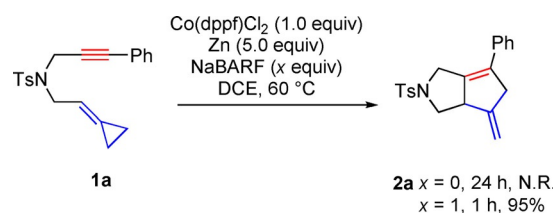
tion yields were obtained, partially because of the Lewis-acidic character of the reducing agent. Similar results were also reported for Co/Al-catalyzed cycloadditions.^[11] It is interesting to find that using Zn/ZnI₂ as activator instead, the oxygen-tethered substrate **1s** and carbon-tethered substrates **1t** and **1u** can participate in the [3+2] reactions, affording the desired product **2s** (90%, 87% ee), **2t** (81%, 88% ee), and **2u** (92%, 88% ee), respectively.^[12] We also tested the substrate **1v** with an aryl group as tether, finding that the reaction took place in high yield of 85%, but almost no ee was obtained.

Experimental and DFT investigation of the asymmetric [3+2] cycloaddition mechanism

We performed mechanistic investigation via both experiments and DFT calculations on the [3+2] cycloaddition of yne-ACPs. Using stoichiometric Co(dppe)Cl₂ and Zn as reductant, no transformation happened, indicating that neutral Co⁰/Co^{II} or Co^I/Co^{III} may not work under the reaction conditions.^[13] In some reported Co^{II}-diphosphine complexes and alkylaluminum reagents for C–C bond formation reactions, the alkylaluminum might act as a reductant as well as an anion abstractor.^[9a,b,14] Using the counter anions NaBARF (sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) as activator,^[15] 95% yield of cycloadduct **2a** was obtained (Scheme 2). The above experiment suggested a unique role of a possible cationic Co^I/Co^{III} catalytic cycle in our reaction. In addition, Co⁰ species may not be excluded since using Et₂Zn as the reductant, which has been proposed to form a Co⁰ species by Dong and co-workers,^[16] only 32% yield of cycloadduct **2a** was obtained (entry 2, Table 1).

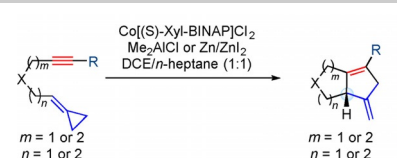
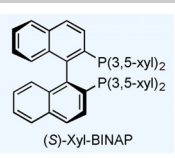
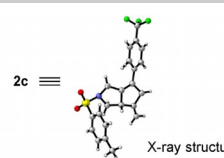
To gain more insights into the catalytic pathway in our reaction system, we performed DFT calculations on the reaction of a model complex **INT1** formed by yne-ACP substrate and a cationic cobalt(II) diphosphine species (Figure 1). A smaller methanesulfonyl protecting group and 1,3-bis(dimethylphosphino)propane (dmpp) were used to reduce the computational cost without sacrificing the understanding of the reaction mechanism. The validation of simplified ligand dmpp had been supported by both experiment and further calculations: experimentally using Co(dpmp)Cl₂ (dpmp = 1,3-bis(dimethylphosphino)propane) as catalyst, **1a** can be converted to **2a** in 74% yield; using dpmp as ligand in calculations, similar results for the key steps were found compared to those from dmpp (see the Supporting Information).

The energy profile was drawn based on the relative Gibbs free energies in DCE solution (ΔG_{DCE}). Note that the suffixes *s* and *t* on the structure numberings refer to the singlet and triplet states, respectively. The first step of the catalytic cycle is the activation of ACPs. The majority of reported transition metal-catalyzed cycloaddition of ACPs and unsaturated partners are initiated by oxidative addition of the metal (typically Pd, Rh, Ni or Ru) to either the proximal or distal C–C bond of the cyclopropane.^[17] However, we found that the distal C–C cleavage of ACPs via **TS1a–s** has an activation free energy of 42.8 kcal mol^{–1} and proximal C–C cleavage of ACPs via **TS1b–s** has an activation free energy of 43.7 kcal mol^{–1}, indicating that these two modes of activation are infeasible. Then a mechanism in which the double bond of the ACPs is first activated was pro-



Scheme 2. Experimental investigation of reaction mechanism. N.R. = no reaction.

Table 2. Scope of reaction.^[a]

Entry	Substrate	Product
		 (S)-Xyl-BINAP
	 2c X-ray structure	
1 ^[b]		1a, Ar = Ph
2 ^[b]		1b, Ar = 4-MeOC ₆ H ₄
3 ^[b]		1c, Ar = 4-CF ₃ C ₆ H ₄
4 ^[b]		1d, Ar = 4-BrC ₆ H ₄
5 ^[b]		1e, Ar = 2-MeOC ₆ H ₄
6 ^[b]		1f, Ar = 2-BrC ₆ H ₄
7 ^[c]		1g, X = O
8 ^[c]		1h, X = S
9 ^[c]		1i, R ¹ = H, R ² = H, R ³ = H
10 ^[c]		1j, R ¹ = H, R ² = CH ₃ , R ³ = CH ₃
11 ^[c]		1k, R ¹ = CH ₃ , R ² = H, R ³ = H
12 ^[c]		1l, R = CH ₃
13 ^[c]		1m, R = cyclopropyl
14 ^[c]		1n, R = CH ₂ OTBS
15 ^[c]		1o, R = CH ₃
16 ^[c]		1p, R = vinyl
17 ^[c]		1q
18 ^[c]		1r
19 ^[d]		1s
20 ^[d]		1t, R = COOMe
21 ^[d]		1u, R = CH ₂ OTs
22 ^[c]		1v
		2a, 2 h, 96%, 91% ee 2b, 3 h, 92%, 91% ee 2c, 6 h, 77%, 92% ee 2d, 3 h, 94%, 89% ee 2e, 3 h, 89%, 91% ee 2f, 3 h, 80%, 88% ee 2g, 0.5 h, 76%, 81% ee 2h, 0.5 h, 92%, 92% ee 2i, 0.5 h, 96%, 83% ee 2j, 0.5 h, 92%, 81% ee 2k, 1 h, 87%, 91% ee 2l, 1 h, 83%, 85% ee 2m, 1 h, 90%, 87% ee 2n, 1 h, 72%, 71% ee 2o, 2 h, 83%, 74% ee 2p, 5 h, 68%, 55% ee 2q, 0.5 h, 95%, 59% ee 2r, 4 h, 13%, 0% ee 2s, 4 h, 90%, 87% ee 2t, 12 h, 81%, 88% ee 2u, 8 h, 92%, 88% ee 2v, 1.5 h, 85%, 7% ee

[a] Isolated yields and ee were determined by high-performance liquid chromatography (HPLC); the reaction was run on 0.08 mmol scale; the reported yield was average of two runs; the absolute configuration of all products was determined by analogy to **2c**, which was confirmed by X-ray analysis. [b] Me₂AlCl (0.5 equiv) was added to the solution of **1** and Co[(S)-Xyl-BINAP]Cl₂ in DCE/n-heptane (1:1) (0.1 M) at 30 °C. [c] Me₂AlCl (1.0 equiv) was added to the solution of **1** and Co[(S)-Xyl-BINAP]Cl₂ in DCE/n-heptane (1:1) (0.1 M) at 60 °C. [d] Co[(S)-Xyl-BINAP]Cl₂ (0.1 equiv), Zn (0.5 equiv), ZnI₂ (0.1 equiv) was used in DCE (0.1 M) at 80 °C.

posed.^[18] This reaction can proceed through coordination of cationic Co^I to the alkyne and alkene followed by oxidative cyclometallation to form cationic Co^{III} metallacycle **INT2-s** with an energy barrier of 16.7 kcal mol⁻¹ (via **TS1 c-s**). Next, ring opening of the cyclopropyl group via **TS2-s** affords the π -allyl metallacycle intermediate **INT3-s**. This step is exergonic by 25.7 kcal mol⁻¹ with a computed activation free energy of 21.9 kcal mol⁻¹. The followed reductive elimination preferentially occurs in the triplet state **TS3-t** with a much lower energy barrier (23.3 kcal mol⁻¹ vs. 33.0 kcal mol⁻¹ in the singlet state **TS3-s** with respect to **INT3-s**). Here, the triplet intermediate

INT3-t may be connected to the corresponding singlet intermediate **INT3-s** by minimum energy crossing point (**MECP2**). Finally, an endergonic process of catalyst transfer between **INT4** and starting material to release the cycloadduct occurs to close the catalytic cycle. In general, the reductive elimination process is the rate-determining step and the overall activation Gibbs activation energy of 23.3 kcal mol⁻¹ (from **INT3-s** to **TS3-t**) is in accordance with our experimental observation that the reaction took place smoothly under mild conditions.

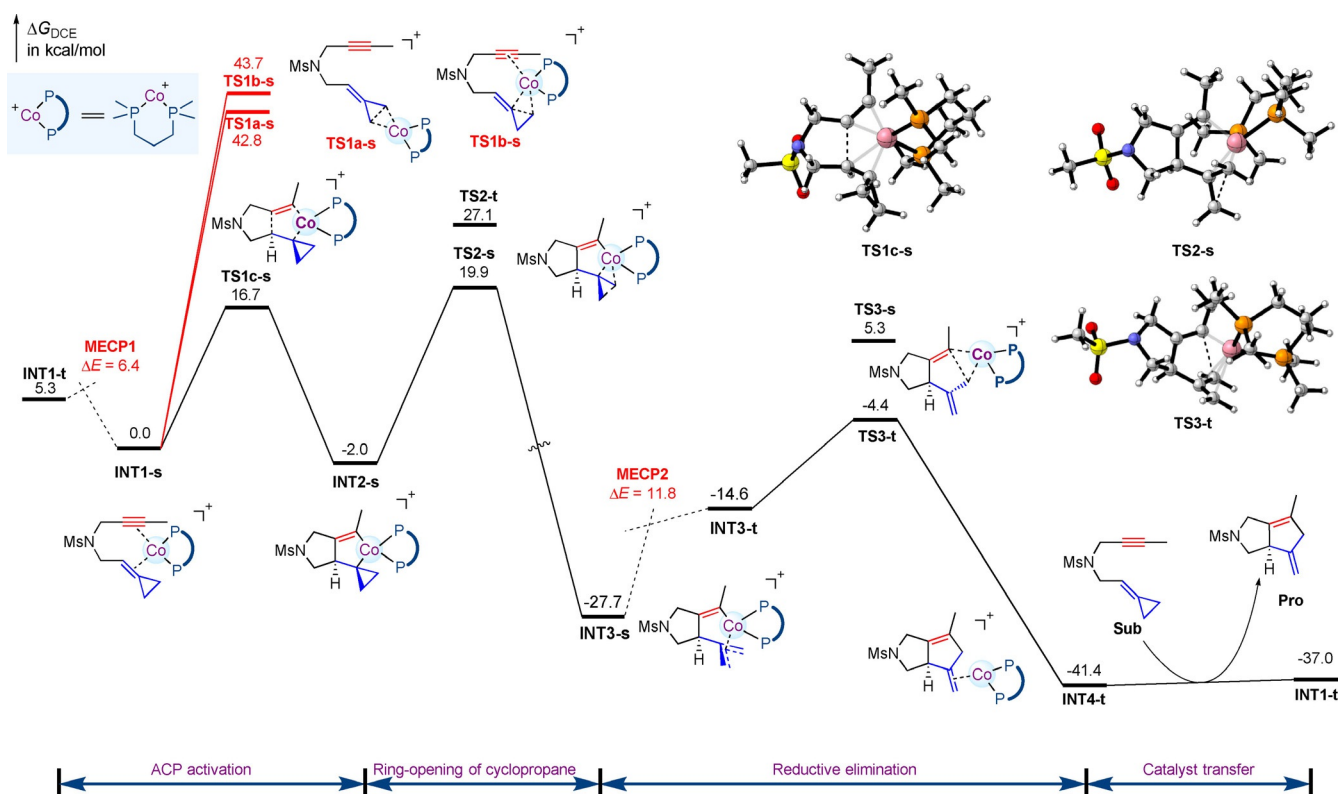


Figure 1. Computed energy surface for the [3+2] cycloaddition catalyzed by a model cobalt(I)-diphosphine species at the SMD(DCE)/M06L/6-311+G(2d,p) (SDD for Co)//B3LYP/6-31G(d) (LANL2DZ for Co) level.

Conclusions

We have developed for the first time a cobalt-catalyzed enantioselective intramolecular [3+2] cycloaddition of yne-ACPs using a commercially available ligand and reductant. This reaction greatly expands the scope of cobalt catalysis in asymmetric synthesis, considering that both bicyclo[3.3.0]octadienes and bicyclo[4.3.0]nonadienes can be obtained in good-to-excellent yields with high *ee*. The experimental and DFT investigations of the reaction mechanism revealed that the reaction starts with oxidative cyclometallation of alkyne and alkene catalyzed by cationic Co^{I} , followed by a ring opening of the cyclopropyl group to afford the π -allyl metallacycle intermediate and a subsequent rate-limiting reductive elimination step to form the cycloadduct. We expect that the present reaction will become a useful tool for synthetic chemists and the mechanism here will be inspiring for understanding/designing of known/new Co-catalyzed reactions.^[12]

Computational Methods

DFT calculations with the Gaussian 09 program^[19] were used to explore the mechanism of the reaction. The B3LYP functional^[20] was used to optimize the geometries of all stationary points in the gas phase with the LANL2DZ basis set^[21] for cobalt and 6-31G(d) basis set^[22] for the other atoms. The keyword "5D" was used to specify that five d-type orbitals were used for all elements in structure optimization. Frequency calculations at the same level were per-

formed to confirm that each stationary point was either a minimum or a transition structure and to evaluate its zero-point energy and the thermal corrections at 298 K. IRC calculations^[23] were carried out to confirm that the key transition state structures connecting the corresponding reactant and product. On the basis of the gas phase optimized structures, the solvation energies ($\Delta G_{\text{solvation}}$) were obtained at the SMD(DCE)/B3LYP/6-31G(d) (LANL2DZ for Co)^[24] level and the single-point energy refinements were performed at M06L/6-311+G(2d,p) (SDD for Co).^[25] Pruned integration grids with 99 radial shells and 590 angular points per shell were used during single-point energy calculations. Gibbs free energies in solution were obtained from sums of the large basis set gas-phase single-point energies, $\Delta G_{\text{solvation}}$ and the gas-phase Gibbs free energy corrections (at 298 K). The minimum energy crossing points (MECP) between the singlet and triplet states were located with the sobMECP program^[26] at the M06L/6-311+G(2d,p) (SDD for Co). All the graphics of molecular structures were prepared using CYLview software.^[27]

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cobalt • carbocycles • alkylidenecyclopropanes • homogeneous catalysis • reaction mechanisms

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