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Pd-Catalyzed Asymmetric Cyclopropanation Reaction of Acyclic Amides with Allyl and Polyenyl Carbonates. Experimental and Computational Studies for the Origin of Cyclopropane Formation

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KEYWORDS: palladium catalysis, cyclopropanation, selectivity, enantioselectivity, (η^3-phenylallyl)Pd complex, DFT studies

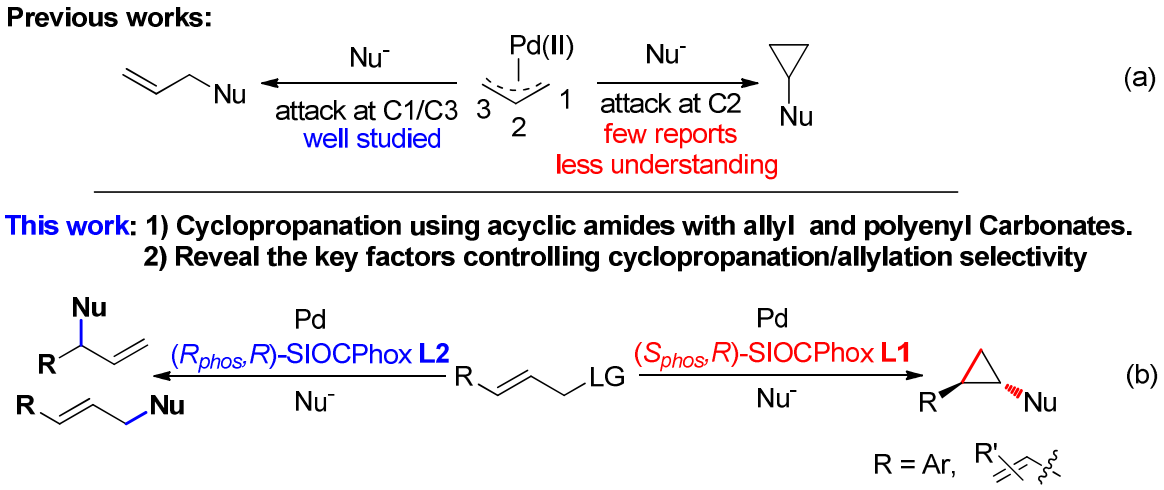
ABSTRACT: Cyclopropanes with three chiral centers were afforded in good to high yields with dr ratio of 4-23:1 and ee of 83-99% in the reaction of acyclic amides with monosubstituted allyl carbonates as well as polyenyl carbonates under the Pd-catalysis in the presence of (S_{phos},R)-SIOCPhox **L1** as the ligand, while allylic alkylated products were provided only if (R_{phos},R)-SIOCPhox **L2** was the ligand. The amide group of product was easily reduced to hydroxymethyl

group in high yield. The active reaction intermediate was determined and transition states for cyclopropanation and allylation were calculated. The origin of cyclopropane formation was investigated by experiments, NMR studies, X-ray analysis of allyl-Pd-ligand complexes and DFT calculations.

INTRODUCTION

Cyclopropanes have widely been presented as the key subunit in many natural products and biologically active compounds, as well as used also as the important building block in organic synthesis.[1] Many efficient protocols have been developed to prepare cyclopropane compounds.[2-5] However the cyclopropanation reactions involving carbenes,[2] carbenoids,[3] and ylides[4] intermediates are among the most important approaches. Pioneering work of Hegedus, the palladium-mediated cyclopropanation via attack of a nucleophile to the central carbon of allyl ligand of a π-allylpalladium chloride, revealed a new way to synthesize cyclopropanes (Scheme 1a).[6] Since then, many researches have focused on the formation of cyclopropane via the Pd-mediated reaction of allyl substrates and nucleophiles. Hoffmann confirmed the attack of nucleophile on the central carbon of allyl ligand of π-allylpalladium complex by isolation of the reaction intermediate formed by the nucleophilic attack on a π-allylpalladium complex.[7] Bäckvall showed that nucleophile favored to attack the terminal carbon of π-allylpalladium complex using a Pd-catalyst with phosphine as ligand while central carbon-attacked product was given when nitrogen ligand was used.[8] Musco and Santi reported a catalytic version of the cyclopropanation reaction using 1,1'-bis(diphenylphosphino)ferrocene (DPPF) as ligand to produce allylation/cyclopropanation products in a ratio of 1.5-6.5:1.[9] Satake realized cyclopropanation using a neutral Pd-catalyst, asymmetric catalytic version of the reaction was also provided though the allylation/cyclopropanation ratio as well as the ee values were rather

lower.[10] Breakthrough appeared when Hayashi and coworkers reported their elegant works on the Pd-catalyzed cyclopropanation with excellent stereoselectivity, and mechanism studies demonstrated that the electronic property of the phosphine ligand has great impact on the reaction.[11] Though significant progress has been made, the types of allyl reagents and nucleophiles suitable for the Pd-catalyzed cyclopropanation were very limited. No successful examples have appeared regarding the highly enantioselective transition metal-catalyzed cyclopropanation with allyl reagents so far. In addition, the factors controlling the selectivities of the cyclopropanation/allylation (c/a selectivity) are far from understanding. To develop the transition metal-catalyzed asymmetric cyclopropanation in high enantioselectivity as well as to understand the reaction mechanism in depth are great challenges.



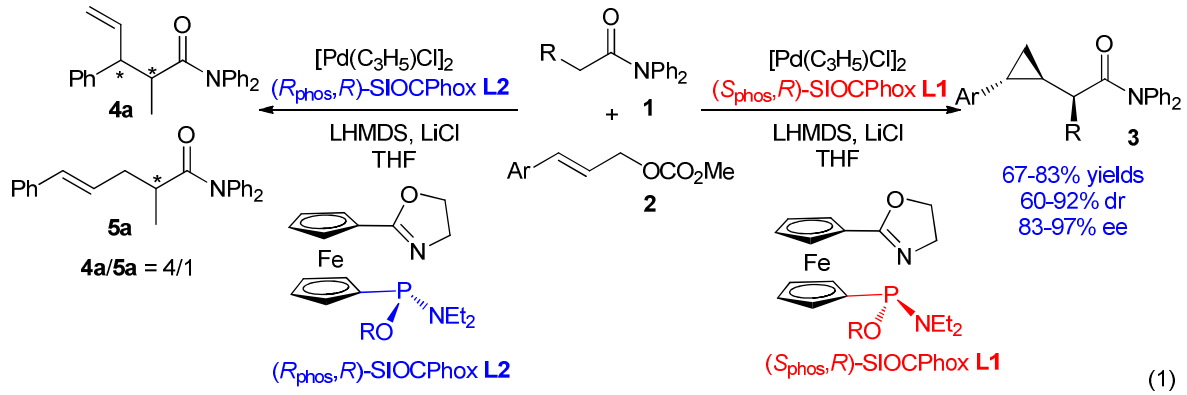
Scheme 1. Allylation vs cyclopropanation in Pd-Catalyzed reaction of allyl reagent with nucleophile

We have studied the palladium-catalyzed asymmetric allylic substitution reaction for years,[12] During the course, we found that the nucleophile could attack the C-2 of the allyl moiety of Pd-complex and reported a highly diastereo- and enantio-selective Pd-catalyzed

cyclopropanation of acyclic amides with substituted allyl carbonates as a communication.[13a] Further studies revealed why the nucleophile attacks the C-2 of the allyl substrate and provided an insight to understand the reaction mechanism by the X-ray diffraction analysis of single crystals of the reaction intermediates, the Pd-ligand-allyl complexes, as well as DFT calculations[14] (Scheme 1b). Based upon the understanding of the reaction course, polyenyl carbonates were applied to this Pd-catalyzed cyclopropanation as well, which afforded the highly functionalized vinylcyclopropanes bearing three continuous chiral centers. Their synthesis via asymmetric and catalytic way is scarce.[15] In this article, we report this Pd-catalyzed asymmetric cyclopropanation and related mechanism studies in detail.

RESULTS AND DISCUSSION

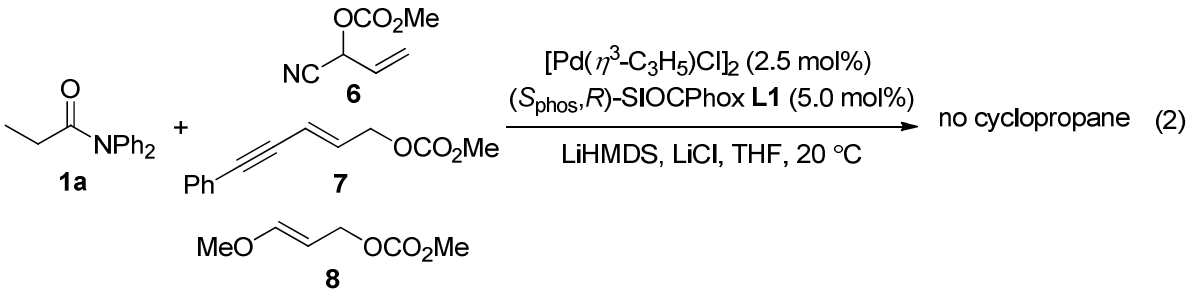
Pd-Catalyzed Cyclopropanation with Allyl and Polyenyl Carbonates. We have studied the reaction of acyclic amides **1** with monosubstituted allyl carbonates **2** under Pd-catalysis,[13a] and found that cyclopropanes **3** were afforded in good yields with high enantioselectivity by using (S_{phos},R)-SIOCPhox **L1** as the ligand while allylic alkylation products **4a** and **5a** were obtained by employing (R_{phos},R)-SIOCPhox **L2** as the ligand (eq 1).[13a] The investigation of the impact of reaction parameters on the reaction revealed that the presence of both Li^+ and Cl^- ions is important for the selectivity of cyclopropanation/allylic alkylation (c/a selectivity) and diastereoselectivity of cyclopropanation (for details, see our preliminary report, ref. 13a).



(1)

R= (*R*)-2'-hydroxy-1,1'-binaphthyl-2-yl

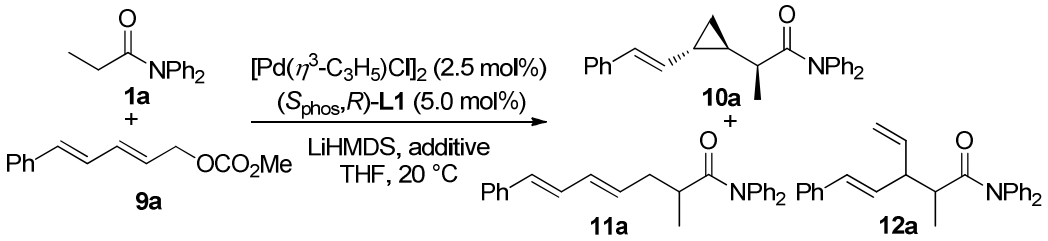
During the experimental and theoretical studies on the origin of cyclopropane formation in this reaction, it was found from the X-ray analysis of single crystals of the Pd-allyl complex **1** (**CP1**) with (S_{phos},*R*)-SIOCPhox **L1** as ligand and the Pd-allyl complex **2** (**CP2**) using (R_{phos},*R*)-SIOCPhox **L2** as ligand respectively that the conjugation between the phenyl ring and the allyl ligand is better in **CP1** than in **CP2** (*vide infra*). DFT calculations suggested that better conjugation should lower the energy of LUMO of the central carbon of π-allylpalladium complex and facilitates the attack on it by nucleophile in the reaction using **L1** as the ligand (*vide infra*).[7c,16] This findings inspired us to explore other allyl substrates having the substituent conjugated with allyl subunit for the cyclopropanation. Thus, three allyl substrates **6-8** bearing cyano, methoxy and phenyl ethynyl group respectively, were tested (eq. 2). However, no desired cyclopropanation occurred but the decomposition of compounds **6-8** was observed.



(2)

Then dienyl carbonate **9a** was tested because the alkene group may have better conjugation ability with allyl group. Pleasingly, the reaction proceeded smoothly with 2.5 mol% of [Pd(η^3-C_3H_5)Cl]$_2$ and 5 mol % of **L1** in THF. The cyclopropane **10a** and allylated products **11a** and **12a** were obtained in 90% yield, with cyclopropanation/allylation ratio being 81/19, dr being 10.5/1 and ee of **10a** being 97% (entry 1, Table 1). Thus, the impact of other reaction parameters on the cyclopropanation was studied (Table 1). Similar with that we found before, LiCl was the best additive (entry 1).[12,13a] When NaCl was applied as additive, both the yield and the ratio of c/a selectivity decreased although the enantioselectivity remained excellent (entry 2). The use of NaI led to very low c/a ratio and diastereoselectivity (entry 3). The reaction was severely retarded in the presence of LiI (entry 4). The absence of additive resulted in a reduced yield, while the dr and the ee values still kept excellent (entry 5). Temperature has great influence on the reaction, which differs with that we observed before:[13a] lower temperature enabled reaction to be sluggish and higher temperature also gave inferior results (entries 6-8 vs. entry 1). The evaluation of the solvent effect on the reaction revealed that the solvents such as CH_3CN, DCE, DMSO, and DMF gave poorer results (data not shown in table).

Table 1. Impact of Reaction Parameters on the Pd-catalyzed Cyclopropanation of Amide **1a** with Dienyl Carbonate **9a**[a]



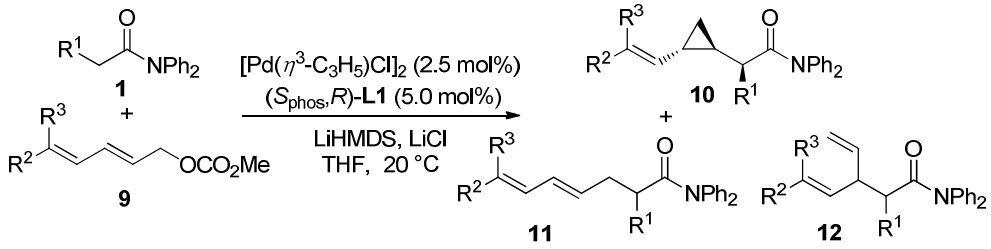
entry	additive	yield[b]	**10a**/**11a**+**12a**[c]	dr[c]	ee[d]
1	LiCl	90%	81/19	10.5/1	97%

2	NaCl	67%	70/30	9.1/1	96%
3	NaI	85%	31/69	4.5/1	--
4	LiI	trace	--	--	--
5	--	66%	74/26	10.4/1	97%
6[e]	LiCl	trace	--	--	--
7[e]	LiCl	68%	70/30	9.0/1	--
8[e]	LiCl	50%	22/78	6.4/1	--

[a]Molar ratio of **1a**/**9a**/[Pd(η^3-C_3H_5)Cl)]$_2$/**L1**/additive/LiHMDS = 100/115/2.5/5/100/120. [b]Isolated yield. [c]Determined by GC. [d]Determined by chiral HPLC. [e]Reaction temperature for entries 6, 7, and 8 is 10, 30, and 45 ^{o}C respectively.

The substrate scope of the reaction was investigated under the optimized reaction conditions and the results are compiled in Table 2. In general, the reaction proceeded smoothly to afford cyclopropanes **16** in high diastereoselectivity (4.1–19.9:1) and excellent enantioselectivity (93–98%). The length of the alkyl chain of the amide **1** exerted little influences on the enantioselectivity of the reaction, while the c/a ratio and diastereoselectivity decreased when the alkyl chain was lengthened (entries 2 and 3 vs 1). For aryl substituted dienyl carbonates **9**, both electron-donating and withdrawing groups of the phenyl ring were well tolerated (entries 4-8). The use of dienyl **9** with a furyl substituent led to the cyclopropane with 97% ee (entry 9). Remarkably, the alkyl substituted dienyls **9j** and **9l** were also suitable substrates for the cyclopropanation with excellent diastereo- and enantioselectivities and in moderate cyclopropane yields (entries 10 and 12). It is noteworthy that the reaction worked well for the *gem*-disubstituted dienyl **9k**, providing the cyclopropane in high c/a ratio, with diastereoselectivity being 19.9/1 and enantioselectivity being 98% (entry 11).

Table 2. Substrate Scope for the Pd-catalyzed Cyclopropanation of Amides **1** with Dienyl Carbonates **9**[a]



entry	R^1, R^2, R^3	yield (%)[b]	**10**/**11**+**12**[c]	dr[c]	ee (%)[d]
1	**a**, Me, Ph, H	90	81/19	10.5/1	97
2	**b**, Et, Ph, H	83	74/26	6.3/1	97
3	**c**, *n*Pr, Ph, H	74	73/27	7.1/1	96
4	**d**, Me, 4-FC_6H_4, H	72	67/33	8.4/1	95
5	**e**, Me, 4-$MeOC_6H_4$, H	78	70/30	12.4/1	>99
6	**f**, Me, 4-BrC_6H_4, H	80	77/23	6.5/1	95
7	**g**, Me, 3-BrC_6H_4, H	80	69/31	4.1/1[e]	93
8	**h**, Me, 2-naphthyl, H	91	74/26	17.6/1	97
9	**i**, Me, 2-furyl, H	85	68/32	8.3/1	97
10	**j**, Me, Me, H	88	55/45	9.5/1	97
11	**k**, Me, Ph, Me	83	94/6	19.9/1	98
12	**l**, Me, -C_5H_{10}-	70	61/39	14.3/1[e]	98

[a]Molar ratio of **1**/**9**/[Pd(η^3-C_3H_5)Cl]$_2$/**L1**/LiCl/LiHMDS = 100/115/2.5/5/100/120. [b]Isolated yield. [c]Determined by GC. [d]Determined by chiral HPLC. [e]Determined by ^{1}H NMR.

The absolute configuration of cyclopropanes **10g** was determined to be (*S*,*R*,*S*) via the X-ray diffraction analysis of its single crystal (Fig 1).

To demonstrate the potential utility of the methodology, the amide group of cyclopropane **10a** was reduced to alcohol **13** with well retention of the diastereo- and enantioselectivities (eq

3).[17] The reaction on larger scale also proceeded well. Treatment of 770 mg of **1a** (3.4 mmol) with 900.0 mg of **9a** (4.1 mmol) using 0.8 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl)]_2$ and 1.6 mol% of (S_{phos},*R*)-**L1** afforded 1.0 g of the mixtures of **10a**, **11a**, and **12a** (80% yield). Recrystallization afforded 0.72 g of cyclopropane **10a** (57% yield) with 99% ee (eq 4).

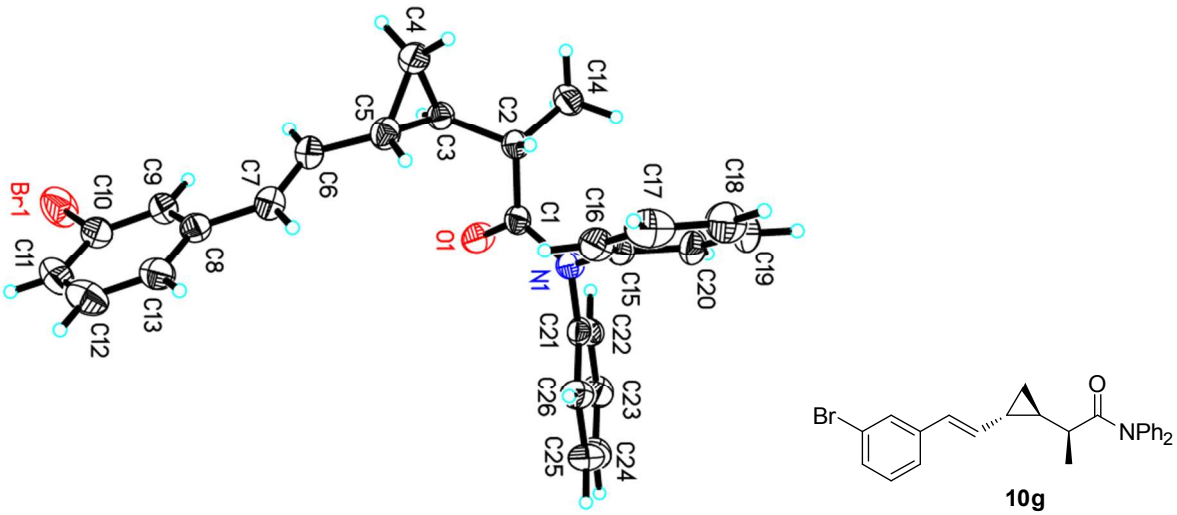
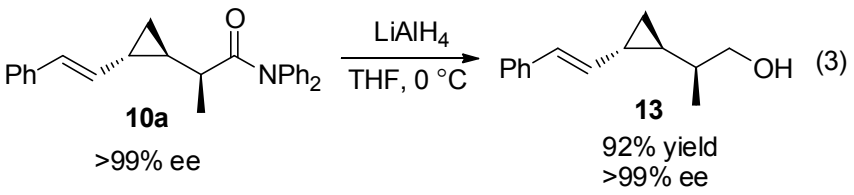
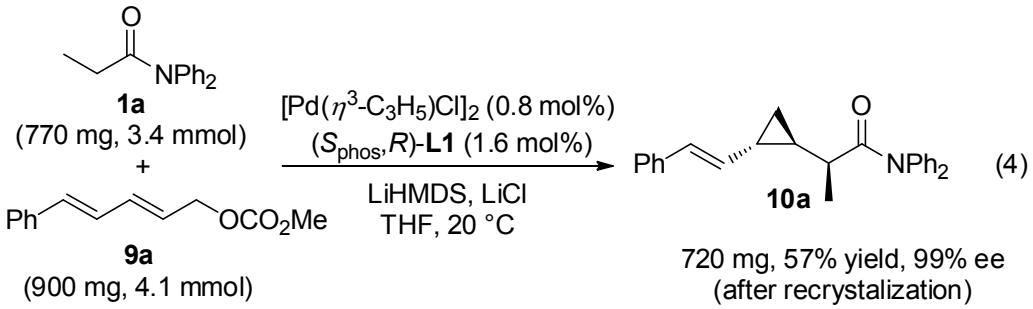
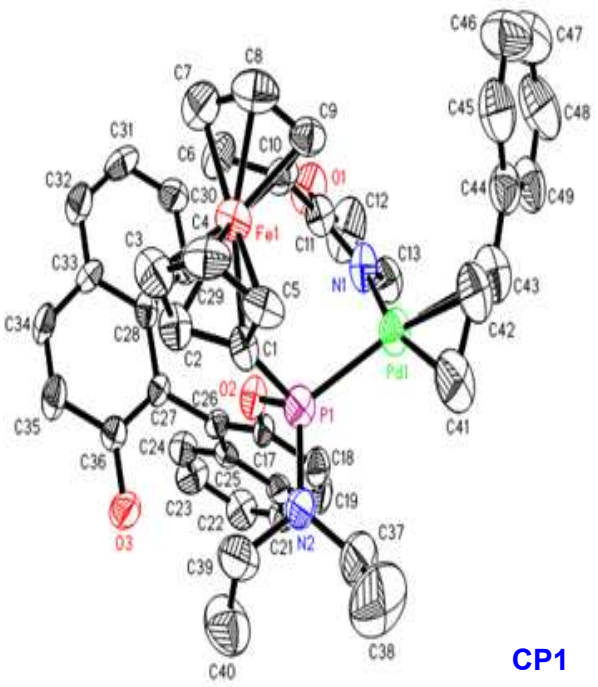


Figure 1. ORTEP Diagram of X-ray diffraction analysis of cyclopropane **10g**.

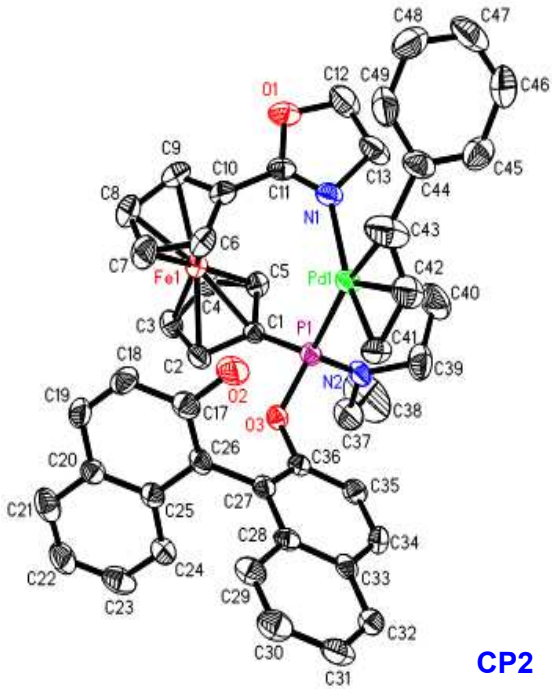




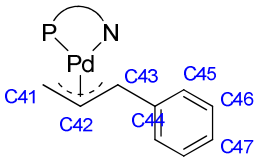
Determination of the active reaction intermediate The above experimental results and our previous studies demonstrated clearly that c/a selectivity was switched when diastereomeric ligands, (S_{phos},R)-SIOCPhox **L1** or (R_{phos},R)-SIOCPhox **L2**, was used (eq. 1).[12e,h,13] Noting that both ligands **L1** and **L2** have the same coordination atoms and backbone except that the configuration on the phosphine atom is (*S*) or (*R*) respectively. To uncover the factors influencing the c/a selectivity, great efforts have been made to define the active reaction intermediates. After trial and error, two crystals of complex **1** (**CP1**) and complex **2** (**CP2**) were acquired by the reaction of [(η^3-phenylallyl)PdCl]$_2$ and AgOTf with (S_{phos},R)-SIOCPhox **L1** and (R_{phos},R)-SIOCPhox **L2,** respectively. Based on the square planar of Pd(II) complex, the position of coordination atoms P and C3 is used to define *trans*/*cis*, P and C3 located at the same side being *cis* while the definition of *endo*/*exo* is depended on the relative orientation of binol subunit and Ph substituent on allyl group.[18] The X-ray analysis of **CP1** and **CP2** showed that both of them were defined as *trans-exo* configuration according to above definition (Fig. 2). ^{31}P NMR spectrum of **CP1** displayed four peaks at 131.6, 130.1, 124.8, 123.1 in a ratio of 0.51:1:0.24:0.24 (See Fig S1, Supporting Information (SI)), which should be related to the isomers with P-C3 *trans or cis* mode in *exo*- or *endo*-configuration (Fig. 3A). ^{1}H NMR with Nuclear Overhauser effect (NOE) (Figure S2, SI) as well as DFT calculations recognized *trans-exo* and *trans-endo* isomers in P-C3 *trans* mode were in a ratio of 66:34[19] (Fig. 3B). Based on above results and the determined absolute configuration of the major reaction product, cyclopropane **10g** (Fig. 1), the P-C3 *trans-exo* isomer could be assigned as the active intermediate (Fig. 3B).



CP1



CP2



CP1	Bond length (Å)	CP2
2.106	Pd-C41	2.119
2.163	Pd-C42	2.169
2.239	Pd-C43	2.261
1.419	C41-C42	1.363
1.386	C42-C43	1.267
	Angle (°)	
119.2	C41-C42-C43	129.2
92.4	P1-Pd1-N1	101.6
	Torsion angle (°)	
4.7	C42-C43-C44-C45	14.0

Figure 2. ORTEP diagram and selected data of X-ray diffraction analysis of **CP1** and **CP2**.

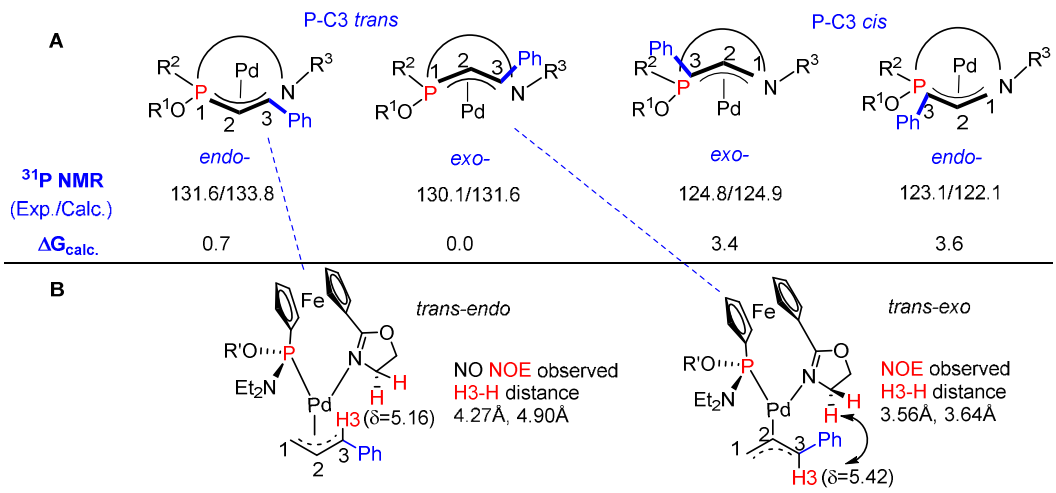


Figure 3. Determination of active reaction intermediates. (**A**) Four possible isomers of **CP1** with *exo*- and *endo*-configurations of (η^3-phenylallyl)PdL with our observed experimental ^{31}P NMR and predicted theoretical ^{31}P NMR. (**B**) Calculated H3-H distances and experimental ^{1}H,^{1}H NOESY of **CP1**.

The *trans-exo* isomer as active intermediate was further confirmed by the reaction of amide **1a** with **CP1** crystal in a molar ratio of 1:1, which afforded 25% yield of products in a ratio of **3a**/**4a**+**5a** being 83/17 with 10.3/1 dr and 95% ee for **3a** (Fig. 4A, b), consistent with that in regio-/diastereo-/enantio- selectivities using the catalytic amount of Pd/**L1** (Figure 4A, a).[13a] Lower yield should be caused by the different counter ion in above reactions (TfO^- *vs* Cl^- ion). Controlled experiments showed that when 110 mol% of AgOTf was added to the reaction,[13a] 20% yields of products were produced with similar selectivities (**3a**/**4a**+**5a** being 82/18, dr ratio being 11/1 and ee being 95% for **3a**) (Fig. 4A, c *vs* a and b). These results suggest that the active *trans-exo* intermediate was favored in the presence of counter ion Cl^- possibly accelerated by the π-σ-π rearrangement,[20] which was supported by our DFT calculations on thermodynamic stability of complexes [(η^3-phenylallyl)Pd**L**] with Cl^- coordination. The *trans-exo* intermediate is the most stable complex among all the calculated π- or σ-intermediates. The calculated energy

difference between *trans-endo* and *trans-exo* intermediates increase to 2.7 kcal/mol under the Cl^- coordination in Figure 4, while it is only 0.7 kcal/mol without Cl^- ion shown in Figure 3B. The results indicate the active π-complex with *trans-exo* configuration tends to be dominated via π-σ-π rearrangement in the presence of Cl^- ion. The similar trend could be found in minor *cis*-isomer as well.

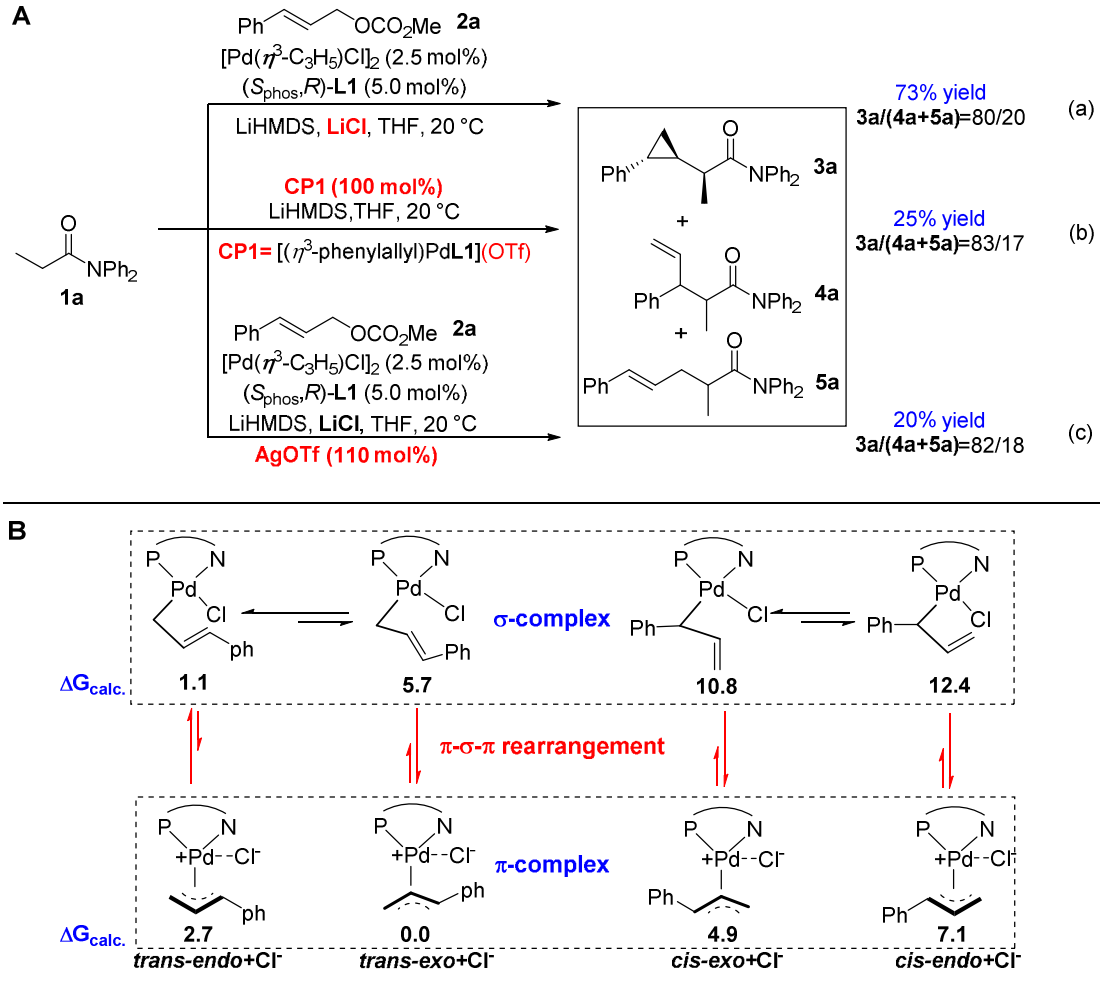
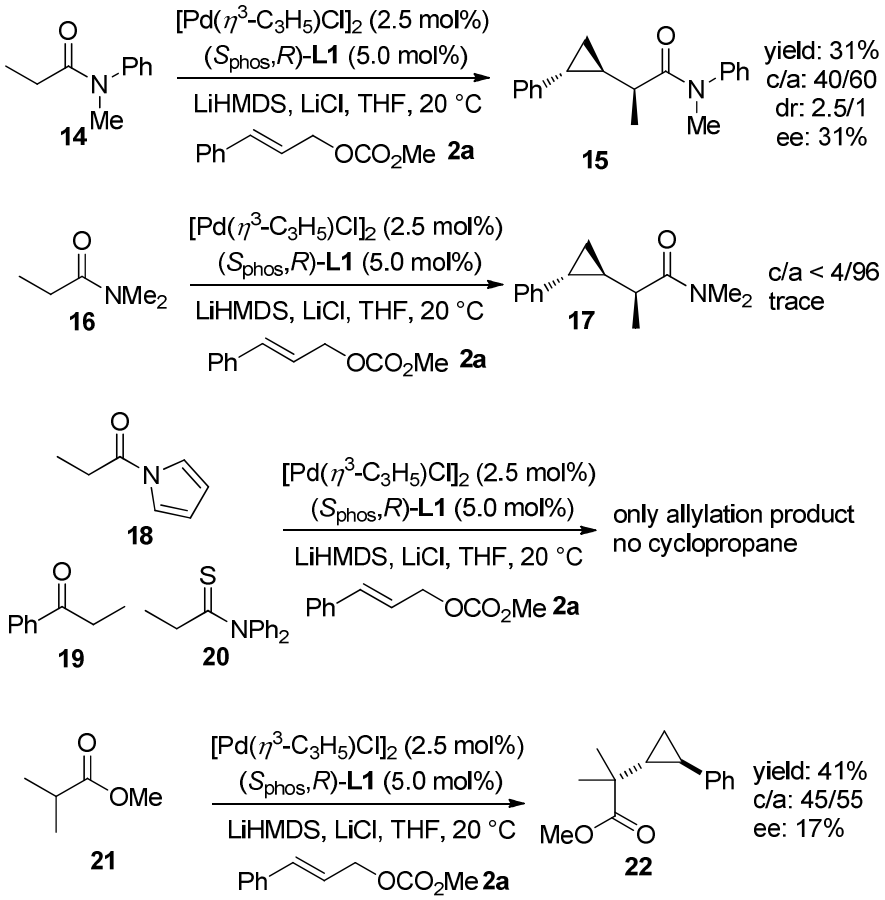


Figure 4. (A) Controlled experiment for active intermediate. (B) Calculated thermodynamic stability of π-σ-π rearrangement for CP1 with Cl^- involved, energy shown in free energy in kcal/mol including CPCM solvent correction (See SI also)

Origin of cyclopropane formation. Closely inspecting the crystal structures of **CP1** and **CP2** (Fig. 2B), the notable difference is the orientation of binol subunit. Due to distinct configuration of P atoms, the orientation of binol subunit in **CP1** is away from its allyl group, while that in **CP2** appears toward allyl group. This orientation difference led to the great changes in bond lengths and bite angles. The bond length of Pd-C43 in both complexes is longer than Pd-C41 due to stronger *trans*-effect of P compared to N.[21] However, the difference of bond length between Pd-C41 and Pd-C43 in **CP2** is larger than that in **CP1**, suggesting that terminal carbon (C43) in **CP2** should be more easily attacked by nucleophiles. The structure of **CP1** exhibits the relative smaller angles for P1-Pd-N1 and C41-C42-C43, and more single bond character of C-C bonds of π-allyl subunit. All these structural information indicates that the allyl-Pd subunit in **CP1** forms a closer palladacyclobutane structure than that in **CP2**. Therefore, these crystal observations suggest that the nucleophile tends to attack the central carbon of allyl subunit of (η3-phenylallyl)PdL in CP1 while attacking the terminal carbon was favoured in CP2.

The property of nucleophile is also an important factor to influence the reaction regarding the reactivity as well as the selectivities.[13b] In order to understand how it affects the reaction, a series of reactions were performed using different kind of carboxylic acid derivatives as nucleophiles (Scheme 2). When the amide **14** with one methyl group instead of Ph group on nitrogen was used in the reaction, 31% yield of cyclopropane **15** with low selectivity was provided. Sluggish reaction occurred if amide **16** with two methyl groups on nitrogen was employed. No cyclopropanation products were observed using pyrrolyl substituent derivatives **18**, ketone **19**, or thioamide **20**. The reaction of methyl isobutyrate **21** could afford cyclopropane **22** in 41% yield, c/a ratio being 1/1.2, and ee of **22** being 17% (Scheme 2). These results could

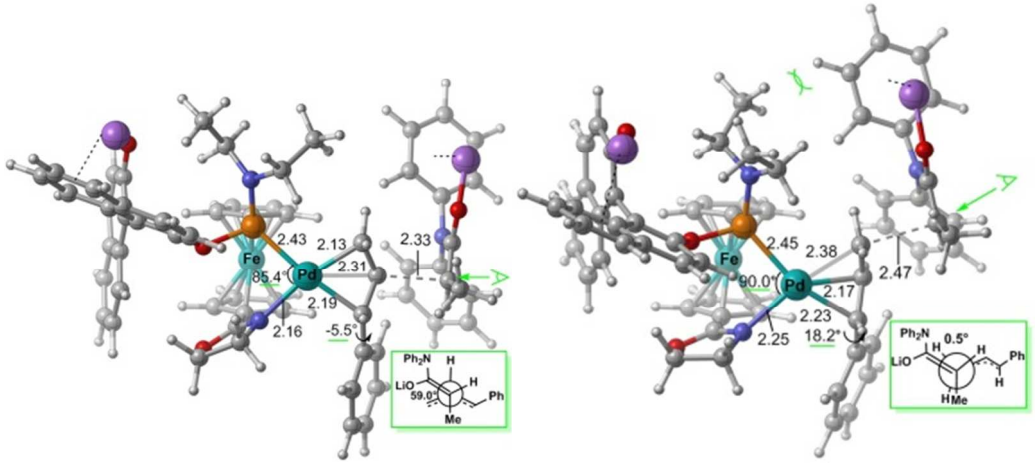
be ascribed to the different stability of the corresponding carbanions. DFT calculations reveal the HOMO energies of carbanions are highly correlated with their reactivity (*vide infra*).



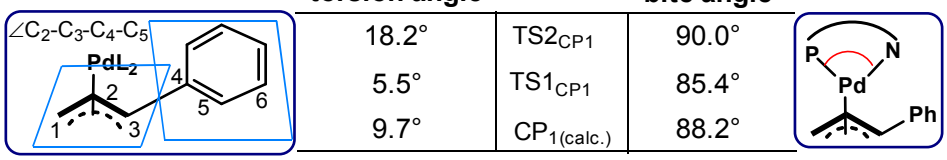
Scheme 2. The Pd-catalyzed reaction of different nucleophiles with allyl reagent **2a**

The results of Scheme 2 indicated that the property of nucleophile singnificantly influences the selectivity of the reaction. For more insights into c/a selectivity, DFT calculations were carried out to locate transition states (TSs) in the nucleophilic attacking step. As shown in Fig. 5, **TS1** and **TS2** are responsible for cyclopropanation and allylic alkylation, respectively. **TS1** with good staggered conformation (59.0°) is 1.7 kcal/mol more stable than **TS2** with eclipsed conformation, suggesting cyclopropane should be major product together with minor allylation

product. Close inspection of both transition states, the bulky NPh_2 group of the nucleophile **1a** prefers to avoid the major steric repulsion with substituent Ph group of the allyl group, as depicted in the Newman projections. From contrasting **TS**s for **CP2**, because of the orientation of binol subunit toward allyl group, the relative **TS** largely favoured to attack the terminal carbon, indicating the overwhelming allylated product should be observed (ΔΔG=6.5 kcal/mol for transition states leading to favorable allylation products, see Fig S4 (SI) for structures). These calculated selectivities are consistent with experimental observation. The **TS1** energy of cyclopropanation from **CP1** (*trans-exo* isomer) appears 3.7-6.4 kcal/mol more stable in free energy than that from other isomers, which evidently supports again our assignment of the active intermediate (*vide supra*) (more unstable TSs were shown in Fig S3, SI).



CP1: TS1 0.0 kcal/mol TS2 1.7 kcal/mol



torsion angle		bite angle
18.2°	$TS2_{CP1}$	90.0°
5.5°	$TS1_{CP1}$	85.4°
9.7°	$CP_{1(calc.)}$	88.2°

Figure 5. The 3D structures, Newman projections and relative energies of transition states. **TS1** and **TS2** are responsible for cyclopropanation and allylic alkylation, respectively. The energies were shown in ΔΔG free energy at level of M06/6-31G(d)/Lanl2DZ//6-

311+G(d,p)/Lanl2DZ with CPCM solvent model correction in THF. Atom colors: Li-purple, P-orange, O-red, N-blue, C-grey, H-white.

It is worthwhile to note that there is a relationship between the torsion angle (C2-C3-C4-C5, Fig 5) and the c/a selectivity. The torsion angles reflect the dihedral angle of two planes of allyl subunit and phenyl rings, observed in crystal structures (Fig 2, 4.7° for **CP1** and 14.0° for **CP2**) and calculated **TS1** for **CP1** (table of Fig. 5). The complex with smaller torsion angle gave rise to better c/a selectivity. Obviously, smaller torsion angle means better conjugative effect between allyl subunit and phenyl ring, which would stabilize **CP1** as well as **TS1** and favor the cyclopropanation. Additionally, our calculated orbital populations of ally subunit in Fig. 6B also reveal a conjugative effect between phenyl substituent and allyl group could stabilize LUMO of **CP1**+Li complex. The orbital overlap is clearly illustrated at the 0.02 iso-value level in **CP1**+Li complex, but not clearly shown in **CP2**+Li, which suggest that the conjugative effect plays an important role in controlling c/a selectivity. These results demonstrate why the presence of aryl substituent on allyl reagents is important in Pd-mediated/catalyzed cyclopropanation and explain also the so called "aryl effect" proposed by Hoffmann.[7c] Based upon these understandings, the allyl substrates were also successfully extended from aryl allyl reagents **2** to polyenyl reagents **9** (*vide supra*).

To further investigate the factors operating the reaction, natural population analysis (NPA) charges and LUMOs of π-allyl Pd-complexes as well as HOMOs of nucleophiles have been analysed by DFT calculations (Fig. 6). It could be found that the tiny positive charges were shown at the central carbon in **CP1** and terminal carbons in **CP2** (Fig. 6A), though the changes of the computed NPA charges at the π-allyl carbon atoms are so small (lower than 0.05) and

could not be evaluated in details. The LUMO of **CP1**+Li shows a large orbital coefficient on middle of allyl part comparing to that of **CP2**+Li and the energy of LUMO in **CP1**+Li is lower than that in **CP2**+Li, suggesting that **CP1**+Li with more stable LUMO is more likely to react with HOMO of Nu^- and thus to form cyclopropane product (Fig. 6B). Calculated energy sequence of nucleophiles' HOMOs follows **1a**>**21**>1**9**>1**8**>**20**, which is clearly associated with their reactivity of cyclopropanation (Scheme 2). As the frontier orbital dependency and the negligible charge difference, we could conclude the central carbon attacking would be largely controlled by orbitals.[22] Higher energy of nucleophile's HOMO and lower energy of π-allyl's LUMO would decrease the energy gap between them which may kinetically facilitate the formation of cyclopropane.

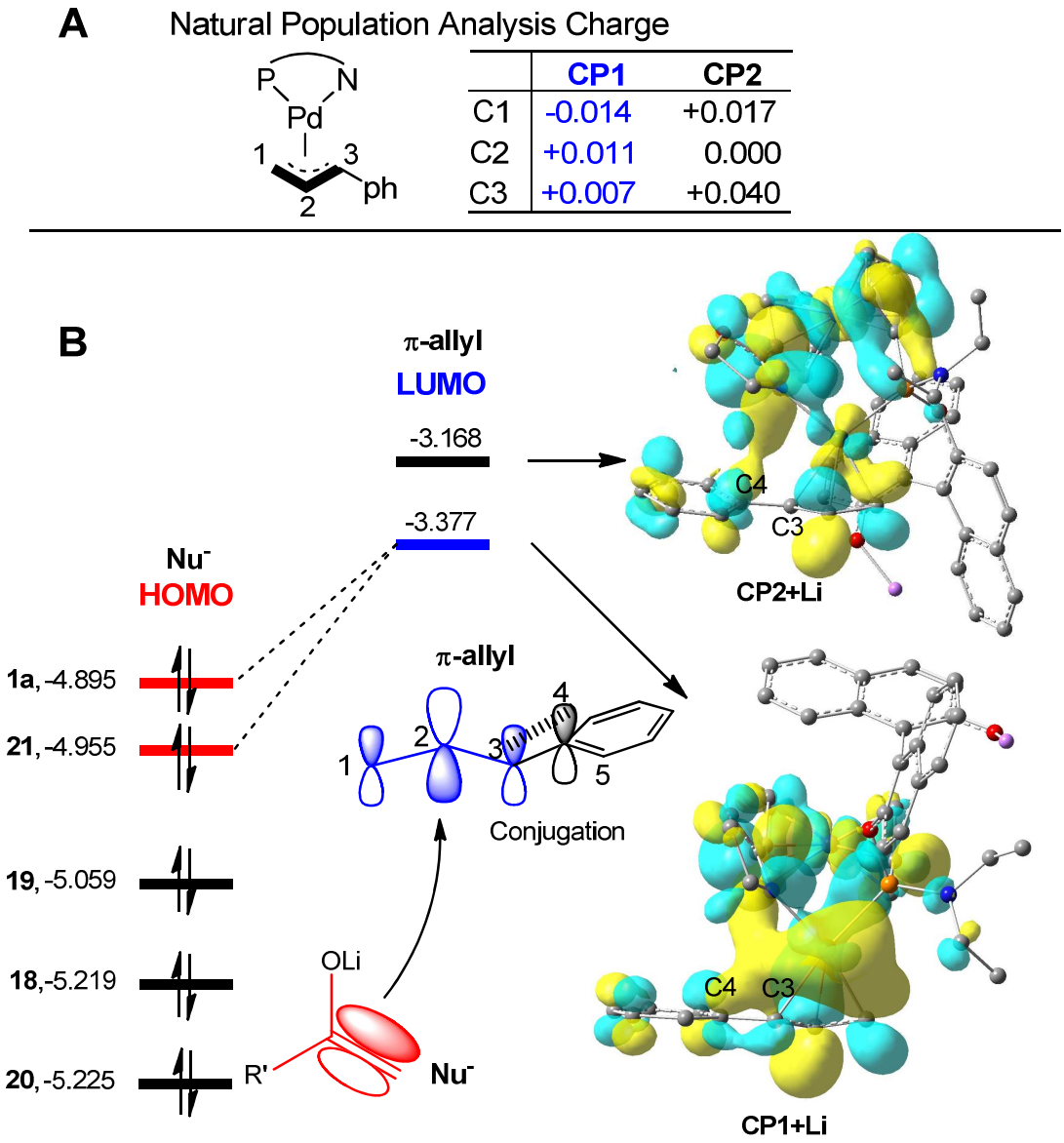
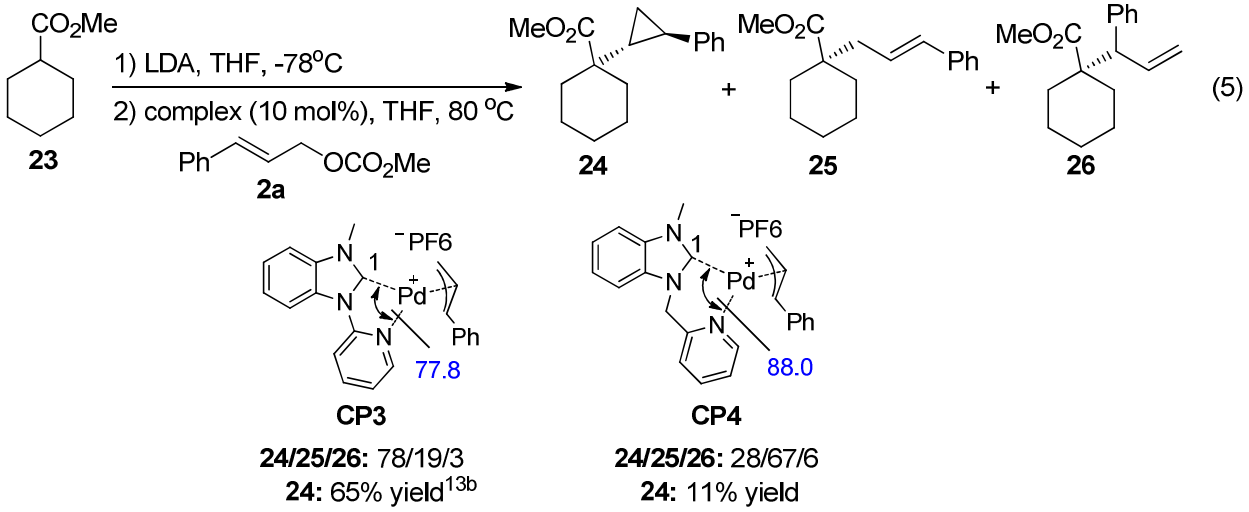


Figure 6. NPA Charges and frontier orbitals of electronic structures. (**A**) Charges in Natural Population Analysis (NPA); (**B**) Frontier orbitals for HOMOs of nucleophiles and LUMOs of π-allyls (iso-value=0.02), Orbital energies are in ev.

We noted that the orbital populations of (η^3-phenylallyl)Pd-ligand partially located on ligand area (Fig. 6B), indicating that the ligand could contribute to those LUMOs, while smaller bite angle of metal with coordination atoms could stabilize **TS1** for cyclopropanation (Fig. 5, table)

and be observed in **CP1** (Fig. 2B). It seems that ligand bite angle also plays a role in the nucleophilic attack at the central carbon to form cyclopropanes.[22] When the angle of our newly designed NHC-Py/Pd/allyl catalysts, **CP3** and **CP4**, increases from 77.8° to 88.0° determined by X-ray analysis, the cyclopropanation ratio dropped from 78% to 28% in Pd-catalyzed cyclopropanation (eq 5).[13b] The data from X-ray analysis of crystal structures, including **CP1**, **CP4**, TMEDA-Pd-allyl, and controlling experimental results afford some supports for this deduction.[23] The findings regarding the relationship between bite-angle and c/a selectivity provide us some useful information on designing new catalyst system.[24]



Conclusions

In conclusion, we realized highly enantioselective cyclopropanation under Pd-catalysis in the reaction of aryl substituted allyl and polyenyl carbonates with acyclic amides. The factors controlling c/a selectivity were investigated through experiments, X-ray diffraction analysis of two palladium-ligand-allyl complexes (**CP1** and **CP2)**, as well as DFT calculations. It revealed that the reaction should be under orbital control, and the characters of both nucleophile and Pd-ally complex with ligand (active intermediate) including bond lengths and bite angles are

important. Conjugative effect between allyl subunit and the substituent on it as well as bite angle of L^1-Pd-L^2 are also important factors to influence c/a selectivity of the reaction. All these information will be great helpful in design of new catalyst and extension of new type of allyl substrate and nucleophile of the reaction.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, analysis data, Computational methods and structure details, NMR and HPLC spectra of products, cif files of complex **1** (**CP1**), complex **2** (**CP2**), complex **3** (**CP3**), complex **4** (**CP4**), and **10g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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