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Taming Chiral Quaternary Stereocenters via Remote H-Bonding Stereoinduction in Palladium-Catalyzed (3+2) Cycloadditions

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Abstract: Ring-opening transformations of donor-acceptor (D-A) cyclopropanes enable the rapid assembly of complex molecules. However, the enantioselective formation of chiral quaternary stereocenters using substrates bearing two different acceptors remains a challenge. Herein, we describe the first palladium-catalyzed highly diastereo- and enantioselective (3+2) cycloaddition of vinyl cyclopropanes bearing two different electron-withdrawing groups, a subset of D-A cyclopropanes. The key to the success of this reaction is the remote stereoinduction through hydrogen bond from chiral ligands, which thereby addressed the aforementioned challenge. A variety of chiral five-membered heterocycles were produced in good yields and with high stereoselectivity (up to 99 % yields, 99:1 er and >19:1 dr). In-depth mechanistic investigations, including control experiments and theoretical calculations, revealed the origin of the stereoselectivity and the importance of H-bonding in stereocontrol.

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Introduction

Donor-acceptor (D-A) cyclopropanes have been evolving for more than 40 years and have been established as a class of versatile reagents in synthetic chemistry.[1] Vicinal electron-donating groups and electron-withdrawing group (EWGs) offer a synergistic "push-pull" effect to activate the cyclopropane ring by polarizing the C–C bond. Moreover, these groups can provide additional handles for catalytic asymmetric transformations of D-A cyclopropanes, which has led to the emergence of many efficient asymmetric catalytic strategies and systems over the last decade (Figure 1a).[2–5] Typically, two identical acceptors have been used in these systems to date. Therefore, despite the remarkable advances in catalytic asymmetric transformations, the formation of chiral quaternary stereocenters[6] remains a challenge when using two different acceptors in D-A cyclopropanes.

Since the pioneering study by Tsuji,[7] activated vinyl cyclopropanes (VCPs), a subset of D-A cyclopropanes, have been widely used D-A in Pd-catalyzed cycloadditions.[8,9] However, only low to moderate diastereoselectivity has

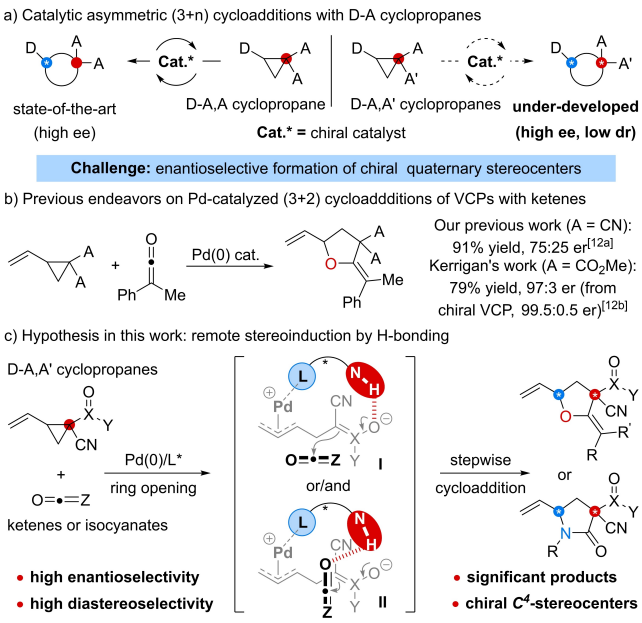


Figure 1. Catalytic asymmetric cycloadditions with D-A cyclopropanes: a) Existing strategy, b) related previous research and c) Pd-catalyzed asymmetric (3+2) cycloadditions with D-A cyclopropanes (this study).

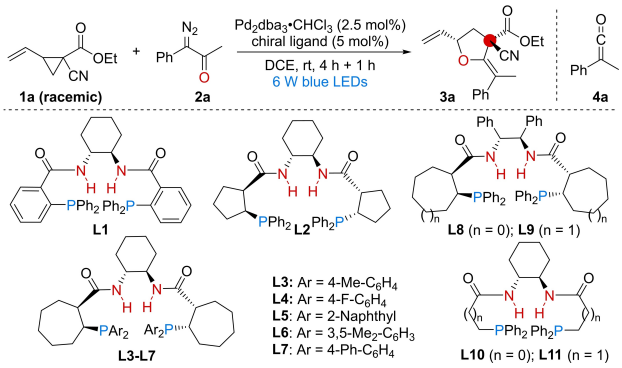
been achieved for VCPs bearing two different EWGs.[10] This was attributed to the chiral environment of the ligand being rather far from the anionic site, thus limiting the scope of successful enantioinduction during the intermolecular nucleophilic addition to the electrophiles. Aiming to address this long standing problem, *we hypothesized that the introduction of H-bonding interactions during asymmetric cycloaddition would help to induce stereoselectivity.*[11] With the Pd-catalyzed (3+2) cycloaddition of VCPs with ketenes as the platform reaction, which was firstlyl disclosed by our group[12a] and Kerrigan's group[12b] independently in 2019 (Figure 1b), we believed that the H-bonding interaction would control the spatial orientation of the anion unit of the π-allyl-Pd intermediate (Mode **I**; Figure 1c) and/or activate and direct the ketenes, during the intermolecular addition step (Mode **II**; Figure 1c). If successful, this would be the first example of the simultaneous stereo-handling of donor and acceptor units in D-A cyclopropane chemistry; as a result, highly enantiselective (3+2) cycloadditions of VCPs with ketenes, as well as their isocyanate analogs, would be realized. Based on this hypothesis and our continued interests in Pd-catalyzed asymmetric cycloadditions,[13,14] in this study, we used a remote H-bonding stereoinduction strategy to perform the first Pd-catalyzed highly diastereo- and enantioselective (3+2) cycloadditions of VCPs bearing a vinyl donor and two different acceptors with ketenes or isocyanates. A wide range of significant chiral tetrahydrofurans and pyrrolidinones[15] bearing chiral quaternary stereocenters were produced efficiently with high enantio- and diastereoselectivities.

Results and Discussion

Optimization of Conditions

To prove our hypothesis, we examined the Pd-catalyzed asymmetric (3+2) cycloaddition in 1,2-dichloroethane (DCE) using model VCP **1a** (racemic, 2:1 dr) and diazo compound **2a**, a precursor to generate ketene **4a** in situ via photo-Wolff rearrangement (Table 1).[12a,13c–e] Using Trost's ligand **L1**, which contains chiral amides and phosphine units,[16a] the reaction proceeded efficiently to afford chiral tetrahydrofuran **3a** in a high yield and with high enantiose-

Table 1: Optimization of reaction conditions.[a]



Entry	L	Solvent	Yield[b]	Er[c]	Dr[b]
1	**L1**	DCE	93	97:3	5:1
2	**L1**	THF	0	ND	ND
3	**L1**	CH_3CN	12	92:8/75:25	3:1
4	**L1**	$CHCl_3$	47	97:3/89:11	2:1
5	**L2**	DCE	71	98:2	10:1
6	**L3**	DCE	67	98:2	>19:1
7	**L4**	DCE	22	98:2	>19:1
8	**L5**	DCE	0	ND	ND
9	**L6**	DCE	28	97:3	>19:1
10	**L7**	DCE	74	98:2	>19:1
11	**L8**	DCE	40	98:2	>19:1
12	**L9**	DCE	27	98:2	8:1
13[d]	**L7**	DCE	81	95:5	>19:1
14[d,e]	**L7**	DCE	88 (85)	98:2	>19:1
15[d,e]	**L10**	DCE	87	95:5	>19:1
16[d,e]	**L11**	DCE	82	95:5	7:1

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.005 mmol), the ligand (0.01 mmol), and 3 mL of the solvent at rt. 4 h +1 h: **2a** in 1.5 mL of the solvent was irradiated by 6 W blue LEDs for 4 h; then, the resulting solution was added to the pre-prepared solution of $Pd_2(dba)_3{\cdot}CHCl_3$ and chiral ligand together with **1a** in 1.5 mL of the solvent and the mixture was stirred at rt for 1 h. [b] Determined by ^{1}H NMR analysis of the reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. [c] Determined by chiral HPLC analysis. [d] 0.6 mmol of **2a** was used. [e] 5 mL of the solvent was used. rt: room temperature; dba: dibenzylideneacetone; DCE: 1,2-dichloroethane; THF: tetrahydrofuran.

lectivity, albeit with a moderate diastereoselectivity (entry 1: 93 % yield, 97:3 er, and 5:1 dr). Changing the solvent decreased the yield remarkably (entries 2–4), which could be attributed to the unfavorable disturbance to the assumed hydrogen bond. To improve the diastereoselectivity, other similar chiral ligands recently developed by Lu[16b] were evaluated (entries 5–12). Remarkably, excellent enantioselectivity and diastereoselectivity were achieved when chiral ligand **L7** bearing a chiral *trans*-cyclohexane-1,2-diamine core and a *cis*-cycloheptane unit was used (entry 10: 74 % yield, 98:2 er and >19:1 dr). Next, further reactions were conducted in which the quantity of **2a** (entry 13) was increased and the reaction mixture was diluted (entry 14), affording the desired product **3a** in 88 % yield and with 98:2 er and >19:1 dr (entry 14). For comparison, Ma's chiral ligands[16c] derived from non-chiral Ph_2P-substituted aliphatic acids were also examined (entries 15 and 16). **L10** afforded the same product **3a** in a similar yield and with >19:1 dr, albeit with a slightly lower enantioselectivity (entry 15).

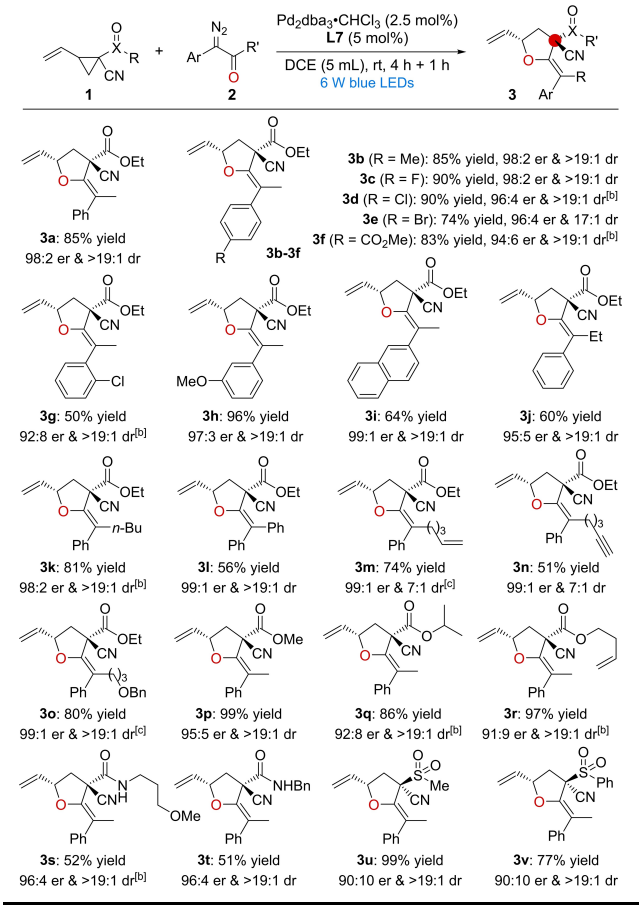
Substrate Scope

After establishing the optimal conditions, we examined the generality of the Pd-catalyzed asymmetric (3+2) cycloadditions between VCPs and diazo compounds. Various electronic characteristics and substitution patterns on the aromatic ring of substrates **2** were tolerated well (**3a–3i**: 52–96 % yields, up to 99:1 er, and >19:1 dr; Table 2). A variety of chiral tetrahydrofurans were afforded, and high yields and excellent enantio- and diastereoselectivities were obtained. The replacement of the methyl group at the ketene by ethyl, phenyl and other functionalized alkyl substituents was favorable, affording the corresponding products with excellent enantioselectivity and in moderate to good yields (**3j–3o**: 51–81 % yields, up to 99:1 er, and >19:1 dr). In some cases, chiral ligand **L10** was used instead of **L7** to achieve higher reaction efficiency and diastereoselectivity (**3d**, **3f**, **3g**, and **3k**).[17] In addition to ethyl ester, other EWGs including methyl ester (**3p**: 99 % yield, 95:5 er, and >19:1 dr), isopropyl ester (**3q**: 86 % yield, 92:8 er, and >19:1 dr) and homoallyl ester (**3r**: 97 % yield, 91:9 er, and >19:1 dr) were tolerated well in this cycloaddition, affording the desired product successfully. Moreover, VCP substrates with 3-methoxypropyl amide (**3s**: 52 % yield, 96:4 er, and >19:1 dr), benzyl amide (**3t**: 51 % yield, 96:4 er, and >19:1 dr), methyl sulfone (**3u**: 99 % yield, 90:10 er, and >19:1 dr) and phenyl sulfone (**3v**: 77 % yield, 90:10 er, and >19:1 dr) were applicable for this cycloaddition. The absolute configuration of chiral product **3t** was established as 3*R*,5*S* by single-crystal X-ray diffraction analysis and the carbon stereocenters adjacent to the sulfonyl group (product **3u** and **3v**) may be reverse from those adjacent to carbonyls.[18]

Next, we applied the remote H-bonded enantioinduction strategy to the Pd-catalyzed asymmetric (3+2) cycloaddition with isocyanates.[19] As summarized in Table 3, aryl isocyanates, regardless of the electronic and steric effects of the substituents, could participate in this reaction successfully. Structurally diverse chiral pyrrolidinones were produced in generally high yields and excellent diastereo- and enantioselectivities when using Ma's ligand **L10** (**6a–6k**: 78–99 % yields, up to 98:2 er, and >19:1 dr).[20] The use of benzyl isocyanate afforded the corresponding products with good enantio- and diastereoselectivity, albeit in a low yield, owing to the reduced reactivity. In addition, this reaction tolerated a variety of activated VCPs, including the ones bearing other esters, benzyl amide, and sulfones; corresponding pyrrolidinones **6m–6t** were afforded in 60–87 % yields and with up to 99:1 er and >19:1 dr. The absolute configuration of chiral products **6n** and **6t** were determined to be 3*R*,5*S* and 3*S*,5*S*, respectively, by single-crystal X-ray diffraction analysis.[18]

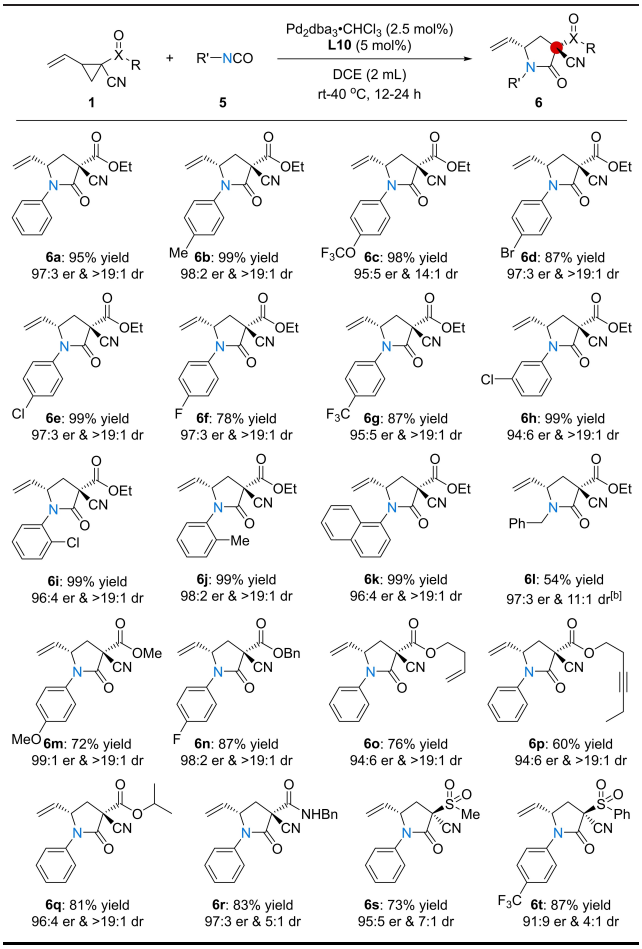
Subsequently, a set of synthetic transformations were performed to prove the utility of these cycloadditions. As shown in Figure 2a–b, a Pd-catalyzed Heck reaction and a Ru-catalyzed cross metathesis reaction are performed. The reactions proceeded smoothly, with the aryl (**8a**) and alkyl (**8b**) groups introduced successfully into the chiral heterocycles. An epoxidation of **3a** with *m*-CPBA by a selective reaction with the electron-rich enol unit facilely afforded the *spiro*-cyclic product **8c** (Figure 2c). Additionally, starting

Table 2: Scope of Pd-catalyzed asymmetric (3+2) cycloadditions with photogenerated ketenes.[a]



[a] Conditions 1: refer to entry 14 in Table 1; isolated yields. [b] **L10** was used as the ligand. [c] 4.0 equiv of α-diazoketones were used.

Table 3: Scope of the Pd-catalyzed asymmetric (3+2) cycloadditions with isocyanates.[a]



[a] Conditions 2: **1** (0.1 mmol), **5** (0.2 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0025 mmol) and **L10** (0.005 mmol) in 2 mL DCE for 12 h at rt; isolated yields. [b] Reaction was performed at 40 °C for 24 h.

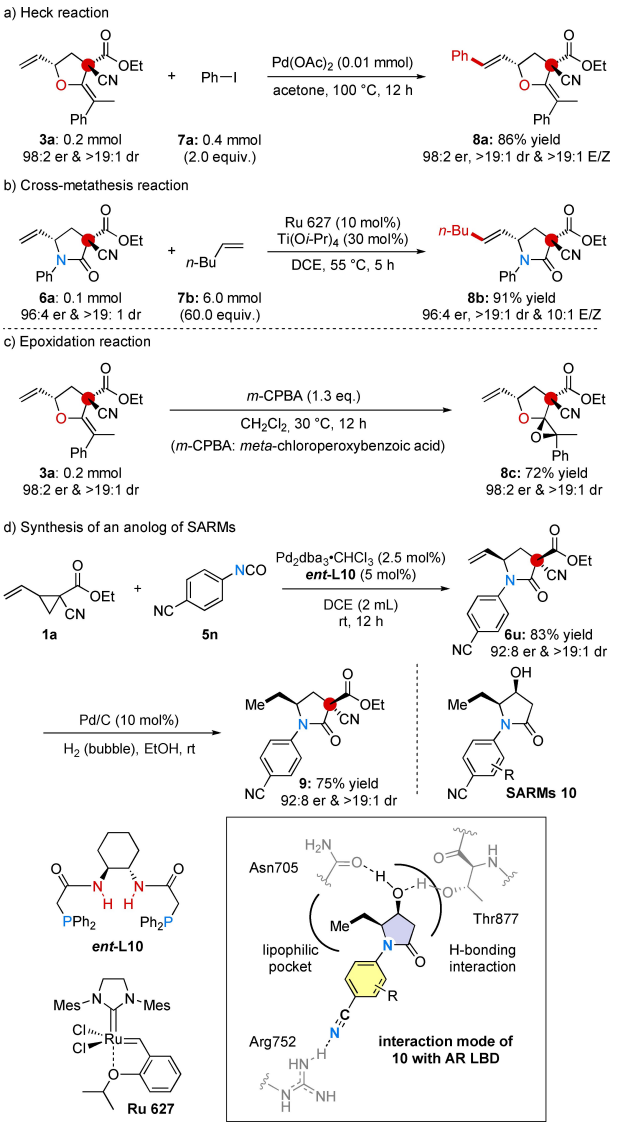


Figure 2. Synthetic transformations of chiral heterocycle products.

from VCP **1a**, isocyanate **5n** and the enantiomer of chiral ligand **L10** (***ent*-L10**), a protocol consisting of Pd-catalyzed asymmetric (3+2) cycloaddition and hydrogenation can provide an enantio-enriched pyrrolidinone **9** (Figure 2d). This molecule, bearing the same chiral skeleton and elemental H-bonding donors that interact with the androgen receptor ligand binding domain (AR LBD), is considered an analog of a type of selective androgen receptor modulators (SARMs; see Figure S2 in Supporting Information).[15c]

Determination of the Mechanism through Stereochemical Analysis

Next, we investigated the reaction mechanism and rationalized the stereochemical outcome of the Pd-catalyzed (3+2) reaction of VCPs with isocyanates as a model. First, the reaction between VCP **1a** and isocyanate **5a** with *N*-methylated chiral ligand **Me-L10** afforded remarkably low enantio- and diastereoselectivities, despite the good yield (Figure 3a). Second, the reaction between the dicyano-substituted VCP **1k** and isocyanate **5g** under the standard conditions afforded product **6v** in 58:42 er (Figure 3b). The first control experiment confirmed the importance of H-bonding from the amide unit in the chiral ligand. The results of the second experiment indicated that non-linear EWGs (i.e., esters, amides, and sulfones) are required as H-bonding acceptors for efficient stereoinduction.[21] Third, the enantio- and diastereo-purities of the recovered racemic VCP **1d** were analyzed by chiral HPLC at approximately 30% conversion, and the racemic VCP **1d** was found to have improved diastereoselectivity (Figure 3c, 3:1 dr→>19:1). This result indicates that the oxidative addition of Pd^0 to VCPs to form Pd-containing dipole intermediates is a reversible process and more rapid than the subsequent cycloaddition. Fourth, four chiral stereoisomers of VCP **1d** were subjected to the standard Pd catalysis conditions, and after stirring for 10 min, the observed mixtures of the stereoisomers were almost identical, with the exception of

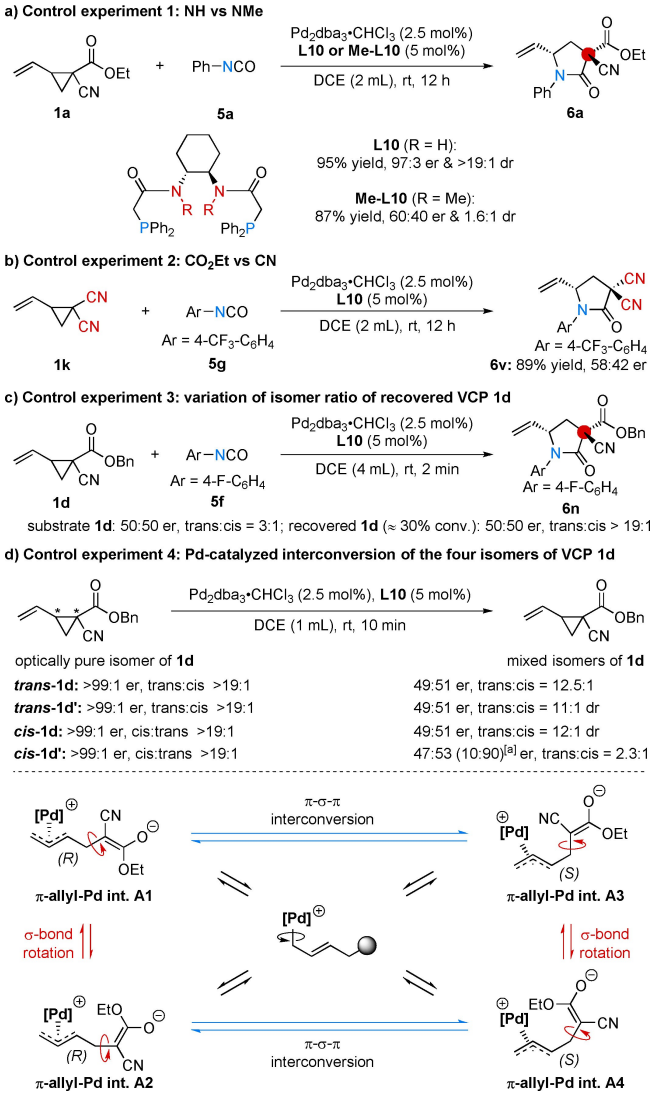


Figure 3. Mechanistical studies on the H-bonding and the stereo-convergence of stereoisomers of VCPs. a) The enantiomer ratio of the minor diastereomer was shown in parentheses.

one minor *cis*-isomer (Figure 3d).[22] The results of these experiments suggested that rapid interconversion occurred between the four stereoisomers of the starting materials under Pd catalysis through π-σ-π interconversion and single-bond rotation of the allyl-Pd intermediates.[5c] The results of the control experiments shown in Figure 3c–d explain the stereo-convergence of the four isomers during the Pd-catalyzed asymmetric (3+2) cycloaddition.

To understand the product stereoselectivity, density functional theory (DFT) calculations, starting from π-allyl-Pd intermediates and isocyanates, were performed. The obtained energy profile is shown in Figure 4a. The energies of the diastereomeric intermediates **A1**–**A4** indicated that **A3** was significantly favored over the other intermediates and that **A1** was the most unfavorable configuration (4.4 kcal mol^{-1} relative to **A3**). Analysis of these structures revealed the existence of the expected H-bonding interactions between the amide of the chiral ligand and the anion unit of the zwitterionic intermediate. The strength of H-bonding and the steric repulsion between the ester and ligand seemed to affect the stability of the four intermediates (please see the structure (.xyz) files **A1**–**A4** in the Supporting Information).[23] The binding of phenyl isocyanate generated four *pre*-TS van der Waals complexes **LS1-1**–**LS1-4** with an altered order of energy, wherein the configuration of **LS1-1** was more favorable than that of **LS1-3** (Figure 4b). This suggested that **A1** was better oriented to facilitate the binding of phenyl isocyanate than **A3**, although it did not have the most stable configuration (Figure 4b). Complex **LS1-1** was stabilized by multiple non-covalent interactions such as H-bonding and π-π interactions, especially the latter, which could not be observed in **LS1-2**–**LS1-4** (refer to the structure (.xyz) files **LS1**–**LS4** in the SI). The subsequent C–C and N–C bond formations over the transition states **TS1** and **TS2**, respectively, still favored **LS1-1** with an overall energy barrier of 18.6 kcal mol^{-1}. In particular, we focused on the rate-determining **TS1** barrier height difference to find an explanation for the product stereoselectivity. The 4.0 kcal mol^{-1} difference between **TS1-1** and **TS1-4** clearly explained the observed enantiomer ratio (97:3), and the 2.2 kcal mol^{-1} difference between **TS1-1** and **TS1-2** well explained the diastereoselectivity of the (3+2) cycloaddition. The reaction profile in Figure 4a and the results of the control experiments in Figure 3c–d suggest that the C–C bond formation step may be the rate- and stereo- determining steps. Analysis of the four calculated transition states for C–C bond formation (Figure 4b and Figure S6; also see the structure (.xyz) files **TS1-1**–**TS1-4** in the Supporting Information for other structures) suggested that the H-bonding activation of phenyl isocyanate by the amide in the chiral ligand and the suitable spatial orientation of the phenyl isocyanate and ester group of π-allyl-Pd intermediates to avoid unfavored steric repulsions may play an important role in the stereocontrol.[24] DFT calculations were employed to investigate the interactions between the phenyl isocyanate and the amide group, and the hydrogen-bonding strength was estimated to be 2.8 kcal mol^{-1}, which represents a significant contribution to the reduction of the energy barrier height. These results explain why (***3R*,*5S*)-6a**, which was generated from **P1** after the release of the [Pd^0] catalyst, became the main final product. Therefore, we concluded that the non-covalent interactions, especially the H-bonding interactions, among the chiral ligands, π-allyl-Pd intermediates, and phenyl isocyanate, governed the stereochemical outcome.

Conclusion

In summary, we developed a Pd-catalyzed asymmetric (3+2) cycloaddition of VCPs with photogenerated ketenes and isocyanates. Diverse chiral tetrahydrofuran and 2-pyrrolidinone derivatives were produced, and good yields and high diastereo- and enantioselectivities were obtained. A possible reaction mechanism and the stereocontrol modes were proposed based on experimental observations and DFT calculations. Remote enantioinduction via the direc-

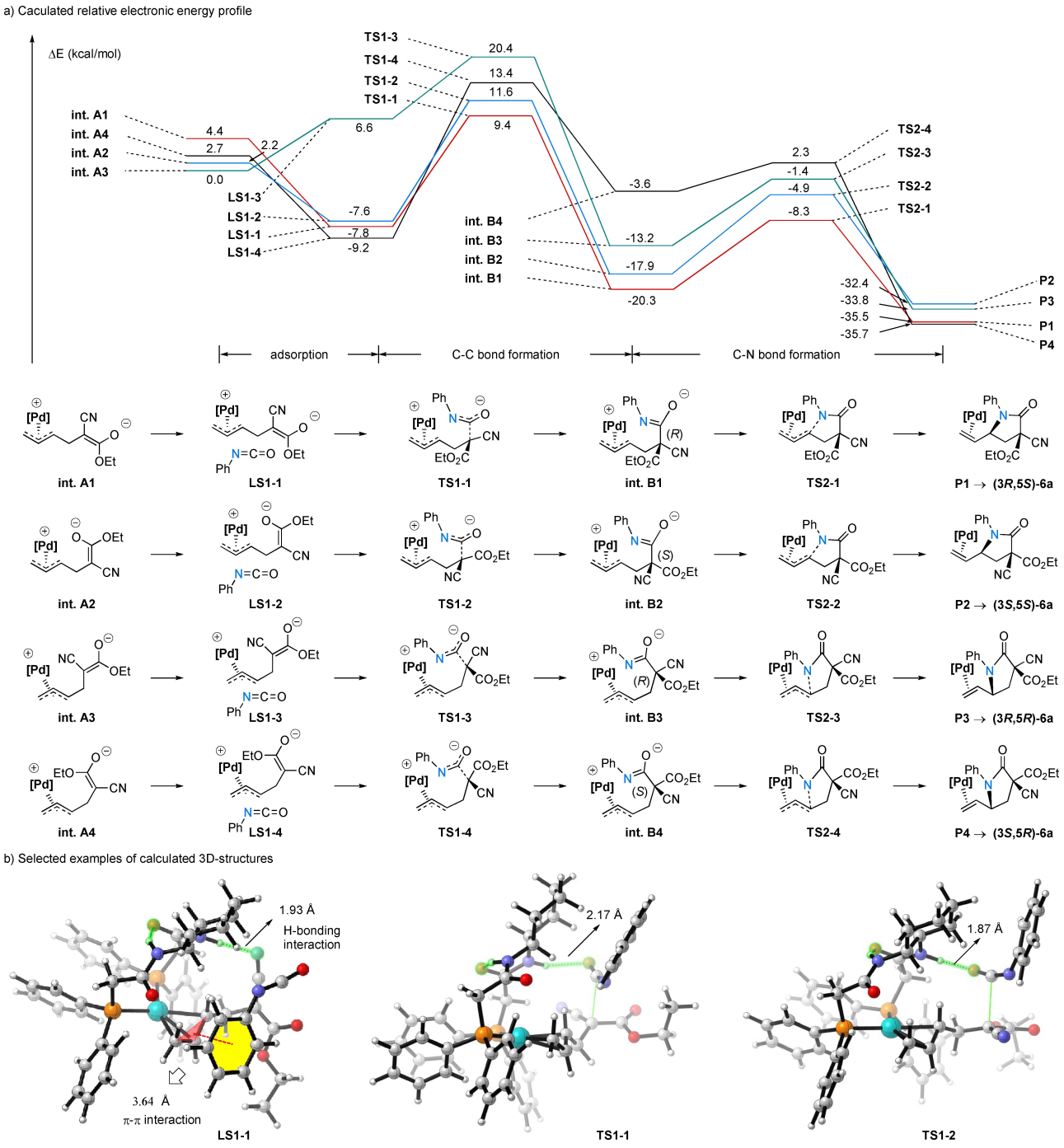


Figure 4. Computational studies to understand the origin of stereoselectivity with chiral ligand **L7**. a) Electronic energy profile of the asymmetric cycloaddition of VCP **1a** and phenyl isocyanate **5a** calculated at the XYGJ-OS[25a]/6-311 + G(d,p), lanl2dz for Pd//ωB97xD[25b]/6-31G(d), lanl2dz for Pd level of theory, using Gaussian09 package.[25c] XYGJ-OS is one of the most advanced fifth-rung DFT with satisfactory accuracy on both hydrogen bond interactions and transition metals.[25d,e] The ligand was omitted in the drawings for clarity. b) Selected key 3D-structures. The ligand is shown to highlight the importance of ligand to substrate interactions in selected structures. All the 12 structure (.xyz) files have been uploaded in SI.

tion of H-bonding from the chiral amide unit in the chiral ligands was found to be key to the enantioselective formation of the chiral quaternary stereocenters. We believe that this study will open a new avenue for the asymmetric ring-opening transformations of D-A cyclopropanes bearing two different acceptor units, thus providing new opportunities for constructing chiral quaternary stereocenters.

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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 supplementary material of this article.

Keywords: Asymmetric Cycloaddition · D-A Cyclopropane · H-Bonding · Palladium Catalysis · Quaternary Stereocenters

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[24] It is worthy of mention that the amide N–H activated isocyanate via a N–H···O hydrogen bond in **TS1-1**, **TS1-2** and **TS1-3**. Additional calculation found that if the isocyanate was flipped to form a N–H···N hydrogen bond with the amide, the barrier height of **TS1** would be increased by 5.3 kcal mol^{-1} (see the structure (.xyz) file TS1-1-N uploaded in Supporting Information).

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