JOC The Journal of Organic Chemistry

Article

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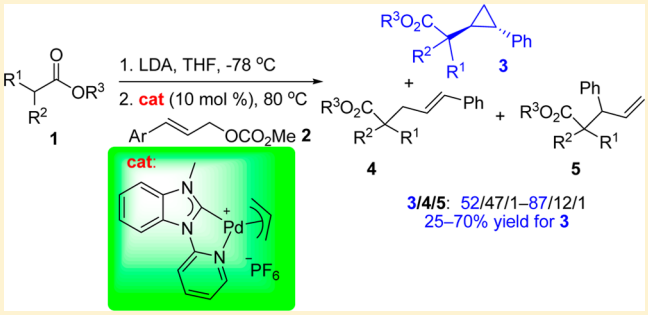
Pyridine-NHC: Effective Ligand in Pd-Catalyzed Cyclopropanation of Esters with Substituted Allyl Carbonates

Jian-Qiang Huang,[†] Chang-Hua Ding,[†] and Xue-Long Hou*[,†,‡]

[†]State Key Laboratory of Organometallic Chemistry, [‡]Shanghai−Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: By consideration of the mechanism of Pd-catalyzed cyclopropanation and allylation, NHC-pyridine compounds were adopted as the ligand in Pd-catalyzed cyclopropanation of esters and monosubstituted allylic reagents. The corresponding cyclopropanes were afforded as major products in moderate to good yields with high cyclopropane/allylation selectivity.



INTRODUCTION

Cyclopropanes exist in a wide range of biologically important compounds.[1] They are also the significant building blocks in organic synthesis.[2] Thus, the synthesis of them has attracted the attention of synthetic chemists for a long time. To date, many strategies have been developed for their synthesis.[2a] Most of the successful examples are the addition of carbenes and carbenoids to alkenes, including the Simmons−Smith reaction,[3c] the transition-metal-catalyzed cyclopropanation of alkenes with diazo compounds,[3b] the Kulinkovich−de Meijere reaction,[3a] the reaction of sulfur ylides with the activated double bonds, and the Michael addition of α-halogenated carbanions to α,β-unsaturated ketones and carboxylic acid derivatives.[4] Some other approaches to cyclopropanes have also appeared.[5] Although many cyclopropanation reactions are available, new synthetically useful methods to cyclopropane derivatives still need to be explored.

The palladium-catalyzed allylic alkylation reaction is one of the most powerful methods for C−C and C−X bond formation under transition-metal catalysis.[6] Most of studies of the reaction focus on the nucleophilic attack to the terminal carbon atoms of a π-allylpalladium intermediate. Hegedus et al. were the first to observe the formation of cyclopropane via the attack of a nucleophile to the central carbon of the π-allylpalladium complex in 1980.[7] Since then, some procedures appeared for the preparation of cyclopropanes by Pd-mediated/catalyzed reaction of allyl reagents with nucleophiles.[8−13] Hoffmann and co-workers reported the cyclopropanation reaction of a Pd-ally complex with nucleophiles in the presence of tetramethyl ethylenediamine (TMEDA) in a stoichiometric manner.[8] Musco and co-workers developed a catalytic version of the reaction with DPPF as ligand to afford allylation and cyclopropanation products in a ratio of 1.5−6.5/1.[9] The Satake group made a substantial improvement using a catalytic amount of neutral Pd-pyridinylpyrazole catalyst in the reaction of esters and allyl reagents, providing cyclopropanes in high yields with three examples.[10] Grigg and Kordes provided an intramolecular version of the reaction with nitrogen as nucleophile.[11] Great achievement was made by Hayashi and co-workers when they reported their elegant works of Pd-catalyzed intramolecular cyclopropanation with excellent stereoselectivity.[12] Recently, we reported a highly diastereo- and enantioselective Pd-catalyzed cyclopropanation of acyclic amides with substituted allyl carbonates.[13]

Though significant progress has been made, the effective catalyst system is still very limited. In addition, we have only a little knowledge regarding what factors influence the attack of a nucleophile to the central carbon of the allyl subunit of the reaction intermediate, the Pd-ligand-ally complex.[8,11,12,14] Obviously, the development of a new catalyst system for Pd-catalyzed cyclopropanation is highly demanded. From the reaction mechanism, the valence state of Pd for allylic substitution is Pd(0) to Pd(II) to Pd(0), whereas that for cyclopropanation should be Pd(0) to Pd(II) to Pd(II) to Pd(0) (Figure 1). Good yields of cyclopropanation products were

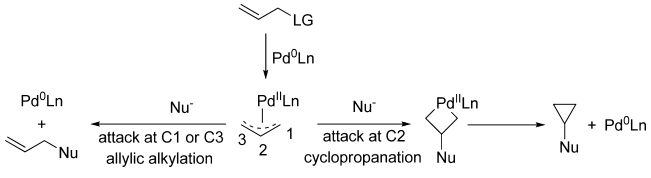
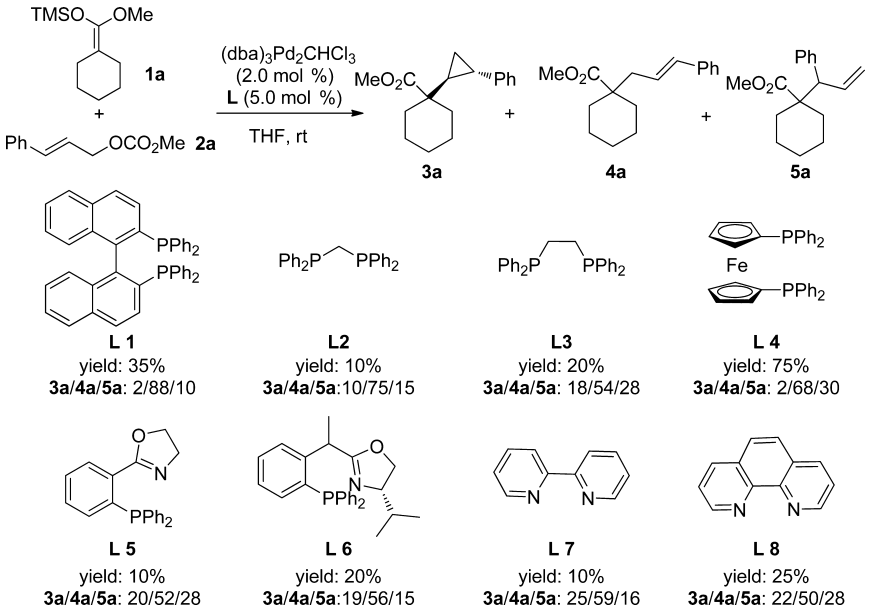


Figure 1. Pd-catalyzed allylic alkylation and cyclopropanation.

Special Issue: Mechanisms in Metal-Based Organic Chemistry

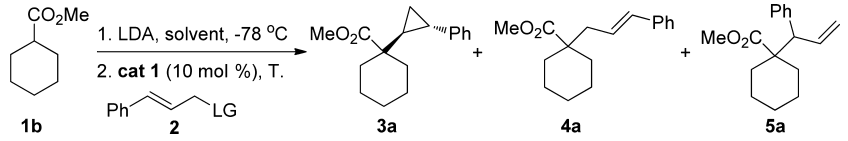
Received: August 13, 2014
Published: October 5, 2014

Scheme 1. Pd-Catalyzed Cyclopropanation with Different Kinds of Ligands[a]



[a]The cyclopropanation/allylation ratio was determined by GC, and the yield was for mixtures of products **3a**, **4a**, and **5a**.

Table 1. Optimization of Reaction Conditions for Pd-Catalyzed Cyclopropanation of Ester 1b with Allyl 2[a]



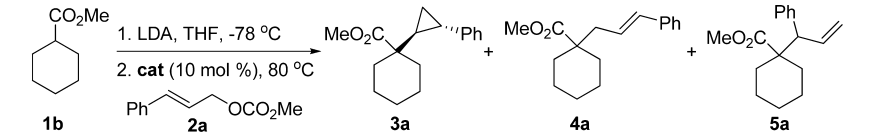
entry	base	*T*	**2**, LG	solvent	**3a**/**4a**/**5a**[b]	yield (%), **3**
1	LDA	rt	**a**, OCO_2Me	THF	53/44/3	30
2	LDA	50 °C	**a**, OCO_2Me	THF	70/25/5	40
3	LDA	65 °C	**a**, OCO_2Me	THF	74/22/4	60
4	LDA	80 °C	**a**, OCO_2Me	THF	78/19/3	65
5	LDA	95 °C	**a**, OCO_2Me	THF	65/30/5	40
6	LDA	80 °C	**b**, OAc	THF	75/20/5	40
7	LDA	80 °C	**c**, OBoc	THF	78/19/3	67
8	LDA	80 °C	**d**, $OPO(OEt)_2$	THF	1/99/-	trace
9	LDA	80 °C	**e**, Cl	THF	5/95/-	trace
10	LDA	80 °C	**a**, OCO_2Me	Et_2O	71/27/2	25
11	LDA	80 °C	**a**, OCO_2Me	toluene	82/17/1	53
12	LDA	80 °C	**a**, OCO_2Me	*o*-xylene	82/16/2	55
13	LiHMDS	80 °C	**a**, OCO_2Me	THF	75/25/1	38
14	NaHMDS	80 °C	**a**, OCO_2Me	THF	50/42/6	15
15	KHMDS	80 °C	**a**, OCO_2Me	THF	20/75/5	8
16[c]	LDA	80 °C	**a**, OCO_2Me	THF	79/18/3	63

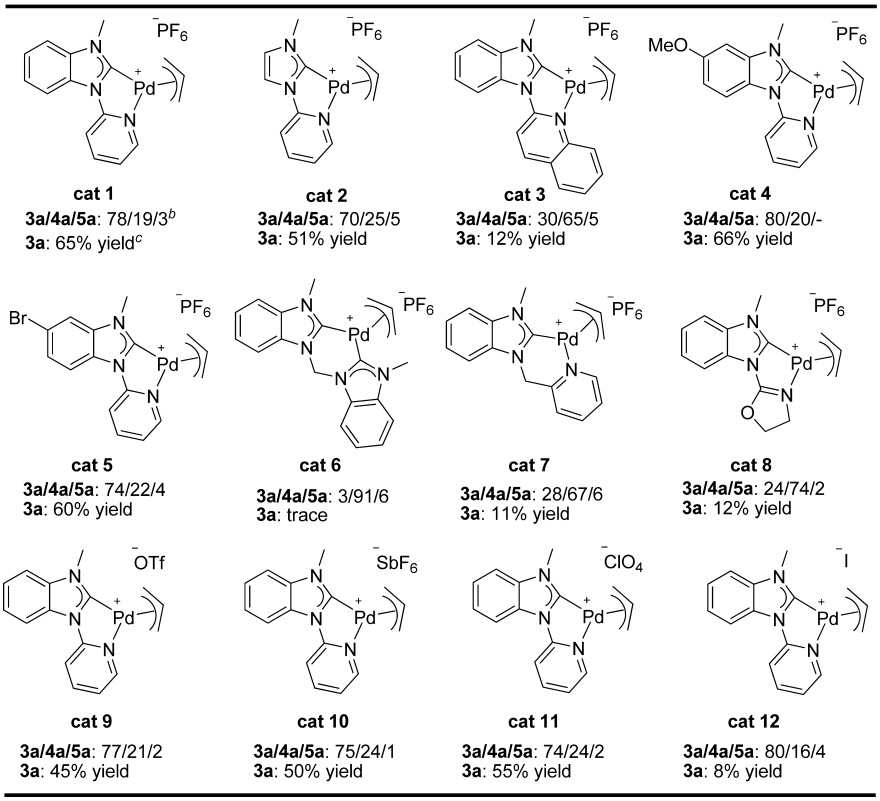
[a]Molar ratio **1b**/**2**/base/**cat 1** = 200/100/200/10. [b]Determined by GC. [c]Under balloon pressure of CO.

afforded by the Hegedus and Hoffmann groups when they used HMPA/Et_3N and TMEDA as ligand, but lower ratios of cyclopropanes were obtained when Musco and co-workers used a diphosphine ligand, though both *N* and *P* are coordination atoms with strong σ-donor character.[7−9] Bäckvall and colleagues had a similar observation that nucleophile favored terminal attack of π-allylpalladium with phosphine ligands while central carbon-attacked product was given if a nitrogen ligand was used in the Pd-catalyzed reaction of an allyl substrate and nucleophile.[14] These results indicate that the nitrogen ligands TMEDA and Et_3N, the tertiary amine, should be beneficial for the cyclopropane formation. However, they could not stabilize a Pd(0) species well, so that made a catalytic reaction impossible. It seems that the properties of coordination atoms, among the factors influencing the selectivity in Pd-catalyzed cyclopropanation reaction, should play the major role. If we have ligands with coordination atoms, which is similar to a tertiary amine but could stabilize both Pd(0) and Pd(II), we may develop a new catalytic system for cyclopropanation. Herein, we reported our results of Pd-catalyzed cyclopropanation of esters with substituted allyl carbonates using NHC-pyridine as ligand.

dx.doi.org/10.1021/jo5018712 | J. Org. Chem. 2014, 79, 12010−12017

Table 2. Impact of Catalysts on Pd-Catalyzed Cyclopropanation of Ester 1b with Allyl 2a[a]





[a]Molar ratio **1b**/**2a**/LDA/**cat** = 200/100/200/10; the ratio of **3a**/**4a**/**5a** was determined by GC.

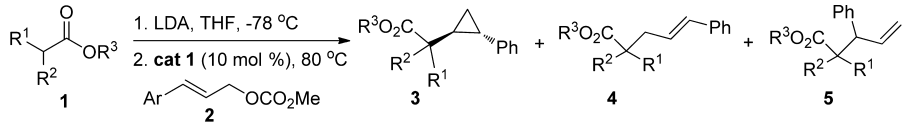
RESULTS AND DISCUSSION

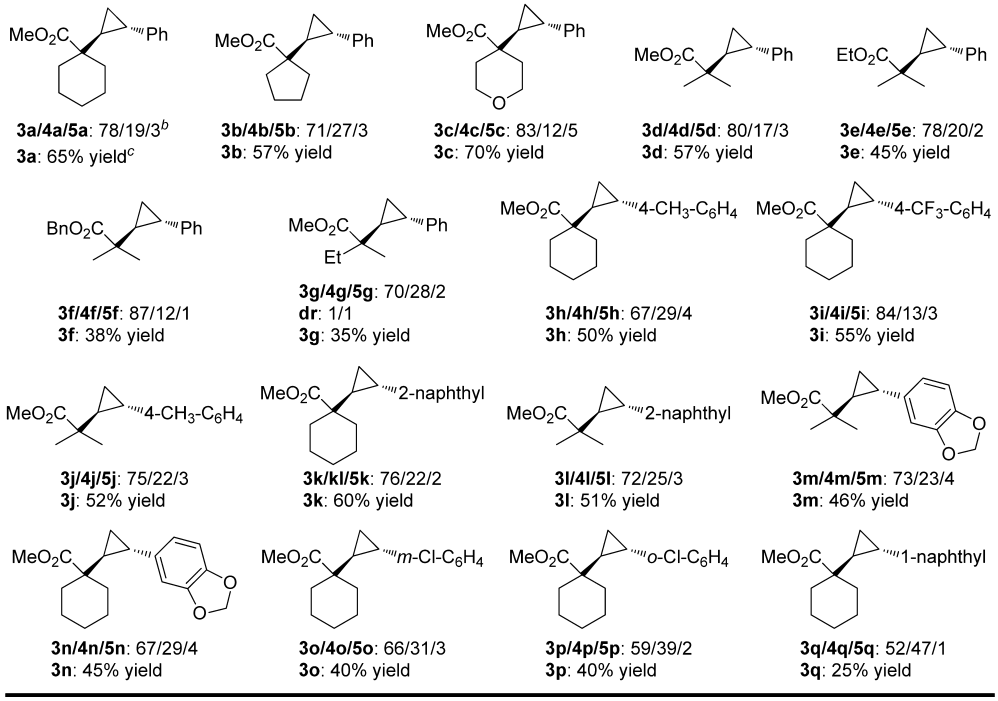
We commenced our investigation with the reaction of 1-methoxy-1-trimethylsilyloxymethylenecyclohexane (**1a**) with cinnamyl carbonate **2a** in the presence of Pd species with some different *P,P*-, *P,N*-, and *N,N*-ligands (Scheme 1). The results clearly demonstrated that the reaction could be catalyzed by Pd/diphosphine ligands; however, the ratio of cyclopropane **3a**/allylation products **4a** and **5a** (c/a ratio) was very low, which increased to about 1/4 if *P,N*-ligands were used. The c/a ratio was a little bit higher, but the yield was only 10% if bipyridine ligand **L7** was the ligand, while the similar results were given if 1,10-phenanthroline **L8** was used. As the N atom is a strong σ-donor, but a weak π-acceptor, the use of a ligand with a coordination atom having similar characteristics may provide products with even better cyclopropanation/allylation selectivity (c/a selectivity). *N*-Heterocyclic carbenes (NHCs) are stronger σ-donors with good π-acceptor character and have widely been used as ligand in transition-metal catalysis.[15] We envisioned that the ligand bearing hybrid nitrogen and NHC might be the choice in Pd-catalyzed cyclopropanation. The synergistic effect of the nitrogen ligand favoring cyclopropane formation and the NHC ligand stabilizing the Pd(0) intermediate may allow the reaction to afford the products with high c/a selectivity.

On the basis of the above consideration, catalyst **1** (**cat 1**)[16] prepared from the pyridine-NHC ligand was used to catalyze the reaction of ester **1b** with allyl reagent **2a** in tetrahydrofuran (THF) using 200 mol % of lithium diisopropylamide (LDA) as the base, affording *trans*-cyclopropane **3a**, and linear and branched allylated ketones **4a** and **5a** in 30% yield with a ratio of 53/44/3 (entry 1, Table 1).[17] These results clearly demonstrated that our strategy is effective and that the use of a ligand with NHC as coordination atom increased the c/a selectivity greatly. Encouraged by these results, further studies of the impact of various parameters on the reaction were performed (Table 1). The c/a selectivity increased when the reaction temperature was raised (entries 1−4, Table 1). The ratio of **3a**/**4a**/**5a** was 78/19/3 when the reaction was conducted at 80 °C (entry 4). Cyclopropane **3a** was obtained as a pure compound in 65% yield after removal of the allylated products **4a** and **5a** by oxidation of the reaction mixture with $RuCl_3/NIO_4$. However, a further rise of the reaction temperature had a negative effect on the c/a selectivity (entry 5 vs 4, Table 1). The leaving group (LG) of allyl reagents **2** played the role in the reaction (entries 6−9, Table 1). The use of acetyl (Ac) and *tert*-butyloxycarbonyl (Boc) as the leaving group led to a similar c/a selectivity as that of methoxycarbonyl (entries 6 and 7, Table 1). However, linear product **4a** was generated predominantely and only a trace amount of cyclopropane **3a** was observed when phosphate and chloride were the leaving group (entries 8 and 9, Table 1). The investigations on the effect of solvents showed that other solvents, such as Et_2O, toluene, and *o*-xylene, gave inferior results, and the formation of

dx.doi.org/10.1021/jo5018712 | J. Org. Chem. 2014, 79, 12010−12017

Table 3. Substrate Scope for Pd-Catalyzed Cyclopropanation of Ester 1 with Allyl 2[a]





[a]Molar ratio of **1**/**2**/LDA/**cat 1** = 200/100/200/10. The ratio of **3**/**4**/**5** was determined by GC; ; only *trans*-cyclopropane **3** was observed.

undetermined byproducts was also observed (entries 10−12, Table 1). The examination of the impact of a base on the reaction indicated that the use of LiHMDS as base led to a decrease of the yield of cyclopropane **3a** (entry 13 vs 4, Table 1), while the nucleophile preferred to attack the terminal positon of the allyl reagent when NaHMDS and KHMDS were employed as base (entries 14 and 15, Table 1). The c/a selectivity and the yield did not improve if the reaction ran under balloon pressure of CO (entry 16 vs 4, Table 1).[7,8] The addition of LiCl as an additive did not also increase the c/a selectivity and the yield of the reaction (not shown in the table).

The influence of the structure of NHC-pyridine ligands on the reaction was also examined (Table 2). It was found that both the benzimidazole skeleton and pyridine of NHC-pyridine ligands should be important for obtaining a high ratio of cyclopropanation product. The reaction using **cat 2**[18] prepared from pyridine imidazolium salt as catalyst afforded **3a** in 51% yield with the ratio of **3a**, **4a**, and **5a** equal to 70/25/5. Linear product **4a** was the major product if **cat 3** with quinoline instead of pyridine was used. The use of **cat 4** and **cat 5** with substituents on the benzimidazole skeleton provided similar results as that of **cat 1**. The **cat 6** with a bis-NHC ligand favered the nucleophilic attack at the terminal position of the allyl reagent. The **cat 7** with a methylene group between NHC and pyridine and **cat 8** with an NHC-oxazoline ligand also favored the formation of linear product **4a**. The reactions using cat **9**−**12**, the same ligand as **cat 1** but with different counterions, gave similar c/a selectivity but an inferior yield of cyclopropane **3a**. When a monodentate NHC ligand derived from 1,3-dimethyl-1*H*-benzo[*d*]imidazol-3-ium iodide was used, the ratio of **3a**/**4a**/**5a** was 27/66/7 and the yield of **3a** was 15% (not shown in Table).

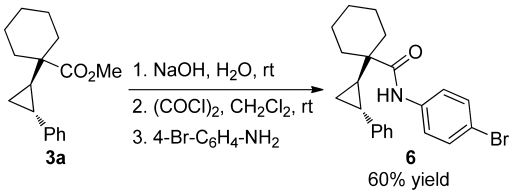
The substrate scope of this Pd-catalyzed cyclopropanation of ester was examined under the optimized reaction conditions (Table 3). The reaction proceeded smoothly in all cases, affording cyclopropanes as major products in moderate to good yields with good c/a selectivity. Various α,α'-disubstituted esters are viable nucleophiles for the cyclopropanation and their structures had a little influence on the c/a selectivity of the reaction (**3a**−**3f**). The yield of cyclopropane decreased if the steric hindrance of the R^3 group of ester **1** increased (**3d** vs **3e** and**3f**). The reaction of ethyl 2-methylbutanoate gave a good c/a selectivity, but with no diastereoselectivity (**3g**). It can be seen that the allyl reagents **2** with various substituents at the *para* or *meta* positions of the phenyl group of allyl reagents **2** (**3h**−**3o**) as well as that with two substituents on the phenyl ring were tolerated in the reaction, providing the corresponding cyclopropanes in moderate yields with good c/a selectivity (**3m**, **3n**). A substituent at the *ortho* position of the phenyl ring of allyl **2** or 1-naphthyl-substutited allyl **2** had a negative effect on the c/a selectivity of the reaction (**3p**, **3q**). The reaction of allyl methyl carbonate with benzyl isobutyrate was also carried out. GC analysis of the reaction mixture indicated that the c/a ratio was 85/15. Because the corresponding cyclopropane is inseparable with benzyl isobutyrate at TLC, the purification of the cyclopropane failed. Methyl propionate, an α-monosubstituted ester, was also used for this reaction, but no cyclopropane was observed (not given in Table 3). When a nonaryl allylic reagent such as (*E*)-but-2-en-1-yl methyl carbonate was used, no

dx.doi.org/10.1021/jo5018712 | J. Org. Chem. 2014, 79, 12010−12017

reaction occurred (not shown in Table 3). The reaction can also proceed smoothly on a 2.5 mmol scale. Treatment of 0.48 g of cinnamyl methyl carbonate (**2a**) with 0.51 g of methyl isobutyrate under the conditions of Table 3 afforded 60% yield of product **3d**, which was purified by flash chromatography on silica gel in the same c/a selectivity. In addition, a reaction of (*Z*)-methyl (3-phenylallyl) carbonate instead of **2a** with methyl isobutyrate gave the cyclopropane **3d** in 55% yield with 77/23 of c/a selectivity. These results indicated that the configuration of the carbon−carbon double bond in the allyl substrates **2** does not influence the selectivity of the reaction, which is in accordance with that the π-allylpalladium species is the reaction intermediate in the Pd-catalyzed allylic alkylation reaction.[6] It should be pointed out that, although the use of esters has been reported as nucleophile in the Pd-catalyzed cyclopropanation,[7,9,10] only the reactions of methyl cyclohexnecarboxylate and ethyl isobutyrate with allyl acetate and cinnamyl acetate appeared.[7,9,10]

The structure of cyclopropanation product **3a** was further determined by conversion of **3a** to amide **6** (Scheme 2), followed by the X-ray diffraction analysis of its single crystal (Supporting Information).

Scheme 2. Transformation of Adduct 3a to Amide 6



To get the information about the active intermediate of the cyclopropanation, **cat 13** was prepared by the reaction of ligand **9** with $[Pd(PhC_3H_4)Cl]_2$ using Ag_2O at room temperature (eq 1, Scheme 3).[19] Its structure was determined by the X-ray diffraction analysis of its single crystal (see Supporting Information). The reaction of ester **1b** with allyl **2a** in the presence of 10 mol % of **cat 13** proceeded smoothly, providing the cyclopropane **3a** in 62% yield with c/a ratio of 79/21 (eq 2, Scheme 3) while that with a stoichiometric amount of **cat 13** gave similar results (eq 3, Scheme 3). These results demonstrated that **cat 13** should be the active intermediate for this cyclopropanation.

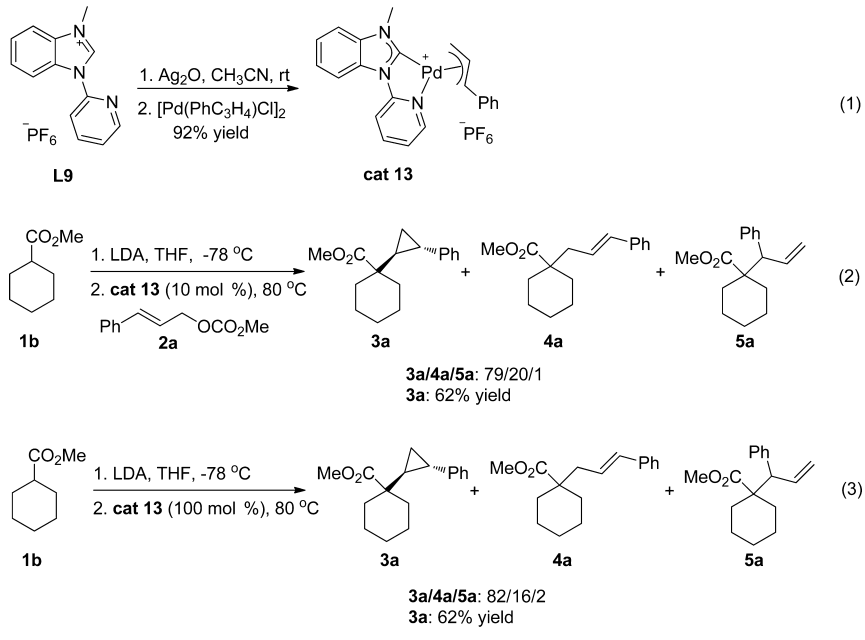
CONCLUSION

An effective catalyst system with pyridine-NHCs as ligand used in Pd-catalyzed cyclopropanation has been developed by consideration of the reaction mechanism, with which a Pd-catalyzed cyclopropanation of esters and monosubstituted allylic substrates was realized, affording cyclopropanes in good yields with high c/a selectivity. The active intermediate of the reaction was determined. The results revealed the importance of the property of coordination atoms of the catalyst in Pd-catalyzed cyclopropanation of allyl substrates with nucleophiles. The information provided by this research should be useful in the design of new ligands and catalysts of Pd-catalyzed cyclopropanation. Further investigations on the influences of coordination atoms and other factors on the reaction as well as the development of new catalyst of Pd-catalyzed cyclopropanation and the applications of the methodologies in organic synthesis are in progress.

EXPERIMENTAL SECTION

General Methods. The reactions were carried out in flame-dried glassware under a dry argon atmosphere. All solvents were purified and dried by using standard methods prior to use. Commercially available reagents were used without further purification. ^{1}H NMR spectra were recorded on an NMR instrument operated at 400 MHz. Chemical shifts are reported in ppm (parts per million) with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). ^{13}C NMR spectra were recorded on an NMR instrument operated at 100 MHz with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 77.1 ppm). Infrared spectra were recorded from thin films of pure samples. MS and HRMS were measured in EI or ESI mode, and the mass analyzer of the HRMS was TOF. Thin-layer chromatography was

Scheme 3. Experiments to Identify the Active Intermediate in the Pd-Catalyzed Cyclopropanation



dx.doi.org/10.1021/jo5018712 | J. Org. Chem. 2014, 79, 12010−12017

performed on precoated glassback plates and visualized with UV light at 254 nm. Flash column chromatography was performed on silica gel. The catalyst **cat 1** was prepared according to the reported procedure.[16]

General Experimental Procedure for Table 3. To a flame-dried Schlenk tube **A** that contained ester **1** (0.4 mmol) was added freshly prepared LDA (0.4 mmol, 0.2 M in THF) at −78 °C, and the resulting mixture was allowed to stir for 1 h. Another Schlenk tube **B** that contained **cat 1** (0.02 mmol), allyl **2** (0.2 mmol), and THF (1 mL) was allowed to stir for 10 min at room temperature. Then, the enolate solution was added to the Schlenk tube **B** and the mixture was allowed to stir at 80 °C until the allyl **2** was consumed completely (monitored by TLC, usually about 1−2 h). After the ratio of products (**3a**/**4a**/**5a**) was determined by GC, the volatiles were removed in vacuo. **Oxidative removal of allylated products:** The above residue was dissolved in EtOAc (2 mL), to which $RuCl_3$ (1.0 mg, 0.005 mmol), benzyltriethylammonium chloride (10.0 mg, 0.04 mmol) and $NaIO_4$ (214.0 mg, 1 mmol) in water (1.0 mL) were added sequentially at room temperature. The resulting solution was stirred for an additional 1 h. EtOAc (8.0 mL) was added to the reaction mixture. The organic layer was separated and washed with water. The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the organic layer was combined, dried (anhydrous Na_2SO_4), filtered, and concentrated in vacuo. Pure product **3** was obtained by preparative TLC.

***trans*-Methyl 1-(2-Phenylcyclopropyl)cyclohexanecarboxylate (3a).** Colorless liquid, 33.5 mg, 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (dt, J = 9.2, 5.2 Hz, 1H), 0.95−1.00 (m, 1H), 1.13−1.30 (m, 6H), 1.59−1.67 (m, 3H), 1.90−1.94 (m, 1H), 2.08−2.13 (m, 2H), 3.69 (s, 3H), 7.05 (m, 2H), 7.11−7.15 (m, 1H), 7.21−7.25 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.2, 18.9, 23.5 (2C), 25.7, 32.4, 32.8, 32.9, 46.8, 51.5, 125.5, 126.0, 128.2, 142.9, 176.1; MS (EI) 81 (12), 91 (29), 104 (33), 115 (20), 117 (100), 118 (16), 258 (M^+, 3); HRMS Calcd for $C_{17}H_{22}O_2$: 258.1620; Found: 258.1618; IR (film) 695, 755, 1135, 1209, 1448, 1726, 2857, 2933 cm^{-1}.

***trans*-Methyl 1-(2-Phenylcyclopropyl)cyclopentanecarboxylate (3b).** Colorless liquid, 27.8 mg, 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87−0.95 (m, 2H), 1.39−1.42 (m, 1H), 1.45−1.51 (m, 2H), 1.58−1.67 (m, 4H), 1.82−1.87 (m, 1H), 2.04−2.11 (2H), 3.68 (s, 3H), 7.06−7.09 (m, 2H), 7.13−7.16 (m, 1H), 7.22−7.27 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.9, 19.9, 24.8, 24.9, 29.3, 33.6, 33.9, 51.9, 53.9, 125.5, 126.0, 128.2, 142.9, 177.9; MS (EI) 91 (23), 104 (53), 115 (18), 117 (100), 118 (16), 244 (M^+, 6); HRMS Calcd for $C_{16}H_{20}O_2$: 244.1463; Found: 244.1466; IR (film) 696, 755, 1073, 1158, 1251, 1727, 2966 cm^{-1}.

***trans*-Methyl 4-(2-Phenylcyclopropyl)tetrahydro-2*H*-pyran-4-carboxylate (3c).** Colorless liquid, 36.4 mg, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.93 (m, 1H), 0.99−1.05 (m, 1H), 1.19−1.26 (m, 1H), 1.53−1.64 (m, 2H), 1.93−1.98 (m, 1H), 2.02−2.06 (m, 2H), 3.35−3.43 (m, 2H), 3.74 (s, 3H), 3.86−3.90 (m, 2H), 7.04−7.06 (m, 2H), 7.14−7.18 (m, 1H), 7.22−7.27 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 10.9, 18.8, 31.6, 32.4, 32.6, 44.9, 51.9, 65.6, 65.6, 125.7, 126.0, 128.3, 142.3, 175.4; MS (EI) 53 (7), 65 (8), 77 (8), 83 (11), 91 (46), 104 (43), 115 (31), 117 (100), 128 (13), 129 (15), 141 (20), 157 (13), 201 (44), 228 (4), 260 (M^+, 3); HRMS Calcd for $C_{16}H_{20}O_3$: 260.1412; Found: 260.1414; IR (film) 698, 765, 1031, 1108, 1138, 1198, 1442, 1728, 2851, 2956 cm^{-1}.

***trans*-Methyl 2-Methyl-2-(2-phenylcyclopropyl)propionate (3d).**[8c,20] Colorless liquid, 24.9 mg, 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (dt, J = 9.2, 5.2 Hz, 1H), 0.94−0.99 (m, 1H), 1.16 (s, 3H), 1.17 (s, 3H), 1.32−1.37 (m, 1H), 1.86−1.90 (m, 1H), 3.68 (s, 3H), 7.07−7.10 (m, 2H), 7.14−7.16 (m, 1H), 7.22−7.27 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.3, 19.1, 23.1, 23.4, 31.0, 41.6, 51.8, 125.5, 126.1, 128.2, 142.9, 177.9; MS (EI) 91 (19), 104 (28), 115 (24), 117 (100), 118 (14), 218 (M^+, 7); HRMS Calcd for $C_{14}H_{18}O_2$: 218.1307; Found: 218.1305; IR (film) 696, 733, 798, 1016, 1089, 1260, 1466, 1731, 2960 cm^{-1}.

***trans*-Ethyl 2-Methyl-2-(2-phenylcyclopropyl)propionate (3e).**[10b,c] Colorless liquid, 20.9 mg, 45% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (dt, J = 9.2, 5.2 Hz, 1H), 0.95−0.99 (m, 1H), 1.15 (s, 3H), 1.16 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.33−1.37 (m, 1H), 1.85−1.91 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 7.07−7.10 (m, 2H), 7.13−7.16 (m, 1H), 7.23−7.27 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.3, 14.2, 19.1, 23.3, 31.1, 41.5, 60.4, 125.5, 126.1, 128.2, 143.0, 177.3; MS (EI) 91 (14), 104 (31), 115 (16), 117 (100), 118 (11), 143 (5), 159 (9), 232 (M^+, 6); HRMS Calcd for $C_{15}H_{20}O_2$: 232.1463; Found: 232.1467; IR (film) 698, 766, 1028, 1138, 1263, 1384, 1469, 1498, 1605, 1726, 2873, 2932, 2979 cm^{-1}.

***trans*-Benzyl 2-Methyl-2-(2-phenylcyclopropyl)propionate (3f).** Colorless liquid, 22.3 mg, 38% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (dt, J = 9.2, 5.2 Hz, 1H), 0.94−0.99 (m, 1H), 1.17 (s, 3H), 1.20 (s, 3H), 1.36−1.40 (m, 1H), 1.85−1.90 (m, 1H), 5.19 (q, J = 12 Hz, 2H), 7.02−7.05 (m, 2H), 7.12−7.16 (m, 1H), 7.20−7.30 (m, 7H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.4, 19.1, 22.9, 23.5, 31.0, 41.7, 66.2, 125.5, 126.1, 127.7, 127.9, 128.2, 128.4, 136.2, 142.8, 177.1; MS (EI) 65 (13), 91 (100), 104 (26), 115 (14), 117 (41), 157 (21), 203 (30), 294 (M^+, 2); HRMS Calcd for $C_{20}H_{22}O_2$: 294.1620; Found: 294.1622; IR (film) 694, 738, 1029, 1077, 1130, 1259, 1456, 1726, 2973 cm^{-1}.

***trans*-Methyl 2-Methyl-2-(2-phenylcyclopropyl)butyrate (3g).** Colorless liquid, 16.2 mg, 35% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82−0.96 (m, 5H), 1.01−1.03 (m, 3H), 1.25−1.35 (m, 1H), 1.54−1.59 (m, 1H), 1.76−1.91 (m, 2H), 3.65−3.69 (m, 3H), 7.06−7.09 (m, 2H), 7.10−7.16 (1H), 7.20−7.27 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 9.1 (9.2), 11.1 (11.4), 17.6 (18.1), 18.8 (19.0), 30.2 (30.4), 31.9 (32.1), 45.8 (45.9), 51.5 (51.6), 125.4 (125.4), 125.9 (126.2), 128.1 (128.2), 142.9 (142.9), 177.0 (177.1); MS (EI) 59 (8), 91 (27), 104 (48), 115 (23), 117 (100), 128 (9), 173 (4), 232 (5); HRMS Calcd for $C_{15}H_{20}O_2$: 232.1463; Found: 232.1462; IR (film) 800, 1007, 1030, 1051, 1498, 1617, 1733, 2361, 2881, 2949, 2971 cm^{-1}.

***trans*-Methyl 1-(2-*p*-Tolylcyclopropyl)cyclohexanecarboxylate (3h).** Colorless liquid, 27.2 mg, 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (dt, J = 9.2, 5.2 Hz, 1H), 0.91−0.97 (m, 1H), 1.10−1.28 (m, 6H), 1.61−1.68 (m, 3H), 1.86−1.91 (m, 1H), 2.08−2.11 (m, 2H), 2.29 (s, 3H), 3.69 (s, 3H), 6.95 (d, J = 4.0 Hz, 2H), 7.05 (d, J = 4.0 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.0, 18.5, 20.9, 23.5, 23.6, 25.7, 32.2, 32.7, 32.9, 46.8, 51.5, 126.0, 128.9, 135.0, 140.0, 176.2; MS (EI) 55 (3), 77 (4), 91 (11), 105 (12), 117 (8), 118 (15), 131 (100), 132 (14), 141 (2), 272 (M^+, 6); HRMS Calcd for $C_{18}H_{24}O_2$: 272.1776; Found: 272.1781; IR (film) 808, 891, 993, 1132, 1202, 1303, 1450, 1516, 1727, 2856, 2929 cm^{-1}.

***trans*-Methyl 1-(2-(4-(Trifluoromethyl)phenyl)cyclopropyl)-cyclohexanecarboxylate (3i).** Colorless liquid, 35.9 mg, 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (dt, J = 9.2, 5.2 Hz, 1H), 1.05−1.10 (m, 1H), 1.15−1.28 (m, 6H), 1.61−1.67 (m, 3H), 1.95−1.99 (m, 1H), 2.08−2.12 (m, 2H), 3.70 (s, 3H), 7.13 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H); ^{19}F NMR (400 MHz, $CDCl_3$) δ −62.3; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.9, 18.8, 23.5, 23.5, 25.7, 32.7, 32.9, 33.2, 46.9, 51.6, 125.1 (q, J = 3.6 Hz), 125.6 (d, J = 270.5 Hz), 126.1, 127.5 (d, J = 32.4 Hz), 147.3 (d, J = 1.6 Hz), 175.9; MS (EI) 55 (17), 67 (21), 79 (24), 81 (100), 95 (30), 109 (54), 141 (28), 154 (29), 159 (20), 172 (31), 185 (64), 186 (21), 266 (23), 326 (M^+, 8); HRMS Calcd for $C_{18}H_{21}O_2F_3$: 326.1494; Found: 326.1489; IR (film) 830, 1015, 1068, 1117, 1162, 1204, 1323, 1452, 1618, 1728, 2933 cm^{-1}.

***trans*-Methyl 2-Methyl-2-(2-*p*-tolylcyclopropyl)propionate (3j).** Colorless liquid, 24.1 mg, 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (dt, J = 9.2, 5.2 Hz, 1H), 0.91−0.96 (m, 1H), 1.15 (s, 3H), 1.16 (s, 3H), 1.28−1.34 (m, 1H), 1.82−1.88 (m, 1H), 2.30 (s, 3H), 3.67 (s, 3H), 6.98 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.1, 18.7, 20.9, 23.1, 23.5, 30.8, 41.6, 51.8, 126.0, 128.9, 135.0, 139.8, 177.8; MS (EI) 91 (15), 115 (9), 118 (9), 131 (100), 132 (13), 173 (5), 232 (M^+, 7); HRMS Calcd for $C_{15}H_{20}O_2$: 232.1463; Found: 232.1460; IR (film) 624, 774, 811, 1136, 1190, 1264, 1468, 1517, 1730, 2350, 2977 cm^{-1}.

***trans*-Methyl 1-(2-(Naphthalen-2-yl)cyclopropyl)cyclohexanecarboxylate (3k).** Colorless liquid, 37.0 mg, 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (dt, J = 9.2, 5.2 Hz, 1H), 1.03−1.09 (m, 1H), 1.18−1.33 (m, 6H), 1.60−1.67 (m, 3H), 2.05−2.16 (m, 3H), 3.70 (s, 3H), 7.18 (dd, J = 8.4, 0.8 Hz, 1H), 7.37−7.44 (m, 2H), 7.48

dx.doi.org/10.1021/jo5018712 | J. Org. Chem. 2014, 79, 12010−12017

(s, 1H), 7.71−7.77 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 11.2, 19.1, 23.1, 23.5, 25.7, 32.6, 32.8, 32.9, 48.9, 51.6, 123.8, 124.9, 125.1, 126.0, 127.2, 127.5, 127.8, 131.8, 133.4, 140.5, 176.2; MS (EI) 67 (3), 79 (3), 115 (4), 128 (4), 141 (12), 152 (12), 154 (15), 165 (11), 167 (100), 178 (3), 191 (2), 249 (3), 308 (M^+,18); HRMS Calcd for $C_{21}H_{24}O_2$: 308.1776; Found: 308.1779; IR (film) 744, 814, 851, 898, 993, 1131, 1201, 1449, 1725, 2855, 2929 cm^{-1}.

***trans*-Methyl 2-Methyl-2-(2-(naphthalen-2-yl)cyclopropyl)-propionate (3l).** Colorless liquid, 27.3 mg, 51% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96−1.06 (m, 2H), 1.19 (s, 6H), 1.42−1.48 (m, 1H), 2.01−2.06 (m, 1H), 3.68 (s, 3H), 7.21 (dd, J = 8.4, 1.6 Hz, 1H), 7.36−7.44 (m, 2H), 7.52 (s, 1H), 7.71−7.77 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 11.4, 19.3, 23.2, 23.4, 31.3, 41.7, 51.8, 124.0, 124.9, 125.2, 126.0, 127.2, 127.5, 127.8, 131.9, 133.5, 140.4, 177.8; MS (EI) 115 (5), 141 (6), 152 (15), 154 (10), 165 (14), 167 (100), 178 (4), 209 (5), 268 (M^+, 19); HRMS Calcd for $C_{18}H_{20}O_2$: 268.1463; Found: 268.1461; IR (film) 650, 745, 815, 851, 969, 1136, 1191, 1265, 1469, 1600, 1728, 2975, 3053 cm^{-1}.

***trans*-Methyl 2-(2-(Benzo[*d*][1,3]dioxol-5-yl)cyclopropyl)-2-methylpropanoate (3m).** Colorless liquid, 24.1 mg, 46% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (dt, J = 9.2, 5.2 Hz, 1H), 0.87−0.94 (m, 1H), 1.15 (s, 6H), 1.23−1.27 (m, 1H), 1.80−1.84 (m, 1H), 3.68 (s, 3H), 5.90 (s, 2H), 6.57−6.60 (m, 2H), 6.68−6.71 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 10.9, 18.9, 23.2, 23.3, 30.6, 41.6, 51.8, 100.8, 106.9, 108.0, 119.4, 136.8, 145.5, 147.6, 177.9; MS (EI) 77 (10), 103 (30), 131 (100), 132 (10), 148 (9), 161 (59), 203 (6), 262 (M^+, 23); HRMS Calcd for $C_{15}H_{18}O_4$: 262.1205; Found: 262.1207; IR (film) 638, 806, 841, 935, 1037, 1136, 1234, 1255, 1437, 1491, 1727, 2884, 2976 cm^{-1}.

***trans*-Methyl 1-(2-(Benzo[*d*][1,3]dioxol-5-yl)cyclopropyl)-cyclohexanecarboxylate (3n).** Colorless liquid, 27.2 mg, 45% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (dt, J = 9.2, 5.2 Hz, 1H), 0.89−0.94 (m, 1H), 1.03−1.09 (m, 1H), 1.16−1.28 (m, 5H), 1.60−1.66 (m, 3H), 1.84−1.89 (m, 1H), 2.07−2.11 (m, 2H), 3.69 (s, 3H), 5.89 (s, 2H), 6.54−6.56 (m, 2H), 6.68 (d, J = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 10.8, 18.7, 23.1, 23.5, 25.7, 32.0, 32.8, 32.9, 46.8, 51.5, 100.7, 106.8, 108.0, 119.3, 136.9, 145.5, 147.6, 176.1; MS (EI) 77 (9), 103 (23), 131 (100), 132 (10), 135 (15), 148 (13), 161 (81), 302 (M^+, 17); HRMS Calcd for $C_{18}H_{22}O_4$: 302.1518; Found: 302.1517; IR (film) 634, 735, 936, 1037, 1132, 1217, 1438, 1490, 1724, 2855, 2930 cm^{-1}.

***trans*-Methyl 1-(2-(3-Chlorophenyl)cyclopropyl)cyclo-hexanecarboxylate (3o).** Colorless liquid, 23.4 mg, 40% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (dt, J = 9.2, 5.2 Hz, 1H), 0.98−1.04 (m, 1H), 1.11−1.31 (m, 6H), 1.60−1.66 (m, 3H), 1.88−1.91 (m, 1H), 2.08−2.12 (m, 2H), 3.70 (s, 3H), 6.91−7.18 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 11.5, 18.6, 23.5, 23.6, 25.7, 32.7, 32.8 (2C), 46.8, 51.6, 124.3, 125.6, 126.0, 129.4, 134.1, 145.2, 176.0; MS (EI) 67 (13), 79 (15), 81 (58), 95 (15), 109 (25), 115 (35), 125 (21), 138 (72), 140 (25), 151 (100), 232 (23), 292 (M^+, 13); HRMS Calcd for $C_{17}H_{21}O_2Cl$: 292.1230; Found: 292.1227; IR (film) 689, 779, 896, 1074, 1132, 1221, 1408, 1450, 1598, 1726, 2982 cm^{-1}.

***trans*-Methyl 1-(2-(2-Chlorophenyl)cyclopropyl)cyclo-hexanecarboxylate (3p).** Colorless liquid, 23.4 mg, 40% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (dt, J = 9.2, 5.2 Hz, 1H), 1.02−1.08 (m, 1H), 1.14−1.30 (m, 6H), 1.62−1.65 (m, 3H), 2.12−2.15 (m, 2H), 2.20−2.28 (m, 1H), 3.71 (s, 3H), 6.88 (dd, J = 7.6, 2.0 Hz, 1H), 7.06−7.16 (m, 2H), 7.32 (dd, J = 7.6, 1.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 10.2, 16.7, 23.5, 23.6, 25.7, 32.2, 32.6, 33.0, 46.7, 51.6, 126.0, 126.6, 126.7, 129.1, 134.8, 140.0, 176.1; MS (EI) 81 (38), 95 (13), 103 (13), 109 (13), 115 (32), 125 (23), 138 (60), 151 (100), 153 (36), 232 (21), 292 (M^+, 11); HRMS Calcd for $C_{17}H_{21}O_2Cl$: 292.1230; Found: 292.1232; IR (film) 680, 751, 1036, 1132, 1201, 1448, 1480, 1726, 2856, 2931 cm^{-1}.

***trans*-Methyl 1-(2-(Naphthalen-1-yl)cyclopropyl)cyclo-hexanecarboxylate (3q).** Colorless liquid, 15.4 mg, 25% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (dt, J = 9.2, 5.2 Hz, 1H), 1.10−1.14 (m, 1H), 1.25−1.35 (m, 6H), 1.60−1.72 (m, 3H), 2.17−2.22 (m, 1H), 2.25−2.29 (m, 1H), 2.37−2.42 (m, 1H), 3.72 (s, 3H), 7.17 (d, J = 7.2 Hz, 1H), 7.36 (m, 1H), 7.14−7.55 (m, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.2 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 9.3, 16.7, 23.6, 23.7, 25.8, 30.5, 32.5, 33.8, 46.9, 51.8, 123.3,124.3, 125.4, 125.6, 125.7, 126.6, 128.4, 133.1, 133.5, 138.4, 176.4; MS (EI) 141 (12), 152 (15), 153 (15), 154 (14), 165 (17), 167 (100), 308 (M^+, 14); HRMS Calcd for $C_{21}H_{24}O_2$: 308.1776; Found: 308.1781; IR (film) 775, 797, 1132, 1201, 1450, 1724, 2855, 2929 cm^{-1}.

Preparation of *trans*-*N*-(4-Bromophenyl)-1-[(1*S*,2*S*)-2-phenylcyclopropyl]cyclohexanecarboxamide (6). Cyclopropane **3a** (0.1 mmol, 25.8 mg) was added to a solution of NaOH (0.5 mmol, 20 mg) in water (2 mL), and the mixture was allowed to stir for 3 h. The reaction mixture was extracted by EtOAc (5 mL × 3), and the organic phase was combined and dried. After volatiles was removed in vacuo, $(COCl)_2$ (1 mL) was added and the resulting mixture was allowed to stir for 1 h at room temperature. The excess $(COCl)_2$ was removed in vacuo. The residue was dissolved in CH_2Cl_2 (3 mL), to which 4-Br-C_6H_4-NH_2 (0.1 mmol, 17.2 mg) was added, and the mixture was allowed to stir for 4 h. After volatiles were removed in vacuo, pure product **6** was obtained by preparative TLC as a white solid (23.4 mg, 60% yield), mp 160−162 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.65 (dt, J = 9.2, 5.2 Hz, 1H), 1.11 (m, 1H), 1.18−1.28 (m, 2H), 1.33−1.42 (m, 2H), 1.43−1.54 (m, 2H), 1.62−1.72 (m, 3H), 1.99−3.07 (m, 3H), 7.05−7.07 (m, 2H), 7.13−7.17 (m, 1H), 7.20−7.27 (m, 2H), 7.33−7.43 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 11.8, 19.4, 23.1, 25.7, 32.8, 33.1, 33.2, 46.6, 116.7, 121.6, 125.8, 126.0, 128.4, 131.8, 137.0, 142.3, 173.8; MS (EI) 67 (13), 91 (44), 95 (13), 115 (16), 117 (100), 118 (11), 123 (35), 397 (M^+, 6), 399 (M^+, 6); HRMS Calcd for $C_{22}H_{24}NOBr$: 397.1041; Found: 397.1039; IR (film) 693, 747, 825, 881, 1009, 1072, 1234, 1285, 1310, 1389, 1488, 1516, 1587, 1649, 2853, 2921, 3340 cm^{-1}.

Preparation of cat 13. To a solution of **L9**[16] (213.2 mg, 0.6 mmol) in CH_3CN (20 mL) was added Ag_2O (76 mg, 0.32 mmol), and the mixture was stirred at room temperature for 5 h. Then, $[Pd(PhC_3H_4)Cl]_2$ (155.4 mg, 0.3 mmol) was added and the mixture was stirred for 3 h. The mixture was filtered through short silica gel, and **cat 13** was obtained as an off-white solid by removal of volatiles under reduced pressure (330 mg, 92%), mp 260 °C (decomposed). ^1H NMR (400 MHz, DMSO-d_6): δ 3.25 (br, 1H), 3.93 (s, 3H), 4.34 (br, 1H), 5.22 (d, J = 12 Hz, 1H), 6.39−6.48 (m, 1H), 6.68 (s, 1H), 7.20 (s, 1H), 7.46−7.75 (m, 7H), 7.84 (s, 1H), 8.15−8.35 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 36.4, 49.9, 91.5, 113.2, 113.4, 113.6, 114.2, 123.0, 125.7, 126.1, 127.7, 128.7, 129.0, 129.7, 134.6, 135.9, 143.2, 146.4, 151.6, 187.1. X-ray-quality crystals was obtained by slow diffusion of Et_2O into the CH_3CN solution of **cat 13**.

Pd-Catalyzed Cyclopropanation of Cinnamyl Carbonate 2a with Methyl Isobutyrate 1d on 2.5 mmol Scale. To a flame-dried Schlenk tube **A** that contained methyl isobutyrate **1d** (510 mg, 5 mmol) was added freshly prepared LDA (5 mmol, 0.2 M in THF) at −78 °C, and the resulting mixture was allowed to stir for 1 h. Another Schlenk tube **B** that contained **cat 1** (130 mg, 0.25 mmol), cinnamyl carbonate **2a** (480 mg, 2.5 mmol), and THF (10 mL) was allowed to stir for 10 min at room temperature. Then, the enolate solution was added to the Schlenk tube **B** and the mixture was allowed to stir at 80 °C until no cinnamyl carbonate **2a** was detected by TLC. The ratio of products **3d**/**4d**/**5d** was 80/2/18 determined by GC. **Oxidative removal of allylated products:** The volatiles of the reaction mixture were removed in vacuo. The residue was dissolved in EtOAc (15 mL), to which $RuCl_3$ (10 mg, 0.05 mmol), benzyltriethylammonium chloride (100 mg, 0.4 mmol) and $NaIO_4$ (1 g, 4.7 mmol) in water (5.0 mL) were added sequentially at room temperature. The resulting solution was stirred for an additional 1 h. EtOAc (20 mL) was added to the reaction mixture. The organic layer was separated and washed with water. The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the organic layer was combined, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel with petroleum ether, followed by petroleum ether/EtOAc (100/1), afforded **3d** (327 mg, 60% yield).

dx.doi.org/10.1021/jo5018712 | J. Org. Chem. 2014, 79, 12010−12017

■ ASSOCIATED CONTENT

Supporting Information

Spectra of compounds **3a**−**3q**, **6**, and X-ray analysis data of **6** and cat **13** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xlhou@sioc.ac.cn (X.-L.H.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Major Basic Research Development Program (2011CB833300), the National Natural Science Foundation of China (21372242, 21272251, 21032007), the Chinese Academy of Sciences, the Technology Commission of Shanghai Municipality, and the Croucher Foundation of Hong Kong.

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