

Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Enol Carbonates

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Abstract: Palladium-catalyzed decarboxylative asymmetric allylic alkylation (DAAA) of allyl enol carbonates as a highly chemo-, regio-, and enantioselective process for the synthesis of ketones bearing either a quaternary or a tertiary α -stereogenic center has been investigated in detail. Chiral ligand **L4** was found to be optimal in the DAAA of a broad scope of cyclic and acyclic ketones including simple aliphatic ketones with more than one enolizable proton. The allyl moiety of the carbonates has been extended to a variety of cyclic or acyclic disubstituted allyl groups. Our mechanistic studies reveal that, similar to the direct allylation of lithium enolates, the DAAA reaction proceeds through an "outer sphere" S_N2 type of attack on the π -allylpalladium complex by the enolate. An important difference between the DAAA reaction and the direct allylation of lithium enolates is that in the DAAA reaction, the nucleophile and the electrophile were generated simultaneously. Since the π -allylpalladium cation must serve as the counterion for the enolate, the enolate probably exists as a tight-ion-pair. This largely prevents the common side reactions of enolates associated with the equilibrium between different enolates. The much milder reaction conditions as well as the much broader substrate scope also represent the advantages of the DAAA reaction over the direct allylation of preformed metal enolates.

Introduction

The formation of carbon–carbon bonds represents the most fundamental process for the synthesis of complex molecules from simple ones. Among carbon–carbon bond forming strategies, enolate alkylation has received intensive attention for decades partially because carbonyl groups, or functional groups easily derived from carbonyl groups, are frequently found in many synthetic targets and they are rich in transformations to many other structural moieties.¹ While significant advances in asymmetric alkylation of enolates have been achieved by using chiral auxiliary approaches,² most notably SAMP/RAMP,³ it is more attractive in terms of atom economy⁴ to develop catalytic enantioselective approaches to meet the environmental and economical requirements of modern chemistry. Many efforts have been made over the past three decades.^{1b,5} Upon the basis of the role of the chiral catalyst, most approaches can be classified into two categories, in one of which the catalyst interacts with the enolate to form a more nucleophilic chiral

complex and in the other, it interacts with the alkylating agent to form a more electrophilic chiral complex. In the first category, one of the most well-studied methods is phase transfer catalysis.⁶ To achieve a high degree of enantioselective control it is essential but difficult to form a well organized transition state involving the enolate, the catalyst and the alkylating agent.⁵ Thus, the enantioselectivity is often found to be very sensitive to a subtle structural change of the substrate and optimization of the reaction conditions is often required for each substrate.⁵ Another straightforward method in this category has been demonstrated by Koga et al., in which a chiral polydentate amine was used to coordinate the metal counterion of the lithium enolate to achieve enantioselectivity in a catalytic fashion, but its scope remains untested.⁷ High enantioselectivities have also been achieved in the recently emerging organocatalyst promoted asymmetric α -alkylation of aldehydes, although by a strict definition, it does not go through enolate intermediates but enamines.⁸ Besides their own limitations, such as the restriction to intramolecular reactions or the use of harsh oxidative reagents,

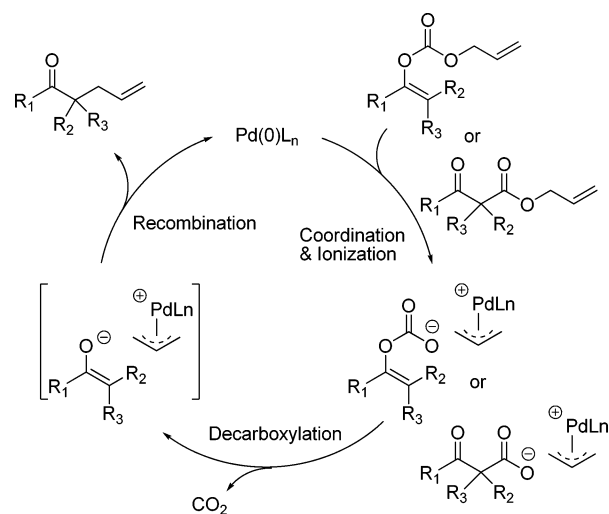
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extending these methods to ketones has not been succeeded. In the second category, a chiral Cr(salen)Cl complex catalyzed asymmetric alkylation of tin enolates with various alkylation agents was developed by Jacobsen and Doyle.⁹ The reaction was proposed to follow a S_N2 type of pathway; the halide in the catalyst served as a Lewis base to activate the tin enolate by the formation of an "ate" complex while the chiral cationic Cr moiety may assist the departure of the halide in the alkylating agent. Transition metal catalyzed enantioselective alkylation of safer and less expensive lithium enolates by activation of the electrophile, however, has almost exclusively focused on a special type of alkylating group - the allylic groups. They can be activated toward nucleophilic substitution by coordinating with a low valent metal complex to form a cationic π -allylmetal complex.^{10–12} Although good yields and high enantioselectivities have been reported, the scope of these reactions was quite narrow, at least partially due to the structural complexity of lithium enolates in solution.¹³ In some cases, a small change of the enolate structure can dramatically affect the yield or enantioselectivity of the reaction.¹⁰ For substrates with more than one enolizable proton, proton transfer between the initially formed enolate and the newly formed product may lead to problems such as loss of regioselectivity and di- or poly-alkylation.¹⁴ These problems caused by the faster equilibration between enolates compared to the alkylation were elegantly avoided in the decarboxylative alkylation of allyl enol carbonates or allyl β -ketoesters, as independently reported by Saegusa¹⁵ and Tsuji.¹⁶ The proposed mechanism includes the coordination of the Pd(0) complex to the allyl moiety, ionization of the carbonate or ester leaving group, Pd-promoted decarboxylation to form the enolate *in situ* and recombination of the enolate and the π -allylpalladium to form the allylated product and regenerate the catalyst (Scheme 1).^{15,16c} Tsuji and co-workers have demonstrated that under these extremely mild and neutral conditions, the reaction preceded with highly conserved regioselectivity.^{16c}

At the time we started to question if we could use a chiral ligand to induce a good enantioselectivity of the reaction while keeping its regiospecificity, there was no enantioselective version of this reaction reported. As our research proceeded, Burger and Tunge reported the first palladium-catalyzed asymmetric DAAA of racemic 1,3-disubstituted allylic β -ketoesters to

Scheme 1. Mechanism of Palladium-Catalyzed Decarboxylative Allylic Alkylation of Enol Carbonates and α,α -Disubstituted β -Ketoesters



generate γ,δ -unsaturated ketones with a β -tertiary chiral center.¹⁷ It should be pointed out that in this report the newly formed asymmetric center is on the electrophile; the control of the stereoselectivity on the allyl moiety is easier than that on the prochiral nucleophile since the allyl moiety is directly attached to the chiral metal complex. In addition, as proposed by Tsuji et al., the reaction probably does not go through the ionization-decarboxylation-alkylation sequence but an alternative ionization-alkylation-decarboxylation pathway; that means that the nucleophile is not an unstabilized ketone enolate but a stabilized β -keto carboxylate.^{16f} Stoltz et al.¹⁸ and our group¹⁹ independently reported the first catalytic enantioselective DAAA reactions of allyl enol carbonates to form simple ketones bearing a quaternary stereogenic α -carbon center. Since then, many expansions and applications of this robust reaction have been reported.²⁰ We were specifically interested in the family of ligands derived from 2-diphenylphosphinobenzoic or 1-naphthoic acid and chiral scalemic diamines, which had been used successfully in inducing excellent enantioselectivity in numerous palladium-catalyzed AAA reactions (Figure 1).²¹ We reported herein a full account in the optimization, scope and mechanistic studies of the decarboxylative asymmetric allylic alkylation (DAAA) of various unstabilized ketone enolates.

Results and Discussion

Preparation of Allyl Enol Carbonates. An allyl enol carbonate was typically prepared by quenching the enolate, generated from the deprotonation of a ketone, with allyl chloroformate at low temperature. The chemo- and regio-selective control of enolate formation has been well documented.^{1b} For ketones with two enolizable centers, either kinetically or thermodynamically

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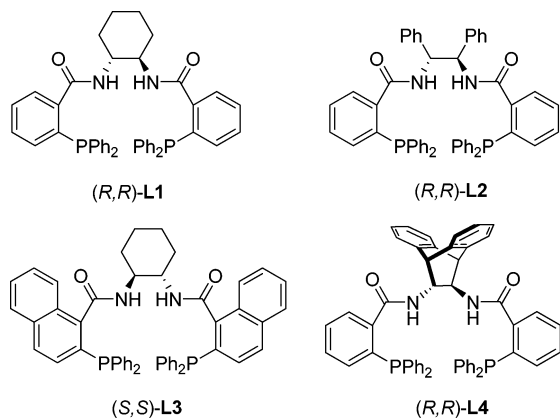
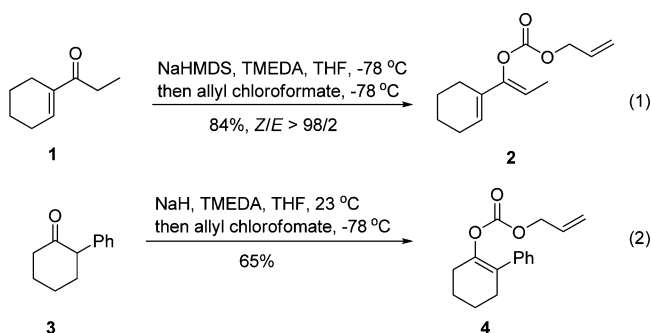


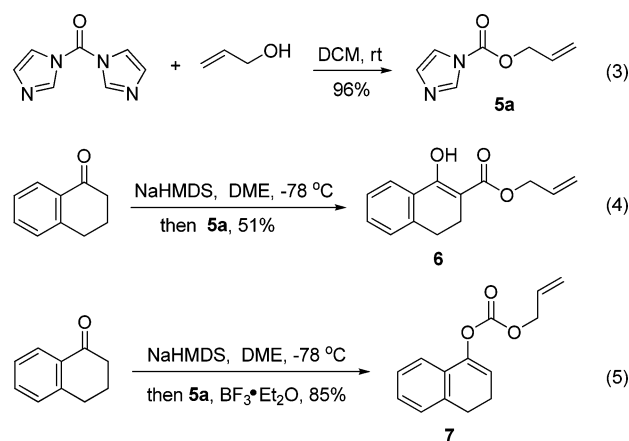
Figure 1. Ligands used in optimization.

controlled enolate formation can be obtained by adjustment of base, solvent, reaction temperature, and, most importantly, the order of addition of the base and the ketone substrate. Most allyl enol carbonates of cyclic ketones were prepared by the method described by Houminer et al.²² In a general procedure (eq 1), 5 mmol of ketone in anhydrous tetrahydrofuran (THF) was slowly added into the solution of 6 mmol of sodium hexamethyldisilazane (NaHMDS) and 6.0 mmol of *N,N,N',N'*-tetramethyl-1,2-ethylenediamine (TMEDA) in anhydrous THF at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 1 h and transferred through a cannula into a solution of 6 mmol of allyl chloroformate in anhydrous THF at $-78\text{ }^{\circ}\text{C}$ and stirred for 5 min. The product was typically purified by flash column chromatography on silica gel; and most enol carbonates are stable for years at refrigerator temperature. Alternatively, the thermodynamically more stable enolates were generated by exposure to sodium hydride and TMEDA at higher temperature, and sequentially quenched with allyl chloroformate at low temperature (eq 2).



The preparation of substituted allyl enol carbonates from the corresponding substituted allylchloroformates is, however, less convenient since substituted allylchloroformates are not commercial available and their preparation involves the use of highly toxic and strictly regulated phosgene. Besides, many chloroformates are not stable to heat and moisture; thus their purification and storage are problematic. Strongly acidic hydrogen chloride generated in the process also limits the range of compatible functional groups. Furthermore, a significant amount of diallyl carbonate is often formed lowering the yield of chloroformate, which is a disadvantage especially for precious allylic alcohols. On the other hand, allyl 1*H*-imidazole-1-

carboxylates are easily prepared in high yields from the corresponding alcohol and carbonyldiimidazole (CDI) under mild conditions (eq 3). They can be purified by flash column chromatography and most are stable for months when refrigerated. Compared with chloroformates, imidazolides are relatively “softer” electrophiles, and thus, the reaction of sodium enolates with **5** gave exclusively the C-acylated product **6**,²³ even in a coordinating solvent DME, which presumably can stabilize the charge-separated ion-pairs, thus favoring the formation of the O-acylated product (eq 4).²⁴ However, by coordinating the more basic nitrogen on the imidazole with an azaphilic Lewis acid, such as BF_3 , to increase the polarity of the carbonyl group as well as to facilitate the leaving of the imidazole group, we were able to tune the complex to a “harder” electrophile, which favored the O-acylation and enol carbonate **7** was obtained exclusively (eq 5).²⁵ As listed in Table 1, a variety of substituted allyl enol carbonates were prepared in this manner in good to excellent yields.



Besides intrinsic electronic and steric effects, the double bond geometry of an acyclic ketone enolate is also controlled by the choice of base, solvent and reaction temperature, etc.^{1b,26} Normally the preformed enolate is geometrically stable at low temperature if there is no external proton source to allow the equilibration between different enolate structures; and it can be rapidly trapped by allyl chloroformate at low temperature. As an example, deprotonation of cyclohexyl ethyl ketone by $(\text{PhMe}_2\text{Si})_2\text{NLi}$ in THF at $-78\text{ }^{\circ}\text{C}$ followed by quenching the produced lithium enolate with allylchloroformate gave *Z*-**15** in 56% yield and greater than 49:1 *Z/E* selectivity (by ^1H NMR), with the formation of a small portion of β -ketoester (Table 2, entry 1). The double bond configuration was assigned by the difference between the chemical shifts of the vinyl proton on

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Table 1. Preparation of Various Substituted Allyl Enol Carbonates

entry	n	R	product	yield
1	1		8	92%
2	1		9	99%
3	1		10	76%
4	1		11	94%
5	1		12	89%
6	1		13	96%
7 ^a	0		14	88%

^a KO^tBu was used as base.

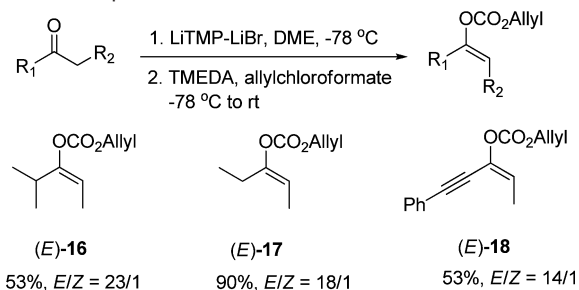
the trisubstituted enol carbonate. As proposed by Pascual et al., the proton *trans* to the carbonate substitution (in the *Z*-isomer) has a lower chemical shift ($\delta = 5.06$) than the one *cis* to the carbonate (in the *E*-isomer, $\delta = 5.17$).²⁷ In the presence of lithium diisopropylamide (LDA)/TMEDA as base, the ratio of *E*-**15** to *Z*-**15** increased to 1:1.6 (entry 2). Switching from LDA to lithium 2,2,6,6-tetramethylpiperidinide-LiBr (LiTMP-LiBr),²⁸ the *E*-**15** was obtained as the major isomer with a 3:1 *E/Z* ratio (entry 3). Several *E*-enol carbonates were prepared in this manner in good yields and high *E/Z* selectivity (Scheme 2).

Palladium-Catalyzed DAAA of Allyl Enol Carbonates to Generate Ketones Possessing an α -Quaternary Center. Using 2-methylcyclohexanone as a model we systematically investigated the DAAA reaction of its allyl enol carbonate **19** by screening chiral ligands, solvents, reaction temperature and substrate concentration. Some results are summarized in Table 3. Among the four chiral ligands listed in Figure 1, **L4** gave the best ee and yield (entry 1–4). Solvent had a small effect on the ee of the reaction when **L4** was used; and the highest ee (85%) was obtained in toluene (entry 4–8). The ee was slightly increased to 87% (entry 9) when the reaction temperature decreased from 23 to 4 °C, but it dropped to 83% at –10 °C (entry 10). The concentration of the substrate did not have a significant effect on the ee and yield of the product (entry 11 and 12). The reaction performed in the presence of 2 mol% Pd gave essentially the same results as that catalyzed by 5 mol% Pd (entry 13).

The asymmetric synthesis of 2-allyl-2-methylcyclohexan-1-one through palladium-catalyzed DAAA reaction of enol carbonate **19** selectively demonstrated the advantage of this method: extremely mild reaction conditions, exclusive regioselectivity, high catalyst efficiency and good enantioselectivity. Compared with our previous results carried out using preformed

Table 2. Control of Double Bond Geometry by the Base in the Formation of Enol Carbonate

entry	base	yield	<i>Z/E</i>
1	(PhMe ₂ Si) ₂ NLi	56%	>49/1
2	LDA, TMEDA	91%	1.6/1
3	LiTMP-LiBr-TMEDA	87%	1/3

Scheme 2. Preparation of *E*-Enol Carbonates

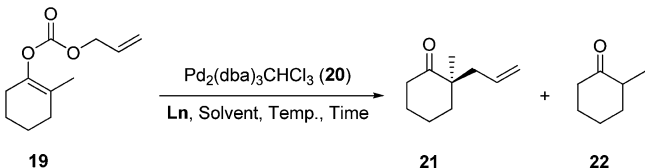
lithium or tin enolates,¹⁰ products obtained through the DAAA of enol carbonates under the above optimized conditions (2.5 mol% **20**, 5.5 mol% (*R,R*)-**L4**, toluene, 23 °C) have much higher enantioselectivity in general (Table 4). For instance, only a poor 6% ee was obtained in the allylation of the preformed tin enolate of 2-methylbenzosuberone. By the DAAA method, however, the ee of **26** was dramatically improved to 91% (entry 2). More interestingly, *R*-**24** was the major enantiomer (88% ee) in the allylation of the preformed lithium or tin enolate of 2-methyltetralone catalyzed by (*S,S*)-**L1**, while the same enantiomer was also found to be the major one in the DAAA reaction of the enol carbonate **23** catalyzed, however, by the (*R,R*)-ligand (entry 1). This means that completely opposite enantioselectivities were obtained by these two approaches. A similar observation was also found in the allylation of 2-methylindanone (entry 3). However, this phenomenon was not observed in the allylation of some other six-membered cyclic ketones, that is, the same enantiomers of **30** and **32** were obtained by both approaches (entry 4 and entry 5). While the chiral scaffold differed in the DAAA (ie **L4**) vs the standard enolate process (ie **L1**), we have shown that the sense of asymmetric induction in each series is independent of the scaffold. The results are given for the best selectivities observed in each case.

One obvious difference between these two methods is that the DAAA reactions of enol carbonates are under neutral conditions and the AAA reactions of preformed lithium or tin enolates are under strong basic conditions. Since there are acidic amide protons in these ligands, under strong basic conditions the ligand must be deprotonated. Therefore, it might be the deprotonation of the ligand that caused the switch of enantioselectivity observed in some cases. To test this hypothesis, we pretreated the Pd/**L4** catalyst with LDA to fully deprotonate the catalyst before it was subjected to the solution of **23** (eq 6). The reaction did not go to completion after 10 h, and the product **24** was obtained in only 31% yield, compared with the 88% yield in 5 min when the neutral catalyst was used. However, almost the same enantioselectivity was obtained with or without deprotonation of the ligand (eq 6). Therefore, it is not likely

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Table 3. Selected Optimization Studies



entry	ligand	solvent	temp	conc.	ee ^b	yield ^c of 21	yield ^c of 22
1	(<i>R,R</i>)-L1	Toluene	23 °C	0.1 M	31%	73%	0
2	(<i>R,R</i>)-L2	Toluene	23 °C	0.1 M	61%	73%	2%
3	(<i>R,R</i>)-L3	Toluene	23 °C	0.1 M	60%	85%	1%
4	(<i>R,R</i>)-L4	Toluene	23 °C	0.1 M	85%	88%	0
5	(<i>R,R</i>)-L4	CH ₂ Cl ₂	23 °C	0.1 M	84%	64%	26%
6	(<i>R,R</i>)-L4	1,4-Dioxane	23 °C	0.1 M	80%	99%	0
7	(<i>R,R</i>)-L4	DME	23 °C	0.1 M	84%	87%	7%
8	(<i>R,R</i>)-L4	THF	23 °C	0.1 M	81%	85%	1%
9	(<i>R,R</i>)-L4	Toluene	4 °C	0.1 M	87%	91%	2%
10	(<i>R,R</i>)-L4	Toluene	-10 °C	0.1 M	83%	84%	6%
11	(<i>R,R</i>)-L4	Toluene	4 °C	0.3 M	85%	94%	4%
12	(<i>R,R</i>)-L4	Toluene	4 °C	0.025 M	87%	92%	0%
13 ^d	(<i>R,R</i>)-L4	Toluene	4 °C	0.3 M	85%	88%	5%

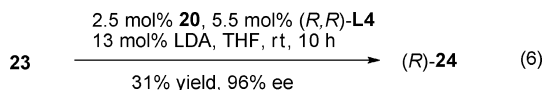
^a Unless otherwise indicated, all reactions were performed on a 0.3 mmol scale at 23 °C employing 2.5 mol% **20** and 5.5 mol% ligand. ^b Ee values were determined by chiral GC. ^c Yields were determined by quantitative GC analysis using decane as internal reference. ^d **20** (1.0 mol%) and **L4** (5 mol%) were used.

Table 4. Reaction of Various Allyl Enol Carbonates^a

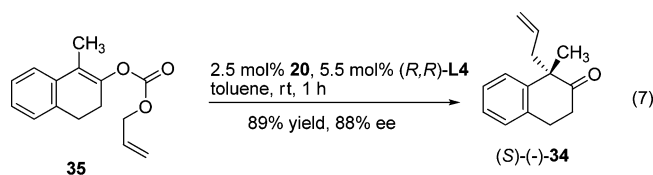
entry	substrate	product	yield ^b ee ^c	Lit. ^d yield, ee
1			88% 99.7% ee <i>R</i> -(+) ^e	99% 88% ee <i>R</i> -(+)
2			94% 91% ee ^f (-)	90% 6% ee (+)
3			98% 76% ee (+)	79% 38% ee (+)
4			64% 82% ee (+)	59% 45% ee (-)
5			99% 95% ee (+)	98% 82% ee (-)

^a All reactions were performed on a 0.3 mmol scale at 0.1 M in toluene at 23 °C for 20 h using 2.5 mol% **20** and 5.5 mol% ligand (*R,R*)-L4. ^b Isolated yields. ^c Ee values were determined by HPLC on a chiral stationary phase. ^d Conditions used were 2.5 mol% [(η^3 -C₃H₅)PdCl]₂, 5.0 mol% (*S,S*)-L1, 2.0 equiv LDA, 1.0 equiv Me₃SnCl, DME, r.t.¹⁰ ^e Absolute configuration and the sign of the optical rotation ([α]_D) of the product.^{9a-f} Ee was determined by GC on a chiral stationary phase.

that the deprotonation of the ligand is the reason causing the observed opposite enantioselectivity in Table 4, entries 1 and 3.



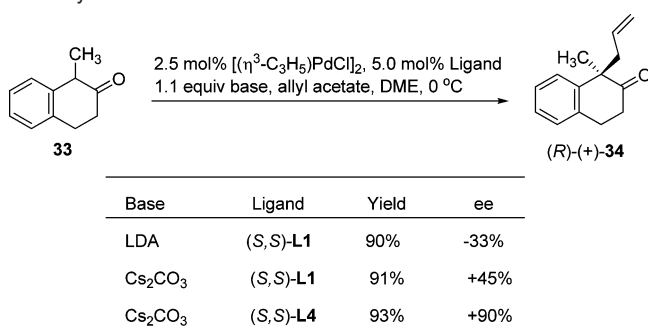
Similarly, our previous studies revealed that palladium-catalyzed AAA of the preformed enolate of 1-methyl-2-tetralone (**33**) was very sensitive to the choice of base. Actually, a completely opposite enantioselectivity was obtained by switching the base from LDA to cesium carbonate (Scheme 3).²⁹ Presumably, the palladium enolate generated *in situ* from the decarboxylation of the enol carbonate should be more like the intermediate in the reaction of less covalently bonded cesium enolate than that in the reaction of more covalently bonded lithium enolate. Indeed, the DAAA reaction of the allyl enol carbonate of 1-methyl-2-tetralone (**35**) catalyzed by Pd-L4 complex (eq 7) gave the same sense of chirality and nearly the same enantioselectivity as the AAA of the cesium enolate.



The observation that opposite enantioselectivity was obtained in the allylation of the lithium enolate of 2-methyl-1-tetralone and the DAAA reaction of its enol carbonate can be probably explained by the structural difference of the nucleophiles. As shown by the cartoons³⁰ in Figure 2, the “naked” enolate approaches the π -allylpalladium-L4 complex by its *Si* face (**A**), to avoid the disfavored steric interaction between the “wall” of the ligand and the phenyl ring of the substrate (**B**). On the other hand, we have disclosed that two equivalents of LDA were necessary for good enantioselectivity in the AAA of lithium enolate.¹⁰ It possibly implies the dimer of one lithium enolate and one LDA is the nucleophile. The aggregation makes the O terminal very bulky so that it prefers to be located at the flap side of the catalyst and leaves its *Re* face exposed to the electrophile (**C**). The fact that enantioselectivity of the allylation

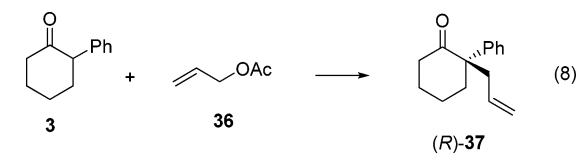
(29) Trost, B. M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3492.

(30) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.

Scheme 3. Counteraction Effect in Palladium-Catalyzed AAA of 1-Methyl-2-tetralone²⁹

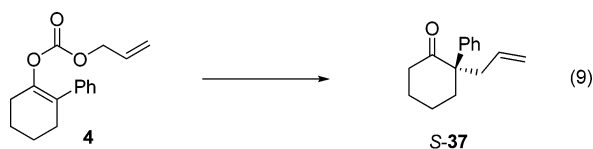
of preformed enolates is very sensitive to structural change of the enolate may also be explained by the complexity of the lithium enolate in solution, which normally exists as a mixture of monomer, dimer and oligomers and the equilibria among them may change with the variation of substrate structure.³¹

However, it is perhaps too simple to say that the DAAA of an enol carbonate is equivalent to the AAA reaction of a charge-separated enolate. For instance, the optimized conditions for the AAA of 2-phenylcyclohexan-1-one (**3**) involved the use of substoichiometric amount of NaHMDS as base and **L3** as ligand in a coordinating solvent 1,2-dimethoxyethane (DME, eq 8).²⁹ The DAAA reaction of **4** in the presence of the same catalyst, however, gave a nearly racemic product (eq 9). Switching from **L3** to **L4** dramatically improved the ee of **37** to over 90% (eq 9).



2.5 mol% $[\eta^3\text{-C}_3\text{H}_5\text{PdCl}]_2$, 5 mol% (S,S)-L3
0.9 equiv NaHMDS, DME, -78 to 23 °C

90%, 88% ee



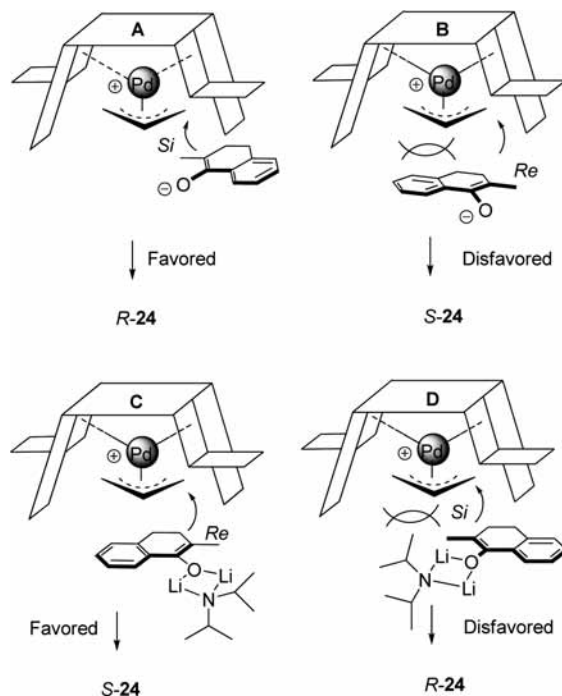
2.5 mol% $\text{Pd}_2\text{dba}_3\text{CHCl}_3$
5.5 mol% (R,R)-L3, dioxane, 23 °C

94%, 4% ee

2.5 mol% $\text{Pd}_2\text{dba}_3\text{CHCl}_3$
5.5 mol% (R,R)-L4, toluene, -78 to 23 °C

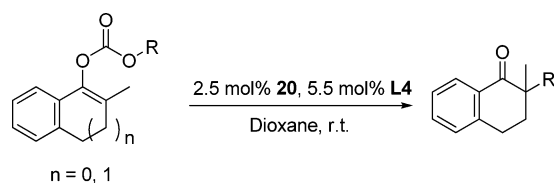
98%, 90.5% ee

Palladium-Catalyzed DAAA of Substituted Allyl Enol Carbonates. The palladium-catalyzed AAA of preformed lithium or tin enolates of ketones has been investigated in our previous work.^{10b} In general, the yields and enantioselectivities were quite sensitive to the substitution changes on the allyl moiety. As a comparison, a variety of 1,1- or 1,2-disubstituted allyl enol carbonates of 2-methyl-1-tetralone were subjected to the optimized conditions (Table 5). The reaction of 2'-methallyl enol carbonate **8** went to completion within 4 h at room temperature to produce the desired product **38** in 89% yield and over 99% ee (Table 5, entry 1), similar to the results of the DAAA of the unsubstituted allyl enol carbonate **23** (Table 3, entry 1), but

**Figure 2.** Cartoon models for the alkylation of charge separated palladium enolate.

much better than the 47% ee obtained by the AAA of the preformed tin enolate. In another example, the reaction of cinnamyl enol carbonate **10** gave cleanly the linear product **39** quantitatively with excellent ee (92.5%), while the yield from the preformed enolate was only 11% (entry 2). The reaction of *cis*-crotyl enol carbonate **12** gave a 4:1 mixture of the linear product **40** and the branched product **41** (entry 3). The *E* isomer of **40** was the major one in a ratio of 11.7:1 to the *Z*-isomer, implying a fast π - σ - π equilibration compared to the decarboxylation and alkylation. Equally good enantioselectivities were achieved for the major product isomer from both the *Z*- and *E*-isomers of the allyl substrates (entry 3 and 4). Surprisingly, prenyl enol carbonate **9** remained intact for 13 h at 23 °C, while at the same temperature the prenylation of the preformed enolate was obtained in good yield (64%), albeit in poor ee (entry 5). It might be because the palladium-involved decarboxylation step is retarded by the steric hindrance of the π -prenylpalladium species. Increasing the reaction temperature to 60 °C did push the reaction of **9** to completion, but the only product found in the crude residue after concentration was 2-methyl-1-tetralone (entry 6). It was formed presumably through the β -hydride elimination of the π -prenylpalladium intermediate followed by reductive elimination of the hydrido-palladium enolate. Elimination from the π -allylpalladium complex to form diene can also occur via a base promoted process. Nevertheless, the palladium-catalyzed decarboxylative prenylation has been successfully applied in the synthesis of spirotryprostatin B, where the corresponding enolate was more stabilized, so the decarboxylation may be more facile.³² We cannot rule out a role for the hardness/softness of the enolate in the two cases although we favor the former explanation. In entry 7, **42** was isolated in 62% yield, over 20:1 dr and over 99% ee. The diastereoselectivity (5:1 dr) in the DAAA of 2-methyl-1-indanone (entry 8) was somehow lower, compared with that of 2-methyl-1-tetralone

(31) Seebach, D. *Angew. Chem., Int. Ed.* **1988**, *27*, 1624.(32) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2007**, *9*, 2763.

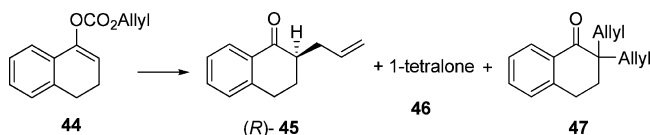
Table 5. Palladium-Catalyzed Decarboxylative AAA of Substituted Allyl Enol Carbonates^a

entry	substrate	time	products ^b	yield	ee (dr)	yield and ee (dr) from preformed enolate ^c
1	8	4 h		89%	>99% ee	82%, 47% ee
2	10	2 h		99%	92.5% ee	11%, NA
3	12	4h	 +	94%	93% ee	-
4	13	2 h	40 (<i>E:Z</i> = 20:1) : 41 (7:1 dr) = 7.4: 1	89%	93% ee	84%, 90% ee (40 : 41 >20:1)
5	9	13 h		0% ^e	-	64%, 13% ee
6 ^d	9	16 h		>95% ^e	-	
7	11	4 h		62%	99% ee (20:1 dr)	-
8	14	4 h		94%	98% ee (5:1 dr)	-

^a All reactions were performed on a 0.2 mmol scale at 0.1 M in dioxane at 23 °C for 20 h using 2.5 mol% **20** and 5.5 mol% ligand (*R,R*)-**L4**; yields are isolated yields; ee values were determined by HPLC on a chiral stationary phase. ^b Absolute and relative stereochemistry were assigned by analogy with compound **24** and **111**. ^c Conditions used were 2.5 mol% [(*η*³-C₃H₅)PdCl]₂, 5.0 mol% (*S,S*)-**L1**, 2.0 equiv LDA, 1.0 equiv Me₃SnCl, DME, rt.^{10b} ^d Reaction was performed at 60 °C. ^e Conversion of the starting material by ¹HNMR.

(entry 7), but the ee of the major diastereomer **43** remained high (98% ee).

To Generate Ketones Possessing an α -Tertiary Center. Since the reaction conditions are mild, we attempted to extend the reaction into the asymmetric syntheses of ketones bearing an α -tertiary center anticipating that no racemization of the α -center or dialkylation would happen. Under the optimized conditions described above, the reaction of **44** went to completion to afford *R*-**45** in over 85% ee, albeit in a moderate yield (62%).³³ A large portion of 1-tetralone (**46**, 29%) and a significant amount of 2,2-diallyl-1-tetralone (**47**, 9%) were obtained as side products (Table 6, entry 1). At lower temperature the yield of **46** increased to 39% and correspondingly the yield of the product decreased to 52% without change of the ee (entry 2). Raising the temperature from 23 to 50 °C in THF decreased the ee and the yield of the desired product and increased the yield of the diallylated product (entry 3 and 4). In the presence of less

Table 6. Selected Optimization Studies for DAAA of Tri-substituted Enol Carbonates^a

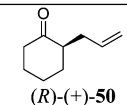
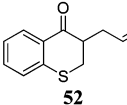
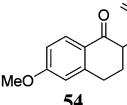
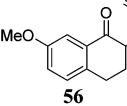
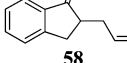
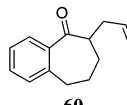
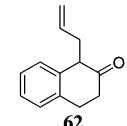
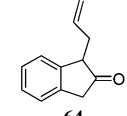
entry	<i>T</i> (°C)	solvent	ee ^b	45	46	47
1	23	PhMe	95%	(62) ^c	(29) ^c	9%
2	4	PhMe	95%	53(52) ^c	36(39) ^c	8%
3	23	THF	94%	51(51) ^c	25(35) ^c	5%
4	50	THF	89%	46(44) ^c	13(20) ^c	19%
5 ^d	50	THF	89%	22(18) ^c	7(10) ^c	38%
6	23	dioxane	97%	81(81) ^c	6	<2%

^a All reactions were performed on a 0.3 mmol scale at 0.1 M for 20 h at 23 °C using 2.5 mol% **20** and 5.5 mol% (*R,R*)-**L4**; yields were measured by quantitative GC analysis using decane as internal reference. ^b Ee values were determined by chiral HPLC. ^c Isolated yields. ^d **20** (1.0 mol%) and (*R,R*)-**L4** (5.0 mol%) were used.

catalyst (2 mol%), diallylation was more severe; **47** was isolated in 38% yield and the yield of the desired product was only 22%

(33) The absolute configuration of **45** was assigned by the comparison of its optical rotation with that known in the literature. Imai, M.; Hagiwara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *Tetrahedron* **2000**, *56*, 179.

Table 7. Summary of the Scope of the Reaction^a

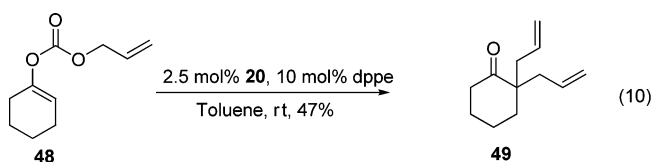
entry	substrate	product	solvent	yield ^b	ee
1	48	 (<i>R</i>)-(+)- 50	toluene	78%	78% ^{c,d}
2	48	(<i>R</i>)-(+)- 50	dioxane	90%	70% ^c
3	51	 52	toluene	89%	93%
4	51	52	dioxane	93%	87%
5	53	 54	dioxane	90%	>99%
6	55	 56	dioxane	97%	97%
7	57	 58	toluene	87%	81%
8	57	58	dioxane	94%	73%
9	59	 60	dioxane	93%	99%
10	61	 62	toluene	85%	0%
11	63	 64	toluene	90%	0%

^a Unless otherwise indicated, all reactions were performed on a 0.3 mmol scale at 0.1 M for 20 h at 23 °C using 2.5 mol% **20** and 5.5 mol% ligand **L4** or 10 mol% dppe; the ee values were determined by chiral HPLC. ^b Yields were isolated yields. ^c Ee values was determined by the analysis of its derivative by chiral GC. ^d [α]_D has the same sign as reported for the *R* configuration.³⁵

(entry 5). The best results were achieved when the reaction was conducted in dioxane at ambient temperature (entry 6).

The reaction scope has also been explored and the results are listed in Table 7. For comparison of this asymmetric process to one using an achiral ligand, the DAA of cyclohexanone with dppe was explored (eq 10). To our surprise, this reaction did not give the desired monoallylated product **50**; instead, 2,2-diallylcyclohexanone **49** was isolated as the major product. However, when **L4** was used as ligand there was little diallylated product and the monoallylated products were isolated in good yields and moderate enantioselectivities (entry 1).³⁴ Generally, better yield was obtained in dioxane than in toluene, but slightly better enantioselectivity was achieved in toluene than in dioxane (entry 1 vs 2; entry 3 vs 4 and entry 7 vs 8). Substrate **51**

containing a sulfur atom is compatible with the Pd catalyst and product **52** was obtained in excellent yield and enantioselectivity (entry 6). The positions of substituents on the aryl ring did not have a significant effect on the reaction and excellent ee's were obtained (entry 8 and 9). The ring size of ketones, however, has a significant impact on the enantioselectivity of the reaction. For instance, 2-allylindanone **58** was obtained in lower ee (81% ee, entry 7) than 2-allyl-1-tetralone **45** (97% ee) while 2-allyl-benzosuberone **60** was obtained in better ee (99% ee, entry 9).



Surprisingly, the DAAA of 2-tetralone and 2-indanone gave essentially *racemic* monoallylated products **62** and **64** (entry 10 and 11), in stark contrast with the 80% ee obtained in the allylation of 1-methyl-2-tetralone under the same reaction conditions (eq 10). This is hard to be explained by the slight structural difference between 2-tetralone and 1-methyl-2-tetralone. Instead, racemization through the equilibration of enolates is possibly a more plausible reason for the complete loss of ee in the product. The equilibration of enolates, which was largely avoided in the DAAA of 1-tetralone, was more severe for 2-tetralone, probably because the later was more acidic, thus the ion-pair of its palladium enolate was much looser so that the enolate can leak out more easily from the solvent cage to equilibrate with the product.

Palladium-Catalyzed DAAA of Allyl Enol Carbonates of Acyclic Ketones. The alkylation of five to seven-membered cyclic ketones is simplified by the fact that the geometry of the enolate is fixed due to the strain in the formation of the *Z*-cyclic enolate. For acyclic enolates the influence of double bond geometry on the stereochemistry of reactions needs to be considered. Both *E* and *Z* isomers of **15** were prepared and submitted to the optimized palladium-catalyzed DAAA conditions. Interestingly, *E*-**15** was more reactive than its isomer and its reaction went to completion in 2 h with **65** being isolated in 94% yield (eq 11), while *Z*-**15** remained mostly unchanged after 4 h as detected by GC analysis. The product was isolated in a lower yield (72%) after 16 h (eq 12). In both cases **65** was the only product, however, the sign of its optical rotation was reversed. Similarly the DAAA of **66** with a 5/95 *Z/E* ratio went to completion in 6 h to afford **67** in quantitative yield and 93% ee (eq 13), while only a trace amount of product was detected in 16 h in the reaction of **66** with a 94/6 *Z/E* ratio (eq 14).

These results indicated that the possible equilibrium between the *E*-enolate and the *Z*-enolate in the presence of a proton source (the product) was avoided and the π -allylpalladium reacted with the enolate from the same face. The different enantioselectivity may be interpreted by models as shown in Figure 3. The *E*-enolate approaching the π -allylpalladium complex from its *Si* face (transition state **A**), with both the cyclohexyl and the methyl groups occupying the “flap” side of the catalyst, should be more favored than that if it reacts from its *Re* face (**B**). Thus, *R*-**65** was the predominating enantiomer

(34) The direct catalytic asymmetric mono-allylation of lithium enolate of cyclohexanone was recently reported. See: Braun, M.; Meletis, P.; Fidan, M. *Synthesis* **2009**, 86, 47.

(35) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, 103, 3081.

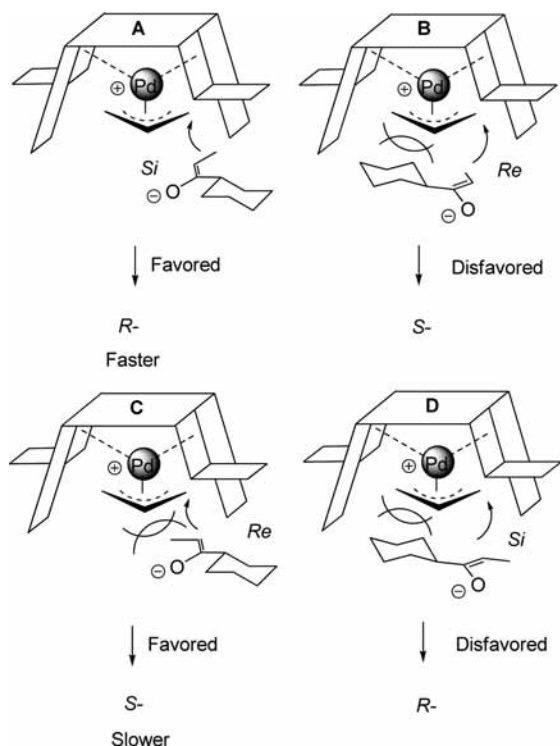
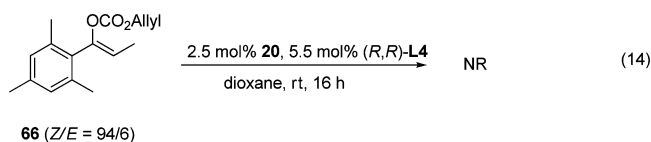
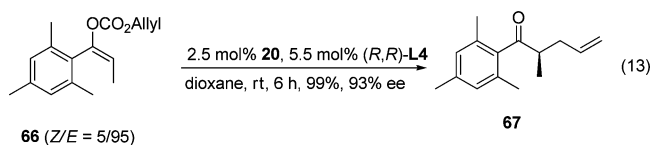
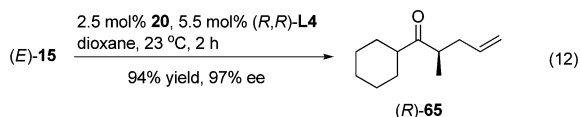
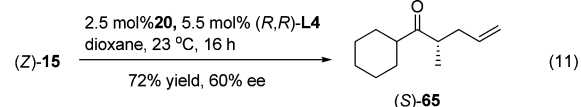


Figure 3. Cartoon models for the explanation of the reactivity and the selectivity of *E*- and *Z*-15.



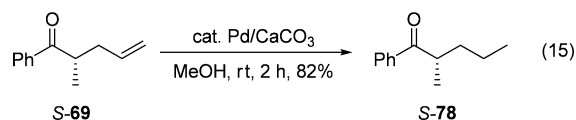
in the reaction of *E*-15. In the allylation of the *Z*-enolate, no matter which side the enolate approaches the π -allylpalladium complex, either the methyl group (C) or the cyclohexyl group (D) has to have some steric interaction with the catalyst. Approach C should be more favored than D, but the energy difference between C and D is smaller than that between A and B, and thus a poorer ee was obtained in the DAAA of *Z*-15.

Z-Enol carbonates are easily accessible if one side of the ketone is sterically bulky, such as phenyl ketones. Several such enol carbonates were made by deprotonating ketones with NaHMDS/TMEDA at -78°C followed by the quenching with allyl chloroformate. All carbonates were isolated with over 98/2

Table 8. DAAA of Allyl Enol Carbonates of Various Phenyl Ketones

entry	R ₂	substrate (<i>Z/E</i>)	product	time (h)	yield	ee
1	Me	68 (>98/2)	S-69	3	96%	94%
2	Et	70 (>98/2)	71	2	94%	94%
3	<i>n</i> -Pent	72 (>98/2)	73	16	93%	92%
4	Bn	74 (>98/2)	75	1	75%	88%
5	<i>i</i> -Pr	76 (>98/2)	77	24	30%	32%

E/Z-selectivity. They were subjected to the palladium-catalyzed DAAA reactions in the presence of **L4** ligand in dioxane at ambient temperature and the results are listed in Table 8. Carbonates bearing a small R₂ group such as CH₃, C₂H₅, C₅H₁₁ and CH₂Ph reacted smoothly to generate the corresponding ketones in excellent yields and ee's (entry 1–4). However, the reaction of carbonate **76** with R₂ = *i*-Pr was sluggish and the desired product **77** was isolated in poor yield and ee (30%, 32% ee, entry 5). The absolute configuration of **69** was assigned to be *S*- by the hydrogenation of **69** to compound **78**, which had an optical rotation of $+25.7$ (EtOH), opposite to the reported optical rotation of *R*-**78** [-15.8 (EtOH), eq 15].³⁶



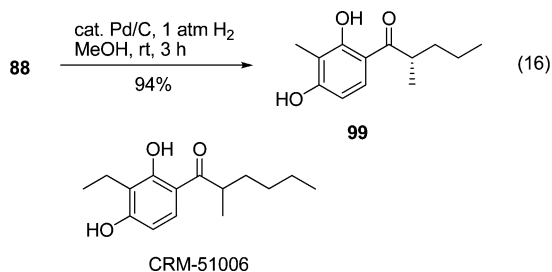
The reaction is compatible with halogen substitutions at either *ortho*-, *meta*-, or *para*- position of the phenyl ring and no significant difference was observed in these reactions compared with that of the unsubstituted one (Table 9, entry 1–3). Remarkably, sterically hindered *ortho*-substitution on the phenyl ring was tolerable; **86** and **88** were isolated in high yields and excellent ee's (entry 4 and entry 5). Compound **88** was cleanly converted to **99**, an analogue of the antitumor compound CRM-51006,^{37,38} by catalytic hydrogenation in methanol to saturate the double bond as well as to remove the benzyl groups (eq 16). Replacement of the electron-rich methoxyl group in **85** with an electron-deficient CF₃ group, apparently shortened the reaction time to 2 h, possibly by facilitating the decarboxylation; the product **90** was obtained in a slightly lower ee (92%) (entry 6). The substrates possessing a more electron-deficient 2'-pyridyl (**91**) or 3'-nitrophenyl group (**93**) were even more reactive, but the corresponding products **90** and **92** were obtained in lower ee's (73% ee and 83% ee respectively, entry 7 and 8). However, the reaction of substrate **95** bearing a more electron-rich but smaller 2'-furyl ring did not give better enantioselectivity (88% ee, entry 9) than that of **69** (94% ee, entry 1), implying the electronic property of the enolate may not be the only factor influencing the enantioselectivity of the reaction.

Beside aryl ketones, the DAAA reactions of alkenyl ketones were also investigated. Enol carbonate **Z-2** was prepared in the same way as aryl ketone enol carbonates. Its DAAA reaction

(36) Wagner, P. J.; Liu, K. C.; Noguchi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 3837–3841.

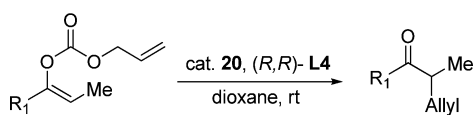
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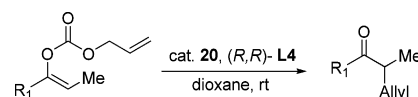
under the standard conditions went to completion in 5 h to afford ketone **100** in 94% yield and 88% ee (Table 10, entry 1). Comparison of the enantioselectivity in the DAAA of **68** (94% ee, Table 8, entry 1), **Z-2** (88% ee) and **Z-15** (60% ee, Scheme 4) may suggest that the enantio-recognition step involves not only steric effects of R_1 and R_2 , but also some electronic effects such as π -stacking interactions between the substrate and the

Table 9. DAAA of Allyl Enol Carbonates of Various Acyclic Aryl Ethyl Ketones



entry	substrate	product	time	yield	ee
1	79 (>98/2)	80	1 h	80%	94%
2	81 (>98/2)	82	1 h	97%	93%
3	83 (>98/2)	84	1 h	94%	93%
4	85 (>98/2)	86	16 h	99%	98%
5	87 (>98/2)	88	3 h	78%	94%
6	89 (>98/2)	90	2 h	94%	92%
7	91 (>98/2)	92	1 h	95%	73%
8	93 (>98/2)	94	1 h	83%	82%
9	95 (>98/2)	96	4 h	89%	88%
10	97 (>98/2)	98	1 h	90%	95%

Table 10. DAAA of Allyl Enol Carbonates of Various Acyclic Alkyl, Alkenyl and Alkynyl Ketones

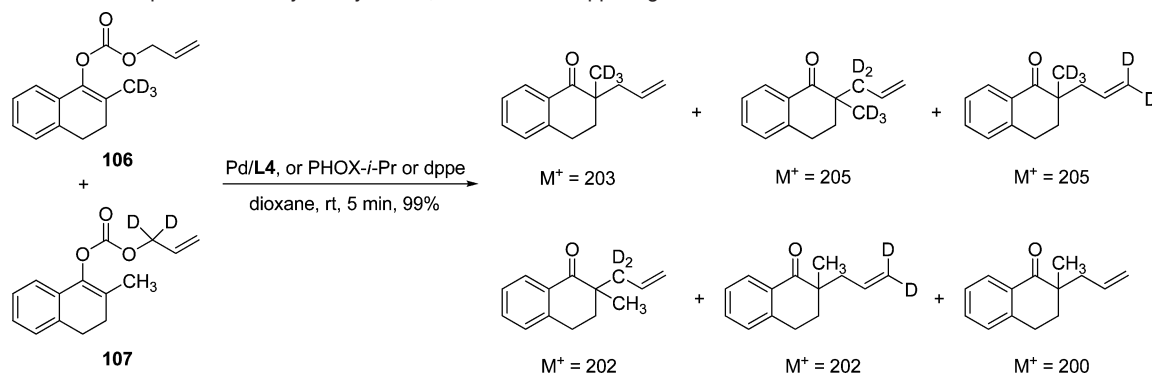


entry	substrate (<i>Z/E</i>)	product	time	yield	ee
1	2 (>98/2)	100	5 h	94%	88%
2	101 (25/1)	102	0.3 h	93%	91%
3	16 (>98/2)	103	16 h	99% ^a	46%
4	16 (1/23)	103	16 h	99% ^a	94%
5	17 (1/18)	104	16 h	99% ^a	88%
6	18 (1/14)	105	2 h	91%	81%

^a Conversion based on GC analysis.

ligand. The higher reactivity of aryl enol carbonate and alkenyl enol carbonate than alkyl enol carbonate indicates that the decarboxylation step is probably the rate determining step since the lower pK_a of the aryl and alkenyl ketones (presumably the inductive effect of sp^2 substituents) should facilitate the decarboxylation. Similarly the reaction of enol carbonate **101**, obtained as a 25/1 *Z/E* isomer mixture, reached full conversion in 15 min to form the corresponding product **102** in 93% yield and 91% ee (entry 2). The DAAA of *Z*-enol carbonate of alkyl ketones was less successful. The reaction of **16** (*Z/E* > 98:2) went to completion in 16 h, detected by GC analysis; however, the ee of the product **103** was only moderate (46% ee) (entry 3). Fortunately, this limitation was overcome by the use of the *E*-isomer; the ee jumped to 94% (entry 4). Similarly, excellent conversions and good ee's of the *E*-enol isomers were obtained when R_1 was as simple as an ethyl group (**17**, entry 5), or when R_1 was a sterically unhindered linear alkynyl group (**18**, entry 6).

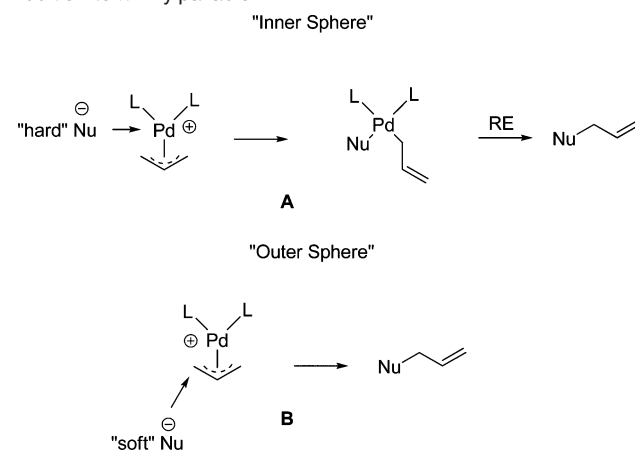
Mechanism Studies of Palladium-Catalyzed DAAA Reaction of Enol Carbonates. The highly conserved regioselectivity in the decarboxylative alkylation of enol carbonates suggests that proton-shuffling between the product and the palladium enolate intermediate is negligible. However, the crossover experiment conducted by Stoltz et al. showed a complete scrambling of the allyl and the ketone moieties.³⁹ To rule out that this is not specific to certain substrates, certain ligands or certain solvents, we performed a similar crossover experiment using deuterium labeled allyl enol carbonate of 2-methyltetralone **106** and **107** in the presence of **L4**, PHOX-*i*-Pr or dppe as ligand in dioxane (Scheme 4). The reaction went to completion within 5 min in all cases. Mass spectral analysis of the products from each reaction clearly showed that four peaks (m/z 200, 202, 203,

Scheme 4. Crossover Experiment Catalyzed by Pd/L4, PHOX-*i*-Pr or dppe Ligand**Table 11.** Acidic Additive Effect in the Palladium-Catalyzed DAAA Reaction

entry	solvent	additive	time (min)	69% (ee%)	108%	109%
1	dioxane	none	120	94 (94)	6	—
2	dioxane	MeCH(CO ₂ Me) ₂	30	94 (94)	6	0
3	dioxane	CH ₂ (CO ₂ Me) ₂	15	90 (93)	10	9
4	dioxane	CH ₂ (COMe) ₂	15	17 (81)	83	91
5	THF	CH ₂ (CO ₂ Me) ₂	10	71 (87)	27	22
6	THF	CH ₂ (COMe) ₂	<5	8 (83)	92	76

and 205) of nearly equal intensity were found implying a complete scrambling of the six possible products. This experiment confirmed complete crossover occurred. Such scrambling suggests that any ion-pair undergoes ion exchange faster than collapse to form products.

If the scrambling in the above crossover experiment occurred at the stage of palladium enolate, which means that palladium enolates are completely charge-separated, then, it is hard to explain why the decarboxylative alkylation reactions of enol carbonates are highly regioselective and the possible diallylation is largely minimized compared with the alkylation of preformed lithium enolates. If the palladium enolate is completely charge-separated, in the presence of an acidic additive the basic “naked” enolate should be protonated by the additive. To regenerate the Pd(0) catalyst, the anion of the additive is required to react with the π -allylpalladium and to simplify the reaction, the alkylation of the additive is best if made irreversible. Taking into account the convenience to tune the acidity of the additive, we decided to use 1,3-dicarbonyl compounds as additives. The pK_a of a simple ketone such as propiophenone is about 24.4 in DMSO, and the pK_a of dimethyl methylmalonate is about 18 in DMSO, so it is acidic enough to protonate the enolate of propiophenone. We subjected enol carbonate **68** to the DAAA reaction in the presence of one equivalent of dimethyl methylmalonate and found no change of the reaction (Table 11, entry 2 vs entry 1). In the presence of one equivalent of the more acidic dimeth-

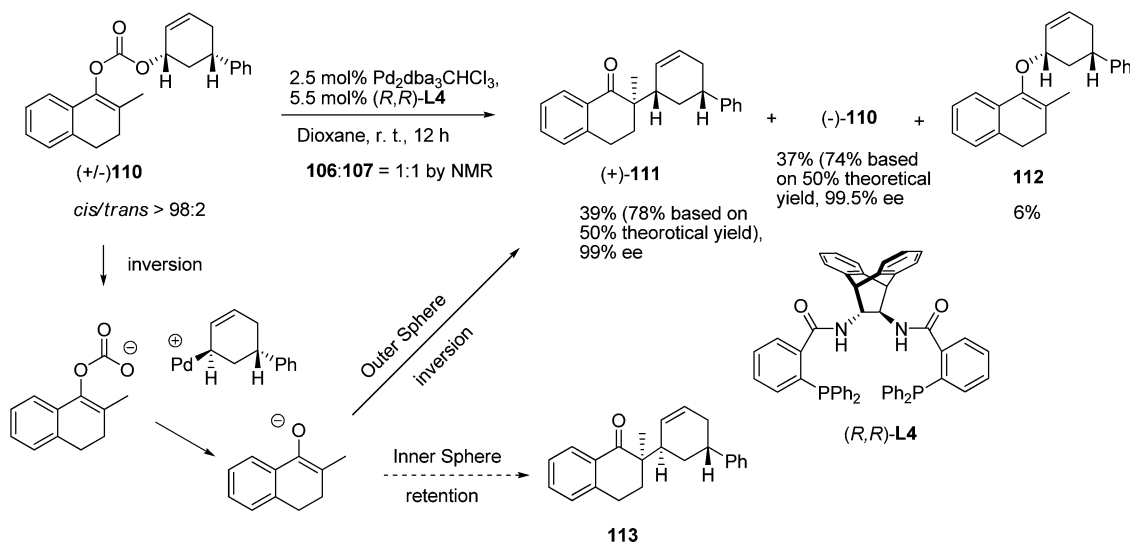
Scheme 5. “Inner Sphere” and “Outer Sphere” Nucleophilic Addition to π -Allylpalladium

ylmalonate (pK_a = 15.9), there was a slight increase in the amount of the protonated product **108** together with the same amount of **109** (entry 3). The addition of one equivalent of acetoacetone (pK_a = 13.3), eventually produced a large amount of proton transfer products; the yield of propiophenone was increased to 83% and allyl acetoacetone was obtained in 91% yield (entry 4). With the other conditions unchanged, the proton-transfer process was more severe in THF than in dioxane (entry 5 vs 3 and entry 6 vs 4).

There lacks pK_a values of enol carbonates in DMSO, however, the pK_a of HCO₃[⊖] is 10.3 in water, which is lower than that of dimethyl malonate (pK_a = 12.9 in water) but higher than that of acetoacetone (pK_a = 9.0 in water). Therefore, it is probable that the protonation did not occur on the enolate but on the carbonate. The carbonate anion is more stabilized than the enolate anion due to the delocalization of the anion on two oxygen atoms, so the palladium carbonate should be more charge separated than that of the palladium enolate. It is probably also the stage that scrambling of the electrophile and nucleophile may occur.

There are two possible mechanistic pathways for the recombination of the π -allylpalladium complex and the enolate. One is an “inner sphere” mechanism: the nucleophile coordinates to the metal followed by a bond-forming reductive elimination (Scheme 5, **A**). The other mechanism is an “outer sphere” one: the nucleophile directly adds to one of the carbons of the allyl moiety and substitutes the Pd complex (Scheme 5, **B**). Arbitrarily, “soft nucleophiles” with pK_a < 20 favored the “outer sphere” pathway and “hard nucleophiles” with pK_a > 20 favored

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Scheme 6. Palladium-Catalyzed DAAA Reaction of *cis*-110

the “inner sphere” pathway.⁴⁰ Previous stereochemistry studies suggested that unstabilized ketone enolates, including potassium,⁴¹ lithium,⁴² tin,⁴³ zinc,⁴⁴ and boron enolates,⁴⁴ attack π -allylpalladium complexes through the “outer sphere” mechanism. Recently, Braun et al. also proved that the palladium-catalyzed allylic alkylation of unstabilized lithium enolate was a net retention-of-configuration process favoring the “outer sphere” mechanism.¹² In the palladium-catalyzed DAAA of enol carbonates, the palladium enolate species are formed in situ as nucleophiles and presumably they may behave similarly as other metal enolates to attack π -allylpalladium through an “outer sphere” pathway. On the other hand, since there is no other counteraction, it is quite reasonable to believe that the palladium enolate may covalently bond or at least form a contact ion-pair, especially in nonpolar solvents such as toluene. This was implied by Tsuji’s early work, which showed that the major competitive pathway of the decarboxylative allylic alkylation of enol carbonates was the formation of conjugated enone, which was proposed involving a β -hydride elimination of the covalently bonded palladium enolate.⁴⁵ Stoltz and Goddard et al. recently reported a theoretical calculation on the mechanism of palladium-catalyzed DAAA reaction in the presence of PHOX-*t*-Bu ligand. The authors claimed that the penta-coordinated π -allylpalladium enolate complex was as stable as the charge separated palladium enolate and the product was formed by the reductive elimination of the η^1 -allylpalladium enolate complex through a seven-membered ring transition state.⁴⁶

Although it is highly likely that the π -allylpalladium complex is in some degree covalently bonded with the enolate, it does not necessarily mean that the covalently bonded palladium enolate is involved in the transition state of the alkylation step.

To shed some light on this question, we synthesized enol carbonate **110** and subjected it to the “standard” conditions we used in the palladium-catalyzed DAAA reactions (Pd₂dba₃CHCl₃, **L4**, dioxane, rt). A nearly perfect kinetic resolution was observed; one enantiomer of **110** reacted rapidly within 1 h to afford the single diastereomer **111** in 39% yield (78% based on 50% theoretical yield) and 99% ee (Scheme 6). The other enantiomer was not touched even after 12 h at rt and it was recovered in 37% yield (74% based on 50% theoretical yield) and 99.5% ee. A small amount of O-alkylation product **112** was also isolated (6%). The relative stereochemistry of **111** was assigned by ¹HNMR and X-ray crystallography (Figure 4). The tetralone moiety and the phenyl group were *cis*. Since the ionization of **110** should most likely follow the same *anti*-addition mechanism as other allyl carbonates, the retention of configuration of the product strongly suggests that the alkylation step should also be an *anti*-nucleophilic addition. Thus, the alkylation is an “outer-sphere” process, not an “inner-sphere” one.

Similar results were observed in the reaction of the *trans*-isomer **114**; only the *trans*- diastereomer **113** was obtained. Compared with the reaction of **110**, the reaction of **114** was significantly slower and was stopped after 8 h. Besides, a significant amount of the O-alkylation product **116**, 2-methyl-1-tetralone (**115**) was also isolated. The reaction rates of the two enantiomers of **114** were also significantly different so that only one reacted in the given reaction time (eq 17).

As a comparison, the preformed lithium enolate prepared by the deprotonation of 2-methyl-1-tetralone (**115**) by LDA was reacted with allyl acetate **117** in the presence of the same

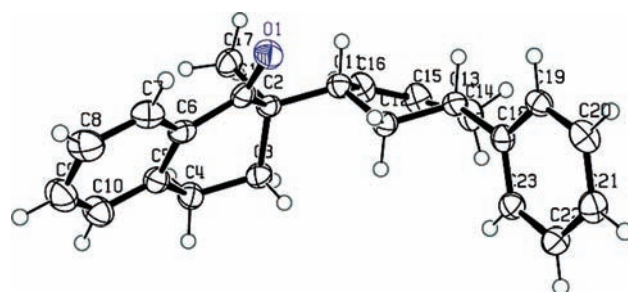
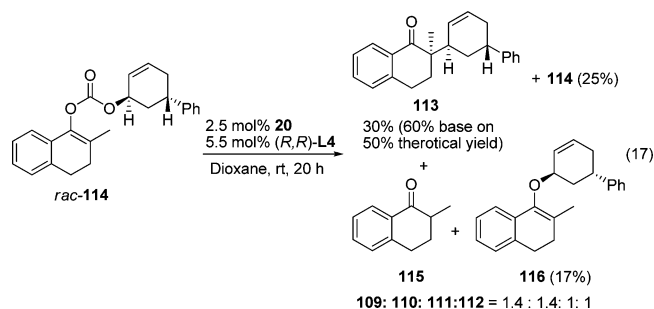
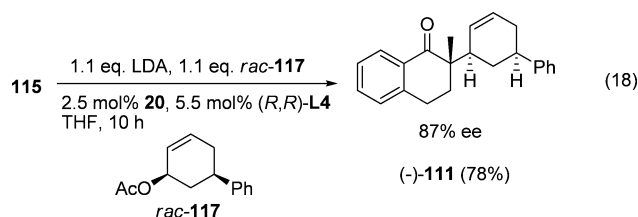


Figure 4. X-ray structure of **111**.

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palladium catalyst (eq 18). Only the *cis*-product **111** was obtained in 78% yield and 87% ee. This is in agreement with Braun's observation that the addition of lithium enolate to π -allylpalladium was an "outer sphere" anti-attack.¹¹ Interestingly, in contrast to the reaction of enol carbonate **110**, the opposite enantiomer (–)-**111** was obtained employing the same enantiomer of ligand **L4**.



On the basis of the above information, we proposed a mechanism as shown in Scheme 7. After the initial ionization, a Pd carbonate intermediate is formed. The decarboxylation step is probably the rate-determining step especially for simple unsubstituted allyl enol carbonates of sterically less hindered ketones. Since the carbonate anion is stabilized by delocalization, it is probably at this stage scrambling of the π -allylpalladium cation and the carbonate anion as well as protonation of the carbonate by an acidic proton source may occur. The decarboxylation must be assisted by the Pd complex;¹⁵ therefore, the enolate is generated in the presence of a π -allylpalladium complex very close to it. Since there is no other counteraction in the system, the unstabilized enolate anion and the cationic π -allylpalladium complex probably form a tight ion-pair caged by solvent molecules. This may explain why less proton-transfer related byproduct were found in dioxane than in THF, since dioxane is better at stabilizing caged ion-pairs.⁴⁷ The palladium enolate ion-pair probably also equilibrates with the covalently bonded palladium enolate, but the alkylation occurs only through an "outer sphere" S_N2 attack of the enolate to the π -allylpalladium complex.

Conclusion

In the presence of enantiopure chiral ligand **L4**, palladium-catalyzed DAAA of enol carbonates is a quite general method for the asymmetric synthesis of cyclic and acyclic ketones with either a quaternary or a tertiary α -center. The reaction conditions are extremely mild; thus, it has quite broad functional group compatibility. Compared with the allylic alkylation of preformed lithium enolates, the nucleophile is structurally much simpler since there is no other counterion in the reaction. This makes the DAAA reaction much more tolerant to the structural diversity of the substrate. As a result, excellent yield and

enantioselectivity were achieved in a broad range of substrates. Our studies suggested that solvent plays important roles in this reaction; for reactions to generate ketones bearing quaternary chiral centers, the nonpolar solvent toluene is the solvent of choice leading to the highest enantioselectivity. For reactions to generate ketones with a tertiary chiral center, dioxane is the best solvent to minimize the equilibrium between the product and the enolate intermediate, and hence minimize the protonated and the diallylated side products.

The DAAA of the enol carbonates of aromatic ketones is faster than that of aliphatic ketones, presumably because the pK_a of aromatic ketones is 2 or 3 units lower than the aliphatic ketones and thus decarboxylation of conjugated ketones is faster. The opposite enantiomers were obtained in the reaction of the *E*-enolate and the *Z*-enolate. This suggests that there is no equilibrium between the *E*-enolate and the *Z*-enolate through the C-bound palladium enolate. We have demonstrated that the *E*-enolate is more reactive than the corresponding *Z*-enolate and better enantioselectivity can be obtained in the allylation of the *E*-enolate as well. For a ketone with a big R_1 group and a small R_2 group, the *Z*-enol carbonate is more readily prepared. In this case, good enantioselectivity can be obtained since most important factor is the interaction between R_1 and the chiral catalyst. For a ketone possesses a small R_1 group and a small R_2 group, the *E* enol carbonates can be readily synthesized by the use of LiTMP-LiBr as base. Generally high enantioselectivities were achieved for the allylation of those ketones via their *E*-enol carbonates.

Mechanistic studies revealed that the palladium enolate forms a tight ion pair in less polar solvents, such as toluene and dioxane. The scrambling of the enolate moiety and the allyl moiety before the alkylation step probably occurs at the palladium carbonate stage, not at the palladium enolate stage. The C–C bond formation is more likely an "outer sphere" S_N2 substitution than the alternative "inner sphere" reductive elimination of the palladium enolate.

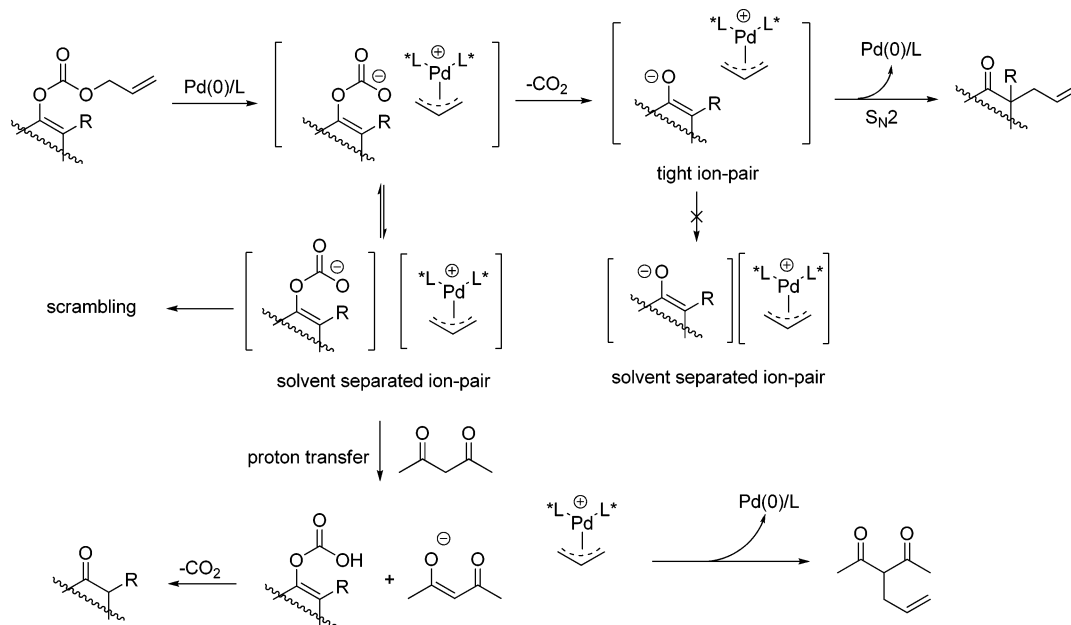
Experimental Section

All reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glasswares with magnetic stirring, unless otherwise indicated. Tris(dibenzylideneacetone)palladium(0) monochloroform complex, $Pd_2dba_3 \cdot CHCl_3$ was prepared by the procedure of Ibers.⁴⁸ Ligands were prepared by literature procedures. All other reagents were used as obtained unless otherwise noted. Flash Chromatography was performed with EM Science silica gel (0.040–0.063 μm grade). 1,4-Dioxane for palladium-catalyzed reactions were freshly distilled from sodium. Other solvents were dried by J. C. Meyer's Solvent Purification System. Proton nuclear magnetic resonance (1H NMR) data were acquired on a Mercury 400 (400 MHz) or on a Varian Unity Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, in parts per million (ppm) downfield from tetramethylsilane. Carbon-13 nuclear magnetic resonance (^{13}C NMR) data were acquired at 100 MHz on a Mercury 400 or at 125 MHz on a Varian Unity Inova 500 spectrometer. Chemical shifts are reported in ppm relative to the center line of a triplet at 77.1 ppm for chloroform-*d*. Infrared (IR) data were recorded as films on sodium chloride plates on a Perkin-Elmer Paragon 500 FT-IR spectrometer. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). Elemental analyses (Anal.) were performed by M.-H.-W. Laboratories of Phoenix, AZ. Chiral HPLC analyses were performed on a Thermo

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Scheme 7. Plausible Mechanism for Palladium-Catalyzed DAAA of Enol Carbonates



Separation Products Spectra Series P-100 or 200 and UV100 (254 nm) using Chiralcel columns (OD-H, AD-H, IA, IB or IC) eluting with heptane/*iso*-propanol mixtures indicated. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter using 5 cm cells and the sodium D line (589 nm) at ambient temperature in the solvent and concentration indicated.

Typical Procedure for the Preparation of the Kinetically Controlled *Z*-Allyl Enol Carbonates. (*Z*)-Allyl 1-Cyclohexenyl-1-propenyl Carbonate (2). To a clean dry 100 mL flask with a magnetic stirring bar was loaded sodium hexamethyldisilazane (Aldrich, 97%, 0.86 g, 4.5 mmol) stored in a glovebox under nitrogen. The flask was cooled in a dry ice-acetone bath for 5 min and THF (20 mL) was transferred to this flask with a syringe. The suspension was warmed to 0 °C with stirring to make a clear solution and TMEDA (freshly distilled from calcium hydride, 0.68 mL, 4.5 mmol) was added. The mixture was cooled to -78 °C again and a solution of 1-cyclohexenyl-1-propanone (1, 520 mg, 3.76 mmol) in 5 mL of THF was added slowly over 5 min. The reaction mixture was stirred for 1 h, and it was transferred through a cannula into a solution of allyl chloroformate (0.48 mL, 4.5 mmol) in 5 mL of THF at -78 °C. The reaction was stirred for 5 min and it was quenched with saturated aqueous ammonium chloride solution (10 mL). The mixture was extracted with diethyl ether (20 mL) twice. The combined organic layer was washed with brine (20 mL), then it was dried over anhydrous magnesium sulfate. After filtration and concentration *in vacuo*, the residue was purified by column chromatography on silica gel to afford the title compound (0.70 g, 84%) after purification by flash column chromatography eluting with 5% diethyl ether in petroleum ether. Colorless oil; $R_f = 0.41$ (Diethyl ether/petroleum ether 1:9); IR (film): $\tilde{\nu}_{\max} = 3047$ (w), 2931 (s), 2861 (s), 1760 (s), 1664 (m), 1448 (s), 1364 (s), 1304 (s), 1248 (s), 1216 (s), 977 (s), 928 (s), 805 (s), 781 cm^{-1} (s); ¹H NMR (400 MHz, CDCl₃): $\delta = 5.97$ (ddt, $J_1 = 17.1$ Hz, $J_2 = 10.4$ Hz, $J_3 = 5.8$ Hz, 1H), 5.87 (bs, 1H), 5.40 (dq, $J_1 = 17.2$ Hz, $J_2 = 1.4$ Hz, 1H), 5.35 (qd, $J_1 = 7.0$ Hz, $J_2 = 0.8$ Hz, 1H), 5.30 (dq, $J_1 = 10.5$ Hz, $J_2 = 1.2$ Hz, 1H), 4.69 (dt, $J_1 = 5.8$ Hz, $J_2 = 1.4$ Hz, 2H), 2.13 (m, 4H), 1.71–1.54 (m, 4H), 1.64 (dd, $J_1 = 7.2$ Hz, $J_2 = 0.6$ Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 153.1, 148.7, 131.7, 130.4, 123.7, 119.2, 110.2, 69.0, 25.4, 24.8, 22.6, 22.2, 11.2$. Anal. calcd for C₁₃H₁₈O₃: C, 70.24; H, 8.16; Found: C, 70.50; H, 7.97.

Typical Procedure for the Preparation of the Kinetically Controlled *E*-Allyl Enol Carbonates. Allyl (*E*)-Pent-2-en-3-yl Carbonate (*E*-17). To a clean dry 100 mL flask was loaded TMP-HBr (500 mg, 2.25 mmol, 1.3 equiv) and 25 mL of DME. To this

rapidly stirred suspension at 0 °C and under nitrogen was added a 2.4 M solution of *n*-BuLi/hexanes (1.70 mL, 4.15 mmol, 2.4 equiv) dropwise over a 3-min period. After being stirred for additional 15 min, the resulting pale yellow solution was cooled to -78 °C and a solution of 3-pentanone (153 mg, 1.78 mmol, 1 equiv) in 1.5 mL of DME was added dropwise. After 15 min, TMEDA (0.62 mL, 4.15 mmol, 2.4 equiv) was added dropwise over a 3-min period. After another 15 min, a precooled (-78 °C) solution of allylchloroformate (241 mg, 2.00 mmol, 1.1 equiv) in 1.4 mL of DME was added at -78 °C. After 30 min at -78 °C the reaction was removed from the bath and was allowed to warm to room temperature. The reaction was quenched with 5% KH₂PO₄ aqueous solution and transferred into a separatory funnel. It was extracted twice with 25 mL of diethyl ether. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with 2–3% diethyl ether in petroleum ether to afford 265 mg of colorless oil (90%). The *E/Z* ratio was determined by ¹H NMR to be 18:1 [by the signal of the CH₃ at $\delta = 1.64$ (d, $J = 7.2$ Hz, major) and 1.59 (dt, $J = 6.9, 1.4$ Hz, minor)]. $R_f = 0.35$ (diethyl ether/petroleum ether 1:9); IR (film): $\tilde{\nu}_{\max} = 2977$ (m), 1756 (s), 1694 (m), 1459 (m), 1386 (m), 1365 (m), 1276 (s), 1245 (s), 1167 (s), 1031 (w), 983 (m), 942 (m), 916 (m), 783 (w), 734 cm^{-1} (m); ¹H NMR (500 MHz, CDCl₃): $\delta = 5.95$ (ddt, $J_1 = 17.2$ Hz, $J_2 = 10.5$ Hz, $J_3 = 5.7$ Hz, 1H), 5.37 (dq, $J_1 = 17.2$ Hz, $J_2 = 1.4$ Hz, 1H), 5.28 (dq, $J_1 = 10.5$ Hz, $J_2 = 1.1$ Hz, 1H), 5.24 (q, $J = 7.2$ Hz, 1H), 4.64 (m, 2H), 2.31 (q, $J = 7.6$ Hz, 2H), 1.64 (d, $J = 7.2$ Hz, 3H), 1.04 (d, $J = 7.6$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 153.8, 150.9, 131.5, 119.1, 111.8, 68.7, 21.8, 11.5, 11.4$. The structure as further confirmed by NOE experiment.

Typical Procedure for the Preparation of the Thermodynamically Controlled Allyl Enol Carbonates. Allyl 2-Phenylcyclohex-1-enyl Carbonate (4). To a clean dry 50 mL three-neck flask with a magnetic stirring bar and a refluxing condenser was loaded a suspension of sodium hydride (60% in mineral oil, 0.44 g, 11.0 mmol) and was purged with nitrogen. The sodium hydride was washed three times with anhydrous hexane under nitrogen. Freshly distilled TMEDA (1.51 mL) and 5 mL of anhydrous THF were added to the flask and the suspension was added to a solution of 2-phenylcyclohexanone (1.74 g, 10.0 mmol) in 5 mL of THF at room temperature. The mixture was heated to reflux for 1 h. After the enolate solution was cooled by an ice-water bath for 5 min, it was transferred through a cannula into a solution of allyl chloroformate (1.07 mL, 10 mmol) in 5 mL of THF at 0 °C. After stirring

for another 15 min, saturated aqueous ammonium chloride (10 mL) was poured into the reaction flask. The mixture was extracted with diethyl ether (20 mL) twice. The combined organic layers were dried over anhydrous magnesium sulfate. After filtration and concentration the residue was purified by column chromatography eluting with 2% diethyl ether in petroleum ether to afford 1.87 g of the title compound (72%). Colorless oil; $R_f = 0.37$ (Diethyl ether/petroleum ether 1:9); IR (film): $\tilde{\nu}_{\max} = 2938$ (s), 1750 (s), 1444 (m), 1367 (m), 1238 (s), 1178 (m), 1036 cm^{-1} (s); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.4\text{--}7.2$ (m, 5H), 5.78 (ddt, $J = 17.2, 10.4, 5.5$ Hz, 1H), 5.20 (ddd, $J = 11.3, 1.5, 1.5$ Hz, 1H), 5.17 (ddd, $J = 4.6, 1.5, 1.5$ Hz, 1H), 4.51 (dt, $J = 5.7, 1.5$ Hz, 2H), 2.42 (m, 2H), 2.33 (m, 2H), 1.84 (m, 2H), 1.76 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 152.9, 143.5, 138.9, 131.4, 128.2, 127.7, 126.9, 118.6, 68.5, 30.2, 27.2, 22.9, 22.6$; HRMS (EI): $[\text{M}]^+$ calcd for $\text{C}_{16}\text{H}_{18}\text{O}_3$, 258.1256; found: 258.1257.

Typical Procedure for the Preparation of the Substituted Allyl Enol Carbonates. 2-Methylprop-2-en-1-yl 1H-imidazole-1-carboxylate. To a clean oven-dried 250 mL flask with a magnetic stirring bar was charged with 1,1'-carbonyldiimidazole (4.86 g, 30.0 mmol) and 100 mL THF under nitrogen. The flask was cooled in an ice-water bath. A solution of 2-methyl-prop-2-en-1-ol (1.44 g, 20.0 mmol) in 30 mL methylene chloride was added slowly and stirred for 2 h. Most solvent was removed *in vacuo* by a rotaevaporator and the crude product was purified by silica gel column chromatography eluted with 1:1 ethyl acetate/petroleum ether to afford 3.23 g of the title compound as a white solid (97%). Mp = 36–38 °C; $R_f = 0.18$ (30% ethyl acetate in petroleum ether); IR (neat): $\tilde{\nu}_{\max} = 1761$ cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): 8.17–8.11 (m, 1H), 7.43 (dd, $J = 3.5, 2.1$ Hz, 1H), 7.07 (dd, $J = 1.5, 0.9$ Hz, 1H), 5.08 (m, 1H), 5.04 (m, 1H), 4.80 (s, 2H), 1.82 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 148.5, 138.3, 137.1, 130.7, 117.1, 114.9, 71.2, 19.4$. HRMS (EI): M^+ calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$ 166.0742, found 166.0737.

2-Methyl-3,4-dihydronaphthalen-1-yl 2-Methylprop-2-en-1-yl Carbonate (8). To the solution of NaHMDS (460 mg, 2.51 mmol) in 5 mL of DME at –78 °C was added 2-methyl-1-tetralone (320 mg, 2.0 mmol) in 2 mL of DME. The solution was stirred at –78 °C for 30 min. Meanwhile, another clean oven-dried 50 mL flask was charged with 2-methylprop-2-en-1-yl 1H-imidazole-1-carboxylate (399 mg, 2.0 mmol) and 5 mL DME. The solution cooled to –78 °C was added boron trifluoride etherate (0.30 mL, 2.4 mmol). The solution was transferred into the solution of enolate through a cannula under nitrogen and stirred for 30 min. One portion of 10 mL saturated aqueous ammonium chloride was poured into the reaction mixture followed by 10 mL diethyl ether. The mixture was taken out from the bath and allowed to warm to ambient temperature. The organic layer was separated and the aqueous layer was extracted once with 10 mL diethyl ether. The organic layer was combined and dried over magnesium sulfate. After filtration and concentration *in vacuo* the crude material was purified by silica gel column chromatography eluted with 10% diethyl ether in petroleum ether to afford the title compound as colorless oil (472 mg, 92%). $R_f = 0.34$ (Diethyl ether/petroleum ether 1:9); IR (film): 1760 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.20\text{--}7.07$ (m, 4H),

5.08 (m, 1H), 4.99 (m, 1H), 4.64 (m, 2H), 2.86 (t, $J = 8.0$ Hz, 2H), 2.39 (dt, $J = 8.1, 1.0$ Hz, 2H), 1.83 (t, $J = 1.0$ Hz, 3H), 1.80 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 153.2, 140.7, 139.3, 135.3, 130.9, 127.4, 127.1, 126.5, 124.5, 120.0, 113.7, 71.7, 29.0, 27.5, 19.4, 16.6$. Anal. calcd for $\text{C}_{16}\text{H}_{18}\text{O}_3$: C, 74.39; H, 7.02; found: C, 74.50; H, 7.12.

Typical Procedure for the Palladium-Catalyzed DAAA Reaction of Allyl Enol Carbonates. 2-Methyl-2-(2-methylallyl)-3,4-dihydronaphthalen-1(2H)-one (38). Two clean oven-dried test tubes were individually charged with a magnetic stirring bar. One test tube was loaded with $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ (5.2 mg, 0.0075 mmol) and (*R,R*)-L4 ligand (9.2 mg, 0.0165 mmol); the other one was loaded with **8** (52 mg, 0.20 mmol). They are sealed and connected with a double-end needle. The system was evacuated and flushed with argon three times at which point 1.0 mL of degassed anhydrous dioxane was added to both of the test tubes. After stirring for 20 min, the orange solution containing the catalyst was transferred into the test tube containing the carbonate substrate. The color of the reaction solution turned to light yellow immediately, and it turned back to orange within 4 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography to afford 38 mg of the title compound as a colorless oil (89%). Chromatography on silica gel, eluent: 3% diethyl ether in petroleum ether. $R_f = 0.44$ (Diethyl ether/petroleum ether 1:9); Colorless oil; IR (film): 1682 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +45.3$ ($c = 1.77, \text{CH}_2\text{Cl}_2, >99\%$ ee); HPLC (Chiralcel AD-H column; 2000:1 Heptane/Isopropanol; flow rate = 1 mL of/min; $t_1 = 15.1$ min (minor), $t_2 = 17.6$ min (major)); ^1H NMR (400 MHz, CDCl_3): $\delta = 8.04$ (m, 1H), 7.46 (dt, $J = 7.5, 1.5$ Hz, 1H), 7.30 (m, 1H), 7.24 (m, 1H), 4.83 (m, 1H), 4.68 (m, 1H), 2.99 (t, $J = 6.5$ Hz, 2H), 2.66 (dd, $J = 13.5, 0.7$ Hz, 1H), 2.23 (dd, $J = 13.5, 0.7$ Hz, 1H), 2.10 (ddd, $J = 13.9, 6.8, 6.8$ Hz, 1H), 1.88 (ddd, $J = 13.9, 5.8, 5.8$ Hz, 1H), 1.65 (m, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 202.2, 143.2, 142.5, 133.0, 131.8, 128.6, 128.1, 126.7, 114.9, 45.0, 44.7, 33.6, 25.5, 24.5, 23.3$. Anal. calcd for $\text{C}_{15}\text{H}_{18}\text{O}$: C, 84.07; H, 8.47; found: C, 84.32; H, 8.55.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences Grant GM13598, for their generous support of our programs. Mass spectra was provided by the Mass Spectrometry Regional Center of the University of California-San Francisco supported by the NIH Division of Research Resources. We thank Chirotech (now Dow) for their generous gifts of ligands and Johnson Matthey for gifts of palladium salts.

Supporting Information Available: Crystallographic data for compound **111** in cif format, experimental procedures, and characterization data for all new compounds in pdf format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA9053948