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# Palladium-Catalyzed Diastereo- and Enantioselective Wagner−Meerwein Shift: Control of Absolute Stereochemistry in the C−C Bond Migration Event

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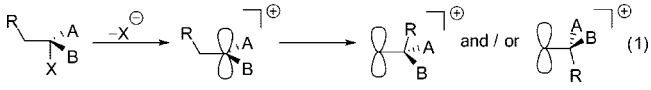
***Abstract:*** Inducing absolute stereochemistry in Wagner−Meerwein shifts was examined in a ring expansion protocol. Initiated by generation of a $\pi$-allylpalladium intermediate by hydropalladation of allenes, the ring expansion of allenylcyclobutanol substrates proceeded with excellent diastereo- and enantioselectivities. The results demonstrate that, during the C−C bond migration process, our chiral catalysts can control the stereochemistry of both the $\pi$-allylpalladium intermediate and the corresponding migration bond. Moreover, the stereochemical outcome of the reaction can be rationalized very well with the working model of the chiral catalyst. The method provides an efficient way to synthesize highly substituted cyclopentanones with an $\alpha$-chiral *O*-tertiary center which has various synthetic applications.

## Introduction

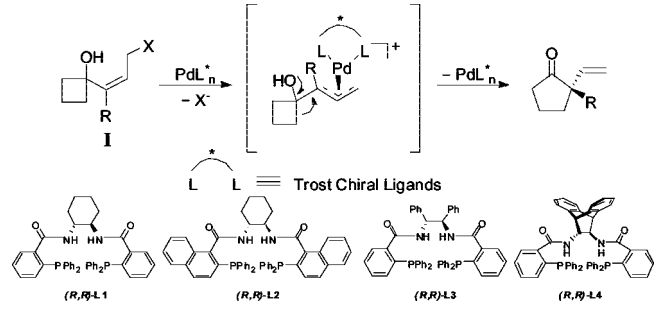
The Wagner−Meerwein shift is a classical intramolecular rearrangement that involves first the generation of a carbocation which is then followed by a 1,2 C−C bond migration.[1] Inducing absolute stereochemistry in such a process is a formidable objective in that it requires the differentiation of the prochiral faces of the carbocation (eq 1).[2]



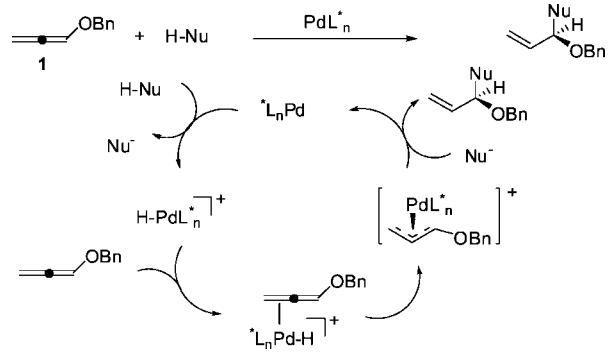

Asymmetric metal complex cations as in the case of $\pi$-allylmetal cations offer a strategy to achieve this objective, as shown in Scheme 1.[3] For substrates such as **I**, the $\pi$-allylpalladium intermediate was generated by the ionization of the allylic leaving group in a process analogous to the palladium-catalyzed asymmetric allylic alkylation (AAA) reactions.[4] With our chiral ligands **L1**−**L4**(Scheme 1), the first enantioselective Wagner−Meerwein shift was developed in a ring expansion protocol.[2]

Recently, utilizing the hydropalladation of allenes to generate the $\pi$-allylpalladium intermediates has allowed the development

***Scheme 1.*** Palladium-Catalyzed Enantioselective Wagner−Meerwein Shift of Cyclobutanols




***Scheme 2.*** Palladium-Catalyzed AAA Reaction with the Allene by Hydropalladation



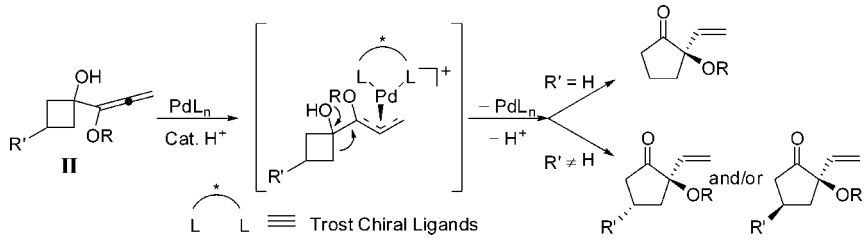

of Pd AAA reactions with allenes (Scheme 2).[5−7] With catalytic amounts of palladium and acid, this reaction is marked with simplicity, synthetic efficiency, and high level of atom economy.[8]

The ease of metalation of the allene **1**, which then provides easy access to the carbinols **II** (Scheme 3), suggested the feasibility of a ring expansion protocol.[9] Given our success in asymmetric intermolecular allylations, the intriguing question

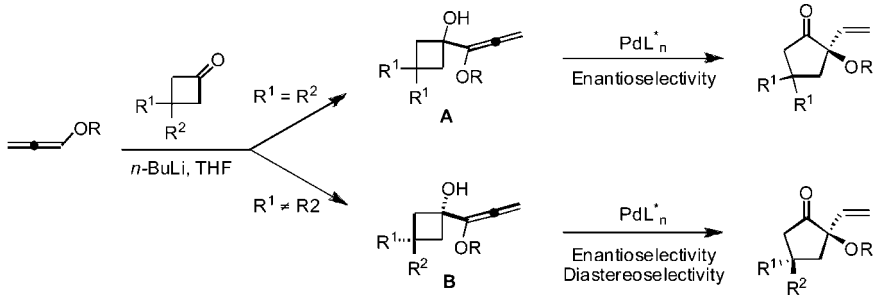
(1) For an overview of Wagner–Meerwein shift and related reactions, see: *Comprehensive Organic Synthesis*, Vol. 3; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Hanson, J. R., Chapter 3.1, pp 705–720; Rickborn, B., Chapter 3.2, pp 721–732 and Chapter 3.3, pp 733–776; Coveney, D. J., Chapter 3.4, pp 777–802.
(2) Trost, B. M.; Yasukata, T. *J. Am. Soc. Chem.* **2001**, *123*, 7162–7163.
(3) Leading reviews of reactions involving chiral $\pi$-allylmetal cations. For Pd, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (b) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1–14. For Mo, see: (c) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159–167. For Cu, see: (d) Yorimitsu, H.; Oshima, K. *Angew Chem., Int. Ed.* **2005**, *44*, 4435–4439. For Rh, see: (e) Evans, P. A.; Leahy, D. K *Chemtracts* **2003**, *16*, 567–578.
(4) For reviews of Pd AAA reactions, see: (a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813–5837. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943.

***Scheme 3.*** Palladium-Catalyzed Asymmetric Wagner−Meerwein Shift of Allenylcyclobutanols




***Scheme 4.*** Designed Reaction Scope




of whether such a method of generating the $\pi$-allylpalladium complex could induce an asymmetric Wagner−Meerwein shift arises.

In the case of substrates such as **II**, where R′ ≠ H, the two bonds that can undergo migration are diastereotopic in nature, and, as a result, a second stereogenic center can be generated in the product. To the best of our knowledge, there are very limited literature examples of diastereo- and enantioselective bond migration events mediated by asymmetric catalysis.[10] Since the bond migration occurs outside the coordination sphere of the metal, the ability for chiral ligands on the palladium to affect the stereochemistry with respect to the prochiral migrating groups seems remote. Nevertheless, our success in inducing stereochemistry of prochiral nucleophiles motivated us to consider such a possibility.[11] However, given that the exact nature of the ion pair plays an important role in the chiral recognition, the question arises whether this analogy to a migrating event which lacks such ion pair character and structure is appropriate.

With this challenge in mind, we decided to fully explore the diastereoselectivity and enantioselectivity of the process not only because of the uniqueness of the mechanism but also because of potential synthetic applications that may arise from this methodology. The ring expansion reaction will provide an efficient way to synthesize highly substituted chiral cyclopentanones with α-chiral *O*-tertiary centers.

## Results and Discussion

**Synthesis of Cyclobutanols.** To examine the scope and the different types of selectivities of the reaction, we prepared two types of allenylcyclobutanols, **A** and **B** (Scheme 4). Ring expansion of type **A** substrates allowed us to examine the enantioselectivity, the functional group compatibility on the allene side chain, and the effect of substituents on the ring. A number of issues arise with type **B** substrates, the first being the question of *cis*/*trans* isomers. Further, the ring expansion creates two stereogenic centers; therefore, both the diastereoselectivity and the enantioselectivity must be examined.

To synthesize type **A** substrates, we first prepared allenes with different alkoxy groups, **1a**−**1h**, by the isomerization of propargyl ethers catalyzed by *t*-BuOK at room temperature (Scheme 5). Cyclobutanone is commercially available. Substi-

(5) For a recent book and reviews of allene, see: (a) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067–3125. (b) Hashimi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590–3593. (c) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133–1150. (d) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773–782. (e) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284–290. (f) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701–712. (g) Krause, N.; Hashmi, A. S. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, 2004. (h) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196–1216. (i) Ohno, H. *Chem. Pharm. Bull.* **2005**, *53*, 1211–1226. (j) Ma, S. *Chem. Rev.* **2005**, *105*, 2829–2872. (k) Ma, S. *Aldrichim. Acta* **2007**, *40* (4), 91–102.

(6) For generation of hydriometal species from protonation, see: Trost, B. M. *Chem. Eur. J.* **1998**, *4*, 2405–2412.

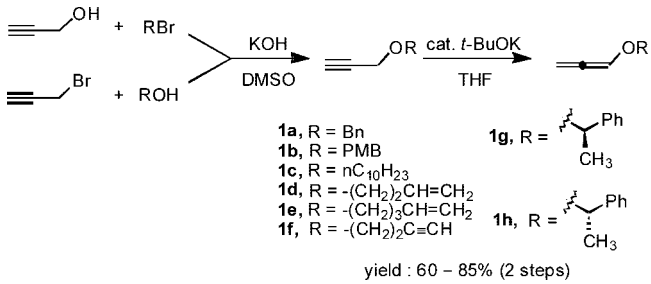
(7) For hydropalladation of allenes, see: (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Soc. Chem.* **1994**, *116*, 6019–20. (b) Yamamoto, Y.; Al-Masum, M. *Synlett* **1995**, 969–970. (c) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N. *Chem. Commun.* **1996**, 381–382. (d) Meguro, M.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 7453–7456. (e) Trost, B. M.; Michellys, P.-Y.; Gerusz, V. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 1750–1753. (f) Trost, B. M.; Jaekel, C.; Plietker, B. *J. Am. Soc. Chem.* **2003**, *125*, 4438–4439. (g) Trost, B. M.; Simas, A. B. C.; Plietker, B.; Jakel, C.; Xie, J. *Chem. Eur. J.* **2005**, *11*, 7075–7082. (h) Trost, B. M.; Xie, J. *J. Am. Soc. Chem.* **2006**, *128*, 6044–45.

(8) For reviews of atom economy, see: (a) Trost, B. M. *Science* **1991**, *254*, 1471–7. (b) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259–81. (c) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705.

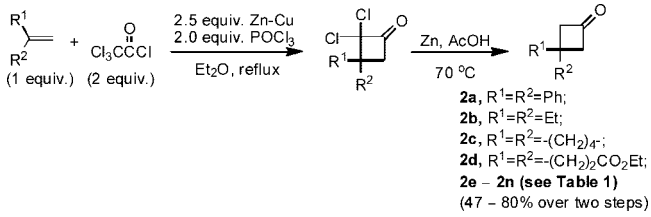
(9) For references of ring expansion reactions involving $\pi$-allylpalladium intermediates with achiral ligands, see: (a) Jeong, I.-Y.; Nagao, Y. *Tetrahedron Lett.* **1998**, *39*, 8677–8680. (b) Jeong, I.-Y.; Shiro, M.; Nagao, Y. *Heterocycles* **2000**, *52*, 85–89. (c) Nagao, Y.; Tanaka, S.; Hayashi, K.; Sano, S.; Shiro, M. *Synlett* **2004**, 481–484. (d) Nagao, Y.; Tanaka, S.; Ueki, A.; Jeong, I.-Y.; Sano, S.; Shiro, M. *Synlett* **2002**, 480–482. (e) Nagao, Y.; Ueki, A.; Asano, K.; Tanaka, S.; Sano, S.; Shiro, M. *Org. Lett.* **2002**, *4*, 455–457. (f) Nemoto, H.; Yoshida, M.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 6450–6451. (g) Yoshida, M.; Nemoto, H.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 8583–8586. (h) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron Lett.* **2000**, *41*, 5089–5092. (i) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron* **2002**, *58*, 7839–7846. (j) Yoshida, M.; Sugimoto, K.; Ihara, M. *Org. Lett.* **2004**, *6*, 1979–1982.

(10) For an enantioselective 1,2 C–C bond migration, see: (a) Brunner, H.; Stohr, F. *Eur. J. Org. Chem.* **2000**, 2777–2786. (b) Reference 2. (c) Reference 7f. (d) Ooi, T.; Saito, A.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 3220–3221. (e) Ohmatsu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 2410–2411.

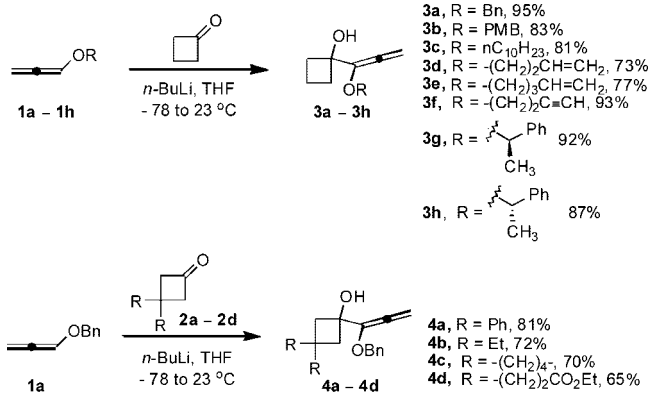
***Scheme 5.*** Preparation of Alkoxyallenes




***Scheme 6.*** Preparation of Substituted Cyclobutanones

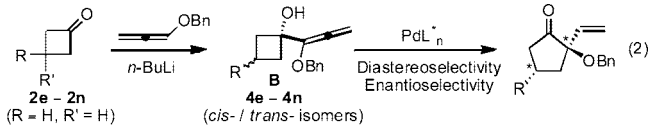



***Scheme 7.*** Preparation of Allenylcyclobutanols **A**



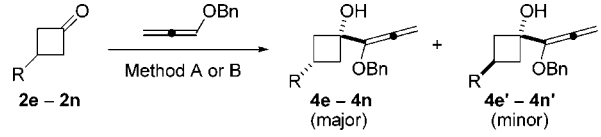

tuted cyclobutanones **2a**−**2n** were synthesized via a classical zinc-catalyzed [2+2] ketene cycloaddition reaction (Scheme 6). Finally, the addition of allenyllithiums generated from allenes **1a**−**1h** to cyclobutanone and substituted cyclobutanones **2a**−**2d** furnished the desired type **A** allenylcyclobutanols **3a**−**3h** and **4a**−**4d** (Scheme 7).

Type **B** allenylcyclobutanols were prepared via the same addition reaction. However, the addition of allenes to the cyclobutanones generated *cis*/*trans* isomers. Since it was anticipated that the *cis*/*trans* stereochemistry of the substrates **B** might also affect the overall stereochemical outcome (eq 2), the first challenge became the diastereoselective formation of the ring expansion substrates **B**, which were not known in the literature. However, a couple of examples indicated that diastereoselective nucleophilic additions to 3-substituted cyclobutanones were possible.[12]




To begin these studies, we chose 3-monosubstituted cyclobutanones **2e**−**2n** because we believed they would result in better diastereoselectivity in the addition reaction. The 3-monosubstituted allenylcyclobutanols **4e**−**4n** were synthesized by reaction of lithiated benzoxyallene **1** with a variety of differently substituted cyclobutanones **2e**−**2n** (Table 1).

***Table 1.*** Preparation of 3-Monosubstituted Allenylcyclobutanols



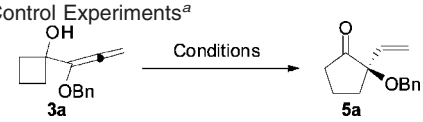

| entry | R | method[a] | yield[b] (%) | d.r.[c] (crude) | d.r.[c] (isolated) |
|---|---|---|---|---|---|
| 1 | Ph (**2e**) | **X** | 85 | 14 : 1 | 15 : 1 |
| 2 | *p*-Br-Ph (**2f**) | **X** | 78 | 10 : 1 | > 20 : 1 |
| 3 | 2-Naphthyl (**2g**) | **X** | 82 | 11 : 1 | > 20 : 1 |
| 4 | *t*-Bu (**2h**) | **X** | 66 | 11: 1 | 18: 1 |
| 5 | MeO2C (**2i**) | **X** | 75 | 10 : 1 | 16 : 1 |
| 6 | BnO (**2j**) | **X** | 70 | 4.2 : 1 | > 20 : 1 |
| | | **Y** | 80 | 10 : 1 | > 20 : 1 |
| 7 | *p*-BrBzO (**2k**) | **X** | 45 | 4.0 : 1 | > 20 : 1 |
| | | **Y** | 76 | 5.4 : 1 | > 20 : 1 |
| 8 | MeO2C (2) (**2l**) | **X** | 50 | 4.2 : 1 | 6.5 : 1 |
| | | **Y** | 70 | 5.8 : 1 | 7.0 : 1 |
| 9 | MeO2C (3) (**2m**) | **X** | 45 | 4.2 : 1 | 5.6 : 1 |
| | | **Y** | 73 | 6.2 : 1 | 7.0 : 1 |
| 10 | EtO2C (4) (**2n**) | **X** | 45 | 4.2 : 1 | 4.5 : 1 |
| | | **Y** | 73 | 5.6 : 1 | 6.4 : 1 |

[a] Method X: Benzyloxyallene was deprotonated with *n*-BuLi at −78 °C, followed by addition of cyclobutanones. Method Y: Benzoxyallene was deprotonated with *n*-BuLi at −78 °C, followed by the addition of 1 equiv of $Et_2Zn$ at 0 °C, and the reaction was stirred at 0 °C for 15 min. The solution was then cooled to −78 °C, followed by the addition of cyclobutanones. [b] Isolated yield of the mixture of diastereomers. [c] The diastereomer ratio (d.r.) values were determined by $^1H$ NMR.

Our results indicated that when bulky substituents were present at the 3-position of the cyclobutanones (entries 1–5), addition of the allenyllithium (method X) led to reactions with high diastereoselectivity (10:1–14:1). On the other hand, less sterically demanding groups at the 3-position (entries 6–10) gave

(11) (a) Trost, B. M.; Schroeder, G. M. *Chem. Eur. J.* **2005**, *11*, 174–184. (b) Trost, B. M.; Xu, J. *J. Am. Soc. Chem.* **2005**, *127*, 17180–17181. (c) Trost, B. M.; Xu, J. *J. Am. Soc. Chem.* **2005**, *127*, 2846–2847.
(12) (a) Lampman, G. M.; Hager, G. D.; Couchman, G. L. *J. Org. Chem.* **1970**, *35*, 2398–402. (b) Sieja, J. B. *J. Am. Soc. Chem.* **1971**, *93*, 130–136. (c) Elgomati, T.; Gasteiger, J.; Lenoir, D.; Ugi, I. *Chem. Ber.* **1976**, *109*, 826–832. (d) Jain, R.; Sponsler, M. B.; Coms, F. D.; Dougherty, D. A. *J. Am. Soc. Chem.* **1988**, *110*, 1356–1366. (e) Dehmlow, E. V.; Bueker, S. *Chem. Ber* **1993**, *126*, 2759–2763. (f) Gil, R.; Fiaud, J.-C. *Bull. Soc. Chim. Fr.* **1994**, *131*, 584–589.

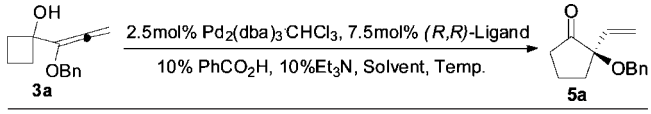
***Table 2.*** Control Experiments[a]




| entry | $Pd_2dba_3 \cdot CHCl_3$ | (*R*,*R*)-**L1** | additives | temp (°C) | conv (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | none | none | none | 60 | <5 | n.d. |
| 2 | none | none | 10 mol% HOAc | 60 | ~10 | n.d. |
| 3 | 5 mol% | 7.5 mol% | none | 60 | ~10 | n.d. |
| 4 | 5 mol% | 7.5 mol% | 10 mol% HOAc | 60 | 100 (85% yield) | 74 |
| 5 | 5 mol% | 7.5 mol% | 10 mol% HOAc | 30 | ~50 (20% yield) | n.d. |
| 6 | 5 mol% | 7.5 mol% | 10 mol% $PhCO_2H$ + 10 mol% $Et_3N$ | 60 | 100 (95% yield) | 83 |
| 7[d] | 5 mol% | 7.5 mol% | 10 mol% $PhCO_2H$ + 10 mol% $Et_3N$ | 30 | ~70 (35% yield)[d] | 85 |

[a] Unless otherwise indicated, all reactions were performed in dichloroethane on a 0.2 mmol scale at 0.1 M for 24 h. [b] Determined by $^1H$ NMR. [c] The enantiomeric excess (ee) values were determined by chiral HPLC. [d] Isolated 35% desired product with other possible products from hydrolysis of **3a**.

***Table 3.*** Optimization of Ring Expansion Reactions[a]




| entry | ligand | solvent | temp (°C) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **L1** | DCE | 60 | 95 | 83 |
| 2 | **L2** | DCE | 60 | 86 | 57 |
| 3 | **L3** | DCE | 60 | 90 | 87 |
| 4 | **L4** | DCE | 60 | 75 | 84 |
| 5 | **L3** | DMSO | 60 | 41 | 64 |
| 6 | **L3** | DMF | 60 | 85 | 79 |
| 7 | **L3** | $CH_3CN$ | 60 | 63 | 82 |
| 8 | **L3** | dioxane | 60 | 40 | 80 |
| 9 | **L3** | THF | 60 | 90 | 80 |
| 10 | **L3** | DME | 60 | 89 | 81 |
| 11 | **L3** | DCE | 40 | 90 | 88 |
| 12 | **L3** | DCE | 30 | 75 | 92 |
| 13[d] | **L3** | DCE | 23 | 60 | 94 |
| 14[d] | **L3** | DCE | 30 | 96 | 92 |

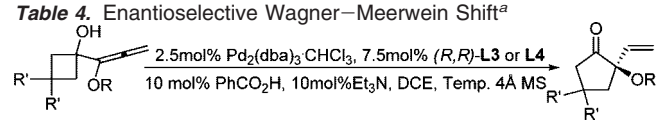
[a] Unless otherwise indicated, all reactions were performed on a 0.2 mmol scale at 0.1 M for 2−24 h. [b] Isolated yield. [c] The ee values were determined by chiral HPLC. [d] Adding 4 Å molecular sieves.

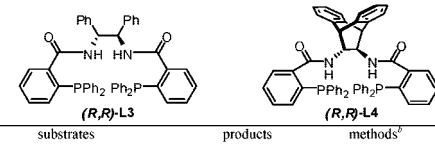
reactions of moderate diastereoselectivity (~4.0:1) with method X. In all cases, diastereomerically enriched compounds could be accessed via the removal of the minor diastereomers by silica gel chromatography. Although the yields of these addition reactions were generally high, significantly lower yields were encountered with substrates bearing ester functionality, presumably due to its susceptibility to nucleophilic attack by the allenyllithium.

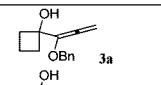
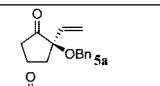
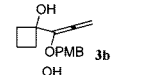
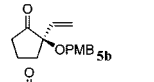
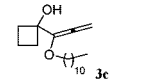
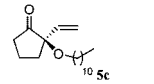
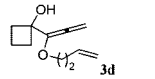
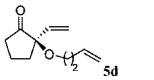
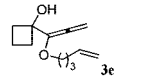
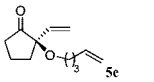
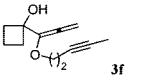
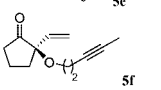
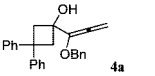
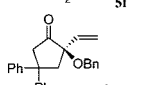
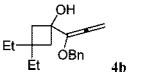
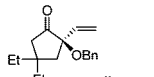
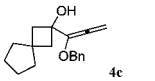
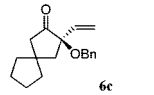
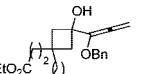
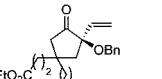
To mitigate the reactivity of the nucleophile, the allenyllithium was replaced with a lithium zincate complex generated from the allenyllithium and diethylzinc. We were pleased to find that the addition reaction to cyclobutanones with this zincate complex (method Y) had greater tolerance for ester groups as well as provided greater diastereoselectivities (entries 6–10, method Y) than the analogous reactions with allenyllithium (method X).

The enhancement of the diastereoselectivity in the addition was presumably due to the greater steric demands of the allenyllithium zincate complexes compared to the simple allenyllithium reagent, which made *trans* addition more favorable. To the best of our knowledge, this reaction is the first example utilizing a lithium zincate complex to improve the chemo- and diastereoselectivity of nucleophilic addition to substituted cyclobutanones.[13]

***Table 4.*** Enantioselective Wagner−Meerwein Shift[a]

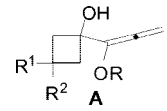



| entry | substrates | products | methods[b] | yield[c] | ee[d] |
|---|---|---|---|---|---|
| 1 |  |  | A | 96% | 92% |
| 2 |  |  | A | 97% | 89% |
| 3 |  |  | A | 100% | 86%[e] |
| 4 |  |  | A | 78% | 87%[e] |
| 5 |  |  | A | 100% | 86%[e] |
| 6 |  |  | A | 88% | 84%[e] |
| 7 |  |  | B | 95% | 95% |
| 8 |  |  | B | 92% | 94% |
| 9 |  |  | B | 93% | 92% |
| 10 |  |  | B | 80% | 94% |

[a] Unless otherwise indicated, all reactions were performed on a 0.5 mmol scale at 0.1 M for 12 h at 23 °C using **L3**. [b] Method A: performed at 30 °C using **L3**. Method B: performed at 60 °C using **L4**. [c] Isolated yield. [d] Unless otherwise indicated, ee values were determined by chiral HPLC. [e] Ee values were determined by chiral GC.

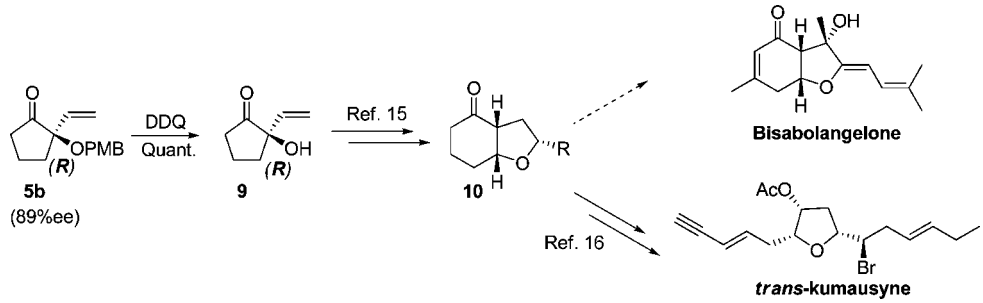
**Rearrangement of Type A Cyclobutanols ($R^1 = R^2$).**



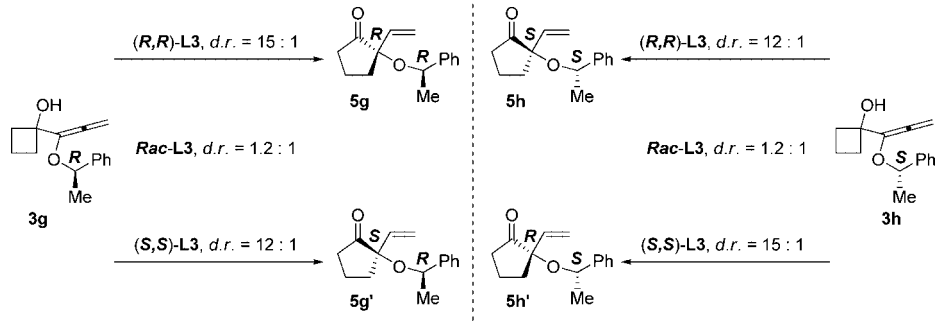

To study the enantioselectivity of the ring expansion reaction, we began with the optimization of the reaction conditions by using benzyloxyallenylcyclobutanol **3a**. Control experiments in Table 2 showed the lack of a background reaction even at 60 °C (entry 1). Furthermore, with either the palladium catalyst or the acid, the reaction times were very long and resulted in low

(13) For a review of lithium zincate complexes, see: Wheatley, A. E. H. *New. J. Chem.* **2004**, *28*, 435–443.

***Scheme 8.*** Assignment of the Absolute Configuration and Synthetic Applications



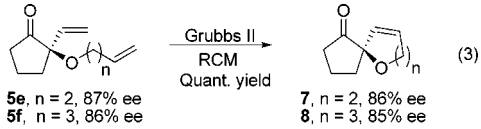

***Scheme 9.*** Ligand Control vs Substrate Control




conversion (entries 2 and 3). Gratifyingly, when both palladium and acid were present (entry 4), the reaction proceeded to full conversion at elevated temperature, which is consistent with the hydropalladation mechanism which requires both the palladium and the acid.[14]

Interestingly, the combination of acid and base, for example benzoic acid and triethylamine, gave the best reactivity and enantioselectivity compared to other additives (entries 6 and 7). This result is consistent with our earlier results on the intermolecular nucleophilic addition of benzyloxyallene **1a**, where controlling the pH is essential for good reactivity and selectivity.[7g] With benzoic acid and triethylamine as the additives, we further optimized the reaction conditions by varying ligands, solvents, and reaction temperatures (Table 3). The optimized reaction conditions afforded the ring expansion product **5a** in a rather impressive 96% yield and 92% ee (entry 14).

We subjected substrates **3a**−**3f** to the optimized reaction conditions. As summarized in Table 4, the reaction was shown to be very general and gave excellent enantioselectivities as well as great functional group tolerance, including benzyl (entry 1), 4-methoxybenzyl (entry 2), alkyl (entry 3), alkene (entries 4 and 5), and alkyne (entry 6). These results potentially provide several approaches for further functionalization, and thereby the ability to access different synthetic targets. For example, ring expansion products **5e** and **5f** were utilized to prepare chiral [4,5] and [4,6] spiro-ring systems such as **5** and **6** via a ring-closing metathesis (eq 3).



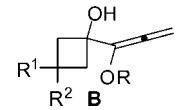

(3)

We also studied substrates with substituents on the cyclobutanol rings, such as 3,3-disubstituted allenylcyclobutanols **4a**−**4d** (entries 7–10). It was found that their reactivity was poorer than that of the unsubstituted cyclobutanols, and lower conversions were obtained at 30 °C. Raising the reaction temperature to 60 °C drove the reaction to completion, albeit with 10–20% decrease in ee using **L3**. Switching to ligand **L4** allowed the ring expansion of 3,3-disubstituted allenylcyclobutanols **4a**−**4d** to be performed at 60 °C with increased reactivity and excellent enantioselectivities. It can be postulated that the rigid backbone of **L4** compared to **L3** makes the enantioselectivity less dependent on the reaction temperature (entries 7–10).

The absolute configuration of the benzyloxy stereocenter was assigned by converting ring expansion product **5b** to **9** (Scheme 8), a known compound whose asymmetric synthesis depended upon a chiral auxiliary. This compound can serve as a useful intermediate for synthesizing natural products, for example, bisabolangelone and *trans*-kumausyne.[15,16]

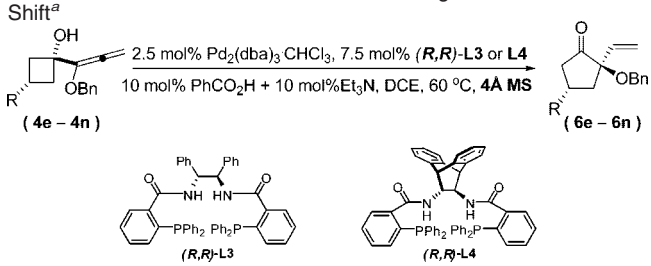
In order to examine the concept of ligand control vs substrate control, we synthesized allenylcyclobutanol substrates **3g** and **3h**, both of which had a chiral alkoxy group on the allene side chain. As shown in Scheme 9, the stereochemical induction in the ring expansion was controlled by our chiral ligands with both enantiomers **3g** and **3h**. Consequently, the chiral side chains had only a slight impact on the stereochemical induction; for example, enantiomer **3g**, which had an alkoxy group with the (*R*) configuration on the side chain, reacted with (*R*,*R*)-**L3** to give a 15:1 dr, compared to a 12:1 dr when (*S*,*S*)-**L3** was employed (Scheme 9). Enantiomer **3h**, which had an alkoxy group with (*S*) configuration on the side chain, gave identical results. For comparison, use of *rac*-**L3** gave a 1.2:1 dr.

**Rearrangement of Type B Cyclobutanols ($R^1 \neq H$, $R^2 = H$).**




After examining the enantioselectivity in the ring expansion reaction, we moved toward examining both diastereo- and

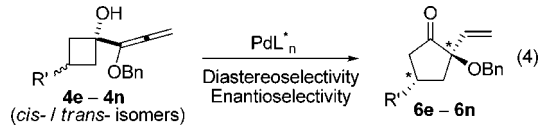
***Table 5.*** Diastereo- and Enantioselective Wagner−Meerwein Shift[a]



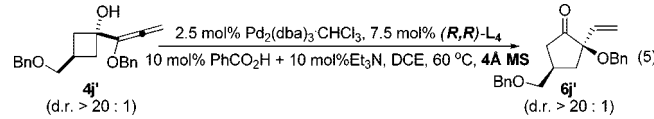

| entry | R[b] | ligand | yield[c] (%) | product d.r.[d] | ee[e] (%) |
|---|---|---|---|---|---|
| 1 | Ph | **L3** | 80 | 8.5 :1 | 83 |
| | **4e / 4e'** = 15 : 1 | | | | |
| 2 | *p*-Br-Ph | **L4** | 78 | 14 : 1 | 90 |
| | **4f / 4f'** > 20 : 1 | | | | |
| 3 | 2-Naphthyl | **L3** | 88 | 14 : 1 | 85 |
| | **4g / 4g'** > 20 : 1 | | | | |
| 4 | *t*-Bu | **L4** | 86 | 10 : 1 | 88 |
| | **4h / 4h'** = 18 : 1 | | | | |
| 5 | $MeO_2C$ | **L4** | 80 | 7.2 : 1 | 88 |
| | **4i / 4i'** = 16 : 1 | | | | |
| 6 | BnO | **L4** | 88 | 10 : 1 | 88 |
| | **4j / 4j'** > 20 : 1 | | | | |
| 7 | *p*-BrBzO | **L4** | 80 | 13 : 1 | 82 |
| | **4k / 4k'** > 20 : 1 | | | | |
| 8 | $MeO_2C$ (2) | **L4** | 73 | 4.2 : 1 | 83 |
| | **4l / 4l'** = 7.0 : 1 | | | | |
| 9 | $MeO_2C$ (3) | **L4** | 68 | 4.4 : 1 | 88 |
| | **4m / 4m'** = 7.0 : 1 | | | | |
| 10 | $EtO_2C$ (4) | **L4** | 71 | 4.2 : 1 | 90 |
| | **4n / 4n'** = 6.4 : 1 | | | | |

[a] Reactions were performed on a 0.2–0.5 mmol scale at 0.1 M overnight. [b] Reactions were run with mixture of diastereomers, the ration of which are shown following the substituents. Structures shown are the major diastereomers. [c] Isolated yield of the major isomers. [d] The dr values were determined by $^1$H NMR. [e] Ee values were determined by chiral HPLC analysis.

enantioselectivity in the reaction with the 3-monosubstituted allenylcyclobutanols, as shown in eq 4. The reaction scope of the ring expansion reaction was examined with substrates **4e**−**4n** as listed in Table 5. The reaction tolerated a variety of structural types, including aryl (entries 1–3), alkyl (entry 4), ether (entry 6), and ester (entries 5, 7–10), and gave high diastereoselectivities and enantioselectivities in most cases.




Since the diastereomeric mixtures resulting from allene additions were not completely separable, the subsequent ring expansions were conducted with the enriched diastereomeric ratio of allenylcyclobutanols obtained after silica gel chromatography. Although the enantioselectivities were independent of the ratio of starting material isomers, the diastereomeric ratios were generally lower than those of the starting materials. This phenomenon could be understood more easily by examining the ring expansion of each diastereomer individually. Toward this end, diastereomers **4j** and **4j′** were fully separated and subjected to the reaction conditions. The ring expansion of the major isomer **4j** gave a 10:1 dr, favoring diastereomer **6j** (Table 5, entry 6), whereas the ring expansion of the minor isomer **4j′** gave a 20:1 dr, favoring diastereomer **6j′** (eq 5). The rationale for a different diastereomeric ratio and diastereomeric outcome will be discussed in the section on mechanism.




The ester side chains in cyclopentanones **6i** and **6m** were utilized in a Claisen condensation to produce 5,5-*cis* and 5,6-*cis* bicyclic products **11** and **12**. Methylation of **12** from the convex face led to *cis* product **13** (Scheme 10). The structures of the bicyclic products were assigned on the basis of NOE study and X-ray single-crystal analysis of product **11**, which also confirmed the absolute configuration of the ring expansion products (Figure 1).

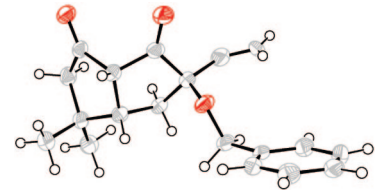
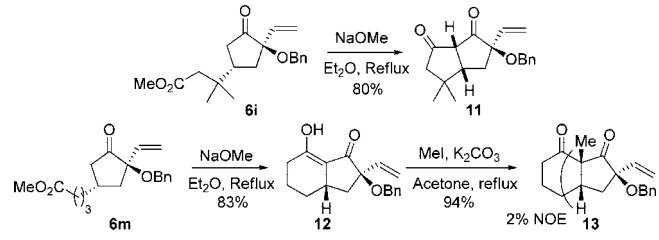


***Figure 1.*** X-ray structure of **11** showing relative configuration. The standard deviation of an observation of unit weight (S)[7] was 0.962. Disorder was encountered with vinyl group (C12a and C12b). Hydrogen on C11 could not be located due to disorder.

***Scheme 10.*** Formation of 5,5- and 5,6-Bicyclic Compounds



***Scheme 11.*** Proposed Working Model for the Enantioselectivity

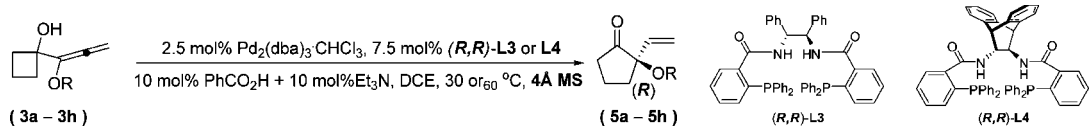
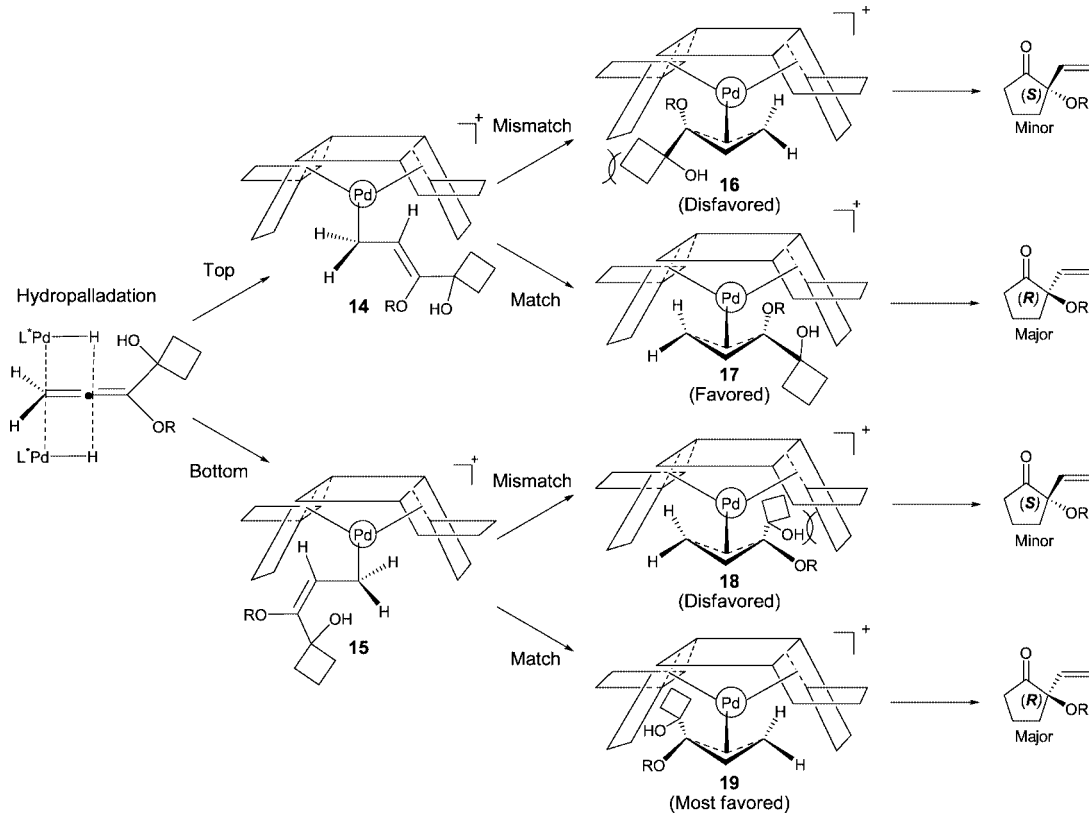



***Chart 1***




**Mechanistic Considerations.** The absolute stereochemistry we obtained with our chiral catalyst could be rationalized very well on the basis of our proposed working model in Scheme 11.[17,18]

The hydropalladation of the allenylcyclobutanol (Chart 1) can occur from either the top or the bottom face of the allene, leading to the formation of $\eta^1$ $\pi$-allylpalladium intermediate **14** or **15**, respectively. Coordination of the palladium to the two $\pi$-faces of the double bond will lead to the formation of either the matched or mismatched $\pi$-allylpalladium intermediate. Intermediate **14** can lead to the formation of *syn* $\pi$-allylpalladium intermediates **16** and **17**. Alternatively, **15** can lead to *anti* $\pi$-allylpalladium intermediates **18** and **19**. Among the four possible $\pi$-allylpalladium intermediates, **16** and **18** are disfavored due to the unfavorable steric interactions between the bulky cyclobutyl groups and the phenyl ring of the chiral ligand. Instead, **17** and **19** are preferred because the cyclobutyl groups are under the flap, thus avoiding the unfavorable steric interactions. Ring expansion of both intermediates **17** and **19** would lead to the major enantiomer with (*R*) configuration. However, according to our previous results, when bulky groups such as a cyclobutyl group are present on the terminal position, they preferred to adopt the *anti* position relative to the $C_2$-H to avoid 1,2-steric interactions.[2] This suggests that intermediate **19** is the favored intermediate overall. Therefore, intermediate **19** should primarily be responsible for the stereochemical outcome of the reaction. As a result, the enantiomer obtained from the reaction indeed had an (*R*) configuration, which was consistent with the prediction of our working model.

For the 3-monosubstituted cyclobutanol substrates, the diastereoselectivity could also be rationalized by the working model shown in Scheme 12. As discussed in Scheme 11, four possible $\pi$-allylpalladium intermediates could be generated in the hydropalladation step. The most favored one is intermediate **17**, in which the bulky cyclobutyl group possessed the *anti* arrangement relative to the $C_2$-H and located under the flap. Therefore, hydropalladation of substrates **20** and **21**should lead to intermediates analogous to those shown in Scheme 11. Because of the 3-substituents, the bonds **a** and **b** undergoing migration are now diastereotopic. Stereoelectronic consideration suggests that the migration event should occur in an antiperiplanar fashion such that the bond that undergoes migration should be *anti* relative to the palladium, i.e., bond **a** in **22** and **25** and bond **b** in **23**and **24**. Only two orientations of the cyclobutanol

(14) Reaction can proceed with Lewis Acid catalysis; for example, Au can catalyze similar reactions, see: Yeom, H.-S.; Yoon, S.-J.; Shin, S. *Tetrahedron Lett.* **2007**, *48*, 4817–4820.

(15) Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Overman, L. E.; Mishra, P. *J. Am. Soc. Chem.* **1991**, *113*, 5365–5378.
(16) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Soc. Chem.* **1991**, *113*, 5378–5384.
(17) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747–760.
(18) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554.

***Scheme 12.*** Proposed Working Model for the Diastereo- and Enantioselectivity

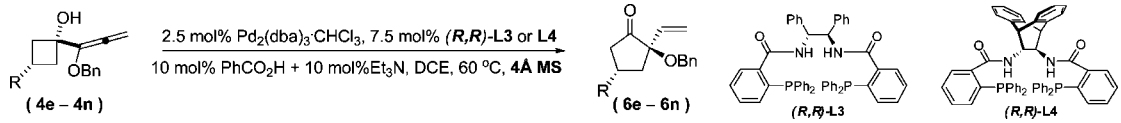
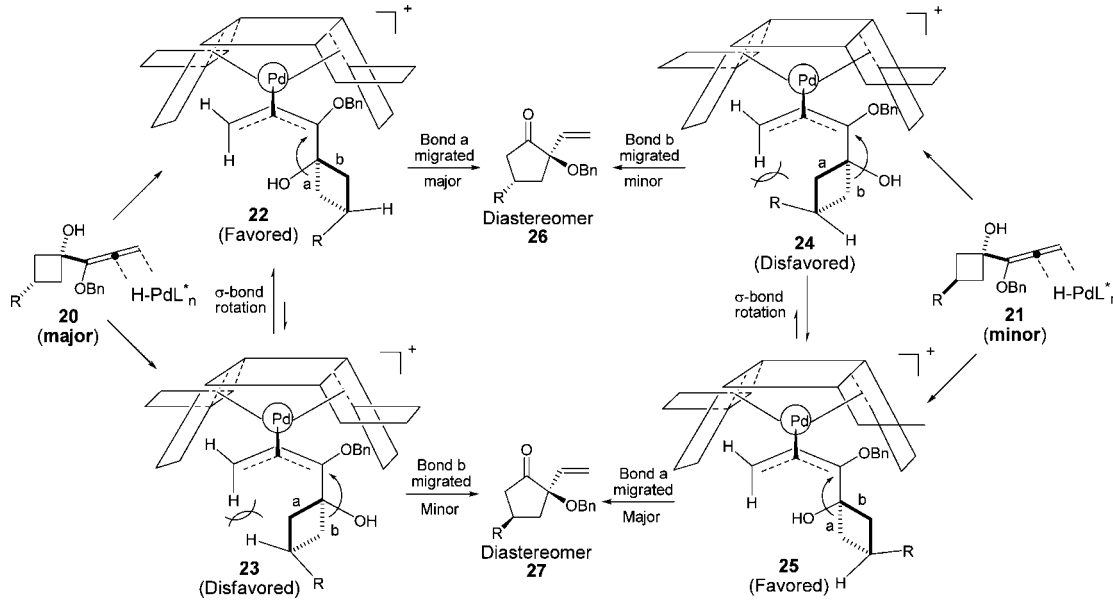



***Chart 2***




will then lead to the migration of bonds **a** and **b**. For the major addition isomer **20**, the favored $\pi$-allylpalladium intermediate can adopt orientations, such as **22** and **23**, where they will lead to the migration of bonds **a** and **b**, respectively. However, in orientation **23**, the bulky cyclobutyl group has a strongly disfavored interaction with the $C_3$-H which is absent in orientation **22**. Thus, **22** is the favored orientation which leads to the migration of bond **a** and the major diastereomer **26**. Similarly, for the minor addition isomer **21**, **25** would be the favored orientation and would lead to the migration of bond **a**, thus leading to the minor diastereomer **27**.

Not only are the major diastereomers from different *cis*/*trans* isomers **20** and **21** different (Chart 2), but also the diastereomeric ratio of the products would be different. For the disfavored orientations **23** and **24**, the latter should be a higher energy intermediate than the former due to stronger steric interaction between the R group (R $\neq$ H) and $C_3$-H. The favored orientations **22** and **25** should have similar stabilities due to the absence of significant steric interactions. Therefore, the energy difference between **24** and **25** should be higher than the one between **22** and **23**. As a result, the diastereomeric ratio for the ring expansion of the minor isomer **21** should be higher than for the major addition isomer **20**. Indeed, this is observed in the independent ring expansions of **4j** and **4j′**, wherein ring expansion of the major isomer **4j** gave a 10:1 dr, favoring diastereomer **6j** (Table 4, entry 6), and ring expansion of the minor isomer **4j′** gave a 20:1 dr, favoring diastereomer **6j′** (eq 5).

## Conclusion

In summary, by applying hydropalladation of allenes, we were able to develop the first asymmetric Wagner−Meerwein shift of allenylcyclobutanol substrates with our palladium catalysts. Diastereoselective preparation of 3-monosubstituted substrates via a novel lithium zincate addition allowed us to examine the diastereoselectivity and led to the creation of two new stereogenic centers in the products. The method provides a general way to synthesize highly substituted chiral cyclopentanones which should have useful synthetic applications. By incorporating an ester side chain in the ring expansion products, 5,5-*cis* and 5,6-*cis* bicyclic compounds were readily accessed as single diastereomers by an intramolecular condensation reaction. The rationalization for diastereoselectivity and enantioselectivity of the reaction using our proposed working model were consistent with experimental results.

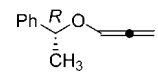
## Experimental Section[22,23]

**General Procedure for Preparation of Allenyl Ethers 1a−1g. Propa-1,2-dienyloxymethyl-benzene (1a).**[7g]


At room temperature, KO*t*Bu (4.3 g, 38.3 mmol) was added into a solution of benzylpropargyl ether (22 g, 130 mmol) in THF (10 mL). The suspension was stirred at room temperature for 3 h, filtered through a Celite pad, and washed with $Et_2O$ (50 mL). The combined solution was concentrated in vacuo and purified by flash chromatography (1% diethyl ether in petroleum ether) to afford **1a** as a light yellowish liquid. Yield: 18 g (82%).

$R_f$ (5% ether/petroleum ether): 0.84. IR (neat): 3034, 2925, 2868, 1953, 1726, 1454, 1442, 1349, 1190, 1043, 893, 737, 698 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.35−7.20 (m, 5H), 6.85 (dd, $J$ = 6.3 Hz, 1H), 5.48 (d, $J$ = 6.1 Hz, 2H), 4.62 (s, 2H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 132.0, 128.2, 123.5, 123.3, 123.1, 118.3, 101.1, 81.8, 66.1, 48.1, 24.8, 23.9, 17.0.

**((*R*)-1-Propa-1,2-dienyloxy-ethyl))-benzene (1g).**

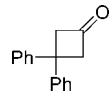


Allenyl ether **1g** was prepared according to the general procedure starting from (*R*)-1-(prop-2-ynyloxy)-ethyl benzene (2.0 g, 12.5 mmol). Yield: 1.4 g (70%, 80% *brsm*), recovered 0.20 g of starting material.

$R_f$ (10% ether/petroleum ether): 0.80. IR (neat): 3064, 3031, 2977, 1953, 1494, 1449, 1273, 1349, 1196, 1068, 1028, 890, 854, 760, 697, 668 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.34−7.24 (m, 5H), 6.22 (t, $J$ = 6.0 Hz, 1H), 5.34 (m, 1H), 5.21 (m, 1H), 4.80 (q, $J$ = 6.5 Hz, 1H), 1.51 (m, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 201.9, 143.1, 128.3, 127.4, 126.0, 120.1, 90.1, 76.6, 23.3, $[\alpha]_D^{24.1}$ = 218.8 ($c$ = 1.40, $CH_2Cl_2$). Anal. Calcd for $C_{14}H_{16}O_2$: C, 82.46; H, 7.55. Found: C, 82.59; H, 7.52.

**General Procedure for Preparation of Substituted Cyclobutanones 2a−2n.** The general procedure involved a zinc-catalyzed ketene [2+2] reaction followed by zinc-catalyzed dehalogenation reduction.[19]

**3,3-Diphenyl-cyclobutanone (2a).**[20]

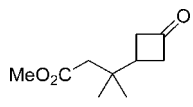



**Zinc-Catalyzed Ketene [2+2] Reaction.** To a stirred suspension of activated Zn−Cu[19] (4.90 g, 75 mmol) and ethene-1,1-diyldibenzene (5.41 g, 30 mmol) in dry $Et_2O$ (70 mL) was added dropwise through an addition funnel, during 2 h at reflux, a solution of trichloroacetic chloride (6.7 mL, 60 mmol) and phosphorus oxychloride (5.7 mL, 60 mmol) in $Et_2O$ (30 mL). The suspension was stirred overnight at reflux. The mixture was cooled to room temperature and then filtered through a pad of Celite. The residue was washed with $Et_2O$ (3 × 15 mL). The combined solution was concentrated and then distilled in a Kugelrohr short-path distillation apparatus (200−250 °C, 0.2 mTorr). The collected liquid was directly taken to the next step.

**Zinc-Catalyzed Dehalogenation Reduction.** The solution of the previous liquid in acetic acid (25 mL) was added dropwise to a vigorously stirred suspension of zinc dust (7.84 g, 120 mmol) in acetic acid (25 mL) at 0 °C. After the addition, the reaction mixture was heated at 70 °C for 2 h. The mixture was allowed to cool to room temperature and then evacuated to get rid of most of the acetic acid. The residue was dissolved in $Et_2O$ (50 mL) and then poured into a separation funnel containing water (50 mL) and $Et_2O$ (50 mL). The organic layer was washed with water (3 × 25 mL), saturated sodium bicarbonate solution (2 × 30 mL), and brine (50 mL) and dried over $MgSO_4$. The solution was then filtered and concentrated, followed by purification with flash chromatography (15% ether in petroleum ether). Yield: 3.5 g (61%) over two steps; white solid; mp = 76−78 °C.

$R_f$ (25% ether/petroleum ether): 0.53. IR (neat): 3082, 3026, 2972, 2924, 1787, 1595, 1580, 1493, 1449, 1375, 1239, 1127, 1084, 1022, 888, 777, 750, 710, 660, 584, $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.35−7.26 (m, 8H), 7.24−7.21 (m, 2H), 3.82 (s, 4H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 205.6, 147.2, 130.3, 128.6, 126.6, 60.5, 42.0.

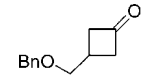
**3-Methyl-3-(3-oxo-cyclobutyl)-butyric Acid Methyl Ester (2i).**




Cyclobutanone **2i** was prepared according to the general procedure for preparation of substituted cyclobutanones starting from methyl 3,3-dimethylpent-4-enoate (4.21 g, 29.6 mmol), except that the purification was done with flash chromatography. Yield: 3.0 g (55%, 70% *brsm*), recovered starting material 0.63 g.

$R_f$ (50% ether/petroleum ether): 0.58. IR (neat): 2963, 1785, 1735, 1469, 1438, 1391, 1326, 1288, 1239, 1210, 1156, 1112, 1047, 1015, 885, 856, 760 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 3.55 (s, 3H), 2.84–2.74 (m, 4H), 2.43–2.38 (m, 1H), 2.15 (s, 2H), 0.94 (s, 6H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 206.6, 171.8, 51.1, 47.3, 44.7, 34.1, 33.1, 23.1. HRMS (EI+): $m/z$ calcd for $C_{10}H_{16}O_3$, 184.1099 ($[M]^+$); found, 183.1013 ($M - H]^+$), 169.0867 ($[M - CH_3]^+$).

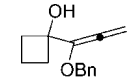
**3-Benzyloxymethyl-cyclobutanone (2j).**[21]




Cyclobutanone **2j** was prepared according to the general procedure for preparation of substituted cyclobutanones staring from allyloxymethyl-benzene (5.50 g, 37.1 mmol). Yield: 6.0 g (58%) over two steps.

$R_f$ (25% ether in petroleum ether): 0.40. IR (neat): 3031, 2857, 1782, 1496, 1454, 1383, 1365, 1206, 1093, 1028, 738, 698 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.37–7.25 (m, 5H), 4.55 (s, 2H), 3.58 (d, $J$ = 6.5 Hz, 2H), 3.15–3.08 (m, 2H), 2.90–2.84 (m, 2H), 2.72–2.64 (m, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 207.4, 137.9, 128.4, 127.7, 127.6, 73.1, 72.8, 49.9, 23.5.

**General Procedure for Preparation of Allenylcyclobutanols 3a−3h. 1-(1-Benzyloxy-propa-1,2-dienyl)-cyclobutanol (3a).**



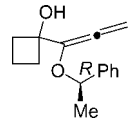

To a stirred solution of benzyloxyallene **3a** (1.46 g, 10.0 mmol) in THF (40 mL) was added dropwise a 2.70 M solution of *n*-BuLi (3.70 mL, 10.0 mmol) in hexane at −78 °C. After stirring was continued for 1 h at −78 °C, cyclobutanone (0.75 mL, 10.0 mmol) was added dropwise to this solution, and stirring was continued for 2 h at −78 °C. The solution was then warmed to room temperature. The reaction mixture was diluted with water (20 mL) and extracted with diethyl ether (3 × 15 mL). The combined extracts were washed with brine, dried over $Mg_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (15% diethyl ether in petroleum ether, silica gel) to give allenylcyclobutanol **3a** as a white solid. Yield: 2.05 g (95%); mp = 43−45 °C.

$R_f$ (25% ether/petroleum ether): 0.30. IR (neat): 3420, 3089, 3062, 3035, 2981, 2936, 2864, 1952, 1495, 1450, 1374, 1244, 1177, 1136, 1096, 1024, 980, 953, 885, 850, 809, 728, 693 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.35−7.20 (m, 5H), 5.58 (s, 2H), 4.67 (s, 2H), 2.67 (s, 1H), 2.37−2.37 (m, 2H), 2.22−2.14 (m, 2H), 1.82−1.73 (m, 1H), 1.61−1.50 (m, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 196.3, 137.5, 135.8, 128.4, 127.9, 127.8, 92.6, 73.8, 71.0, 34.6, 12.8. HRMS (EI+): $m/z$ calcd for $C_{14}H_{16}O_2$, 216.1150 ($[M]^+$); found, 216.1148.

**1-[1-(1-(*R*)-Phenyl-ethoxy)-propa-1,2-dienyl]-cyclobutanol (3g).**

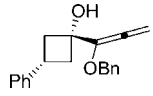
Allenylcyclobutanol **3g** was prepared according to the general procedure for preparation of allenylcyclobutanols starting from allenyl ether **1g** (0.65 g, 4.06 mmol) and cyclobutanone (1.5 mL, 4.05 mmol). Yield: 0.85 g (92%).

(19) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879.
(20) Cao, W.; Erden, I.; Grow, R. H.; Keeffe, J. R.; Song, J.; Trudell, M. B.; Wadsworth, T. L.; Xu, F.; Zheng, J. *Can. J. Chem.* **1999**, *77*, 1009.
(21) Rammeloo, T.; Stevens, C. *Chem. Commun.* **2002**, *3*, 250.
(22) Some experimental details have been described: Trost, B. M.; Xie, J. *J. Am. Soc. Chem.* **2006**, *129*, 6044–6045.
(23) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC-655683 (**7**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Rd., Cambridge CB21EZ, UK (fax +44 1223-336-033; E-mail data_request@ccdc.cam.ac.uk).



$R_f$ (25% ether/petroleum ether): 0.35. IR (neat): 3424, 3086, 3063, 3031, 2977, 2943, 1954, 1494, 1450, 1372, 1244, 1206, 1181, 1133, 1091, 1028, 956, 910, 885, 760, 731, 699, 546 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$7.33−7.23 (m, 5H), 5.47 (d, $J$ = 7.8 Hz, 1H), 5.30 (d, $J$ = 7.8 Hz, 1H), 4.85 (q, $J$ = 6.5 Hz, 1H), 2.70 (broad, 1H), 2.32−2.26 (m, 2H), 2.20−2.14 (m, 2H), 1.77−1.71 (m, 1H), 1.52 (d, $J$ = 6.5 Hz, 3H), 1.54−1.46 (m, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 196.9, 143.3, 134.2, 128.2, 127.3, 125.8, 91.9, 76.1, 73.6, 34.5, 34.2, 23.2, 12.6. $[\alpha]_D^{24.8}$ = 154.6 ($c$ = 2.30, $CH_2Cl_2$). HRMS (EI+): $m/z$ calcd for $C_{15}H_{18}O_2$, 230.1307 ($[M]^+$); found, 230.1310.

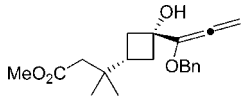
**1-(1-Benzyloxy-propa-1,2-dienyl)-3-phenyl-cyclobutanol (4e).**



**Method A.** To a stirred solution of benzyloxyallene (161 mg, 1.1 mmol) in THF (7 mL) was added dropwise a 2.43 M solution of *n*-BuLi (0.45 mL, 1.1 mmol) in hexane at −78 °C. After stirring was continued for 1 h at −78 °C, a solution of cyclobutanone **2e** (146 mg, 1.0 mmol) in THF (3 mL) was added dropwise, and stirring was continued for 2 h at −78 °C. The solution was then warmed to room temperature. The reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (3 × 5 mL). The combined extracts were washed with brine, dried over $Mg_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (20% diethyl ether in petroleum ether, silica gel) to give the desired allenylcyclobutanol as a yellowish liquid. Reaction dr = 14:1 (by $^1H$ NMR). Isolated yield of the major isomer **4e**: 260 mg (85%), dr = 15:1 (by $^1H$ NMR).

**Major diastereomer 4e.** $R_f$ (50% ether/petroleum ether): 0.60. IR (neat): 3416, 3028, 2934, 1954, 1603, 1496, 1454, 1378, 1238, 1155, 1094, 1029, 892, 751, 697 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$7.38–7.15 (m, 10H), 5.63 (s, 2H), 4.71 (s, 2H), 3.03 (m, 1H), 2.87(s, 1H), 2.82–2.77 (m, 2H), 2.37–2.32 (m, 1H), 0.82 (s, 9H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 196.1, 144.8, 137.2, 135.5, 128.4, 128.2, 127.9, 127.8, 126.6, 125.9, 92.7, 71.0, 69.7, 42.4, 30.6. HRMS (EI+): $m/z$ calcd for $C_{20}H_{20}O_2$, 292.1463 ($[M]^+$); found, 292.1467. Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89. Found: C, 81.91; H, 7.03.

**3-[3-(1-Benzyloxy-propa-1,2-dienyl)-3-hydroxy-cyclobutyl]-3-methyl-butyric Acid Methyl Ester (4i).**

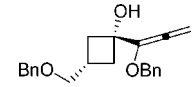


Allenylcyclobutanol **4i** was prepared according to the general procedure Method A, starting from the benzoxyallene (715 mg, 4.89 mmol) and cyclobutanone **2i** (900 mg, 4.89 mmol). Reaction dr = 10:1 (by $^1H$ NMR). Isolated yield of the major isomer **4i**: 1.20 g (75%), dr = 16:1 (by $^1H$ NMR).

**Major diastereomer 4i.** $R_f$ (50% ether/petroleum ether): 0.46. IR (neat): 3449, 3032, 2954, 1954, 1735, 1452, 1369, 1324, 1235, 1124, 1015, 889, 826, 737, 697 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.36–7.26 (m, 5H), 5.58 (s, 2H), 4.67 (s, 2H), 3.62 (s, 3H), 2.77 (broad, 1H), 2.27–2.23 (m, 2H), 2.12 (s, 1H), 1.96–1.92 (m, 2H), 1.85–1.79 (m, 2H), 0.95 (s, 6H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 196.1, 172.7, 137.2, 135.6, 128.3, 127.8, 127.7, 92.4, 70.9, 68.8, 51.1, 44.6, 35.8, 35.5, 34.0, 23.6. HRMS (EI+): $m/z$ calcd for $C_{20}H_{26}O_4$, 330.1831 ($[M]^+$); found, 330.1840. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.56; H, 7.72.

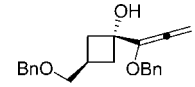
**3-Benzyloxymethyl-1-(1-benzyloxy-propa-1,2-dienyl)-cyclobutanol (4j). Method B.** To a stirred solution of benzyloxyallene (146 mg, 1.0 mmol) in THF (7 mL) was added dropwise a 2.50 M solution of *n*-BuLi (0.40 mL, 1.0 mmol) in hexane at −78 °C. Stirring was continued for 1 h at −78 °C, and then the solution was warmed to 0 °C and a 1.0 M solution of $Et_2Zn$ in hexane (1.0 mL, 1.0 mmol) was added. The resulting solution was stirred at 0 °C for 15 min and cooled to −78 °C, followed by the addition of a solution of cyclobutanone **2j** (190 mg, 1.0 mmol) in THF (3 mL), and stirring was continued for 2 h at −78 °C. The solution was then warmed to room temperature. The reaction mixture was diluted with saturated $NH_4Cl$ (10 mL) and extracted with diethyl ether (3 × 5 mL). The combined extracts were washed with brine (10 mL), dried over $Mg_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (30% diethyl ether in petroleum ether, silica gel) to give allenylcyclobutanol **4j** as a yellowish oil. Reaction dr = 10:1 (by $^1H$ NMR). Isolated yield of the major isomer **4j**: 269 mg (80%), dr > 20:1 (by $^1H$ NMR).

**Major diastereomer 4j.**



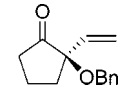
$R_f$ (50% ether/petroleum ether): 0.53. IR (neat): 3448, 3065, 3033, 2962, 2934, 2875, 1954, 1744, 1498, 1456, 1377, 1287, 1222, 1185, 1130, 1080, 1008, 887, 734, 696 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.34–7.26 (m, 10H), 5.57 (s, 2H), 4.67 (s, 2H), 4.51 (s, 2H), 3.47 (d, $J$ = 6.5 Hz, 2H), 2.98 (s, 1H), 2.54–2.50 (m, 2H), 2.20–2.14 (m, 1H), 1.99–1.95 (m, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 196.1, 138.3, 137.3, 135.7, 128.3, 127.8, 127.7, 127.6, 127.5, 92.7, 74.5, 73.0, 70.9, 70.6, 38.0, 25.9. HRMS (EI+): $m/z$ calcd for $C_{22}H_{24}O_3$, 336.1725 ($[M]^+$), 245.1178 ($[M - Bn]^+$); found, 245.1185 ($[M - Bn]^+$). LRMS (ESI+): $m/z$ calcd for $C_{22}H_{24}O_3$, 359.1 ($[M + Na]^+$); found, 359.1 ($[M + Na]^+$).

**Minor diastereomer 4j′.**



$R_f$ (50% ether/petroleum ether): 0.45. IR (neat): 3448, 3065, 3033, 2962, 2934, 2875, 1954, 1744, 1498, 1456, 1377, 1287, 1222, 1185, 1130, 1080, 1008, 887, 734, 696 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.35–7.26 (m, 10H), 5.51 (s, 2H), 4.64 (s, 2H), 4.48 (s, 2H), 3.42 (d, $J$ = 7.2 Hz, 2H), 2.73–2.67 (m, 1H), 2.49 (s, 1H), 2.29–2.25 (m, 2H), 2.21–2.17 (m, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 196.3, 138.5, 137.3, 136.6, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 93.2, 74.1, 72.9, 72.3, 70.9, 36.5, 26.4. HRMS (EI+): $m/z$ calcd for $C_{22}H_{24}O_3$, 336.1725 ($[M]^+$); found, 336.1728.

**General Procedure for Palladium-Catalyzed Ring Expansion Reactions. 2-Benzyloxy-2-vinyl-cyclopentanone (5a).**

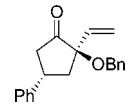


Dichloroethane (DCE) (25 mL, which was dried and freeze–pump–thaw degassed) was added into the mixture of $Pd_2(dba)_3 \cdot CHCl_3$ (65.8 mg, 63.6 $\mu$mol) and (*R*,*R*)-stilbene ligand **L3** (150.3 mg, 0.191 mmol) within a flask which was three times evacuated and flushed with argon. The mixture was stirred under argon at room temperature for 15 min. It was then cannulated into the allenylcyclobutanol **3a** (550 mg, 2.54 mmol) with 4 Å molecular sieves, three times evacuated and flushed with argon, followed by addition of $PhCO_2H$ (0.2 5 mL, 1 M in $CH_2Cl_2$, 0.25 mmol) and $Et_3N$ (0.25 mL, 1 M in $CH_2Cl_2$, 0.25 mmol) respectively via syringe. After stirring under argon at 30 °C for 12 h, the mixture was filtered through a Celite pad, concentrated, and purified by direct flash

chromatography (5% diethyl ether in petroleum ether, silica gel) to give the desired product **5a** (530 mg, 96%). Racemic product was prepared using the same procedure with racemic standard Trost ligand **L1**.

$R_f$ (25% ether/petroleum ether): 0.50. IR (neat): 3085, 3058, 3022, 2958, 2913, 2877, 1746, 1492, 1451, 1401, 1379, 1157, 1130, 1080, 1053, 931, 808, 736, 695, 659 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.35–7.20 (m, 5H), 5.92 (dd, $J$ = 17.5 Hz, 11 Hz, 1H), 5.46 (dd, $J$ = 11 Hz, 0.9 Hz, 1H), 5.41 (dd, $J$ = 17.5 Hz, 0.9 Hz 1H), 4.52 (d, $J$ = 11.5 Hz, 1H), 4.48 (d, $J$ = 11.5 Hz, 1H), 2.41−2.25 (m, 2H), 2.24−2.18 (m, 1H), 2.14−2.02 (m, 2H), 1.88−1.79 (m, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 196.3, 137.5, 135.8, 128.4, 127.9, 127.8, 92.6, 73.8, 71.0, 34.6, 12.8. $[\alpha]_D^{24.8}$ = −68.58 ($c$ = 1.70, $CH_2Cl_2$). Enantiomeric excess was determined to be 92% ee by chiral HPLC (Chiralpak OD, heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, $t_1$ = 17.22 min (major), $t_2$ = 20.25 min). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.90; H, 7.36.

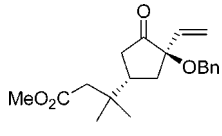
**2-Benzyloxy-4-phenyl-2-vinyl-cyclopentanone (6e).**




DCE (2 mL, which was dried and freeze–pump–thaw degassed) was added into the mixture of $Pd_2(dba)_3 \cdot CHCl_3$ (5.2 mg, 5.0 $\mu$mol) and (*R*,*R*)-stilbene ligand **L3** (11.8 mg, 0.015 mmol) within a flask which was three times evacuated and flushed with argon. The mixture was stirred under argon at room temperature for 15 min. It was then cannulated into a flask charged with allenylcyclobutanol **4e** (58.5 mg, 0.20 mmol) and 4 Å molecular sieves, three times evacuated and flushed with argon, followed by addition of $PhCO_2H$ (20 $\mu$L, 1.0 M in $CH_2Cl_2$, 0.020 mmol) and $Et_3N$ (20 $\mu$L, 1.0 M in $CH_2Cl_2$, 0.020 mmol) respectively via syringe. After stirring under argon at 60 °C for 6 h, the mixture was filtered through a Celite pad, concentrated, and purified by direct flash chromatography (10% diethyl ether in petroleum ether, silica gel) to give the desired product **6e**: dr = 8.3:1 (by $^1H$ NMR). Isolated yield of the major isomer **6e**: 47 mg (89%); 88% ee.

**Major diastereomer 6e.** $R_f$ (25% ether in petroleum ether): 0.69. IR (neat): 3030, 2924, 2855, 1741, 1652, 1497, 1455, 1274, 1215, 1058, 994, 930, 803, 761, 698 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.37–7.28 (m, 10H), 6.08 (dd, $J_1$ = 18.0 Hz, $J_2$ = 10.8 Hz, 1H), 5.49 (dd, $J_1$ = 18.0 Hz, $J_2$ = 1.0 Hz, 1H), 5.47 (dd, $J_1$ = 10.8 Hz, $J_2$ = 1.0 Hz, 1H), 4.58 (d, $J$ = 11.6 Hz, 1H), 4.44 (d, $J$ = 11.6 Hz, 1H), 2.91 (ddd, $J_1$ = 19.0 Hz, $J_2$ = 7.9 Hz, $J_3$ = 2.7 Hz, 1H), 2.66 (ddd, $J_1$ = 13.8 Hz, $J_2$ = 6.0 Hz, $J_3$ = 2.7 Hz, 1H), 2.41 (dd, $J_1$ = 19.0 Hz, $J_2$ = 11.1 Hz, 1H), 2.05 (dd, $J_1$ = 13.9 Hz, $J_2$ = 12.1 Hz, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 211.9, 142.7, 138.2, 134.3, 129.7, 128.7, 128.4, 127.6, 126.8, 126.7, 119.6, 83.5, 66.6, 44.7, 44.3, 37.3. HRMS (EI+): $m/z$ calcd for $C_{18}H_{24}O_2$, 272.1776 ($[M]^+$); found, 272.1781. $[\alpha]_D^{22.0}$= −64.17 ($c$ = 1.56, $CH_2Cl_2$). Enantiomeric excess was determined to be 88% ee by chiral HPLC (Chiralpak ODH, 220 nm, heptane/*i*-PrOH = 99:1, 0.8 mL/min, $t_1$ = 20.28 min (major), $t_2$ = 22.03 min).

**3-(3-Benzyloxy-4-oxo-3-vinyl-cyclopentyl)-3-methyl-butyric Acid Methyl Ester (6i).**

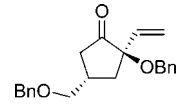



Cyclopentanone **6i** was prepared from allenylcyclobutanol **6i** (132.2 mg, 0.40 mmol) according to the general procedure for ring expansion with (*R*,*R*)-anthracene ligand **L4** (24.4 mg, 0.030 mmol) at 60 °C: dr = 7.2:1 (by $^1H$ NMR). Isolated yield of the major isomer **6i**: 106 mg (80%); 88% ee.

**Major diastereomer 6i.** $R_f$ (25% ether in petroleum ether): 0.43. IR (neat): 3089, 3031, 2963, 2877, 1738, 1632, 1610, 1453, 1372, 1328, 1232, 1095, 940, 826, 735, 698 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.34–7.24 (m, 5H), 6.00 (dd, $J_1$ = 18.2 Hz, $J_2$ = 10.8 Hz, 1H), 5.45–5.42 (m, 2H), 4.50 (d, $J$ = 11.6 Hz, 1H), 4.36 (d, $J$ = 11.4 Hz, 1H), 3.64 (s, 3H), 2.57–2.44 (m, 2H), 2.30–2.25 (m, 1H), 2.22 (s, 2H), 2.04 (dd, $J_1$ = 18.2 Hz, $J_2$ = 10.6 Hz, 1H), 1.66 (m, 1H), 1.00 (s, 3H), 0.99 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 212.1, 172.1, 138.3, 134.5, 128.2, 127.43, 127.40, 119.2, 83.5, 66.3, 51.3, 45.0, 41.2, 38.5, 37.2, 34.3, 24.0, 23.9. HRMS (EI+): $m/z$ calcd for $C_{20}H_{26}O_4$, 330.1831 ($[M]^+$); found, 330.1845. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.58; H, 8.05. $[\alpha]_D^{25.2}$ = −21.12 ($c$ = 1.10, $CH_2Cl_2$). Enantiomeric excess was determined to be 88% ee by chiral HPLC (Chiralpak AD, 220 nm, heptane/*i*-PrOH = 99.5:0.5, 220 nm, 1.0 mL/min, $t_1$ = 21.28 min (major), $t_2$ = 24.67 min).

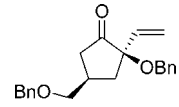
**2-Benzyloxy-4-benzyloxymethyl-2-vinyl-cyclopentanone (6j).** Cyclopentanone **6j** was prepared from allenylcyclobutanol **4j** (168 mg, 0.50 mmol) according to the general procedure for ring expansion with (*R*,*R*)-anthracene ligand **L4** (30.5 mg, 0.0375 mmol) at 60 °C. d.r. = 10:1 (by $^1H$ NMR). Isolated yield of the major isomer **6j**149 mg (88%), 88% ee.

**Major diastereomer 6j.**



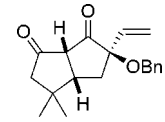

$R_f$ (25% ether in petroleum ether): 0.45. IR (neat): 3088, 3064, 3031, 2929, 2858, 1740, 1654, 1622, 1496, 1454, 1366, 1346, 1211, 1187, 1104, 1027, 992, 936, 736, 697 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.40–7.23 (m, 10H), 6.01 (dd, $J_1$ = 18.0 Hz, $J_2$ = 10.8 Hz, 1H), 5.46–5.41 (m, 2H), 4.52 (s, 2H), 4.50 (d, $J$ = 11.0 Hz, 1H), 4.36 (d, $J$ = 11.0 Hz, 1H), 3.52–3.43 (m, 2H), 2.84–2.74 (m, 1H), 2.64–2.57 (m, 1H), 2.40–2.34 (m, 1H), 2.13 (dd, $J_1$ = 19.1 Hz, $J_2$ = 10.8 Hz, 1H), 1.80 (dd, $J_1$ = 14.0 Hz, $J_2$ = 10.8 Hz, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 212.4, 138.3, 138.2, 134.5, 129.0, 128.40, 128.38, 128.32, 127.7, 127.6, 127.5, 119.4, 83.2, 73.1, 72.7, 66.4, 40.4, 39.3, 32.4. HRMS (EI+): $m/z$ calcd for $C_{22}H_{34}O_3$, 336.1725 ($[M]^+$); found, 336.1726. Anal. Calcd for $C_{14}H_{16}O_2$: C, 78.23; H, 7.88. Found: C, 78.41; H, 7.70. $[\alpha]_D^{26.3}$ = −43.97 ($c$ = 1.60, $CH_2Cl_2$). Enantiomeric excess was determined to be 88% ee by chiral HPLC (Chiralpak AD, 220 nm, heptane/*i*-PrOH = 99:1, 0.8 mL/min, $t_1$ = 12.13 min (major), $t_2$ = 13.84 min).

**Minor diastereomer 6j′.**




$R_f$ (25% ether in petroleum ether): 0.31. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.36–7.26 (m, 10H), 5.87 (dd, $J_1$ = 17.7 Hz, $J_2$ = 10.6 Hz, 1H), 5.46 (dd, $J_1$ = 10.7 Hz, $J_2$ = 0.9 Hz, 1H), 5.40 (dd, $J_1$ = 17.7 Hz, $J_2$ = 0.9 Hz, 1H), 4.65 (d, $J$ = 11.4 Hz, 1H), 4.52 (s, 2H), 4.45 (d, $J$ = 11.4 Hz, 1H), 3.50 (dd, $J_1$ = 6.0 Hz, $J_2$ = 1.5 Hz, 2H), 2.54–2.36 (m, 3H), 2.19 (dd, $J_1$ = 18.5 Hz, $J_2$ = 8.7 Hz, 1H), 1.99 (dd, $J_1$ = 12.8 Hz, $J_2$ = 10.1 Hz, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 214.2, 138.4, 138.1, 135.3, 128.4, 128.3, 127.7, 127.6, 127.5, 125.5, 119.9, 85.2, 73.3, 73.2, 66.8, 40.0, 37.3, 31.2, 30.3.

**(2*R*,7*R*,8*S*)-2-Benzyloxy-4,4-dimethyl-2-vinyl-hexahydro-pentalene-1,6-dione (11).**



Cyclopentanone **6i** (49.6 mg, 0.15 mmol) was dissolved in 15 mL of $Et_2O$, followed by addition of NaOMe (12.2 mg, 0.225 mmol). The solution was heated at reflux under $N_2$ overnight, quenched with aqueous saturated $NaHCO_3$, and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by silical gel flash chromatography (25% $Et_2O$ in petroleum ether) to give a white solid. Reaction dr > 10:1. A single isomer was isolated. Yield: 38 mg (85%). The solid was dissolved in $Et_2O$. Slow evaporation of solvent afforded the white crystal which was used for X-ray analysis.

$R_f$ (50% ether in petroleum ether): 0.59. IR (neat): 3032, 2959, 2927, 2869, 1767, 1719, 1454, 1374, 1267, 1116, 1060, 948, 876, 741, 699 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.35–7.26 (m, 5H), 6.00 (dd, $J_1 = 18.1$ Hz, $J_2 = 10.8$ Hz, 1H), 5.46 (dd, $J_1 = 10.8$ Hz, $J_2 = 1.0$ Hz, 1H), 5.45 (dd, $J_1 = 18.0$ Hz, $J_2 = 1.0$ Hz, 1H), 4.53 (d, $J = 11.5$ Hz, 1H), 4.29 (d, $J = 11.5$ Hz, 1H), 3.38 (dd, $J_1 = 7.8$ Hz, $J_2 = 2.6$ Hz, 1H), 2.94 (m, 1H), 2.42 (ddd, $J_1 = 14.3$ Hz, $J_2 = 7.0$ Hz, $J_3 = 2.8$ Hz, 1H), 2.28 (d, $J = 18.4$ Hz, 1H), 2.13 (d, $J = 18.4$ Hz, 1H), 1.64 (dd, $J_1 = 14.4$ Hz, $J_2 = 12.0$ Hz, 1H), 1.16 (s, 3H), 1.09 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 207.9, 202.1, 137.8, 133.3, 128.4, 127.7, 127.6, 120.1, 85.2, 66.9, 62.8, 49.2, 46.2, 38.2, 35.9, 30.2, 23.5. HRMS (EI+): *m/z* calcd for $C_{19}H_{22}O_3$, 298.1569 ($[M]^+$), 207.1022 ($[M - Bn]^+$); found, 207.1028 ($[M - Bn]^+$). LRMS (ESI+): *m/z* calcd for $C_{19}H_{22}O_3$, 299.2 ($[M + H]^+$), 321.2 ($[M + Na]^+$); found, 299.2 ($[M + H]^+$), 321.2 ($[M + Na]^+$). $[\alpha]_D^{22.8} = -73.55$ ($c = 1.50$, $CH_2Cl_2$).

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**Supporting Information Available:** Complete experimental details, spectra, X-ray structure report, and X-ray crystallographic data (CIF) for **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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