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Palladium-Catalyzed Asymmetric Allylic Alkylation of *meso*- and *dl*-1,2-Divinylethylene Carbonate

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The development of new reactions that produce enantiomerically pure compounds from inexpensive readily available achiral or racemic starting materials represents a continuing major challenge. In our efforts directed toward this goal, we have explored palladium-catalyzed asymmetric allylic alkylation (Pd AAA) processes that rely on either the ionization of enantiotopic leaving groups or nucleophilic addition to chiral π-allylpalladium complexes as the enantiodetermining steps.[1,2] Herein we wish to report the first example whereby both methods of enantiodiscrimination act in concert to produce chiral materials in high enantiomeric excess (ee).

On the basis of the successful palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) of racemic butadiene monoepoxide,[3] we postulated that a triene monoepoxide, or surrogate thereof, may behave similarly and generate two new stereogenic centers in high optical purity. The reaction products using heteroatom nucleophiles would hopefully be monoprotected diols and N-protected amino alcohols with both heteroatoms and all six carbon atoms differentiated in the reaction. Use of these diols in efficient synthetic schemes has recently been reported,[4] but the starting materials are prepared from the chiral pool and require multi-step procedures. A catalytic enantioselective preparation of these synthons would provide direct access to either enantiomer in a single operation.

The parent triene monoepoxide required, hexatriene monoepoxide, was predicted to be more difficult to prepare and handle than desired, so 1,2-divinylethylene carbonate[5] (**2** and **3**) was chosen as a surrogate. Reductive dimerization[6] of **1** followed by cyclization provided the *dl*- and *meso*-isomers **2** and **3** as a 1:1 mixture of separable diastereomers in good yield.

The products of the Pd AAA of **2** and **3** by the well-established double inversion mechanism[7] were expected to be diastereomers **4** and **5**, respectively, neglecting the regiochemistry of the nucleophilic addition (Scheme 1). With the goal of finding both a nitrogen and an oxygen nucleophile that would serve as easily deprotected functional groups in the product, preliminary studies focused on employing phthalimide **6** in the desired reaction (Table 1). When the *dl*-carbonate **2** was allowed to react with phthalimide in the presence of 5 mol % of π-allylpalladium chloride dimer **7**, 15 mol % of racemic **8**, and 5 mol % of Na_2CO_3 in CH_2Cl_2,[3] the only product isolated was the expected amino alcohol **9**[8] in 81% yield (entry 1, Table 1). Using ligand (*R*,*R*)-**8** with 5 and 2 mol % of **7** (entries 2 and 3), **9** was again isolated as the sole product in >99% ee but with 44 and 43% yield, respectively, due to kinetic resolution of racemic **2** (vide infra).

The reaction was next attempted with the cyclic carbonate **3** (entries 4−6) to determine how well the catalyst system would work with a dienyl *meso* compound, a class of substrates that has not been explored in intermolecular Pd AAA reactions.[9] To our surprise, using both racemic **8** and (*R*,*R*)-**8**, *the only product formed was the unexpected syn diastereomer* **9** (entries 4 and 5). In both reactions, the yield was acceptable, and in entry 5, the ee was

Scheme 1. Pd AAA of *meso*- and *dl*-1,2-Divinylethylene Carbonate

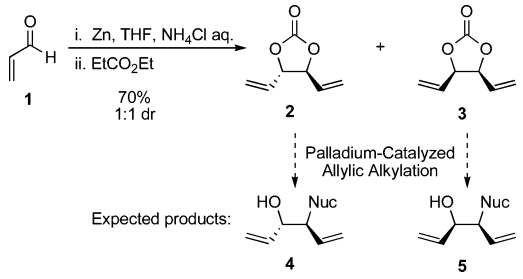
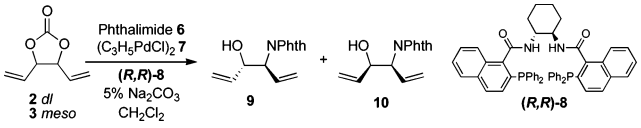


Table 1. Initial Optimization Studies



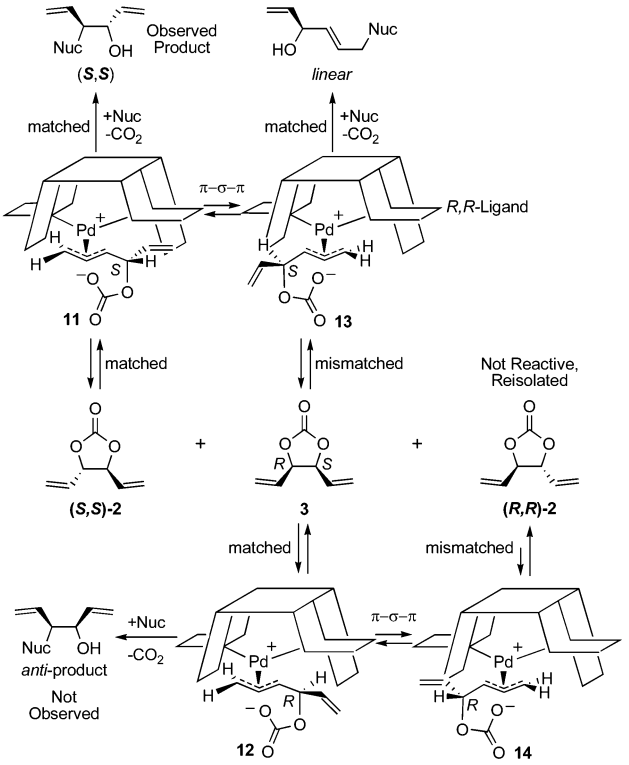
entry	carbonate	**7** (%)[a]	product	yield (%)[b]	ee (%)
1[c]	**2**	5[d]	**9**	81	
2[c]	**2**	5	**9**	44	>99
3[c]	**2**	2	**9**	43	>99
4[c]	**3**	5[d]	**9**	71	
5[c]	**3**	5	**9**	74	>99
6[c]	**3**	2	**9**	71	>99
7[e]	**2**+**3**[f]	1	**9**	74[g]	>99

[a] $(C_3H_5PdCl)_2$:**8** = 1:3. [b] All yields based on mmol **2** and/or **3**. [c] On 0.5 mmol scale, 16 h reaction time with 1.1 equiv of **6**. [d] *rac*-**8**. [e] On 5.0 mmol scale, 72 h reaction time with 0.77 equiv of **6**. [f] A 1:1 mixture of **2**:**3**. [g] (*R*,*R*)-**2** (16%) was also recovered in 91% ee.

>99%. The catalyst loading could also be reduced (2 mol % of **7**, entry 6) while maintaining both yield and ee. Since **2** and **3** are prepared in the same reaction and both exclusively gave product **9** with excellent ee, the reaction was carried out on a 1:1 mixture of **2** and **3** obtained from **1**. Under optimized conditions with prolonged reaction time, the process performed equally well giving **9** with >99% ee using 1 mol % of **7** in 74% yield (based on charged **2** + **3**) wherein the maximum theoretical yield is 75% based upon the dual enantiodiscrimination mechanisms. Interestingly, the cyclic carbonate (*R*,*R*)-**2**, recovered in 16% yield (theoretical max 25%), has a 91% ee, indicative of a kinetic resolution of racemic **2** by the chiral catalyst system.

The mechanistic scenario for this process to occur was intriguing based on our prior observations. Previously, two discrete situations with different mechanistic circumstances have been observed whereby the enantiodetermining steps of the reactions are postulated to be separate steps of the catalytic cycle. When nucleophilic addition to the initially formed π-allyl occurs faster than equilibration, the ionization step of the catalytic cycle is the stage at which the enantioselectivity is determined, and overall retention of stereochemistry is observed. If interconversion of the diastereomeric

Scheme 2. Mechanism of Pd-Catalyzed AAA of *meso*- and *dl*-Divinylethylene Carbonate

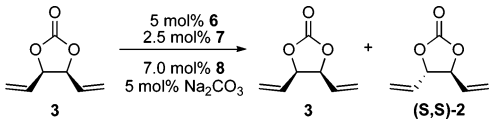


π-allylpalladium complexes is faster than nucleophilic addition, the addition step is enantiodetermining, and products that have overall inversion of stereochemistry may arise by an outer sphere process. Under ideal conditions, coupling these two pathways may provide a suitable manifold for the conversion of racemic diastereomeric starting materials into a single compound in high ee. If reactions of **2** and **3** are treated separately (Table 1, entries 1−3 vs 4−6), both types of enantiodiscrimination are postulated to be occurring.

Using the wall and flap diagram to represent the chiral ligand scaffold,[10] the proposed mechanism of this transformation is illustrated in Scheme 2. In matched processes, both ionization of the leaving group and nucleophilic addition occur from under the flap of the ligand to avoid contact with the wall. When considering how these cyclic carbonates interact with the catalyst, treatment of the kinetic resolution of racemic **2** is straightforward. Employing ligand (*R*,*R*)-**8**, (*S*,*S*)-**9** is produced from (*S*,*S*)-**2** leaving unreacted (*R*,*R*)-**2** in high optical purity. This is consistent with the model, in that ionization of (*S*,*S*)-**2** is predicted to be a matched pair using (*R*,*R*)-**8**. Considering how **3** would ionize leads to the conclusion that the product of matched ionization (**3** → **12**) would retain the *R* stereocenter and lead to the unobserved product **10** after intermolecular alkylation. While intermolecular alkylation of **12** appears reasonable, the competing intramolecular alkylation leading back to **3** by the pendant carboxylate is likely kinetically favored. Due to relative rates, this sets up a Curtin−Hammett-type situation where the rapid and reversible matched ionization is unproductive. Mismatched ionization leads to **13**, which undergoes $\pi-\sigma-\pi$ interconversion to relieve steric repulsion between the substrate and the wall of the ligand. This process gives **11** which is then alkylated in an intra- or intermolecular fashion to provide (*S*,*S*)-**2** or the observed product (*S*,*S*)-**9**.

Since a 1:2:1 ratio of (*S*,*S*)-**2**:**3**:(*R*,*R*)-**2** is used in the reaction (Table 1, entry 7), the proposed mechanism explains how **2** and **3** can be converted into the same product and predicts a maximum yield of 75%, but it also suggests that **3** could be converted to **2** under the reaction conditions. To probe this issue, the reaction was run with only enough **6** to form the active catalyst (Table 2). Under the standard conditions, only a trace amount of carbonate **3** remained, and **2** was isolated in 14% yield (entry 1). The low recovery is likely due to decomposition of the π-allylpalladium complexes formed after decarboxylation. When the reaction is run under an atmosphere of CO_2, the mass recovery improves significantly and provides (*S*,*S*)-**2** in 75% ee (entry 2). Further evidence to support the proposed mechanism was obtained by running the reaction at lower temperature to determine if there is any effect on ee. Since we propose that both (*S*,*S*)-**2** and (*S*,*S*)-**9** are formed from **3** by a mismatched ionization (**3** → **13**, Scheme 2), a reverse temperature effect should be observed because at lower temperature the selectivity should shift toward the product of the matched reaction. This is indeed the case. When the reaction is conducted at −25 °C (entry 3), the ee of recovered (*S*,*S*)-**2** is significantly lower, indicating that the matched ionization leads instead to (*R*,*R*)-**2**.

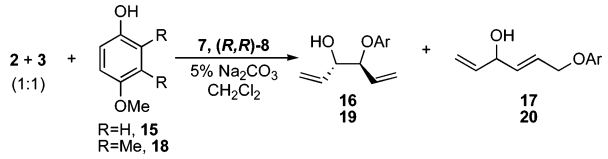
Table 2. Interconversion of **2** and **3**



entry	temp (°C)	yield **3** (%)	yield **2** (%)	ee (*S*,*S*)-**2** (%)
1[a]	25	trace	14	nd
2[b]	25	21	21	75
3[b]	−25	64	12	53

[a] N_2, 1 atm. [b] CO_2, 1 atm.

Table 3. Optimization of AAA with Phenol Nucleophiles

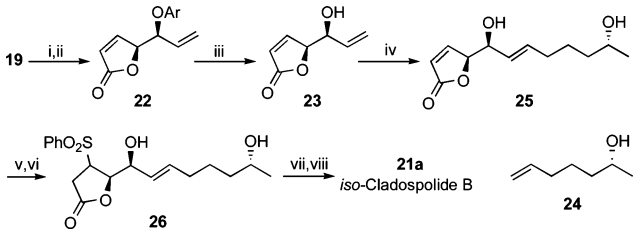


entry	phenol	**7** (%)[a]	b:l	product	yield (%)	ee (%)
1	**15**	2.5[b]	1.5:1	**16**	69[c]	
2	**15**	2.5	1.3:1	**16**	59[c]	99
3[d]	**15**	2.5	1.2:1	**16**	nd	nd
4[e,f]	**15**	2.5	2.3:1	**16**	nd	nd
5[e−g]	**15**	2.5	2.3:1	**16**	nd	nd
6[g]	**18**	2.5[b]	7.5:1	**19**	77	
7[f−h]	**18**	0.8	12:1	**19**	64	98

[a] $(C_3H_5PdCl)_2$:**8** = 1:3. [b] *rac*-**8**. [c] Combined yield. [d] *dl*-Isomer only. [e] **15** added over 5 h. [f] Temperature = 0 °C. [g] No base added. [h] With 0.77 equiv of **18**.

To probe the robustness of this system and for synthetic purposes, the use of oxygen nucleophiles to produce monoprotected 1,2-diols was studied (Table 3). Employing *p*-methoxyphenol **15**, the desired branched product **16** was formed along with the linear product **17**. While the combined yields and ratios required improvement (entries 1 and 2), **16** was obtained in 99% ee. Several modifications were made to the reaction conditions in an attempt to improve this ratio. While use of only the *dl*-isomer **2** had very little impact (entry 3), slow addition of the nucleophile at 0 °C both with and without Na_2CO_3 improved the ratio to 2.3:1 (entries 4 and 5). Although only a modest improvement, these experiments seemed to indicate that decreasing the rate of nucleophilic attack would improve the yield of the branched product. Instead of further changes in the reaction conditions, the phenol was modified to slow the reaction. Use of the more sterically hindered phenol **18** with racemic ligand

Scheme 3. Synthesis of *iso*-Cladospolide B[a]

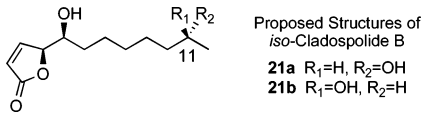


[a] Conditions: (i) Acryloyl chloride, DMAP, Et_3N, CH_2Cl_2, 71%; (ii) 10 mol % of Grubbs 2nd generation catalyst (**27**), CH_2Cl_2, 70%; (iii) CAN, CH_3CN/H_2O, 70%; (iv) **24** (5 equiv), **27** (10 mol %), CH_2Cl_2, 73%; (v) PhSH, Et_3N (5 mol %), CH_2Cl_2, 77%; (vi) oxone, $MeOH/H_2O$, 82%; (vii) H_2, 10% Pd/C; (viii) DBU, CH_2Cl_2, 82% (2 steps).

improved the ratio from 1.5:1 to 7.5:1 (entries 1 and 6) and also gave **19**[11] in higher yield. When the catalyst loading, equivalents of **18**, and temperature were lowered, **19** was isolated in 64% yield (theoretical max 75%) with 98% ee in a 12:1 ratio with **20** (entry 7).

Under the optimized conditions (Table 3, entry 7), (*R*,*R*)-**2** could be reisolated from the reaction mixture, and although differences are observed, the same mechanism (Scheme 2) is proposed to be operative. Appearance of the linear products **17** and **20** is likely due to matched nucleophilic addition to π-allylpalladium complex **13**. Additional evidence of this was obtained by assignment of the absolute stereochemistry. While racemic material failed to separate on a variety of chiral stationary phase HPLC columns, both the configuration and ee could be determined by NMR.[12] After conversion to the *O*-methyl mandalate ester, the major product was determined to be of the *S* configuration and the ee was 60%. These data are also consistent with the proposed mechanism. The principal difference between the phenol and phthalimide reactions is the solubility of the nucleophile. Phthalimide is only partially soluble, while the phenols completely dissolve under the reaction conditions. With phthalimide, proper balance is achieved, but the higher concentration of phenol present increases the rate of nucleophilic addition relative to equilibration of the π-complexes and leads to a less regioselective reaction.

The impetus for developing this chemistry was for application to the synthesis of natural products containing 1,2-amino alcohols or 1,2-diols, two relatively simple structures being the proposed structures of *iso*-cladospolide B **21a,b**.[13] The stereochemistry of *iso*-cladospolide B (**21a**) was originally postulated to be analogous to that of the macrolide cladospolide B,[13c,d] but recent reports indicate a discrepancy as **21b** was proposed based on NMR studies of material isolated from a marine fungus culture of a different source and by analogy to pandangolides 1 and 1a of known stereochemistry that were also isolated.[13e]



Our strategy relies on a union of two fragments of defined stereochemistry to establish both the absolute and relative configuration. To this end, the alcohol **19** was acylated with acryloyl chloride, and ring-closing metathesis (RCM) provided **22** (Scheme 3). Deprotection and cross-metathesis (CM) with the olefin **24**[14] assembled the carbon framework in good yield.

Chemoselective reduction of the allylic olefin proved more difficult than anticipated and required that the butenolide olefin be protected. Conjugate addition of thiophenol and oxidation of the resultant sulfide to the sulfone followed by hydrogenation and elimination provided **21a** in 52% yield over four steps. The optical rotation, $[\alpha]^{23}_D$ −87.5 (*c* 0.25, MeOH aq.) {lit.[13a] $[\alpha]_D$ −90 (*c* 0.23, MeOH)}, and spectral data for synthetic **21a** matched the data reported for the natural material.[13a,c,d] Additionally, **21b** was prepared by an analogous route from **23** and *ent*-**24**, and the spectroscopic data were indistinguishable from **21a** within experimental error. The optical rotation, $[\alpha]^{23}_D$ −60.4 (*c* 0.23, distilled MeOH), matched the literature value for recently isolated material {lit.[13e] $[\alpha]_D$ −61 (*c* 16.6, MeOH)}. Both diastereomers appear to be natural products that are structurally related to known macrolides, and **21b** should be referred to as 11-*epi*-*iso*-cladospolide B.

In summary, an efficient preparation of synthetically useful intermediates in high ee from a mixture of the cyclic carbonates *dl*- and *meso*-1,2-divinylethylene carbonate has been developed whereby two different modes of asymmetric induction give the same product in excellent ee. This process, combined with ring-closing and cross-metathesis, provides rapid access to a wide range of useful synthons from the feedstock chemical acrolein. Further studies to understand the mechanism and the broad utility of the products will be the subjects of future reports.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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