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Ligand Controlled Highly Regio- and Enantio-selective Synthesis of α-Acyloxyketones by Palladium Catalyzed Allylic Alkylation of 1,2-Enediol Carbonates

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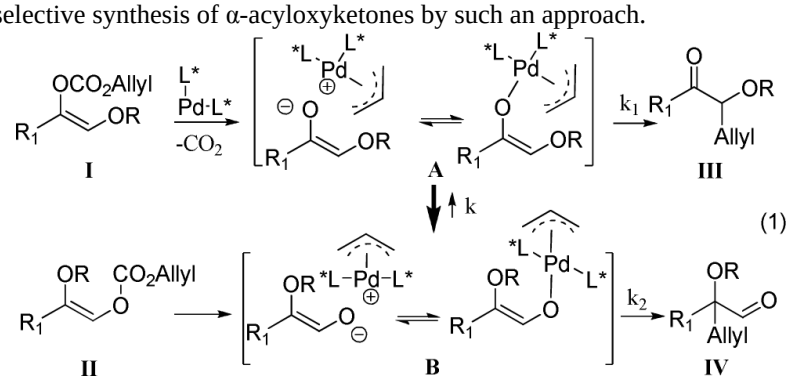
α-Hydroxy carbonyl compounds represent a structural type of both synthetic and biological importance. We previously noted that the enol allyl carbonates of α-siloxycarbonyl compounds underwent smooth palladium catalyzed decarboxylative asymmetric allylic alkylation (AAA) [1] to allylated α-siloxyaldehydes using a Pd complex bearing the $\mathbf{L_{anth}}$ ligand regardless of the regioisomeric nature of the starting material (ie. **I** or **II** in eq. 1).[2] The regioselectivity may be interpreted as a faster equilibration between the Pd enolate **A** and **B** compared to the rate of alkylation which occurs faster via **B** (ie. $k > k_2 > k_1$). However, if **A** and **B** exist as either tight ion-pairs or covalently bonded enolates as we proposed before,[1c] the Pd catalyst should be involved in **both** R migration and enolate alkylation steps. Thus, by tuning the ligand and the potential migrating group, we envisioned that we could change the reaction pattern in favor of the formation of α-hydroxyketones **III**, which have attracted much attention due to their versatile roles in organic synthesis.[1k, 3] Herein, we report our success in the highly regio- and enantio-selective synthesis of α-acyloxyketones by such an approach.



Initially we investigated the role of ligands by using carbonate **1a** (R = *tert*-butyldimethylsilyl, TBS) as the substrate, which as we reported previously, in the presence of $\mathbf{L_{anth}}$ decarboxylatively alkylated to the corresponding siloxyaldehyde **4a** with high regioselectivity (Table 1, entry 1). **PHOX** ligands, which, similar to $\mathbf{L_{anth}}$, have also been successfully used to catalyze the decarboxylative AAA of enol allyl carbonates, favored the formation of the aldehyde product in a ratio of 4.2 to1; however, the ee of **3a** was much lower (17%, entry 4). In contrast to these results, varying our ligands to $\mathbf{L_{std}}$ and $\mathbf{L_{stlb}}$, slightly favored the formation of the ketone product (entry 2 and 3). The best selectivity (**3a**/**4a** = 17/1) was achieved by using

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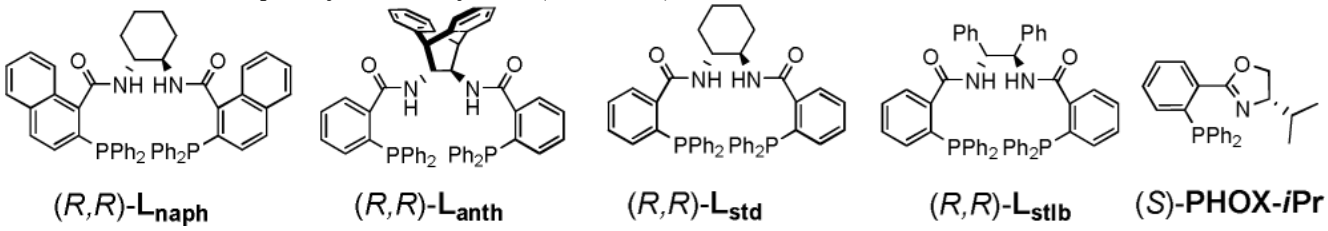
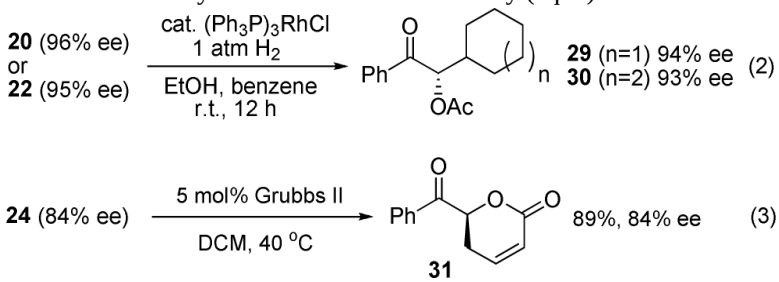
L_{naph} (entry 5). Replacement of OTBS with OAc almost completely suppressed the formation of the aldehyde product (entry 6). Changing solvent from dioxane to 1,2-dimethoxyethane (DME), kept the excellent regioselectivity but also improved the ee of **3b** to 90% (entry 7).[4] The ligand-dependence of the product distribution of **1b** was similar to that of **1a**, although in all cases the ketone product was the major one (entry 8−11). Besides acetoxy other ester groups were also investigated and **3d** with R = pivaloyl (Piv) had the highest ee value (94%, entry 13). Starting from **2** (R = TBS or Piv), which, after decarboxylation initially generated the more stable Pd enolate **B**, only the aldehyde product was exclusively generated in the presence of **L_{naph}** (entry 14 and 15).This suggests that the equilibrium between **A** and **B** is slower than the alkylation steps ($k < k_1$, k_2), in stark contrast to the reaction catalyzed by **L_{anth}**. The same reaction catalyzed by **PHOX** ligand (entry 16), however, gave a similar amount of aldehyde **4a** (**3a**/**4a** = 1/7.7) as in the reaction of entry 4 (**3a**/**4a** = 1/4.2), implying a faster equilibrium and comparably slower alkylation ($k > k_1 \approx k_2$).



The scope of the reaction has been investigated and the results are summarized in Table 2. Besides the aromatic ketones (entry 1−5), enones such as **12b** and **12d** (entry 6 and 7), as well as aliphatic ketones such as **14** and **16** (entry 8 and 9) can be obtained in good yields and high ee's. In general, pivolate protected α-hydroxyketones have moderately higher ee's than the corresponding acetate protected ones; however, acetate is easier to be removed without loss of the enantioselectivity of the α-hydroxyketone. Substrates with a substituted allylic moiety also reacted with full conversions, in some cases at slightly warmer temperature (40 °C) (entry 10 −12). The dr's of the corresponding products are over 95/5, and the ee values of the major diastereomers are higher than that of **3b**. These high dr's are reflected in the excellent ee's of **29** and **30** by the hydrogenations of **20** and **22** respectively (eq. 2). More interestingly, OR can be a functionalized group as in **24**, **26**, and **28** (entry 13−15). Such functionality can be useful in further structural elaboration as illustrated by the treatment of **24** with Grubbs II catalyst to afford lactone **31** without any erosion of enantioselectivity (eq. 3).



In summary, the palladium catalyzed decarboxylative AAA of 1,2-enediol carbonates can be precisely controlled by the selection of the ligand to generate either regio-isomer. Interestingly, although acyl migration in sodium enolates is fast even at −78 °C,[5] such equilibration is much slower with these Pd enolates and shows a ligand dependence. In the case of using **L_{naph}** as ligand it is slower than the alkylation, so that no migration is observed even above room temperature. This supports the concept that the decarboxylative AAA of ketones reacts through a tight ion pair or covalently bonded Pd enolate intermediates.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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4. The absolute configuration was assigned by the NMR study of the corresponding O-methylmandelate ester. Trost BM, Belletire JL, Godleski S, McDougal PG, Balkovec JM, Baldwin JJ, Christy ME, Ponticello GS, Varga SL, Springer JP. J. Org. Chem 1986;51:2370.
5. Observed in the preparation of substrates. See Supporting Information for details.

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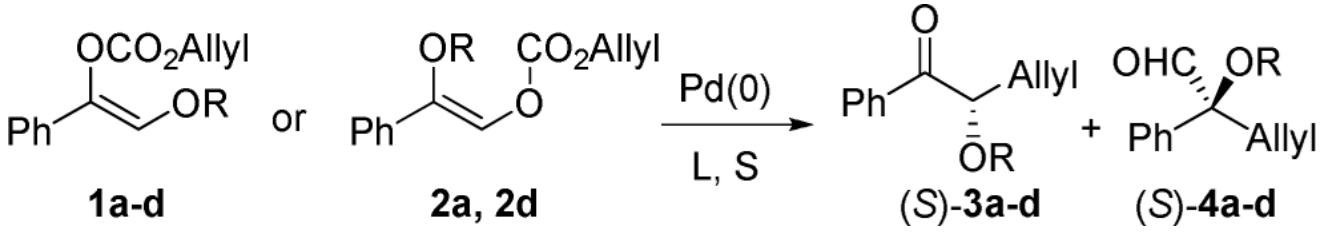
Table 1

Selected Optimization Studies[a]



entry	substrate (R)	ligand	solvent	yield[b]	3/4[c]	ee of 3[d]
1	**1a** (TBS)	L_{anth}	dioxane	95%	1/33	-
2	**1a**	L_{std}	dioxane	93%	2.7/1	77%
3	**1a**	L_{stlb}	dioxane	93%	2.8/1	91%
4	**1a**	**PHOX**	dioxane	77%	1/4.2	−17%
5	**1a**	L_{naph}	dioxane	91%	17/1	85%
6	**1b** (Ac)	L_{naph}	dioxane	99%	98/2	82%
7	**1b**	L_{naph}	DME	**99%**	**98/2**	**90%**
8	**1b**	L_{anth}	DME	27%	3/2	25%
9	**1b**	L_{std}	DME	93%	25/1	79%
10	**1b**	L_{stlb}	DME	53%	7/1	83%
11	**1b**	**PHOX**	DME	46%	11/1	−11%
12	**1c** (Bz)	L_{naph}	DME	95%	98/2	74%
13	**1d** (Piv)	L_{naph}	DME	**99%**	**98/2**	**94%**
14	**2a** (TBS)	L_{naph}	dioxane	99%	2/98	-
15	**2d** (Piv)	L_{naph}	DME	79%	2/98	-
16	**2a** (TBS)	**PHOX**	dioxane	88%	1/7.7	−18%

[a]Unless otherwise indicated, all reactions were performed on a 0.2 mmol scale at 0.1 M concentration at 23 °C for 16 h, using 2.5 mol% $Pd_2(dba)_3CHCl_3$ and 5.5 mol% ligand.

[b]The yields were combined isolated yields of **3** and **4**.

[c]The molar ratios of **3** and **4** were determined by ^{1}H-NMR of the crude products.

[d]The ee values were determined by HPLC on a chiral stationary phase.

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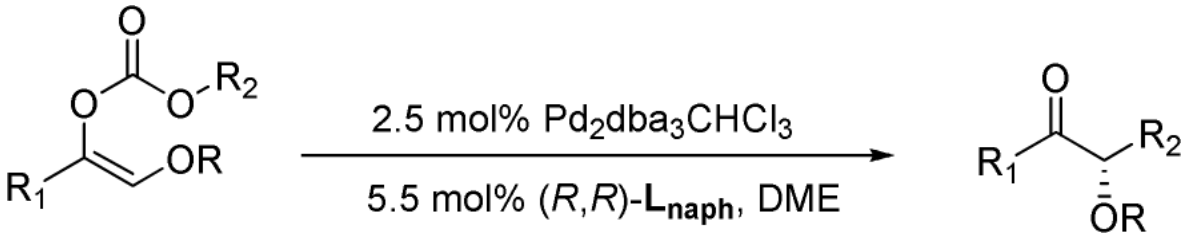
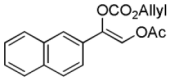
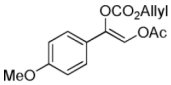
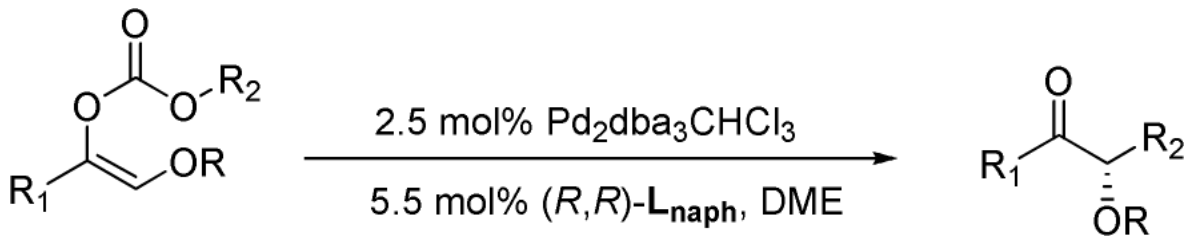
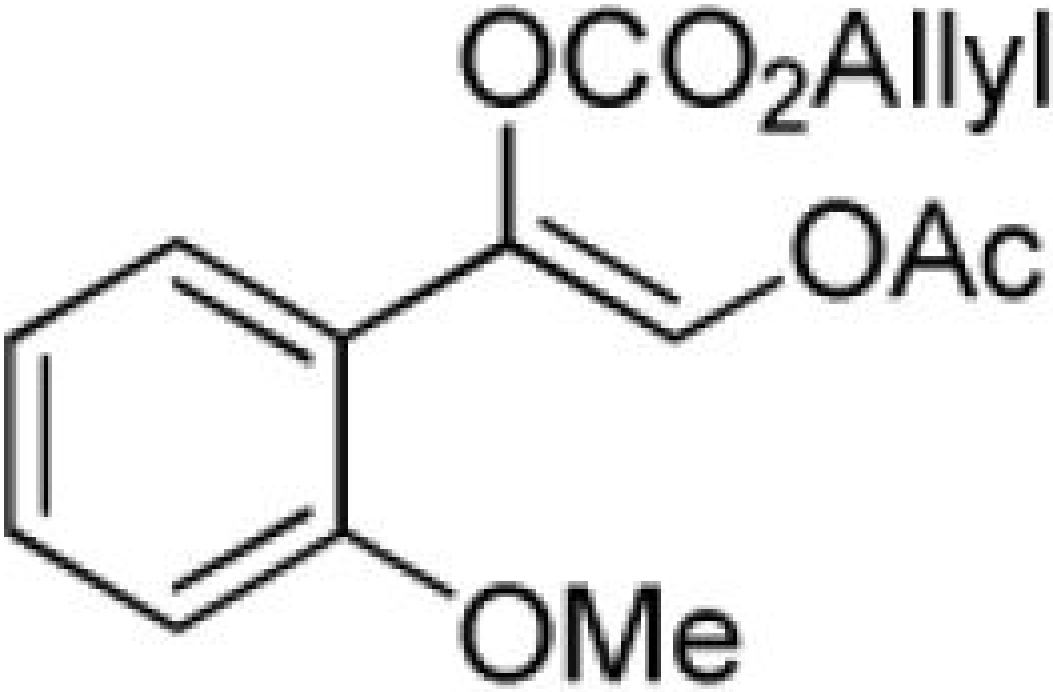
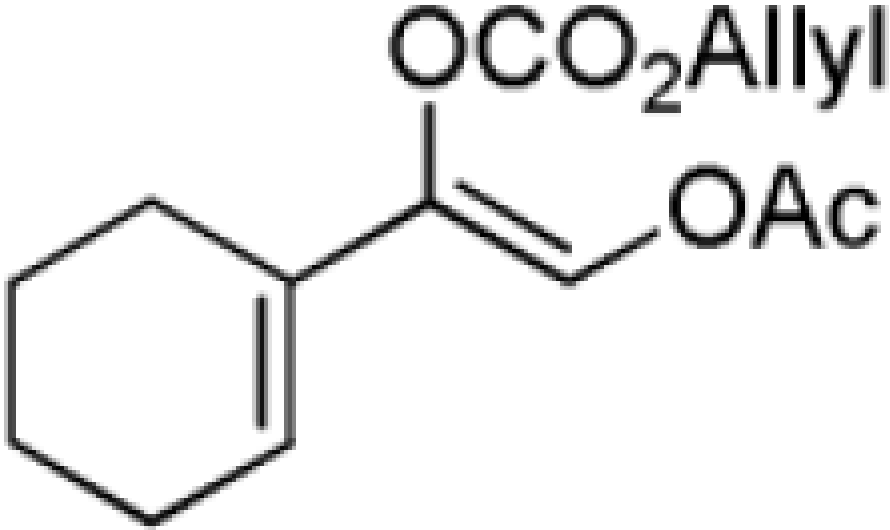
Table 2

Reaction Scope.[a]



entry	substrate
1	 **5b**
2	**5d** (R_3 = Piv)
3[b]	 **7b**
4	**7d** (R_3 = Piv)



entry	substrate
5	 **9**
6	 **11b**

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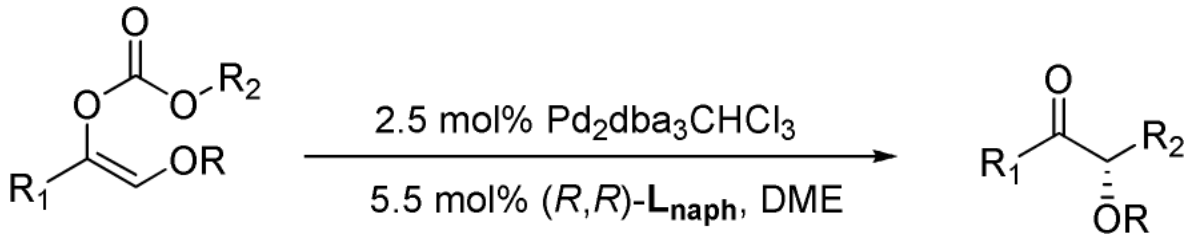
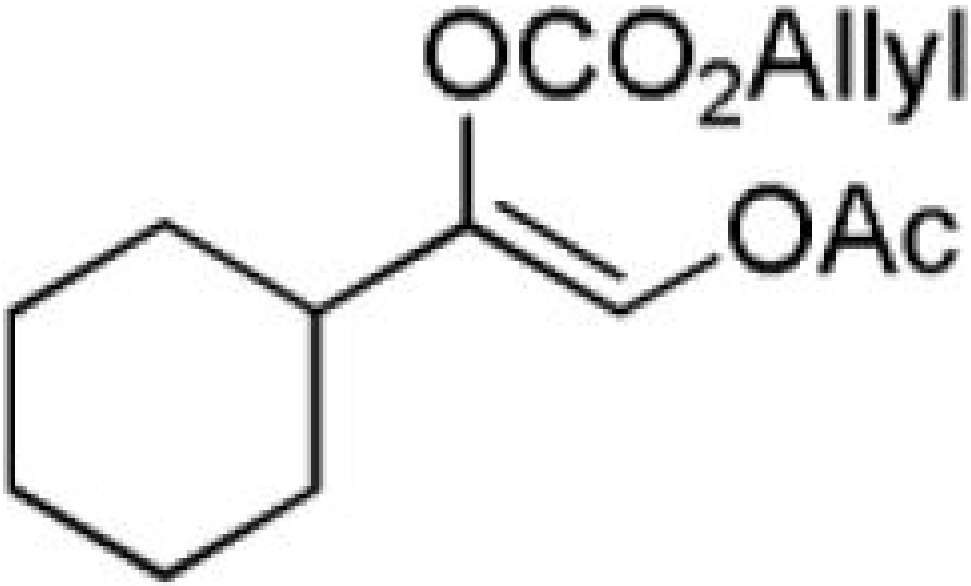
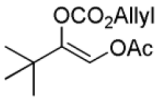


entry	substrate
7	**11d** (R_3 = Piv)
8	 **13**
9	 **15**

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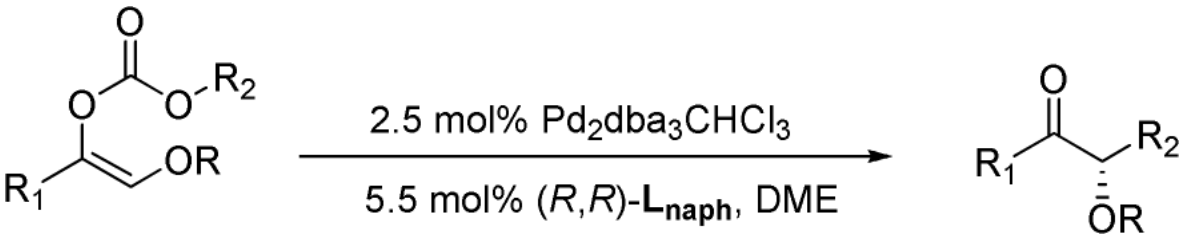

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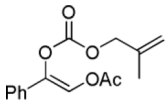
10[c]	 **17**

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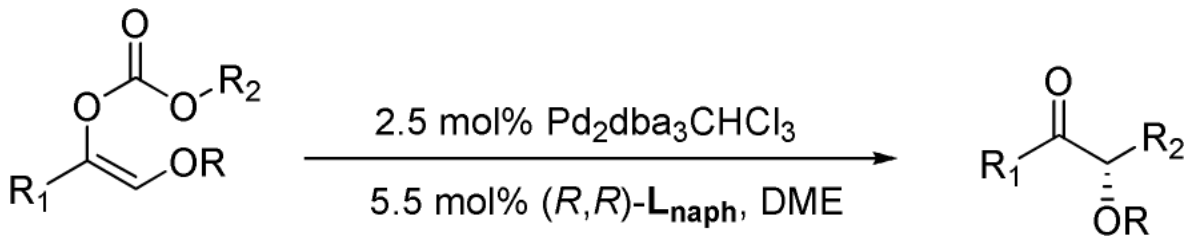

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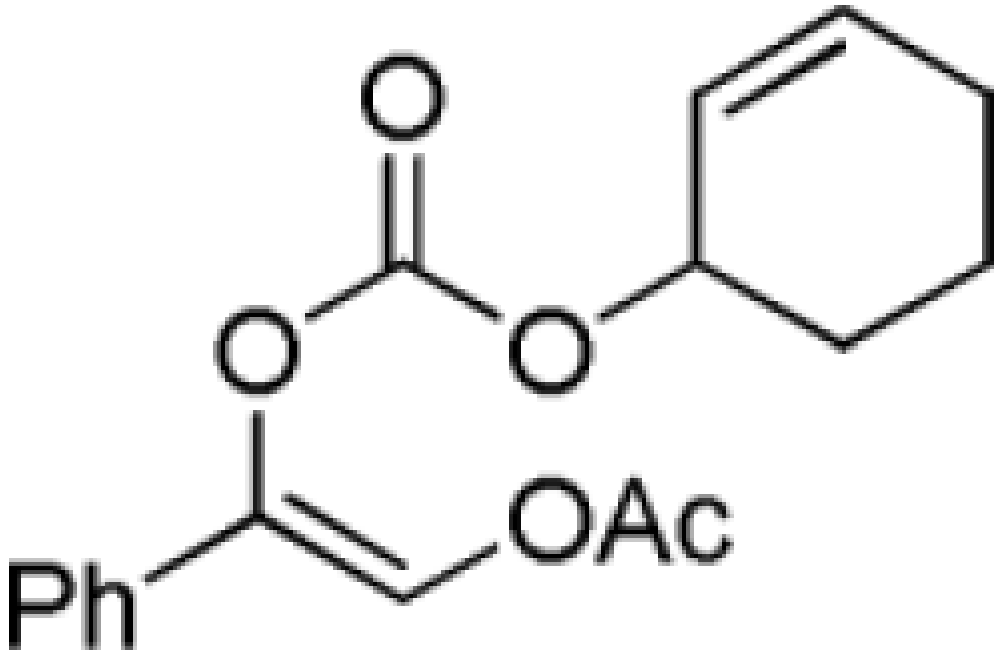
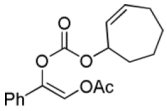
11	 **19**
12[c]	 **21**

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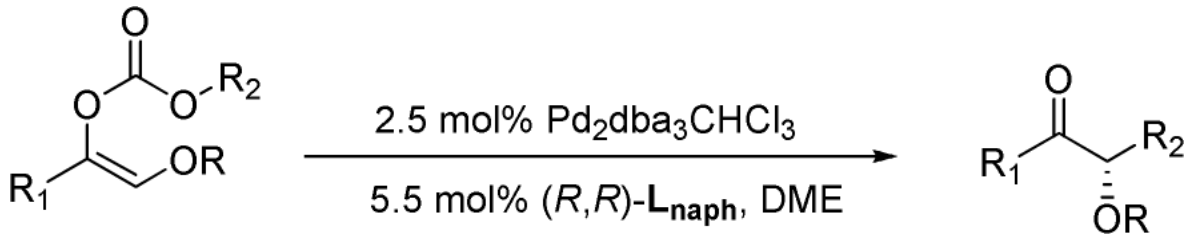
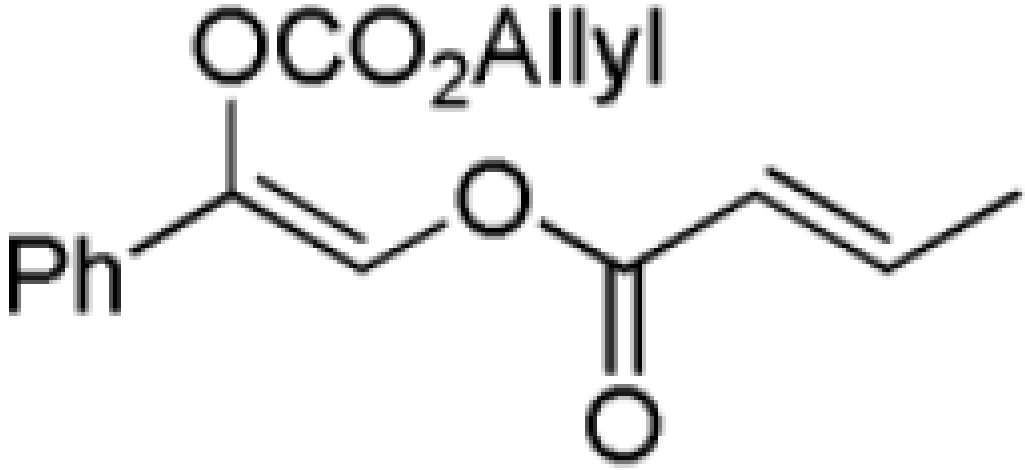
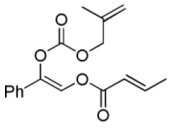


entry	substrate
13	 **23**
14	 **25**

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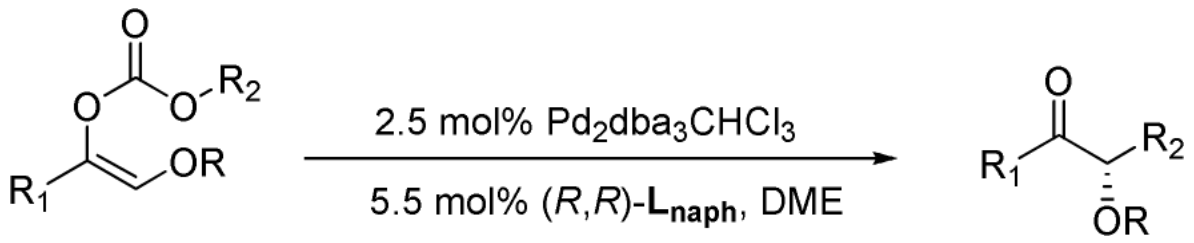
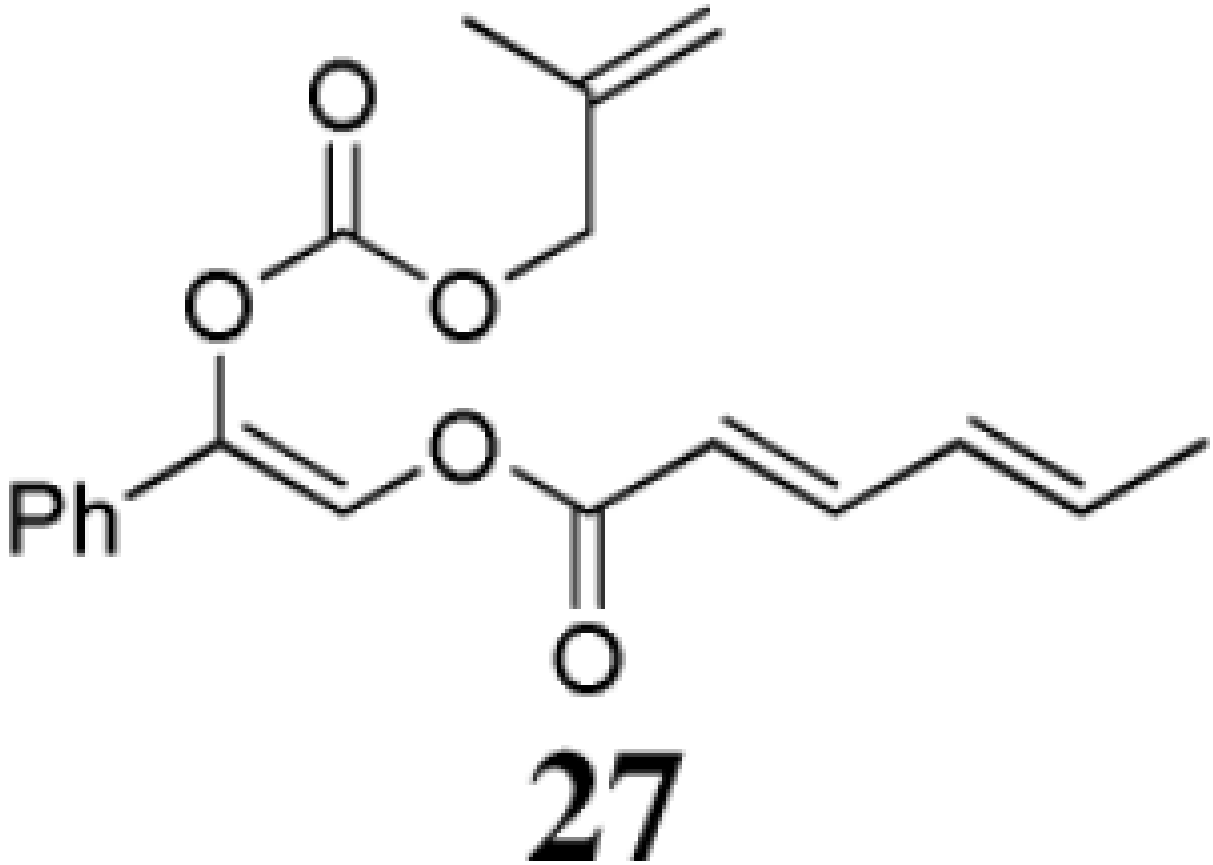


entry	substrate
15	 **27**

[a] All reactions were performed on a 0.2 mmol scale at 0.1 M in DME at 23 °C for 16 h, using 2.5 mol% $Pd_2(dba)_3CHCl_3$ and 5.5 mol% **L**$_{\mathbf{naph}}$; the yields were isolated yields and ee values were determined by chiral HPLC.

[b] Reaction was performed at 4 °C.

[c] Reaction was performed at 40 °C.

[d] Greater than 95/5 dr.

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