Communication

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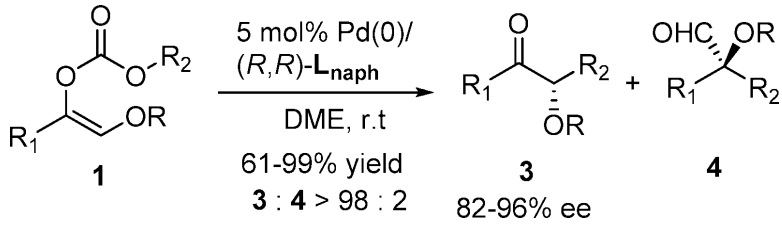

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Ligand Controlled Highly Regio- and Enantioselective Synthesis of α-Acyloxyketones by Palladium-Catalyzed Allylic Alkylation of 1,2-Enediol Carbonates

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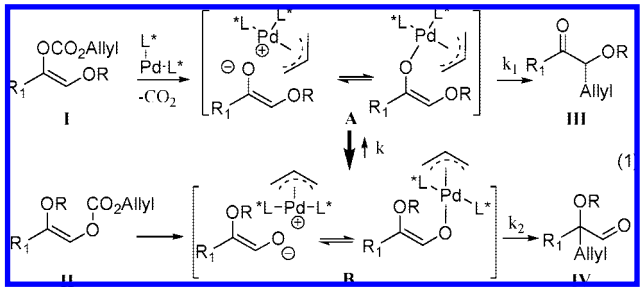
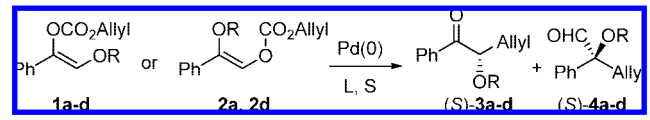
α-Hydroxy carbonyl compounds represent a structural type of both synthetic and biological importance. We previously noted that the enol allyl carbonates of α-siloxycarbonyl compounds underwent smooth palladium catalyzed decarboxylative asymmetric allylic alkylation (AAA)[1] to allylated α-siloxyaldehydes using a Pd complex bearing the L_{anth} ligand regardless of the regioisomeric nature of the starting material (i.e., 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** (i.e., $k > k_2 > k_1$). 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 because of their versatile roles in organic synthesis.[1k,3] Herein, we report our success in the highly regio- and enantioselective synthesis of α-acyloxyketones by such an approach.



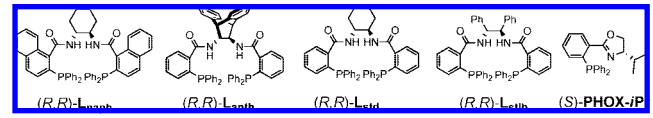
Initially we investigated the role of ligands by using carbonate **1a** (R = *tert*-butyldimethylsilyl, TBS) as the substrate, which as we reported previously, in the presence of $\mathbf{L_{anth}}$ decarboxylatively alkylated to the corresponding siloxyaldehyde **4a** with high regioselectivity (Table 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 to 1; 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 $\mathbf{L_{naph}}$ (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

Table 1. Selected Optimization Studies[a]



entry	substrate (R)	ligand	solvent	yield[b]	3/4[c]	ee of 3[d]
1	**1a** (TBS)	$\mathbf{L_{anth}}$	dioxane	95%	1/33	-
2	**1a**	$\mathbf{L_{std}}$	dioxane	93%	2.7/1	77%
3	**1a**	$\mathbf{L_{stlb}}$	dioxane	93%	2.8/1	91%
4	**1a**	**PHOX**	dioxane	77%	1/4.2	−17%
5	**1a**	$\mathbf{L_{naph}}$	dioxane	91%	17/1	85%
6	**1b** (Ac)	$\mathbf{L_{naph}}$	dioxane	99%	49/1	82%
7	**1b**	$\mathbf{L_{naph}}$	DME	**99%**	**49/1**	**90%**
8	**1b**	$\mathbf{L_{anth}}$	DME	27%	3/2	25%
9	**1b**	$\mathbf{L_{std}}$	DME	93%	25/1	79%
10	**1b**	$\mathbf{L_{stlb}}$	DME	53%	7/1	83%
11	**1b**	**PHOX**	DME	46%	11/1	−11%
12	**1c** (Bz)	$\mathbf{L_{naph}}$	DME	95%	49/1	74%
13	**1d** (Piv)	$\mathbf{L_{naph}}$	DME	**99%**	**49/1**	**94%**
14	**2a** (TBS)	$\mathbf{L_{naph}}$	dioxane	99%	1/49	-
15	**2d** (Piv)	$\mathbf{L_{naph}}$	DME	79%	1/49	-
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.

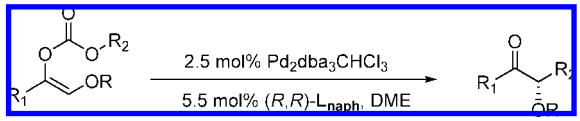


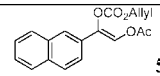
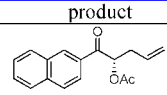
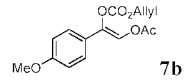
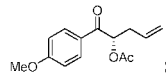
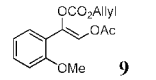
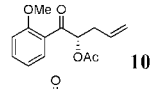
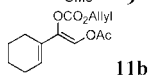
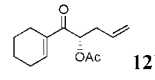
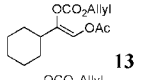
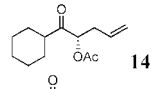
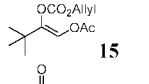
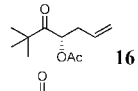
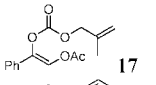
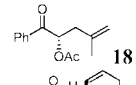
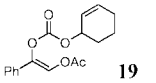
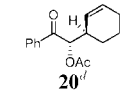
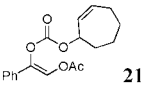
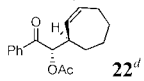
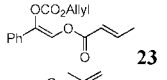
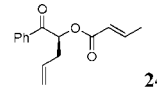
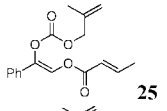
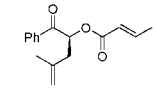
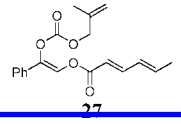
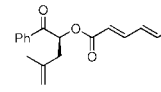
was exclusively generated in the presence of $\mathbf{L_{naph}}$ (entry 14 and 15). This suggests that the equilibrium between **A** and **B** is slower than the alkylation steps ($k < k_1, k_2$), in stark contrast to the reaction catalyzed by $\mathbf{L_{anth}}$. The same reaction catalyzed by **PHOX** 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

10.1021/ja8038954 CCC: $40.75

Table 2. Reaction Scope[a]

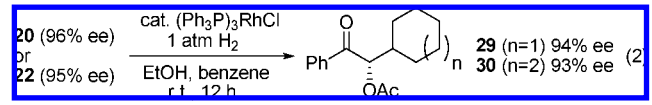


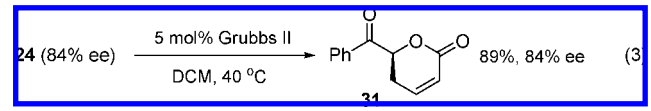
entry	substrate	product	yield	ee
1	 **5b**	 **6b**	98%	89%
2	**5d** (R_3 = Piv)	**6d**	99%	91%
3[b]	 **7b**	 **8b**	84%	87%
4	**7d** (R_3 = Piv)	**8d**	96%	95%
5	 **9**	 **10**	83%	92%
6	 **11b**	 **12b**	96%	89%
7	**11d** (R_3 = Piv)	**12d**	97%	90%
8	 **13**	 **14**	61%	83%
9	 **15**	 **16**	65%	82%
10[c]	 **17**	 **18**	96%	94%
11	 **19**	 **20**[d]	97%	96%
12[c]	 **21**	 **22**[d]	99%	95%
13	 **23**	 **24**	92%	84%
14	 **25**	 **26**	93%	94%
15	 **27**	 **28**	88%	93%

[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 % $\mathbf{L_{naph}}$; 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.

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 regioisomer. 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 $\mathbf{L_{naph}}$ 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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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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