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Enantioselective Synthesis of α-Tertiary Hydroxyaldehydes by Palladium-Catalyzed Asymmetric Allylic Alkylation of Enolates

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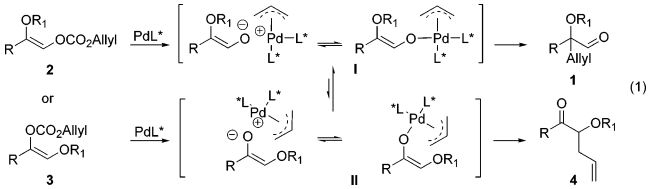
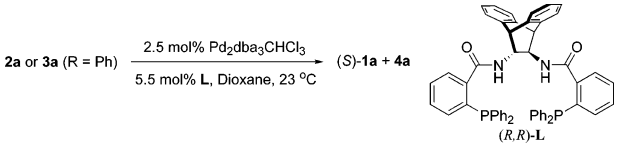
α-Hydroxyaldehydes are very versatile building blocks for the synthesis of natural products as well as clinical drugs.[1] Chiral α-hydroxyaldehydes enjoy the added benefit of being a potential source of introducing other stereogenic centers. Up to now, the access of such compounds in enantiomerically enriched form can be classified as a chiral pool approach,[1] a chiral auxiliary approach,[2] or a transformation from other enantioenriched compounds, such as 1,2-diols,[3a−c] α-hydroxy acids,[3d] and cyanohydrins,[3e] synthesized by other enantioselective methods. However, to our knowledge, catalytic enantioselective synthesis of α-tertiary hydroxyaldehydes directly from prochiral precursors has not been reported.[4] In the course of studying palladium-catalyzed asymmetric allylic alkylation (AAA) of simple ketone enolates,[5] we postulated that treatment of enol carbonate **2** or **3** bearing a shiftable OR_1 group with a proper chiral palladium catalyst presumably could regio- and enantioselectively generate R_1 protected α-tertiary hydroxyaldehydes **1** (eq 1). Substrates **2** and **3** can be made from readily available α-halo or α-hydroxy ketones.[6] Herein, we report the first example of a palladium-catalyzed highly enantioselective synthesis of α-tertiary hydroxyaldehydes resulting from a novel competition and demonstrate its synthetic utility in a formal synthesis of (*S*)-oxybutynin.[7]



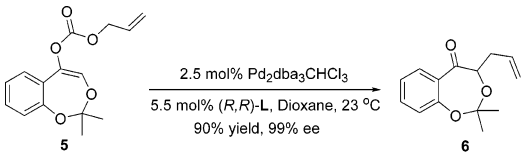
We initially subjected **2a-1** and **3a-1**, respectively, to our previously reported conditions (2.5 mol % of $Pd_2(dba)_3CHCl_3$ and 5.5 mol % of (*R,R*)-**L** in 1,4-dioxane at 23 °C).[5] Although the reaction of **2a-1** was significantly faster, the only product from either was aldehyde (*S*)-**1a** with excellent yields and enantiomeric excesses (ee's) (Table 1, entries 1 and 2).[8] As summarized in Table 1, the scope of the R_1 group was explored. With few exceptions, the reaction favored the formation of aldehyde **1a** independent of the oxygen substituent, while in several cases of reactions with achiral ligand 1,2-bis(diphenylphosphino)ethane (dppe) as ligand, the major product was ketone **4a** (Table 1, entries 6, 8, and 10). The reaction of **3a-3** with a TIPS or **3a-8** with a mesitoyl group was slower than that with a less bulky group in the same class; in both cases, a significant amount of ketone **4a** was isolated (Table 1, entries 4 and 12). Presumably, if the equilibrium between enolate **I** and **II** is faster than the allylation, the reaction should proceed through the former since it is more stable than **II** both electronically and sterically. On the other hand, if the rate of allylation became faster than the rate of enolate equilibration as may be occurring in the case of acetyl (Table 1, entry 7) or with dppe as ligand, then an increasing amount of ketone is observed (Table 1, entries 6, 8, and 10). Substrate **3a-9** with an unshiftable methoxymethyl (MOM) group had very poor conversion under the same conditions, perhaps due to the chelation of the intermediate enolate with the Pd catalyst (Table 1, entry 13). Support for this contention is derived from the observation that the reaction of **3a-1** was severely inhibited by the addition of an equal amount of **3a-9** (6% conversion in contrast to a full conversion in 1 h in the absence of **3a-9**). In addition, The *E*-enolate generated from **5** cannot chelate to the catalyst and reacted readily (eq 2).

Table 1. Various Hydroxy Protecting Groups are Suitable[a]



entry	SM	R_1	time	yield% of **1a**	ee% of **1a**	yield% of **4a**
1	**2a-1**	TBDMS	1/4 h	93	92	0
2	**3a-1**	TBDMS	1 h	86	91	0
3	**2a-2**	TMS	1/4 h	99	92	0
4	**3a-3**	TIPS	5 h	67	91	9
5	**2a-4**	benzoyl	2 h	93	81	0
6[b]	**2a-4**	benzoyl	2 h	11		75
7	**3a-5**	acetyl	7 h	40	91	60[c]
8[b]	**3a-5**	acetyl	1/2 h	24		67
9	**2a-6**	piv	4 h	90	91	0
10[b]	**2a-6**	piv	4 h	36		55
11	**2a-7**	CO_2Me	4 h	71[d]	86	0
12	**3a-8**	mesitoyl	36 h	10	91	36[e]
13	**3a-9**	MOM	16 h	<5		

[a] The structure of the substrates was confirmed with HMBC and NOE NMR data; unless otherwise indicated, all reactions were performed at 23 °C on a 0.2 mmol scale at 0.1 M using 2.5 mol % of **2** and 5.5 mol % of ligand; yields were isolated yields; ee's of **1a** and **4a** were determined by chiral HPLC. [b] 5.5 mol % dppe was used as the ligand. [c] With 21% ee. [d] Product partially hydrolyzed on silica gel column. [e] With 13% ee.



Although various R_1 groups are suitable, we selected the most commonly used TBDMS as the hydroxy protecting group and investigated the scope of the nucleophilic moiety (Table 2). In general, excellent yields and ee's were obtained with R as different as aryl, alkenyl, or alkynyl groups (Table 2). For substrates where R are alkenyl groups, only the α-alkylated aldehydes are generated, no γ-alkylated enal is observed (entries 9 and 10).[9] Since the silicon migration of trans enediolate is not likely as in substrate **11**, it reacted to afford ketone **4i** in 95% yields and 99% ee, while its cis isomer **2i** converted to aldehyde **1i** in 76% yield and 89% ee under the same conditions (entries 12 and 15). In the case of tetrasubstituted enol carbonate **7** (entry 13), α-tertiary siloxy ketone **8** generated from the corresponding *E*-enolate favored formation of

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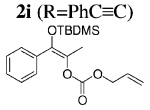
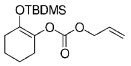
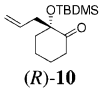
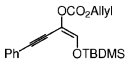
Table 2. Reactions with Different Nucleophilic Moieties[a]

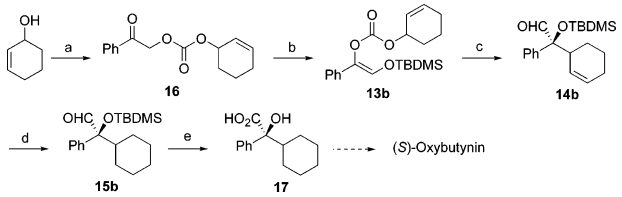
	substrate	product	time	yield	ee
1	**2a** (R=Ph)	(*S*)-**1a**	1/4 h	93%	92%
2	**3a** (R=Ph)	(*S*)-**1a**	1 h	89%	91%
3	**2b** (R=*p*-MeOPh)	**1b**	1/4 h	94%	92%
4	**3b** (R=*p*-MeOPh)	**1b**	2 h	86%	92%
5	**2c** (R=2-Naphthyl)	**1c**	1/4 h	92%	85%
6	**3c** (R=2-Naphthyl)	**1c**	1/2 h	94%	85%
7	**2d** (R=*o*-NO_2Ph)	**1d**	12 h	69%	79%
8	**3d** (R=*o*-NO_2Ph)	**1d**	12 h	69%	72%
9	**2e** (R=2-furyl)	**1e**	1/2 h	81%	93%
10	**2f** (R=1-cyclohexenyl)	**1f**	7 h	93%	98%
11	**2g** (R=2-methyl-1-propenyl)	**1g**	5 h	89%	98%
12	**2i** (R=PhC≡C)	**1i**	1/4 h	76%	89%
13	 **7**	 (*R*)-**8**	12 h	94%	80%
14	 **9**	 (*R*)-**10**	10 h	96%	64%
15	 **11**	**4i**	2 h	95%	99%

[a] All reactions were performed on a 0.2 mmol scale at 0.1 M in dioxane at 23 °C using 2.5 mol % of $Pd_2(dba)_3CHCl_3$ and 5.5 mol % of ligand **L**; the yields were isolated yields, and ee values were determined by chiral HPLC.

Table 3. Reactions with Different Electrophilic Moieties

entry	substrate	time	yield	dr	ee of major	ee of minor	ee of **15**
1	**13a** ($n = 1$)	1 h	quant.	2.5:1	92%	87%	43%
2	**12b** ($n = 2$)	2 h	quant.	11:1	>99%		84%
3	**13b** ($n = 2$)	16 h	quant.	11:1	>99%		
4	**12c** ($n = 3$)	16 h	quant.	50:1	>99%		99%
5	**13c** ($n = 3$)	16 h	30%	50:1	>99%		

Scheme 1. Formal Synthesis of (*S*)-Oxybutynin[a]

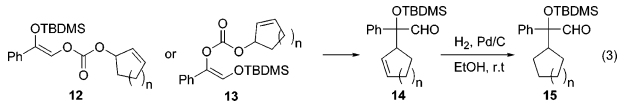


[a] Reagents and conditions: (a) NaH, CO_2, THF, then $PhCOCH_2Br$, DMF, 23 °C, 42%; (b) NaHMDS, TBSCl, THF, −78 to 23 °C, 83%; (c) 2.5 mol % of $Pd_2(dba)_3CHCl_3$, 5.5 mol % of **L**, 1,4-dioxane, 23 °C, 99% (dr 11:1); (d) H_2, cat. Pd/C, EtOH, 23 °C, 96%, 84% ee; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 23 °C, 95% (recrystallization from hexane/DCM, >99% ee).

the *R*-enantiomer.[10] The reaction also works for the synthesis of a cyclic α-tertiary siloxy ketone **10** with a moderate ee in favor of the *R*-enantiomer (entry 14).[11]

Variation of the allyl moiety to cycloalkenyl as in **12** led to **14** quantitatively (eq 3). The regioisomer **13b** reacted slower than **12b** but still in quantitative yield, whereas the reaction of **13c** proceeded only in 30% conversion. The diastereomeric ratio (dr) of **14** increased from 2.5:1 to over 50:1 with increasing cycloalkenyl ring size. Removal of one of the stereogenic centers by hydrogenation of the C=C double bond gave compounds **15a**−**c** ($n = 1$−3). The ee of **15** reflected the dr of **14**. **15b** was converted into the key intermediate **17** for the synthesis of (*S*)-oxybutynin in 95% yield, wherein one recrystallization increased the ee to over 99% (Scheme 1).

In summary, we report the first catalytic asymmetric synthesis of α-tertiary hydroxyaldehydes by palladium-catalyzed allylic



alkylation of siloxy enol carbonates. The excellent selectivity toward aldehyde was achieved by using chiral ligand **L**, which is in stark contrast to dppe, which favors ketone formation. The reaction proceeds under very mild conditions and generates an α-tetrasubstituted stereogenic center with excellent yield and enantiomeric excess. Further investigation of the mechanism, reaction scope, and its application in organic synthesis is ongoing.

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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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