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

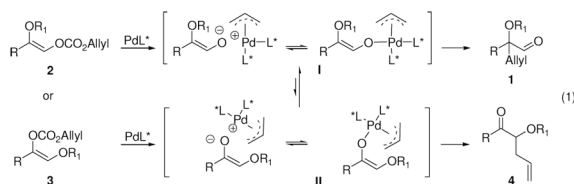**Barry M. Trost**[*], **Jiayi Xu**, and **Markus Reichle**
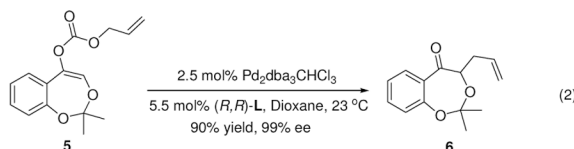*Department of Chemistry, Stanford University, Stanford, California 94305-5080.*

Abstract

Chiral α-tertiary hydroxyaldehydes are very versatile building blocks in synthetic chemistry. Herein, we reported the first examples of a catalytic asymmetric protocol for the synthesis of such compounds from readily available α-halo or α-hydroxy ketones or enol silyl ethers with excellent yields and enantioselectivity. Its synthetic utility is demonstrated in the short, efficient formal synthesis of (*S*)-oxybutynin. In this process, the chiral ligand controls with the regioselectivity as well as enantioselectivity.

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 enantio-enriched 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 demonstrated its synthetic utility in a formal synthesis of (*S*)-oxybutynin.[7]
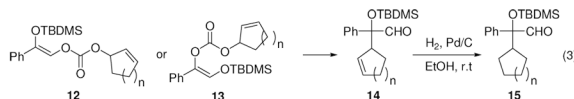

We initially subjected **2a-1** and **3a-1** respectively to our previously reported conditions (2.5 mol% $Pd_2(dba)_3CHCl_3$ and 5.5 mol% (*R,R*)-**L** in 1,4-dioxane at 23 °C).[5] Although the reaction of **2a-1** was significantly faster, the only product from either was aldehyde (*S*)-**1a** with excellent yields and ee's (Table 1, entry 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 *O*- substituent while, in several cases, reactions with achiral ligand 1,2-bis (diphenylphosphino)ethane (dppe) as ligand the major product was ketone **4a** (Table 1, entry

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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, entry 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, entry 6, 8 and 10). Substrate **3a-9** with an un-shiftable 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 derives 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** can not chelate to the catalyst and reacted readily (eq. 2).

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 (entry 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 (entry 12 and 15). In the case of tetra-substituted enol carbonate **7** (entry 13), α-tertiary siloxy ketone **8** generated from the corresponding *E*-enolate favored formation of 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 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 **15 a-c** (n =1,2, or 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 towards 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-tetra-substituted stereogenic center with excellent yield and enantiomeric excess. Further investigation of the mechanism, reaction scope and its application in organic synthesis are ongoing.
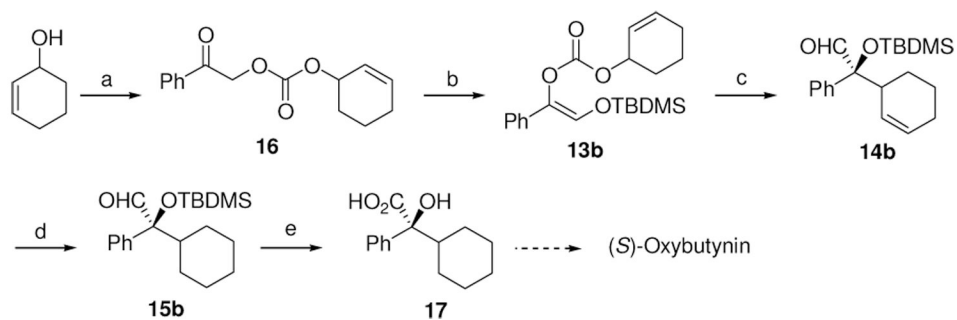
Supplementary Material

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8. The absolute configuration of **1a** was determined by reduction of CHO to CH_2OH followed by removal of TBDMS and comparison of the optical rotation of the product 1,2-diol ($[\alpha]_D{}^{24} = -45.2$ (c 1.2, $CHCl_3$)) with the reported data for (2*R*)-1,2-dihydroxy-2-phenylpent-4-ene ($[\alpha]_D{}^{20} = +43.4$ (c 1.2, $CHCl_3$)).Agami C, Couty F, Lequesne C. Tetrahedron 1995;51:4043.

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10. The absolute configuration of **8** was determined by removal of TBDMS and comparison of the optical rotation of the product ($[\alpha]_D{}^{24} = -91.3$ (c 1.05, benzene)) with the reported data for (*S*)-3-hydroxy-3-phenyl-hex-5-en-2-one ($[\alpha]_D{}^{26} = +124.7$ (c 0.635, benzene)).Soai K, Ishizaki M. J. Org. Chem 1986;51:3290.

11. The absolute configuration of **10** was determined by removal of TBDMS and comparison of the optical rotation of the product ($[\alpha]_D{}^{23} = -73.4$ (c, 2.6, $CHCl_3$)) with the reported data for (*S*)-2-allyl-2-hydroxy-cyclohexanone ($[\alpha]_D = +136.6$ (c 2, $CHCl_3$)).Compain P, Goré J, Vatèle JM. Tetrahedron 1996;52:6647.

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 °C to 23 °C, 83%; (c) 2.5 mol% $Pd_2(dba)_3CHCl_3$, 5.5 mol% 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).

Table 1

Various Hydroxy Protecting Groups are Suitable.[a]

2a or 3a (R = Ph) $\xrightarrow[\text{5.5 mol\% L, Dioxane, 23 °C}]{\text{2.5 mol\% Pd}_2\text{dba}_3\cdot\text{CHCl}_3}$ (S)-1a + 4a

(R,R)-L

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$_2$Me	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 were 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% 2 and 5.5 mol% 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

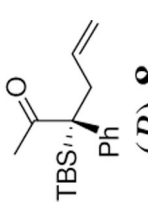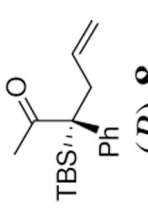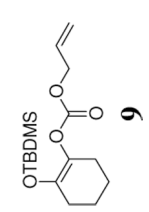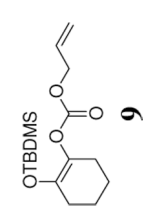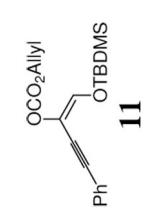[c] With 21% ee

[d] Product partially hydrolyzed on silica gel column

[e] With 13% ee.

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-NO₂Ph)	**1d**	12 h	69%	79%
8	**3d** (R=o-NO₂Ph)	**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%

Table 3

Reactions with different electrophilic moieties.

	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%	-	