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Direct Enantioselective Organocatalytic Hydroxymethylation of Aldehydes Catalyzed by α,α-Diphenylprolinol Trimethylsilyl Ether

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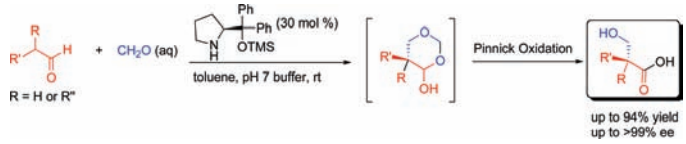
ABSTRACT



The direct enantioselective hydroxymethylation of aldehydes utilizing α,α-diphenylprolinol trimethylsilyl ether as an organocatalyst is described. The intermediate α-substituted *β*-hydroxyaldehydes were not isolated but converted to the more readily isolable derivatives. For example, the derived hydroxy acids were isolated in up to 94% yield with excellent enantioselectivity.

α-Substituted *β*-hydroxy aldehydes and carboxylic acids are very useful chiral building blocks.[1] The need for an efficient, enantioselective method for preparing these building blocks can be seen from their widespread use in complex molecule synthesis.[1] To date, we are aware of only one report in the literature describing enantioselective hydroxymethylation of aldehydes utilizing organocatalysis.[2] However, in our hands, that literature protocol failed to reproduce the reported levels of enantioselectivity (>99% reported, 70% ee observed). In addition, that report suggested that the scope of substrates may be rather limited and did not afford easily isolable chiral building blocks useful for further transformations. Evans first reported the preparation of these chiral building blocks utilizing enolate chemistry and stoichiometric chiral auxiliaries to install the desired stereochemistry.[3] Although use of chiral auxiliary based methods affords excellent stereoselectivity, they require multiple operations and recycling of the auxiliaries limiting their practicality on scale-up.

Thus, we sought to develop a practical and scalable method for enantioselective hydroxymethylation of aldehydes. We report herein the results of our studies that established that efficient catalytic enantioselective hydroxymethylation can be achieved. Employing biphasic mixtures of acceptable organic solvents and suitably buffered formalin provided the desired stable chiral building blocks in very good to excellent yields. We first sought to establish an efficient catalytic cycle. Subsequently, we envisioned use of α,α-diphenylprolinol trimethylsilyl ether (**1**) as a chiral amine organocatalyst since **1** has found use as a relatively general organocatalyst for α-functionalization of aldehydes.[4,5]

(1) For selected examples, see: Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313. Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 597–599. Evans, D. A.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10899–10905. Troy Lister, M. V. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2560–2564.

(2) Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 6117–6119.

(3) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739. Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.

(4) For recent reviews, see: Palomo, C.; Mielgo, A. *Asian J. Chem.* **2008**, *3*, 922–948. Palomo, C.; Mielgo, A. *Angew. Chem, Int. Ed.* **2006**, *45*, 7876–7880. Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492. Marigo, M.; Jorgensen, K. A. *Chem. Commun.* **2006**, 2001–2011.

(5) For examples, see: Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797. Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215.

(6) Igarashi, M. T.; Masaru, *J. Heterocycl. Chem.* **1995**, *32*, 807–810. Kimpe, N. D. V.; Roland, B. L. D.; Schamp, N. *Chem. Ber.* **1983**, *116*, 3846–3857. Nagel, M.; Hansen, H.-J. *Synlett* **2002**, 692–696.

(7) Mori, K.; Ohki, M.; Matsui, M. *Tetrahedron* **1970**, *26*, 2821–2824.

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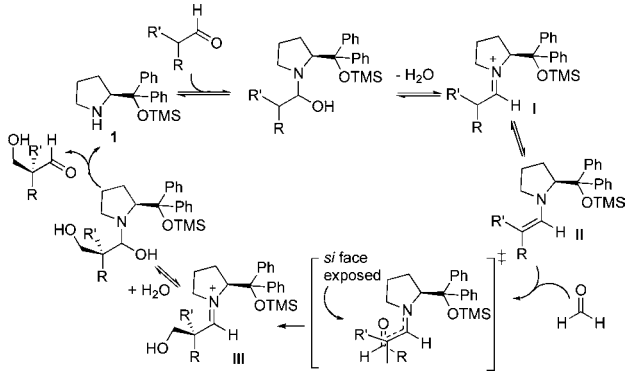
A likely mechanism for catalytic hydroxymethylation of aldehydes is outlined in Scheme 1. The enamine **II**, derived

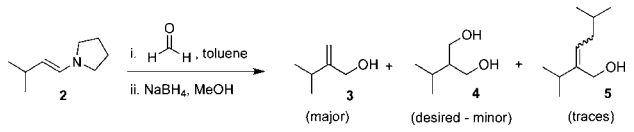
Scheme 1. Plausible Mechanism for the Hydroxymethylation of Aldehydes Catalyzed by **1**



from chiral amine **1** and the aldehyde, is postulated to react with formaldehyde from the less hindered *si* face owing to nonbonded interactions with the sterically demanding amine α-substituent. Hydrolysis of the resulting iminium ion completes the catalytic cycle.

To demonstrate the required catalytic cycle in nonpolar organic solvents, we began with the reaction of the preformed pyrrolidine enamine **2** derived from isovaleraldeyde (Scheme 2).[6] In preliminary experiments, we found that enamine **2**

Scheme 2. Initial Experiment with Pyrroline Enamine **2**



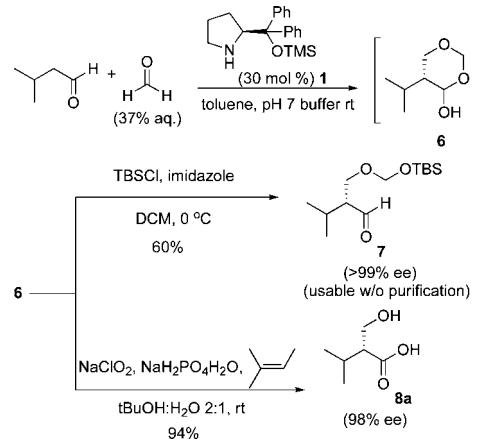
upon reaction with ∼3.0 equiv of 37% aq fomaldehyde in a variety of solvents afforded principally allylic alcohol **3**[7] after reduction with $NaBH_4$ accompanied by minor amounts of the desired diol **4**.[2] Upon further investigation, we determined that the undesired elimination was promoted by formic acid. A similar result had been reported by Pihko during development of a process α-methylenation of aldehydes.[8] The sample of formalin solution we employed was found to have pH ∼5 owing to accumulation of HCO_2H over time resulting from air oxidation of HCHO.[9]

Upon the basis of that observation, we buffered the formaldehyde solution with NaOAc and/or the reaction medium with a commerical pH 7 phosphate buffer which was found to surpress the undesired formation of **3**.

Formalin proved to be the optimal source of formaldehyde. We also found that adjusting the concentration of the reaction mixture to 0.5 M completely suppressed formation of **5** arising from aldol dimerization of isovaleraldehyde and provided acceptable reaction rates.[10] The desired hydroxymethylation reaction occurred in a variety of solvents; however, significantly better yields were observed in nonpolar solvents that were immiscible with formalin (i.e., toluene, hexane, DCM, $CHCl_3$). Under such biphasic reaction conditions, we were pleased that the desired hydroxymethylation proceeded using a catalytic amount (20−30 mol %) of pyrrolidine affording **4** in good yield (after in situ reduction with $NaBH_4$) in ∼12 h at rt. A further decrease in catalyst loadings led to unacceptably long reaction times.

Having established the catalytic cycle for hydroxymethylation, we then examined the asymmetric variant. Treatment of isovaleraldehyde with 20−30 mol % of prolinol ether **1** in a biphasic mixture of toluene and ∼3.0 equiv of buffered 37% aq formaldehyde (commercial formalin) with efficient mixing unexpectedly afforded principally the cyclic hemiacetal(s) **6** of the desired β-hydroxyaldehyde in which 2 equiv of formaldehyde had been incorporated (Scheme 3). Since

Scheme 3. Derivitization of the Intermediate α-Substituted β-Hydroxyaldehydes[a,b,c]



[a] Yields based on isolated yields after chromatography. [b] Enantiomeric excess determined by chiral GC analysis. [c] Absolute configuration assigned by comparison of the sign of optical rotation to known **8a**.

6 and the derived β-hydroxyaldehyde were difficult to handle and purify owing to their proclivity for oligomerization, we expected that TBS protection or Pinnick oxidation of **6** would provide more readily isolable materials suitable for further transformation.[11,12] The structure of **6**, which was unstable to isolation/purification, was inferred from the formation of silyl ether **7** (90% yield, >99% ee) upon treatment of crude **6** with TBSCl/imidazole. As noted previously, aldehyde **7** and congeners proved sensitive to racemization upon chro-

(8) Kallianos, A. G.; Warfield, A. H.; Simpson, M. I. U.S. Patent 3, 704, 714, December 5, 1972.

(9) Erkkila, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538–2541.

(10) Joshi, L. D.; Srivastava, A. C.; Dutta, B. K. *Fert. Technol.* **1976**, *13*, 128–30.

(11) For a review, see: Raach, A.; Reiser, O. *J. Prakt. Chem.* **2000**, *342*, 605–608.

(12) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348–6359. Hosokawa, T.; Yamanaka, T.; Itotani, M.; Murahashi, S.-I. *J. Org. Chem.* **1995**, *60*, 6159–6167.

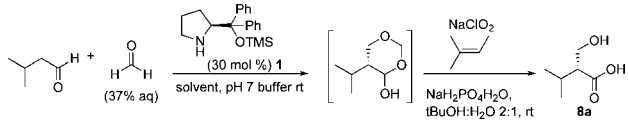
matographic purification; however, these materials were obtained sufficiently pure for further use.[12]

Formation of **6** was surprising and potentially fortuitous since the stability of **6** may be responsible for the high degree of enantioselectivity observed by preserving the chirality at the newly generated α chiral center given the ease of racemization of such aldehydes.[12]

Alternatively, Pinnick oxidation ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene) of **6** afforded (*R*)-2-(hydroxymethyl)-3-methylbutanoic acid **8a** in excellent yield (94%) and enantiospecificity (98% ee) as also shown in Scheme 3.

Since the reaction performed well in biphasic media, we set out to investigate whether the nature of the organic solvent affected the observed enantioselectivity. Indeed, employing more polar solvents such as CH_2Cl_2 (71% ee) and $CHCl_3$ (79% ee) degraded the enantioselectivity ∼20% relative to that observed in the most nonpolar solvents hexane (93% ee) and toluene (98% ee). It is noteworthy that the decrease in % ee is correlated with the solubility of water in the organic phase (Table 1).

Table 1. Effect of Solvent on the Enantioselectivity



entry	solvent	time (h)	ee (%)[a]
1	DCM	15	71
2	$CHCl_3$	15	79
3	hexane	15	93
4	toluene	15	98

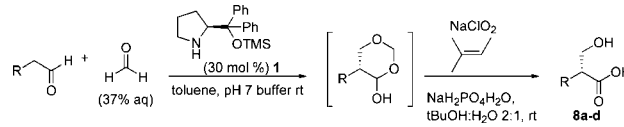
[a] Enantiomeric excess determined by chiral GC analysis of methyl ester.

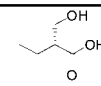
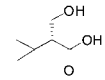
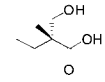
Having determined optimal reaction conditions, we set out to examine structurally diverse aldehydes including those bearing substituents and branched side chains. We found that most aldehyde branching patterns are tolerated (Table 2). Reaction of three linear and *β*-branched aliphatic aldehydes afforded the desired *β*-hydroxy acids **8a**−**c** in 71−94% yield and 92−99% ee. It is especially noteworthy that α branching is also tolerated providing hydroxy acid **8d** bearing a fully substituted chiral center in >99% ee but somewhat lower yield (50%) possibly owing to the slower reaction rate. The absolute configuration of all the products **8a**−**j** were assigned by comparison or analogy to known hydroxy acids **8a**,**c**,**j**.[13−15]

Further investigation of the scope has shown that the method tolerates a wide array of functional groups, including esters, alkynes, and protected nitrogen and oxygen functional

(13) Jin, Y. *Synlett* **1998**, 1189–1190.
(14) Takacs, J. M.; Jaber, M. R.; Vellekoop, A. S. *J. Org. Chem.* **1998**, *63*, 2742–2748.
(15) Monteil, T.; Danvy, D.; Plaquevent, J.-C.; Duhamel, L.; Duhamel, P.; Gros, C.; Schwartz, J.-C.; Lecomte, J.-M. *Synth. Commun.* **2001**, *31*, 211–218.

Table 2. Effect of Carbon Branching for the Hydroxymethylation of Aldehydes

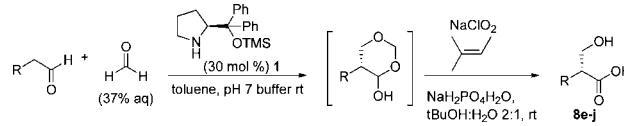


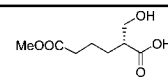
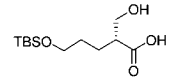
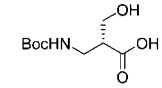
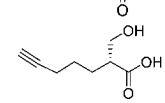
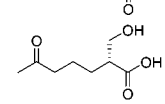
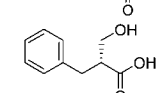
entry		product	time(h)	yield (%)[a]	ee (%)[b]
1	**8a**		15	94	98
2	**8b**		12	75	92
3	**8c**		20	71	95
4	**8d**		48	50	>99

[a] Yields based on isolated yields after chromatography. [b] Enantiomeric excess determined by chiral GC analysis of methyl esters (see Supporting Information).

groups. As seen from Table 3, the results for a variety of substrates are uniformly very good to excellent. The precursor aldehydes afforded the corresponding *β*-hydroxy acids

Table 3. Functional Group Tolerance for the Hydroxymethylation of Aldehydes

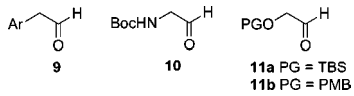


entry		product	time(h)	yield (%)[a]	ee (%)[b]
1	**8e**		15	92	>99
2	**8f**		12	86	>99
3	**8g**		15	80	>99
4	**8h**		12	60	96
5	**8i**		15	64	>99
6	**8j**		12	93	90

[a] Yields based on isolated yields after chromatography. [b] Enantiomeric excess determined by chiral GC analysis of methyl esters (see Supporting Information).

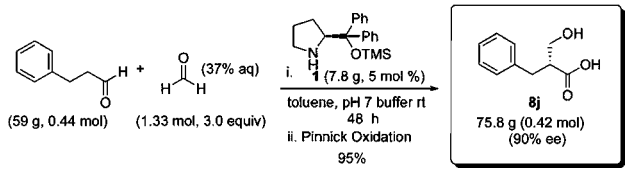
8e−**j** in 60−93% yields in 90−99% ee. Noteworthy chemoselectivity is observed for α-hydroxymethylation of an aldehyde in the presence of a methyl ketone in the formation of acid **8i**.[16] No interaction of the intermediate enamine with the electrophilic functional groups was noted in formation of acids **8e** and **8h,i**.

However, limitations in subtrate scope were encountered. Aldehydes of the general structures **9**−**11** failed to undergo hydroxymethylation using the standard conditions outlined above. For **9**, the low reactivity may result from formation of an unusually stable enamine upon reaction with amine **1**. Such aldehydes have been employed in organocatalytic reactions but normally require higher reaction temperatures and the presence of acid to catalyze reaction.[17] In our case, use of harsher conditions would surely lead to elimination and/or erosion of enantiocontrol. As are the aldehydes **10** and **11** bearing α heteroatoms, the resulting enamines are notoriously unstable decomposing under our reaction conditions. Aldehydes such as **10** and **11** have also been employed successfully in organocatalytic reactions, but different catalyst frameworks and nonaqueous reaction conditions are required.[18] Furthermore, substrates where a carbonyl functionality is present five atoms removed from the enamine, afforded only α-methylenated products presumably owing to assisted elimination by interaction with the terminal functional group.



The hydroxymethylation is readily scalable. Catalyst loadings can be decreased to 5 mol % without loss of % ee or significant increase in reaction time as shown for preparation of **8j** (Scheme 4). On scale, the exothermic Pinnick oxidation step must be conducted at 0 °C.

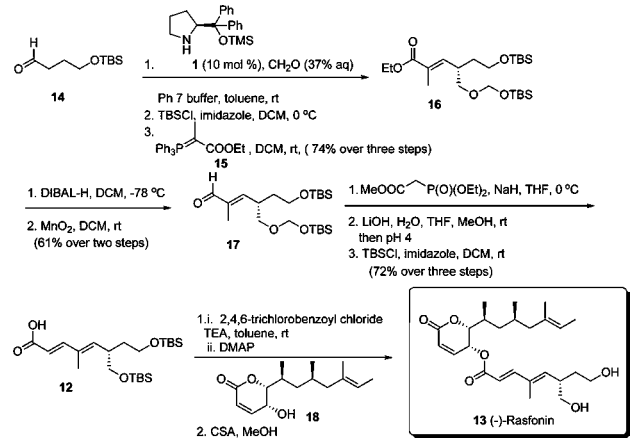
Scheme 4. Large-Scale Example of Hydroxymethylation



Our methodology was applied to a shortened synthesis of the acid side chain (−)-**12** of (−)-Rasfonin **13** prepared previously by our group (Scheme 5).[19] Organocatalytic

(16) When an equimolar amount of **1** and acetone were mixed in an NMR tube, no detectable enamine formation was observed at rt.

Scheme 5. Application of the Hydroxymethylation of Aldehydes to the Synthesis of (−)-Rasfonin



hydroxymethylation of aldehyde **14**,[20] followed by TBS protection of the resulting alcohol and Wittig reaction with ylide **15**, provided the ester **16** (98% ee) in 74% yield over three steps without purification of any intermediates. Ester **16** was transformed through the related aldehyde **17** via Wittig olefination to acid **12** which was coupled to pyrone alcohol **18** using a Yamaguchi coupling.[19,21] Desilylation gave (−)-Rasfonin **13** identical to a sample of synthetic (−)-Rasfonin.[19,21]

In summary, we have disclosed a practical method for the α-hydroxymethylation of aldehydes affording, after derivatization, bench stable and in some cases crystalline solid materials which can be utilized as chiral building blocks in total synthesis. Further studies to expand the scope of enamine catalysis to a variety of aldehyde functionalization reactions are currently underway.

Acknowledgment. We are grateful for support of these studies by Novartis Pharma AG and Novartis Pharmaceuticals Corp.

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.

OL9017479

(17) Sulzer-Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Synthesis* **2007**, 1729–1732.
(18) Ian Storer, R.; MacMillan, D. W. C. *Tetrahedron* **2004**, *60*, 7705–7714.
(19) Boeckman, R. K., Jr.; Pero, J. E.; Boehmler, D. J. *J. Am. Chem. Soc.* **2006**, *128*, 11032–11033.
(20) Barrett, A. G. M.; Flygare, J. A.; Spilling, C. D. *J. Org. Chem.* **1989**, *54*, 4723–4726.
(21) Akiyama, K.; Yamamoto, S.; Fujimoto, H.; Ishibashi, M. *Tetrahedron* **2005**, *61*, 1827–1833.