ORGANIC LETTERS

2005
Vol. 7, No. 18
3861−3864

Asymmetric Glycolate Aldol Reactions Using Cinchonium Phase-Transfer Catalysts

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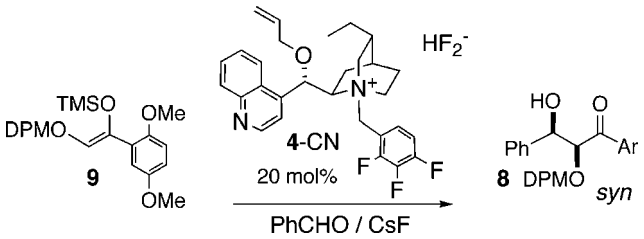
Received May 11, 2005

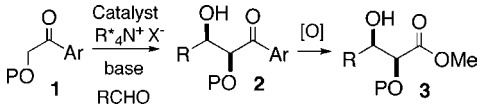
ABSTRACT



Cinchona phase-transfer catalysts (PTC) were developed for glycolate aldol reactions to give differentially protected 1,2-diol products. Silyl enol ether 9 reacted to generate benzhydryl-protected products. *O*-Allyl trifluorobenzyl cinchonium hydrofluoride CN-4 (20 mol %) catalyzed the addition of 9 to benzaldehyde to give 8 as a single *syn*-product in 76% yield and 80% ee. Recrystallization enriched the product to 95% ee, and a Baeyer–Villiger reaction transformed the product into useful ester intermediates.

Phase-transfer catalysis (PTC) is an attractive, general approach to asymmetric synthesis where an enolate ion, formed in situ, is paired with an enantiopure quaternary ammonium cation. Partitioning to the organic phase is thus facilitated, allowing the enolate to selectively react with an organic soluble electrophile. Glycine alkylations, enone epoxidation, conjugate additions, and other asymmetric transformations have been successfully developed using this strategy.[1] We now report a new PTC asymmetric glycolate aldol reaction, which employs a silyl enol ether derivative of aryl ketone **1** to give differentially protected *syn*-products **2** that are readily converted to 1,2-diol esters **3** (Scheme 1). PTC has numerous advantages including the use of inexpensive, cinchona alkaloid catalysts, which are readily available in pseudo-enantiomeric antipodes, simple hydroxide bases, and mild conditions performed in either liquid−liquid or liquid−solid mode over an extended temperature range. Systematic variation of cinchona-based and other nonnatural catalysts (Scheme 2) have led to steady improvements for

Scheme 1. Glycolate Aldol



glycine alkylations with *N*-(diphenylmethylene)glycine *tert*-butyl ester for the synthesis of amino acids.[2]

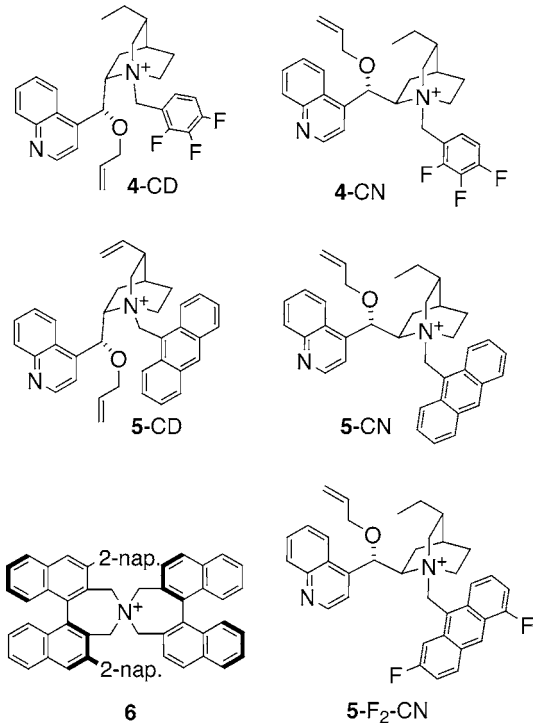
In contrast to glycine alkylation, PTC aldol reactions are far less common. Protected glycine has been reacted with aldehydes under various PTC conditions to give β-hydroxy-α-amino acids.[3,4] Although problems with *syn*/*anti* selectivity

(1) (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013−3028. (b) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961−998. (c) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *3*, 3−15.

(2) (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353−2354. (b) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775−8778. (c) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. (d) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595−8598. (e) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000−13001. (f) Ooi, T.; Kameda, K.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519−6520. (g) Jew, S.; Yoo, M.; Jeong, B.; Park, I. Y.; Park, H. *Org. Lett.* **2002**, *4*, 4245−4248. (h) Park, H.; Jeong, B.; Yoo, M.; Lee, J.; Park, M.; Lee, Y.; Kim, M.; Jew, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036−3038.

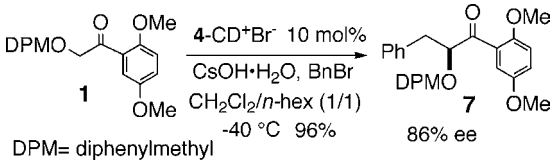
10.1021/ol051096a CCC: $30.25
Published on Web 08/11/2005

Scheme 2. Phase Transfer Catalysts Investigated



and product isolation are typical. Maruoka and co-workers have recently developed bis-binaphthyl catalysts that give glycine aldol products with high selectivity.[5] In an effort to extend the PTC process to oxygenated glycolate products, we previously reported asymmetric PTC-catalyzed alkylations with oxygenated substrates using the novel alkoxyacetophenone **1** (Scheme 3).[6] The nature of the protecting

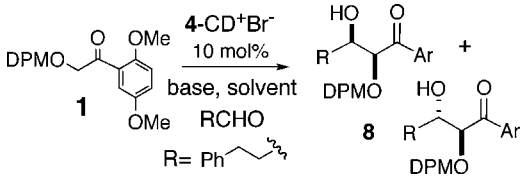
Scheme 3. PTC Alkylation



group and substitution pattern on the aryl ketone proved to be critical for high selectivity and good reaction rates. This method provides a convenient route to a variety of alkylated hydroxy products with high selectivity. Previous to this work, asymmetric glycolate alkylation was limited to chiral auxiliaries.[7]

Initially the direct aldol reaction of DPM (diphenylmethyl)-protected 2,5-dimethoxyacetophenone **1** was explored using the *N*-trifluorobenzyl cinchonidinium catalyst of Park and Jew[2g] **4**-CD$^+$Br$^-$ (Table 1). Solid-liquid-phase conditions

Table 1. PTC Aldol with Ketone **1**



base	solvent	yield (%)	*syn*/*anti*	ee (%, *syn*)
CsOH·H_2O	THF	45	3/1	0[a]
NaOMe	THF	83	2.5/1	0[a]
NaOH	toluene	53	4/1	7[b]
NaOH	toluene	45	4/1	22[b,c]

[a] The temperature was −40 °C. [b] The reaction was conducted at 0 °C with 1% aqueous NaOH. [c] **4**-CN$^+$Br$^-$ was used as catalyst.

with either cesium hydroxide or sodium methoxide in THF gave product **8** from dihydrocinnamaldehyde with poor diastereoselectivity and no enantioselectivity. Liquid−liquid conditions with 1% aqueous sodium hydroxide and toluene showed only slight improvement in the *syn*/*anti* ratio. Use of other bases (not shown) including sodium carbonate and phosphazines (BTPP)[2b] failed to give product. The catalyst was then changed to the pseudo-enantiomeric **4**-CN$^+$Br$^-$ with only slight improvement in the enantioselectivity, 22% ee for the *syn*-product. Surprisingly, this change to the cinchonium catalyst **4** resulted in production of the same enantiomeric product. Use of ammonium chloride as an additive in toluene, THF, or other solvents did not improve the yield or selectivity. Use of Maruoka's bis-binaphthyl catalyst **6** gave only trace product with little selectivity (7%, 6% ee).[2f] Self-condensation products were not observed under any conditions with dihydrocinnamaldehyde used as the test substrate. Benzaldehyde with **4**-CD$^+$Br$^-$ and NaOH gave a very low yield (15%) under these conditions.

The silyl enol ether of **1** was then made and explored under Corey's cinchonium fluoride catalyst conditions.[4] Compound **1** was treated with LDA and trapped with TMSCl to give **9** (Scheme 4) as a stable white solid, which is simply purified by filtration and crystallization. Fortunately, as a silyl enol ether, **9** is easily manipulated, unlike the corresponding silyl ketene acetal of the protected glycine used in previous PTC aldol studies, which is easily hydrolyzed.

Reaction of **9** with benzaldehyde under PTC conditions gave the differentially protected aldol product **8** following

(3) (a) Gasparski, C. M.; Miller, M. J. *Tetrahedron* **1991**, *47*, 5367−78. (b) Yoshikawa, N.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 8289−96. (c) Shimizu, S.; Shirakawa, S.; Suzuki, T.; Sasaki, Y. *Tetrahedron* **2001**, *57*, 6169. (d) Arai, S.; Hasegawa, K.; Nishida, A. *Tetrahedron Lett.* **2004**, *45*, 1023. (e) Mettath, S. Srikanth, G. S. C.; Dangerfield, B. S.; Castle, S. L. *J. Org. Chem.* **2004**, *69*, 6489−6492.

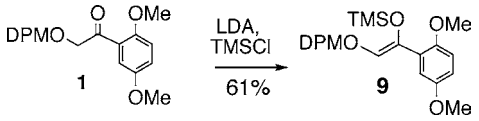
(4) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843−3846.

(5) (a) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542−4522. (b) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685−9694. For other recent catalytic glycolate aldol reactios, see: Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368.

(6) Andrus, M. B.; Hicken, E. J.; Stephens, J. S. *Org. Lett.* **2004**, *6*, 2289−2292.

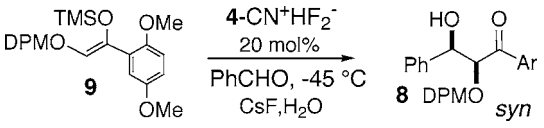
(7) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165−2167.

Scheme 4. Silyl Enol Ether Synthesis



treatment with cesium fluoride and water (Table 2). In dry THF with the hydrogen difluoride catalyst **4**-$CN^+HF_2^-$ at −45 °C the yield of **8** was low (35%); however, the selectivity was dramatically improved to 75% ee. In all cases with this substrate, a single *syn*-diastereomer was obtained. Protected glycine PTC aldol reactions typically give a mixture of diastereomers. Use of DME and other solvents explored did not improve the yield. Using the corresponding cinchonidinium catalyst **4**-$CD^+HF_2^-$, the isolated yield increased to 52%; however the selectivity dropped to 41% ee. Surprisingly, use of reagent grade THF with **4**-$CN^+HF_2^-$ improved the rate of the reaction, requiring 1.5 h for completion, and the yield and selectivity also increased (78%, 75% ee). Trace water in this case appears to improve the catalyst turnover and the selectivity. Use of the Corey−Lygo catalyst[4] **5**-$CN^+HF_2^-$ extended the reaction time and improved the selectivity (78% ee) with a lower yield (52%). Using the optimal catalyst **4**-$CN^+HF_2^-$, the temperature was lowered to −55 °C, to give **8** in 76% yield and 80% ee. Use of the novel difluoroanthracenyl catalyst **5**-F_2-$CN^+HF_2^-$, recently found in the bromide form to give highly selective glycine alkylations,[8] improved the aldol reaction in **8** with 83% ee. Unfortunately, the isolated yield dropped to 40% in this case. Variations of the aryl group of the silyl enol ether **9** were also explored (not shown). With phenyl in place of the 2,5-dimethoxyphenyl group, the aldol product with benzaldehyde was obtained in 58% yield and greatly reduced 15% ee selectivity. With the 2-methoxyphenyl substrate variation, 52% ee was obtained in 23% yield. 4-Methoxy and 2,4-methoxy variants gave only trace aldol product. Various solvents and combinations were also explored under

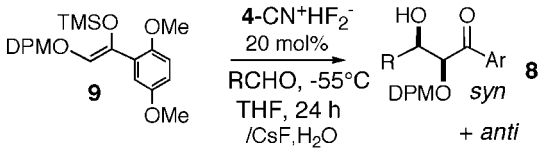
Table 2. PTC Aldol with Silyl Ether **9**

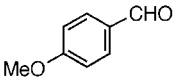
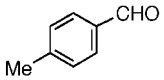
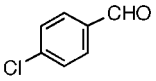
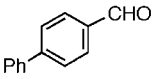
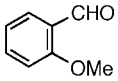
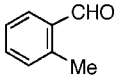
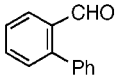
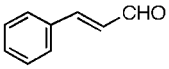
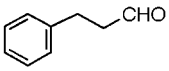
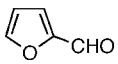
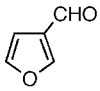
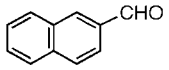


solvent	catalyst	time (h)	yield (%)	ee (%)
THF	**4**-$CN^+HF_2^-$	24	35	75
DME	**4**-$CN^+HF_2^-$	24	19	37
THF	**4**-$CD^+HF_2^-$	24	52	41
THF[a]	**4**-$CN^+HF_2^-$	1.5	78	75
THF[a]	**5**-$CN^+HF_2^-$	11	52	78
THF[a,b]	**4**-$CN^+HF_2^-$	24	76	80
THF[b]	**5**-F_2-$CN^+HF_2^-$	24	40	83
THF/DMF[a,c]	**4**-CN^+HF_2	19	87	80

[a] Reagent grade solvent used. [b] Reaction conducted at −55 °C. [c] Reaction conducted at −78 °C.

Table 3. PTC Aldol Addition with Various Aldehydes



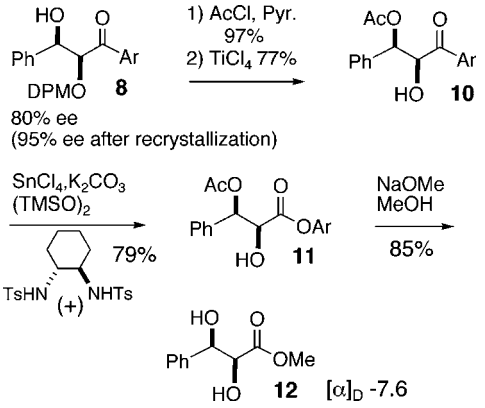
entry	RCHO	yield%	*syn/anti*	ee%
1	PhCHO	76	>99/1	80
2		30	>99/1	83
3		58	>99/1	78
4		85	10/1	65
5		77	>99/1	75
6		70	>99/1	77
7		57	>99/1	75
8		45	20/1	83
9		36	>99/1	44
10		23	2/1	45
11		86	6/1	53
12		33	>99/1	62
13		69	>99/1	79

these aldol conditions. Finally, use of a 1/1 reagent THF/DMF solvent mixture with **4**-$CN^+HF_2^-$ proved superior, with 87% yield and 80% ee for the *syn*-product **8**. Reagent grade THF used alone proved to be the most practical and general solvent for the other aldehyde substrates.

Optimized conditions with **4**-$CN^+HF_2^-$ in reagent grade THF were used with a wide range of aldehydes (Table 3). In most cases, a single *syn*-diastereomer **8** was again produced. Aromatic aldehydes all reacted with good to excellent results. 4-Biphenylcarboxaldehyde (Table 3, entry 5) and *o*-methoxybenzaldehyde (Table 3, entry 6) with yields and selectivities from 70% to 80% were typical. Unfortunately, alkyl and α,β-unsaturated aldehydes reacted with lower yield and selectivity (Table 3, entries 9 and 10). 2-Naphthaldehyde (Table 3, entry 13) was also efficient again with a single *syn*-diastereomer in 79% ee. Although conclu-

(8) Andrus, M. B.; Ye, Z.; Zhang, J. *Tetrahedron Lett.* **2005**, *46*, 3839−3842.

Scheme 5. Structure Proof and Elaboration



sions concerning mechanistic details are premature at this time, it can be pointed out that the C2 stereocenter in the product **8** is *S* using either the cinchonine catalyst **4**-CN or cinchonidine **4**-CD as demonstrated below. This is consistent with the major *S*-isomer obtained previously for alkylation of **1** using **4**-CD.[6]

Fortunately, the enantioselectivity of the aldol product was significantly raised on crystallization (Scheme 5). The major (2*S*,3*R*) *syn*-diastereomer **8**, obtained from addition to benzaldehyde originally at 80% ee, was enriched to 95% ee (65%) following crystallization and filtration of a racemic, conglomerant solid. Elaboration to differentially protected products and proof of the absolute stereochemistry were carried out from this intermediate. Treatement with acetyl chloride and pyridine gave an acetate intermediate, which was unambiguously confirmed by single-crystal X-ray analysis.[9] This intermediate was then subjected to titanium chloride at low temperature to effect removal of the diphenylmethyl (DPM) group. The resultant hydroxy ketone **10** (Ar = 2,5-dimethoxyphenyl) was subjected to Shibizaki modified Baeyer−Villiger conditions,[10] involving stiochiometric TMS-peroxide, catalytic tin tetrachloride, and (±)-cyclohexyl bis-sulfonamide, to give aryl ester **11** in 79% isolated yield. Transesterification, with concomitant acetate hydrolysis, gave the known (*S*,*R*)-diol methyl ester **12**.[11]

In summary, a new approach to asymmetric glycolate aldol additions has been developed using readily available catalysts under mild PTC conditions. Differentially protected *syn*-1,2-diols are produced with very high diastereoselectivity and good enantioselectivity. Simple recrystallization and Baeyer−Villiger oxidation generate highly enantioenriched ester diol products. Refinements to the substrate and catalyst are anticipated to lead to further improvements and synthetic applications.

Acknowledgment. We are grateful to the American Chemical Society Petroleum Research Fund (41552-AC1) and the BYU Cancer Research Center for funding.

Supporting Information Available: Experimental procedures and characterization for selected compounds and spectral, HPLC, and X-ray data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051096A

(9) See Supporting Information for details.

(10) (a) Sawanda, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521−10532. (b) Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971−974.

(11) Deng, J.; Hamada, Y.; Shiori, T. *Synthesis* **1998**, 627−638.