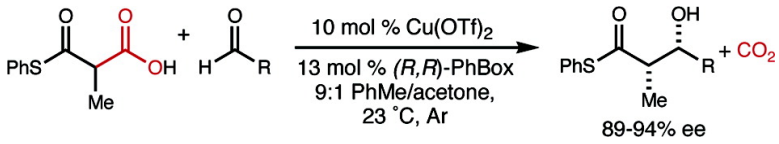
Communication

Catalytic Enantioselective Thioester Aldol Reactions That Are Compatible with Protic Functional Groups

Derek Magdziak, Gojko Lalic, Hong Myung Lee, Kevin C. Fortner, Allen D. Aloise, and Matthew D. Shair

J. Am. Chem. Soc., **2005**, 127 (20), 7284-7285• DOI: 10.1021/ja051759j • Publication Date (Web): 28 April 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 17 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 04/28/2005

Catalytic Enantioselective Thioester Aldol Reactions That Are Compatible with Protic Functional Groups

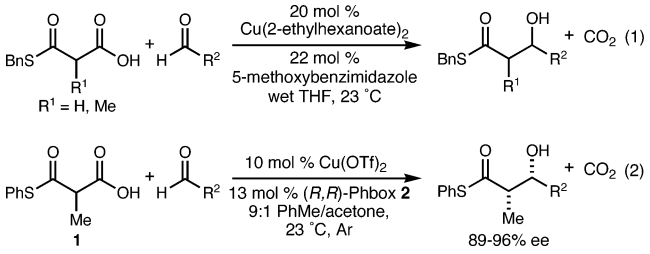
Derek Magdziak, Gojko Lalic, Hong Myung Lee, Kevin C. Fortner, Allen D. Aloise, and Matthew D. Shair*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received March 19, 2005; E-mail: shair@chemistry.harvard.edu

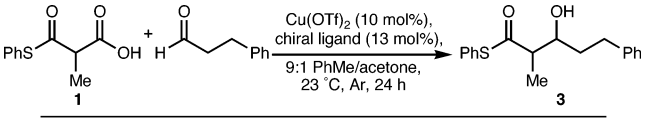
Catalytic enantioselective aldol reactions of carboxylic acid derivatives have undergone continuous development over the last 20 years.[1] An important recent advance was reported by Evans and co-workers who achieved Ni(II) bis(oxazoline)-catalyzed enantioselective imide aldol reactions with in situ enolate formation in the presence of enolizable aldehydes.[2,3] Our interest in the reactivity of malonic acid half thioesters (MAHTs) led to the discovery that MAHTs can be used in Cu(II)-catalyzed decarboxylative thioester aldol reactions, which also involve in situ generation of the nucleophile (Scheme 1, eq 1, R^1 = H, Me).[4] Since these reactions were performed in the presence of a carboxylic acid (the MAHT), an alcohol (from the product), and in wet THF, we believed that they might also be compatible with aldehydes bearing unprotected protic functional groups.[5] This communication reports (Scheme 1, eq 2) highly enantioselective and diastereoselective methyl malonic acid half thioester (MeMAHT) aldol reactions that are compatible with protic functional groups and enolizable aldehydes and that afford syn *S*-phenyl thiopropionates.

Scheme 1

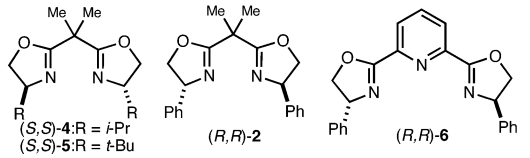


Initial attempts to render the thioacetate aldol reaction (Scheme 1, eq 1, R^1 = H)[4a] enantioselective by the addition of chiral ligands and $Cu(OAc)_2$ led to low enantioselectivities.[4b] We speculated that a more Lewis acidic Cu(II) complex, such as $Cu(OTf)_2$, possessing less coordinating counterions may be necessary for the formation of a MAHT−Cu(II)−chiral ligand ternary complex. This led to our discovery that highly enantioselective thiopropionate aldol reactions could be achieved by adding 1.2 equiv of *S*-phenyl MeMAHT (**1**)[6] to 10 mol % $Cu(OTf)_2$ followed by 13 mol % (*R*,*R*)-Phbox (**2**) and 1.0 equiv of aldehyde (Scheme 1, eq 2), affording preferentially the syn diastereomer. The use of an *S*-phenyl ester was necessary for high enantioselectivity and high reactivity. Although this reaction (eq 2) could be performed in wet solvents without diminution of enantioselectivity, the yields fluctuated, leading us to use dry solvents. While most Cu(II) bis(oxazoline)-catalyzed reactions are conducted with a preformed complex comprising a 1:1 ratio of CuX_2:bis(oxazoline),[7] the MeMAHT aldol reaction did not occur under these conditions. The reaction afforded the highest yields when performed with a 3 mol % excess of bis(oxazoline), possibly due to its secondary role as a base in the reaction.

Table 1. Effects of Bis(oxazoline) Ligands



Entry[a]	Ligand	% Yield	syn:anti[b]	% ee[c,d] (config)[e]
1	(*S*,*S*)-*i*-Prbox **4**	83	3.2:1	87 (*S*)
2	(*S*,*S*)-*t*-Bubox **5**	trace		
3	(*R*,*R*)-Phbox **2**	89	11:1	93 (*R*)
4	(*R*,*R*)-Phpybox **6**	NR	-	-



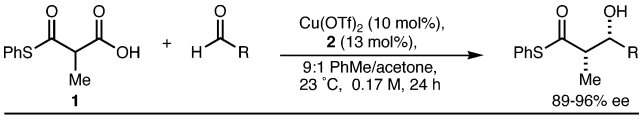
[a] 1.2 equiv of **1**, 1.0 equiv of aldehyde. [b] Syn:anti ratios were determined by HPLC. [c] Enantiomeric excess of the syn diastereomer. [d] Enantiomeric excess was determined by chiral HPLC. [e] The absolute configuration of the secondary alcohol is provided in parentheses.

Of the four bis(oxazoline) ligands (**2**, **4**−**6**) evaluated in the aldol reaction (Table 1), **2** afforded aldol adduct **3** (entry 3) in the highest yield (89%), the highest enantioselectivity (93%), and the highest diastereoselectivity (11:1 favoring the syn isomer). The aldol reaction with *i*-Prbox (**4**) occurred, albeit in lower yield, ee, and diastereoselectivity (entry 1). Interestingly, the reaction was suppressed by *t*-Bubox (**5**) and Phpybox (**6**) (entries 2 and 4). Taken together, these results suggest that the aldol reaction requires a catalyst capable of forming a pentacoordinate Cu(II) complex[7e] with one aldehyde as a ligand, an arrangement that is energetically prohibitive for a MeMAHT−Cu(II)−**5** complex.[7a] Also, the reaction may require two open equatorial positions, an arrangement geometrically prevented by **6**.[7b] Both requirements are possible with **2** and **4**.[7c]

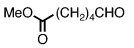
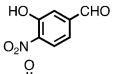
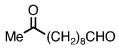
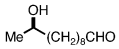
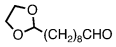
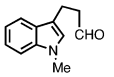
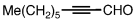
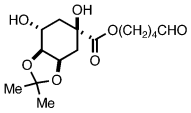
We evaluated a diverse set of aldehydes, many bearing protic functionality, using our optimized conditions (Table 2). For instance, the MeMAHT aldol reaction afforded good yields (70−79%) and enantioselectivites (91−92%) with aldehydes bearing unprotected hydroxyl groups (entries 5 and 11). Even 4-nitro-3-hydroxybenzaldehyde (entry 3), a phenol that would normally protonate metal enolates, underwent the aldol addition to afford the product in 83% yield and 93% ee. Other functionalities compatible with the reaction included a methyl ketone (entry 4), Lewis acid-sensitive acetals and ketals (entries 6 and 11), and an indole-containing aldehyde susceptible to acid-catalyzed cyclization (entry 7). α-Branched aldehydes reacted more sluggishly, requiring in the case of cyclohexanecarboxaldehyde two equivalents of aldehyde (entry 10) to reach 71% yield. Limitations of the reactions are α,β-unsaturated aldehydes and aromatic aldehydes lacking electron-

10.1021/ja051759j CCC: $30.25

Table 2. Scope of the MeMAHT Aldol Reaction



1

Entry[a]	RCHO	% Yield	syn:anti[d]	% ee[e,f]
1	$Me(CH_2)_6CHO$	80	9:1	92 (*R*)
2		83	10:1	94
3		83	9:1	93 (*S*)
4		71	6.5:1	93
5		79	8:1	91
6[b]		79	7.6:1	94
7		83	8:1	94
8		59	2.2:1	96 (*S*)
9[c]		73	7.5:1	89
10[c]		48 (71[g])	36:1	93
11[b]		70	5.5:1	92

[a] 1.2 equiv of **1**, 1.0 equiv of aldehyde. [b] 0.1 M for 48 h. [c] For 60 h. [d] Syn:anti ratios were determined by HPLC or by NMR analysis. [e] Enantiomeric excess was determined by chiral HPLC. [f] Configuration of the secondary alcohol provided in parentheses when determined, or assigned by analogy. [g] With 2 equiv of aldehyde.

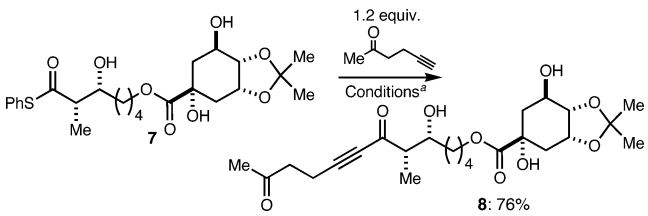
withdrawing groups, both of which were unreactive; however, octynal (entry 8) was reactive.

Notably, enantioselectivites were ≥89% for the aldehydes listed in Table 2, irrespective of their steric and electronic properties. In each reaction, little or no aldehyde self-condensation was detected, and no more than 2% α,β-unsaturated thioester was observed, highlighting the selective activation of MeMAHTs in the presence of enolizable aldehydes and the mildness of the reaction conditions.

One advantage of using thioesters as carboxylic acid equivalents is their participation in Pd-catalyzed cross-couplings to generate ketones under neutral conditions.[8] An exemplary reaction is provided in Scheme 2 in which unprotected aldol adduct **7** (from entry 11, Table 2) was directly coupled with 5-hexyne-2-one to afford **8**.[8b] In principle, MeMAHT aldol reactions combined with Pd-catalyzed cross-couplings should provide rapid access to a wide range of enantiomerically enriched α-methyl-β-hydroxyketones without recourse to protecting groups.

There are several reasons why these aldol reactions are unique. First, in most cases two-point binding aldehydes are required to achieve >90% ee in Cu(II)(box)-catalyzed reactions.[9] This is one of the few reactions that achieve high enantioselectivities with one-point binding aldehydes.[10] This could be due to the two-point binding capability of the MeMAHT, a hypothesis that awaits future mechanistic studies. Second, the conditions are remarkably mild. The reaction reported here is formally an aldol reaction between a thioester and an aldehyde where the strongest base is 3 mol % of excess **2**. The lack of strong Lewis acids or strongly basic intermediates generated during the course of the reaction enables

Scheme 2[a]



[a] Reagents and conditions: 10 mol % $Pd(dppf)Cl_2$, 25 mol % trifurylphosphine, 2 equiv of Cu(I), 1 equiv of *i*-Pr_2NEt, DMF, 50 °C, 6 h.

it to be compatible with hydroxyl groups, phenols, enolizable aldehydes, enolizable methyl ketones, and carboxylic acids—functionalities that would normally be incompatible with ester enolates. Third, MAHTs provide a unique way of activating esters as nucleophiles—a carboxylate group that is lost as CO_2 during the course of the reaction provides traceless activation. The functional group compatibility and the utility of the thioester group in the products may make this aldol reaction useful in complex molecule synthesis.

Acknowledgment. We gratefully acknowledge support from Novartis, Merck Research Labs, GlaxoSmithKline, and the Arthur C. Cope Fund.

Supporting Information Available: Representative experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Recent review of catalytic, enantioselective aldol reactions: (a) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65−75. For a review of catalytic, enantioselective Mukaiyama aldol reactions with silyl ketene acetals, see: (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 3, pp 997−1065.

(2) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706−8707.

(3) For other catalytic enantioselective aldol reactions with esters or their derivatives involving in situ generation of the nucleophile, see: (a) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352−5353. (b) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945−7946. (c) Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829−1831.

(4) (a) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852−2853. (b) Orlandi, S.; Benaglia, M.; Cozzi, F. *Tetrahedron Lett.* **2004**, *45*, 1747−1749. See also: (c) Lou, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440−11441.

(5) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209−217.

(6) MeMAHT (**1**) was prepared in 12 g batches in one step from commercially available starting materials, in 94% yield, and without chromatography following crystallization (see Supporting Information). **1** is a colorless solid that can be stored on the benchtop for at least 2 months without loss of activity in the aldol reaction.

(7) (a) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jorgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888−1898. (b) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (d) Jorgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605−613. For an exception, see: (e) Juhl, K.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420−2421.

(8) (a) Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87−96. (b) Tokuyama, H.; Miyazaki, T.; Yokoshima, S.; Fukuyama, T. *Synlett* **2003**, 1512−1514. (c) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554−3557 and references therein.

(9) See, for example: (a) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936−7943. (b) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814−5815.

(10) (a) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692−12693. (b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582−7594.

JA051759J