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Direct Carbon−Carbon Bond Formation via Reductive Soft Enolization: A Kinetically Controlled *syn*-Aldol Addition of α-Halo Thioesters and Enolizable Aldehydes

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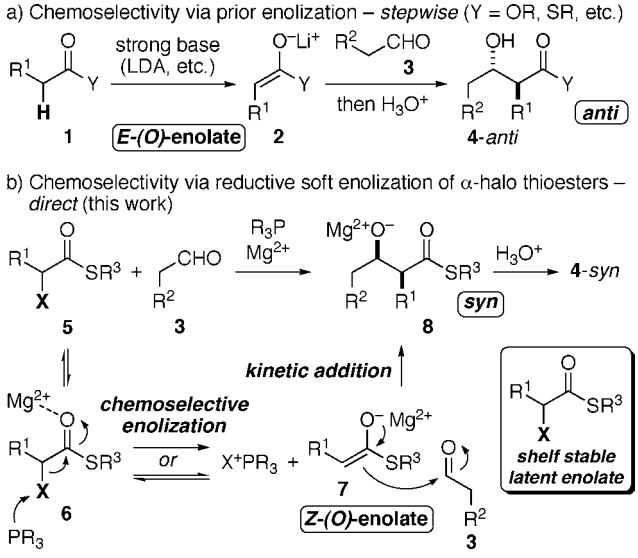
Abstract: The *direct* addition of enolizable aldehydes and α-halo thioesters to produce *β*-hydroxy thioesters enabled by reductive soft enolization is reported. The transformation is operationally simple and efficient and has the unusual feature of giving high *syn*-selectivity, which is the opposite of that produced for (thio)esters under conventional conditions. Moreover, excellent diastereoselectivity results when a chiral nonracemic α-hydroxy aldehyde derivative is used.

The development of a generally applicable direct aldol addition[1] in which a carboxylate derivative and enolizable aldehyde are combined in the presence of a base (etc.) has been a long-standing yet unrealized goal in the field of organic synthesis. Unfortunately, side reactions between, for example, the base and electrophile complicate this transformation. Introduced in 1951,[2] prior enolate formation[3] (cf. Scheme 1a) provides a way of circumventing these issues and has led to some of the most important reactions known. While effective, the stepwise procedures used to generate the enolates are time-consuming, particularly if trapping is involved, and require that all manipulations be conducted under anhydrous conditions and, when strong bases are used, at low temperature. Given these factors along with the importance of the aldol reaction,[4] a general, direct transformation applicable to enolizable aldehydes remains highly desirable. In what follows, we describe the first *direct* addition of enolizable aldehydes and α-halo thioesters to produce simple *β*-hydroxy thioesters. Reductive soft enolization provides access to the nucleophile in situ, thus obviating the need for prior enolate formation. Moreover, this transformation has the unusual feature of producing *syn*-selectivity, which is the opposite of that produced for (thio)esters under conventional conditions. The yield and diastereoselectivity are as good or better than these traditional methods. In addition, the reactions proceed at room temperature, open to the air in untreated solvents. The products of these reactions are valuable and versatile intermediates that provide access to a rich variety of carbonyl derivatives.

The main factor that must be controlled in a direct reaction between an enolizable aldehyde and a carboxylate derivative to form the corresponding *β*-hydroxy carboxylate system is the chemoselectivity of enolization. Since aldehydes are more susceptible to deprotonation than simple carboxylate derivatives, a nonbasic means of enolization is desirable. The second key factor is the stereoselectivity of the addition, which is most easily managed when the reaction is kinetically controlled.

We have been studying the base mediated soft enolization[5] of Mg^{2+}-activated thioesters in the development of direct versions of certain fundamental carbon−carbon bond-forming reactions.[6,7] It occurred to us that a simple modification of this strategy could provide both the chemoselectivity and kinetic control needed for a

Scheme 1. Select Approaches to the Aldol Addition of Carboxylate Derivatives and Enolizable Aldehydes

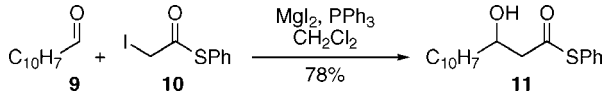


stereoselective direct aldol addition. To achieve this, readily accessible and easily managed α-halo thioesters[8] would be used in combination with Ph_3P and a Mg^{2+} salt to facilitate *reductive* soft enolization.[9] By analogy to our base mediated reactions,[6] Mg^{2+} coordination (**5** → **6**) would polarize the thioester carbonyl, thus allowing Ph_3P to abstract X^+ and generate the magnesium enolate (**6** → **7**).[10] Since a base would not be present, enolization of the aldehyde should not compete, providing the required chemoselectivity. Our expectation of kinetic control in the addition step (**7** + **3** → **8**) was based on the anticipated stability of magnesium aldolate **8** under the reaction conditions. In analogous amine mediated reactions, retro-aldol addition (cf. **8** → **7** + **3**) occurs,[1i] likely due to participation of the amine through lone pair donation to Mg^{2+}.[11] In the proposed reductive aldol reaction, the related interaction with Ph_3P would be unlikely given its soft nature.[12] Thus, the retro-aldol reaction would not occur, resulting in a kinetic addition step. When viewed in this way, α-halo thioesters represent a convenient shelf-stable latent enolate,[13] able to be liberated and utilized under mild conditions.

We began our studies by testing the Ph_3P-mediated reductive aldol addition using different α-halo thioesters and magnesium salts. Gratifyingly, the reaction proceeded under a range of conditions.[8] However, our best results were obtained using a combination of MgI_2 and α-iodo thioester **10** (Scheme 2), so these conditions were employed for the remainder of our studies.[14]

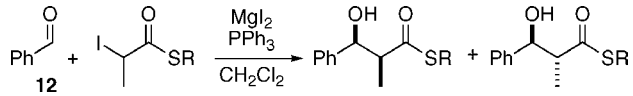
With suitable conditions available, we examined the diastereoselectivity of the transformation with α-iodo propionoate thioester **13** (Table 1). Interestingly, the major product was the *syn* isomer,

Scheme 2. Aldol Addition via Reductive Soft Enolization



which is the opposite of that normally obtained for the aldol addition of (thio)esters under typical hard enolization conditions.[3] However, only a 3:1 ratio of diastereomers was produced. In pioneering work on the development of an *anti*-selective aldol addition, Heathcock and Pirrung showed that increasing the steric bulk of the ester component led to an increase in diastereoselectivity.[15] Thus, various thioesters derived from more sterically demanding thiols were examined. As with the previous study, an increase in steric bulk did correlate to an increase in diastereoselectivity. However, in contrast to that work, the *syn*-, not the *anti*-diastereomer, was preferentially formed. In the case of **16** the selectivity was >20:1 in favor of the *syn*-product,[8] so this thioester was used for the remainder of our work.

Table 1. Effect of Thioester on Diastereoselectivity[a]

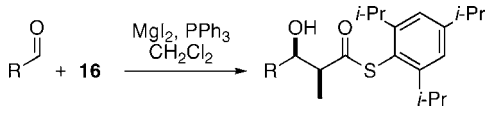


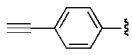
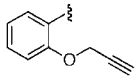
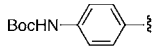
entry	thioester	aldol product	*syn:anti*	yield (%)
1	**13** R = Ph	**17**	3:1	83
2	**14** R = *t*-Bu	**18**	3.7:1	85
3	**15** R = 2,6-$(Me)_2C_6H_3$	**19**	15.3:1	78
4	**16** R = 2,4,6-$(i\text{-}Pr)_3C_6H_2$	**20**	>20:1	89

[a] 1.2 molar equiv of α-iodo thioester, 1.0 molar equiv of benzaldehyde, 1.2 molar equiv of MgI_2, 1.2 molar equiv of PPh_3 in CH_2Cl_2 (concn 0.2 M).

We next investigated the scope of the transformation using a variety of aldehydes (Table 2). We were pleased to find that the diastereoselectivity was excellent in all cases. As expected, the transformation worked equally well with enolizable aldehydes (entries 3−7). A particularly impressive example is seen in entry 7, where the aldol addition proceeded in high yield and selectivity despite the presence of the strongly acidic α-protons of aldehyde **25**. Aldehydes having other base-sensitive functionality were also tested (entries 8−10) and underwent the reaction smoothly.

Table 2. Scope of the Reductive Soft Enolization Aldol Addition[a]

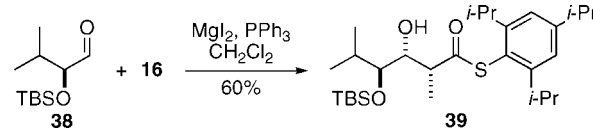


entry	aldehyde	aldol product	*syn:anti*	yield (%)
1	**12** R = Ph	**20**	>20:1	89
2	**9** R = $C_{10}H_7$	**29**	>20:1	65
3	**21** R = C_6H_{11}	**30**	>20:1	87
4	**22** R = $CH_3(CH_2)_2$	**31**	>20:1	68
5	**23** R = $CH_3(CH_2)_6$	**32**	>20:1	77
6	**24** R = $Ph(CH_2)_2$	**33**	>20:1	68
7	**25** R = Bn	**34**	>20:1	80
8	**26** R = 	**35**	>20:1	72
9	**27** R = 	**36**	>20:1	62
10	**28** R = 	**37**	>20:1	89

[a] 1.2 molar equiv of **16**, 1.0 molar equiv of aldehyde, 1.2 molar equiv of MgI_2, 1.2 molar equiv of PPh_3 in CH_2Cl_2 (conc 0.2 M).

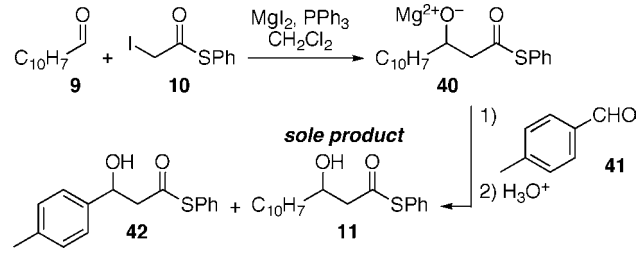
The transformation also proceeds in a highly diastereoselective manner with aldehydes having an α-stereogenic center. As an initial indication of this, when aldehyde **38** was subjected to the aldol reaction with **16**, only compound **39** was formed (Scheme 3).[16]

Scheme 3. Diastereoselective Aldol Addition to Aldehyde **38**



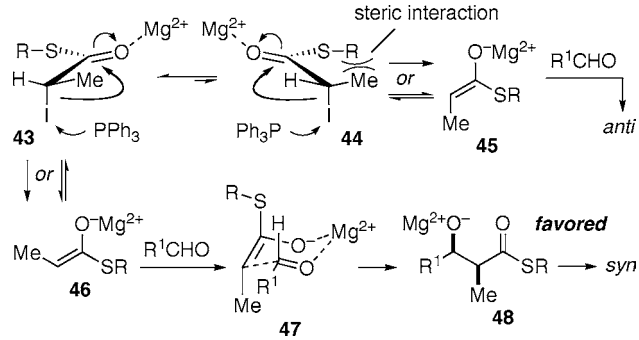
To confirm our expectation of kinetic control in the addition step, the reaction between **9** and **10** was carried out. However, after 18 h rather than quenching the reaction with acid, *p*-tolualdehyde (**41**) was added. The mixture was stirred for an additional 18 h and then quenched. The sole product was **11** (Scheme 4). The lack of incorporation of *p*-tolualdehyde confirms the predicted stability of the aldolate intermediate (cf. **40**) and supports the notion of a kinetically controlled addition.

Scheme 4. Kinetic Reactivity Studies



A model accounting for the observed stereoselectivity based on a kinetically controlled addition step is shown in Scheme 5. Enolization presumably occurs through an open transition state in a manner analogous to LDA-mediated enolization in the presence of chelating ligands.[17] Alternatively, it is reversible and favors the thermodynamically more stable *Z*-(*O*)-enolate (**46**). In either case, a greater proportion of **46** forms as the steric bulk of the thioester increases, which is consistent with the trend observed in Table 2. Irreversible, kinetic addition of **46**[18] to the aldehyde through the lower energy Zimmerman−Traxler transition state (**47**) then gives the *syn*-aldol product via aldolate **48**.

Scheme 5. Stereochemical Model



In summary, we have developed the first Mg^{2+} promoted direct addition of α-halo thioesters and enolizable aldehydes to produce *β*-hydroxy thioesters via reductive soft enolization. The *syn*-selective nature of this reaction is the opposite of that obtained for simple (thio)esters using amide bases (LDA, etc.) and so provides a convenient complementary approach to this key transformation. Moreover, the kinetic control exhibited in the addition step makes

it ideal for the development of direct, stereocontrolled aldol additions, as demonstrated by the preparation of **39**. Further studies of this reaction will focus on elucidating its mechanism and extending the scope of the asymmetric process in a catalytic fashion.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For lead references on metal-mediated direct aldol addition reactions, see: (a) Shibasaki, M.; Matsunaga, S.; Kumagai, N. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, Chapter 6. (b) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595–1601. (c) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1871–1873. (d) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004. (e) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393. (f) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127–1130. (g) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706–8707. (h) Wei, H.; Li, K.; Zhang, Q.; Jasoni, R.; Hu, J.; Pare, P. *Helv. Chim. Acta* **2004**, *87*, 2354–2357. (i) Yost, J.; Zhou, G.; Coltart, D. *Org. Lett.* **2006**, *8*, 1503–1506. (j) Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 8704–8705. For lead references on organocatalytic direct aldol addition reactions, see: (k) Tanaka, F.; Barbas, C. F., III. In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; Chapter 2. (l) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387. (m) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267. (n) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799. (o) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289.

(2) Hauser, C. R.; Puterbaugh, W. H. *J. Am. Chem. Soc.* **1951**, *73*, 2972.

(3) Heathcock, C. H. *Mod. Synth. Methods* **1992**, *6*, 1–102.

(4) (a) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2. (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, pp 997−1065. (c) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: 1991; Vol. 2, pp 133−179. (d) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press, 1991; Vol. 2, pp 181−238. (e) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: 1991; Vol. 2, pp 239−275.

(5) For pioneering examples of soft enolization, see: (a) Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622–2624. (b) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624–2626. (c) Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877–4879.

(6) For example, see: Zhou, G.; Lim, D.; Coltart, D. M. *Org. Lett.* **2008**, *10*, 3809–3812.

(7) For examples of thioesters in organocatalysis, see: (a) Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2008**, *47*, 4588–4591. (b) Utsumi, N.; Kitagaki, S.; Barbas, C. F., III. *Org. Lett.* **2008**, *10*, 3405–3408. For Malonic acid half-thioesters, see: (c) Lubkoll, J.; Wennemers, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6841–6844. (d) Ricci, A.; Petterson, D.; Bernardi, L.; Fini, F.; Fochi, M.; Herrera, R. P.; Sgarzani, V. *Adv. Synth. Catal.* **2007**, *349*, 1037–1040. (e) Kohler, M. C.; Yost, J. M.; Garnsey, M. R.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 3376–3379.

(8) See the Supporting Information for details.

(9) A related transformation employing $TiCl_4$ is known but requires prior enolate formation and the use of anhydrous conditions at −78 °C. See: Hashimoto, Y.; Kikuchi, S. *Chem. Lett.* **2002**, 126–127.

(10) In the absence of Mg^{2+} salts, phosphonium salt formation would be expected to occur over time.

(11) Sano, S.; Miyamoto, M.; Mitani, T.; Nagao, Y. *Heterocycles* **2006**, *68*, 459–463.

(12) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533–3539.

(13) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389.

(14) Attempts to conduct the transformation in a catalytic fashion by trapping the aldolate intermediate with either TMSCl or TMSOTf were not successful. Cf. refs 1e−g.

(15) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1728–1728. Heathcock, H. C.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, 4087–4095.

(16) 60% yield due to incomplete conversion. See the Supporting Information for stereochemical assignment.

(17) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650–657.

(18) Attempts to trap the *Z*-(*O*)-enolate as the corresponding silyl ketene acetal by exclusion of the aldehyde and addition of either TMSCl or TMSOTf were unsuccessful. These results are consistent with those obtained from similar experiments employing base mediated soft enolization. See refs 1e−g. The assumption of *Z*-(*O*)-enolate formation is made based on the *syn*-selective nature of the addition reaction, coupled with the high likelihood that it proceeds through a closed transition state.

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