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A Facile and Efficient *Anti*-Selective Four-Component Direct Aldol Addition via Chemoselective Thioester Enolate Formation

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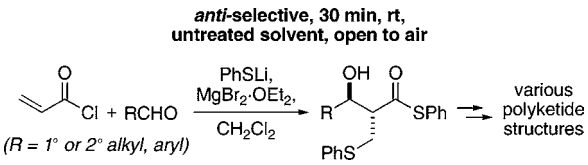
ABSTRACT



A facile and efficient four-component *anti*-selective direct aldol addition of thioester enolates has been developed that is fully compatible with enolizable aldehydes and able to be conducted using untreated reagent-grade CH_2Cl_2 open to the air. The thioester enolates are generated in situ via an acylation/conjugate addition sequence using commercially available PhSLi and acryloyl chloride, thus avoiding prior enolate formation while maintaining complete chemoselectivity. The organosulfur products are convertible into various polyketide-based structures.

The importance of the aldol addition reaction cannot be overstated. Extensive research has resulted in remarkable advances in stereo-, regio-, and chemoselectivity.[1] Much of the control that is possible stems from the use of carboxylate-derived, preformed enolates.[1] Although effective, the stepwise procedures used to generate such enolates are time-consuming, particularly if enolate trapping is involved, and require that all manipulations be conducted under anhydrous conditions and, when strong bases are used, at low temperatures. The desire to develop milder and operationally simplified methods for carbon−carbon bond formation has spawned a renewed interest in the *direct* aldol reaction.[2] To be of general use, such a direct reaction must possess control elements to ensure chemoselective enolate formation. The chemoselectivity issue arises when the aldehyde acceptor has one or more α-protons, as it too can enolize, leading predominantly to self-addition products. Overcoming this selectivity challenge is, thus, the critical first step in developing a generally applicable direct aldol addition. Herein, we describe an *anti*-selective, four-component direct aldol addition of thioesters that is fully compatible with enolizable aldehydes. Significantly, the transformation can be conducted open to the air using commercially available, untreated solvent.

Due to their strong nucleophilicity, thiols can be selectively acylated in the presence of other common nucleophiles[3] and readily undergo conjugate addition.[4] Thus, we reasoned that combining two equivalents of a thiolate, along with one equivalent each of an α,β-unsaturated acid chloride and an aldehyde, would initiate a four-component cascade sequence leading to a single aldol addition product (Scheme 1). The first thiolate equivalent and the acid chloride would combine

(1) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; 2 vols.

(2) See for example: (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392−393. (b) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127−1130. (c) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706−8707. (d) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852−2853. (e) Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284−7285. (f) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972−6973. (g) Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 8704−8705. (h) Yost, J. M.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2006**, *8*, 1503−1506. (i) Zhou, G.; Yost, J. M.; Coltart, D. M. *Synthesis* **2007**, 478−482.

(3) Coltart, D. M. *Tetrahedron* **2000**, *56*, 3449−3491, and refs therein.

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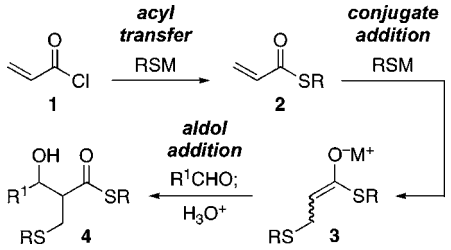
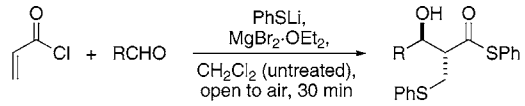
Scheme 1. Four-Component Direct Aldol Addition Reaction

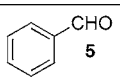
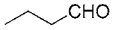
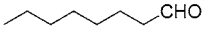
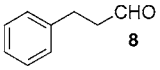
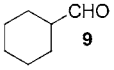


to generate an α,β-unsaturated thioester (**1** → **2**), which would be followed by 1,4-addition of the second thiolate equivalent to give a thioester enolate (**3**) and, ultimately, aldol addition (**3** → **4**). This chemoselective mode of enolate formation would preclude aldehyde enolization and, consequently, self-addition. Thus, the need for prior enolate formation would be eliminated, while maintaining the level of chemoselectivity associated with such techniques. Moreover, since the cascade sequence is initiated by thiolate addition, background reactions involving trace amounts of moisture in the atmosphere or solvent should not be a factor, and low temperatures would not be required, further simplifying the process. Additionally, the organosulfur aldol products could participate in numerous subsequent transformations, leading to an array of useful structures.

To test the feasibility of the proposed four-component aldol addition reaction, PhSNa (2 equiv) was added to a mixture of acryloyl chloride (**1**) (1 equiv) and benzaldehyde (**5**) (1 equiv) in CH_2Cl_2.[5] However, no aldol adduct was obtained, and instead, protonated **3** (R = Ph) was isolated in 92% yield. Varying the solvent and counterion (Li^+, K^+) gave no improvement. We next tried PhSLi in the presence of $MgBr_2 \cdot OEt_2$,[2h,i] which gave the aldol addition product (**11**) in 67% yield within only 30 min. Remarkably, the reaction was highly selective for the *anti* diastereomer, which is uncommon in aldol additions,[1,6] with an *anti*−*syn* ratio of 13:1. Prolonged reaction time did not improve the yield or affect the diastereomeric ratio. However, the efficiency was improved using 3 equiv of PhSLi, 1.5 equiv of **1**, 1.2 equiv of $MgBr_2 \cdot OEt_2$, and 1 equiv of **5**, which gave 88% yield of **11**, with the same *anti*−*syn* ratio (Table 1, Entry 1). As hypothesized, control experiments showed no difference between anhydrous[7] and nonanhydrous[8] conditions. We also ruled out an alternative reaction pathway initiated by thiolate 1,4-addition to **1** to give an acid chloride enolate intermediate, which would then undergo aldol addition, followed by Cl → S acyl transfer to give **4**. This was done by conducting the reaction with only 1.5 equiv of PhSLi (equimolar to **1**), along with **5** (1 equiv) and $MgBr_2 \cdot OEt_2$ (1.2 equiv), which gave acrylate thioester **17** in 93% conversion, with <4% of **11**.

Table 1. Direct Aldol Addition Reaction with Various Aldehydes



entry	aldehyde	addition product (*anti*-shown)	yield (%)	*anti*-*syn*
1	 **5**	**11** R = Ph	88	13:1
2	 **6**	**12** R = $(CH_2)_2CH_3$	71	11:1
3	 **7**	**13** R = $(CH_2)_6CH_3$	68	16:1
4	 **8**	**14** R = $(CH_2)_2Ph$	71	14:1
5	 **9**	**15** R = C_6H_{11}	81	>20:1
6	 **10**	**16** R = $CH(CH_3)_2$	76	>20:1

With simple and efficient conditions established for the aldol addition with **5**, we investigated the reaction scope with other aldehydes, both with and without α-protons (Table 1). In all cases, the four-component transformation proceeded efficiently with short reaction times. No aldehyde self-addition products were obtained, thus confirming the compatibility of the method with enolizable aldehydes. Adding further to the significance of this result was that, in each case, the *anti* product was strongly favored over the more commonly obtained *syn* diastereomer.[1,6]

We next investigated the origin of the *anti*-selectivity. Assuming standard models,[1] this could originate from either kinetic addition of the *E-(O)*-enolate to the aldehyde or from the relative thermodynamic stability of the *anti* and *syn* products. Several attempts to trap the enolate or kinetic addition intermediate under a variety of conditions were unsuccessful. However, we did establish that the reaction is reversible, suggesting that the diastereoselectivity is thermodynamically controlled. To do this, PhSLi was added to a mixture of $MgBr_2 \cdot OEt_2$, **1**, and **5**, and after the reaction was complete (30 min), 4-methylbenzaldehyde was added and the reaction was continued for 30 min. This gave an approximately 1:1 mixture of addition products **11** and **4** (R = Ph, R^1 = 4-MeC_6H_4), with a 13:1 *anti*−*syn* ratio in each case.

The inherent thermodynamic preference for the *anti* or *syn* addition product with different acrylate derivatives was examined (Table 2). With the exception of **20**, all thioesters

(4) See for example: Kamimura, A.; Omata, Y.; Mitsudera, H.; Kakehi, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4499−4504. Kamimura, A.; Mitsudera, H.; Asano, S.; Kakehi, A.; Noguchi, M. *Chem. Commun.* **1998**, 1095−1096. Kamimura, A.; Mitsudera, H.; Asano, S.; Kidera, S. Kakehi, A. *J. Org. Chem.* **1999**, *64*, 6353−6360. Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 1509−1512. Armitage, M. A.; Lathbury, D. C.; Mitchell, M. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1551−1552. Shono, T.; Matsumura, Y.; Kashimura, S.; Hatanaka, K. *J. Am. Chem. Soc.* **1979**, *101*, 4752−4753.

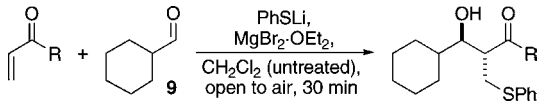
(5) Initial experiments were done using anhydrous conditions.

(6) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727−1728. Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976−4977. Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387−395.

(7) Dry CH_2Cl_2; Ar atmosphere.

(8) Untreated Aldrich ACS-grade CH_2Cl_2; open to air.

Table 2. Effect of Acrylate Structure on Diastereoselectivity

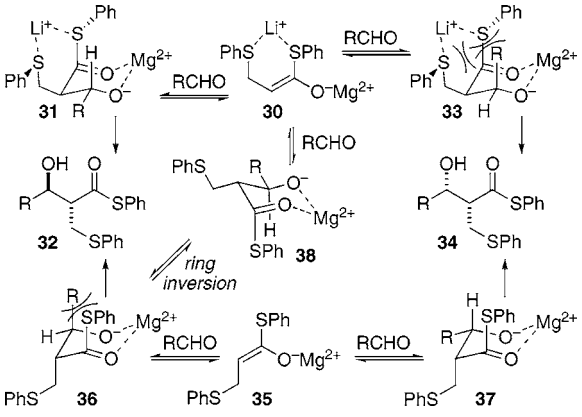


entry	α,β-unsaturated carboxyl	aldol adduct (*anti*-shown)	yield (%)	*anti*−*syn*
1	**17** R = SPh	**15** R = SPh	79	>20:1
2	**18** R = SC_6H_3−2,6-Me	**24** R = SC_6H_3−2,6-Me	60	11:1
3	**19** R = SEt	**25** R = SEt	82	4:1
4	**20** R = S*t*-Bu	**26** R = S*t*-Bu	77	1.5:1
5	**21** R = OPh	**27** R = OPh	72	2:1
6	**22** R = O*t*-Bu	**28** R = O*t*-Bu	78	1:1
7	**23** R = NHPh	**29** R = NHPh	64	2:1

showed a significant preference for the *anti* product. The oxoesters and the amide showed modest or no *anti*-selectivity.

Earlier in our study (see above), we had established that the addition reaction proceeded only when Mg^{2+} was added, implying that the thiolate Li^+ may have only a passive role in the transformation. To test this, we attempted the aldol addition with **1**, **9**, and $MgBr_2{\cdot}OEt_2$, but using PhSMgBr in place of PhSLi. This gave aldol addition product **15** with a 2:1 preference for the *syn* product, suggesting that Li^+ was actually a key component in achieving *anti*-selectivity. To confirm the importance of PhSLi in this regard, the reaction using PhSMgBr was repeated but, after 30 min, PhSLi was added and the reaction was continued for 30 min. The ratio of the aldol addition products **15** obtained from this procedure was restored to >20:1 in favor of the *anti* product. Taken collectively, these results show that the stereochemical outcome of the reaction is strongly tied to the nature of the thiolate counterion. A rationale (Scheme 2) for this outcome

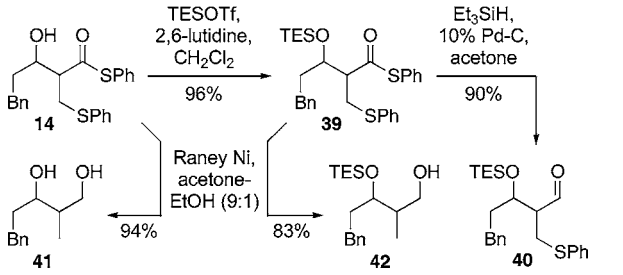
Scheme 2. Stereochemical Model of the Aldol Addition



that is consistent with a reversible process is that, in the presence of Li^+, coordination with sulfur[9] leads to the *E*-(*O*)-enolate (**30**), which then reacts via the lower-energy Zimmerman−Traxler transition state to give intermediate **31** preferentially over **33** and, consequently, the *anti* product (**32**). In the absence of Li^+, both the *E*-(*O*)-enolate (**30** minus Li^+) and *Z*-(*O*)-enolate (**35**) exist, allowing *syn* product **34** to form via **37**, in addition to **32**. However, when PhSLi is added to the latter system prior to work up, *syn* intermediate **37** is converted to Li^+-complexed *E*-(*O*)-enolate **30** via a thermodynamically driven conformational ring inversion of **36** to **38**. Addition from **30** then gives *anti* product **32**, analogously to the first reaction containing only PhSLi.

As an initial demonstration of the utility of the organosulfur products in subsequent transformations, **14** was silylated to **39** and treated under Fukuyama reduction[10] conditions to give aldehyde **40** in high yield (Scheme 3).

Scheme 3. Representative Transformations of **14**



As well, diols **41** and **42** were prepared from **14** and **39**, respectively, by treatment with Raney nickel.

In conclusion, we have developed a facile and efficient *anti*-selective four-component direct aldol addition of thioester enolates that is fully compatible with enolizable aldehydes and able to be conducted open to the air using untreated, reagent-grade solvent. Our method avoids the need for prior enolate formation while maintaining complete chemoselectivity. Mechanistic investigations of this highly practical and stereochemically intriguing reaction are underway, as is the development of related asymmetric versions.

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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.

OL702240P

(9) Olmstead, M. M.; Power, P. P. *J. Am. Chem. Soc.* **1990**, *112*, 8008−8014.

(10) Tokuyama, H.; Yokoshima, S.; Shao-Cheng, L.; Li, L.; Fukuyama, T. *Synthesis* **2002**, 1121−1123.