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Graphical Abstract

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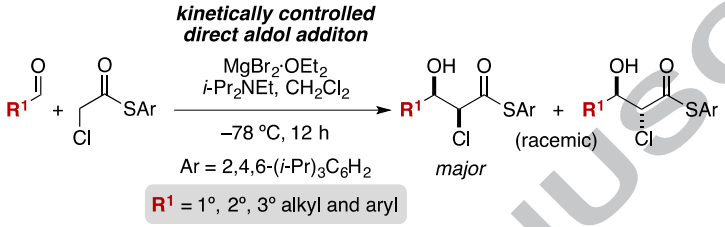

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A Kinetically Controlled Direct Aldol Addition of α-Chloro Thioesters via Soft Enolization

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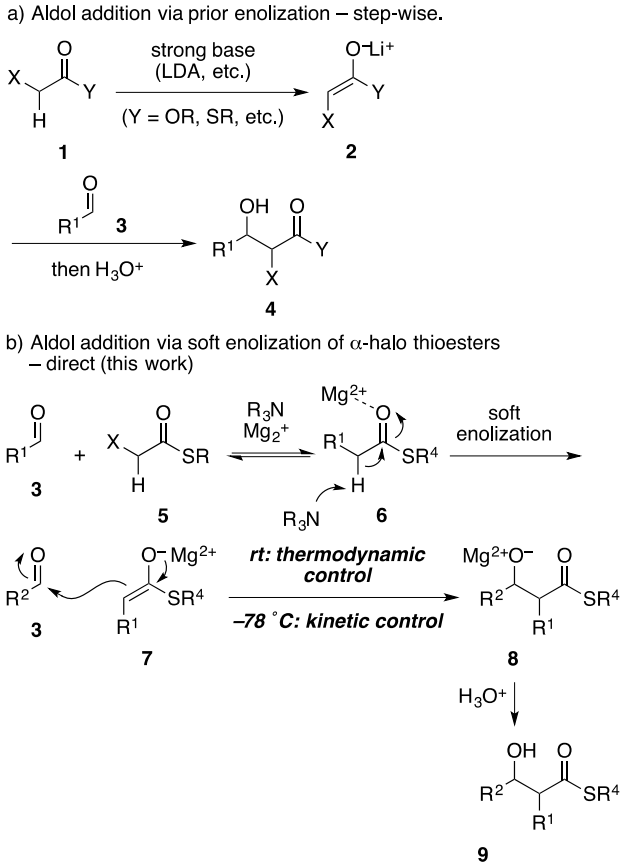
ABSTRACT

Herein we report that simple α-chloro thioesters undergo soft enolization and direct aldol addition to aldehydes in the presence of $MgBr_2{\cdot}OEt_2$ and *i*-Pr_2NEt. At –78 ºC the reaction proceeds in a kinetically controlled manner giving good diastereoselectivity. Significantly, the transformation is applicable to both enolizable and nonenolizable aldehydes. Moreover, excellent stereoselectivity results when a chiral nonracemic α-hydroxy aldehyde derivative is used. To our knowledge, this is the first report of a kinetically controlled soft enolization-based aldol addition.

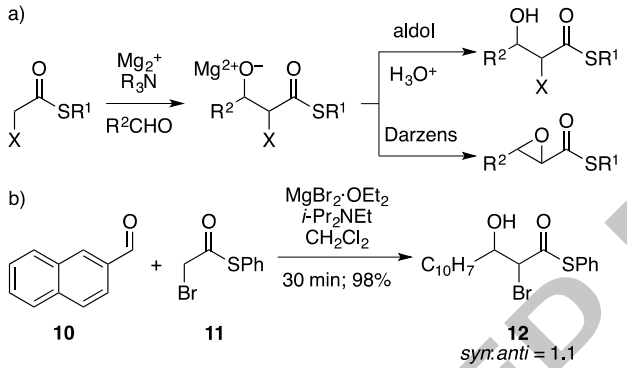
α-Halo-β-hydroxy carboxylic acid derivatives are useful synthetic intermediates that are typically prepared by the aldol addition of a pre-formed enolate and an aldehyde.[1] Notwithstanding the effectiveness of this approach, the step-wise procedures required to generate the enolates are time consuming, especially if trapping is involved. The α-halo enolates may be generated via hard enolization using a strong base such as LDA and then trapped with a silylating agent if needed to give the corresponding silyl ketene acetal or related species. In another approach α-halo silyl ketene acetals and their boronyl analogs may be generated via soft enolization. Here, a relatively weakly basic amine is used in combination with a silylating or boronylating agent to induce deprotonation. Given the sensitivity of the above approaches to water, all manipulations must be conducted under anhydrous conditions and, when strong bases are used, at low temperature (Scheme 1a). Soft enolization may also be conducted in a direct manner[2,3] thereby circumventing these stepwise procedures. In this case the enolate precursor (α-halo ester, α-halo thioester, etc.) and aldehyde are combined and then treated with a amine base and a Lewis acid in such a way that the enolate precursor is chemoselectively converted to its corresponding enolate (Scheme 1b). This then adds to the aldehyde giving the desired α-halo-β-hydroxy carboxylate product. A further advantage of this direct approach is that it may often be carried out under non-anhydrous conditions. We have been exploring this approach to enolization with thioesters in the development of direct versions of certain key carbon–carbon bond-forming reactions.[4] We recently extended this strategy to the synthesis of α-halo-β-hydroxy thioesters via a thermodynamically controlled process that gave modest diastereoselectivity.[5] In what follows, we describe the further development of this $MgBr_2{\cdot}OEt_2$-promoted direct aldol addition



Scheme 1 Hard and soft enolization-based aldol additions.

reaction between α-halo thioesters and aldehydes that utilizes soft enolization. In particular we show that when the transformation is conducted at –78 °C it proceeds under kinetic control and gives significantly improved diastereoselectivity. To our knowledge this is the first report of a kinetically controlled soft enolization-based aldol reaction. Moreover, we show that excellent stereoselectivity results when a chiral nonracemic α-hydroxy aldehyde derivative is used.

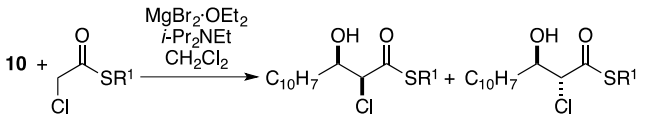
The possibility of competing Darzens reaction[6] to produce the corresponding α-epoxy thioesters (Scheme 2a) is a practical concern associated with the proposed transformation. However, our previous experiences led us to believe that the magnesium aldolate intermediate formed upon addition of the enolate and aldehyde would be sufficiently stable under the reaction conditions to prevent epoxide formation.[7] This was confirmed in our initial studies[5] by conducting the aldol addition with aldehyde **10** and α-bromo thioester **11** under soft enolization conditions (Scheme 2b). The desired α-bromo-β-hydroxy thioester (**12**) was formed rapidly and in excellent yield from this reaction with no epoxide formation.

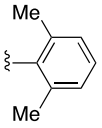
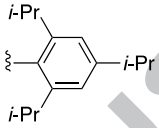
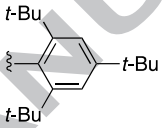


Scheme 2 a) Possible reaction pathways. b) $MgBr_2 \cdot OEt_2$-promoted direct aldol reaction of **10** and **11**.

In our previous work we had investigated the effect of the halogen of the α-halo thioester on the reaction and found the chloro species to be preferred.[5] Moreover, we established that the 2,4,6-triisopropylphenyl thioester gave the best outcome in terms of both diastereoselectivity and yield at room temperature (Table 1, entries 1-4). With this as a starting point we further investigated the effect of temperature on the diastereoselectivity of the reaction. While we suspected that lower reaction temperatures might well correlate with improved diastereoselectivity, we were concerned that they might significantly hinder the reaction rate making the transformation impractical. However, in the event the overall reaction times were slowed, but not to an extent that was unmanageable. As can be seen in Table 1, while at room temperature *S*-phenyl α-chlorothioacetate (**13**) failed to exhibit any appreciable diastereoselectivity, at –78 ºC a *syn:anti* ratio of 1.9:1 was observed (entry 5). The *dr* increased to 8.2:1 when the *S*-(2,6-dimethyl)phenyl thioester **14** was used in the reaction at –78 ºC (entry 6). The greatest effect on the *dr* was due to the use of 2,4,6-triisopropylphenyl α-chloro thioacetate (**15**), with a *syn:anti* ratio of 11:1 at –78 ºC. While the trend pointed to the bulkier thioesters giving aldol products with higher *syn:anti* ratios, we found a discrepancy when using 2,4,6-tri-*tert*-butylphenyl thioacetate **16**. Initial trials with the usual 1.2 equivalents of this thioester resulted in a 17:1 *syn:anti* ratio, but with only 60% conversion after 14 h. By using two equivalents of the thioester (**16**), the conversion increased, but the *dr* was

Table 1 Effect of the thioester and temperature on diastereoselectivity.

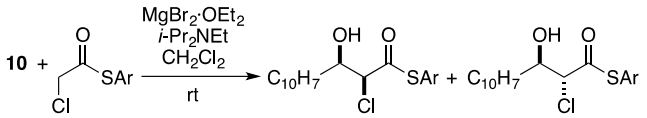


entry	thioester	product	temp (°C)	time (h)	*syn:anti*	conversion (%)
1	**13** R^1 = Ph	**17**	24	0.5	1.2:1	98
2	**14** R^1 = 	**18**	24	0.5	2.5:1	97
3	**15** R^1 = 	**19**	24	0.5	5.2:1	97
4	**16** R^1 = 	**20**	24	1	4.5:1	90
5	**13**	**17**	–78	5	1.9:1	72
6	**14**	**18**	–78	5	8.2:1	65
7	**15**	**19**	–78	12	11:1	85
8	**16**	**20**	–78	12	17:1	60
9[b]	**16**	**20**	–78	12	9:1	87
10	**15**	**19**	–40	12	5.3:1	85
11	**15**	**19**	–60	12	9:1	85

[a]1 molar equiv of **10**, 1.2 molar equiv of thioester, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-Pr_2Net. [b]2 molar equiv of thioester used.

depleted to 9:1. The reaction was also tried at –40 and –60 ºC (entries 10 and 11) but was found to be less effective than at –78 ºC. Thus, we used thioester **15** at –78 ºC for our subsequent studies.

Table 2 Varying bases in the $MgBr_2 \cdot OEt_2$-Promoted Aldol Addition Reaction.



15 (Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$)

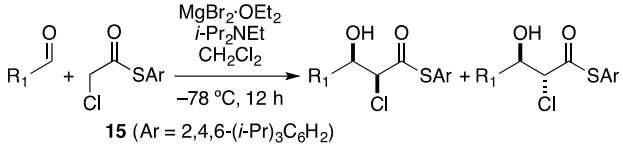
entry	base	time(h)	*syn:anti*	conversion (%)	pK_a[b]
1	*i*-Pr_2NEt	0.5	5.2:1	98	11.44
2	NEt_3	4	3:1	87	10.75
3	piperidine	24	1.5:1	16	11.22
4	pyridine	24	2:1	3	5.21
5	pyrrolidine	24	1.6:1	10	11.27
6	*n*-Bu_3N	7	1.7:1	85	10.89
7	DABCO	22	1.9:1	39	8.9
8	2,6-lutidene	21	3.2:1	22	6.75
9	2,2,6,6-tetramethyl-piperidine	4	1.2:1	86	10.89

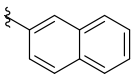
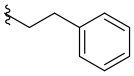
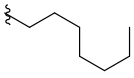
[a]1 molar equiv of **10**, 1.2 molar equiv of thioester, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-Pr_2Net. [b]Of conjugate acid of base.

In a further attempt to improve the transformation, a variety of amine bases was tested for their effect on diastereoselectivity and conversion (Table 2). Of the amines tried *i*-Pr_2NEt gave the highest *syn:anti* ratio (5.2:1) in the reaction of 2-napthaldehyde and thioester **15** at room temperature, as well as the greatest conversion (98%) (entry 1). The sp^3-hybridized bases *i*-Pr_2NEt, NEt_3, and *n*-Bu_3N gave consistently high conversions (entries 1, 2 and 6). Interestingly, 2,2,6,6-tetramethylpiperidine also gave a high conversion (86%) to the aldol product, whereas piperidine failed to give a similar result (entries 3 and 9).

The scope of the reaction was explored next using thioester **15** and a variety of aldehydes (Table 3). The transformation proceeded efficiently with aromatic aldehydes and also worked well with the highly sterically-hindered aldehyde **18**. Notably, when the reaction was carried out with enolizable aldehydes possessing a single α-proton (**19** and **20**, entry 4 and 5), the aldol product was produced in good yield. Encouraged by this result aldehydes **21** and **22** were tested in the addition reaction. Unfortunately, while the desired products (**27** and **28**, respectively) did form, they were obtained in a somewhat lower yield due to competing aldehyde self addition.

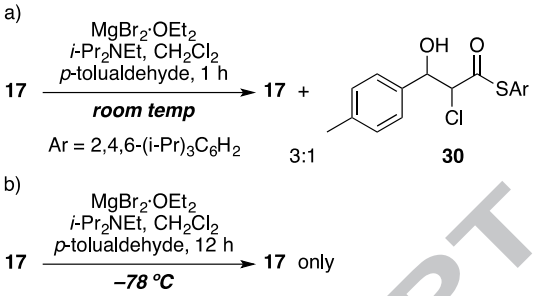
Table 3 Scope of the $MgBr_2{\cdot}OEt_2$-promoted aldol addition using thioester **15** and various aldehydes.



entry	aldehyde	product	*syn:anti*	yield (%)
1	**10** R^1 = 	**17**	11:1	80
2	**14** R^1 = 	**23**	9:1	77
3	**18** R^1 = 	**24**	6:1	81
4	**19** R^1 = 	**25**	3:1	87
5	**20** R^1 = 	**26**	3:1	96
6	**21** R^1 = 	**27**	2:1	40
7	**22** R^1 = 	**28**	3:1	52

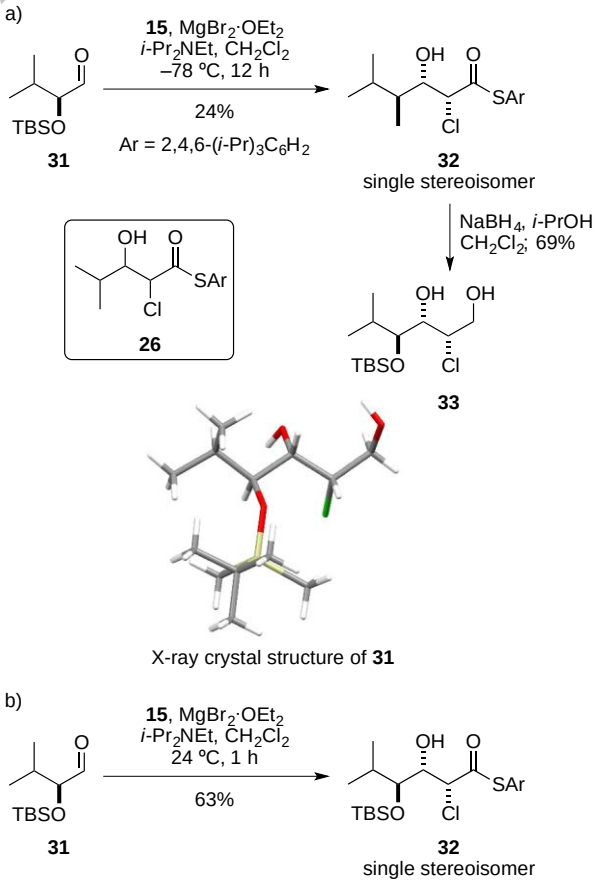
[a]1 molar equiv of aldehyde, 1.2 molar equiv of thioester, and 1.4 molar equiv of $MgBr_2{\cdot}OEt_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-Pr_2Net.

Having discovered that the diastereoselectivity varied with reaction temperature, we examined whether the reaction was operating under thermodynamic or kinetic control at rt and –78 °C. We speculated that at room temperature the reaction was



Scheme 3 Kinetic/thermodynamic control studies.

under thermodynamic control and thus reversible, while at –78 °C it was under kinetic control and irreversibly formed the *syn* isomer in excess. If the reaction was reversible at room temperature, then by placing the pure aldol product **17** in the standard reaction conditions of 1.4 equiv of $MgBr_2{\cdot}OEt_2$ and 2.0 equiv of *i*-Pr_2NEt in CH_2Cl_2 without starting thioester and aldehyde present, then when *p*-tolualdehyde (**29**) was introduced to the system the initial aldol product **17**, as well as the newly formed **30** should both be observed after 30 min (Scheme 3a). Indeed, when this experiment was conducted, a 3:1 ratio of **17** to aldol product **30** resulted. A similar control experiment was performed at –78 °C for 12 h (Scheme 3b) and resulted in the re isolation of only **17** with no crossover product **30** detected, indicative of an irreversible reaction.



Scheme 4 Aldol addition to chiral nonracemic aldehyde **28**.

We next tested the use of a chiral, nonracemic aldehyde (**31**) in a cursory investigation of broader asymmetric induction. Remarkably, when **15** and **31** were combined under the aldol

reaction conditions, the desired addition product (**32**) was obtained as a single diastereomer, albeit in low (24%) yield. Interestingly, a byproduct was also formed to a small extent that was identified to be **26** (*syn:anti* = 2:1). **26** is formally the aldol addition product of **15** and isobutyraldehyde, however, there was no trace of isobutyraldehyde contamination in any of the reagents or solvents used. It appears that some form of decarbonylation may be occurring in the reaction mixture that ultimately gives rise to **26**. In an effort to improve the reaction yield, the aldol addition was carried out at room temperature. We were very pleased to find that not only did the yield of the desired product increase, but it was still obtained as a single stereoisomer. Byproduct **26** was also formed in this reaction.

In conclusion, we have developed a kinetically-controlled aldol addition of α-chloro thioesters and aldehydes. The reaction proceeds at –78 ºC in very good yield, and with good *syn*-diastereoselectivity. Significantly, it is also amenable to the use of enolizable aldehydes, albeit with somewhat poorer yields. Very interestingly, when conducted using chiral, nonracemic aldehyde **31** at room temperature, a single stereoisomeric product (**32**) was obtained in 63% yield. Further studies of this promising transformation employing chiral nonracemic aldehydes are underway and will be reported in due course.

Acknowledgments

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References and notes

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at X.

Highlights

- Direct aldol additon
- Soft enolization
- Syn-selective aldol
- Kinetically controlled soft enolization process