Asymmetric Synthesis

Construction of C–S Bonds with a Quaternary Stereocenter through a Formal Michael Reaction: Asymmetric Synthesis of Tertiary Thiols**

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There are several reactions for the asymmetric construction of C–S bonds, often with excellent results in terms of efficiency and selectivity.[1,2] Among them, the Michael reaction, that is, the conjugate addition of nucleophiles to electron-deficient olefins,[3] has received special attention. This approach is very attractive not only because of the availability of a broad range of Michael acceptors and the suitability of the simultaneous formation of both a new C–S bond and a stereocenter, but also because the conjugate addition step provides a reactive species that may be trapped by electrophiles leading to tandem processes of significant synthetic value. Several approaches have been documented for diastereo-[4] and enantiocontrol[5,6] in the conjugate addition of sulfur-based nucleophiles to Michael acceptors. To the best of our knowledge, however, construction of quaternary C–S systems[7] through this reaction remains essentially unexplored within

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the asymmetric endeavor.[8] There are three conceptual restraints that may be invoked for this omission: a) the attenuated reactivity of β,β-disubstituted Michael acceptors;[9] b) the inherent difficulty in controlling π-facial diastereo- and enantioselectivity in these substrates;[8] and c) virtual thermodynamic equilibration of the stereoisomeric products through an addition–elimination mechanism,[10] which makes kinetic stereocontrol rather challenging. Yet, the asymmetric construction of quaternary stereocenters, particularly from β,β-disubstituted Michael acceptors, is a very difficult synthetic task.[11,12]

Our hypothesis was that the above restraints might be counterbalanced if an intramolecular version of the Michael-type approach could be implemented (Figure 1). In this

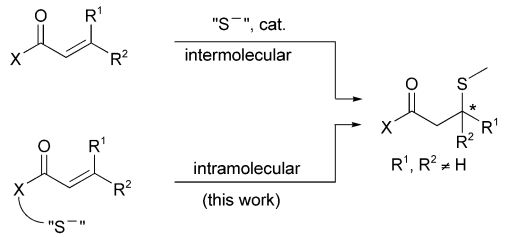
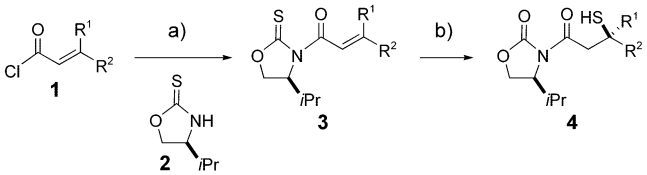


Figure 1. Intermolecular and intramolecular variants of the Michael-type addition of sulfur nucleophiles to enoyl systems as a route to C–S bonds with a quaternary stereocenter.

instance, the favorable entropy usually associated with an intramolecular process might help to solve the reactivity problem, whilst at the same time, a sufficiently high π-facial discrimination could also be exerted because of the intramolecular nature of the chirality transfer.

To validate this hypothesis, we have formulated the approach outlined in Scheme 1 on the basis of previous



Scheme 1. Preparation of Michael acceptors **3** and their intramolecular reaction leading to tertiary thiols **4**. Conditions: a) NaH, THF, −78 °C. b) $BF_3{\cdot}Et_2O$ then H_2O.

observations made in our laboratory.[13,14] Accordingly, several β,β-disubstituted *N*-enoyl oxazolidine-2-thiones, **3**, were prepared from **1** and **2**, and their intramolecular reaction in the presence of Lewis acids[15] examined, whereby the chiral oxazolidine-2-thione moiety was expected to act not only as the controller of the reaction stereochemistry but also as the sulfur transfer reagent. We were pleased to find that tertiary thiols **4** were indeed formed with good to excellent yields and, most significantly, with high diastereoselectivity under the action of an appropriate Lewis acid. The most satisfactory results in terms of both reactivity and stereoselectivity were obtained with $BF_3{\cdot}Et_2O$. Among the Lewis acids tested,[16] $SnCl_4$ also led to a clean reaction, but longer reaction times and in general lower diastereoselectivities were obtained. For a variety of substrates examined (Table 1) the diastereoselectivity of the reactions carried out at −30 °C ranged from

Table 1: $BF_3{\cdot}Et_2O$-promoted intramolecular Michael-type addition of sulfur in β,β-disubstituted enoyl systems **3** leading to tertiary thiols **4**.[a]

Compound	R^1	R^2	*T* [°C]	*t* [h]	d.r.[b]	Yield [%][c]
3a	Me	Ph	−78	13	n.d.	<40
			−30	9	>99:1	80
			25	52	86:14	n.d.
3b		4-MeC_6H_4	−30	7	97:3	77
			25	5	73:27	89[d]
3c		4-ClC_6H_4	−30	9	92:8	72
			25	5	90:10	90[d]
3d		4-BrC_6H_4	−30	72	98:2	76
			25	24	96:4	42
3e		4-$MeOC_6H_4$	−30	7	52:48	65
3f		3-$MeOC_6H_4$	−30	120	93:7	83
3g		4-CNC_6H_4	−30	36	92:8	73[e]
3h		4-$NO_2C_6H_4$	−30	12	91:9	70
3i	Et	Ph	−30	10	98:2	77
3j	*n*Bu	Ph	−30	15	96:4	68

[a] Reactions conducted at 0.5 mmol scale and 0.1 M substrate concentration. Ratio of **3**:$BF_3{\cdot}OEt_2$ 1:2. For details, see Supporting Information. [b] Determined by ^1H and/or ^{13}C NMR spectroscopy. [c] Yields of isolated compound after purification by column chromatography. [d] Yield of crude product. [e] Reaction performed at 0.2 mmol scale.

very high to essentially perfect, while even at 25 °C diastereoselectivity remained high in some instances (compounds **3c**,**d**). Curiously, whilst the β-4-methoxyphenyl substituted enoyl derivative **3e** brought about almost no diastereoselection, the enoyl compound **3f** bearing the 3-methoxyphenyl substituent showed quite good diastereoselectivity. On the other hand, from comparison of the results with substrates **3a**, **3i**, and **3j**, it appears that the size of the "small" substituent at the β position does not influence selectivity very much and high d.r. values are regularly observed.

The assigned configuration for the adducts was established by a single-crystal X-ray crystallographic analysis of the *p*-nitrobenzoyl derivative **5**,[17] and by assuming a uniform reaction mechanism. In this respect, the sense of the asymmetric induction can be explained by assuming a preferential attack of sulfur on the *Si* face of the enoyl β carbon atom with no interference of the *i*Pr group (model **A**), Figure 2.

In an effort to add some insight into the reaction mechanism, several substrates with variable *E*/*Z* composi-

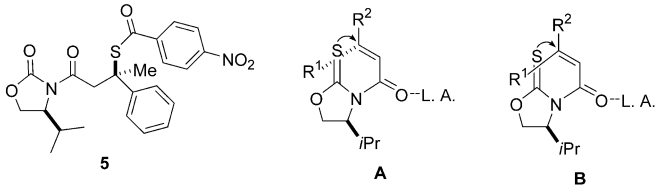


Figure 2. The attacking trajectories of sulfur onto (**A**) the *Si* face and (**B**) the *Re* face of the enoyl β-carbon, showing the distal and proximal alignments, respectively, of *i*Pr group and (R^1R^2C=C) moiety, and structure of **5**.

tions were prepared[18] and the outcomes of their reactions were examined. Strikingly, it was found that the reaction diastereoselectivity was essentially the same regardless of the *E*/*Z* composition of the starting enoyl substrate **3**,[19] Table 2.

Table 2: Reaction diastereoselectivities obtained from substrates **3** of variable *E*/*Z* compositions.[a]

Compound	R^1	R^2	Substrate **3** *E*/*Z* ratio[b]	Product **4** d.r.[b]
3d	Me	4-BrC_6H_4	100:0	92:8
			30:70	92:8
3g	Me	4-CNC_6H_4	100:0	92:8
			83:13	92:8
3j	*n*Bu	Ph	100:0	96:4
			50:50	96:4
			0:100	96:4

[a] Reactions conducted at 0.5 mmol scale and 0.1 M substrate concentration. Ratio of **3**:BF_3·OEt_2 1:2. [b] Determined by 500 MHz ^{1}H NMR spectroscopy.

The same behavior was also observed for substrate **6** (Figure 3), which bears a structurally different oxazolidine-2-thione auxiliary.[20] These results show that products with very high diastereomeric purity may be accessible from

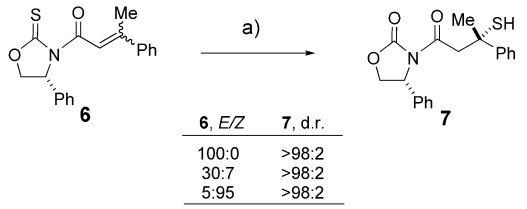
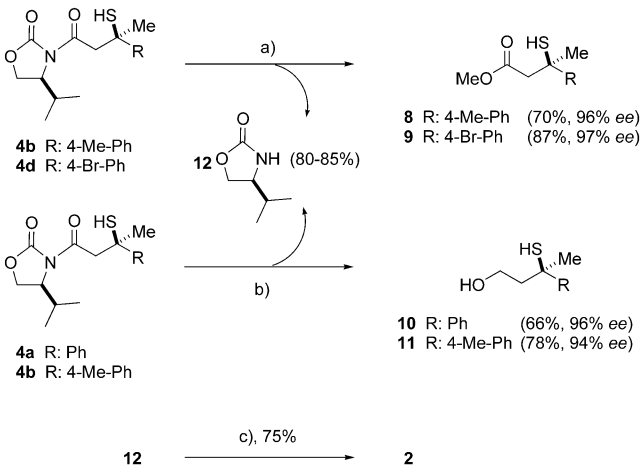


Figure 3. Uniform diastereoselectivity sense and level regardless of the *E*/*Z* composition of substrate **6**. Conditions: a) BF_3·Et_2O, −30 °C then H_2O.

configurationally nonhomogeneous β,β-disubstituted Michael acceptors, a feature that is of practical interest.[21]

Although at the present time we do not have a rational explanation for the above observations,[22] the excellent diastereoselectivity attained in these reactions is also of particular interest, since treatment of the thiol adducts such as **4b** and **4d** with $Sm(OTf)_3$ (Tf = trifluromethanesulfonyl) in MeOH[23] provides the β,β-disubstituted β-sulfanyl carboxylic esters **8** and **9**, respectively. Likewise, treatment of **4a** and **4b** with $NaBH_4$[24] leads to the corresponding 1,3-hydroxythiols **10**[25] and **11**. In each case, the oxazolidinone **12** is produced and can be transformed into the oxazolidine-2-thione **2** for reuse by treatment with Laweson's reagent (Scheme 2).

In conclusion, it has been shown that β,β-disubstituted *N*-enoyl oxazolidine-2-thiones react upon the action of Lewis acids through a highly stereoselective intramolecular Michael-type process. This transformation allows for the construction of C–S bonds with a quaternary stereocenter and results in the formation of functionalized tertiary sulfanyls in very high enantioselectivity. Further studies are underway to clarify the mechanism of this reaction.



Scheme 2. Elaboration of adducts into enantiopure sulfanyl-bearing esters and alcohols bearing a quaternary stereocenter, and recycling of the chiral auxiliary. Conditions: a) $Sm(OTf)_3$, MeOH, RT; b) $NaBH_4$, THF/H_2O. c) Lawesson's reagent, 1,4-Dioxane, reflux.

Experimental Section

General Procedure: BF_3·Et_2O (1.0 mmol, 0.127 mL) was added dropwise by syringe to a solution of the corresponding *N*-enoyl oxazolidine-2-thione (**3**; 0.5 mmol) in methylene chloride (8 mL) under a nitrogen atmosphere at −30 °C (bath temperature) or at the corresponding temperature (see Table 1). The resulting mixture was stirred at the same temperature until signals corresponding to starting material were no longer visible in the ^{1}H NMR spectra of the extracted samples. The mixture was then poured into a saturated solution of sodium bicarbonate (20 mL) and the layers were separated. The organic layer was washed with brine (50 mL), dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The crude material was purified by silica gel chromatography by using a mixture of ethyl acetate and hexane (10:90) as eluent.

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[17] CCDC-228804 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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