Stereoselective Conjugate Addition

Highly Diastereoselective Conjugate Addition to Alkylidene Bis(Sulfoxides): Asymmetric Synthesis of (+)-*erythro*-Roccellic Acid**

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The conjugate addition of a nucleophile to an electron-deficient olefin is a key transformation for the synthesis of highly functionalized molecules.[1] Facial control relying on an appended chiral auxiliary as an electron-withdrawing moiety has been extensively studied,[2] and, despite recent advances in catalytic asymmetric processes,[3] this strategy still has important advantages such as predictability and generality. Whereas most methods for conjugate additions to olefins have dealt with chiral acrylic systems,[4] sulfoxides and congener auxiliaries have also been subject to versatile applications.[5] However, in the latter case, high diastereoselectivities have generally been reached when the acceptor is part of a ring, and/or an extra carbonyl moiety has been introduced so that additional steric constraints or chelation controls can operate.[6]

In this context alkylidene bis(sulfoxides) are appealing candidates[7] for asymmetric conjugate additions. Two types of these compounds have been developed: namely the 1,1-bis-*p*-tolyl derivatives[8] and the cyclic dithioacetal dioxides, which were studied more extensively by Aggarwal et al.[9] While these compounds have been utilized mainly as highly diastereoselective chiral ketene equivalents in cycloaddition[10] and epoxidation reactions,[11] their behavior as Michael acceptors has not been exploited.

Our approach has relied on (*S,S*)-bis-*p*-tolylsulfinyl acceptors **1** because of their direct availability from (−)-

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menthol as a cheap chiral source.[8d] Moreover, structural examination of these substrates based on X-ray analysis of **1a** and **1c**[12] provided valuable information (see Figure 1 for the X-ray structure of **1a**). By introducing a dummy ligand (LP)

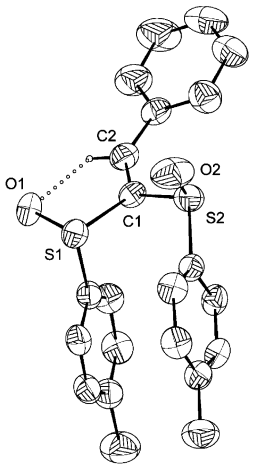
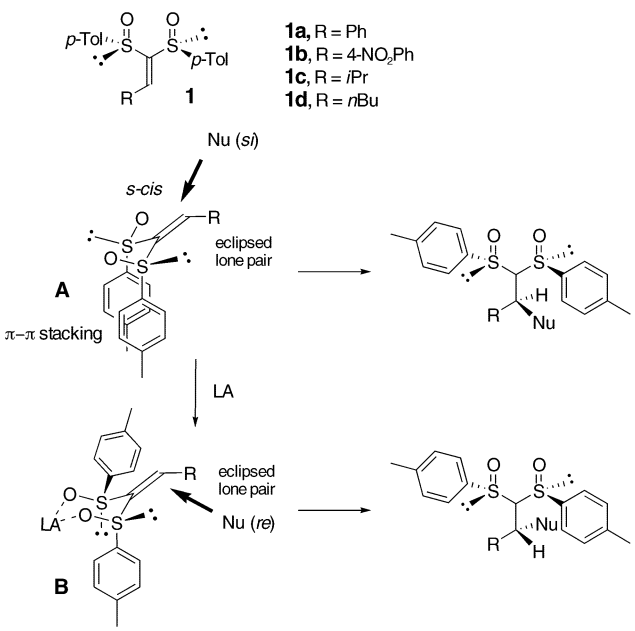


Figure 1. X-ray structure of **1a**.



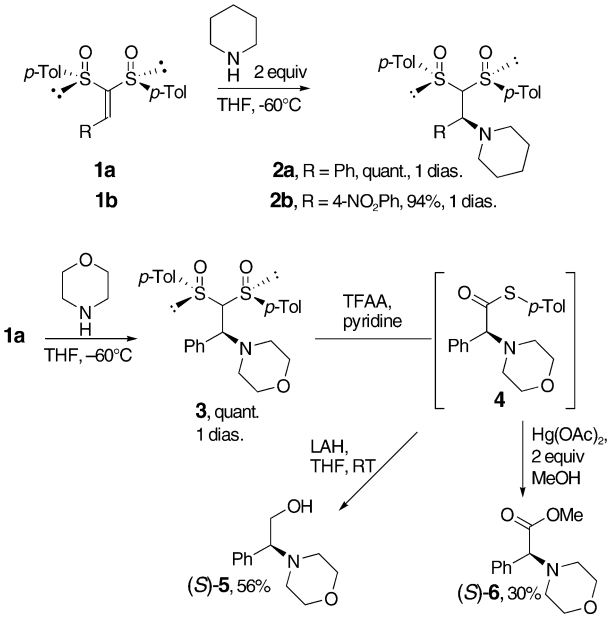
Scheme 1. Dual mode of stereoselection.

in the structures of **1a** and **1c** in place of the lone pair, it was possible to deduce a dihedral angle C2-C1-S2-LP of 28° for **1a** and 14° for **1c**, which suggests that the lone pair of one sulfinyl group is quasi-eclipsing the *syn* R group on the alkene. Then, C2-C1-S1-O1 dihedral angles (4° for **1a** and 13° for **1c**) were even more consistent with an *s-cis* conformation of the other sulfinyl group. An additional intriguing feature of this *s-cis* arrangement is the interaction between the vinylic proton and the O1 atom (d(H–O1) = 2.28 Å for **1a** and **1c**). It is remarkable that these data corroborate the ab initio calculations by Tietze et. al on simpler vinylsulfoxides.[13] Finally, intramolecular π-stacking interactions between *p*-tolyl groups were established based on the following values[14] (distance between centroids: 3.53 Å for **1a**, 3.66 Å for **1c**, and ring normal–centroid vector angles of 25° for **1a**, and 27° for **1c**).

All these observations indicated to us that a dual mode (**A** or **B**) of diastereoselection was possible. If we assume that the conformations in solution are the same as those in the solid state, then the two interacting *p*-tolyl groups should lock the lower *re* face and promote the attack of the incoming nucleophile from the opposite *si* face (mode **A**, Scheme 1). In contrast, in presence of a proper Lewis acid (LA), a new organization of the reacting system based on chelation by the two sulfinyl groups should take place (mode **B**). This would favor attack from the *re* face, which minimizes steric interactions with the *p*-tolyl group present on the *si* face. Finally, a further attractive feature of this system is that the bis-sulfinyl moiety can serve as a masked carbonyl group,[15] which could be liberated after a Pummerer reaction.[8d]

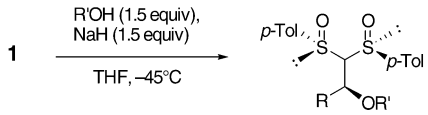
To probe these points, we initially focused on the addition of amines to **1a** and **1b**. In contrast with the known reactivity of simple vinylsulfoxides,[16] this process provided amino adducts **2a** and **2b** more efficiently (quantitative yield at −60 °C) and in a completely diastereoselective manner following mode **A**. These amino adducts proved also to be versatile precursors of enantiopure amino esters and amino alcohols, as demonstrated by the transformation of **3** into (*S*)-**5** and (*S*)-**6**[17] via the Pummerer adduct **4** (Scheme 2).

The addition of oxygenated nucleophiles required some optimization. Sodium alkoxides were the best nucleophiles and afforded adducts in high yields with total stereoselectivity following mode **A**, which sets an *S* absolute configuration at the α-alkoxy center.[18] It is worthy of note that products **10**



Scheme 2. Diastereoselective addition of amines to compounds **1a** and **1b** and derivatizations. dias = diastereomer, LAH = lithium aluminum hydride, RT = room temperature, TFAA = trifluoroacetic anhydride.

and **11** are promising building blocks for the preparation of enantiopure diols and furan or pyran derivatives, respectively (Scheme 3, Table 1).



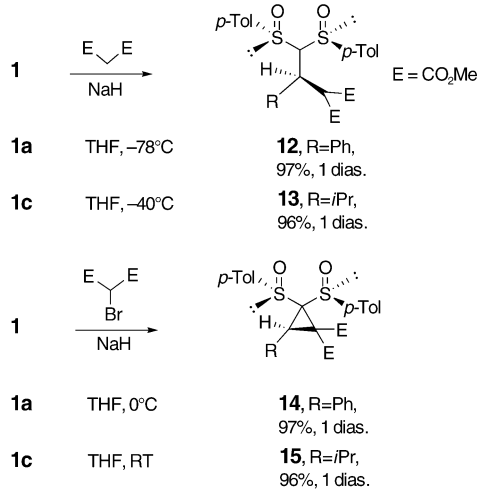
Scheme 3. Diastereoselective addition of alkoxides.

Table 1: Addition of sodium alkoxides to Michael acceptors **1**.

Precursor	R′	Prod.	Yield [%]	d.r., abs. conf.[a]
1a	Me	**7**	90	>98:2, *S*
1c	Me	**8**	94	>98:2, *S*
1c	Et	**9**	93	>98:2, *S*
1c	Bn	**10**	84	>98:2, *S*
1c	propargyl	**11**	82	>98:2, *S*

[a] abs. conf.: absolute configuration of the α-alkoxy center.

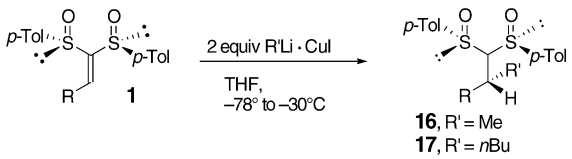
To further extend the scope of these Michael additions, we examined C–C bond formation with stabilized carbon nucleophiles such as sodium dimethylmalonate. High yields and complete stereoselectivity based on mode **A** were also observed (adducts **12**[19] and **13**, Scheme 4). More interest-



Scheme 4. Diastereoselective C–C bond formation.

ingly, when the sodium anion of bromomalonate was used, the intriguing cyclopropane derivatives **14** and **15**, whose structure and absolute configuration were confirmed by X-ray analysis,[12] were also obtained in the same fashion.

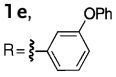
Because of the known complexation of copper salts with bis(sulfoxides) through sulfinyl oxygen atoms,[20] and previous results by Posner et al.,[21] we consider copper-based reagents to be good in Michael additions under chelation control (mode **B**, Scheme 5). Presumably also, formation of the initial Cu/olefin π-complex[22] with the double bond would be



Scheme 5. Addition of copper reagents leads to a reversed diastereoselection.

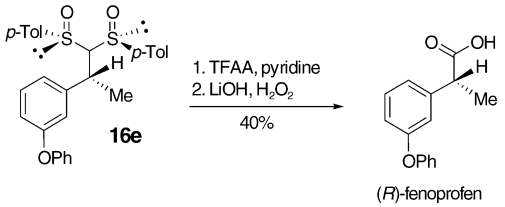
precluded on the *si* face because of the steric hindrance from the close *p*-tolyl group. Thus, addition reactions proceeded smoothly, affording products **16a, 16c–e**,and **17** in good yields and as single diastereomers with *R* absolute configuration at the newly alkylated center (Table 2).[23]

Table 2: Addition of copper reagents to alkylidene acceptors **1**.

Precursor	R′	Prod.	Yield [%]	d.r., abs. conf.[a]
1a	Me	**16a**	89	>98:2, *R*
1c	Me	**16c**	96	>98:2, *R*
1d	Me	**16d**	85	>98:2, *R*
1e, R= 	Me	**16e**	98	>98:2, *R*
1c	*n*Bu	**17**	77	>98:2, *R*

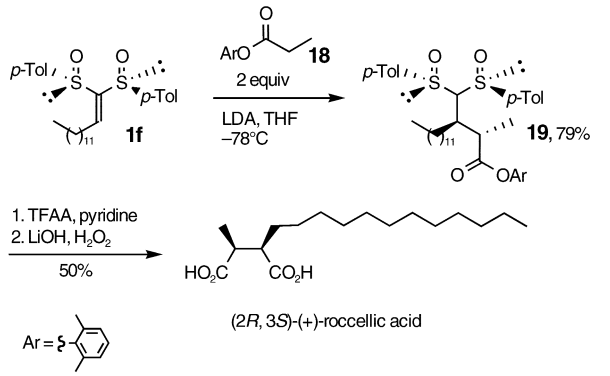
[a] abs. conf.: absolute configuration of the alkylated center.

Derivatization of alkylidene **16e** through a Pummerer reaction and saponification provided the *R* enantiomer of fenoprofen (Scheme 6). *R* Enantiomers of profens have recently found applications in rheumatology,[24] and several members of this family should be readily available by this approach.



Scheme 6. Application to the synthesis of (*R*)-fenoprofen.

Finally, exposure of alkylidene acceptor **1f** to the lithium enolate of Heathcock's ester[25] **18** afforded adduct **19** (79% yield) accompanied by minor diasteromers (10% yield; Scheme 7). The major diastereomer **19** was then engaged in a Pummerer reaction, followed by a double saponification to result in the first asymmetric synthesis of (+)-*erythro*-roccellic acid. Isolated from lichens,[26] and recently synthesized in a racemic form by Argade et al.,[27] roccellic acid exhibits a palette of biological activities such as plant growth promotion/inhibition and antituberculosis activity.[27] Remarkably, the succinate motif is found in a myriad of biologically relevant derivatives,[28] which this chemistry should render easily accessible.



Scheme 7. Synthesis of (+)-*erythro*-roccellic acid.

In conclusion, we have shown that alkylidene bis(sulfoxide) derivatives are exceptional partners in high-yielding and totally diastereoselective Michael additions. The use of heteronucleophiles (amines and alkoxides) paves the way to enantiopure α-amino and α-hydroxy acids as well as β-amino alcohols and diols. C–C bond formation can also be achieved and the stereoselection conveniently controlled by means of chelation or lack of chelation by the choice of the counterion (Li^+, Na^+ vs. Cu^+). A new route to enantiopure succinate derivatives is also open, as demonstrated by the first asymmetric synthesis of (+)-*erythro*-roccelic acid, which relies on the highly diastereoselective addition of a lithium ester enolate to an appropriate, readily available bissulfinyl acceptor.

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