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Sulfinyl-Mediated Stereoselective Overman Rearrangements and Diels–Alder Cycloadditions

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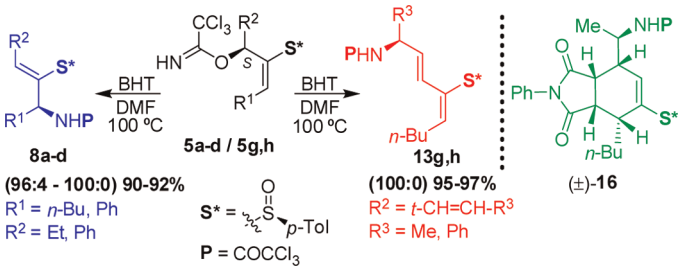
ABSTRACT



The Overman rearrangement of allylic sulfinyl trichloroacetimidates affords sulfinyl trichloroacetamides with high stereoselectivity and excellent yields. Bis-allylic substrates lead to amido 2-sulfinyl butadiene derivatives in excellent yields, with total chemo- and diastereoselectivity. The Diels–Alder cycloaddition of related dienes is controlled by the sulfoxide moiety.

The synthesis of chiral allylic amines is still a challenge from different standpoints such as synthetic methodology,[1] applications,[2] medicinal chemistry,[3] and synthesis of natural products.[4] This sustained interest has prompted organic chemists to develop a number of routes to these valuable building blocks. A general approach entails the addition to imines of suitable nucleophiles such as electron-deficient alkenes (aza-Morita-Baylis-Hillman,[5a] α-lithiated vinyl sulfoxides[5b,c]) or reductive couplings with alkynes.[6] An alternative route relies on metal-catalyzed allylic aminations, promoted by Ir,[7] Pd,[8] Pt, and even Fe.[9] Finally, the hydroamination of 1,3-dienes is also an important contribution in this field.[10]

Aside from the above, the thermal or metal-catalyzed [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates

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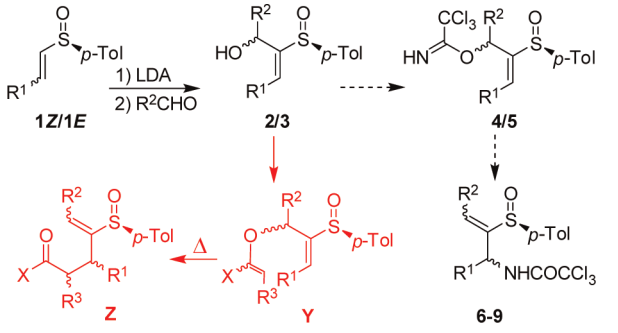
(Overman Rearrangement)[11] is perhaps one of the most general routes to allylic amine derivatives.[12] In this paper we report our preliminary results on the Overman rearrangement of sulfinyl allylic trichloroacetimidates that occur with good diastereoselectivities and complete chemoselectivity in some cases and maintain the useful alkenyl sulfoxide fragment.

Enantiopure sulfoxides are synthetically versatile chiral auxiliaries.[13] In recent years, we have pursued novel strategies involving readily available α-hydroxy vinyl sulfoxides **2**/**3** (Scheme 1)[14,15] including the highly diastereoselective Claisen rearrangement of enol ethers **Y** to carbonyl derivatives **Z** with generation of up to two stereogenic centers while preserving the useful vinyl sulfoxide.[16] Building upon these precedents we decided to undertake a study on the preparation of trichloroacetimidates **4**/**5** and their transformation into enantiopure allylic trichloroacetamides **6**–**9** with a stereodefined alkenyl sulfoxide moiety by Overman rearrangement.

Scheme 1. Proposed Sulfinyl-Mediated Overman Rearrangement



In most cases, the required trichloroacetimidates **4**/**5** (Table 1) were prepared uneventfully under standard conditions (Cl_3CCN, DBU, CH_3CN, rt) in almost quantitative yields after column chromatography from the appropiate alcohols **2**/**3**. However, the ^1H NMR spectra of isomers **5** with R^1 = *n*-Bu indicated clearly that two inseparable species were present in solution (73:27 mixture, for **5a**). While the major products were clearly the expected trichloroacetimidates, the minor products were tentatively assigned sulfurane structures, presumably in equilibrium with the trichloroacetimidates (see Supporting Information), since, remarkably, the yields and diastereoselectivities of the rearrangements are not compromised in those cases (see below).

After considerable experimentation with solvents and reaction temperatures, the optimal conditions found for the Overman rearrangement of trichloroacetimidate **4a** (Table 1) involved heating at 100 °C in DMF in the presence of a small amount of BHT; thus, a 92:8 mixture of amides **6a** and **7a** was obtained in 90% yield (Table 1, entry 1). Encouraged by this result, we selected substrates **4a**–**d** and diastereoisomers **5a**–**d** to evaluate the effect of representative R^1 and R^2 groups on the viability and selectivity of the rearrangement, and the results are gathered in Table 1, entries 1–8. The yields and selectivities found for these processes were excellent in most cases, with isomers **5** being slightly more reactive and selective than isomers **4**. In all examples, the predominant resulting isomer had a *Z* geometry, in sharp contrast with recent findings on related unsaturated esters that led mainly to *E* isomers.[17,18] This methodology nicely complements our previous synthesis of allylic sulfinyl amine derivatives.[5b,c]

The influence of the geometry of the vinyl sulfoxide was then addressed, and *Z* substrates (±)-**10b** and (±)-**11b**[19] were submitted to these conditions to produce *E* trichloroacetamides (±)-**9b** and (±)-**7b**, respectively, as single isomers and in excellent yields (Table 1, entries 9 and 10).

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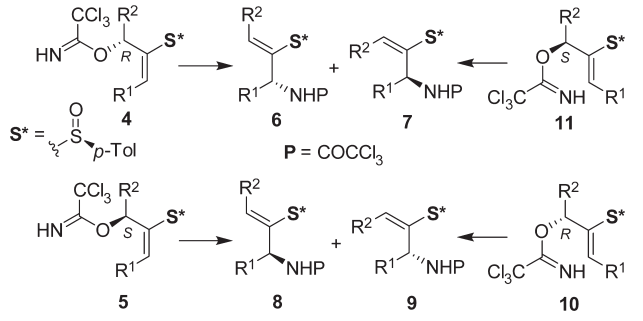
(17) See ref 11 in: Lee, S. I.; Moon, S. Y.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2010**, *12*, 3234–3237. The relative configuration of final products **6** and **8** was assigned from their *Z* geometry (NOE), the relative configuration of the starting materials, and the accepted mechanism for the Overman rearrangement.

(18) The rearrangement of the sulfone analog of **5a** afforded an 80:20 *Z*/*E* mixture of the sulfones related to **8a** and **9a**, with identical data to those obtained by oxidation of **8a** and **9a**. See Supporting Information.

(19) Racemic (*Z*)-sulfinyl alcohols were prepared from the corresponding alkynyl sulfides (Kabanyane, S. T.; MaGee, D. I. *Can. J. Chem.* **1992**, *70*, 2758–2763) by Pd-catalyzed hydroestannylation (Magriotis, P. A.; Brown, J. T.; Scott, M. E. *Tetrahedron Lett.* **1991**, *32*, 5047–5051), tin–lithium exchange, condensation with an aldehyde, and diastereoselective oxidation with *m*-CPBA. For an enantioselective synthesis of (*Z*)-sulfenyl alcohols, see: Berenguer, R.; Cavero, M.; García, J.; Muñoz, M. *Tetrahedron Lett.* **1998**, *39*, 2183–2186.

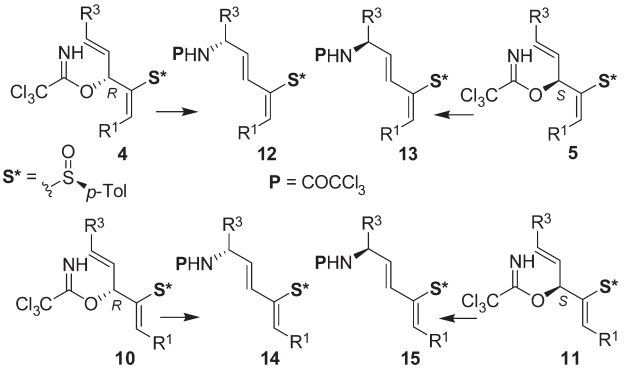
Table 1. Scope of the Sulfinyl-Mediated Overman Rearrangement[a]



entry	SM	R^1	R^2	major product[a]	dr (yield %)[b,c]
1	**4a**	*n*-Bu	Et	**6a**	92:8 (90%)
2	**5a**	*n*-Bu	Et	**8a**	96:4 (90%)
3	**4b**	*n*-Bu	Ph	**6b**	70:30 (75%)
4	**5b**	*n*-Bu	Ph	**8b**	100:0 (92%)
5	**4c**	Ph	Et	**6c**	100:0 (83%)
6	**5c**	Ph	Et	**8c**	100:0 (91%)
7	**4d**	Ph	Ph	**6d**	100:0 (51%)
8	**5d**	Ph	Ph	**8d**	100:0 (91%)
9	(±)-**10b**	*n*-Bu	Ph	(±)-**9b**	100:0 (85%)
10	(±)-**11b**	*n*-Bu	Ph	(±)-**7b**	100:0 (95%)

[a] Reactions were performed in DMF with a catalytic amount of BHT at 100 °C. [b] Ratio determined by ^{1}H NMR analysis of crude reaction mixtures. [c] Combined yield after chromatography.

Table 2. Overman Rearrangement of Bis-allylic Substrates[a]



entry	SM	R^1	R^3	product[a]	yield %
1	**4e**	*n*-Bu	H	**12e**	91%
2	**5e**	*n*-Bu	H	**12e**	99%
3	**4f**	Ph	H	**12f**	92%
4	**5f**	Ph	H	**12f**	98%
5	**4g**	*n*-Bu	Ph	**12g**	92%
6	**5g**	*n*-Bu	Ph	**13g**	95%
7	**4h**	*n*-Bu	Me	**12h**	80%
8	**5h**	*n*-Bu	Me	**13h**	97%
9	(±)-**10h**	*n*-Bu	Me	(±)-**14h**	88%
10	(±)-**11h**	*n*-Bu	Me	(±)-**15h**	95%

[a] Reactions were performed in DMF with a catalytic amount of BHT at 100 °C.

Having established the generality of the methodology we examined the behavior of bis-allylic substrates with the expectation that the different natures of the alkenes potentially involved in the rearrangement could provide a useful level of chemoselectivity, often elusive in the known examples of this transformation.[20] In this manner, diastereomeric trichloroacetimidates **4e** and **5e** (R^3 = H), prepared smoothly from the alcohol precursors, were submitted to the standard reaction conditions, to produce excellent yields of aminodiene **12e** with complete chemoselectivity (Table 2, entries 1 and 2). Likewise, phenyl-substituted diene **12f** was obtained in excellent yields and as a single isomer from acetimidates **4f** and **5f** (Table 2, entries 3 and 4).

Encouraged by these results, the creation of an additional stereocenter by placing a substituent at the reactive alkene ($R^3 \neq$ H) was examined, and to our delight, the rearrangement took place with complete chemo- and stereoselectivity to produce dienes **12g**, **13g**, **12h**, and **13h** in excellent yields (Table 2, entries 5–8). It should be pointed out that these trichloroacetimidates (**4g**, **5g**, **4h**, and **5h**) were used as crude products since they were unstable to purification on silica gel and, therefore, the yields are reported from the starting alcohols. Finally, geometric isomers (±)-**10h** and (±)-**11h**, as crude products, were submitted to the rearrangement conditions to afford respectively the *E*,*Z* aminodienes (±)-**14h** and (±)-**15h** as single isomers.

These results may be tentatively accounted for in terms of diastereomeric transition states derived from chairlike reactive conformations **A**–**D** (Figure 1). For *E* vinyl sulfoxides **5a**–**d**, with an S-*cis* alkene and S=O bonds,[21] while conformer **B** would have a severe R^1–R^2 1,3-diaxial interaction and the *p*-Tol group would point toward the incoming unsaturated moiety for the rearrangement, conformer **A** would display a favorable arrangement of stereocontrolling elements.

In the case of *Z* vinyl sulfoxides **10b**, the process appears to be primarily controlled by $A^{1,2}$ strain rather than 1,3-diaxial interactions with conformer **C** displaying a severe 1,2-strain between the *p*-Tol and R^2 moieties that results in high stereoselectivity to produce the *E* rearrangement product **9**, presumably through conformer **D**.[22] For bis-allylic substrates, the process seems to follow the accepted stereochemical outcome for the [3,3]-sigmatropic Overman rearrangement albeit with unprecedented complete chemoselectivity.

(20) Chemoselective Overman rearrangement on bis-allylic trichloroacetimidates continues to be a challenge, since poor selectivity (60:40) has been achieved. See: (a) Birtwistle, D. H.; Brown, J. M.; Foxton, M. W. *Tetrahedron* **1988**, *44*, 7309–7318. (b) Commerçon, A.; Ponsinet, G. *Tetrahedron Lett.* **1990**, *31*, 3871–3874. See also ref 11a and 11d.

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(22) A similar trend is followed for isomers **4** and **11**.

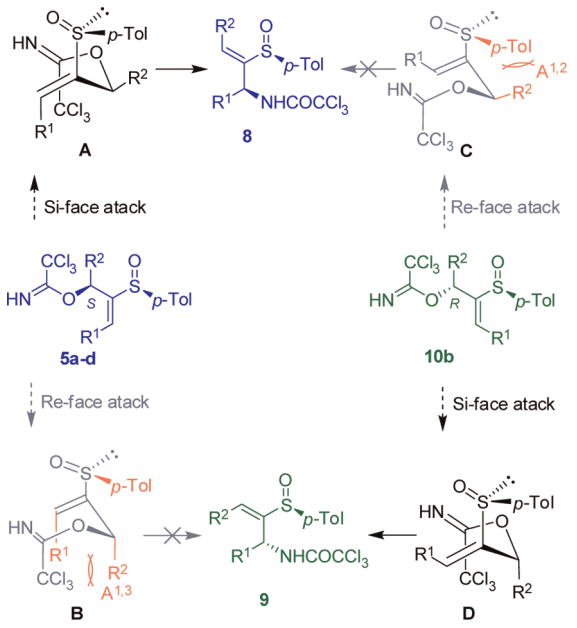
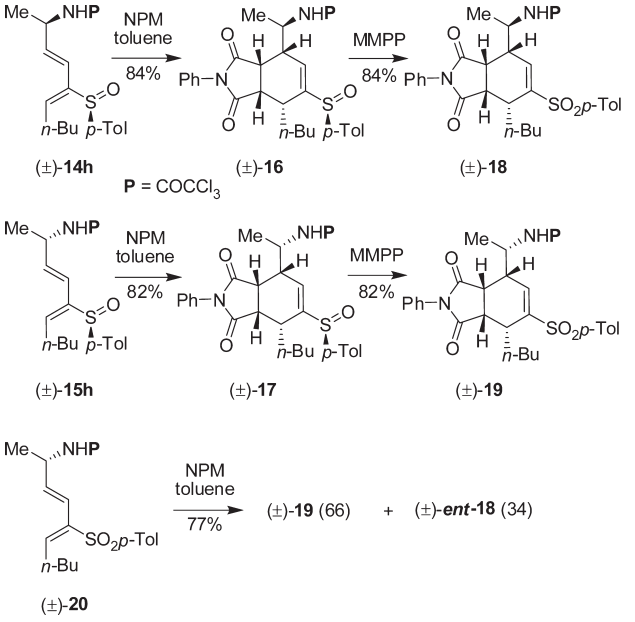


Figure 1. Stereochemical outcome.

At this stage we pursued exploratory experiments on the behavior of our sulfinyl amido dienes in diastereoselective Diels–Alder processes, and the results are summarized in Scheme 2.[23] The reaction between our diastereomeric dienes (±)-**14h** and (±)-**15h** with *N*-phenylmaleimide (NPM) in toluene at rt afforded excellent yields of α-endo cycloadducts (±)-**16** and (±)-**17** respectively as single isomers and preserving the valuable alkenyl sulfoxide moiety. Oxidation with MMPP gave the related sulfonyl cycloadducts (±)-**18** and (±)-**19** respectively as single isomers.

To determine the intrinsic stereodirecting capabilities of the chiral allylic amide residue under these conditions,[24] we examined the cycloaddition between amido sulfonyl diene (±)-**20**, prepared by oxidation of (±)-**15h**, that gave rise to a 66:34 mixture of (±)-**19** and (±)-***ent*-18**,[25] with identical spectral data to those found before. These results conclusively establish that the stereochemical outcome of the Diels–Alder cycloaddition of our sulfinyl dienes is primarily controlled by the chiral sulfur atom.

Scheme 2. Sulfinyl-Directed Diels–Alder Cycloadditions



In conclusion, the first examples of the Overman rearrangement of allylic sulfinyl trichloroacetimidates to afford sulfinyl trichloroacetamides have been described. The rearrangement of bis-allylic substrates involves exclusively the alkene that does not bear the sulfinyl substituent to afford amido 2-sulfinyl butadienes. Selected examples of these dienes undergo highly diastereoselective Diels–Alder cycloadditions controlled exclusively by the chiral sulfur atom. We are currently exploring the scope, limitations, and synthetic applications of these methodologies.

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Supporting Information Available. Experimental procedures, compound characterization, NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.

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(25) The *ent* nomenclature is used to facilitate comparison of the data.