Asymmetric Synthesis of Cyclopropane-1,1-Dicarboxylates from a γ-Alkoxy-Alkylidenemalonate

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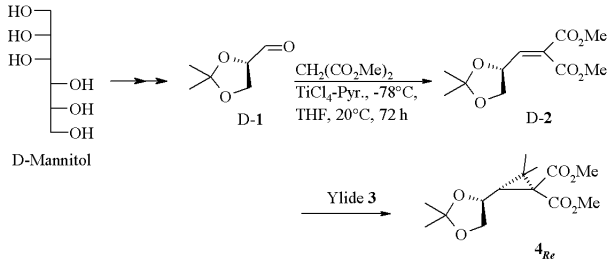
Abstract: 2-Metallo-2-sulfonylpropanes and 2-metallo-2-nitropropanes react with the dimethyl alkylidenemalonate derived from the acetonide of D-glyceraldehyde to produce the Michael adduct or the corresponding dimethyl cyclopropane-1,1-dicarboxylate. The nature of the product formed and the relative configuration of the cyclopropane derivative depends upon the nature of the leaving group and the conditions used (solvent and counter ion).

Key words: asymmetric synthesis, Michael adduct, cyclopropane derivative

2-Metallo-nitroalkanes and 2-metallo-alkylsulfones add to α,β-unsaturated esters and alkylidenemalonates in a Michael mode, under a large variety of conditions and produce γ-nitro and γ-sulfonyl esters.[1,2] The adducts derived from alkylidenemalonates further react under forced conditions, in polar solvents, and lead to cyclopropane-1,1-dicarboxylates in reasonably good yields.[2] The latter transformation offers, over the one involving phosphorus and sulfur ylides and the same electrophiles, the advantage to transfer the same isopropylidene moiety from reagents of lower molecular weight.

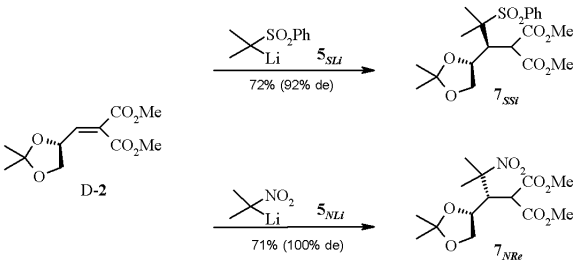
We recently reported[3] that isopropylidene diphenylsulfurane $\mathbf{3}_S$ and isopropylidene triphenylphosphorane $\mathbf{3}_P$ react on the *(Re)*-face of the dimethyl alkylidenemalonate D-**2** derived from D-glyceraldehyde acetonide D-**1** and produce the corresponding dimethyl cyclopropane-1,1-dicarboxylate $\mathbf{4}_{Re}$ almost as a single diastereoisomer (Scheme 1).



Scheme 1

Extension of this reaction to 2-metallo-2-nitropropanes[4] $\mathbf{5}_N$ and 2-metallo-2-sulfonylpropanes $\mathbf{5}_S$ should provide interesting informations on the intimate mechanism of these specific reactions as well as on that of organometallics with γ-heterosubstituted-α,β-unsaturated esters which still remains unclear.[3,5]

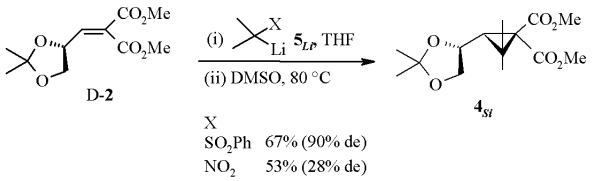
We were rather surprised to find that 2-lithio-2-sulfonylpropane $\mathbf{5}_{SLi}$ and 2-lithio-2-nitropropane $\mathbf{5}_{NLi}$ behave differently with the dimethyl alkylidenemalonate D-**2**. Thus, 2-lithio-2-sulfonylpropane $\mathbf{5}_{SLi}$ reacted in THF almost exclusively on the *(Si)*-face and lead to the γ-sulfonyl malonate[6a] $\mathbf{7}_{SSi}$ (THF, 20 °C, 0.5 h) whereas 2-lithio-2-nitropropane $\mathbf{5}_{NLi}$ reacted, under similar conditions, exclusively on the *(Re)*-face, providing after hydrolysis the γ-nitro malonate[6a] $\mathbf{7}_{NRe}$ (Scheme 2).



Scheme 2

The same starting materials afforded, as expected, dimethyl cyclopropane-1,1-dicarboxylates **4** when the reactions were instead carried out in DMSO at 80 °C (Scheme 3).[6b] Both reactions provided the same stereoisomer resulting from the cyclopropanation of dimethyl alkylidenemalonate D-**2** by its *(Si)*-face but their diastereoselectivity are very different: $\mathbf{4}_{Si}$ was produced with very high stereocontrol from 2-lithio-2-sulfonylpropane $\mathbf{5}_{SLi}$ (DMSO, 80 °C, 66h)[6b,7] and as a mixture of stereoisomers from 2-lithio-2-nitropropane $\mathbf{5}_{NLi}$ (DMSO, 80 °C, 24h).[3,6b,7] Thus whereas the open chain derivative and the cyclopropane arose from the attack of the same face of D-**2** from $\mathbf{5}_{SLi}$ they resulted from a different face of attack from $\mathbf{5}_{NLi}$.

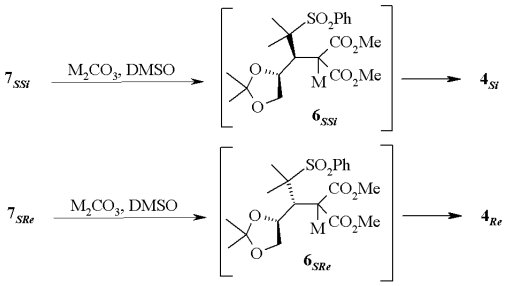
In order to understand these conflicting results, we undertook a more detailed study aimed to determine which of the reactions takes place under kinetic or thermodynamic



Scheme 3

control. We found that addition of 2-lithio-2-sulfonylpropane $\mathbf{5}_{SLi}$ to D-**2** is slightly dependent upon the conditions used. Complete diastereoselection was observed when the reaction was performed in THF-HMPA (D-**2**/HMPA:1/4; -78 °C, 0.5 h, yield in $\mathbf{7}_S$:76%, $\mathbf{7}_{SSi}/\mathbf{7}_{SRe}$:100/0)[8] instead of THF alone and slightly lower selectivity was found when the reaction was performed in ether (-78 °C, 0.5 h, 72%, $\mathbf{7}_{SSi}/\mathbf{7}_{SRe}$:92/8).

We have proven that these reactions occur under kinetic control since the same $\mathbf{7}_{SSi}/\mathbf{7}_{SRe}$ ratio of stereoisomers is obtained whether the reaction is quenched at -78 °C or at room temperature, after short or long reaction time. We have also secured that no epimerization is taking place when each stereoisomer $\mathbf{7}_{SRe}$ or $\mathbf{7}_{SSi}$ is treated with a base at room temperature (K_2CO_3 in DMSO, 20 °C, 10 h) or even at 80 °C. Under the latter conditions however, ring closure was readily achieved and lead with complete stereocontrol (Scheme 4) to the dimethyl cyclopropane-1,1-dicarboxylates $\mathbf{4}_{Si}$ from $\mathbf{7}_{SSi}$ (K_2CO_3, DMSO, 80 °C, 3 h, 84%, 100% de) and to its stereoisomer $\mathbf{4}_{Re}$ from $\mathbf{7}_{SRe}$ (K_2CO_3, DMSO, 80 °C, 0.7 h, 77%, 100% de)



Scheme 4

We have also found that the rate of this reaction depends not only upon the nature of the counter-ion (it is much faster with cesium than with lithium, Scheme 4, Table 1) but also upon the nature of the stereoisomer used ($\mathbf{7}_{SRe}$ reacts faster than $\mathbf{7}_{SSi}$, Scheme 4, Table 1).[9]

The reaction of 2-metallo-2-nitropropane $\mathbf{5}_N$ with alkylidenemalonate D-**2** is more complex. The $\mathbf{7}_{NSi}/\mathbf{7}_{NRe}$ ratio of stereoisomers is highly dependent upon the solvent and the conditions used (temperature and time). Although a single stereoisomer ($\mathbf{7}_{NRe}$) was formed in THF[10] (Scheme 2), substantial amounts of the other stereoisomer ($\mathbf{7}_{NSi}$) was produced when the reaction was performed in DMSO at room temperature. Under these conditions the diastereoisomeric ratio changed with the reaction time to give $\mathbf{7}_{NRe}$ slowly from 2-lithio-2-nitropropane (Table 2, entry 1) and more rapidly when the reaction was instead performed with its potassium analogue (Table 2, entry 3). This suggests that this reaction is under thermodynamic control.

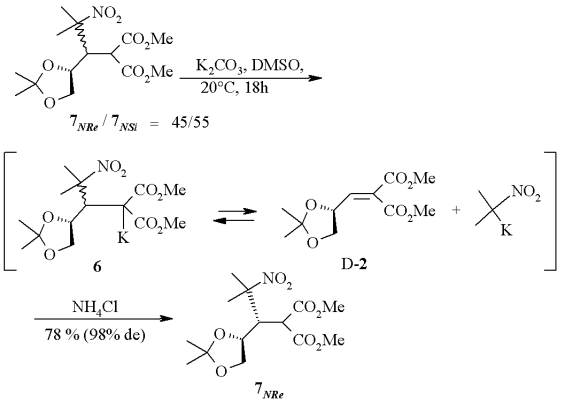
Table 1 Rate of the reaction of $\mathbf{7}_{SRe}$ and $\mathbf{7}_{SSi}$ with metal carbonates

Entry	$Me_2CM(NO_2)$ DMSO, 80°C	Time/half reaction $\mathbf{7}_{SRe}$ [h]	Time/half reaction $\mathbf{7}_{SSi}$ [h]
1	Li	55	>140
2	Na	1.4	28
3	K	0.35	0.9
4	Cs	0.25	0.4

Table 2 Stereochemistry of the γ-nitro malonates $\mathbf{7}_N$ according to reaction time

Entry	$Me_2CM(NO_2)$ DMSO, 20°C	Yield of $\mathbf{7}_N$ ($\mathbf{7}_{NRe}/\mathbf{7}_{Nsi}$) after 1 h reaction [%]	Reaction time [h] ($\mathbf{7}_{NRe}/\mathbf{7}_{Nsi}$)
1	Li	96 (77/23)	24 (86/14)
			48 (98/2)
2	Na	94 (80/20)	
3	K	77 (90/10)	3.5 (98/2)
4	Cs	99 (97/3)	

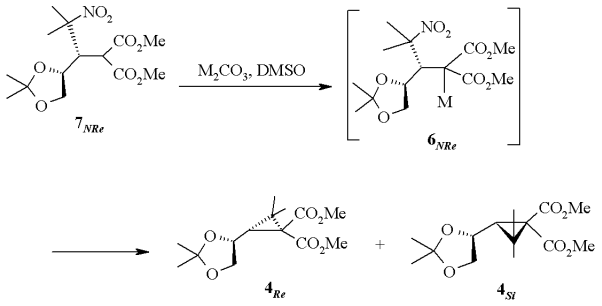
We have independently proven the presence of an equilibrium by reacting a 45/55 mixture of $\mathbf{7}_{NRe}/\mathbf{7}_{NSi}$ artificially enriched in $\mathbf{7}_{NSi}$, with K_2CO_3 in DMSO 20 °C and found (Scheme 5) that it provides, after 18 h, almost exclusively the $\mathbf{7}_{NRe}$ adduct (98% de).



Scheme 5

The cyclization of $\mathbf{7}_{NRe}$ to **4**, carried out in DMSO under different conditions implying alkali metal carbonates at 80 °C and potassium carbonate at 40 °C, lead every time

to a mixture of the two diastereoisomers $\mathbf{4}_{Re}/\mathbf{4}_{Si}$ (45/55 to 35/65, Scheme 6, Table 3). Careful monitoring by ^{1}H NMR of the reaction described in Table 3, entry 5 shows that D-**2** is formed as an intermediate.



Scheme 6

Table 3 Stereochemistry of the cyclopropane **4** obtained from γ-nitro malonates $\mathbf{7}_N$ depending upon the base used.

Entry	M (in M_2CO_3) DMSO, [T °C]	Yield in **4** ($\mathbf{4}_{Re}/\mathbf{4}_{Si}$)
1	Li [80]	72 (45/55)
2	Na [80]	81 (45/55)
3	K [80]	88 (40/60)
4	Cs [80]	90 (40/60)
5	K [40]	76 (35/65)

In conclusion, we have shown that 2-lithio-2-sulfonylpropane reacts under kinetic control with alkylidenemalonate D-**2** in DMSO to provide dimethyl cyclopropane-1,1-dicarboxylate $\mathbf{4}_{Si}$ almost as a single diastereoisomer. This is diastereoisomeric to the one ($\mathbf{4}_{Re}$) formed when isopropylidene diphenylsulfurane-$LiBF_4$ $\mathbf{3}_S$ or isopropylidene triphenylphosphorane-LiI $\mathbf{3}_P$ are used instead.[3]

Dimethyl cyclopropane-1,1-dicarboxylate $\mathbf{4}_{Si}$ was also formed from 2-lithio-2-nitropropane but with much lower diastereoselection. This result is even more puzzling since the open chain 1,4-adduct $\mathbf{7}_{NRe}$ which is isolated if the reaction is performed under milder conditions, has the opposite stereochemistry (it is derived from the (*Re*)-face attack) and is formed under thermodynamic control.

Apparently, the formation of the $\mathbf{4}_{Si}$ adduct from $\mathbf{7}_{NRe}$ requires the formation of $\mathbf{7}_{NSi}$ as an intermediate which is the least stable of both diastereoisomers and which must cyclize to $\mathbf{4}_{Si}$ faster than $\mathbf{7}_{NRe}$ do to produce $\mathbf{4}_{Re}$. We would have expected that $\mathbf{7}_N$ behaves as $\mathbf{7}_S$: this is apparently not the case. Results are opposite to the one observed with the sulfone derivatives! What are the reasons for such discrepancies? We are working towards this end in trying to understand the intimate mechanism of each of these reactions.

Acknowledgement

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References and Notes

(1) (a) Yechezkel, T.; Ghera, E.; Ramesh, N. G.; Hassner, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2423. (b) Ferreira, A. R. G.; Dias, A. G.; Pinto, A. C.; Costa, P. R. R.; Miguez, E.; da Silva, A. J. R. *Tetrahedron Lett.* **1998**, *39*, 5305. (c) Costa, J. S.; Dias, A. G.; Anholeto, A. L.; Monteiro, M. D.; Patrocinio, V. L.; Costa, P. R. R. *J. Org. Chem.* **1997**, *62*, 4002.

(2) Krief, A.; Hevesi, L.; Chaboteaux, G.; Mathy, P.; Sevrin, M.; DeVos, M.-J. *J. Chem. Soc., Chem. Commun.* **1985**, 1693. (b) Chaboteaux, G.; Krief, A. *Bull. Soc. Chim. Belg.* **1985**, *94*, 495. (c) Krief, A.; DeVos, M.-J. *Tetrahedron Lett.* **1985**, *26*, 6115. (d) Ono, N.; Kamimura, A.; Kaji, A. *Synthesis* **1984**, 226.

(3) Krief, A.; Provins, L.; Froidbise, A. *Tetrahedron Lett.* **1998**, *39*, 1437 and references cited.

(4) 2-metallo-2-nitropropanes are better described as nitronates anions. Description as 2-metallo-2-nitropropanes in the text is only used for consistency and does not reflect the reality.

(5) (a) Krief, A. in "*Organic Synthesis. A Chemistry for the 21st Century Monograph*", International Union of Pure and Applied Chemistry, Trost, B. M., Ed; Blackwell Scientific Publications **1994**, 337. (b) Krief, A.; Dumont, W.; Pasau, P.; Lecomte, P. *Tetrahedron* **1989**, *45*, 3039. (c) Mulzer, J.; Kappert, M. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 63.

(6) [5] (a) The two stereoisomers of $\mathbf{7}_S$ have been separated (Thick layer preparative liquid chromatography on SiO_2, pentane/ether 1/1, $\mathbf{7}_{SSi}$ Rf:0.4, $\mathbf{7}_{SRe}$ Rf :0.55) and the stereochemistry of the major stereoisomer ($\mathbf{7}_{NRe}$ and $\mathbf{7}_{SSi}$) of each of the above mentioned reactions has been unambiguously assessed by X-ray crystallography.[7] (b) The stereochemistry of the dimethyl cyclopropane-1,1-dicarboxylates $\mathbf{4}_{Re}$ and $\mathbf{4}_{Si}$ have been assessed by comparison with an authentic sample[3]. (c) The stereochemistry of the dimethyl cyclopropane-1,1-dicarboxylates $\mathbf{4}_{Si}$ has been also assessed by X-ray crystallography.[7]

(7) (a) Baudoux, G.; Norberg, B.; Provins, L.; Froidbise, A.; Krief, A.; Evrard G. *Acta Cryst.* **1998**, *C54*, 834.

(8) $\mathbf{4}_{Si}$ is produced (65%) as a single stereoisomer by performing the reaction in one pot by (i) 1,4-addition in THF-HMPA at -78 °C for 2 h, (ii) heating the mixture to 20 °C, (iii) adding DMSO and heating the mixture at 80 °C for 60 h. Notice that $\mathbf{7}_{SSi}$ does not cyclize when heated at 80 °C in THF-HMPA.

(9) These reactions have been followed by GC[2] using 1,3,5-trimethoxybenzene as an internal standard (Hewlett-Packard 5890A, capillary column, SE 30 HL; 30m x 0.2 mm, film thickness 0.33 μm, injector and detector :250 °C, oven from 100 °C to 220 °C at 10 °C/min., Rt = 3.5 min.). Under similar conditions the cyclopropane derivatives have the following retention times: $\mathbf{4}_{Re}$ Rt = 5.1 min. $\mathbf{4}_{Si}$ Rt = 5.3 min.

(10) A 97/3 mixture of $\mathbf{7}_{NRe}/\mathbf{7}_{NSi}$ is formed in 70% yield when the reaction is performed in THF-HMPA.

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