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Asymmetric Michael Addition of Chiral Enaminoesters to Phenyl Vinyl Sulfone and 1,1-bis(Phenylsulfonyl)ethylene

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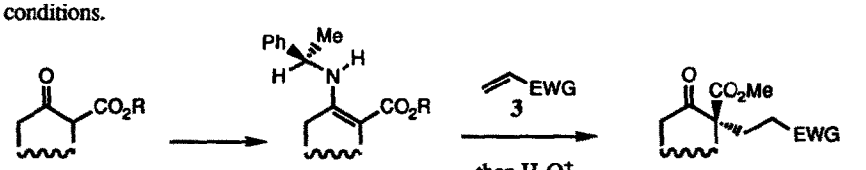
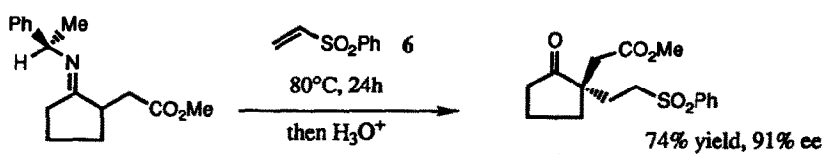
Abstract : *Enaminoester (S)-9 was added to phenyl vinyl sulfone, leading to adduct (S)-10. In contrast addition of 9 to 1,1-bis(phenylsulfonyl) ethylene gave (R)-16.*

It has been established that chiral enamino-esters **2**, derived from ketoesters **1** and optically active 1-phenylethylamine, add to electrophilic alkenes **3** leading, after hydrolytic work-up, to adducts **4** with good to excellent stereoselectivity[1]. The reaction parameters in these additions depend strongly on the nature of electrophile **3**. Thus the addition of **2** to acrylonitrile[2] or methyl vinyl ketone[3] requires the presence of $ZnCl_2$, while the addition to *tert*-butyl acrylate[3] requires the activation either by a Lewis acid ($MgBr_2$) or by high pressure. In contrast enaminoesters **2** add readily to the very reactive di-*tert*-butyl methylenemalonate[4] under mild thermal conditions.



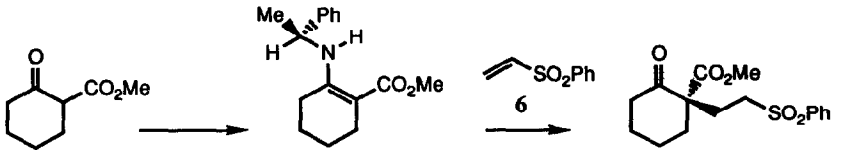
1 **2** **4** ee: 80-95%

Introduction of at least "three-carbon-atom" appendages in adducts **4** results from the utilization of the aforementioned electrophilic alkenes. In connection with our program devoted to the enantioselective synthesis of natural products, we have recently directed our attention to the use of "two-carbon-atom" electrophiles in these Michael additions. To attain this end, we thought to replace the carbon-bearing electrophilic functions in the preceding Michael acceptors by an easily removable heteroatom-bearing group. In this respect, phenyl vinyl sulfone **6** appeared a valuable candidate, since we have previously shown that its addition to imine **5** led to the desired adduct **7** with excellent selectivity[5].



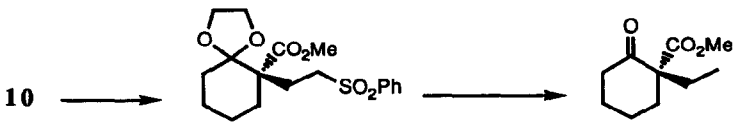
5 **7** 74% yield, 91% ee

Addition of enaminoester (*S*)-**9**[3], prepared from ketoester **8** and (*S*)-(-)-1-phenylethylamine (96 % ee), to **6** was thus examined. Not surprisingly this enaminoester proved to be much less reactive than imine **5** : all attempts at conversion [**9** + **6** → **10**] under thermal or Lewis acid-catalyzed ($MgBr_2$, $AlCl_3$, Et_2AlCl) conditions actually failed. In contrast, *activation by high pressure* (THF, 14 Kbar, 40°C, 66h, then 2 N AcOH) led to the desired adduct (*S*)-**10**[6] (85 % yield, 94 % ee). Based upon the ee of the initial chiral auxiliary amine being 96 %, *the efficacy of the "chirality transfer" in the present asymmetric process is 98 %.*



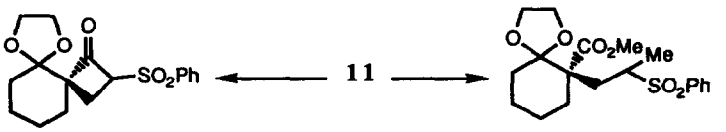
8 **9** **10**

Determination of the ee and of the absolute configuration in adduct **10** was made by correlating this compound with known ketoester (*R*)-**12**[7]. For this purpose **10** was converted into ketal **11**[8] (Dean-Stark trap, 10 eq of ethylene glycol, cat. TsOH, 12h in refluxing, toluene, 85 % yield), which upon desulfonation ("activated" Mg, MeOH, 50°C, then 3 N HCl)[9] led to **12**[10] (80 % yield). One should note that the *S* configuration is observed in adduct **10**, in agreement with the proposed transition state model for these Michael addition reactions[1].



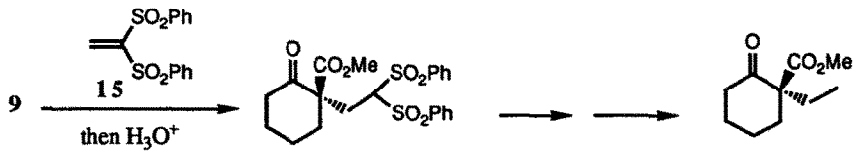
11 **12**

Formation of the anion in the α-position to the phenylsulfonyl group in **11** was then attempted, since such anionic species are known to be powerful and versatile intermediates in organic synthesis. However it was suspected that this anion could react intramolecularly with the ester function, leading to cyclobutanone **13**. This was indeed observed when **11** was treated with an excess of LDA in THF at -78°C, and the resulting mixture was warmed up to 20°C : the spiro derivative **13**[11] was produced, as an essentially single diastereomer, with a 80 % yield. Nevertheless, when MeI was added to the anion of **11**, preformed at -78°C, the expected methylated derivative **14**[12] (essentially a single diastereomer) was obtained with an excellent yield (85 %). This experiment thus demonstrates that the condensation of anion of **11** with an *external* electrophile has priority over the *internal* displacement of the methoxy group.

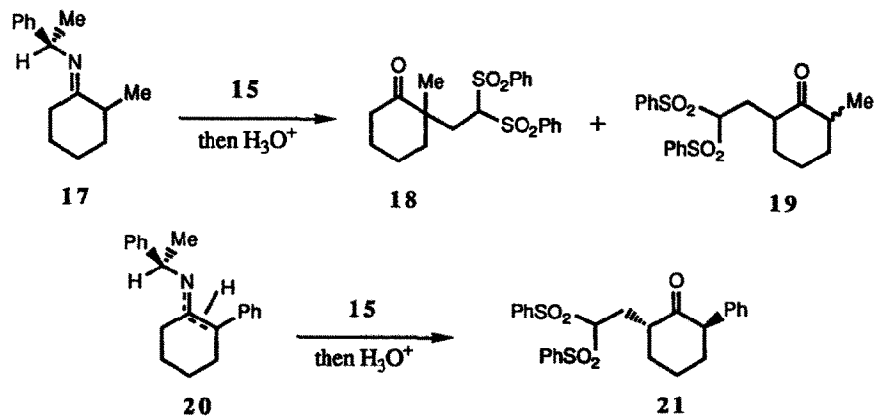


13 **14**

Although conversion [**9** → **10**] is particularly efficient, we next turned to the use of a "two-carbon-atom "electrophilic alkene more reactive than phenyl vinyl sulfone **6**, in order to avoid the need of high pressures as activating conditions. In this regard 1,1-bis(phenylsulfonyl)ethylene **15**[13] seemed very attractive. Indeed this compound is a powerful Michael acceptor which reacts with a great variety of nucleophiles under very mild operating conditions[14]. As expected, addition of enaminoester (*S*)-**9** to **15** proceeded smoothly (THF, O°C, 4h) leading to adduct **16**[15] with a 90 % yield. However, quite surprisingly, the configuration of **16** was found to be mainly *R* (50 % ee), by correlating with (*ent*)-**12** (*i* : dioxolanation; *ii* : Mg, MeOH, 50°C; *iii* : 3 N HCl ; 70 % overall yield). This stereochemical finding is thus in contradiction with the cyclic, chair-like transition state model which we have proposed for these Michael additions[1]. Consequently, a dramatic change in the mechanism of reaction [**9** + **15** → **16**], compared to preceding related addition pathways [**5** + **6** → **7**], [**9** + **6** → **10**], and others[1], should necessarily be evoked, perhaps an acyclic transition state.



One should note that the peculiar electrophilic alkene **15** exhibits an "abnormal" (and unprecedented) behaviour, not only in terms of stereochemistry (considering the "inversion" of the sense of induction in addition [**9** + **15** → **16**]), but also in terms of regiochemistry. Indeed, an important loss of regiocontrol was observed in the addition of this electrophile with imines **17** and **20**, which are known to react with "common" Michael acceptors, like methyl acrylate, essentially at *the more* substituted α-position of the imine function[1]. Thus addition of **15** to imine **17** (THF, O°C, 1h) led to a 1:4 mixture of regioisomeric adducts **18** and **19**[16], respectively (the latter compound being obtained as a 2.3:1 mixture of *trans/cis* stereomers) with an overall yield of 70 %. Similarly imine **20**[17] added to acceptor **15** (THF, 20°C, 5h), giving with a 35 % yield adduct **21**[18] (single *trans* diastereomer, ee not determined).



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6 - **10** : solid; mp 73-74°C; $[\alpha]_D^{25}$ -50.6 (c=8, MeOH); IR (KBr) 1725 cm^{-1} (br); ^1H NMR (200 MHz, $CDCl_3$) δ 1.4-2.25 (m, 6H) 2.45 (m, 4H) 3.0 (m, 1H) 3.3 (m, 1H) 3.70 (s, 3H) 7.6 (m, 3H) 7.9 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3 27.2 27.7 36.5 40.7 51.9 52.7 59.6 128.0 129.3 133.8 138.7 171.6 206.9.

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8 - **11** : solid; mp 65-66°C; $[\alpha]_D^{20}$ -9.6 (c=5.6, MeOH); IR (KBr) 1725 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2 22.8 25.4 31.7 32.4 52.0 52.9 53.7 64.3 64.8 110.4 128.1 129.3 133.7 139.0 173.1.

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10 - (*R*)-**12** : oil; $[\alpha]_D^{20}$ -82.4 (c=5.7, EtOH); the ee (94 %) was determined by 200 MHz ^1H NMR, on the methoxy resonance; having added Eu (hfc)$_3$ as shift reagent. Lit[7] : $[\alpha]_D$ -9.03 (ee = 11 %).

11 - **13** solid; mp 136-137°C; IR (CH_2Cl_2) 1775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35-1.75 (m, 8H) 2.0 (m, 1H) 2.32 (dd, J=12.6 7.3 Hz, 1H) 2.58 (dd, J=12.6 10.6 Hz, 1H) 3.9 (m, 4H) 4.62 (dd, J=10.6 7.3 Hz, 1H) 7.5 (m, 2H) 7.6 (m, 1H) 7.9 (m, 2H).

12 - **14** : ^1H NMR (200 MHz, $CDCl_3$) δ 1.12 (d, J=6.7 Hz, 3H) 1.3-2.2 (m, 9H) 2.43 (dd, J=14.5 1.9 Hz, 1H) 3.0 (m, 1H) 3.62 (s, 3H) 3.87 (m, 4H) 7.55 (m, 3H) 7.8 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9 20.3 22.8 29.1 30.2 31.8 51.8 52.6 56.5 64.5 64.9 110.7 129.0 133.6 136.9 174.0.

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15 - **16** : solid; mp 145-146°C; $[\alpha]_D^{25}$ + 27.8 (c=5.7, acetone); IR (KBr) 1730 1710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.2-2.1 (m, 6H) 2.37 (dd, J=17.0 3.4 Hz, 1H) 2.5 (m, 2H) 3.06 (dd, J=17.0 4.9 Hz, 1H) 3.81 (s, 3H) 4.80 (dd, J= 4.9 3.4 Hz, 1H) 7.5 (m, 3H) 7.8 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4 27.1 28.2 35.7 41.0 53.2 58.5 78.7 129.0 129.6 130.4 134.3 134.7 136.7 138.3 171.3 205.6. The ee (50 %) in this adduct was determined by ^1H NMR, on the methoxy signal, having added Eu (hfc)$_3$ as shift reagent.

16 - Regio- and diastereomeric ratios in mixture [**18** + **19**] were determined by ^1H NMR (200 MHz, $CDCl_3$) δ **18** : 0.87 (s, 3H) 4.60 (dd, 1H); **19** *trans* 1.01 (d, 3H) 4.75 (dd, 1H); **19** *cis* : 0.88 (d, 3H) 4.92 (dd, 1H).

17 - Compound **20**, prepared by condensation of 2-phenylcyclohexanone with (*S*)-1-phenylethylamine, proved, in fact, to be a mixture of imine and tautomeric secondary enamine.

18 - **21** : solid; mp 55-55.5°C; IR (KBr) 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.3-2.7 (m,8H) 2.8 (m, 1H) 3.67 (dd, J=6 6 Hz, 1H) 4.60 (dd, J=8 3.5 Hz, 1H) 7.0-7.9 (m, 15H); ^{13}H NMR (50 MHz, $CDCl_3$) δ 20.8 26.6 31.3 33.1 45.9 54.2 80.6 126.9 127.5 127.9 128.7 129.0 129.2 129.4 134.4 137.6 138.0 212.4.