Pergamon

Tetrahedron Letters, Vol. 38, No. 41, pp. 7131-7134, 1997

0040-4039/97 $17.00 + 0.00

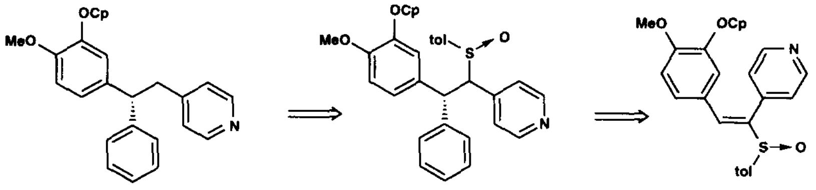
PII: S0040-4039(97)01766-8

Nickel Catalyzed Addition of Organozincates to Optically Pure Vinylic Sulfoxides. Synthesis of the Phosphodiesterase IV Inhibitor L-765,527 (CDP-840).

Ioannis N. Houpis*#, Audrey Molina*, Ilias Dorziotis, Robert A. Reamer, R.P. Volante, and Paul J. Reider
Merck Research Laboratories, Process Chemistry, P.O. Box 2000, Rahway, N.J. 07065
e-mail address: ioannis_houpis@merck.com

***Summary**: $Ph_3ZnMgCl$ was added to the optically pure sulfoxide **3** in the presence of $Ni(acac)_2$ to give, after desulfurization, the phosphodiesterase IV inhibitor **1** in good yield and 92% enantiomeric excess.*

Optically pure sulfoxides have been used as readily accessible "chiral auxiliaries" for a diverse range of reactions such as conjugate additions, Diels-Alder reactions, and sigmatropic rearrangements.[1] Indeed, in the last decade, the utility of the sulfoxide functionality has increased as asymmetric sulfide oxidation technology has been refined.[2] Our interest in the chemistry of chiral sulfoxides was spurred by our need to prepare **1**, a clinical candidate for the treatment of asthma. Retrosynthetic analysis indicated that vinyl sulfoxide **3** would be an appropriate precursor to **1**.

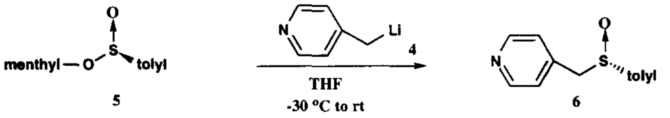


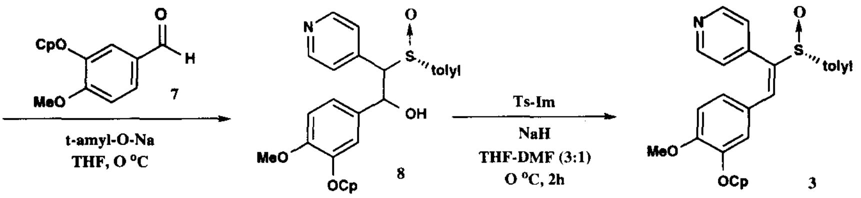
1 **2** **3**

Cp = cyclopentyl

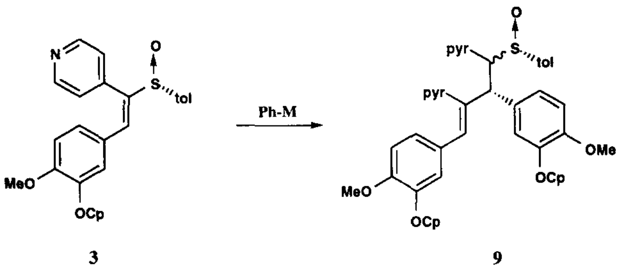
This letter describes a study involving the addition of nucleophiles such as organo-lithium, magnesium, titanium, aluminum and zincate reagents to sulfoxide **3**. The best results were ultimately achieved by the use of organozincate reagents via Ni catalysis.[3]

The synthesis of **3** was carried out by the sequence shown below: (a) addition of lithium picolinate **4** (n-BuLi, 1.0 eq; picoline, 1.5 eq; THF, 23 °C) to menthyl sulfinate **5**;[4] (b) deprotonation of the pyridyl sulfinate **6** with *t*-amyl-ONa (1.1 eq; THF; 0 °C) in the presence of aldehyde **7** to give adduct **8** as a single diastereomer;[5] and (c) treatment of the latter with tosyl imidazole in the presence of NaH in THF-DMF (3:1) to give **3**, as the sole isomer, in 66% recrystallized yield. This yield could be improved to ca. 80% via a two-step process involving formation of the corresponding acetate followed by elimination with NaH or DBU.[6]





Reaction of **3** with common organometallic reagents proved disappointing (eq 1). The expected adduct, **2**, was not formed with any of the reagents shown, instead the dimer **9** was produced in high yield. The latter results from attack of the organometallic reagent on the sulfur, followed by expulsion of the corresponding vinyl anion, which in turn adds to another molecule of **3**. This reaction occurred rapidly even at -78 °C, irrespective of the solvent, order of addition or equivalents of the reagents shown in eq 1. It became apparent that hard nucleophiles could not effect the desired conjugate addition and attack on sulfur seemed to be the kinetically preferred mode of reactivity.[6]



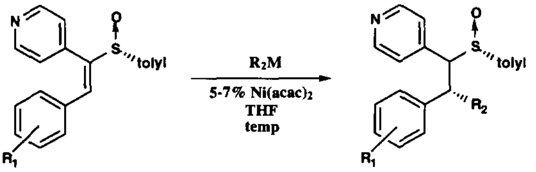
(eq 1)

$\mathrm{Ph\text{-}M = PhLi;\ PhMgBr;\ Ph_2Mg; PhCeCl_2;\ Ph_2CuCNLi_2}$

We next turned our attention to transition metal catalyzed processes and the results are shown in eq 2 and Table I. Organotitanium reagents, although useful for conjugate additions to hindered enones,[7] afforded no reaction with olefin **3** other than partial double bond isomerization of the starting material (entries 1, 2). Organoaluminum reagents, on the other hand, gave a clean reaction with olefin **3** under Ni(acac)$_2$ catalysis. However, a mixture of phenyl and ethyl adducts (1.2:1 ratio) was observed (entry 3). More interestingly, PhAlMe$_3$Li gave exclusive Me group migration (entry 4) while only reduction was observed with PhAl(^{i}Bu)$_3$Li (entry 5).

The first successful conjugate addition was observed with the lower order cuprate Ph_2CuLi (entry 6) in the presence of $Ni(acac)_2$. However, this process had limited utility due to the low stability of the cuprate at the reaction temperature (-5 to 0 °C). Interestingly Ph_2CuLi did not react with **3** in the absence of $Ni(acac)_2$ and $Ph_2CuCNLi_2$ gave only the dimer **9** when reacted with **3** without $Ni(acac)_2$.

The synthesis of **2** (and consequently **1**) was subsequently accomplished in high, reproducible yield by use of the organozincate reagents derived from $ZnCl_2$ and PhLi or PhMgBr (entries 8 and 9).[8] The preformed organozincate (2 eq $ZnCl_2$; 6 eq PhLi or PhMgBr in THF; 0 to 23 °C) was added to a solution of olefin and $Ni(acac)_2$ at -25 °C and the resulting deep burgundy solution was stirred for 4 hours. The reaction was quenched with NH_4Cl and the pH was adjusted to 10 with NH_4OH. The adduct **2** was isolated in ca. 90% yield.



(eq 2)

TABLE I

Entry	Organometallic[a]	R_1	R_2	Temp (°C)	Yield	% ee[b]
1	$LiPhTi(OPr^i)_4$	p-OMe; m-OCp	Ph	23	NR	–
2	$LiPh_2Ti(OPr^i)_3$	p-OMe; m-OCp	Ph	23	NR	–
3	$LiPhAlEt_3$	p-OMe; m-OCp	Ph:Et (1.2:1)	23	82%	–
4	$LiPhAlMe_3$	p-OMe; m-OCp	Me	23	75-80%	d
5	$LiPhAl(Bu^i)_3$	p-OMe; m-OCp	H	23	–	e
6	Ph_2CuLi	p-OMe; m-OCp	Ph	-5	50%	65-70%
7	PhZnCl	p-OMe; m-OCp	Ph	23	15%	f
8	Ph_3ZnLi	p-OMe; m-OCp	Ph	-25	>90%	82%
9	$Ph_3ZnMgBr$	p-OMe; m-OCp	Ph	-25	>90%	92%
10	$Et_3ZnMgCl$	p-OMe; m-OCp	Et	-25	60%[c]	88%
11	$Ph_3ZnMgCl$	CF_3	Ph	-25	62%[c]	71%
12	$Ph_3ZnMgCl$	Cl	Ph	-25	80%	89%
13	$Et_3ZnMgCl$	Cl	Et	-25	75%	64%
14	Bu_3ZnLi	p-OMe; m-OCp	Bu	-25	87%	75-80%
15	Me_3ZnLi	p-OMe; m-OCp	Me	23	80%	65%

(a) No reaction was observed in the absence of $Ni(acac)_2$. (b) The ee was determined after desulfurization on a Chiralpack-OD column using Supercritical Fluid Chromatographic techniques. (c) Yield after desulfurization. (d) Only the Me adduct was observed by crude NMR. The ee was not determined. (e) Only the 1-4 reduction product was obtained. (f) The ee was not determined.

A number of points should be raised about this reaction: (a) THF was the optimum solvent with lower polarity solvents having a detrimental effect on the ee; (b) the order of addition was essential, as addition of the olefin to a solution of the zincate followed by Ni(acac)$_2$ required a reaction time of 24 hours compared to 4 hours for the reverse addition mode; (c) the reaction temperature (-25 °C) was important for catalyst activation, (e.g. addition of the zincate at -35 °C gave a light brown reaction mixture instead of the deep burgundy color of the active system and no reaction was observed); (d) methyl migration (entry 15) was considerably more sluggish than Ph, Et, or Bu migration unlike the corresponding Al reagents (entries 4 and 5);[9] (e) the substituents and the electronic nature of R_1 played an important role with electron deficient aromatic substituents substantially reducing the ee (entry 11); (f) vinyl or acetylynic zincates did not add to **3**, however, there are indications that the corresponding zincates were unstable and we are currently investigating solutions to this problem; (g) under the mild conditions required for this reaction, alkyl groups could be successfully added without complications from β-hydride elimination; (h) addition of external ligands (bipyridine, PPh$_3$, or bisoxazolines) to the reaction mixture of Ni(acac)$_2$, zincate and the olefin inhibited the reaction.[10]

The synthesis of **1** was completed by desulfurization of **2** with Zn^0 in THF/AcOH (10:1) at 23 °C to give the desired product in 70-75% yield. Aluminum amalgam could also be used for this transformation.

In conclusion, the combination of organozincates and Ni(acac)$_2$ added to vinyl sulfoxide **3** to afford our target **1** in good yield and enantiomeric excess. The use of zincates in other processes is under intense investigation in our group.

References and Notes

1. (a) Solladie, G. *Synthesis*, **1981**, 185. (b) Posner, G.H. *Acc. Chem. Res.* **1987**, *20*, 72. (c) Walker, A.J. *Tetrahedron:Asymmetry* **1992**, *3*, 961. (d) Casey, M.; Manage, A.C.; Gairns, R.S. *Tetrahedron Lett.* **1989**, *30*, 6919. (e)Toru,T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**,*115*,10464. (f) Alonso, I.; Carretero, J.C.; Ruano, J.L.G.; Cabrejas, L.M.M.; Lopez-Solera, I.; Raithby,P.R. *Tetrahedron Lett.* **1994**, *35*, 9461. (g) Burgess, K.; Henderson, I.*Tetrahedron Lett.* **1989**, *30*,4325. (h) Marino, J.P.; Laborde, E.; Deering, C.F.; Paley, R.S.; Ventura, M.P *J. Org. Chem.* **1994**, *59*, 319.
2. (a) Pitchen, P.P.; Dunach, E.; Deshmukh, M.N.; Kagan, H.B. *J. Am. Chem. Soc.* **1984**, *106*, 8188. (b) Zhao,S.H.; Samuel, O.; Kagan, H.B. *Tetrahedron*, **1987**, *43*, 5135. (c) Holland, H.L. *Chem.Rev.* **1988**, *88*, 473.
3. Organozincate additions to activated and unactivated C=C have been reported: (a) Knochel, P.; Vaupel, A. *Tetrahedron Lett.* **1995**, *36*, 231. (b) Knochel, P. *Synlett* **1995**, 393 and references therein.(c) Savchenko, A. V.; Montgomery, J. *J. Org.Chem* **1996**,*61*, 1562.(d) Schwartz, J.; Loots, M.J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333.
4. For details on the general synthesis of chiral sulfoxides using **5**, see ref 1a and 1b.
5. The amount of base was crucial. Excess reagent caused a shift of the equilibrium towards **6** and **7.**
6. Indeed after this study was completed, an interesting report appeared where hindered vinyl sulfoxides were used for generation of vinyl Grignards in high yield: Satoh, T.; Tahano, K.; Someya, H.;Matsuda, K. *Tetrahedron Lett.* **1995**, *36*, 7097.
7. Flemming, S.; Kabbara, J.; Nickish, K.; Neh, H.; Westermann, J. *Tetrahedron Lett,* **1994**, *35*, 6075.
8. These reagents have been used for addition to enones both with and without Ni catalysis; (a) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679. (b) Kjonaas, R. A.;Watson, R.A. *Tetrahedron Lett.* **1986**, *27*, 1437. (c) Kjonaas, R.K.; Hoffer, R.K. *J. Org.Chem.* **1988**,*53*, 4133. (d) Takahashi, Y.; Nakazawa, M.; Kanoh, M. Yamamoto, K. *Tetrahedron Lett.* **1990**, *31*, 7349. (e) Singer, R. D.; Vaughan, A. *Tetrahedron Lett.* **1995**,*36*, 5683.
9. This migratory trend has been observed.[8d] In addition, Me$_3$ZnLi has been used in an ingenious way to effect catalytic cuprate additions to enones: Lipshutz, B.H.; Wood, M.R., Tirado R. *J.Am.Chem.Soc.* **1995**, *117*, 6126 and references therein.
10. The order of addition of the external ligand was not important. Inhibition was observed regardless if the ligand was added before or after the zincate.

(*Received in USA* 30 *July* 1997; *revised* 19 *August* 1997; *accepted* 20 *August* 1997)