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ENANTIOSELECTIVE ADDITION OF CHIRALLY MODIFIED METHYLTITANIUM REAGENTS TO AROMATIC ALDEHYDES

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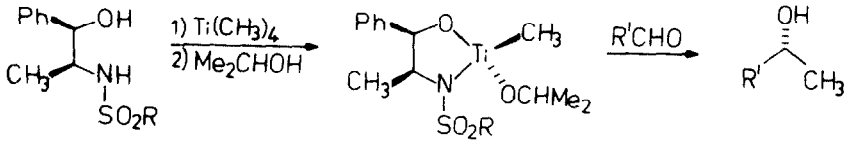
Summary: N-Sulfonylated derivatives of norephedrine are excellent ligands for chirally modified methyltitanium reagents, the latter reacting enantioselectively with aromatic aldehydes (ee ~ 90%) to form R-configurated carbinols.

Much research has gone into developing enantioselective versions of Grignard-type additions to aldehydes, particularly methods based on complexation of RLi and RMgX with chiral amines and ethers[1]. Admirable results have been reported, but no general procedures. The enantioselective addition of methyl groups appears to be especially difficult[1]. Another approach is the use of organometallics which are chirally modified in the form of optically active ligands such as certain allylboron reagents (ee=80-99%)[2]. Since organotitanium reagents have proven to be very stereoselective in many other situations[3], application in the area of enantioselective additions would seem to be possible. However, so far the results have been far from being uniformly acceptable[3-5]. Phenyl additions to aromatic aldehydes are useful (ee ~ 90%)[5], but such groups as

methyl pose problems. A synthetic and mechanistic uncertainty is the fact that many titanium reagents having bidendate ligands undergo rapid ring-opening oligomerization and/or exist as aggregates[3-4]. In this Letter we describe a method based on readily available norephedrine which appears to be general for the highly enantioselective addition of methyl groups to aromatic aldehydes.

N-Sulfonylation of norephedrine using $RSO_2Cl/NEt_3/Et_2O$ afforded good yields of the novel sulfonamides 1. These were treated with $Ti(CH_3)_4$ followed by the addition of isopropanol to the intermediate dimethyltitanium compounds. The formula 2 is only a formal representation, since the H and ^{13}C NMR spectra show a multitude of peaks not in line with a single monomeric or dimeric species. Inspite of the undefined nature of the reagents, they were tested in addition reactions with aldehydes (Table 1)[6]. The ee-values were determined by the Mosher method using MTPA-Cl[7] or by capillary GC analysis of the N-isopropyl carbamate of 3 on a König column[8].



1 2 3

In all cases the products 3 have the R-configuration, as proven by polarimetric comparison with known compounds. Table 1 shows that unacceptable ee-values are generally obtained in case of aliphatic aldehydes (entries 9 -13). In contrast, pronounced stereoselectivity is observed in reactions with aromatic aldehydes, particularly if the R group at sulfur in 1 is mesityl (entries 5-8). If it is methyl (entry 4), ee is lowest. Thus, a prerequisite for high enantioselectivity seems to be the presence of an aromatic ring at sulfur.

In case of the reaction sequence with R = p-tolyl and R' = phenyl, the effect of alcohols other than isopropanol was tested. In all cases enantioselectivity turned out to be lower than in entry 1 of Table 1: C_2H_5OH (ee = 48%);

$t\text{-}C_4H_9OH$ (ee = 58%); C_6H_5OH (ee = 12%); CF_3CH_2OH (ee = 50%); CCl_3CH_2OH (ee = 69%).

Table 1. Enantiomeric Addition 2 + R'CHO → 3

Entry	R	R'	isol.yield of 3 (%)	ee (%)
1	p-tolyl	phenyl	78	85
2	p-tolyl	o-nitrophenyl	91	79
3	p-tolyl	1-naphthyl	96	81
4	methyl	phenyl	89	62
5	mesityl	phenyl	93	88
6	mesityl	o-nitrophenyl	86	90
7	mesityl	o-methylphenyl	75	88
8	mesityl	1-naphthyl	92	90
9	p-tolyl	n-heptyl	81	60
10	p-tolyl	isobutyl	53	43
11	p-tolyl	1-(ethyl)propyl	64	76
12	mesityl	n-heptyl	82	58
13	mesityl	1-(ethyl)propyl	70	31

Due to the undefined nature of the reagents, any detailed interpretation is meaningless. However, it should be noted that in addition to the non-epimerizing chiral centers of the norephedrine ligand system, titanium itself represents a chiral center which is not likely to be configurationally stable[9]. Either the absolute configuration at titanium is of little importance, or one of the (equilibrating) epimers is much more reactive than other species. The latter phenomenon would be an example of the Curtin-Hammett principle in stereoselective C-C bond formation.

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References and Notes

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6) The suspension of $TiCl_4$ (3.0 mmol) in 50 ml of dry ether is slowly treated with 12 mmol of a CH_3Li/ether solution (Merck) at -70°C under dry N_2. Stirring is continued until a clear green solution is obtained ($\sim$30 min.). The ligand 1 (3.0 mmol) in ether is slowly added, the solution allowed to reach -30°C (2 h) and isopropanol (192 mg; 3.2 mmol) added. The solution is stirred for 30 min. during which the temp. reaches $\sim$ -10°C. It is cooled to -78°C and an aldehyde (2.7 mmol) added. Stirring is continued overnight during which room temp. is reached and the solution is poured on sat. NH_4F/H_2O. The aqueous phase is extracted twice with Et_2O, the combined org. phases washed with NH_4Cl/H_2O and H_2O and dried over $MgSO_4$. Kugelrohr distillation affords the carbinols 3.

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