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SECOND-GENERATION AUXILIARY FOR THE ASYMMETRIC ADDITION OF METALATED TETRAHYDROISOQUINOLINES TO ALDEHYDES

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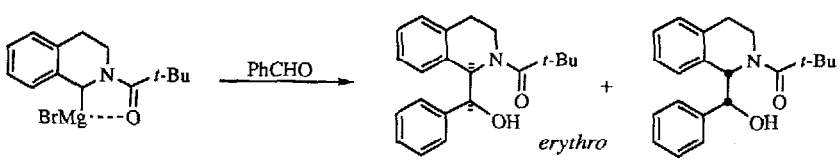
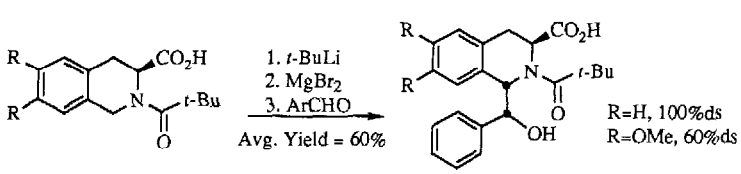
Abstract: *The selectivity of asymmetric addition of tetrahydroisoquinolyloxazoline Grignard reagents to aldehydes has now been improved to 78-82% ds through the use of a camphor-derived auxiliary. The new auxiliary has broad applicability, with overall yields of chemically and diastereomerically pure addition products now in the 50-58% range.*

In 1984, the chemistry of dipole-stabilized anions[1] was advanced by Seebach's observation that tetrahydroisoquinoline Grignards add to aldehydes diastereoselectively (Eq. 1).[2] This behavior is in contrast to the corresponding lithium compound, which shows no selectivity in its addition reactions.[2,3] Our recent mechanistic studies[4] have shown that this difference is due to a change in mechanism: the lithium addition occurs by single electron transfer whereas the magnesium addition occurs by the polar pathway proposed by Seebach.[3]



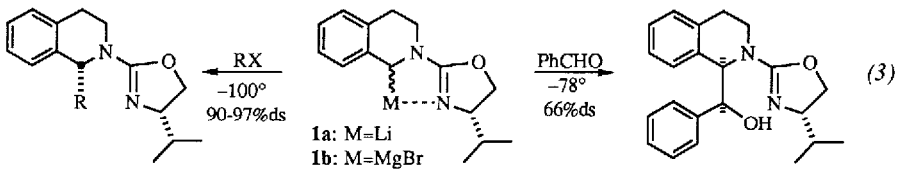
(1)

Seebach's methodology proved to be useful for the diastereoselective synthesis of racemic aporphine, phthalide, and protoberberine alkaloids.[5] In subsequent work, a chiral isoquinolyl pivalamide derived from phenylalanine was used in a synthesis of enantiomerically pure addition products (Eq. 2).[6] Unfortunately, substitution of dimethoxyphenylalanine (necessary for several natural products) in the sequence produced anomalous results, and the high diastereoselectivity (ds) was lost.[6]



(2)

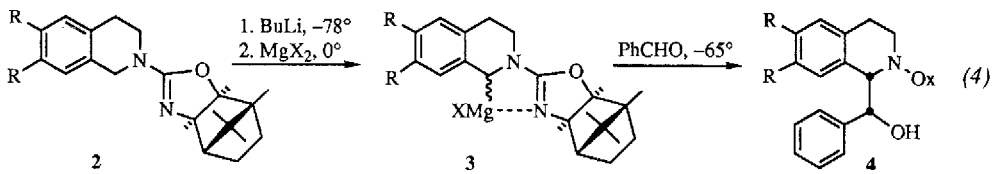
We recently began an investigation into a face selective addition of tetrahydroisoquinoline Grignards mediated by an oxazoline chiral auxiliary.[7] In the reactions of isoquinolyloxazolines such as **1a** with alkyl halides, selectivities as high as 97:3 were achieved.[8] Additions of the isoquinolyloxazoline Grignard **1b** to benzaldehyde showed 100% *erythro* selectivity, but the diastereomer ratio was not as high as hoped: 66:33:0:0.[7] The absolute configuration of the major diastereomer was correlated to bicuculline diol, and it was thus established that the sense of asymmetric induction in the alkylations and the carbonyl additions are opposite (Eq. 3).[7,9]



(3)

Because of the significant potential of these asymmetric carbonyl additions for the synthesis of enantiomerically pure alkaloids, we have surveyed a number of oxazoline chiral auxiliaries for this process, and report that we have identified a new auxiliary that affords significantly improved selectivity *at higher temperatures* than previously reported, and which facilitates the separation of the unwanted diastereomer. We also note an anomaly in the addition of dimethoxyisoquinoline Grignards that is reminiscent of that reported by Seebach[6] (Eq. 2), a speculative hypothesis of its source, and a solution to the problem.

A number of substituted oxazolines were tested;[10] although the details of the search will be reported in the full paper, it is important to note that *erythro* selectivity was observed in all cases.[11] The camphor derivative **2** (R=H, Eq. 4) produced an addition product, **4** (R=H), that could be purified to 100% de by recrystallization in 50% overall yield. We also note an interesting temperature effect: the selectivity for the addition of **3** (R=H) to PhCHO *increases* when the temperature of the reaction is raised from −78° (employed previously[7,9]) to −65°. The reasons for this effect are unclear, but may be related to the ability of the metalated carbon to epimerize at a rate that is competitive with the rate of carbonyl addition.[12] We now consider this auxiliary to be the best for accomplishing the asymmetric carbonyl addition.



2 3 4 (4)

R	X	Yield*	Crude ds
H	Br	50%	80%
MeO	Cl	58%	82%
-OCH_2O-	Cl	53%	78%

* After purification to 100% de by recrystallization or chromatography.

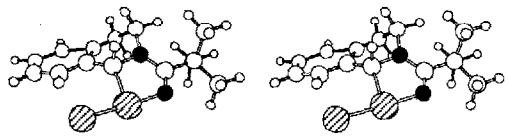


Figure 1. Stereo view of tetrahydroisoquinoline pivalamide Grignard. Three THFs of solvation are deleted for clarity. Coordinates taken from ref. 3.

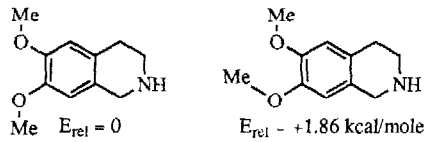


Figure 2. Relative energies of 6,7-dimethoxyisoquinoline *syn* and *anti* methoxy conformers.

In testing this method for the synthesis of oxygenated derivatives, including some isoquinoline alkaloids, we noticed that the 6,7-dimethoxy derivative **2** (R=OMe, X=Br) did not show the expected *erythro* selectivity. Instead, a mixture of *erythro* and *threo* addition products were obtained. This surprising result stands in contrast to the *erythro* selectivity observed for the 6,7-methylenedioxy analogs.[7,9] The crystal structure of the tetrahydroisoquinoline Grignard shown in equation 1 shows the bromine *trans* to the carbonyl oxygen, as shown in Figure 1.[3] Our calculations[13] show that the most stable conformation of a 6,7-dimethoxyisoquinoline has the methyls oriented away from each other, as shown in Figure 2. This conformation could perturb the geometry of the octahedral complex by interfering with the large bromine, thereby causing a change in mechanism that results in lost selectivity. If this were true, we hypothesized that exchanging the bromine for a smaller chlorine might alleviate the problem. In the event, it did: transmetalation with $MgCl_2 \cdot Et_2O$ restored the *erythro* selectivity with the original oxazoline auxiliary and exhibited the same high selectivity with the camphor-derived auxiliary as was observed with the unsubstituted isoquinoline.

As before,[7,9] the auxiliary may be removed and recovered in good yield by LAH reduction. Utilization of this method in natural product synthesis will be reported shortly. An optimized procedure for the preparation of isoquinolyloxazoline **2a**, its metalation and addition to benzaldehyde follows:

Preparation of 2 (R=H). To a solution of 26 mL (50.2 mmol) of phosgene (1.93M in toluene[14]) and 4 mL Et_3N in 20 mL THF at –78° was added slowly a solution of 1.66 g (12.5 mmol) of 1,2,3,4-tetrahydroisoquinoline in 20 mL of THF. After stirring for 1 h at –78° the mixture was warmed to room temperature. Excess phosgene was removed by stirring at room temperature under aspirator pressure. The mixture was diluted with 20 mL of THF, recooled to –78°, and treated with a solution of 2.0 g (11.8 mmol) of (1*R*, 2*S*, 3*R*, 4*S*)-3-*exo*-amino-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane[15] and 4 mL Et_3N in 20 mL THF. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water and extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried with $MgSO_4$. The solution was condensed to near dryness and diluted with ether. The urea derivative precipitated and was collected by filtration to afford ~2.75 g (~70%). Cyclization was accomplished by refluxing a solution of 2.5 g (7.6 mmol) of the urea and 9.3 g (61 mmol) of $POCl_3$ in 40 mL toluene overnight. After condensing the solution to near dryness, the residue was quenched with aqueous sodium carbonate and extracted with CH_2Cl_2. The organic layers were combined, washed with brine and dried with $MgSO_4$. Condensation of the residue and column chromatography (silica gel, 20:1 CH_2Cl_2:EtOH) afforded ~1.9 g of **2** (R=H,~80%). The same procedure is used for 6,7-dimethoxy- and 6,7-methylenedioxyisoquinolyl oxazolines.

General Procedure for the Metalation and Carbonyl Addition of 2. To a 0.1 M solution of **2** in THF at –78° was added 1.2 eq of 1.6M *n*-BuLi in hexane. After the solution was stirred at this temperature for 20

minutes, 1.5 eq. of MgX_2[16] was added. The mixture was stirred at 0° for 20 minutes to achieve transmetalation (the solution changed color from red to yellow), then cooled to –65°. To this solution was added 1.5 eq of aldehyde and the mixture was maintained at this temperature for 48 h. The reaction was then quenched with aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried with $MgSO_4$, and condensed. The addition product was purified either by recrystallization or column chromatography (silica gel, 2-4:1 EtOAc:Hexane).

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