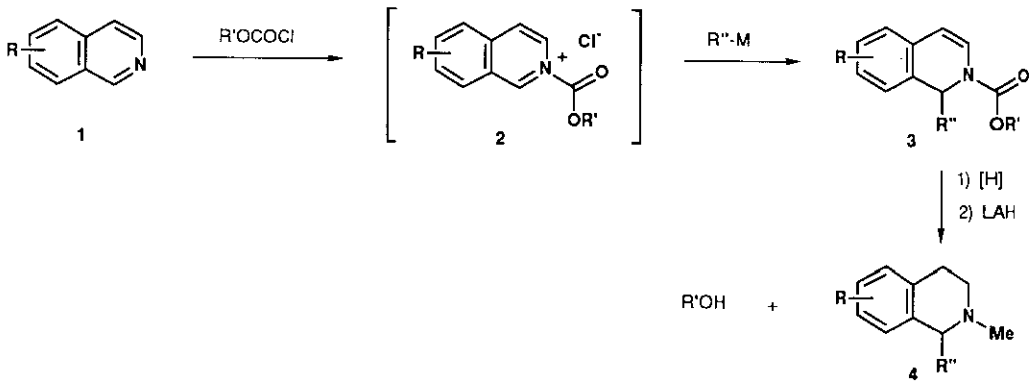
NUCLEOPHILIC ADDITION TO HOMOCHIRAL *N*-ACYLISOQUINOLINIUM SALTS. ASYMMETRIC SYNTHESIS OF (+)-CARNEGINE

Daniel L. Comins* and Mohamed M. Badawi
Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204, USA

Abstract - The asymmetric addition of methyl nucleophiles to homochiral *N*-acylisoquinolinium salts was studied and utilized in a synthesis of the tetrahydroisoquinoline alkaloid, (+)-carnegine.

Analogous to the pyridine series,[1] isoquinolines (**1**) react with chloroformates to form *N*-acylisoquinolinium salts (**2**), which are attacked by nucleophiles, i.e. Grignard reagents, to give dihydroisoquinolines (**3**).[2] Subsequent reduction of the double bond and the carbamate group would give 1,2,3,4-tetrahydroisoquinolines

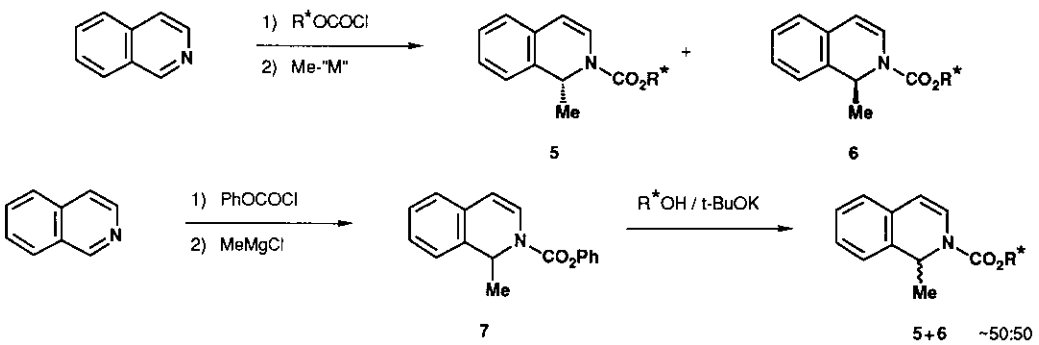


(**4**), a class of heterocyclics of considerable interest due to their abundance in nature and their biological activity.[3]

The use of a homochiral chloroformate to prepare **2** in situ appeared to have potential for imparting some diastereofacial differentiation during the nucleophilic addition step. Once developed, this chiral auxiliary mediated procedure could be used to prepare tetrahydroisoquinolines (**4**) in an enantioselective manner.[4] Prompted by our recent results on the diastereoselective addition of Grignard reagents to homochiral 1-acylpyridinium salts,[5] we examined the addition of methyl nucleophiles to chiral *N*-acyl salts of isoquinolines.

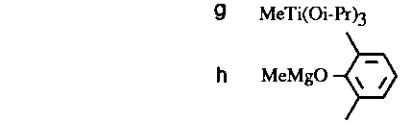
The chiral *N*-acyl salt was prepared in situ by the addition of (-)-8-phenylmenthyl chloroformate[5] to

isoquinoline in THF or toluene (-23°C, 30 min). Addition of a methyl nucleophile gave a mixture of diastereomers (**5**) and (**6**) as shown in Table I. To accurately determine the diastereoselectivity of the Grignard reaction, a 50:50 mixture of **5** and **6** was prepared. Isoquinoline was treated with phenyl chloroformate and then methylmagnesium chloride to give the dihydroisoquinoline (**7**) in 89% yield. Reaction of **7** with the potassium salt of (-)-8-phenylmenthol in THF effected a carbamate exchange providing a 51:49 mixture of **5** and **6** in 79% yield.



Of the classical methyl Grignard reagents, methylmagnesium iodide gave the best result effecting an 80% yield and 64% de (entry f). Two attempts at raising the asymmetric induction by increasing the bulk of the

Table I. Diastereoselective synthesis of **5** and **6** (R^* = (-)-8-phenylmenthyl)

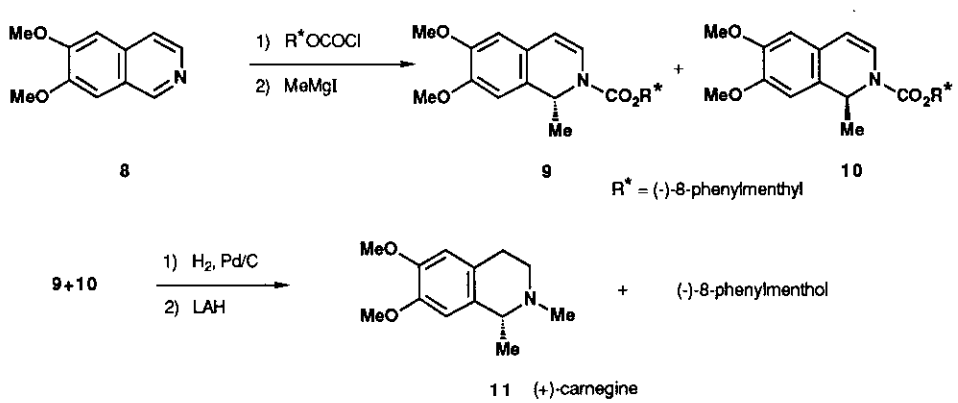
Entry[a]	R-M	Solvent	Temp °C	Yield[b]	Diastereomeric Ratio[c]
a	MeMgCl	THF	-23	76	77:23
b		THF	-78	48	71:29
c		Toluene/THF	-23	71	82:18
d		Toluene/THF	-78	24	86:14
e	MeMgI	THF	-23	80	80:20
f		Toluene/THF	-23	80	82:18
g	$MeTi(Oi\text{-}Pr)_3$	THF	-23	79	78:22
h		Toluene/THF	-23	36	78:22

[a] The reactions were generally performed on a 1.0-mmol scale. After addition of R-M, the mixture was stirred for 2 h at the indicated temperature and quenched with 20% aqueous ammonium chloride. [b] Yield of purified products (**5** + **6**) obtained as a mixture from radial preparative layer chromatography. [c] The diastereomeric ratio was determined by hplc (silica gel, EtOAc/hexanes).

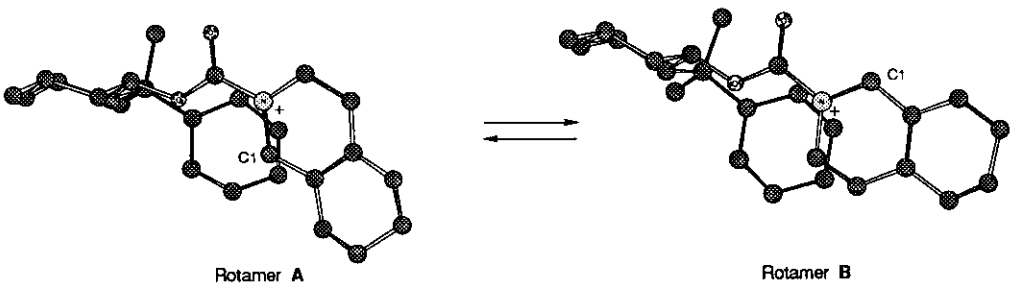
nucleophile were unsuccessful. Methyltitanium triisopropoxide[6] added to the *N*-acylisoquinolinium salt at the desired position but with only 56% de (entry g). A bulky, modified[7] methyl Grignard reagent gave a similar result (entry h).

Several (-)-8-arylmenthols have been prepared and studied as chiral auxiliaries for various asymmetric reactions.[8,9] The menthol derivative (-)-8-(4-phenoxyphenyl)menthol has been shown to be a more effective chiral auxiliary than (-)-8-phenylmenthol in certain diastereoselective processes.[9] The chloroformate of (-)-8-(4-phenoxyphenyl)menthol ($COCl_2$, quinoline, toluene, room temperature) was treated with isoquinoline and methyl Grignard (THF, -23°C) to give the diastereomeric products (**5**) and (**6**) (R* = (-)-8-(4-phenoxyphenyl)menthyl) in 56% yield and 46% de. It is not clear at this time why the bulkier chiral auxiliary is less effective in this asymmetric reaction.[10]

To test if this asymmetric synthesis could be used to prepare naturally occurring 1,2,3,4-tetrahydroisoquinolines in an enantioselective manner, and to determine the absolute configuration of the newly formed stereogenic center in the major diastereomer (Table I), we carried out a synthesis of carnegine (**11**). Reaction of (-)-8-phenylmenthyl chloroformate, 6,7-dimethoxyisoquinoline[11] (**8**) and methylmagnesium iodide (toluene/THF, -23°C) gave an 82% yield of diastereomers (**9**) and (**10**) in a ratio of 78:22. The diastereomeric ratio could be increased to 83:17 by performing the reaction at -78°C, but the chemical yield was reduced to 26%. A mixture of **9** and **10** (81:19) was reduced by catalytic hydrogenation to give the corresponding tetrahydro intermediates (95%), which on treatment with LAH (THF, reflux, 8 h) afforded (+)-carnegine (**11**)[12] (65%) [$[\alpha]_D^{21}$ + 30.0° (c 3.2, benzene)] and (-)- 8-phenylmenthol (71%). Based on the literature,[13] our (+)-carnegine is 62% optically pure with the major enantiomer possessing the R configuration.



Two low-energy "reactive conformations" of the intermediate *N*-acylisoquinolinium salt are depicted below as rotamers **A** and **B**. There appears to be very little energy difference between these conformations,[14] which



Rotamer **A** Rotamer **B**

indicates an additional factor must be responsible for the observed diastereoselectivity. Since "reactive conformation" **A** would lead to the observed major diastereomer, it seems reasonable that π-π interaction between the phenyl ring of the chiral auxiliary and the electron-deficient azomethine bond at C1 of **A** stabilizes the transition state.[15] Additional studies on the mechanism and scope of this asymmetric synthesis are in progress.

ACKNOWLEDGMENT

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