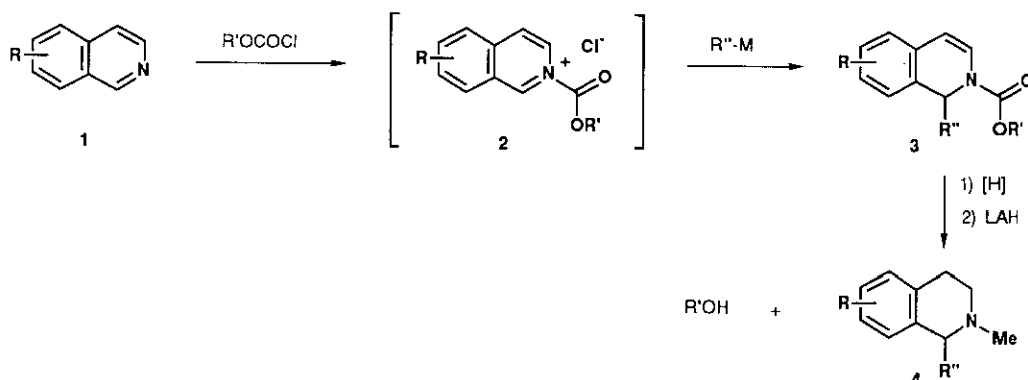


NUCLEOPHILIC ADDITION TO HOMOCHIRAL *N*-ACYLISOQUINOLINIUM SALTS.  
ASYMMETRIC SYNTHESIS OF (+)-CARNEGINE

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

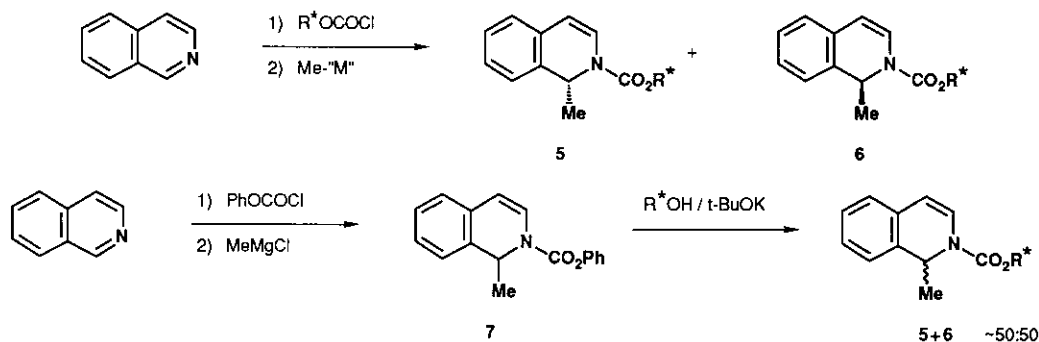


(**4**), a class of heterocyclics of considerable interest due to their abundance in nature and their biological activity.<sup>3</sup>

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.<sup>4</sup> Prompted by our recent results on the diastereoselective addition of Grignard reagents to homochiral 1-acylpyridinium salts,<sup>5</sup> 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<sup>5</sup> 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)

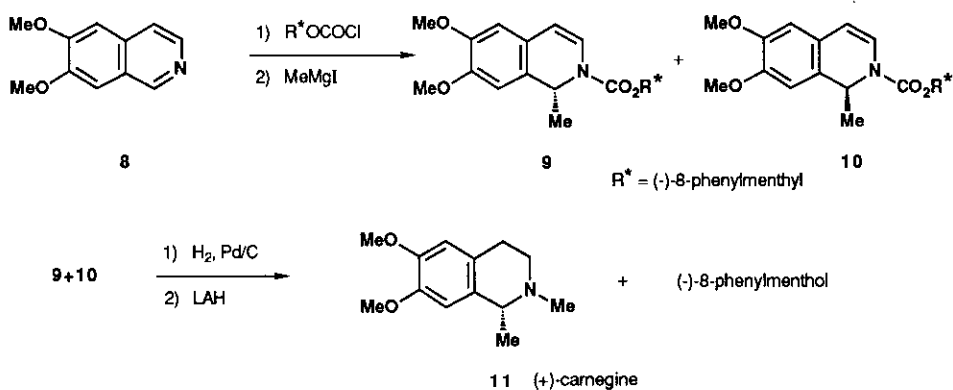
Entry <sup>a</sup>	R-M	Solvent	Temp °C	Yield <sup>b</sup>	Diastereomeric Ratio <sup>c</sup>
a	MeMgCl	THF	-23	76	77:23
b		THF	-78	48	71:29
c		Toluene/THF	-23	71	82:18
d		Toluene/THF	-78	24	86:14
e	MeMgI	THF	-23	80	80:20
f		Toluene/THF	-23	80	82:18
g	MeTi(Oi-Pr) <sub>3</sub>	THF	-23	79	78:22
h	MeMgO 	Toluene/THF	-23	36	78:22

<sup>a</sup> 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. <sup>b</sup> Yield of purified products (**5** + **6**) obtained as a mixture from radial preparative layer chromatography. <sup>c</sup> The diastereomeric ratio was determined by hplc (silica gel, EtOAc/hexanes).

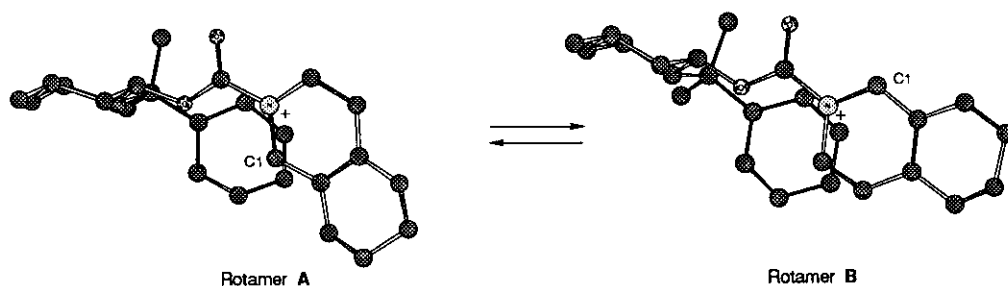
nucleophile were unsuccessful. Methyltitanium triisopropoxide<sup>6</sup> added to the *N*-acylisoquinolinium salt at the desired position but with only 56% de (entry g). A bulky, modified<sup>7</sup> methyl Grignard reagent gave a similar result (entry h).

Several (-)-8-arylmenthols have been prepared and studied as chiral auxiliaries for various asymmetric reactions.<sup>8,9</sup> The menthol derivative (-)-8-(4-phenoxyphenyl)menthol has been shown to be a more effective chiral auxiliary than (-)-8-phenylmenthol in certain diastereoselective processes.<sup>9</sup> The chloroformate of (-)-8-(4-phenoxyphenyl)menthol (COCl<sub>2</sub>, 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.<sup>10</sup>

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<sup>11</sup> (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)<sup>12</sup> (65%) [ $[\alpha]_D^{21} + 30.0^\circ$  (c 3.2, benzene)] and (-)-8-phenylmenthol (71%). Based on the literature,<sup>13</sup> 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,<sup>14</sup> which



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  $\pi$ - $\pi$  interaction between the phenyl ring of the chiral auxiliary and the electron-deficient azomethine bond at C1 of A stabilizes the transition state.<sup>15</sup> Additional studies on the mechanism and scope of this asymmetric synthesis are in progress.

#### ACKNOWLEDGMENT

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