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DIASTEREOSELECTIVE ADDITION OF ORGANOMETALLIC REAGENTS TO CHIRAL IMINIUM IONS: SYNTHESIS OF (*S*)-(+)-CRYPTOSTYLINE I.

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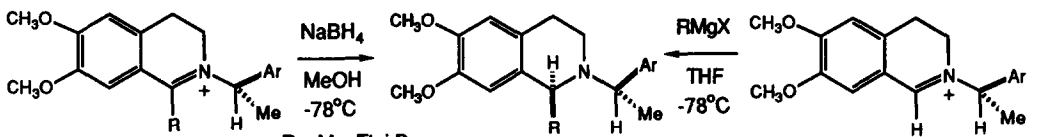
Abstract: Iminium ion **2c** participates in stereoselective nucleophilic addition reactions with Grignard reagents. Analysis of the products from reaction of 5-hexenylmagnesium bromide with iminium ion **2a** suggests that these reactions proceed by a polar (two electron) mechanism. The utility of this chemistry is demonstrated in a stereospecific synthesis of (*S*)-(+)-cryptostyline I.

We are interested in determining the factors which influence the sense and extent of stereoselection associated with the addition of various nucleophiles to iminium ions. Previous publications from these laboratories[1] have revealed that iminium ions **1a-c** undergo highly stereoselective hydride reduction with $NaBH_4$ in methanol to afford (1*S*)-1,2-disubstituted-1,2,3,4-tetrahydroisoquinolines. This letter describes complementary experiments involving nucleophilic addition of organometallic reagents to iminium ions **2a-c**.

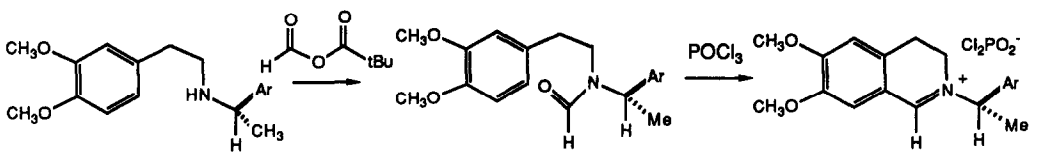


1a: Ar = Ph
1b: Ar = 2-ClPh
1c: Ar = 2,6-Cl_2Ph

3

2a: Ar = Ph
2b: Ar = 2-ClPh
2c: Ar = 2,6-Cl_2Ph

Iminium ions **2a-c** were prepared by a two step procedure involving formylation of amines[1] **4a**, **4b**, or **4c** with formyl pivalyl anhydride[2] followed by refluxing the resultant formamides in a mixture of phosphorus oxytrichloride and benzene.[1] We focused our attention on the study of addition of Grignard reagents to iminium ions **2a-c**, since other common alkyl organometallic reagents expressed approximately the same extent of diastereoselection[3] in their reaction with **2a**. The results of the Grignard reagent addition experiments are presented in Table 1.

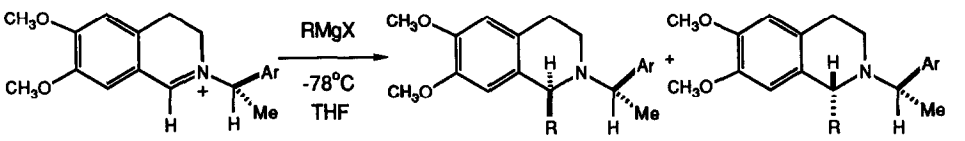


4a: Ar = Ph
4b: Ar = 2-ClPh
4c: Ar = 2,6-Cl_2Ph

Ar = Ph (96%)
Ar = 2-ClPh (95%)
Ar = 2,6-Cl_2Ph (97%)

2a: Ar = Ph
2b: Ar = 2-ClPh
2c: Ar = 2,6-Cl_2Ph

Table 1



2a-c **D_1** **D_2**

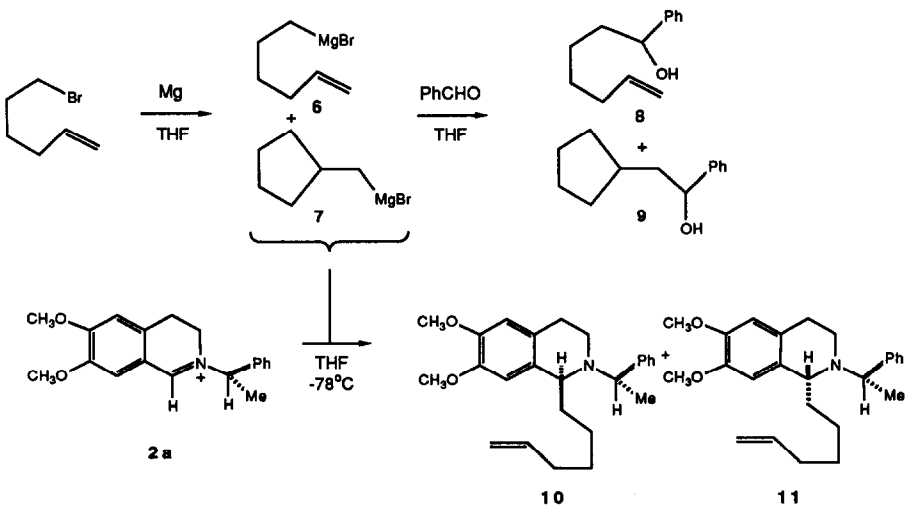
Ar	Substrate	RMgX[a]	D_1:D_2[b]	(%)[c]
Ph	(2a)	MeMgBr	58:42	(82)
Ph	(2a)	EtMgBr	77:23	(82)
Ph	(2a)	i-PrMgCl	58:42	(81)
Ph	(2a)	i-BuMgBr	58:42	(82)
2-ClPh	(2b)	MeMgBr	54:46[d]	(84)
2-ClPh	(2b)	EtMgBr	78:22	(86)
2-ClPh	(2b)	i-PrMgCl	74:26	(78)
2-ClPh	(2b)	i-BuMgBr[e]	61:39	(90)
2,6-Cl_2Ph	(2c)	MeMgBr	85:15	(89)
2,6-Cl_2Ph	(2c)	EtMgBr	94:6	(85)
2,6-Cl_2Ph	(2c)	i-PrMgCl	98:2	(83)
2,6-Cl_2Ph	(2c)	i-BuMgBr	87:13	(88)

a: Reaction performed in THF at -78°C. b: Analytical ratios were determined by HPLC on 5 μ silica with UV detection (254 nm). c: All yields are for material purified by liquid chromatography and represent yields for cyclization-nucleophilic addition starting from the formamides. d: Ratio determined by 300 MHz ^{1}H NMR. e: Reaction performed in CH_2Cl_2 at -78°C.

Both iminium ions **2a** (Ar=Ph) and **2b** (Ar=2-ClPh) displayed only marginal stereoselectivity in their reactions with the various Grignard reagents. Iminium ion **2c** (Ar=2,6-Cl_2Ph) expressed good to excellent levels of diastereoselection in its reactions with the Grignard reagents. The ratio of diastereomeric products obtained in each reaction was determined by analytical HPLC. The configuration of the newly generated stereogenic center in the products D_1 and D_2 was determined by direct comparison with known compounds[1] or by analogy (R=*i*-Bu, Ar=Ph,2-ClPh, 2,6-Cl_2Ph).[4]

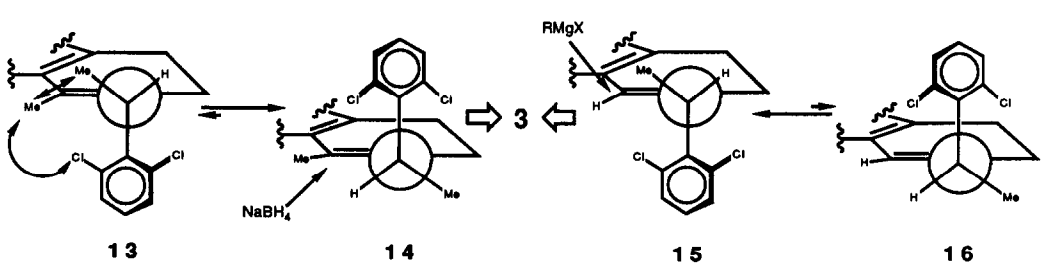
An interesting observation emerging from these experiments is that the major diastereoisomer resulting from either hydride reduction of **1a-c** or Grignard addition to **2a-c** is **3**. This surprising result can be attributed to either a change in reaction mechanism or a change of substrate geometry in the transition state of the nucleophilic addition reaction as the character of the substrate and/or nucleophile changes. Thus, one possible explanation of the apparently conflicting results is that one process occurs by a polar mechanism and the other by a path involving single electron transfer. In order to gain insight into this question, the radical probe 5-hexenylmagnesium bromide[5] was reacted with iminium ion **2a**.

1-Bromo-5-hexene has been reported to undergo cyclization to cyclopentylmethylmagnesium bromide to the extent of 4-13% during formation of the Grignard reagent.[5b,6] We assayed the ratio of **6**:**7** by addition of the Grignard solution to benzaldehyde, and analysis of the reaction products by capillary GC. The ratio of **8**:**9** and hence **6**:**7** was 96:4. Consequently in our experiments, the maximum possible amount of cyclization of 5-hexenyl bromide which occurred during formation of the Grignard reagent was 4%. Addition of an aliquot of this same solution to iminium ion **2a** resulted in an 86% isolated yield of diastereomeric adducts **10** and **11**. We independently reacted cyclopentylmethyllithium[7] with **2a** and obtained the expected addition products. We were not able to detect either diastereomer of cyclopentylmethyl adducts in the unfractionated mixture obtained from 5-hexenylmagnesium bromide addition to **2a**. We conclude that addition of Grignard reagents to iminium ions



2a-c occurs by a polar (two electron) process, or that if single electron transfer does occur, combination of the resultant caged radical pair occurs faster than 10^5 s^{-1}.

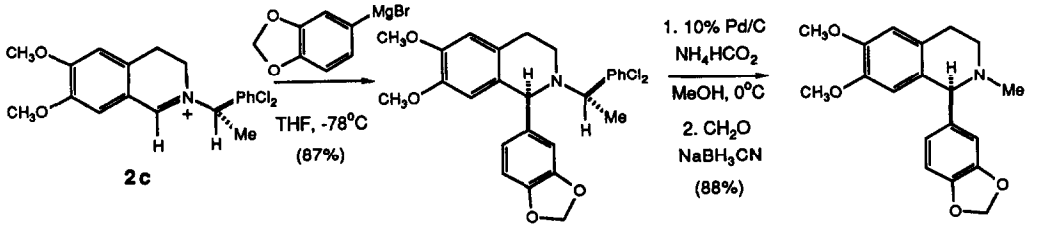
Table 1 reports that the extent of stereoselection observed in the addition of Grignard reagents to iminium ions **2a-c** is significant only for substrate **2c**. The precision of stereoselection of hydride reduction[1] of iminium ions **1a-c** is highest for substrate **1c**. Assuming both sets of reactions proceed by polar mechanisms, this data can be accommodated by presuming that nucleophilic addition occurs preferentially to certain select "reactive conformations" of each substrate. These "reactive conformations" provide maximum transition state stabilization by orbital overlap between the iminium ion π^* orbital and a suitably aligned σ^* orbital linking the stereogenic center and the 2,6-dichlorophenyl moiety.[8,9] We presume that Curtin-Hammett kinetics are operative, and that such conformers react faster than others due to a stabilizing stereo**electronic** effect expressed in the transition state of the nucleophilic addition reaction.[9] In order to assess the intramolecular **steric** effects present in the two competing "reactive conformations" available to either **1c** or **2c**, molecular mechanics calculations of conformers **13** and **14** (models for **1c**) and **15** and **16** (models for **2c**) were performed.[10] (Conformer **14** was calculated[10] to be 4.4 kcal/mol more stable **13**, conformer **15** was calculated[10] to be 0.5 kcal/mol more stable than **16**.) The structure of the transition state of these addition reactions thus appears to resemble a geometry approximated by nucleophilic attack on the least hindered face of the more stable "reactive conformation" of each substrate. We reason that within each pair of "reactive



conformations", the non-bonded repulsions and other strain factors of the most stable conformation are minimized. Since the transition state is sensitive to these same non-bonded repulsions it seems reasonable that the transition state in which these repulsions are minimized will also be more stable.[11]

Finally, 3,4-methylenedioxyphenyl magnesium bromide reacted with chiral iminium ion **2c** to afford a single diastereo-

meric adduct in 87% yield. Hydrogenolytic removal of the chiral directing group[12] (97%) followed by *N*-methylation[13] (91%) afforded (*S*)-(+)-cryptostyline I: $[\alpha]_D$ 56° (*c* 1.8, $CHCl_3$); lit.[14] $[\alpha]_D$ 56° (*c* 2.7, $CHCl_3$).



These results in conjunction with the data in Table 2 indicate that nucleophilic addition to substrates **2** occurs with practical levels of stereoselection only for substrate **2c** and only with secondary or aryl Grignard reagents. Nevertheless, the chemistry provides access to chiral 1-aryl-1,2,3,4-tetrahydroisoquinolines, and as such complements other very elegant methods.[15]

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10. MM2 parameters for iminium ions do not currently exist. Iminium ion conformers **13-16** were modeled with olefinic counterparts (replace nitrogen with carbon) in molecular mechanics calculations (MM2 87).
11. Limited evidence in support of the hypothesis that these reactions are governed by iminium ion structure and not either the solvent or the structure of the nucleophile was provided by reaction of the very nucleophilic $LiEt_3BH$ with **1a** in THF at -78°C which afforded **3** (R=Me) as the major product (D_1:D_2 of 80:20).
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