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Lewis Acid-Mediated Nucleophilic Alkylations on Chiral [6,3a,4]Oxadiazaindano[5,4-*a*]isoquinolines. Asymmetric Synthesis of 1-Alkyl Substituted Tetrahydroisoquinolines

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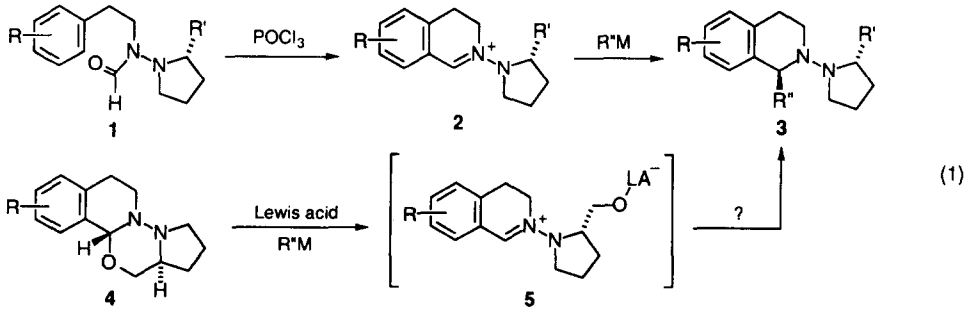
Abstract: Lewis acid-mediated nucleophilic alkylation of the chiral [6,3a,4]oxadiazaindano[5,4-*a*]isoquinoline derivatives with various organometallic reagents leads to highly enantioselective synthesis of 1-alkyl substituted tetrahydroisoquinolines. This methodology was applied to the asymmetric synthesis of (–)-salsolidine and (+)-*O*-methylarmepavine. Copyright © 1996 Elsevier Science Ltd

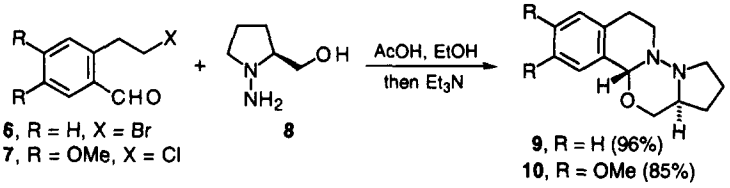
Due to widespread occurrence in nature and marked physiological action, 1-substituted tetrahydroisoquinoline alkaloids have long offered intensive targets for synthesis.[1] In this regard, the enantioselective construction of 1-substituted tetrahydroisoquinolines has attracted growing attention in the last decade.[2] We have recently described[3] the efficient enantioselective synthesis of 1-alkyl and 1-aryl substituted tetrahydroisoquinolines based on nucleophilic addition to chiral "hydrazonium ions"[4] **2** generated by Bischler–Napieralski reaction (eq 1), and demonstrated the application to the synthesis of various tetrahydroisoquinoline alkaloids. In an extension of this hydrazonium strategy, we envisioned another pathway to generate chiral hydrazonium ions **5** via cleavage of cyclic N–O acetals **4** due to preferential coordination of Lewis acids with the oxygen atom, leading to **3** with inversion of the C-1 configuration as hypothetically depicted in eq 1. Herein we detail our observations on the asymmetric alkylation of tetrahydroisoquinolines using unusual chiral tetracyclic heterocycles, namely (11b*R*,13a*S*)-2,3,7,11b,13,13a-hexahydro-1*H*,6*H*-[6,3a,4]oxadiazaindano[5,4-*a*]isoquinolines **4**, with organometallic reagents, and report application of a developed method to the enantioselective synthesis of alkaloids.



(1)

The required chiral [6,3a,4]oxadiazaindano[5,4-*a*]isoquinolines **9** and **10** were readily obtained in 96% and 85% yield, respectively, as single isomers by treating the *o*-(2-haloethyl)benzaldehydes **6** and **7** with (*S*)-1-amino-2-pyrrolidinemethanol (**8**) according to the Yamato's method[5] (Scheme 1). The stereochemistry at C-11b and a cis A/B ring junction in **9** were unambiguously assigned by ^{1}H NMR NOE experiments (Figure 1).

Scheme 1



6, R = H, X = Br
7, R = OMe, X = Cl

8

9, R = H (96%)
10, R = OMe (85%)

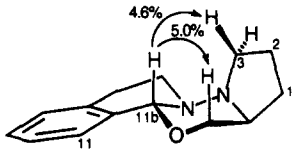


Figure 1. Selected NOEs of **9** at 400 MHz ^{1}H NMR.

On the chiral 1,3,4-oxadiazine derivative **9** thus obtained, nucleophilic addition of organometallic reagents for alkylation at C-11b was first examined without addition of Lewis acids (Table 1). The methyl and benzyl Grignard reagents (4.0 equiv) reacted at 0 °C, affording the diastereomeric adducts **11a/12a** and **11b/12b**, respectively, with poor retentive diastereoselection (61:39 and 57:43, entries 1 and 2, respectively).[6] The retentive selectivity was remarkably enhanced to 97:3 when the triisopropoxy organotitanium (4.0 equiv) was used at room temperature (entry 3). The use of 1.1 equiv of trimethylaluminum gave a poor retentive selectivity (55:45, entry 4) as by the Grignard reagents. However, more interestingly, when 3.0 equiv of trimethylaluminum was used, the stereochemical outcome was turned over to be inversive manner, affording a 19:81 mixture of the diastereomers **11a/12a** in favor of the inversive adduct **12a** (entry 5).

9

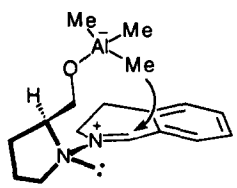
11a, R = Me
11b, R = Bn

12a, R = Me
12b, R = Bn

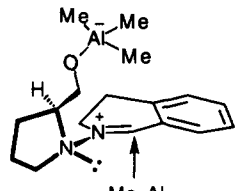
Table 1. Nucleophilic alkylation of the chiral [6,3a,4]oxadiazaindano[5,4-*a*]isoquinoline derivative **9**.

Entry	Nucleophile (equiv)	Solvent	Temperature	Products	Ratio[a]	Yield, %[b]
1	MeMgBr (4.0)	THF	0 °C	**11a/12a**	61 : 39	68
2	BnMgBr (4.0)	THF	0 °C	**11b/12b**	57 : 43	95
3	BnTi(O*i*-Pr)$_3$ (4.0)	THF	rt	**11b/12b**	97 : 3	73
4	Me_3Al (1.1)	$CHCl_3$	rt	**11a/12a**	55 : 45	92
5	Me_3Al (3.0)	$CHCl_3$	rt	**11a/12a**	19 : 81	81

[a]Determined by HPLC analysis. [b]Isolated yield of the diastereomeric mixture.



A (1.1 equiv of Me_3Al)

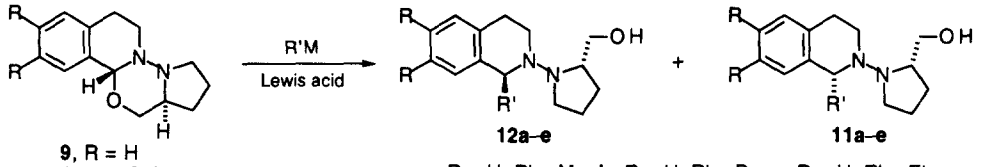


B (3.0 equiv of Me_3Al)

The reversal of the stereoselectivity of retention and inversion brought about by the stoichiometry of the organoaluminum reagent is possibly accounted for by assuming hydrazonium transition state models **A** and **B**, both arising from cleavage of the N–O acetal to form tight ion pairs between the aluminum ate complex and the hydrazonium ion. In the case of using 1.1 equiv of Me_3Al (entry 4), as illustrated by **A** the hydrazonium ion pair may lead to internal alkyl delivery to produce the retentive diastereomer **11a**. On the other hand, since the

alkyl aluminum reagents can act as an acid-base complexed agents,[7] when 3.0 equiv of Me_3Al was employed (entry 5) 1 equiv of the reagent would serve to form the hydrazonium ion pair which may undergo external nucleophilic attack by the remaining reagent as illustrated by **B** in a manner similar to that proposed by us previously.[3] Thus, facial selectivity may arise from the pyramidal stability of the trivalent nitrogen in the auxiliary pyrrolidine ring, leading to the preferential formation of the inversive diastereomer **12a**.

The above observation associated with inversive stereoselection with Me_3Al as an acid-base complexed agent prompted us to carried out the inversive alkyl introduction to the tetrahydroisoquinoline with organometallic reagents in the presence of Lewis acids. Thus, the 1,3,4-oxadiazine derivative **9** or **10** was precomplexed with Lewis acids [$Al(t\text{-}BuO)_3$, Et_2AlCl, $BF_3{\cdot}Et_2O$] and allowed to react with organometallic reagents. As expected, all the reactions under Lewis acid conditions resulted in the preferential formation of the inversive diastereomers **12a–e** with good to excellent stereoselectivity (Table 2).



9, R = H
10, R = OMe

12a–e

11a–e

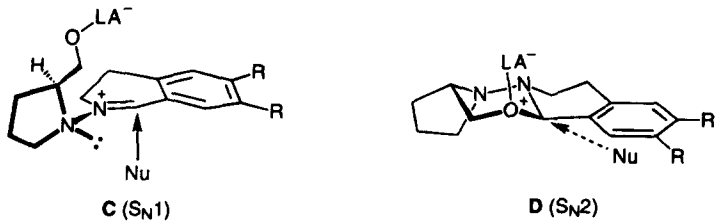
a, R = H, R' = Me; **b**, R = H, R' = Bn; **c**, R = H, R' = Et;
d, R = OMe, R' = Me; **e**, R = OMe, R' = *p*-$MeOC_6H_4CH_2$

Table 2. Nucleophilic alkylation of the chiral [6,3a,4]oxadiazaindano[5,4-*a*]isoquinoline derivatives **9** and **10** in the presence of Lewis acids.

Entry	Compd	R'M (equiv)	Lewis acid (equiv)	Solvent	Temp, °C	Products	Ratio[a]	Yield, %[b]
1	**9**	MeLi (3)	$Al(t\text{-}BuO)_3$ (1.5)	Et_2O	20	**12a/11a**	76 : 24	61
2	**9**	MeMgBr (4)	Et_2AlCl (4)	THF	−70	**12a/11a**	91 : 9	95
3	**9**	Me_2CuLi (4)	$BF_3{\cdot}Et_2O$ (4)	Et_2O	−50	**12a/11a**	90 : 10	69
4	**9**	EtMgBr (4)	Et_2AlCl (4)	THF	−95	**12c/11c**	96 : 4	83
5	**9**	BnMgCl (4)	Et_2AlCl (4)	THF	−95	**12b/11b**	97 : 3	96
6	**10**	MeMgBr (4)	Et_2AlCl (4)	THF	−80	**12d/11d**	95 : 5	86
7	**10**	$ArCH_2MgCl$[c] (2)	Et_2AlCl (4)	THF	−80	**12e/11e**	>99 : 1	76

[a]Determined by HPLC analysis. [b]Isolated yield of the diastereomeric mixture. [c]Ar = *p*-$MeOC_6H_4$

The reverse stereochemical results obtained in employing the combination of Lewis acids and organometallic reagents can be explained by an S_N1 mechanism via a hydrazonium ion pair **C**, which closely resembles the stereoselective manner **B** described above on the aluminum ate complex, leading to enantioselective delivery of the alkyl group to the more exposed *si* face of the hydrazonium ion. However, it is a current issue that Lewis acid-mediated nucleophilic substitution of N,O-acetals can occur by iminium ion (S_N1) or direct displacement (S_N2) mechanisms.[8,9,10] Our results observed for the N,O-acetals **9** and **10** are also



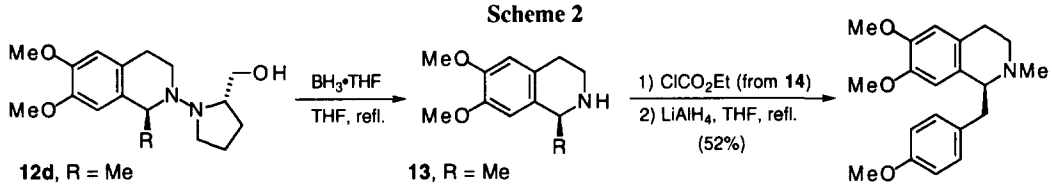
C (S_N1)

D (S_N2)

consistent with an alternate pathway involving the direct nucleophilic displacement of a Lewis acid–ether complex depicted as **D**, thus allowing an inversive alkylation and remaining the possibility of the S_N2 mechanism for the preferential formation of the inversive products **12a–e**.

To demonstrate the synthetic potential of this Lewis acid-mediated asymmetric alkylation, we envisioned alkaloid synthesis by utilizing the enantiomerically pure 1-substituted tetrahydroisoquinoline derivatives. Thus, the inversive diastereomers **12d** and **12e**, both chromatographically separable as single isomers, were subjected to reductive N–N bond cleavage by treatment with BH_3•THF in refluxing THF to furnish (–)-salsolidine (**13**) (58% yield), $[\alpha]^{27}_D$ –58.4 (*c* 0.57, EtOH) [lit.[11] $[\alpha]^{27}_D$ –59.5 (*c* 4.39, EtOH)], and **14** (56% yield), $[\alpha]^{21}_D$ –19.1 (*c* 1.37, $CHCl_3$), respectively. Compound **14**, which is referred to as a vasorelaxant GS-389 (racemate),[12] underwent carbamoylation followed by reduction with $LiAlH_4$, leading to the first enantioselective synthesis of (+)-*O*-methylarmepavine (**15**),[13,14] mp 62–64 °C (hexane); $[\alpha]^{23}_D$ +83.7 (*c* 0.35, $CHCl_3$) [lit.[13] $[\alpha]^{23}_D$ +68.7 (*c* 1.165, $CHCl_3$)], in 52% yield, identical in all respects to the natural alkaloid.

Scheme 2



12d, R = Me
12e, R = *p*-$MeOC_6H_4CH_2$

13, R = Me
14, R = *p*-$MeOC_6H_4CH_2$

15

In conclusion, we have proved that the Lewis acid-mediated nucleophilic alkylation of chiral [6,3a,4]oxadiazaindano[5,4-*a*]isoquinoline derivatives using a variety of organometallic reagents proceeds sufficiently in an excellent inversive diastereoselectivity to furnish some class of 1-alkyltetrahydroisoquinolines. The further application to enantioselective alkaloid synthesis on our strategy is under investigation.

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