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Diastereoselective [4 + 2] Type Cycloaddition of 1-Azatriene Iron-tricarbonyl Complex: Asymmetric Synthesis of a Piperidine Alkaloid

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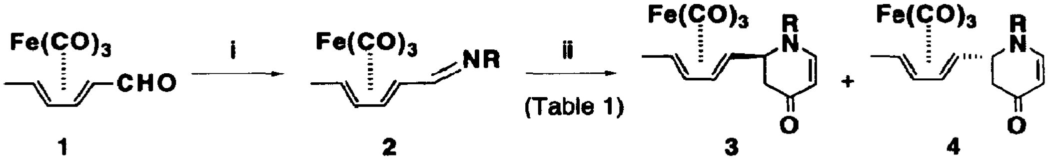
Abstract: A $LiClO_4$ catalyzed cycloaddition reaction of 1-azatriene iron-tricarbonyl complex **2b** with Danishefsky's diene proceeds in highly stereoselective manner to give diastereomerically pure 2-substituted dehydropiperidinone derivative **3b**. The chiral cycloadduct **3b*** is converted into a biologically active piperidine alkaloid SS20846A in 3 steps, by which its absolute configuration is revealed as 2*S*,4*S*.

Construction of nitrogen heterocycles through the use of imine-dienophiles in [4 + 2] type cycloadditions has received much attention in recent times.[1] The use of Lewis acids to counteract the low reactivity has further increased their potential in synthesis.[2] The majority of the reported investigations on this topic have dealt with the diastereoselectivity with C-1 or C-2 substituted chiral dienes[3] and chirally modified dienophiles derived from chiral aldehydes[4] or chiral amines[5], although Lewis acids have also received increasing attention as chiral catalysts for asymmetric cycloadditions.[6]

Our own investigation in this area focuses on the stereodirecting potentiality of **2** as the chiral dienophile, which was demonstrated as a good acceptor giving rise to single diastereomers of secondary amines in a nucleophilic addition reaction with organometallic reagents.[7] In this paper, we wish to describe a diastereoselective [4 + 2] type cycloaddition reaction of **2** with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) mediated by a catalytic amount of lithium perchlorate ($LiClO_4$) suspended in dichloromethane (CH_2Cl_2).

The imine-complex **2a-d** were prepared by condensation of the racemic dienal complex **1**[7] and the corresponding amines. The [4 + 2] type cycloaddition of the benzylimine complex **2a** with Danishefsky's



Scheme 1: i) RNH_2, MS 3A, benene; ii) Danishefsky's diene, Lewis Acid (see Table 1)
a: R = Bn, b: R = *p*-$MeOC_6H_4$, c: R = Ph, d: R = *p*-ClC_6H_4

Table 1. [4 + 2] type cycloaddition reaction of 1-azatriene iron-tricarbonyl complexes **2b-d** mediated by Lewis acids

entry	substrate	reaction conditions	yield[a] (%)	d.e. (**3** / **4**)
1	**2b**	$AlCl_3$ (1.1 eq.), CH_2Cl_2, -78 °C → -30 °C, 6 h	59	63[b]
2		$AlCl_3$ (0.2 eq.), CH_2Cl_2, -78 °C → -30 °C, 6 h	28	45[b]
3		TMSOTf (1.1 eq.), CH_2Cl_2, -78 °C → -30 °C, 8 h	77	74[b]
4		$LiClO_4$ (5 M solution), ether, r.t., 1 h	89	86[b]
5		$LiClO_4$ (2.0 eq.), CH_2Cl_2, r.t., 3 h	87	81[b]
6		$LiClO_4$ (1.1 eq.), CH_2Cl_2, r.t., 3 h	80	> 95[b]
7		$LiClO_4$ (0.2 eq.), CH_2Cl_2, r.t., 8 h	93	> 95[b]
8		$LiClO_4$ (0.2 eq.), THF, r.t., 8 h	73	77[b]
9	**2c**	$AlCl_3$ (1.1 eq.), CH_2Cl_2, -78 °C → -30 °C, 6 h	70	30[c]
10		$LiClO_4$ (0.2 eq.), CH_2Cl_2, r.t., 2 h	92	81[c]
11	**2d**	$LiClO_4$ (0.2 eq.), CH_2Cl_2, r.t., 0.5 h	82	79[c]

[a] Isolated yields of cycloadducts **3** and **4**. [b] Deduced from the 500MHz ^{1}H-NMR spectra of the diastereomeric mixture. [c] Determined from the isolated yields.

diene mediated by several Lewis acids was sluggish and resulted in recovery of the aldehyde **1** along with small amount of desired products **3a** and **4a**. On the other hand, treatment of the more reactive aromatic imine complexes **2b-d** under the above reaction conditions afforded the desired cycloadducts **3b-d**[8] and **4b-d** in reasonable yields. Some examples are listed in Table 1. The table suggests that (1) employment of a catalytic amount of $LiClO_4$ in CH_2Cl_2[9] gave the best selectivity than that of 5 molar solutions of $LiClO_4$ in ether[10] and stoichiometric amount of conventional Lewis acids (e.g. $ZnCl_2$,[11] TMSOTf[12]) and (2) electron-donating groups on the aromatic ring of the aldimines enhances the stereoselectivity (p-$MeOC_6H_4$ > Ph > p-ClC_6H_4), whereas reaction rate of the cycloaddition tends to decrease (entry 7, 10 and 11).

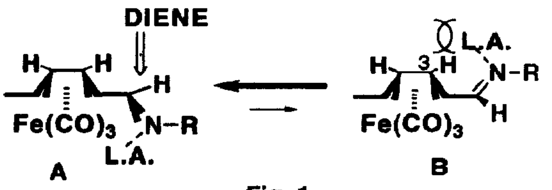
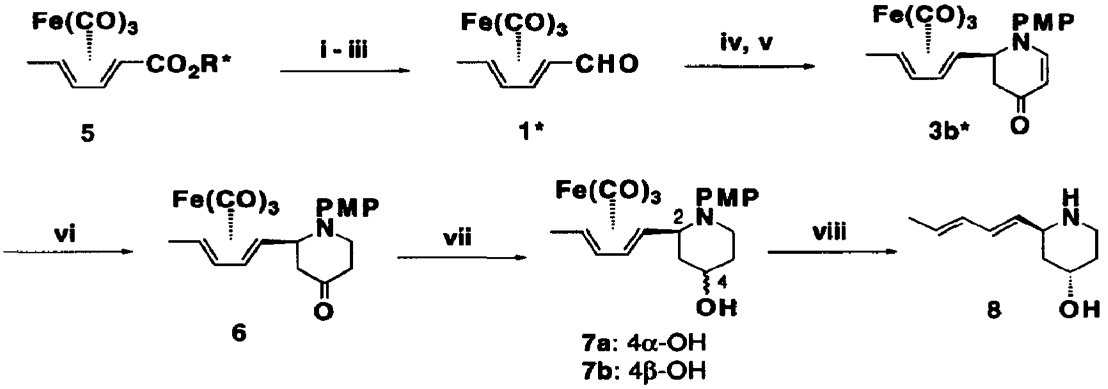


Fig. 1

From the stereochemical outcome of the major products, reaction process should be described as follows in analogy to the nucleophilic addition of organometals (Fig. 1).[7] In the presence of Lewis acids, transoid conformation **A** is considered to be more stable than cisoid one **B** owing to the severe steric repulsion between the substituents of nitrogen and vinyl-proton at C-3. Consequently, the diene should approach preferentially from the *re*-face of the C=N bond in conformation **A** and the (6*SR*,7*RS*)-diastereomers **3b-d** are predominantly obtained.[13] The difference of diastereoselectivity demonstrated by the Lewis acids employed might be attributed to their ability of chelation to the imine which influenced to the equilibrium of conformation **A** and **B** in a transition state.

The practicability of the new method is illustrated by the following asymmetric synthesis of SS20846A, which was isolated from *Streptomyces* sp. S20846 and has a restrictive action upon the digestive system.[14] For this purpose, chiral non-racemic cycloadduct **3b*** was synthesized from the known chiral



Scheme 2: i) KOH, EtOH, H_2O, reflux (89%); ii) $(COCl)_2$, CH_2Cl_2, 0 °C; iii) $(PPh_3)_2CuBH_4$, Ph_3P, acetone (81%); iv) *p*-$MeOC_6H_4NH_2$, MS 3A, benzene; v) Danishefsky's diene, cat. $LiClO_4$, CH_2Cl_2 (93%); vi) L-Selectride, CH_2Cl_2, -78 °C (80%); vii) $NaBH_4$, $CeCl_3$•$7H_2O$, MeOH, 0 °C (77%); viii) CAN, CH_3CN, -30 °C (64 %)

complex **5** in 5 steps.[15] Namely, hydrolysis and chlorination of **5** was followed by reduction with $(PPh_3)_2CuBH_4$[16] to give chiral aldehyde **1*** ($[\alpha]_D^{22}$ −112°: c = 0.77, $CHCl_3$)[17] in 72 % overall yield. The desired product **3b***, obtained as a single isomer by the catalytic $LiClO_4$ mediated cycloaddition of PMP (*p*-methoxyphenyl)-imine derivative of **1***, was reduced by L-Selectride to give rise to 1,4-reduction product **6** in 80 % yield. Subsequently, $NaBH_4$ reduction in methanol in the presence of cerium chloride at 0 °C gave the desired product **7a** as a major product (77 %: **7a** : **7b** = 70 : 30).[18] Finally, simultaneous deprotection of iron-tricarbonyl and PMP-group[19] with CAN furnished SS20846A **8** in 64% yield as an optically active form. The synthetic sample **8** is identical to the natural product as judged by a comparison of their spectral data including the sign of $[\alpha]_D$,[14] which indicates that natural SS20846A ($[\alpha]_D^{20}$ −15°: c = 1.00, $CHCl_3$) has the same (2*S*,4*S*)-configuration as **8** ($[\alpha]_D^{24}$ −15.2°: c = 0.53, $CHCl_3$). Herein we could achieve the first asymmetric synthesis of SS20846A along with the determination of its absolute configuration.

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