Tetrahedron Letters, Vol. 34, No. 38, pp. 6069-6072, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

ABSOLUTELY DIASTEREOSELECTIVE 1,2-NUCLEOPHILIC ADDITION OF ORGANOMETALLIC REAGENTS TO IMINES USING DIENE-IRON TRICARBONYL CHIRALITY

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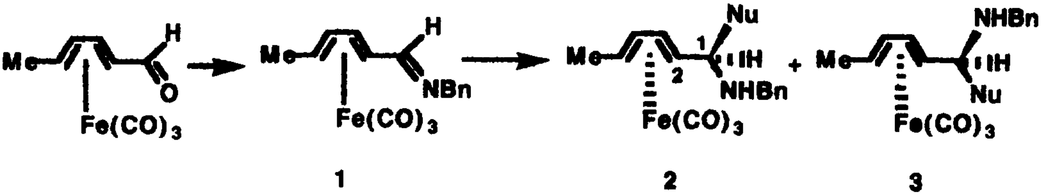
Abstract: 1-Imino-*E*,*E*-butadiene-iron tricarbonyl complex **1** reacts with various organometallic nucleophiles in a stereoselective manner, and especially by use of organocerium reagents, only single diastereomers **2** were obtained in good yields.

Although a lot of literature on the stereoselective 1,2-addition of organometallic reagents to α- and/or β-substituted imines have been reported aiming the synthesis of β-lactam antibiotics and amino acid derivatives, there are few methods exhibiting perfect diastereofacial selectivity independent of the nucleophile's property.[1] Recently, acyclic and functionalized butadiene-iron tricarbonyl complexes have been demonstrated to be valuable intermediates in organic synthesis to construct stereogenic centers utilizing the chirality of iron tricarbonyl moiety.[2] Concerning stereoselectivity of the 1,2-nucleophilic additions to C=O double bond, it has been manifested that organometallic reagents react with dienone complexes stereoselectively,[2g,3] but those reagents generally offer a diastereomixture of the secondary alcohols by the reaction with dienal complexes.[2f,4] The point of this work is whether such addition to imine complexes occurs stereoselectively or not. The high diastereoselectivity opens a route to optically active secondary amines, since optically pure dienal complexes are now available in large scale.[5] Herein we wish to describe the stereoselective nucleophilic addition of organocerium reagents ($RCeCl_2$ or $RMgX\text{-}CeCl_3$) to the 1-imino-*E*,*E*-diene complex **1**, resulting in the (1*RS*,2*RS*)-amine complexes **2**.



a: Nu = n-Bu, b: Nu = allyl, c: Nu = Me, d: Nu = Ph

Table 1. Reaction of Organometallic Nucleophiles with 1-Imino-*E*,*E*-diene Complex 1

entry	organometal	solvent	temperature (°C)	yield[d] (%) 2	3	d. e. (%)
1	*n*-BuLi	THF	-78	0[e]	0[e]	---
2	*n*-BuLi, BBr_3	toluene	-78	46	0	100
3	allylMgBr	ether	-78	40	0	100
4	$(allyl)_2CuMgBr\cdot BF_3$[a]	THF	-78	46	16	48
5	*n*-$BuCeCl_2$[b]	THF	-78	74	0	100
6	$MeCeCl_2$[b]	THF	-78	69	0	100
7	$PhCeCl_2$[b]	THF	-78	57	0	100
8	MeMgBr, $CeCl_3$[c]	THF	-30	70	0	100
9	PhMgBr, $CeCl_3$[c]	THF	-30	95	0	100
10	allylMgBr, $CeCl_3$[c]	THF	-30	79	0	100

a) Prepared from allylmagnesium bromide (3.4 *eq.*), CuI (3 *eq.*), and borontrifluoride etherate (9 *eq.*) according to the procedure of ref. 8a. b) Prepared according to the procedure of ref. 8b. c) Prepared according to the procedure of ref. 8c. d) Isolated yield. e) The reaction gave a complex mixture.

1-Imino-*E*,*E*-diene complex **1** was prepared by the condensation of the known dienal complex[6] and benzylamine in the presence of molecular sieves 4A in benzene at room temperature. The results of 1,2-nucleophilic addition of several organometallics to **1** are summarized in Table 1. Whereas the reaction of **1** with organolithium and Grignard reagent gave **2a**[7] and **2b**[7] in a high diastereoselective manner, respectively, these reagents are not suitable for the aimed reaction because of low chemical yield (entry 2-3). The most successful organometallic reagents in the nucleophilic attack to imines are usually organocopper[8a] and organocerium[8b] derivatives. Therefore, we next examined the reactivity of these none-basic organometallic reagents. None-Lewis acidic allylcopper reagent reacted with **1** smoothly in tetrahydrofuran (THF) at -78°C to afford a separable epimeric mixture of **2b**[7] and **3b**[7] in good yield but with moderate stereoselectivity (entry 4). On the other hand, treatment of **1** with *n*-butylcerium reagent, prepared *in situ* from *n*-butyllithium and cerium(III) chloride, at -78°C for 15 min provided the alkylated secondary amine not only in good yield but also with excellent diastereoselectivity. Similarly, exposure of methyl- and phenylcerium reagents as nucleophiles to **1** provided the corresponding secondary amines **2c**[7] and **2d**[7] in good yields and highly stereoselective manner, respectively (entry 6 and 7). It is worthy to note that organocerium reagents can be replaced by the mixing system prepared from the

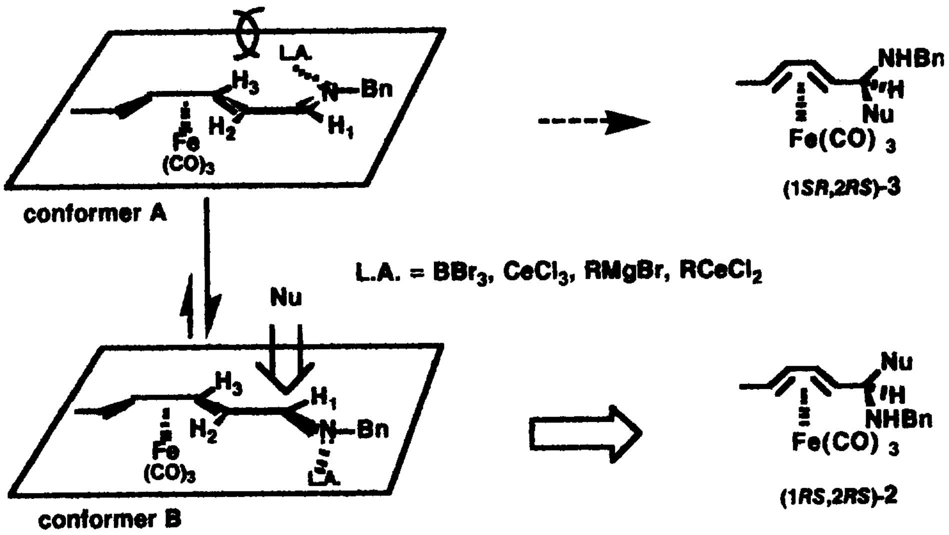


Fig. 1 Reaction Mechanism of Organometallic Addition to the Imine Complex 1

corresponding Grignard reagents (5 *eq.*) and cerium(III) chloride (5 *eq.*) without loss of stereoselectivity (Entry 8-10).[8c]

Such high diastereoselectivity in the presence of Lewis acids such as boron tribromide and cerium(III) chloride, and also Lewis acidic organometals (organomagnesium and organocerium derivatives) in comparison with copper reagents could be explained as follows. Among the two major conformers of 1 (A and B),[9] the chelated complex of conformer B by Lewis acid is more stable than that of conformer A because of severe steric hindrance in the latter case (Fig. 1). Therefore nucleophiles attack from the opposite side of the bulky tricarbonyl iron unit in the chelated conformer B to yield 2 stereoselectively. On the other hand, none Lewis acidic organocopper reagent adds to C=N double bond of both conformers (A and B) from the upper side, resulting in the diastereomixture of 2 and (1*SR*,2*RS*)-amine 3.

In conclusion, considering of the perfect diastereoselectivity and the easy access to both enantiomers of the 1-imino-*E*,*E*-diene-iron complexes, our method might be one of the best tools to synthesize optically active natural products containing nitrogen atom. The asymmetric synthesis of biologically active alkaloids are now undergoing in our laboratory.

Acknowledgement. The present work was partially supported by the Takeda Chemical Industries, Ltd. Foundation and Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

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9) Irradiation of a proton (H_1) led to an increase of the integration of both protons of H_2 and H_3, which means that the imine complex 1 exists as equilibrium mixture of both conformers A and B.

(Received in Japan 3 April 1993; accepted 26 May 1993)