Electronic and Steric Control in Regioselective Addition Reactions of Organolithium Reagents with Enaldimines†

Kiyoshi Tomioka,* Yoshito Shioya, Yasuo Nagaoka, and Ken-ichi Yamada

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida Sakyo-ku, Kyoto 606-8501, Japan

tomioka@pharm.kyoto-u.ac.jp

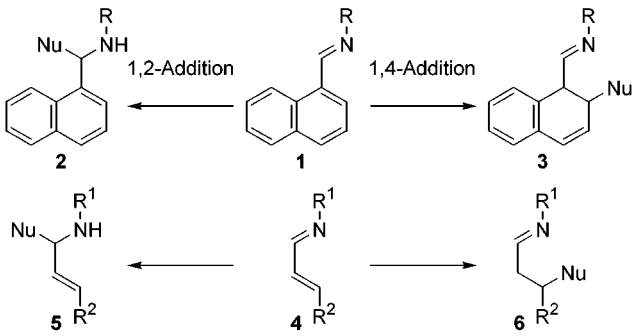
Received May 17, 2001

A reaction mode of imines derived from naphthalene-1-carbaldehyde and acyclic α,β-unsaturated aldehydes with organolitium reagents was dependent on the characteristic nature of a substituent on the imine nitrogen atom. An imine having an electron-withdrawing aryl group on the nirtogen atom behaves as a 1,2-directing imine toward organolithium reagents. In contrast, an imine bearing an alkyl or a bulky aryl group favors 1,4-addition of organolithium reagents. Electronic and steric tuning of a substituent on the imine nitrogen atom for a reaction mode was rationalized on the basis of molecular orbital calculations.

Introduction

A conjugate addition reaction of organometallic reagents with α,β-unsaturated carbonyl compounds and their equivalents is a powerful and fundamental method in forming a carbon−carbon bond.[1] These substrates are, however, ambident in their nature and undergo 1,4- and 1,2-additions. An oxazoline trick has been demonstrated by Meyers as a milestone toward a modern carbanion and heterocyclic chemistry applicable to a 1,4-selective asymmetric conjugate addition reaction of organolithium reagents.[2] It was further and considerable progress to extend this trick to a 1,4-selective addition reaction of organolithium reagents with a naphthalene nucleus.[3,4] Steric modification in a carbonyl moiety has been proven as an alternative methodology effective for a 1,4-selective conjugate addition of organolithium reagents.[5] Pioneering works by Seebach[6] and Cooke[7] have demonstrated that sterically hindered α,β-unsaturated trityl ketones and BHA esters serve as the Michael acceptors, affording the corresponding 1,4-selective addition products.[8] The BHA method was also extended to a 1,4-selective addition reaction of a naphthalenecarboxylate.[9,10] Steric masking and nucleophilic activation of naphthalenyl ketone by an external aluminum-based bulky Lewis acid has been impressive advance of 1,4- and 1,6-selective addition reactions.[11] An enaldimine **4** derived from an enal and an amine has been also developed as a good Michael acceptor equivalent to the corresponding α,β-unsaturated aldehyde (Scheme 1).[12] The imine method was also extended to a 1,4-selective reaction of imines **1** bearing a naphthalene nucleus.[13] The 1,2- and 1,4-selectivity has been shown to be dependent on a type of organometallic reagents[14] and the ion-pair structure of organometallic reagents.[15] It was interesting for us to learn that the 1,2-

Scheme 1. 1,2- and 1,4-Selective Addition Reactions



† We dedicate this work to Prof. A. I. Meyers for his accomplishment of oxazoline- and imine-based methodology on the occasion of his retirement.

(1) For reviews, see: (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. III, Chapter 31. (b) Tomioka, K. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 12. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061.

(2) For reviews on oxazolines chemistry, see: (a) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297−2360. (b) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991−1002.

(3) For the use of 1,3-oxazoline as an activating group for naphthalene additions, see: (a) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611−4624. (b) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292−2294. (c) Kolotuchin, S. V.; Meyers, A. I. *J. Org. Chem.* **2000**, *65*, 3018−3026.

(4) Interesting 1,6-addition of lithium amides has been reported. (a) Shimano, M.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 5714−5715. (b) Shimano, M.; Matsuo, A. *Tetrahedron* **1998**, *54*, 4787−4810.

(5) (a) Tomioka, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 1739−1740. (b) Tomioka, K.; Shindo, M.; Koga, K. *J. Org. Chem.* **1990**, *55*, 2276−2277.

(6) Seebach, D.; Ertas, M.; Locher, R.; Schweizer, W. B. *Helv. Chim. Acta* **1985**, *68*, 264−282.

(7) Cooke, M. P., Jr. *J. Org. Chem.* **1986**, *51*, 1637−1638.

(8) Xu, F.; Tillyer, R. D.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron*: *Asymmetry* **1998**, *9*, 1651−1654.

(9) Shindo, M.; Koga, K.; Asano, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 4955−4968.

(10) Application of the bulky ester in the nucleophilic aromatic substitution reaction has been extensively studied by Miyano. A review: Hattori, T.; Miyano, S. *J. Synth. Org. Chem.* **1997**, *55*, 121−131. Leading reference: Hattori, T.; Komuro, Y.; Hayashizaka, N.; Takahashi, H.; Miyano, S. *Enantiomer* **1997**, *2*, 203-213.

(11) Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091−9092.

(12) Kogen, H.; Tomioka, K.; Hashimoto, S.; Koga, K. *Tetrahedron* **1981**, *37*, 3951−3956.

(13) For the use of oxazolidine/imine system as an activating group for naphthalene additions, see: (a) Mokhallatie, M. K.; Muralidharan, K. R.; Pridgen, L. N. *Tetrahedron Lett.* **1994**, *35*, 4267−4270. (b) Meyers, A. I.; Brown, J. D.; Laucher, D. *Tetrahedron Lett.* **1987**, *28*, 5283−5286. (c) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266−8268.

(14) (a) Pridgen, L. N.; Mokhallatie, M. K.; Wu, M.-J. *J. Org. Chem.* **1992**, *57*, 1237−1241. (b) Meyers, A. I.; Brown, J. D.; Laucher, D. *Tetrahedron Lett.* **1987**, *28*, 5279−5282.

10.1021/jo015766b CCC: $20.00
Published on Web 09/21/2001

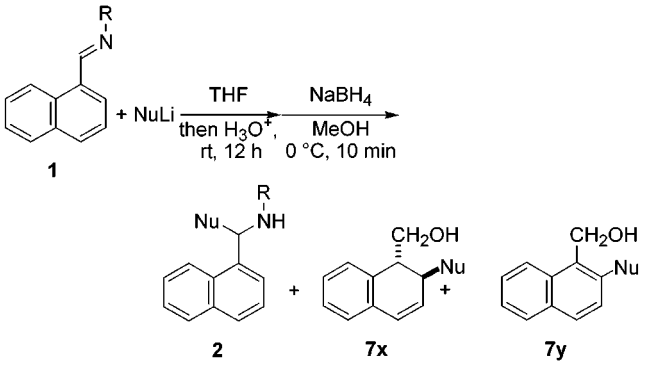
and 1,4-regioselectivity was dependent on the nature of an imine.[16] An imine prepared by condensation of an aryl aldehyde with an amine is a typical example to realize amine dependency of the reaction pattern. Thus, the imine **1** derived from naphthalene-1-carbaldehyde and an alkylamine such as cyclohexylamine undergoes 1,4-selective conjugate-type addition with organolithium reagents giving 2-alkylated 1,2-dihydronaphthalenecarbaldehydes, after hydrolysis of **3**. In contrast, the imine **1** derived from an arylamine such as 4-methoxyaniline undergoes 1,2-selective addition reaction with organolithium giving the corresponding alkylated amine **2**. It was also more interesting to learn that 1-substituted 2-naphthaleneimine was a good 1,4-selective acceptor giving a nucleophilic aromatic substitution product in a high yield.[17] Similar reaction pattern dependency has been observed in the reaction of an imine **4** derived from α,β-unsaturated aldehyde, affording 1,4- and 1,2-selective products **6** and **5**.

Selectivity control in a bond-forming reaction is the focus in the recent synthetic chemistry. Electronic and steric factors are the elements for regioselectivity control. We have already described that the degree of a LUMO coefficient is an essential factor in the reaction of organolithium reagents with naphthalenecarbaldehyde imines.[18,19] The current report summarizes our efforts to address the relationship between 1,2- and 1,4-regioselectivity and imine variables. One goal of the studies was to define the essential electronic and structural features of the α,β-unsaturated imines required for high 1,2- and 1,4-regioselectivity.

Results and Discussion

Alkylimines **1a**,**b** of naphthalene-1-carbaldehyde were 1,4-selective acceptors predominantly affording the corresponding alcohols **7** (Table 1, run 1−4). Treatment of cyclohexylimine **1a** (R = c-Hex) with butyllithium in THF at −78 °C for 3 h and acidic hydrolysis followed by sodium borohydride reduction of the aldehyde provided 2-butylated alcohols **7** as a mixture of dihydro and aromatized naphthalenes **7x**,**y** in 83% yield (Table 1, run 1). A trace amount of the 1,2-addition product (<1%) was observed by ^{1}H NMR in basic extracts from the reaction mixture. The reaction with phenyllithium at −45 °C was more selective, giving 2-phenylated naphthalenes **7** in 57% yield without production of the 1,2-addition product (Table 1, run 2). In this reaction, no 1,2-addition product could be observed in basic extracts. Butylimine **1b** (R = Bu) was a less bulky 1,4-selective acceptor predominantly giving **7** (Table 1, runs 3 and 4). It is reasonably understandable that phenyllithium is a softer nucleophile[20] and reacts with **1a**,**b** in a 1,4-conjugate addition pattern and that butyllithium is a harder nucleophile and gave a small amount of 1,2-addition amines **2** as the side product.

Table 1. 1,2- and 1,4-Selective Addition Reactions with Imine 1



run	**1**	R	Nu	*T*/°C	time/h	**2**/%	**7**/%	**x**:**y**
1	**a**	*c*-Hex	Bu	−78	3	<1	83	74:9
2	**a**	*c*-Hex	Ph	−45	3	0	57	24:33
3	**b**	*n*-Bu	Bu	−78	3	5	64	64:0
4	**b**	*n*-Bu	Ph	−45	3	0	76	39:37
5	**c**	4-MeOC$_6$H$_4$	Bu	−78	1	79	6	6:0
6	**c**	4-MeOC$_6$H$_4$	Ph	−78	1	90	4	4:0
7	**d**	Ph	Bu	−78	1	83	6	4:2
8	**d**	Ph	Ph	−78	1	99	1	0:1
9	**e**	4-CF$_3$C$_6$H$_4$	Bu	−78	1	89	0	0:0
10	**e**	4-CF$_3$C$_6$H$_4$	Ph	−78	1	99	0	0:0

In contrast, arylimines **1c**,**d**,**e** (R = 4-MeOC$_6$H$_4$, Ph, 4-CF$_3$C$_6$H$_4$) were 1,2-selective acceptors giving the corresponding amines **2** as major products (Table 1, runs 5−10). 4-Methoxyphenyl and phenylimines **1c**,**d** (R = 4-MeOC$_6$H$_4$, Ph) were not perfect 1,2-selective acceptors, giving a small amount of 1,4-products **7**, while 4-trifluoromethylphenylimine **1e** (R = 4-CF$_3$C$_6$H$_4$) was a perfect acceptor giving 1,2-addition amine **2** without production of 1,4-adduct **7** (Table 1, runs 9 and 10). Electronic control is apparently a factor determining 1,2- and 1,4-selectivity. The most electron-withdrawing group, CF$_3$, favors a 1,2-addition. An electron-donating MeO group is still in favor of 1,2-addition, though the relative ratio of 1,4-addition is increased.

Understanding the factors governing regioselectivity is a long-standing challenge[21,22] and essential for further development of more effective asymmetric reactions of the enimines. We carried out molecular orbital calculations of **1**.[23]

Structures **1** were fully optimized with MOPAC (PM3, precise mode). MOPAC calculations were shown to be comparable with the ab initio (HF/STO-3G) method under the Cs constraint.[24] Calculation of methylimine **1ab** (R = Me) as a model of cyclohexyl and butylimines

(15) (a) Cohen, T.; Abraham, W. D.; Myers, M. *J. Am. Chem. Soc.* **1987**, *109*, 7923−7924. (b) Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14−15.

(16) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429−4438.

(17) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 4, 8732−8733.

(18) Tomioka, K.; Okamoto, T.; Kanai, M.; Yamataka, H. *Tetrahedron Lett.* **1994**, *35*, 1891−1892.

(19) For the use of a carboxylate as an activating group for naphthalene additions, see: Plunain, B.; Mortier, J.; Vaultier, J. *J. Org. Chem.* **1996**, *61*, 5206−5207.

(20) Ho, T.-L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977.

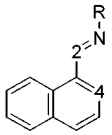
(21) Similar regioselectivity has been reported in the reaction of ketimines without clear explanation. Keuk, B. P.; Mauze, B.; Miginiac, L. *Synthesis* **1977**, 638.

(22) For theoretical treatment for regioselectivity of electrophilic addition to an ambident ketone or aldehyde, see: Lefour, J.-M.; Loupy, A. *Tetrahedron* **1978**, *34*, 2597−2605 and references therein.

(23) Calculations were carried out with an IBM RS6000 using the GAUSSIAN 92 program: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J.; Pople, J. A. *GAUSSIAN 92, Revision B*; Gaussian Inc.: Pittsburgh, PA, 1992. PM3 calculations were also carried out using MOPAC.

(24) Results for the s-trans isomers are nearly the same as s-cis, and the difference in the method of calculation (HF/3-21G, HF/STO-3G, and PM3) has little influence on a qualitative conclusion. Tomioka, K.; Okamoto, T.; Kanai, M.; Yamataka, H. *Tetrahedron Lett.* **1994**, *35*, 1891−1892.

Table 2. LUMO Coefficients and Regioselectivity of 1

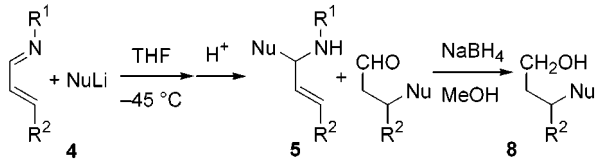


1

R	**1**	C2	C4	|C2 LUMO| − |C4 LUMO|	1,2/1,4 (PhLi)[a]
Me	**ab**	+0.212	−0.325	−0.113	0:100
4-$MeOC_6H_4$	**c**	+0.320	−0.322	−0.002	23:1
Ph	**d**	+0.330	−0.324	+0.006	99:1
4-$CF_3C_6H_4$	**e**	+0.382	−0.298	+0.084	100:0

[a] These ratios correspond to the ratios of **2** to **7** in Table 1.

Table 3. 1,2- and 1,4-Selective Addition Reactions with Imine 4



4 **5** **8**

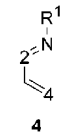
run	**4**	R^1	R^2	Nu	time/h	**5**/%	**8**/%
1	**a**	*c*-Hex	Me	Bu	2	0	74
2	**a**	*c*-Hex	Me	Ph	2	0	81
3	**b**	*c*-Hex	Ph	Bu	1	25	69
4	**b**	*c*-Hex	Ph	Ph	2	0	99
5	**c**	Ph	Me	Bu	1	92	0
6	**c**	Ph	Me	Ph	1	32	51
7	**d**	Ph	Ph	Bu	1	99	0
8	**d**	Ph	Ph	Ph	1	92	0
9	**e**	2,6-(i-Pr)$_2$$C_6H_3$	Ph	Me[a]	3	0	61
10	**e**	2,6-(i-Pr)$_2$$C_6H_3$	Ph	Bu	1	0	92
11	**e**	2,6-(i-Pr)$_2$$C_6H_3$	Ph	Ph	1	0	91

[a] The reaction was carried out at −20 °C.

1a,**b** was carried out (Table 2). The values of LUMO coefficients at each reaction site (2- and 4-positions) and the absolute value differences between these coefficients for the optimized geometries are summarized for comparison. Comparison of LUMO coefficients of **1ab** (R = Me) and **1c**,**d** (R = Ar) revealed that the experimentally observed regioselectivity is rationalized by the relative magnitude of the LUMO coefficients. The methylimine **1ab** has a larger coefficient at the 4-position, and the major reaction course for **1a**,**b** was 1,4-addition. The arylimine **1e** has a larger coefficient at the 2-position than the 4-position, being consistent with the exclusive 1,2-addition for **1e**. The coefficients are almost equal at the 2- and 4-positions for the arylimines **1c**,**d**, for which the 1,2-adduct was the selective product along with formation of a small amount of 1,4-adduct. This is easily understandable by considering that the 1,4-addition leads to the unfavorable transition state rather than the 1,2-addition due to the breakdown of the naphthalene aromaticity. The substituent R-dependency of the LUMO coefficient magnitude of **1** is ascribable to the electron-withdrawing nature of the aryl and the donating nature of the alkyl groups of **1**, respectively.

Acyclic enaldimines **4** derived from cinnamaldehyde and crotonaldehyde were also examined their behavior toward organolithium reagents (Table 3). Cyclohexylimine **4a** (R^1 = *c*-Hex, R^2 = Me) was cleanly converted to the corresponding 1,4-selective addition products **8** (R^2 = Me, Nu = Bu, Ph) (Table 3, runs 1 and 2). Reaction of cinnamaldehyde imine **4b** (R^1 = *c*-Hex, R^2 = Ph) with phenyllithium was selective, giving **8** (R^2 = Ph, Nu = Ph) in a quantitative yield (Table 3, run 4). Reaction with harder butyllithium was, however, not so selective, giving **8** in 69% yield along with a 1,2-addition product **5** (R^1 = *c*-Hex, R^2 = Ph, Nu = Bu) in 25% yield (Table 3, run 3). In contrast, phenylimines **4c**,**d** (R^1 = Ph) reacted in a 1,2-selective mode except for the reaction of **4c** with softer phenyllithium (Table 3, run 6), affording the corresponding amines **5c**,**d** as a sole isomer (Table 3, runs 5, 7, and 8). It was impressive that arylimine **4e** (R^1 = 2,6-diisopropylphenyl), having two bulky isopropyl groups at the 2,6-positions of a phenyl ring, directed a 1,4-selective addition whether butyl- or phenyllithium was used (Table 3, runs 10 and 11). It was noteworthy that even methyllithium selectively reacted in a 1,4-manner to provide the corresponding adduct **8** (Table 3, run 9).

Table 4. LUMO Coefficients and Regioselectivity of 4



4

R^1	**4**	Φ/deg	C2	C4	|C2 LUMO| − |C4 LUMO|	1,2/1,4 (PhLi)[a]
Me	**ab**		+0.472	−0.560	−0.088	0:100
Ph	**cd**	0	+0.462	−0.377	+0.085	100:0
		44.7	+0.454	−0.403	+0.051	
2,6-(i-Pr)$_2$-C_6H_3	**ee**	91	+0.486	−0.556	−0.070	0:100

[a] These ratios correspond to the ratios of **5** to **8** in Table 3.

Cooperative 1,4-selectivity by cyclohexylimine and the characteristic nature of softer phenyllithium favors 1,4-addition, and competition with harder butyllithium allows for a partial contamination of the 1,2-addition pathway. It is also responsible for 1,2-addition that 1,4-addition results in loss of resonance stabilizing energy of cinnamaldehyde-derived imine **4b**. The relative magnitude of LUMO coefficients of these acyclic imines was also useful in understanding reaction selectivity (Table 4). Calculations were carried out with imines of acrolein **4**. Methylimine **4ab** (R^1 = Me), as a model of cyclohexylimines **4a**,**b**, indicated that the C4 position has a coefficient larger than C2, suggesting 1,4-selective reaction as has been observed. Phenylimine **4cd**, as a model of **4c**,**d**, is quite interesting in that rotation of an N−Ph σ bond affects the relative magnitude of coefficients at C2 and C4. Thus, the coefficient at C2 is larger than that at C4 when the dihedral angle of C2−N−C=C(Ph) is 0 degree (Φ = 0). This conformation is the most stable structure of **4cd**. Imaginative rotation of the N−Ph bond from 0 to 44.7° dihedral angle increases the C4 coefficient and decreases the C2 coefficient. Rotation of the N−Ph bond brings about the slippage from the conjugate plane of C=N and Ph (R^1), corresponding to replacement of the aryl group of the imine part by an alkyl group. The dihedral angle of the most stable structure of 2,6-diisopropylphenylimine **4ee** (R^1 = 2,6-diisopropylphenyl) is 91°, almost perpendicular due to the steric bulk of isopropyl group, and conjugation of the imine C=N double bond with the aryl group is completely lost (Figure 1). The absolute value of the calculated LUMO coefficient at C4 is larger than that at C2, which indicates the 1,4-selective reaction. Steric hindrance by the isopropyl group and the frontier molecular orbital cooperate in directing the 1,4-selective addition reaction.

The 1,4-directing effect of a 2,6-diisopropylphenyl group was demonstrated in an asymmetric conjugate

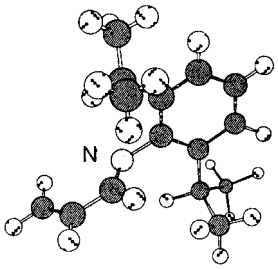


Figure 1. Model for **4ee**.

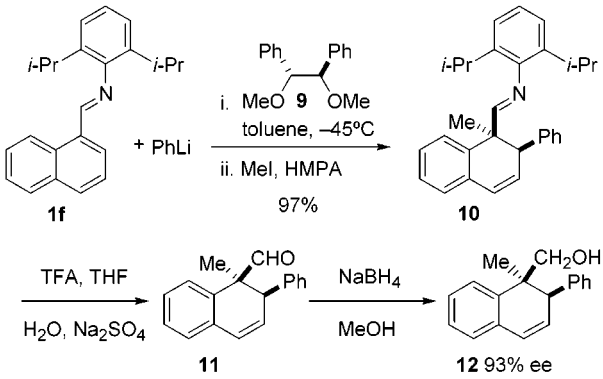
addition reaction of phenyllithium with imine **1f** (Scheme 2). The reaction was conducted in the presence of a chiral diether **9**[25] in toluene at −45 °C and then was treated with methyl iodide, giving **10** in 97% yield. Hydrolysis afforded a chiral aldehyde **11**[3a] in 82% yield. The ee was determined to be 93% by a chiral stationary-phase HPLC of reduction alcohol **12**.

Conclusion

Thus, it became clear that the relative magnitude of the LUMO coefficient is one of the essential factors governing the substituent-dependent regioselectivity of the ambident enimines. A bulky aryl group can increase C4 LUMO coefficients through slippage from conjugation. Cooperation of this electronic and steric control by the aryl group directs a 1,4-selective addition reaction. An electron-withdrawing aryl group can increase C2 LUMO coefficients and directs a 1,2-selective addition reaction.

(25) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351−9357.

Scheme 2. Asymmetric 1,4-Addition of Phenyllithium to Imine



We believe that LUMO coefficient as well as steric control would become an essential methodology for designing a selective reaction.

Acknowledgment. We gratefully acknowledge financial support from the Ministry of Education, Science, Sports and Culture, Japan Society for Promotion of Science (RFTF-96P00302), and the Science and Technology Agency, Japan. We are grateful to M. Shindo (Tokushima University) and T. Okamoto (Osaka University) for contributions to the early stages of the work.

Supporting Information Available: General experimental procedure and spectroscopic and analytical data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO015766B