

HETEROCYCLES, Vol. 73, 2007, pp. 255 - 261. © The Japan Institute of Heterocyclic Chemistry
Received, 11th July, 2007, Accepted, 4th October, 2007, Published online, 9th October, 2007. COM-07-S(U)65

**LEWIS BASE CATALYZED AZA-DIELS-ALDER TYPE REACTIONS
BETWEEN DANISHEFSKY'S DIENES IN THE PRESENCE OF LEWIS
BASE CATALYSTS.
AN EFFICIENT METHOD FOR THE SYNTHESIS OF
SUBSTITUTED 2,3-DIHYDROPYRIDIN-4-ONES**

Takayuki Kitazawa, Yuji Maruyama, and Teruaki Mukaiyama*

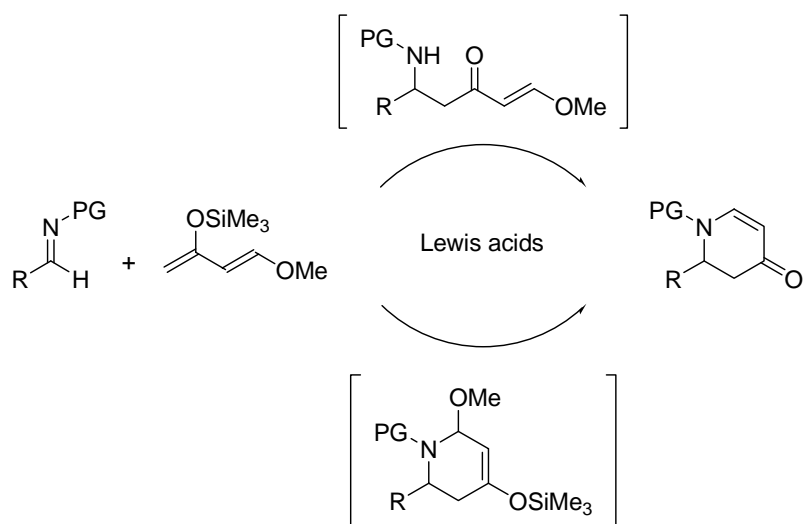
Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI), Toshima, Kita-ku,
Tokyo 114-0003, Japan and Kitasato Institute for Life Sciences, Kitasato
University, 5-9-1, Shirokane, Minato-ku, Tokyo 108-8641, Japan

Dedicated to Professor Ivar Ugi.

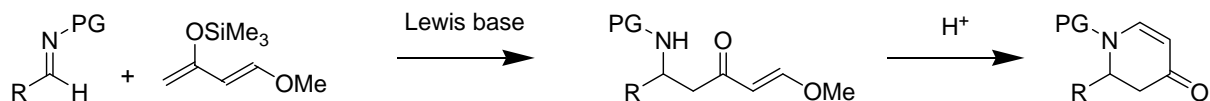
Abstract – Aza-Diels-Alder type reactions of various imines with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) derivatives catalyzed by Lewis bases such as lithium methoxide are described. The reaction proceeds via a stepwise pathway, i.e. first by an imino-aldol reaction followed by the acid mediated annulation to afford the corresponding 2,3-dihydropyridin-4-ones in high yields. An appropriate choice of the substituents on nitrogen plays important roles both in addition of the silyl enolates and in the subsequent annulation to form the desired cycloadducts.

Among the biologically active compounds such as pharmaceuticals, agrochemicals and natural products, 2,3-dihydropyridin-4-ones are often recognized as key intermediates to form piperidine alkaloids. To obtain 2,3-dihydropyridin-4-ones, one of the most fundamental methods is to allow 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's Diene) to react with imines, that is the well known aza-Diels-Alder reaction.¹ Since aza-Diels-Alder reactions promoted by Lewis acid catalyst were first reported, even more effective Lewis acid catalysts have been developed (Scheme 1).² On the other

hand, there are no reports on Lewis base mediated aza-Diels-Alder reactions. Recently, it was reported from our laboratory that silyl enolates are activated by Lewis base catalysts,³ and particularly, Danishefsky's dienes are effectively activated by a catalytic amount of Lewis base such as lithium methoxide and afforded 2,3-dihydropyran-4-ones in high yields on treatment with carbonyl compounds.⁴ As a course of our continuous study on Lewis base catalyzed reactions, this method was next applied to the reactions with imines in place of the above mentioned carbonyl compounds (Scheme 2). In this communication, the first example of Lewis base catalyzed aza-Diels-Alder type reactions is described.

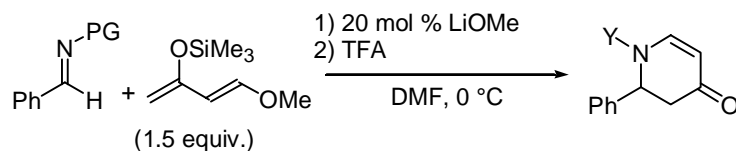


Scheme 1. Lewis Acid Catalyzed Aza-Diels-Alder Reactions



Scheme 2. Lewis Base Catalyzed Aza-Diels-Alder Reactions

In the first place, a reaction between Danishefsky's diene and imines derived from benzaldehyde was tried in the presence of a catalytic amount of lithium methoxide in DMF, which was previously proved to be the best reaction conditions of hetero Diels-Alder type reactions (Table 1).

Table 1. Lithium methoxide catalyzed aza-Diels-Alder reactions of various imines with Danishefsky's diene

Entry	PG	Yield (%)	Entry	PG	Yield (%)
1	Ts	complex mixture	5	P(O)Ph ₂	trace
2	<i>o</i> -Ns	complex mixture	6	Benzyl	trace
3	PMP	trace	7	Allyl	trace
4	Ph	trace	8	CO ₂ ^t Bu	89*

o-Ns = *o*-nitrobenzenesulfonyl, PMP = *p*-methoxyphenyl

* PG = H in cycloadduct

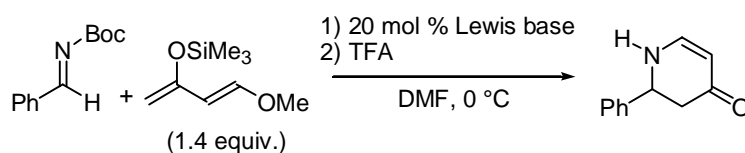
Y = H in entry 8

The substituents on imine nitrogen atom were chosen for the protective groups to be removed easily by well known procedures. When imines having strong electron withdrawing *N*-sulfonyl group were used, the starting materials disappeared after 24 hours, which was checked by TLC analysis. However, several spots besides the target adduct were also observed by the TLC analysis (entries 1 and 2). In addition, it was shown that the acid mediated cyclization was not successful due to the low nucleophilicity of the sulfonamide. The addition of Danishefsky's diene to *N*-aryl imines and *N*-diphenylphosphinoyl imine proceeded very sluggishly and the desired pyridones were not obtained (entries 3-5). As shown in entries 6 and 7, *N*-benzyl imine and *N*-allyl imine were non-reactive. When *N*-*t*-Butoxycarbonyl (Boc) imine was used, the desired 2,3-dihydropyridin-4-one was obtained in 89 % overall yield with the deprotection of Boc group during the acid mediated annulation (entry 8). When the reaction was carried out at room temperature, the reaction mixture became complex and the yield of the desired cycloadduct became lower.

Next, effects of other Lewis base catalysts were examined (Table 2). The alkoxide anions except ammonium methoxide showed similar activities to lithium methoxide (entries 1-5). When Lewis bases such as phenoxide anion and carboxylate anion were used, only a trace amount of the desired product was

obtained (entries 6-9). Tetrabutylammonium fluoride, a commonly used fluoride anion source, was not effective (entry 10).

Table 2. Effects of various Lewis base catalysts in the aza-Diels-Alder reactions

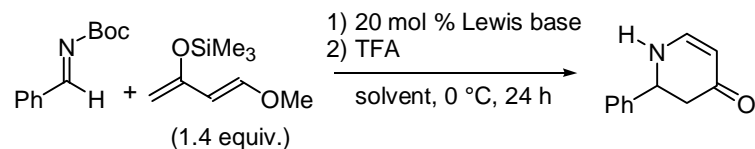


Entry	Lewis Base	Yield (%)	Entry	Lewis Base	Yield (%)
1	LiOMe	89	6	LiOPh	N.R.
2*	LiOMe	69	7	Bu ₄ NOPh	trace
3	NaOMe	54	8	LiOAc	N.R.
4	Bu ₄ NOMe	trace	9	Bu ₄ NOAc	trace
5	KO ^t Bu	37	10	TBAF	10

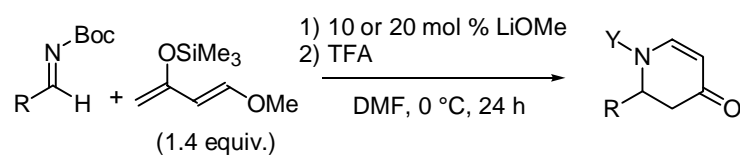
* 10 mol% LiOMe was used.

Then, effect of solvents was examined (Table 3). When the reaction was carried out in DMSO or pyridine, the reaction proceeded similarly to afford the pyridone in good yields (entries 2 and 3), but solvents such as CH₂Cl₂, THF, and toluene were not applicable under this reaction conditions (entries 4-6). Because of the low solubility of lithium methoxide in these solvents, it was considered that the Lewis base catalysts did not dissolve in the reaction media and thus, no reaction proceeded at all.

The above aza-Diels-Alder type reactions were next examined by using other substrates (Table 4). N-Boc imines derived from the substituted benzaldehydes reacted as smoothly as well under the optimized conditions and afforded the pyridones in high yields (entries 1-4). Imines derived from hetero-aromatic aldehydes also gave the corresponding cycloadducts in good yields (entries 5 and 6). Not only the above imines prepared from aromatic aldehydes, those derived from aliphatic aldehydes gave the cycloadducts in good yields (entry 7). In addition to N-Boc imines, the imine derived from ethyl glyoxylate and *p*-anisidine was also applicable to this aza-Diels-Alder type reaction and afforded the N-PMP protected pyridones in good yield (entry 8).

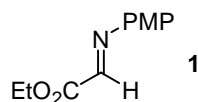
Table 3. Effects of solvents in lithium methoxide catalyzed aza-Diels-Alder reactions.

Entry	Solvent	Yield (%)	Entry	Solvent	Yield (%)
1	DMF	89	4	CH ₂ Cl ₂	N.R.
2	DMSO	72	5	THF	N.R.
3	pyridine	50	6	toluene	N.R.

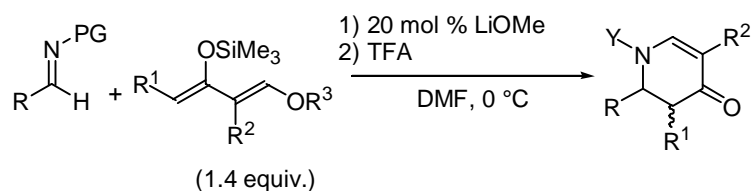
Table 4. Lithium methoxide catalyzed aza-Diels-Alder reactions

Entry	R	Yield (%)	Entry	R	Yield (%)
1	Ph	89	5*	2-furyl	80
2	4-MeOC ₆ H ₄	73	6	3-pyridyl	37
3	4-BrC ₆ H ₄	46	7*	^t Bu	61
4*	2-MeC ₆ H ₄	82	8	1	73

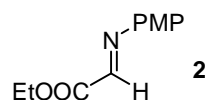
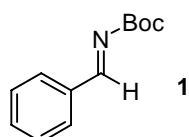
* 10 mol% LiOMe was used
 Y = H in entries 1-7
 Y = PMP in entry 8



Next, this aza-Diels-Alder type reaction was tried by using other Danishefsky's dienes⁵ (Table 5). Then, the Danishefsky's diene with methyl groups at 2- and 4-positions was also activated effectively to afford the desired products in excellent yields, but the observed diastereoselectivities turned out to be low. The diastereoselectivities were slightly improved when α -benzyloxy substituted Danishefsky's diene⁶ was used.

Table 5. Aza-Diels-Alder reactions Using Substituted Danishefsky's dienes

Entry	Imine	R ¹	R ²	R ³	Y	Yield (%)	d.r.
1	1	Me	Me	Me	H	91	77 / 23
2	1	BnO	H	^t Bu	H	86	81 / 19
3	2	Me	Me	Me	PMP	>99	73 / 27
4	2	BnO	H	^t Bu	PMP	70	79 / 21



It is noted that the lithium methoxide catalyzed aza-Diels-Alder type reactions using aldimines proceeded smoothly to construct the corresponding 2,3-dihydro-4-pyridin-2-one skeletons, frequently found structures in such biologically active compounds as pharmaceuticals and natural products, in good to excellent yields under mild Lewis basic conditions. Further studies on this type of reactions are in progress.

ACKNOWLEDGEMENTS

This study was supported in part by the Grant of the 21st Century COE Program from Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

REFERENCES AND NOTES

- (a) W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Tetrahedron Organic Chemistry Series, Pergamon, Elmsford, New York, 1990, Vol. 8. (b) D. L. Boger and S. N. Weinreb, *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, Sandiego, CA, 1987. (c) Kerwin Jr.

- and S. Danishefsky, *Tetrahedron Lett.*, 1982, **23**, 3739.
- (a) S. Weinreb, *Comprehensive Organic Synthesis*. (b) B. M. Trost and I. Fleming, *Hetero dienophile additions to dienes*, Pergamon Press: Oxford, 1991, **5**, 401. (c) H. Waldmann, *Synthesis*, 1994, 535.
 - (a) aldol reaction: H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, 2002, **31**, 182; T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, 2003, **32**, 462; T. Nakagawa, H. Fujisawa, Y. Nagata, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 1555; Y. Kawano, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, 2005, **34**, 422. (b) Michael reaction and related reaction: T. Mukaiyama, T. Nakagawa, and H. Fujisawa, *Chem. Lett.*, 2003, **32**, 56; T. Nakagawa, H. Fujisawa, Y. Nagata, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 236; T. Tozawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, 2004, **33**, 1454; H. Nagao, Y. Yamane, and T. Mukaiyama, *Chem. Lett.*, 2007, **36**, 8. (c) Mannich-type reaction: H. Fujisawa, E. Takahashi, T. Nakagawa, and T. Mukaiyama, *Chem. Lett.*, 2003, **32**, 1036; E. Takahashi, H. Fujisawa, T. Yanai, and T. Mukaiyama, *Chem. Lett.*, 2005, **34**, 216. (d) 2,3-Wittig rearrangement: Y. Sato, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, 2005, **34**, 588; Y. Sato, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, 2005, **34**, 1188; Y. Sato, H. Fujisawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 1275.
 - T. Mukaiyama, T. Kitazawa, and H. Fujisawa, *Chem. Lett.*, 2006, **35**, 328; T. Kitazawa and T. Mukaiyama, *Heterocycles*, 2006, **69**, 417.
 - Z. Fu, B. Gao, Z. Yu, L. Yu, Y. Huang, X. Feng, and G. Zhang, *Synlett*, 2004, **10**, 1772.
 - Y. Ymashita, S. Saito, H. Ishitani, and S. Kobayashi, *J. Am. Chem. Soc.*, 2003, **125**, 3793.