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New method for activation of aldimines in cycloaddition of lithium ynolates with *N*-2-methoxyphenyl imines leading to β-lactams

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Abstract

The cycloaddition of the *N*-2-methoxyphenyl aldimines with lithium ynolates was efficiently accelerated via chelation to give β-lactam enolates, which immediately reacted with one more equivalent of the imine to give β-lactams (2:1 adducts) in good yields, while *N*-4-methoxyphenyl imines were inert towards lithium ynolates.

Keywords: ynolates; imines; azetidinones; chelation.

Aldimines are known to have versatile and useful electrophilic functionality.[1] However, in contrast to aldehydes, aldimines, because of their lower reactivity, often require activation of the imine (e.g., introduction of strong electron-withdrawing groups or use of Lewis acids[2]) and/or harsh conditions for the addition of nucleophiles.

Previously, we reported that lithium ynolates **1**,[3] prepared by the method that we developed, react with aldehydes to give β-lactones (2:1 adducts) at –78°C.[4] Similarly, aldimines would be expected to react with ynolates to afford β-lactam enolates. Barrett et al.[5] and Murai et al.[6] reported that phenyl-substituted and silyl-substituted ynolates added to aldimines bearing an electron-withdrawing substituent to provide β-lactams (2:1 adducts) at –60°C and α,β-unsaturated amides at room temperature, respectively. Recently, we also reported that lithium ynolates added to *N*-sulfonyl imines to give β-lactams **2** (1:1 adducts) at –78°C (Scheme 1).[7]

However, unactivated imines such as *N*-4-methoxyphenyl imines (e.g., **3**) were much less reactive towards lithium ynolates (Scheme 2). Further attempts to promote addition using various Lewis acids ($TiCl_4$, Me_3Al, BF_3 etc.) were likewise not effective.[8] Herein, we describe a novel method for activation of imines via chelation with lithium and the first successful example of cycloaddition of lithium ynolates with *unactivated* aldimines having an *N*-2-methoxyphenyl substituent.[9]

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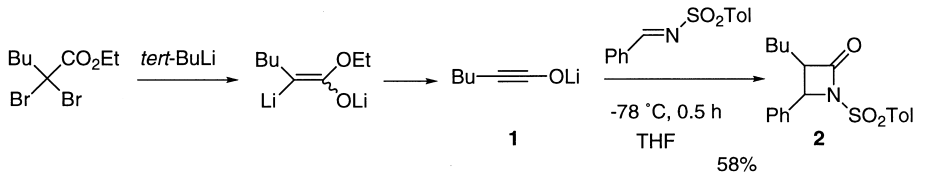
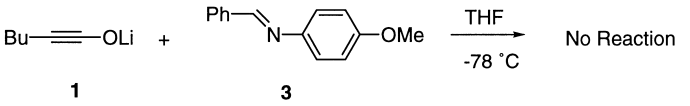


Scheme 1.



Scheme 2.

We thought that if the imino nitrogen and another coordination site on a group attached to the imine chelated the lithium cation of the lithium ynolate, then the imino group would be more effectively activated, and the ynolate would be nearer the substrate (Fig. 1).

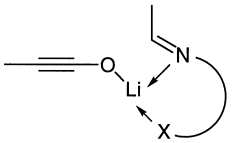
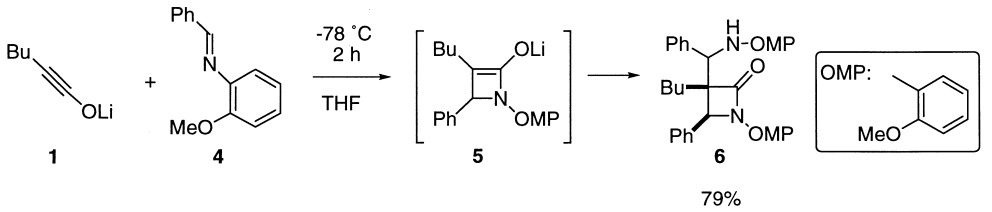


Figure 1.

Based on this idea, we attempted the cycloaddition of the lithium ynolate with the *N*-2-methoxyethyl imine; however, the reaction proceeded very slowly. We then used the *N*-2-methoxyphenyl (OMP) aldimine as a substrate, expecting the 2-methoxy group to act as another coordination site. The imine **4** was added to a THF solution of the lithium ynolate **1**, prepared from the dibromo ester and *tert*-BuLi, at –78°C. Amazingly, the starting imine disappeared in 2 h at –78°C and, after workup, followed by isolation of the major products, the β-lactams **6** containing two equivalents of the starting imine unit were produced in 79% yield as a single isomer (Scheme 3).



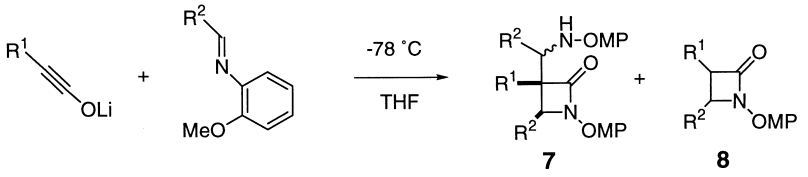
Scheme 3.

Compared with the reaction of 4-methoxyphenyl imines, this one was considerably accelerated by the 2-methoxy moiety. Since the nucleophilicity of the intermediate β-lactam enolate **5** was much higher than that of the ynolate, the 2:1 adducts **6** were obtained, even though only one

equivalent of the imine **4** was added.[5] The electron-donating *N*-substituent, i.e., the methoxyphenyl group, clearly increased the nucleophilicity of the lactam enolates, while the 1:1 adducts (β-lactams) were generated preferentially when *N*-tosyl imines were used.

To confirm the new method of activation of imines in the cycloaddition, we examined reactions using several ynolates and *N*-2-methoxyphenyl imines. As shown in Table 1, when imines of aryl aldehydes were used, the reaction proceeded smoothly to give the adducts. The bulky imine (R^2 = *tert*-Bu, entry 4) did not afford the desired products. Primary and secondary carbon-substituted ynolates gave the β-lactams **7** (2:1 adducts) in good yields. The cyclohexyl-substituted ynolate provided the disubstituted β-lactams **8** (1:1 adducts) in 45% yield in addition to the 2:1 adducts (entry 9).

Table 1
Cycloaddition of ynolates with *N*-2-methoxyphenyl imines affording β-lactams[a]



7 **8**

Entry	R^1	R^2	Time (h)	Yield of **7** (%)	(diastereomer ratio[b])	Yield of **8** (%)
1	Me	phenyl	0.5	96	1:1	0
2	Me	1-naphthyl	1.5	88	2:1	0
3	Me	2-naphthyl	0.5	93	3:1	0
4	Me	*tert*-Bu	>12	0	-	0
5	Me	4-(MeO_2C)C_6H_5	0.5	97	3:1	0
6	Bu	phenyl	2.0	79	single	0
7	Bu	1-naphthyl	1.5	78	single	0
8	Bu	2-naphthyl	0.7	74	single	0
9	cyclohexyl	phenyl	0.5	52	single	45[c]

[a] Conditions: Lithium ynolate, prepared from dibromoester (1.2 mmol) and *tert*-BuLi (4.8 mmol), and imine (1.0 mmol) in THF (8 mL) were employed.
[b] The stereochemistry on the the β-lactam ring was determined by nOe experiments, but the relative configulation of the third stereogenic center (next to amine) has not been determined.
[c] Mixture of diastereomers (1:1).

In conclusion, we have developed a new method for activation of aldimines via chelation in cycloaddition of lithium ynolates with aldimines.[10]

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References

1. For reviews see: (a) Bloch, R. *Chem. Rev*. **1998**, *98*, 1407–1438. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946. (c) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Schreiber, S. L., Ed.; Pergamon: Oxford, 1991; Vol. 1, pp. 355–396. (d) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon: Oxford, 1991; Vol. 2, pp. 975–1006.
2. (a) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc*. **2000**, *122*, 762–766. (b) Kobayashi, S.; Nagayama, S. *J. Org. Chem*. **1997**, *62*, 232–233. (c) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc*. **1997**, *119*, 10049–10053 and references therein.
3. For a review see: Shindo, M. *Chem. Soc. Rev*. **1998**, *27*, 367–374.
4. (a) Shindo, M. *Tetrahedron Lett*. **1997**, *38*, 4433–4436. (b) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411–2422.
5. (a) Adlington, R. M.; Barrett, A. G. M.; Quayle, P.; Walker, A.; Betts, M. J. *J. Chem. Soc*., *Chem. Commun*. **1981**, 404–405. (b) Barrett, A. G. M.; Quayle, P. *J. Chem. Soc*., *Perkin Trans. 1* **1982**, 2193–2196.
6. Kai, H.; Iwamoto, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc*. **1996**, *118*, 7634–7635.
7. Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* **1998**, *49*, 113–116.
8. A lanthanaid triflate activated cycloaddition of silyl ynol ether to 4-methoxyphenyl imines has been reported by us: Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* **2000**, *52*, 545–548.
9. There have been many reports on stereocontrol of addition of organometallics to imines via chelation. Utilizing the *N*-2-hydroxyphenyl function, Kobayashi achieved high enantioselectivity and reaction acceleration in the asymmetric Mannich reaction and Strecker reaction: Ishitani, H.; Kobayashi, S. *Tetrahedron Lett*. **1996**, *41*, 7357–7360; Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc*. **1997**, *119*, 7153–7154; Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem*., *Int. Ed*. **1998**, *37*, 3186–3188; Kobayashi, S.; Hasegawa, Y.; Ishitani, H. *Chem. Lett*. **1998**, 1131–1132; Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc*. **1998**, *120*, 431–432; Kobayashi, S.; Busujima, T.; Nagayama, S. *Synlett* **1999**, 545–546; Ishitani, H.; Kitazawa, T.; Kobayashi, S. *Tetrahedron Lett*. **1999**, *40*, 2161–2164; Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem*. **1999**, *64*, 4220–4221; Kobayashi, S.; Kusakabe, K.; Ishitani, H. *Org. Lett*. **2000**, *2*, 1225–1227; Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc*. **2000**, *122*, 762–766. See also: Adrian Jr., J. C.; Barkin, J. L.; Hassib, L. *Tetrahedron Lett*. **1999**, *40*, 2457–2460.
10. **Note added in proof:** After submission of the revised manuscript, Yamamoto et al. reported the acceleration of addition of lithium ester enolates to *N*-2-methoxyphenyl aldimines: Saito, S.; Hatanaka, K.; Yamamoto, H. *Org. Lett*. **2000**, *2*, 1891–1894.