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Lithium Amide Assisted Asymmetric Mannich-Type Reactions of Menthyl Acetate with PMP-Aldimines

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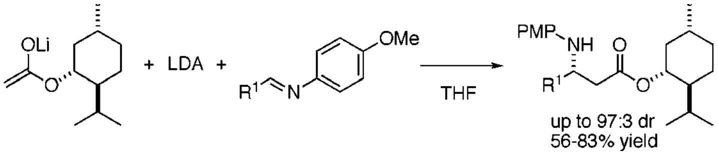
ABSTRACT



A lithium enolate of menthyl acetate added to PMP-imines, in the presence of an equimolar amount of lithium diisopropylamide, affords the Mannich-type addition products in high stereoselectivity.

There have been few reports[1,2] on the asymmetric Mannich-type reactions of acetate lithium enolates with stable *N*-substituted imines[3,4] of poor electrophilicity.[5] In contrast, propionates and other α-substituted acetate analogues have been used in the asymmetric Mannich-type reactions.[6] Success of the Mannich reaction with a chiral acetate is limited to the Yamamoto protocol, which uses 2-methoxyaniline-derived aldimines and Lewis acid additives.[7] We have been investigating the chiral-ligand-controlled asymmetric addition reaction[8] of lithium ester enolates with aldimines derived from aldehydes and 4-methoxyaniline (PMP−NH$_2$).[9] Either the ternary complex reagent of α-substituted ester lithium enolates having a chiral bidentate ligand and a lithium amide as components or the binary reagent of a lithium enolate coordinated by a tridentate ligand enhanced the reactivity of an enolate toward PMP-imines, giving the

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[1] Reviews: (a) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447−1465. (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (c) Kobayashi, S. Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. (d) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, pp 923−961. (e) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, 563−572.

[2] For asymmetric Mannich-type reactions using a chiral acetate equivalent with achiral activated imines, see: (a) Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328−6343. (b) Palomo, C.; Oiarbide, M.; González-Rego, M. C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063−1066 and references therein.

[3] Other than stable *N*-aryl imines, chiral sulfinyl imines have been the good reaction partners. (a) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1−15. (b) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819−7832 and references therein.

[4] Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044−1070.

[5] For recent asymmetric Mannich-type reactions using a ketene derivative, see: (a) Müller, R.; Röttele, H.; Henke, H.; Waldmann, H. *Chem. Eur. J.* **2000**, *6*, 2032−2043. (b) Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271−2274. (c) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635. (d) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964−12965. (e) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507−2515.

[6] For examples, see: (a) Ojima, I.; Habus, I. *Tetrahedron Lett.* **1990**, *31*, 4289−4292. (b) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 9030−9032.

[7] (a) Saito, S.; Hatanaka, K.; Yamamoto, H. *Org. Lett.* **2000**, *2*, 1891−1894. (b) Saito, S.; Hatanaka, K.; Yamamoto, H. *Tetrahedron* **2001**, *57*, 875−887.

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β-lactam products in high enantioselectivities. However, an acetate itself, in place of α-substituted esters, was not a reactive partner in the reaction, and PMP-imines were recovered mostly unchanged. After many trials, we finally reached a simple solution for this problematic reaction by using a lithium amide as an assisting agent.

We systematically studied the influence of the *para* substituents of the aniline-derived aldimines **3** (R^1 = Ph) on the reaction efficiency using menthyl acetate **1** (Scheme 1).

Scheme 1. Mannich-Type Reaction of Imine **3** with Menthyl Acetate **1** via Lithium Enolate **2**, Giving **4**

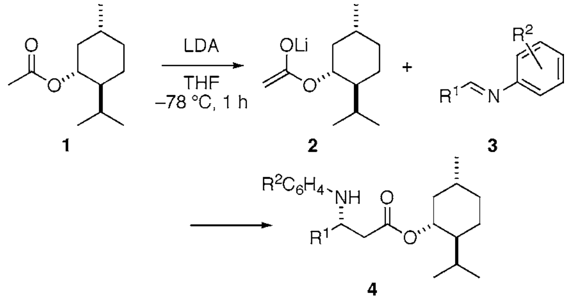

Table 1. Mannich-Type Reaction of **1** with **3** (R^1 = Ph) at −78 °C

entry	**3** (R^1 = Ph)	R^2	*t* (h)	**4** (R^1 = Ph)	yield (%)	dr
1	**a**	4-MeO	5	**a**	0	
2	**b**	4-H	5	**b**	62	93:7
3	**c**	4-CF_3	0.3	**c**	87	80:20
4	**d**	4-CO_2*i*-Pr	0.3	**d**	80	72:28
5	**e**	4-CN	0.3	**e**	95	60:40
6	**f**	4-NO_2	0.3	**f**	98	56:44
7	**g**	2-MeO	3	**g**	86	84:16

The lithium enolate **2** was generated by treatment of a THF solution of **1** with a slight excess of lithium diisopropylamide (LDA) at −78 °C for 1 h and was then treated with **3**. Contrary to the lack of the addition product **4a** (R^1 = Ph, R^2 = 4-MeO) with PMP-imine **3a** (R^1 = Ph, R^2 = 4-MeO) (Table 1, entry 1),[10] imines **3b**−**3f** of anilines bearing electron-withdrawing substituents or no substituent at the 4-position were good partners for the Mannich-type reaction at −78 °C for 0.3 h (5 h for **3b**) to afford **4b**−**4f** (R^1 = Ph) in good to high yields [62% (93:7 diastereomer ratio (dr)) with **3b** (R^2 = 4-H), 87% (80:20 dr) with **3c** (R^2 = 4-CF_3), 80% (72:28 dr) with **3d** (R^2 = 4-CO_2*i*-Pr), 95% (60:40 dr) with **3e** (R^2 = 4-CN), and 98% (56:44 dr) with **3f** (R^2 = 4-NO_2) (entries 2−6)].[11] As expected from Yamamoto's report,[7] the reaction with **3g** (R^2 = 2-MeO) proceeded under the same conditions to give **4g** in 86% yield and 84:16 dr (entry 7).

Hammett σ-constants and pK_a values of the 4-substituted anilines are likely to be the key to the success and failure of the Mannich reaction. For example, imines **3b**−**3f** derived from anilines bearing 4-NO_2 (σ[12] 0.81), 4-CN (0.71), 4-CO_2*i*-Pr (0.68 for CO_2Et), 4-CF_3 (0.53), and 4-H (0) groups are good reaction partners, and **3a** bearing 4-MeO (−0.28) is not. The pK_a values[13] of 4-NO_2 (21), 4-CN (26), and 4-H (31) anilines are smaller than or nearly equal to that (30 for $MeCO_2$*t*-Bu) of an acetate. These apparently indicate two critical points: (1) electron-withdrawing groups (R^2) at the 4-position of aniline increase the reactivity of the imine functionality, and (2) the initially formed lithium amide species of **4** plays the important role in the reaction (Figure 1). When the lithium amides of the products **4** are more stable as a result of the electron-withdrawing 4-R^2 group or internal coordination (2-MeO), the efficiency of the reaction is higher and vice versa.

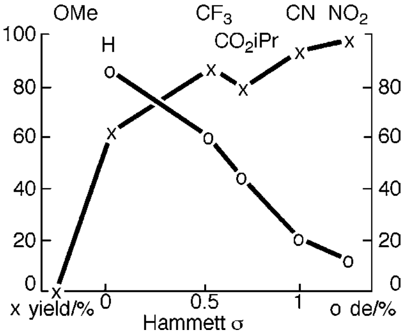

Figure 1. Hammett σ-constant, yield (×) and dr (○) of the reaction.

The diastereoselectivity is inversely proportional to the value of the Hammett σ-constants of R^2, implying the important role of the reactivity of the imine functionality (Figure 1). The reaction with more reactive imines likely proceeds through a looser organization of the transition state, leading to lower diastereoselectivity down to 56:44 dr with **3f** (R^2 = NO_2). Less reactive imines react through a tighter transition state to afford better diastereoselectivity up to 93:7 dr with **3b** (R^2 = H).

These experiments and analyses led us to the expectation that the least activated imine **3a** would provide the highest diastereoselectivity if the reaction proceeded. As a simple solution to the problem we applied the concept of ternary reagent control[9] that enables activation of a lithium ester enolate by forming a complex with a lithium amide and a

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[10] The reaction at higher temperature resulted in the production of a messy mixture.

[11] The diastereomer ratio was determined by ^{1}H NMR (doublet Me protons appearing at around 1 ppm) of the crude product.

[12] *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; Smith, M. B., March, J., Eds.; John Wiley & Sons Inc.: NY, 2001.

[13] The pK_a values in DMSO quoted from the Bordwell pK_a table.

chiral ligand. For the reaction in THF, a binary complex of a lithium enolate with a lithium amide would be the reagent of choice.[14]

To our delight, the reaction at −30 °C for 4 h of a binary complex of menthyl acetate enolate (**2**-LDA), generated by treatment of **1** with 2.25 equiv of LDA in THF, converted PMP imine **3a** to the desired adduct **4a** (R^1 = Ph, R^2 = 4-MeO) in 76% yield and 96:4 dr (Table 2, entry 1). The use of other lithium amides, derived from dicyclohexylamine, isopropylcyclohexylamine, or tetramethylpiperidine, had little influence on the reaction to afford **4a** with the same high selectivity of 94:6−93:7 dr and 56−80% yields. The binary reagent (**2**-LDA) also converted **3b** in 3.5 h to **4b** with 96:4 improved dr (entry 2). Under these conditions, no improvement in the diastereoselectivity was observed in the reaction with activated imines **3c**−**3f**.

Table 2. Mannich-Type Reaction of Imine **3** with **1** via Binary Reagent of **2**-LDA

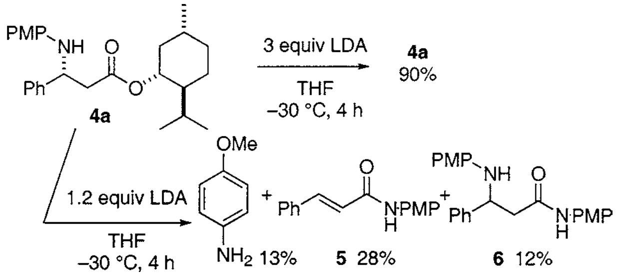
$$\mathbf{1} \xrightarrow[\text{THF, −78 °C, 1 h}]{\text{LDA, 2.25 eq}} \mathbf{2}\text{-LDA} + \mathbf{3} \xrightarrow[\text{−40 to −20 °C, 3−4 h}]{} \mathbf{4}$$

entry	3	R^1	R^2	4	yield (%)	dr
1	**a**	Ph	4-MeO	**a**	76	96:4
2	**b**	Ph	H	**b**	58	96:4
3	**h**	4-$CF_3C_6H_4$	4-MeO	**h**	74	97:3
4	**i**	4-$MeOC_6H_4$	4-MeO	**i**	56	96:4
5	**j**	1-Naph	4-MeO	**j**	65	82:18
6	**k**	2-Naph	4-MeO	**k**	83	94:6

The 4-substituents of benzaldehyde derivatives were not so influential on the reaction. The 4-trifluoromethyl- and 4-methoxybenzaldehyde imines **3h** and **3i** (R^1 = 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, R^2 = 4-MeO) were converted at −30 °C in the presence of an excess of LDA to **4h** in 74% yield and 97:3 dr and **4i** in 56% yield and 96:4 dr (entries 3 and 4). In the absence of an excess of LDA, the starting imines were recovered without formation of detectable amount of the adducts. Other than benzaldehyde imines, PMP imines of 1- and 2-naphthaldehydes **3j** and **3k** (R^1 = 1- and 2-Naph) were converted at −40 °C for 3 h to **4j** in 65% and 82:18 dr and **4k** in 83% and 94:6 dr (entries 5 and 6).

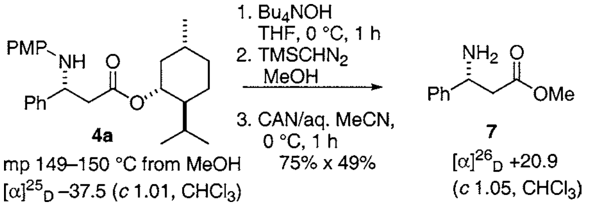
The deuterium oxide quench of the reaction with **3a** revealed that the α-position of ester **4a** was deuterized at 80%, indicating the conversion of the initially formed lithium amide of the adduct to its dianion. The stability of the dianion of the adduct was confirmed by treatment of **4a** with 3 equiv of LDA to recover **4a** in 90% yield without any loss of diastereo-integrity (Scheme 2). On the other hand, treatment of **4a** with 1.2 equiv of LDA gave the recovery of **4a** in a trace amount, along with 4-methoxyaniline in 13% yield, *N*-PMP cinnamoylamide **5** in 28% yield, and its PMP-amine 1,4-adduct **6** in 12% yield. These products seemed to arise through elimination of 4-methoxyaniline from **4a** via its lithium enolate and subsequent 1,2-addition to a carbonyl group of cinnamate followed by 1,4-addition.[15] Thus the stability of the lithium amide of **4a** is also one of the controlling factors of the reaction. It is important to note that LDA plays a dual role in the activation of the lithium enolate and the lithiation of the unstable initial adduct into the stable dianion.

Scheme 2. Stability of **4a** upon Treatment with LDA



The PMP group of (−)-**4a**, diastereomerically enriched to over 99:1 dr in 70% yield by recrystallization from methanol, was easily removed by a CAN oxidation to afford optically pure (*R*)-**7**[15] (Scheme 3).

Scheme 3. Conversion of Enantiomerically Pure **4a** to **7**



In conclusion, we have developed a new and simple methodology for the Mannich-type reaction of a chiral acetate with arylaldimines, in which the use of a binary reagent composed of a lithium acetate enolate and a lithium amide is key to the success. It is also important to note that a simple chiral auxiliary, menthol, is operative as an efficient stoichiometric stereocontrolling group.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2886−2887.