A Ternary Complex Reagent for an Asymmetric Reaction of Lithium Ester Enolates with Imines

Hiroki Fujieda,[†] Motomu Kanai,[†] Takeshi Kambara,[‡] Akira Iida,[‡] and Kiyoshi Tomioka*,[‡]

Faculty of Pharmaceutical Sciences Kyoto University, Sakyo, Kyoto 606-01, Japan ISIR, Osaka University Mihogaoka, Ibaraki, Osaka 567, Japan

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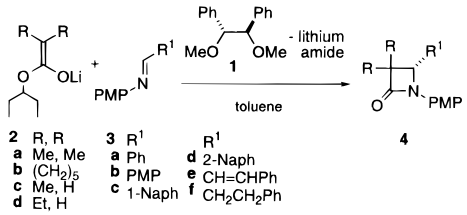
Lithium ester enolate is among the established, powerful carbonucleophiles in the formation of carbon−carbon bonds.[1] The extended application of the reagent into asymmetric reactions has been a considerable challenge in synthetic organic chemistry.[2] Indeed, there have been significant achievements in the development of the chiral ester[3] and its equivalents such as oxazoline,[4] acyloxazolidinone,[5] and acylsultam,[6] even though these require at least a stoichiometric amount of a chiral auxiliary. Another promising approach relies on a chiral external ligand, which opens a catalytic way to an asymmetric reaction.[7] The use of a stoichiometric amount of a chiral lithium amide or chiral amine has been reported as an external chiral ligand that forms a chiral, binary complex with a lithium ester enolate.[8] The binary complex of the lithium ketone enolate−lithium amide has been demonstrated by X-ray crystallography and NMR studies.[9,10] However, the asymmetric addition of the lithium ester enolate to the azomethine group in the presence of an external chiral ligand is quite undeveloped in comparison with efforts on record in the area of asymmetric addition of the chiral lithium enolate to a chiral imine.[11] We have been involved in the development of both stoichiometric and catalytic asymmetric reactions of organolithiums with the aid of chiral external ligands.[12,13] We describe herein the stoichiometric and catalytic asymmetric reactions of lithium ester enolates **2** with imines **3** based on a ternary complex reagent, which comprises three components: a chiral ether ligand (**1**), an achiral lithium amide, and **2**, giving the corresponding β-lactams **4** in high enantiomeric excess (ee).



The reaction of lithium ester enolate **2a**, generated from 3-pentyl isobutylate (2.0 equiv) and lithium diisopropylamide (LDA, 2.2 equiv), with benzaldehyde anisidine imine **3a** in the presence of a chiral ether (**1**) (2.6 equiv)[14] in toluene at −20 °C for 7 h gave the corresponding β-lactam (*S*)-**4aa**[15] in 95% yield.[16] The enantioselectivity was determined to be 60% ee by chiral HPLC (DAICEL Chiralcel OD, *i*-PrOH/hexane = 1/100). After fruitless trial to improve the enantioselectivity, we finally found that coexistence of another lithium amide affects the selectivity and reactivity of **2a**. Thus, upon further addition of LDA (2.2 equiv), both the selectivity and reactivity were improved to afford (*S*)-**4aa** in 87% ee and 80% yield at −60 °C for 5 h.

The enantioselectivity and reactivity of the ternary complex depend on the size and nature of the lithium amide used as shown in Table 1 (entries 2−8). The lithium amide derived from bulky secondary amine such as 2,2,6,6-tetramethylpiperidine (LTMP) proved to have an unfavorable effect on reactivity and enantioselectivity and gave **4aa** in 26% ee and in low yield at −20 °C (entry 6).[17] The reaction in the presence of lithium cyclohexyl-*tert*-butylamide[18] proceeded at −50 °C to give, however, **4aa** in 55% ee and low yield (entry 5).[17] Lithium diphenylamide derived from more acidic diphenylamine gave **4aa** in 50% ee at −20 °C (entry 8). Fortunately, the lithium amides derived from cyclohexylisopropylamine (LICA) and

[†] Osaka University.
[‡] Kyoto University.

(1) Caine, D. In *Carbon-Carbon Bond Formation*; Augustine, R. L., Ed.; Marcel Dekker, Inc.: New York, 1979; p 85. Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, 317.

(2) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapters 1 and 2.

(3) Braun, M.; Devant, R. *Tetrahedron Lett.* **1983**, *24*, 4405−4408. Tanaka, F.; Node, M.; Tanaka, K.; Mizuchi, M.; Hosoi, S.; Nakayama, M.; Taga, T.; Fuji, K. *J. Am. Chem. Soc.* **1995**, *117*, 12159 and references cited therein.

(4) Lutomski, K. A.; Meyers, A. I. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 3.

(5) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739. Paloma, C.; Berree, F.; Lindent, A.; Villalgordo, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1861−1862. Hashimoto, N.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1994**, *35*, 721. Davies, S. G.; Doisneau, G. J.-M.; Prodger, J. C.; Sanganee, H. J. *ibid.* **1994**, *35*, 2369−2376. Sudo, A.; Saigo, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2153−2156.

(6) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397−1401.

(7) Bosnich, B. *Asymmetric Catalysis*; Martinus Nijhoff Publishers: Dordrecht, The Netherlands, 1986. Tomioka, K. *Synthesis* **1990**, 541−549. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons, Inc.: New York, 1994.

(8) Ester enolate: Yamashita, T.; Mitsui, H.; Watanabe, H.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 961−962. Mulzer, J.; de Lasalle, P.; Chucholowski, A.; Blaschek, U.; Bruntrup, G. Jibril, J.; Huttner, G. *Tetrahedron* **1984**, *40*, 2211−2218. Ando, A.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1620−1621. Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1. Uragami, M.; Tomioka, K.; Koga, K. *Tetrahedron: Asymmetry* **1995**, 6, 701−704. Ketone enolate: Hogeveen, H.; Menge, W. M. P. B. *Tetrahedron Lett.* **1986**, *27*, 2767−2770. Ando, A.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1987**, 656−658. Tomioka, K.; Shindo, M.; Koga, K. *Chem. Pharm. Bull.* **1989**, *37*, 1120−1122. Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1657−1658.

(9) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. Seebach, S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539−5541; **1990**, *112*, 8602−8604. Galiano-Roth, A. S.; Kim, Y. J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *Ibid.* **1991**, *113*, 5053−5055. Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

(10) Catalytic asymmetric alkylation of a lithium ketone enolate has been reported: Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829−8831.

(11) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. Kleinman, E. F. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 4.1. Baldoli, C.; Buttero, P. D. *J. Chem. Soc., Chem. Commun.* **1991**, 982−983. Fujioka, H.; Yamanaka, T.; Matsunaga, N.; Fujii, M.; Kita, Y. *Synlett* **1992**, 35−36. Ojima, I.; Park, Y. H.; Sun, C. M.; Brigaud, T.; Zhao, M. *Tetrahedron Lett.* **1992**, *33*, 5737−5740. Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151−1152. Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243−3245. Shimizu, M.; Teramoto, Y.; Fujisawa, T. *Tetrahedron Lett.* **1995**, *36*, 729−732.

(12) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732−8733. Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527−2533. Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Ibid.* **1996**, *7*, 2483−2484.

(13) A recent situation of the external ligand-controlled asymmetric reaction of organolithiums with imines has been summarized: Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999−1004.

(14) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266−8268.

(15) The first and second **a**'s of **4aa** refer to **2a** and **3a**, respectively. For example, **4bc** comes from **2b** and **3c**.

(16) The absolute configuration of (+)-(*S*)-**4aa** was unambiguously determined by converting to the *N*-demethoxyphenyl-β-lactam, the antipode of which was obtained by chemical conversion from (*R*)-D-phenylglycine (Kaseda, T.; Kikuchi, T.; Kibayashi, C. *Tetrahedron Lett.* **1989**, *30*, 4539−4542. Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Ibid.* **1982**, *23*, 465−468). The absolute configurations of other compounds were also determined by chemical correlation with (*R*)-D-phenylglycine. The absolute configurations of **4ac**, **4ad**, and **4ba** were tentatively assigned by analogy.

(17) The reaction gave a mixture of complex products.

(18) Stowell, J. C.; Padegimas, S. J. *Synthesis* **1974**, 127−128.

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Table 1. Asymmetric Reaction of the Ternary Complex of Lithium Ester Enolates **2** with Imines **3**, Giving **4**

entry	R, R	R^1	lithium amide	temp/°C[a]	time/h[a]	**4**	ee/%[a] (*cis*, *trans*)	yield/%[a] (*cis*, *trans*)
1	Me, Me	Ph	none	−20	7	**4aa**	60	95
2	Me, Me	Ph	LDA	−60	5		87	80
3	Me, Me	Ph	LICA	−50	4		88	85
4	Me, Me	Ph	$LiNcHex_2$	−50	4		86	76
5	Me, Me	Ph	LiNtBucHex	−50	1		55	22
6	Me, Me	Ph	LTMP	−20	1		26	12
7	Me, Me	Ph	LHMDS	−20	2		73	99
8	Me, Me	Ph	$LiNPh_2$	−20	7		50	60
9	Me, Me	PMP	LICA	−50	20	**4ab**	80	70
10	Me, Me	1-Naph	LICA	−50	15	**4ac**	75	40
11	Me, Me	2-Naph	LICA	−50	15	**4ad**	90	85
12	Me, Me	CH═CHPh	LICA	−78 (−20)	9 (7)	**4ae**	75 (60)	40 (59)
13	Me, Me	$(CH_2)_2Ph$	LDA	−78 (−40)	1 (15)	**4af**	90 (77)	80 (84)
14	$(CH_2)_5$	Ph	LICA	−50	15	**4ba**	75	83
15[b]	Me, H	Ph	LICA	−78 (−78)	10 s (0.5)	**4ca**	76, 73 (38, 16)	51, 13 (18, 2)
16[b]	Et, H	Ph	LDA	−78 (−40)	20 (2)	**4da**	70, 51 (52, 42)	54, 12 (45, 2)

[a] The numbers in parentheses represent temperature, time, ee, and yield obtained without a lithium amide. [b] The reaction was carried out by using 1.4 equiv of the ester.

dicyclohexylamine resulted in the increase of the reactivity of **2a** to afford **4aa** in 88 and 86% ees at −50 °C, respectively (entries 3, 4). It is also interesting that, while lithium hexamethyldisilazide (LHMDS) exhibited a slight activation effect,[19] however, it gave **4aa** in improved 73% ee (entry 7).

The influence of the amine, produced *in situ* by the lithium amide deprotonation of the ester, is marginal. Thus, the reaction of **2a**, prepared from the corresponding trimethylsilyl enol ether and BuLi, with **3a** in the presence of LDA and **1** gave **4aa** in comparable ee and yield.

The reaction of the appropriate ternary complex generally gives **4** in higher ee than the binary complex without assistance by a lithium amide (entries 9−16). It is also noteworthy that the imine **3f** bearing an extra methylene group at the α position does not suffer from deprotonation by a lithium amide, and is a suitable substrate to give (*S*)-**4af** in 90% ee and 80% yield (entry 13).

The ternary complex is the most reactive, even if an equilibrium between the binary complexes is possible. In the absence of both excess LDA and **1**, the lithium ester enolate **2a** reacted with **3a** in a toluene solvent at room temperature for 2 h to give racemic **4aa** in 99% yield, whereas no reaction took place below −20 °C to result in recovery of the imine. In the presence of excess LDA, **2a** reacted with **3a** at −20 °C for 3 h to give racemic **4aa** in 67% (30% recovery of **3a**), and upon addition of the chiral ether **1** the reaction smoothly took place at −60 °C for 5 h to give (*S*)-**4aa** in 87% ee and 80% yield. Thus, the reactivity of **2a** increases in the order of **2a** alone, **2a** + LDA, **2a** + **1**, and **2a** + **1** + LDA, indicating that coexistence of the lithium amide and chiral ether ligand is essential to increase the reactivity of the lithium ester enolate. This difference in the reactivity opens a new way to the catalytic process.

(19) The reaction was very sluggish below −20 °C.

The catalytic asymmetric process (0.2 equiv of **1**) is exemplified by the following: A solution of 3-pentyl isobutylate (2.0 mmol) and **1** (0.2 mmol) in toluene (3 mL) was added to a preformed solution of LDA (4.4 mmol) in toluene (9 mL) at −78 °C. The mixture was stirred at −25 °C for 1.5 h and cooled to −78 °C; to this solution was then added a solution of **3f** (1.0 mmol) in toluene (1.5 mL). After stirring at −78 °C for 20 h, usual workup and purification through silica gel column chromatography (AcOEt/hexane = 1/5) gave (*S*)-**4af** in 82% ee and 75% yield. The chiral ligand **1** was recovered for reuse in 99% yield.

Similarly, the catalytic reaction of **2a** with **3a** in the presence of LICA (2.4 equiv) and **1** (0.2 equiv) gave **4aa** in 75% ee and 80% yield. Since the same reaction of **2a** with **3a** in the presence of **1** (0.2 equiv) without LICA gave **4aa** in 50% ee, the advantage of the catalytic process of the ternary complex is apparent.

Although further studies are required to elucidate the precise nature of the ternary complex and improve the selectivity,[20] we believe that the results demonstrated here would provide the basis for a catalytic asymmetric reaction of the lithium ester enolate.

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Supporting Information Available: Details of the experimental procedure, characterization data, and determination of the absolute configuration (6 pages). See any current masthead page for ordering and Internet access instructions.

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(20) Recently we have been focusing our efforts to find an appropriate chiral external ligand other than **1**. It is worth noting that (−)-sparteine, which is highly effective in some other reactions (Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516−2518), gave (*R*)-**4aa** in an unsatisfactory 9% ee.