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Direct Catalytic Asymmetric Mannich-Type Reaction of α-Sulfanyl Lactones

Sho Takechi,[†,‡] Naoya Kumagai,[*,†] and Masakatsu Shibasaki[*,†,§]

Institute of Microbial Chemistry (BIKAKEN), Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and JST, ACT-C, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

nkumagai@bikaken.or.jp; mshibasa@bikaken.or.jp

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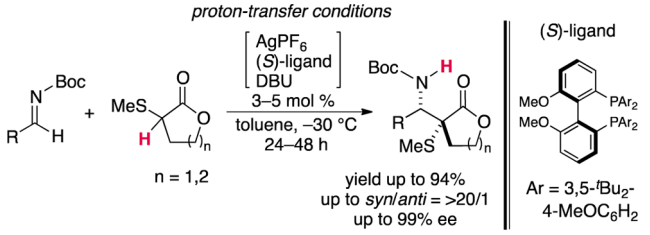
ABSTRACT



Catalytic asymmetric Mannich-type reactions of α-sulfanyl lactones to aldimines were promoted by a chiral Ag complex/DBU binary catalyst. The reaction proceeded in a *syn*-selective manner in high enantioselectivity. Alkylative activation of the sulfide of the Mannich adduct allowed for the formation of trisubstituted aziridines.

Catalytic asymmetric Mannich reactions offer direct access to the optically active β-amino carbonyl architecture,[1] which serves as a synthetically useful chiral building block for biologically important nitrogen-containing compounds.[2] Among them, a direct type of reaction in which the generation of active enolates and enantioselective addition are integrated in one pot meets the increasing demand for the development of environmentally benign processes; preformation of active enolate species in separate processes and coproduction of undesirable wastes can be avoided.[3] Although considerable effort has been devoted to developing direct Mannich reactions during the past decade, there is still room for improvement: readily enolizable aldehydes or ketones have been selected as privileged pronucleophiles,[3] while less acidic pronucleophiles

[†] Institute of Microbial Chemistry (BIKAKEN), Tokyo.
[‡] The University of Tokyo.
[§] JST, ACT-C.

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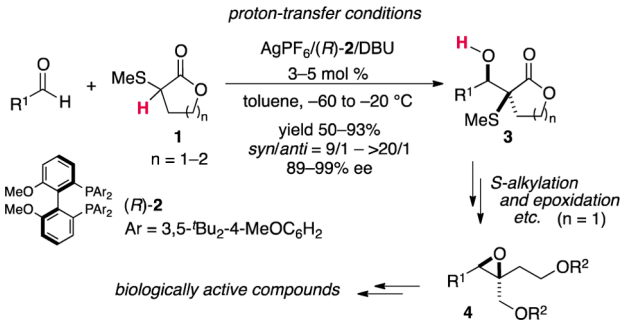
in the carboxylic oxidation state have been largely neglected because of their reluctance to form active enolates through in situ deprotonation.[4,5]

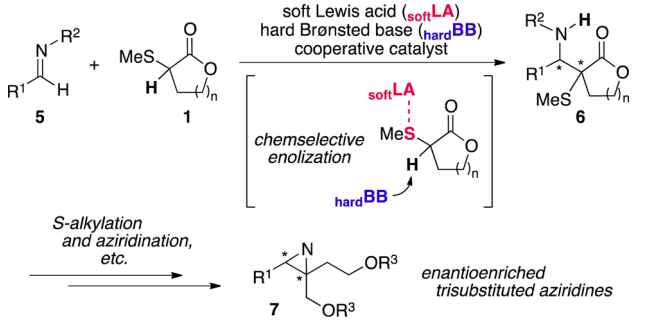
Scheme 1. Direct Catalytic Asymmetric Aldol Reaction of α-Sulfanyl Lactones **1**



Recently, we reported a direct catalytic asymmetric aldol reaction of α-sulfanyl lactones **1** promoted by a soft Lewis acid/hard Brønsted base cooperative catalytic system comprised of $AgPF_6$, a BIPHEP-type ligand (*R*)-**2**, and DBU.[6,7] Soft–soft interaction between Ag and the sulfanyl moiety afforded in situ chemoselective activation of α-sulfanyl lactones **1** to catalytically generate the corresponding enolates by the synergistic action of the mild Brønsted base (Scheme 1).[6] Even in the presence of highly enolizable α-nonbranched aliphatic aldehydes, preferential enolate formation of **1** proceeded to afford the corresponding aldol products **3** with high stereoselectivity, highlighting the potency of chemoselective activation through soft–soft interaction. The sulfanyl moiety of the product **3** served as a latent leaving group upon S-alkylation to produce trisubstituted epoxide **4**, endorsing the utility of the products as chiral building blocks.

On the basis of the robustness of the chemoselective activation strategy of α-sulfanyl lactones **1** with the cooperative catalytic system and productive replacement of the sulfanyl group after the reaction,[6] we envisaged developing a direct catalytic asymmetric Mannich-type reaction of aldimine **5** and α-sulfanyl lactones **1**, which is in the carboxylic acid oxidation state (Scheme 2).[8] Analogous manipulation of the Mannich product **6** would produce enantiomerically enriched trisubstituted aziridines **7**. Although there are a few leading examples of the enantioselective synthesis of trisubstituted aziridines by coupling of imines and α-diazocarbonyl compounds,[9–11] potentially explosive α-diazocarbonyl compounds are required and our protocol offers complementary access.

Scheme 2. Direct Catalytic Asymmetric Mannich-Type Reaction of α-Sulfanyl Lactones **1**



Initial investigations of the $AgPF_6$/(*S*)-**2**/DBU binary catalyst system,[6,12] which was prepared by mixing the components in a 1:1:1 molar ratio, in Mannich-type reactions were conducted with a five-membered α-sulfanyl lactone **1a** and various *N*-protected aldimines derived from 4-fluorobenzaldehyde **5a–c**. At room temperature, the reaction using Ts-protected aldimine **5a** afforded *syn*-adduct **6aa** predominantly with excellent enantioselectivity, albeit with modest reactivity (Table 1, entry 1). The aldimine bearing *N*-diphenylphosphinoyl ($P(O)Ph_2$) group **5b** exhibited worse reactivity, and the enantioselectivity decreased significantly (entry 2).[13] In contrast, the reaction of *N*-Boc protected aldimine **5c** reached completion under identical conditions, affording *syn*-adduct **6ac** in 89% ee (entry 3). **5c** was much more soluble in toluene than **5a** and **5b**, and the reaction could be performed at −30 °C under homogeneous conditions, affording the product **6ac** in almost perfect stereoselectivity (entry 4).

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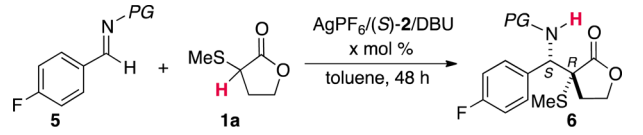
Table 1. Direct Catalytic Asymmetric Mannich-Type Reaction of α-Sulfanyl Lactones **1a** and Aldimines **5a**–**c**[a]



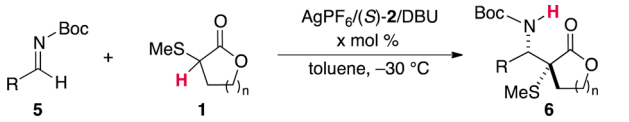
	imine **5**							ee[d](*syn*)
entry	PG =		x	product	temp (°C)	yield[b] (%)	*syn*/*anti*[c]	(%)
1	Ts	**5a**	5	**6aa**	rt	67	>20/1	99
2	$P(O)Ph_2$	**5b**	5	**6ab**	rt	18	>20/1	63
3	Boc	**5c**	5	**6ac**	rt	74	12/1	89
4[e,f]	Boc	**5c**	5	**6ac**	−30	85	>20/1	99
5[e]	Boc	**5c**	3	**6ac**	−30	89	>20/1	99

[a] $AgPF_6$/(*S*)-**2**/DBU = 1:1:1. **1a**: 0.2 mmol. **5**: 0.24 mmol, 0.2 M. [b] Determined by ^1H NMR analysis with $(CHCl_2)_2$ as an internal standard. [c] Determined by ^1H NMR analysis. [d] Determined by chiral stationary phase HPLC. [e] Run at 0.5 M. [f] Reaction time was 24 h.

The catalyst loading could be reduced to 3 mol % with no loss of stereoselectivity (entry 5).[14] Irrespective of the protecting group on the nitrogen, *syn*-(2*R*,3*S*)-adducts were predominantly obtained,[15] suggesting that the C–C bond formation between the Ag-enolate of **1a** and imines **5** proceeded through a similar transition state irrespective of the protecting group on the nitrogen.

The scope of the direct catalytic Mannich-type reaction of **1** with Boc imines is summarized in Table 2.[16] Although *syn*-adducts were predominantly produced with uniformly high enantioselectivity, the reactivity and diastereomeric ratio were dependent on the electronic nature of the substituents on the aromatic ring. Aromatic imines bearing electron-deficient substituents **5c**,**d**,**e** produced Mannich adducts in high diastereo- and enantioselectivity (entries 1–3). As the electron density of the aromatic ring increased, the diastereoselectivity decreased steadily (entries 4–6). Prochiral-face selection of approaching imines was compromised with electron-rich imines, presumably because the higher Lewis basicity of the imine nitrogen had a negative effect. The particularly low yield in the reaction of MeO-substituted imine **5h** was ascribed to its intrinsic low electrophilicity (entry 6). Replacing the 4-MeO group with an electron-withdrawing 4-TfO group enhanced both the reactivity and stereoselectivity (entry 7). The reaction could be run on 2.3 g scale with no detrimental effect, and facile recrystallization provided optically pure product **6ai** in 75% yield (entry 8). Imines having a heteroaromatic ring were applicable to the present catalysis (entries 9, 10). A pyridyl group could potentially coordinate to Ag and compromise the stereochemical outcome, but imine **5j** was

Table 2. Direct Catalytic Asymmetric Mannich-Type Reaction of α-Sulfanyl Lactones **1** and Boc-Aldimines **5**[a]



	imine **5**		**1**							ee[d]
entry	R =		*n* =		x	time (h)	product	yield[b] (%)	*syn*/*anti*[c]	(%)
1	$4\text{-}FC_6H_4$	**5c**	1	**1a**	3	48	**6ac**	79	>20/1	99
2	$4\text{-}ClC_6H_4$	**5d**	1	**1a**	3	48	**6ad**	78	>20/1	99
3	$4\text{-}NO_2C_6H_4$	**5e**	1	**1a**	3	48	**6ae**	87	>20/1	99
4	Ph	**5f**	1	**1a**	3	24	**6af**	80	14/1	96
5	$4\text{-}MeC_6H_4$	**5g**	1	**1a**	5	48	**6ag**	70	7/1	97
6	$4\text{-}MeOC_6H_4$	**5h**	1	**1a**	5	48	**6ah**	42	6/1	97
7	$4\text{-}TfOC_6H_4$	**5i**	1	**1a**	5	24	**6ai**	79	>20/1	96
8[e]	$4\text{-}TfOC_6H_4$	**5i**	1	**1a**	5	24	**6ai**	75	>20/1	>99
9	3-pyridyl	**5j**	1	**1a**	5	48	**6aj**	89	>20/1	94
10	2-furyl	**5k**	1	**1a**	3	48	**6ak**	94	6/1	97
11	$^nC_5H_{11}$	**5l**	1	**1a**	5	48	**6al**	71	>20/1	99
12	3-pyridyl	**5j**	2	**1b**	5	48	**6bj**	88	>20/1	82
13[f]	$PhCH_2CH_2$	**5m**	2	**1b**	5	50	**6bm**	49	>20/1	96
14	Ph	**5f**	3	**1c**	5	48	**6cf**	0	–	–

[a] $AgPF_6$/(*S*)-**2**/DBU = 1:1:1. **1**: 0.2 mmol. **5**: 0.24 mmol. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Ee of *syn*-adduct, determined by chiral stationary phase HPLC. [e] 2.3 g of **5i** were used. Yield and stereoselectivity were determined after recrystallization. [f] 1.5 equiv of imine **5m** (0.3 mmol) were used.

served as an electron-deficient imine and afforded the *syn*-adduct in high stereoselectivity (entry 9). The reaction conditions were sufficiently mild to allow the reaction with the nonbranched aliphatic imine **5l**, which is susceptible to tautomerization to the corresponding enamine (entry 11). Whereas six-membered α-sulfanyl lactone **1b** could be applicable as a pronucleophile, less reactivity or lower enantioselectivity was observed (entries 12, 13). The present catalytic system failed to promote the reaction of ε-lactone **1c**, probably because of reluctant formation of the enolate (entry 14).

Further manipulation of the Mannich adducts is outlined in Scheme 3. Oxidation of the sulfanyl group of **6af** with *m*CPBA followed by *syn*-elimination of the transient sulfoxide under elevated temperature gave α,β-unsaturated

(14) The reaction in the absence of either $AgPF_6$ or DBU produced no desired product, suggesting that cooperative catalysis of a soft Lewis acid and hard Brønsted base is essential.

(15) See Supporting Information.

(16) The absolute configuration of **6af** was determined by X-ray crystallographic analysis.

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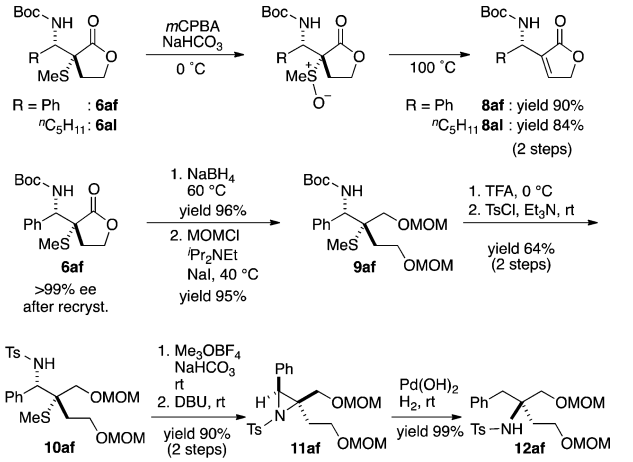
(19) Azirine formation with Boc amide resulted in poor yield.

Scheme 3. Transformations of the Product



butyrolactone **8af**, which is analogous to aza-Morita–Baylis–Hillman products from 2-furanone.[17,18] This procedure could be applied to Mannich adduct **6al**, derived from aliphatic imine to afford corresponding product **8al** in 84% yield. Facile recrystallization provided enantiomerically pure **6af**, which was reduced by $NaBH_4$, and newly generated primary alcohols were protected by a MOM group to give **9af**. The protecting group on nitrogen was converted from Boc to Ts,[19] and subsequent treatment with Meerwein's salt afforded an *S*-methylated sulfonium intermediate, which was transformed into trisubstituted aziridine **11af** with DBU. Hydrogenolysis of the aziridine **11af** over $Pd(OH)_2$ produced α,α-disubstituted α-amino acid derivative **12af**.

In summary, we have developed a catalytic asymmetric Mannich-type reaction of α-sulfanyl lactones and aldimines promoted by the soft Lewis acid/hard Brønsted base cooperative catalyst $AgPF_6$/(*S*)-**2**/DBU. Two contiguous stereogenic centers were newly constructed in a preferential *syn*-configuration with high enantioselectivity. The *β*-amino-α-methylthio scaffold embedded in the adduct was utilized to give enantioenriched trisubstituted aziridine, a pivotal intermediate for α,α-disubstituted α-amino acid derivatives.

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

The authors declare no competing financial interest.