Asymmetric Aldol Reaction

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A Direct Catalytic Asymmetric Aldol Reaction of α-Sulfanyl Lactones: Efficient Synthesis of SPT Inhibitors**

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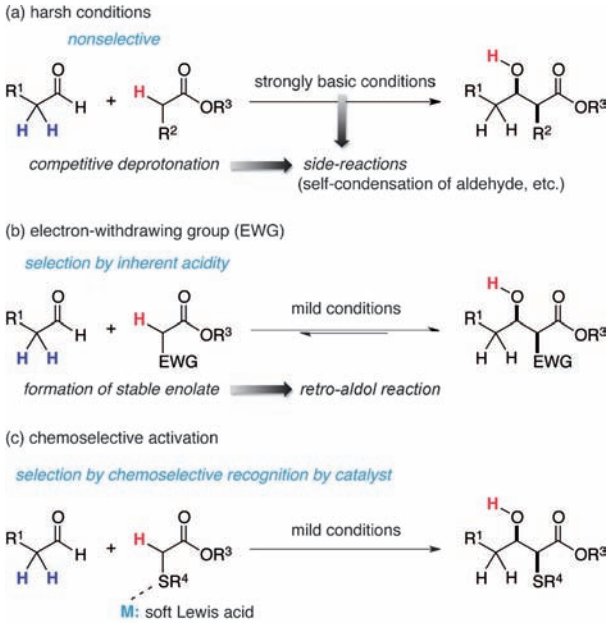
The direct catalytic asymmetric aldol reaction continues to attract interest because it employs a well-known and robust transformation for the efficient and atom-economical production of enantiomerically enriched β-hydroxy carbonyl compounds. An aldol donor and acceptor are used directly, without the need for the pre-formation or pre-activation of the enolate species, for enantioselective C–C bond formation.[1,2] The in situ catalytic generation of active enolates from aldol donors is the initial step in direct aldol reactions and thus the scope of the aldol donor is usually limited to carbonyl compounds bearing α protons of relatively high acidity, e.g. aldehydes and ketones that are amenable to facilitated deprotonation or enamine formation.[1] Aldol donors in the carboxylic acid oxidation state are not substrates for enamine formation and the harsh reaction conditions that are required for their catalytic deprotonation[3] severely limits the scope of compatible aldol acceptors (aldehydes), and frequently promote side reactions (Scheme 1 a). The development of direct aldol reactions that involve esters as aldol donors is still in its infancy and currently relies on the presence of additional electron-withdrawing groups to lower the deprotonation barrier (Scheme 1 b).[4] The scope of this approach is limited because the inherent acidity of these aldol donors means that under the proton-transfer conditions of the direct aldol reaction, the retro-aldol reaction also occurs.[5] To address the above problems and achieve the catalytic generation of ester enolates and subsequent C–C bond formation, we reasoned that a chemoselective activation strategy would promote the aldol reaction and not the undesired side reactions, under mild conditions. Specifically, we sought to take advantage of a soft–soft interaction to differentiate between esters (aldol donors) and aldehydes (aldol acceptors) by introducing the sulfide functionality at the α position of the ester aldol donor (Scheme 1 c). Although the electronegativity values of sulfur and carbon atoms are similar, α-sulfanyl carbonyl compounds have an inherently more acidic α proton than the parent carbonyl compounds because the sulfide functionality stabilizes the α carbanion through appreciable stereoelectronic effects.[6] We hypothesized that α-sulfanyl esters would be more susceptible to deprotonation than aldehydes in the presence of a soft Lewis acid as a result of an activation involving selective coordination of the Lewis acid to the α-sulfanyl moiety. Furthermore, such an activation of the sulfide-containing product would be disfavored because of steric hindrance and thus the retro-aldol reaction would be suppressed.



Scheme 1. Strategies for direct aldol reaction of esters as aldol donor.

Our recent development of soft Lewis acid/hard Brønsted base cooperative catalysis,[7,8] led us to initially explore a chemoselective activation strategy using a soft Lewis acid/amine binary catalytic system. Early in our investigation, we observed that α-sulfanyl lactones **1** were superior substrates to acyclic α-sulfanyl esters in the direct aldol reaction.[9] Initially, a range of soft Lewis acids were screened in combination with biphep-type ligand (*R*)-**4** and DBU for the reaction of 2-methylsulfanyl-γ-butyrolactone (**1a**) and 3-phenylpropanal (**2a**; Table 1). $AgPF_6$ was superior in terms of catalytic activity, thus affording *syn* **3aa** preferentially, in 68% yield and 98% *ee* after 2 hours at 0°C (Table 1, entries 1–

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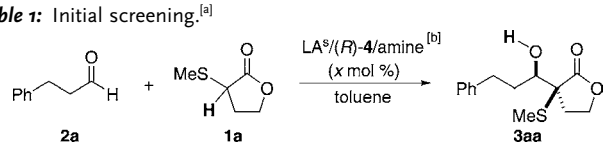
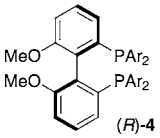
Table 1: Initial screening.[a]



2a **1a** **3aa**

Entry	Soft Lewis acid	Amine	*x*	*T* [°C]	*t* [h]	Yield[d] [%]	*Syn*/*Anti*[e]	*ee* [%] (*syn*)
1	CuOTf[c]	DBU	5	0	2	5	>20:1	–
2	$AgPF_6$	DBU	5	0	2	68	13:1	98
3	$[Pd(CH_3CN)_4](BF_4)_2$	DBU	5	0	2	trace	–	–
4	$Ni(OTf)_2$	DBU	5	0	2	trace	–	–
5	$AgClO_4$	DBU	5	0	2	79	6.7:1	95
6	$AgSbF_6$	DBU	5	0	2	51	14:1	98
7	$AgPF_6$	*i*Pr_2NEt	5	0	20	1	–	–
8	$AgPF_6$	TBD	5	0	2	86	2.1:1	82
9	$AgPF_6$	DBU	5	−20	20	98	>20:1	99
10	$AgPF_6$	DBU	3	−20	48	93[f]	18:1	99

[a] **1a**: 0.2 mmol, **2a**: 0.24 mmol. [b] Soft Lewis acid/(*R*)-**4**/amine = 1:1:1. [c] CuOTf·$^1/_2$toluene was used. [d] Determined by ^{1}H NMR analysis with $(CHCl_2)_2$ as an internal standard. [e] Determined by ^{1}H NMR analysis. [f] Yield of isolated product. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, LA^s = soft Lewis acid, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene, Tf = trifluoromethanesulfonyl.

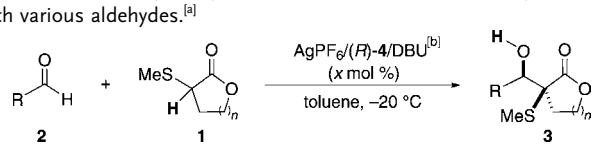


(*R*)-**4**

Ar = 3,5-(*t*Bu)$_2$-4-MeOC$_6$H$_2$

TBD

Table 2: Direct catalytic asymmetric aldol reaction of α-sulfanyl lactones with various aldehydes.[a]



2 **1** **3**

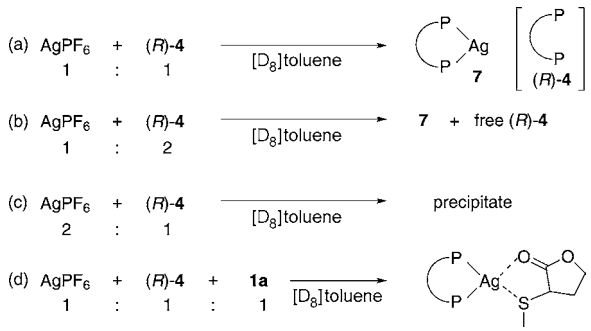
Entry	R	**2**	*n*	**1**	*x*	**3**	*t* [h]	Yield[c] [%]	*Syn*/*Anti*[d]	*ee* [%] (*syn*)
1	$Ph(CH_2)_2$	**2a**	1	**1a**	3	**3aa**	48	93	18:1	99
2	nC_7H_{15}	**2b**	1	**1a**	5	**3ab**	48	77	13:1	99
3	*i*Bu	**2c**	1	**1a**	5	**3ac**	48	81	10:1	99
4	$BnOCH_2$	**2d**	1	**1a**	3	**3ad**	48	85	9:1	99
5	$PMBOCH_2$	**2e**	1	**1a**	3	**3ae**	24	81	13:1	98
6	$TBSOCH_2$	**2f**	1	**1a**	5	**3af**	48	87	>20:1	98
7	H (formalin)	**2g**	1	**1a**	5	**3ag**	24	50	–	89
8	$CbzNH(CH_2)_2$	**2h**	1	**1a**	5	**3ah**	48	89	10:1	98
9	$EtO_2C(CH_2)_2$	**2i**	1	**1a**	5	**3ai**	72	70	13:1[e]	99
10	2-py-$(CH_2)_2$	**2j**	1	**1a**	5	**3aj**	36	58	14:1	98
11[g]	$Ph(CH_2)_2$	**2a**	2	**1b**	3	**3ba**	24	79	>20:1	99
12[h]	$BnOCH_2$	**2d**	2	**1b**	3	**3bd**	15	92	>20:1	99
13	$BnOCH_2$	**2d**	3	**1c**	5	**3cd**	24	trace[f]	–	–
14[g]	2-furyl	**2k**	1	**1a**	5	**3ak**	48	50	15:1	96

[a] **1**: 0.2 mmol, **2**: 0.24 mmol. [b] $AgPF_6$/(*R*)-**4**/DBU = 1:1:1. [c] Yield of isolated product. [d] Determined by ^{1}H NMR analysis of the crude mixture. [e] Determined after column chromatography. [f] Based on ^{1}H NMR analysis. [g] Reaction temperature was −60 °C. [h] Reaction temperature was −50 °C. Bn = benzyl, Cbz = benzyloxycarbonyl, PMB = *p*-methoxybenzyl, py = pyridyl, TBS = *tert*-butyldimethylsilyl.

4).[10] Among the silver salts examined, $AgSbF_6$ exhibited comparable catalytic activity to $AgPF_6$ (Table 1, entries 2, 5, and 6). With regard to the base, the use of the weaker amine base *i*Pr_2NEt failed to promote the reaction, even after 20 hours of stirring the reaction mixture, and the use of the guanidine-type base, TBD, led to conversion to product **3aa** but with decreased stereoselectivity (Table 1, entries 7 and 8).[11] When the $AgPF_6$/(*R*)-**4**/DBU binary catalyst system was used, the reaction proceeded at −20 °C to give **3aa** in excellent stereoselectivity (Table 1, entry 9; *syn*/*anti* = 20:1, 99% *ee* for the *syn* product), and under these reaction conditions the catalyst loading could be lowered to 3 mol% without significant impact (Table 1, entry 10).[12]

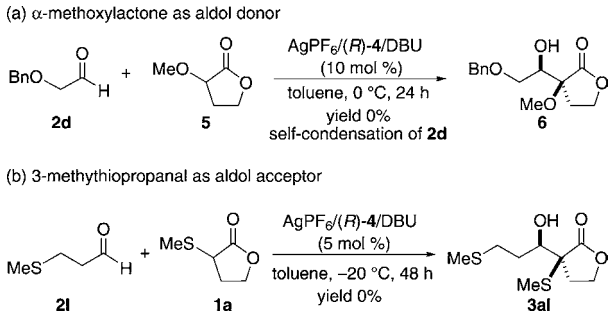
The use of the $AgPF_6$/(*R*)-**4**/DBU binary catalyst was an efficient protocol for the direct asymmetric aldol reaction of α-sulfanyl lactones **1** with a wide range of aldehydes (Table 2). α,α-Nonbranched aldehydes, which are susceptible to self-aldol reactions under strongly basic conditions because of their high propensity toward enolization, afforded the desired aldol products in good yield and selectivity (Table 2, entries 1–10); this selectivity is believed to result from the preferential enolization of **1a**, because of the soft–soft interaction between the Ag and the α-sulfanyl group. Aldehydes with alkyl substituents and those with oxygen-containing substituents were compatible, thus delivering the desired products in high *syn* selectivity and enantioselectivity (entries 1–6). Notably, the use of formalin was successful, thus representing an operationally simple enantioselective hydroxymethylation and indicating that the present catalytic system is not sensitive to moisture (Table 2, entry 7). Aldehydes bearing a carbamate or ester group (**2h** and **2i**) were also compatible (Table 2, entries 8 and 9). The use of α-pyridyl-substituted aldehyde **2j** resulted in the isolation of the desired product **3aj** with high stereoselectivity but in only moderate yield; the lower yield was attributed to competitive coordination of the pyridyl moiety to the silver catalyst (Table 2, entry 10). The reactions of six-membered lactone, 2-methylsulfanyl-δ-valerolactone (**1b**) with aldehydes **2a** and **2d**, were conducted at a lower temperature (−60 and −50 °C, respectively) to give the products **3ba** and **3bd**, respectively, with high stereoselectivity (Table 2, entries 11 and 12). A significantly slower reaction was observed with seven-membered lactone **1c**, with only a trace amount of product **3cd** being detected after 24 hours (Table 2, entry 13). The reaction of furfural (**2k**) with α-sulfanyl lactone **1a** was conducted at low temperature (−60 °C) to afford the aldol product in moderate yield (Table 2, entry 14).[13]

Our mechanistic hypothesis, involving the preferential activation of **1**, was supported by the following experiments. ^{1}H and ^{31}P NMR spectroscopy and mass spectrometry indicated that a 1:1 Ag/(*R*)-**4** complex was predominantly formed when $AgPF_6$ and (*R*)-**4** were mixed in a 1:1 ratio in [D_8]toluene (Scheme 2a).[14–16] Although for a Ag/binap catalyst system there is literature precedent for the formation of multiple complexes, the composition of which depends on the stoichiometry of the Ag salts and binap, the steric bulk of (*R*)-**4** would prevent the formation of the 1:2 Ag/(*R*)-**4** complex, even when (*R*)-**4** was added in excess (Scheme 2b).[17,18] An attempt to form the 2:1 Ag/(*R*)-**4** complex by mixing $AgPF_6$ and (*R*)-**4** in a 2:1 stoichiometry,



Scheme 2. Formation of Ag complexes based on ^{1}H and ^{31}P NMR spectroscopy analyses and mass spectrometry.

led to the immediate formation of a precipitate, which is presumably high-molecular-weight coordination oligomers formed through aggregation (Scheme 2c).[15] The addition of α-sulfanyl lactone **1a** to a solution of the 1:1 Ag/(*R*)-**4** complex **7** in toluene led to the formation of a new species, as indicated by the formation of a new set of resonances in the ^{1}H NMR spectrum and an upfield shift in the ^{31}P NMR spectrum (Scheme 2d). This result is consistent with the formation of a complex, in which the α-methylsulfanyl group of **1a** is coordinated to the metal center of Ag complex **7**, thus activating the α position of **1a** for deprotonation by DBU and thereby generating a Ag enolate in a chiral environment.[15] In contrast, analysis of the ^{1}H and ^{31}P NMR spectra of a mixture obtained by the addition of 2-methoxy-γ-butyrolactone (**5**), an oxygen analogue of **1a**, to complex **7** did not indicate the formation of a new species.[15] When the direct aldol reaction between aldehyde **2d** and **5** with the $AgPF_6$/(*R*)-**4**/DBU binary catalyst was attempted, the desired aldol product **6** was not observed and many side products were seen; these side products are presumably attributable to the enolization/self-condensation of the aldehyde **2d** (Scheme 3a). This finding is consistent with the absence of an activating interaction between the aldol donor **5** and the Ag complex **7**, thus leading to the preferential deprotonation of the aldehyde **2d**. The catalytic cycle was completely inhibited by the presence of an aldehyde bearing a methylsulfanyl group, **2l**, a result that is most likely attributable to competitive coordination of **2l** to the Ag complex **7** (Scheme 3b).[19] A kinetic study indicated that the rate of the reaction had a nearly first-order dependency on the concentrations of the aldehyde and the



Scheme 3. Control experiments.

catalyst, but a zero-order dependence on the concentration of α-sulfanyl lactone **1a**;[15] such a rate law supports a fast and quantitative coordination of **1a** to the Ag complex and a rate-limiting aldol addition step involving the metal-coordinated enolate and the aldehyde. A transition-state model based on the calculated structure of the Ag/(*R*)-**4**/enolate complex is depicted in Figure 1.[20] The methyl group on the sulfur atom is placed out of the enolate plane to occupy the open space, thus

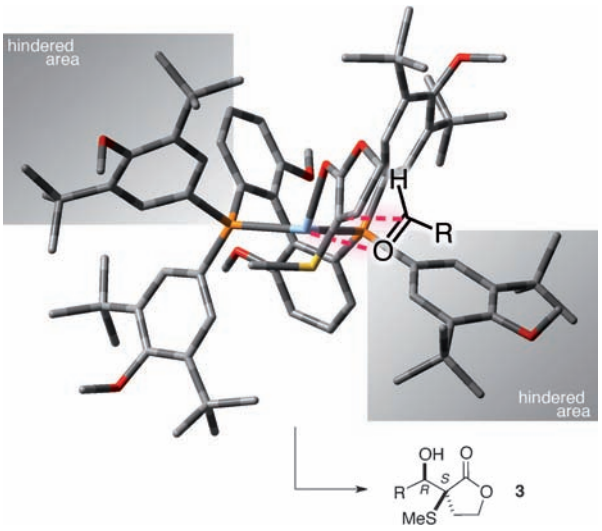
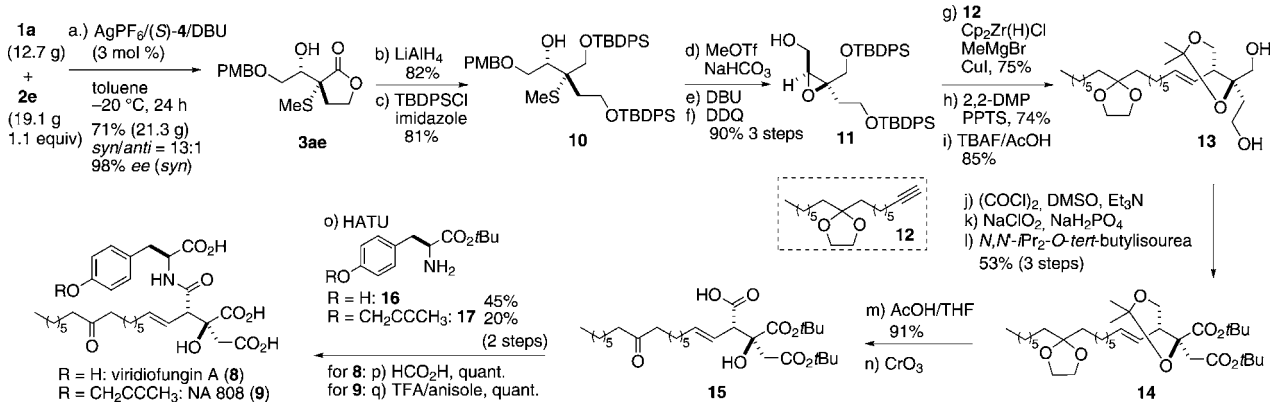


Figure 1. Proposed transition state.

in an asymmetric environment, presumably because this conformation facilitates maximal overlap of the C(Me)–S σ* and enolate π orbitals.[7a,b] With the methyl group shielding one side of the enolate, the aldehyde would then preferentially approach the alternative side of the enolate, thus affording the aldol product **3** with the observed stereochemistry.

We then turned our attention to the synthetic utility of this direct aldol reaction. Specifically, the use of the α-methylsulfanyl group of the aldol product **3ae** as a latent leaving group would allow for an efficient incorporation of the polar head group of viridiofungin A (**8**)[21,22] and NA808 (**9**),[22,23] which are known serine palmitoyl transferase (SPT) inhibitors. SPT is a rate-limiting enzyme in sphingolipid biosynthesis and inhibitors thereof may serve as potential drugs that block the proliferation of the hepatitis C virus.[23–25] The direct catalytic asymmetric aldol reaction between aldehyde **2e** and α-sulfanyl lactone **1a**, was scaled up to a 19.1 g reaction, with respect to the aldehyde, without any adverse effects on catalytic efficiency, thus affording **3ae** in 71% yield with *syn*/*anti* = 13:1 and 98% *ee* (Scheme 4). Reduction of the lactone **3ae** with $LiAlH_4$ and selective protection of the resulting primary alcohols as their TBDPS ethers gave **10**. S-Methylation using MeOTf and subsequent treatment with DBU afforded an epoxide with the liberation of Me_2S. Removal of the PMB group using DDQ gave the known epoxide **11**,[23] which was then subjected to an epoxide-opening reaction with a *trans*-vinyl cuprate, which was generated from terminal alkyne **12**. The resulting 1,3-diol was protected as the



Scheme 4. Synthesis of SPT inhibitors, viridiofungin A and NA 808. Reaction conditions: a) $AgPF_6$/(*S*)-**4**/DBU = 1:1:1 (3 mol%), toluene, −20 °C, 24 h, 71%, *syn*/*anti* = 13:1, 98% *ee* (*syn*); b) $LiAlH_4$ (6 equiv), THF, reflux, 1 h, 82%; c) TBDPSCl (2.2 equiv), Imidazole (6.0 equiv), DMF, RT, 2 h, 81%; d) MeOTf (1.2 equiv), $NaHCO_3$ (2 equiv), diethyl ether, RT, 16 h; e) DBU (4 equiv), diethyl ether, RT, 1 h, 95% (2 steps); f) DDQ (2.0 equiv), CH_2Cl_2/H_2O (20:1), RT, 1.5 h, 95%; g) **12** (5.2 equiv), $Cp_2Zr(H)Cl$ (5.5 equiv), MeMgBr (10.3 equiv), CuI (0.4 equiv), THF, −25 °C, 36 h, 75%; h) PPTS (1 mol%), CH_2Cl_2/2,2-DMP (5:4), RT, 37 h, 74%; i) TBAF (2.2 equiv), AcOH (2.0 equiv), THF, RT, 50 h, 85%; j) $(COCl)_2$ (8 equiv), DMSO (16 equiv), Et_3N (26 equiv), CH_2Cl_2, −78 °C, 1 h; k) $NaClO_2$ (10 equiv), NaH_2PO_4 (7.5 equiv), 2-methylbut-2-ene (70 equiv), *t*BuOH/H_2O (3:1), 0 °C, 4 h; l) *N*,*N*'-diisopropyl-*O*-*tert*-butylisourea (10 equiv), CH_2Cl_2, RT, 48 h, 53% (3 steps); m) AcOH/H_2O/THF (4:1:5), RT, 3 h, 91%; n) CrO_3 (2.5 equiv), acetone, −78 to 0 °C, 1 h; o) for **8** (R = H): **16** (3 equiv), HATU (3 equiv), iPr_2NEt (3 equiv), DMF, RT, 14 h, 45% (2 steps), for **9** ($R = CH_2CCH_3$): **17** (HCl salt) (2 equiv), HATU (2 equiv), iPr_2NEt (4 equiv), DMF, RT, 10.5 h, 20% (2 steps); p) for **8**: HCO_2H, RT, 1 h, quantitative; q) for **9**: anisole (9 equiv), TFA, 0 °C to RT, 16 h, quantitative. Cp = cyclopentadienyl, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, 2,2-DMP = 2,2-dimethoxypropane, DMSO = dimethylsulfoxide, HATU = (7-azabenzotriazol-1-yl)tetramethyluronium hexafluorophosphate, PPTS = pyridinium *p*-toluenesulfonate, quant. = quantitative yield, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TFA = trifluoroacetic acid.

acetonide and the TBDPS groups were removed to give diol **13**. Oxidation of the primary alcohols to the carboxylic acids and then esterification to the *tert*-butyl esters gave **14**. Hydrolysis of both the acetonide and the ketal under acidic conditions followed by Jones oxidation gave carboxylic acid **15**. Amide coupling reaction between L-tyrosine derivatives **16** and **17** and carboxylic acid **15** proceeded smoothly using HATU and subsequent hydrolysis of the *tert*-butyl esters using HCO_2H or TFA/anisole furnished **8** and **9**, respectively.

In summary, we have developed a direct catalytic asymmetric aldol reaction between α-sulfanyl lactones **1** and aldehydes that is promoted by a chiral Ag/DBU binary catalyst. Chemoselective activation of α-sulfanyl lactones **1** in the presence of aldehyde, made possible through specific coordination of the sulfur atom to the Ag cation, resulted in the preferential enolization of **1** and gave the desired aldol products **3** with high stereoselectivity. The efficient and stereospecific displacement of the sulfide functionality of the product **3ae** facilitated a rapid access to a densely functionalized tertiary alcohol in optically active form, which was subsequently used as an intermediate in an enantioselective synthesis of viridiofungin A (**8**) and NA 808 (**9**).

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[9] The catalytic generation of active enolates from acyclic α-sulfanyl esters did not occur under the reaction conditions .

[10] The absolute configuration of the product **3aa** was determined by X-ray crystallographic analysis. See the Supporting Information.

[11] When the reaction using the TBD base was allowed to proceed for 20 hours at 0 °C, the product was isolated with reversed diastereoselectivity and significantly decreased enantioselectivity, presumably because the retro-aldol reaction takes place (yield 82 %, *syn*/*anti* = 1:3.5, 21 % *ee* for the *syn* isomer). Even after only 2 h, the retro-aldol reaction was believed to occur, thus reducing the stereoselectivity.

[12] A further decrease of the catalyst loading resulted in a significantly lower conversion of substrate. The reaction in the absence of either $AgPF_6$ or DBU did not proceed.

[13] The retro-aldol reaction was prominent when aldehyde **2k** was used in the direct aldol reaction at −20 °C. The retro reaction was suppressed at lower temperature and the aldol product was obtained in high stereoselectivity, albeit with moderate yield.

[14] Tiny amount of 1:2 Ag/(*R*)-**4** complex was observed.

[15] See the Supporting Information for further details.

[16] Although the possibility of the formation of 2:2 and 3:3 Ag/(*R*)-**4** complexes etc. cannot be completely excluded, a dominant peak corresponding to 1:1 Ag/(*R*)-**4** complex **7** in the mass spectrum and an ^{107}Ag–^{31}P coupling constant (419 Hz) strongly suggested the formation of 1:1 Ag/(*R*)-**4** complex **7**.

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