Asymmetric Catalysis

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A Designed Amide as an Aldol Donor in the Direct Catalytic Asymmetric Aldol Reaction**

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Abstract: *The direct catalytic asymmetric aldol reaction offers efficient access to β-hydroxy carbonyl entities. Described is a robust direct catalytic asymmetric aldol reaction of α-sulfanyl 7-azaindolinylamide, thus affording both aromatic and aliphatic β-hydroxy amides with high ee values. The design of this transformation features a cooperative interplay of a soft and a hard Lewis acid, which together facilitate the challenging chemoselective enolization by a hard Brønsted base.*

The aldol reaction is a robust and widely used transformation of carbonyl compounds to construct β-hydroxy carbonyl units.[1] For the reliable coupling of aldol acceptors and aldol donors, preactivated aldol donors, for example, metal enolates or enol silyl ethers, are commonly used. Given the broad utility of β-hydroxy carbonyl fragments in organic synthesis, significant advances have been made to devise catalytic stereoselective aldol reactions based on the use of preformed enolates as aldol donors.[2,3] Since the first report of the intermolecular direct catalytic asymmetric aldol reaction which features in situ or direct generation of nucleophilically active enolates,[4] direct use of aldol donors has gained increasing attention in catalytic asymmetric aldol reactions.[1,5] The bottleneck in direct aldol methodology is the reluctance of enolate formation from aldol donors, and fairly acidic latent enolates such as ketones and aldehydes have been preferably adopted.[5] In this context, direct aldol reactions using less acidic carbonyl compounds, having a carboxylic acid oxidation state, have been much less explored because of their reluctance to form enolates.[6–13] Only the pioneering example of a direct catalytic asymmetric aldol reaction using amide-based aldol donors (N-Boc amide) has been reported with limited substrate scope and moderate *ee* values.[14] Specifically, the chemoselective formation of the active enolate of an amide aldol donor in the presence of an inherently more acidic aldehyde acceptor in a catalytic system is a formidable challenge. To address this issue, we designed a new amide aldol donor to override the intrinsic low acidity of amides so that the active enolate can be preferentially formed. Herein we report a direct catalytic asymmetric aldol reaction of α-sulfanyl 7-azaindolinylamide as an aldol donor, a reaction promoted by a Ag/Li-based cooperative asymmetric catalyst. This new aldol donor allows direct aldol reaction in a highly diastereo- and enantioselective fashion without self-condensation of the aldehydes.

We reasoned that the bidentate coordination of soft Lewis-basic functionalities, installed at suitable positions of an amide, to a soft Lewis-acidic metal might facilitate the chemoselective activation over aldehydes. The thus designed α-sulfanyl 7-azaindolinylamide (**1**), predominantly as the *E*-amide rotamer,[15,16] would form the seven-membered chelated structure **A** with the soft Lewis acid, in which the chelation would induce tilting the indolino group so as to partially break the amide conjugation (Figure 1). Moreover,

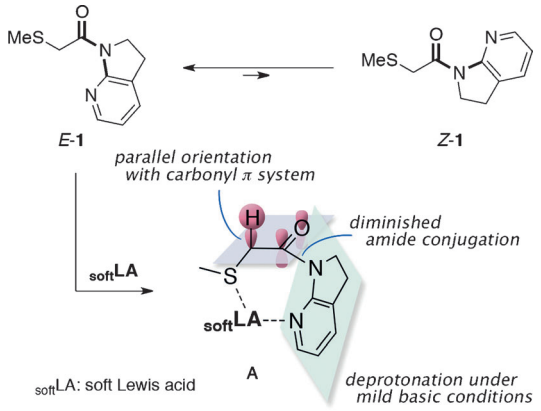

Figure 1. Working hypothesis for enolate formation from α-sulfanyl 7-azaindolinylamide (**1**). LA = Lewis acid.

the cyclic alignment would fix the α-C–H bond of the amide suitable for deprotonation, thus allowing enolate formation by the action of a mild Brønsted base. We anticipated that diminished amide conjugation and conformational restriction would work synergistically to generate an amide-derived enolate in the presence of a more enolizable aldehyde.[17]

Our recent development of soft Lewis acid/hard Brønsted base cooperative catalysis[18] led us to initially screen various cationic soft Lewis acids in combination with (*R*)-BINAP (**4**) and the lithium salt of 2,2,5,7,8-pentamethylchromanol as a Brønsted base (Table 1). Attempted reactions, in which isobutyraldehyde (**2a**) was used as the model substrate,

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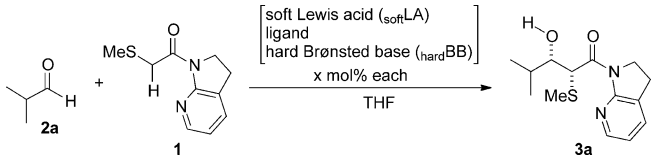
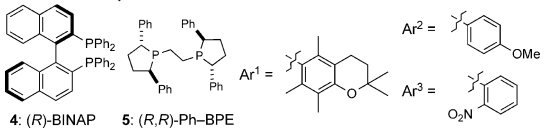
Table 1: Initial screening.[a]



Entry	softLA	Ligand	hardBB	x	Additive (x mol%)	T [°C]	t [h]	Yield [%][b]	anti/syn[b]	ee [%][c]
1	$CuPF_6$[d]	**4**	$LiOAr^1$	10	–	−40	24	82	23:77	15
2	$Ni(OTf)_2$	**4**	$LiOAr^1$	10	–	−40	24	79	28:72	1
3	$AgPF_6$	**4**	$LiOAr^1$	10	–	−40	24	64	18:82	38
4	$AgBF_4$	**4**	$LiOAr^1$	10	–	−40	24	86	31:69	57
5	$AgBF_4$	**5**	$LiOAr^1$	10	–	−60	24	72	9:91	43
6	$AgBF_4$	**5**	$LiOAr^2$	10	–	−60	24	49	9:91	63
7	$AgBF_4$	**5**	DBU	10	–	−60	24	0	–	–
8	$AgBF_4$	**5**	$NaOAr^2$	10	–	−60	24	0	–	–
9	$AgBF_4$	**5**	$KOAr^2$	10	–	−60	24	0	–	–
10[e]	(Ag)	**5**	$AgOAr^3$	10	–	−60	24	0	–	–
11	$AgBF_4$	**5**	$LiOAr^2$	10	LiOTf	−60	24	89	9:91	99
12	–	**5**	$LiOAr^2$	10	LiOTf	−60	24	0	–	–
13	$AgBF_4$	**5**	–	10	LiOTf	−60	24	0	–	–
14	$AgBF_4$	**5**	$LiOAr^2$	8	LiOTf	−60	36	87	9:91	99

[a] **1**: 1.0 mmol, **2a**: 1.2 mmol. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis. [d] Tetrakis(acetonitrile) complex was used. [e] $^-OAr^3$ anion was expected to function as base. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.



4: (*R*)-BINAP **5**: (*R*,*R*)-Ph–BPE

indicated that $AgBF_4$ served as a suitable Lewis acid to afford the corresponding *syn*-aldol product **3a** preferentially at −40 °C with moderate stereoselectivity (entries 1–4). Extensive screening of ligands identified (*R*,*R*)-Ph-BPE **5** as the preferred ligand and **3a** was produced in promising stereoselectivity at −60 °C (entry 5). Fluctuating stereoselectivity was observed as a result of the retro-aldol reaction. This was prevented by switching to the less basic $Li(OC_6H_4$-*p*-OMe) to obtain higher stereoselectivity in a reproducible manner (entry 6). Amine bases and the sodium or potassium aryloxides were ineffective, thus suggesting that the lithium cation plays a key role in promoting the reaction (entries 7–9). This assumption is in line with the ineffectiveness of **5**/$AgOAr^3$ as a cooperative catalyst (entry 10).[19,20] This finding directed us to use LiOTf as an additive, which led to an enhanced catalytic performance and higher *ee* value (entry 11). Control experiments in the absence of either the soft Lewis acid or Brønsted base failed, thus indicating that the cooperative effect was crucial for promoting the reaction (entries 12 and 13). The catalyst loading could be reduced to 8 mol% without any detrimental effect (entry 14). In striking contrast, the structurally related amide **6**, derived from 2-aminopyridine, completely failed the reaction under otherwise identical reaction conditions despite the likely formation of the bidentate chelation to a silver cation (Figure 2).[21] This outcome is presumably because flexible rotation along the C(py)–N(amide) bond allowed the formation of the chelated complex with a silver cation without breaking the planarity of the amide functionality.

The substrate scope of aliphatic aldehydes under the optimized reaction conditions is summarized in Table 2.[22] The present catalytic system afforded the desired aldol products in a highly chemoselective manner even with α,α-nonbranched aldehydes and no self-aldol products were observed (entries 2–6 and 8–11). *syn*-Products were obtained preferentially with high yield and *ee* value. In some cases, the addition of 2-methylthioethanol (**7**) was beneficial to improving stereoselectivity (entries 6, 9, and 11). The reaction conditions were sufficiently mild and **3h** was obtained without lactonization (entry 10). The present direct aldol reaction was also performed on gram scale (entry 6).

Next we tested whether this catalytic system would be applicable to aromatic aldehydes. The initial attempt to conduct the reaction with 2-(trifluoromethyl)benzaldehyde (**2i**) afforded a striking reaction outcome, namely the diastereoselectivity was switched to *anti*

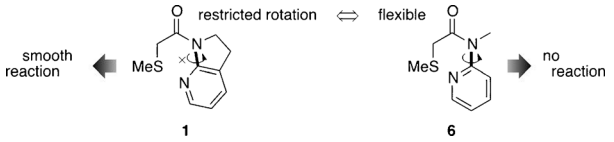
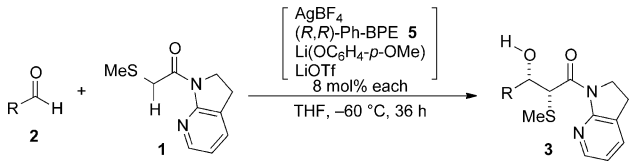


Figure 2. Structural features of the reactive amide **1** and unreactive amide **6**.

selective and a nearly racemic product, **3i**, was obtained (Figure 3a). Close inspection of the reaction profile revealed the following: 1) the reaction proceeded much faster with aromatic aldehydes than with aliphatic aldehydes, and 2) significant retro-aldol reaction was observed as evidenced by the continuous decrease in stereoselectivity during the course of the reaction (Figure 3d; time course marked with red open-circles). To protect the product from undesired re-entry into the catalytic cycle, we sought a simple molecule bearing a similar functional-group array as the aldol product, which may serve as a dummy ligand. We found that **7** fulfilled this role. The desired aldol product **3i** was obtained in *anti*-selective fashion with high *ee* value when **7** was used in a tenfold amount relative to the catalyst (Figure 3b,c). Whereas 1 equivalent of **7** relative to the catalyst was insufficient for the aromatic aldehyde to prevent the retro-aldol reaction, it was effective for the less reactive aliphatic aldehydes, and a marginal increase in stereoselectivity was

Table 2: *syn*-Selective direct catalytic asymmetric aldol reaction of **1** with aliphatic aldehydes.[a]



Entry	R	Additive (8 mol%)	3	Yield [%][b]	*anti*/*syn*	*ee* [%][c]
1	*i*Pr (**2a**)	–	**3a**	87	9:91	99
2	*n*Pr (**2b**)	–	**3b**	86	6:94	97
3	*n*-heptyl (**2c**)	–	**3c**	83	8:92	98
4	*i*Bu (**2d**)	–	**3d**	91	14:86	93
5	$Ph(CH_2)_2$ (**2e**)	–	**3e**	94	11:89	97
6[d]	$Ph(CH_2)_2$ (**2e**)	**7**	**3e**	91	10:90	97
7	*c*Hex (**2f**)	–	**3f**	85	9:91	95
8	$PMBO(CH_2)_2$ (**2g**)	–	**3g**	72	17:83	98
9	$PMBO(CH_2)_2$ (**2g**)	**7**	**3g**	86	11:89	99
10	$EtO_2C(CH_2)_2$ (**2h**)	–	**3h**	86	16:84	89
11	$EtO_2C(CH_2)_2$ (**2h**)	**7**	**3h**	86	9:91	97

[a] **1**: 1.0 mmol, **2a**: 1.2 mmol. [b] Yield of the isolated products. [c] *Ee* of *syn*-diastereomer determined by HPLC analysis. [d] 5.0 mmol of **1** and 6.0 mmol of **2e** were used.

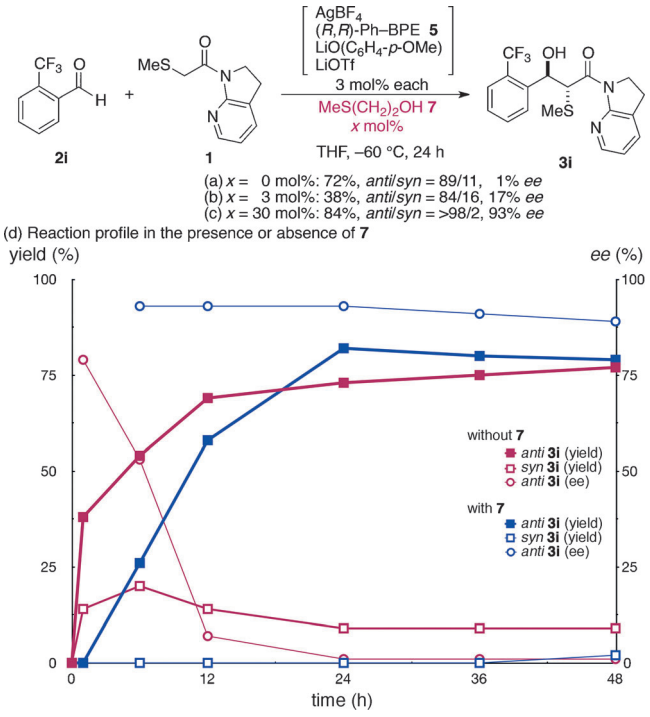
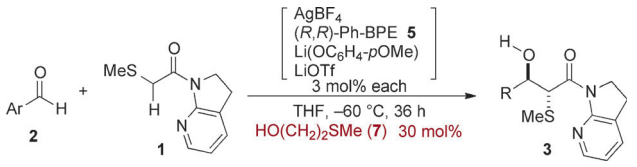


Figure 3. Initial attempt of the aldol reaction using the aromatic aldehyde **2i** and the effect of $MeS(CH_2)_2OH$ (**7**).

observed (Table 2, entries 6, 9, and 11). The beneficial effect of the additive **7** in preventing the retro-aldol reaction was evident from the consistent *ee* value during the course of the reaction (Figure 3d). The modified catalyst system was successfully applied to aromatic aldehydes with *anti* diastereoselectivity (Table 3).[21] Aromatic aldehydes bearing an *ortho* substituent afforded the desired products with high

Table 3: *anti*-Selective direct catalytic asymmetric aldol reaction of **1** with aromatic aldehydes.[a]



Entry	Ar	3	Yield[b] [%]	*anti*/*syn*	*ee* [%][c]
1	*o*-$CF_3C_6H_4$ (**2i**)	**3i**	84	>98:2	93
2[d]	*o*-$CF_3C_6H_4$ (**2i**)	**3i**	75	>98:2	93
3	*o*-$NO_2C_6H_4$ (**2j**)	**3j**	92	>98:2	91
4	*o*-FC_6H_4 (**2k**)	**3k**	76	81:19	99
5	*p*-$CF_3C_6H_4$ (**2l**)	**3l**	75	75:25	95
6	*p*-ClC_6H_4 (**2m**)	**3m**	86	81:19	85
7	*p*-IC_6H_4 (**2n**)	**3n**	73	86:14	97
8	C_6H_5 (**2o**)	**3o**	65	83:17	93
9	1-naphthyl (**2p**)	**3p**	86	92:8	84

[a] **1**: 1.0 mmol, **2a**: 1.2 mmol. [b] Yield of isolated product. [c] *Ee* of *anti*-diastereomer determined by HPLC analysis. [d] 5.0 mmol of **1** and 6.0 mmol of **2i** were used.

yields and excellent *ee* value (entries 1–4). The exclusive *anti* selectivity was observed when sterically demanding groups were present (entries 1–3). The halogenated benzaldehydes **2k**,**m**,**n** were also compatible in this reaction (entries 4, 6, and 7), as well as **2o** and 1-naphthaldehyde (**2p**; entries 8 and 9). The reaction using **2i** was performed on a 1 g scale (entry 2).

To gain insight into the silver complex, we performed spectroscopic analysis of the catalyst solution. Whereas a dense white suspension was formed by mixing $AgBF_4$/**5** in a ratio 1:1 in THF, the addition of LiOTf afforded a solution of $AgBF_4$/**5**/LiOTf = 1:1:1. ESI-MS analysis of the solution identified $[Ag/\mathbf{5}]^+$, $[Ag/(\mathbf{5})_2]^+$, $[Ag_2/(\mathbf{5})_2]^{2+}$, $[Ag_2/(\mathbf{5})_2/(OTf)]^+$, and minor peaks for a complex bearing three molecules of **5**, thus suggesting that LiOTf dissociated the higher-order complexes.[23] Crystallography of a single crystal obtained from the same solution revealed a dimeric complex of $Ag_2/(\mathbf{5})_2/(OTf)_2$ (**8**; Figure 4). The same crystal was grown from solutions of $AgBF_4$/**5**/LiOTf/**7** = 1:1:1:1 and $AgBF_4$/**5**/LiOTf/**1** = 1:1:1:1, which would be a major species in solution phase as suggested by ^{31}P NMR analysis.[23] Monomeric and dimeric silver complexes would be in equilibrium, with a preference of the latter, but it is unclear which of the complexes is responsible for promoting the present reaction. In ESI-MS analysis, the monomeric Ag/**7** complex $[Ag/\mathbf{5}/\mathbf{7}]^+$ was observed.[23] This complex underlies the proposed role of **7** in preventing the undesired retro-aldol reaction.[24]

The 7-azaindolinylamide moiety behaves as a Weinreb amide to prevent overreaction owing to the six-membered chelating structure **B** (Scheme 1).[25] Treatment of the unprotected aldol product **3i** with *n*-butyllithium led to the clean formation of the corresponding ketone **9** without overreaction. After protection with a TBS group, reductive desulfurization proceeded smoothly with nBu_3SnH/AIBN to give **11**. Treatment with DIBAL-H afforded the aldehyde **12** without over-reduction. Reduction to the primary alcohol **13** pro-

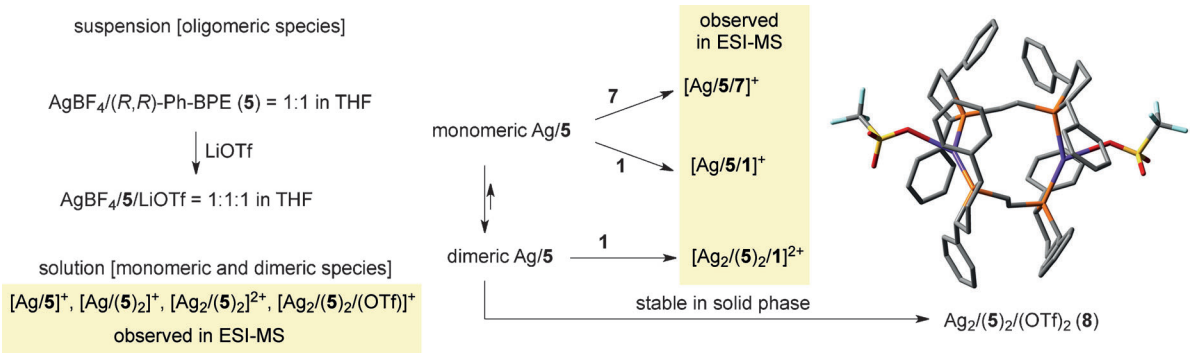
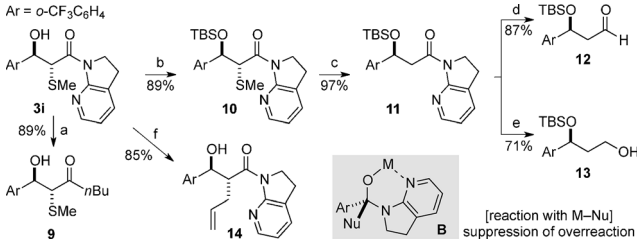


Figure 4. Plausible catalytic species.



Scheme 1. Transformation of the aldol product. a) *n*BuLi, THF, −78 °C, 1.5 h, 89%. b) TBSOTf, 2,6-lutidine, THF, RT, 24 h, 89%. c) nBu_3SnH, AIBN, benzene, reflux, 2.5 h, 97%. d) DIBAL-H, THF, −40 °C, 2 h, 87%. e) $LiEt_3BH$, THF, RT, 16 h, 71%. f) nBu_3Sn(allyl), AIBN, benzene, reflux, 24 h, 85%.

ceeded with $LiEt_3BH$. Subjection of **3i** to Keck allylation conditions replaced the SMe group with an allyl group to afford the *anti*-oriented **14** exclusively.[26] In contrast, **10** gave the diastereomixture of allylated compounds under the identical reaction conditions, thus suggesting that hydrogen bonding played a key role in rendering the reaction highly diastereoselective.[27]

In summary, we have developed a direct catalytic asymmetric aldol reaction of α-sulfanyl 7-azaindolinylamide (**1**). Breaking the conjugation of an amide through bidentate chelation to a Lewis acid is proposed for the preferential formation of the amide enolate in the presence of readily enolizable aldehydes. Both aliphatic and aromatic aldehydes were successfully used as aldol acceptors and divergent diastereoselectivity was observed. Tactical use of the dummy product **7** effectively suppressed the undesired retro-aldol reaction. The beneficial effect of 7-azaindolinyl-amide to prevent the overreaction with organometallic reagents is favorable for various transformations.

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[21] A series of structurally related amides were unreactive. See Supporting Information.
[22] Details on the determination of relative and absolute configuration are summarized in Supporting Information. α-(Methylthio)propionamide did not serve as a pronucleophile in this catalytic system.
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