Asymmetric Catalysis

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Catalytic Asymmetric Mannich-Type Reaction of *N*-Alkylidene-α-Aminoacetonitrile with Ketimines**

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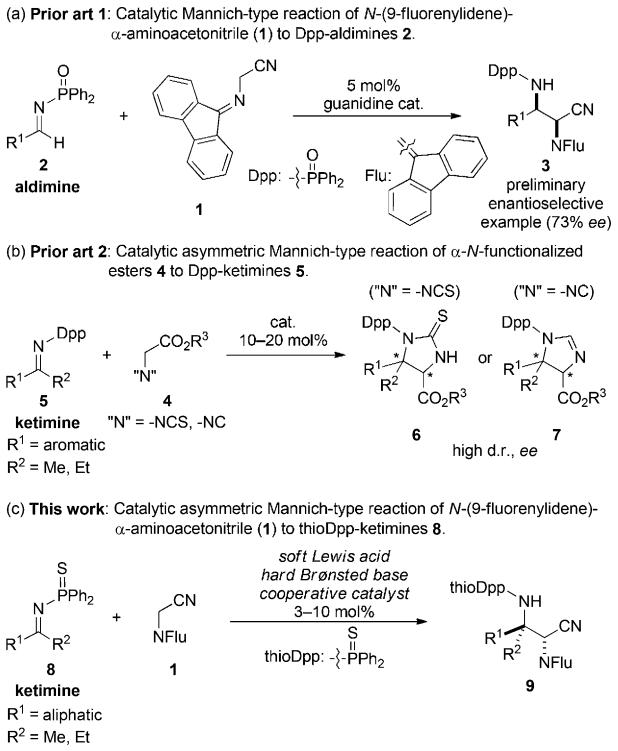
Abstract: *Optically active vicinal diamines are versatile chiral building blocks in organic synthesis. A soft Lewis acid/hard Brønsted base cooperative catalyst allows for an efficient stereoselective coupling of N-alkylidene-α-aminoacetonitrile and ketimines to access this class of compounds bearing consecutive tetra- and trisubstituted stereogenic centers. The strategic use of a soft Lewis basic thiophosphinoyl group for ketimines is the key to promoting the reaction, and aliphatic ketimines serve as suitable substrates with as little as 3 mol% catalyst loading.*

Given the possible divergent functional group interconversions, nitrile-based pronucleophiles have gained growing attention in asymmetric carbon–carbon bond-forming catalysis to produce enantioenriched compounds decorated with a nitrile functionality.[1] For the rapid assembly of multiple functional groups at the stereogenic center, an α-cyano carbanion bearing α-heteroatom groups is an intriguing class of active nucleophile.[2,3] Acetonitriles containing an *N*-alkylidene functionality (Schiff base) are an archetypal pronucleophile because of the facilitated generation of a nucleophilically active α-cyano carbanion assisted by the imino group.[4–8] In contrast to numerous literature precedents on carbon–carbon bond formation using this useful pronucleophile, catalytic and enantioselective reactions have met with only limited success.[9,10] Recently, Kobayashi et al. showed the particular utility of *N*-(9-fluorenylidene)-α-aminoacetonitrile (**1**) as a highly active pronucleophile in a Mannich-type reaction with *N*-(diphenylphosphinoyl)aldimines **2** which had superior catalytic efficiency (Scheme 1a).[11,12] The reaction was rendered asymmetric by using a chiral guanidine catalyst with moderate enantioselectivity. In our continuing research program on nitrile-based pronucleophiles and cooperative catalysis,[5] we envisioned merging these concepts to develop a highly stereoselective reaction of *N*-alkylidene-α-aminonitrile promoted by a cooperative soft Lewis acid/hard Brønsted base catalyst. We selected the Mannich-type reaction of *N*-(9-fluorenylidene)-α-aminoacetonitrile (**1**) with *N*-(diphenylthiophosphinoyl)ketimines as a rational and formidable objective because 1) both nitrile and thiophosphinoyl functionalities can be activated by a soft Lewis acid; 2) direct catalytic asymmetric addition of in situ generated nucleophiles to ketimines is underdeveloped; and 3) densely functionalized α,β-diamino nitriles bearing consecutive tetra- and trisubstituted stereogenic centers are produced. Recent advances in ester-based pronucleophiles have enabled the direct catalytic asymmetric addition of α-*N*-functionalized (α-isothiocyanato and α-isocyano) esters **4** to *N*-Dpp-ketimines **5**[13] to afford the analogous α,β-diamino esters with concomitant intramolecular cyclization to thioureas **6** or imidazolines **7** (Scheme 1b).[14–16] These reactions were largely limited to aromatic ketimines, and the excessive stability of the thiourea and imidazoline products complicated further elaboration. Herein, we report a catalytic asymmetric addition of *N*-(9-fluorenylidene)-α-aminoacetonitrile (**1**) to *N*-thioDpp-ketimines **8**. A series of aliphatic ketimines afforded the desired products in a highly stereoselective manner with as little as 3 mol% catalyst loading. Two



Scheme 1. Background for this work.

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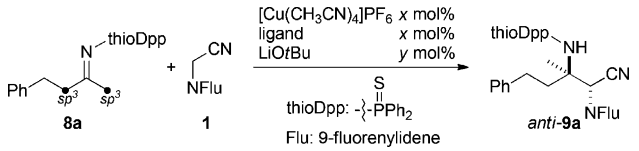
different *N*-protecting groups on the product could be removed selectively.

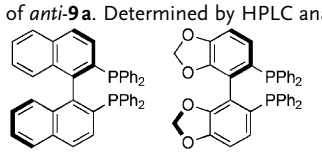
We set out to evaluate the soft Lewis acid/hard Brønsted base cooperative catalytic system[17] in the Mannich-type reaction of *N*-(9-fluorenylidene)-α-aminoacetonitrile (**1**) with *N*-thioDpp-ketimine **8a**,[18] which bears two sp^3-hybridized carbon atoms directly attached to the imino carbon atom. On the basis of the particular efficiency of Cu^I in the activation of the thioDpp group,[19] several bisphosphine ligands were screened with readily available $[Cu(CH_3CN)_4]PF_6$. The combined use of LiO*t*Bu as a Brønsted base resulted in the catalytic asymmetric Mannich-type reaction being promoted in THF at −60 °C to give **9a** (Table 1, entries 1–6). Biaryl-type ligands and (R,R_p)-Taniaphos preferred the formation of the *anti* isomer (entries 1–5), whereas quinoxaline-based alkyl phosphine (*R*,*R*)-QuinoxP* gave the *syn* isomer preferentially (entry 6). (*R*)-DMM-Garphos was optimal both in terms of catalytic efficiency and stereoselectivity, and lowering the reaction temperature to −78 °C improved the *anti*/*syn* ratio and enantioselectivity (entry 7). Decreasing the amount of Cu^I complex (5 mol%) relative to LiO*t*Bu (10 mol%) had a negative effect on the *anti*/*syn* ratio, while maintaining high enantioselectivity for the *anti* isomer (entry 8). This effect is solvent dependent: switching the solvent to toluene resulted in the predominant formation of the *anti* isomer, even with 5 mol% of the Cu^I complex (entry 9). This finding was ascribed to the competitive racemic reaction pathway promoted by LiO*t*Bu, as confirmed by control experiments outlined in Scheme 2. Unexpectedly, LiO*t*Bu alone catalyzed the Mannich-type reaction of **1** and **8a** in THF at −78 °C to

Table 1: Initial screening.[a]



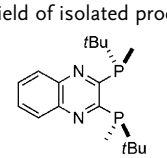
Entry	Ligand	*x*	*y*	Solvent	*T* [°C]	*t* [h]	Conv.[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	(*R*)-Binap	10	10	THF	−60	12	99	59:41	39
2	(*R*)-Segphos	10	10	THF	−60	12	72	69:31	54
3	(*R*)-Garphos	10	10	THF	−60	12	99	62:38	38
4	(*R*)-DMM-Garphos	10	10	THF	−60	12	99	85:15	88
5	(R,R_p)-Taniaphos	10	10	THF	−60	12	47	68:32	−79
6	(*R*,*R*)-QuinoxP*	10	10	THF	−60	12	52	35:65	12
7	(*R*)-DMM-Garphos	10	10	THF	−78	24	83	91:9	94
8	(*R*)-DMM-Garphos	5	10	THF	−78	24	45	42:58	90
9	(*R*)-DMM-Garphos	5	10	toluene	−78	24	96	91:9	94
10	(*R*)-DMM-Garphos	3	5	toluene	−78	24	91[e]	91:9	94

[a] **1**: 0.1 mmol, **8a**: 0.11 mmol. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [d] Enantiomeric excess (*ee*) of *anti*-**9a**. Determined by HPLC analysis. [e] Yield of isolated product.

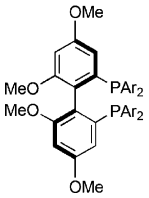


(*R*)-Binap

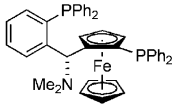
(*R*)-Segphos



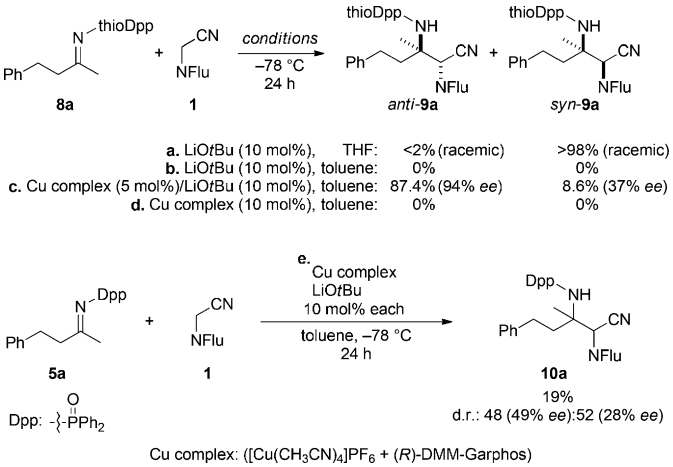
(*R*,*R*)-QuinoxP*



(*R*)-Garphos:
Ar = Ph
(*R*)-DMM-Garphos:
Ar = 3,5-Me_2-4-OMe-C_6H_2



(R,R_p)-Taniaphos

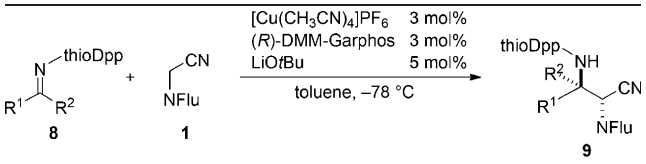


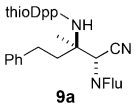
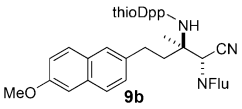
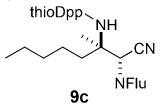
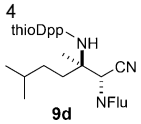
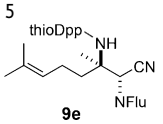
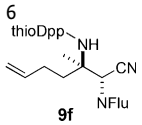
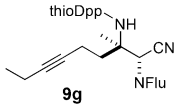
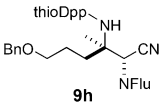
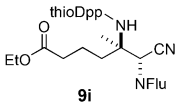
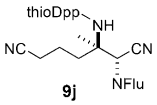
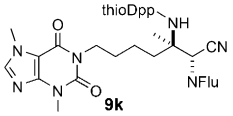
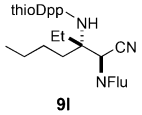
Scheme 2. Control experiments.

give almost exclusively racemic *syn*-**9a** (Scheme 2a). In the presence of excess LiO*t*Bu (entry 8), *anti*-**9a** was mostly produced with high enantioselectivity by the cooperative catalyst, while some fraction of the LiO*t*Bu worked independently to increase the production of racemic *syn*-**9a**. In marked contrast, the racemic pathway was completely suppressed in toluene (Scheme 2b), and this is consistent with the observed high *anti*/*syn* ratio even with the decreased amount of Cu^I complex when switching the solvent from THF to toluene (entry 9 and Scheme 2c). The catalyst loading can be further reduced to 3 and 5 mol% of the Cu^I complex and LiO*t*Bu, respectively, with a comparable catalytic efficiency (entry 10). No trace of product **9a** was obtained in the absence of the Brønsted base (Scheme 2d). The analogous *N*-Dpp-ketimine **5a** resulted in much lower conversion and stereoselectivity under the reaction conditions, thus suggesting that the specific activation of the thioDpp group by Cu^I complex was crucial for the formation of a carbon–carbon bond and efficient stereochemical discrimination (Scheme 2e).

The identified catalytic system was valid for a range of aliphatic *N*-thioDpp-ketimines **8** (Table 2).[20] An attempted gram-scale reaction proceeded without any detrimental effect to give the comparable reaction outcome (entry 1). Ketimines bearing a pendant substituted naphthyl group and a linear or branched alkyl chain served as suitable substrates to afford predominantly the *anti* products with high enantioselectivity

Table 2: Substrate generality.[a]

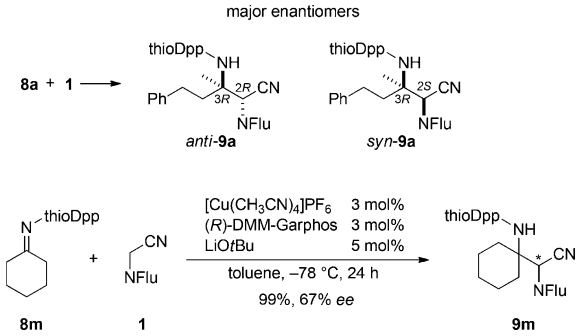


1  **9a**	2  **9b**	3  **9c**
48 h, 95 %	48 h, 91 %	72 h, 88 %
anti/*syn* = 91:9	*anti*/*syn* = 93:7	*anti*/*syn* = 90:10
93 % *ee* (*anti*)	94 % *ee* (*anti*)	91 % *ee* (*anti*)
1.09 g scale		
4  **9d**	5  **9e**	6  **9f**
48 h, 97 %	48 h, 96 %	72 h, 92 %
anti/*syn* = 95:5	*anti*/*syn* = 91:9	*anti*/*syn* = 90:10
95 % *ee* (*anti*)	90 % *ee* (*anti*)	90 % *ee* (*anti*)
7  **9g**	8  **9h**	9  **9i**
72 h, 97 %	72 h, 88 %	72 h, 95 %
anti/*syn* = 83:17	*anti*/*syn* = 88:12	*anti*/*syn* = 92:8
88 % *ee* (*anti*)	91 % *ee* (*anti*)	92 % *ee* (*anti*)
10  **9j**	11[b]  **9k**	12[c]  **9l**
48 h, 99 %	72 h, 85 %	72 h, 61 %
anti/*syn* = 85:15	*anti*/*syn* = 83:17	*anti*/*syn* = 77:23
87 % *ee* (*anti*)	84 % *ee* (*anti*)	83 % *ee* (*anti*)

[a] **1**: 0.2 mmol, **8**: 0.22 mmol. Yields of isolated products are given. The *anti*/*syn* ratio was determined by ^{1}H NMR spectroscopic analysis of the crude mixture. The *ee* value was determined using HPLC analysis. [b] 6 mol % of $[Cu(CH_3CN)_4]PF_6$/(*R*)-DMM-Garphos and 10 mol % LiO*t*Bu were used. [c] The reaction was conducted at −60 °C. 10 mol % of $[Cu(CH_3CN)_4]PF_6$/(R,R_p)-Taniaphos and 30 mol % LiO*t*Bu were used to give the enantiomeric product.

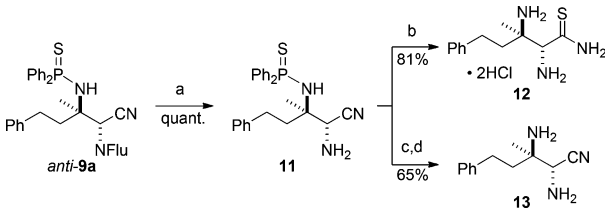
(entries 2–4). Unsaturated bonds, including internal alkynes, were compatible (entries 5–7). Oxygen functionalities, for example, a benzyl ether and an ester group did not have a negative impact on the catalytic efficiency (entries 8 and 9). Xanthine and nitrile functionalities, which can potentially coordinate to the Cu^I complex to disturb the desired catalysis, were compatible, albeit with a marginal loss in stereoselectivity (entries 10 and 11). This reaction system was fairly sensitive to steric factors. The reaction using a ketimine bearing an ethyl group resulted in considerably lower conversion (entry 12). In this specific case, (R,R_p)-Taniaphos performed best as the chiral ligand to afford the desired product **9l** with reasonably high yield and stereoselectivity.

The relative and absolute configurations of the major enantiomers of *anti*-**9a** and *syn*-**9a** were determined by X-ray crystallographic analysis to have identical absolute configuration at the tetrasubstituted stereogenic centers (Scheme 3).[21] Taking the observed diastereo- and enantioselectivity into account, the present catalytic system exhibited higher performance for differentiating the prochiral face of ketimines rather than that of α-cyano carbanions. This is in line with the observed moderate enantioselectivity (67 % *ee*) of cyclic ketimine **8m**, where the trigonal imino carbon is not prochiral.



Scheme 3. Stereochemical analysis of the Mannich-type reaction.

The 9-fluorenylimine moiety of the product was selectively hydrolyzed by 1 N HCl(aq) to give **11** (Scheme 4). Hydrolysis of the thiophosphinoyl group under acidic conditions was more intractable, and strongly acidic conditions or high reaction temperatures resulted in a complicated mixture, probably because of elimination of thiophosphinamide and subsequent decomposition. Gentle warming (40 °C) in 12 N HCl(aq)/MeOH (1:4) slowly gave primary thioamide **12** with two free vicinal amino groups. Intramolecular delivery of the sulfur atom would be involved. Considering the known divergent transformations of primary thioamide to various functional groups and heterocycles,[17c,22] **12** can be viewed as a useful chiral building block. The thioDpp group was readily transformed to a Dpp group with H_2O_2, and subsequent chemoselective hydrolysis of the Dpp amide with 12 N HCl(aq)/THF (1:1) at 40 °C proceeded with the nitrile group intact, thereby affording diamino nitrile **13**.



Scheme 4. Transformation of the product. a) 1 N HCl(aq), THF, RT, 5 h, quant. b) 12 N HCl(aq)/MeOH (1:4), 40 °C, 5 days, 81 %. c) 12 N HCl (aq)/MeOH (1:4), 30–35 % H_2O_2 aq., RT, 0.5 h. d) 12 N HCl(aq)/THF (1:1), 40 °C, 3 days; then 2 N NH_3(aq), 65 % (2 steps).

In conclusion, a direct catalytic asymmetric Mannich-type reaction of *N*-(9-fluorenylidene)-α-aminoacetonitrile and *N*-

(diphenylthiophosphinoyl)ketimines has been developed. Ketimines bearing sp^3 substituents on the imine carbonyl group were generally used with high diastereo- and enantioselectivity. The use of the soft Lewis basic ketimine was the key to promoting the reaction with a soft Lewis acid/hard Brønsted base cooperative catalyst.

Keywords: asymmetric catalysis · copper · ketimines · Mannich reaction · nitriles

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[1] For reviews, see a) S. Arseniyadis, K. S. Kyler, D. S. Watt, *Org. React.* **1984**, *31*, 1; b) F. F. Fleming, B. C. Shook, *Tetrahedron* **2002**, *58*, 1; c) J. G. Verkade, P. B. Kisanga, *Aldrichimica Acta* **2004**, *37*, 3.

[2] D. Enders, J. P. Shilvock, *Chem. Soc. Rev.* **2000**, *29*, 359.

[3] a) G. Stork, A. A. Ozorio, A. Y. W. Leong, *Tetrahedron Lett.* **1978**, *19*, 5175; b) J. D. Albright, *Tetrahedron* **1983**, *39*, 3207; c) D. Enders, J. Kirchhoff, P. Gerdes, D. Mannes, G. Raabe, J. Runsink, G. Boche, M. Marsch, H. Ahlbrecht, H. Sommer, *Eur. J. Org. Chem.* **1998**, 63, and references therein.

[4] For reviews on the utility of glycine Schiff bases (*N*-alkylidene-α-amino esters), see a) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013; b) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506; c) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584.

[5] Alkylation of *N*-alkylidene-α-aminoacetonitriles: a) M. J. O'Donnell, T. M. Eckrich, *Tetrahedron Lett.* **1978**, *19*, 4625; b) D. Ferroud, J. P. Genet, R. Kiolle, *Tetrahedron Lett.* **1986**, *27*, 23; c) J. P. Genet, S. Juge, S. Achi, S. Mallart, J. R. Montes, G. Levif, *Tetrahedron* **1988**, *44*, 5263; d) F. Rose-Munch, K. Aniss, *Tetrahedron Lett.* **1990**, *31*, 6351; e) J. E. Baldwin, R. M. Adlington, N. P. Crouch, C. J. Schofield, N. J. Turner, R. T. Aplin, *Tetrahedron* **1991**, *47*, 9881; f) I. M. Wyzlic, A. H. Soloway, *Tetrahedron Lett.* **1992**, *33*, 7489; g) Y. Q. Wu, T. Lawrence, J. Q. Guo, P. M. Woster, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2811; h) C. Chengzhi, D. Buechler, D. Lowe, S. Urwyler, G. Shapiro, *Tetrahedron* **1994**, *50*, 5735; i) A. Gaucher, P. Dorizon, J. Ollivier, J. Salaün, *Tetrahedron Lett.* **1995**, *36*, 2979; j) L. Ridvan, N. Abdallah, R. Holakovsky, M. Tichy, J. Závada, *Tetrahedron: Asymmetry* **1996**, *7*, 231; k) P. Dorizon, J. Ollivier, J. Salaün, *Synlett* **1996**, 1071; l) A. Mazón, C. Nájera, J. Ezquerra, C. Pedregal, *Tetrahedron Lett.* **1997**, *38*, 2167; m) M. E. Fox, I. C. Lennon, V. Farina, *Tetrahedron Lett.* **2007**, *48*, 945; n) J. E. Baldwin, R. M. Adlington, J. W. Bird, C. J. Schofield, *J. Chem. Soc. Chem. Commun.* **1989**, 1615; o) M. Selva, A. Bomben, P. Tundo, *Synth. Commun.* **1999**, *29*, 1561; p) P. Dorizon, G. Su, G. Ludvig, L. Nikitina, R. Paugam, J. Ollivier, J. Salaün, *J. Org. Chem.* **1999**, *64*, 4712; q) A. Enright, F.-R. Alexandre, G. Roff, I. G. Fotheringham, M. J. Dawson, N. J. Turner, *Chem. Commun.* **2003**, 2636; r) M. McLaughlin, R. M. Mohareb, H. Rapoport, *J. Org. Chem.* **2003**, *68*, 50; s) I. Bergner, T. Opatz, *Synthesis* **2007**, 918; t) D. Tasheva, A. Petrova, S. Simova, *Synth. Commun.* **2007**, *37*, 3971; u) T. Nawrath, J. S. Dickschat, B. Kunze, S. Schulz, *Chem. Biodiversity* **2010**, *7*, 2129; v) E. Shinkevich, J. Deblander, S. Matthijs, J. Jacobs, N. De Kimpe, K. A. Tehrani, *Org. Biomol. Chem.* **2011**, *9*, 538; w) Y. Zhang, L. Pan, Y. Zou, X. Xu, Q. Liu, *Chem. Commun.* **2014**, *50*, 14334.

[6] Cycloaddition of *N*-alkylidene-α-aminoacetonitriles: a) O. Tsuge, S. Kanemasa, K. Yorozu, K. Ueno, *Chem. Lett.* **1985**, 1601; b) O. Tsuge, K. Ueno, S. Kanemasa, K. Yorozu, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1809; c) O. Tsuge, S. Kanemasa, K. Yorozu, K. Ueno, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3359; d) S. Kanemasa, H. Yamamoto, E. Wada, T. Sakurai, K. Urushido, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2857.

[7] Aldol reaction of *N*-alkylidene-α-aminoacetonitriles: a) V. Dryanska, *Synth. Commun.* **1990**, *20*, 1055; b) V. Dryanska, O. Angelova, J. Macicek, L. Shishkova, P. Denkova, S. Spassov, *J. Chem. Res.* **1995**, 268.

[8] Mannich-type reaction of *N*-alkylidene-α-aminoacetonitriles: V. Dryanska, D. Tasheva, *Synth. Commun.* **1992**, *22*, 63.

[9] Catalytic conjugate addition: O. Marrec, C. Christophe, T. Billard, B. Langlois, J.-P. Vors, S. Pazenok, *Adv. Synth. Catal.* **2010**, *352*, 2825.

[10] Catalytic asymmetric 1,3-dipolar cycloaddition: R. Robles-Machín, I. Alonso, J. Adrio, J. C. Carretero, *Chem. Eur. J.* **2010**, *16*, 5286.

[11] For the utility of *N*-(9-fluorenylidene) α-amino ester for catalytic asymmetric Mannich reactions, see S. Kobayashi, R. Yazaki, K. Seki, Y. Yamashita, *Angew. Chem. Int. Ed.* **2008**, *47*, 5613; *Angew. Chem.* **2008**, *120*, 5695. For a unique use of the 9-fluorenyl group for the imine–imine coupling reaction, see M. Matsumoto, M. Harada, Y. Yamashita, S. Kobayashi, *Chem. Commun.* **2014**, *50*, 13041.

[12] a) Y.-J. Chen, K. Seki, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2010**, *132*, 3244; b) Y. Yamashita, M. Matsumoto, Y.-J. Chen, S. Kobayashi, *Tetrahedron* **2012**, *68*, 7558.

[13] S. M. Weinreb, R. K. Orr, *Synthesis* **2005**, 1205.

[14] G. Lu, T. Yoshino, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2011**, *50*, 4382; *Angew. Chem.* **2011**, *123*, 4474.

[15] I. Ortín, D. J. Dixon, *Angew. Chem. Int. Ed.* **2014**, *53*, 3462; *Angew. Chem.* **2014**, *126*, 3530.

[16] M. Hayashi, M. Iwanaga, N. Shiomi, D. Nakane, H. Masuda, S. Nakamura, *Angew. Chem. Int. Ed.* **2014**, *53*, 8411; *Angew. Chem.* **2014**, *126*, 8551. There are two examples where aliphatic *N*-Dpp-ketimines were used with high enantioselectivity, albeit with lower diastereoselectivity and yield.

[17] Recent reviews on cooperative catalysis: Lewis acid/Brønsted base: a) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187; b) N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2011**, *50*, 4760; *Angew. Chem.* **2011**, *123*, 4856; Lewis acid/Lewis base: c) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491; d) D. H. Paull, C. J. Abraham, M. T. Scerba, E. Alden-Danforth, T. Lectka, *Acc. Chem. Res.* **2008**, *41*, 655; Lewis acid/Brønsted acid and Lewis acid/Lewis acid: e) H. Yamamoto, K. Futatsugi, *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; *Angew. Chem.* **2005**, *117*, 1958; f) H. Yamamoto, K. Futatsugi in *Acid Catalysis in Modern Organic Synthesis* (Eds.: H. Yamamoto, K. Ishihara), Wiley-VCH, Weinheim, **2008**.

[18] Synthesis of *N*-thioDpp-imines: a) X. Xu, C. Wang, Z. Zhou, Z. Zeng, X. Ma, G. Zhao, C. Tang, *Lett. Org. Chem.* **2006**, *3*, 640; b) X. Xu, C. Wang, Z. Zhou, Z. Zeng, X. Ma, G. Zhao, C. Tang, *Heteroat. Chem.* **2008**, *19*, 238.

[19] Utility of *N*-thioDpp-imines in catalytic asymmetric reactions: a) L. Yin, Y. Otsuka, H. Takada, S. Mouri, R. Yazaki, N. Kumagai, M. Shibasaki, *Org. Lett.* **2013**, *15*, 698; b) L. Yin, H. Takada, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2013**, *52*, 7310; *Angew. Chem.* **2013**, *125*, 7451; c) L. Yin, Y. Bao, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2013**, *135*, 10338; d) Y. Kawato, N. Kumagai, M. Shibasaki, *Chem. Commun.* **2013**, *49*, 11227.

[20] The reaction using a representative aromatic *N*-thioDpp-ketimine derived from acetophenone under the optimized reaction conditions (at −60 °C) gave only trace amounts of the product.

[21] See the Supporting Information for details.

[22] T. S. Jagodzinski, *Chem. Rev.* **2003**, *103*, 197.

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