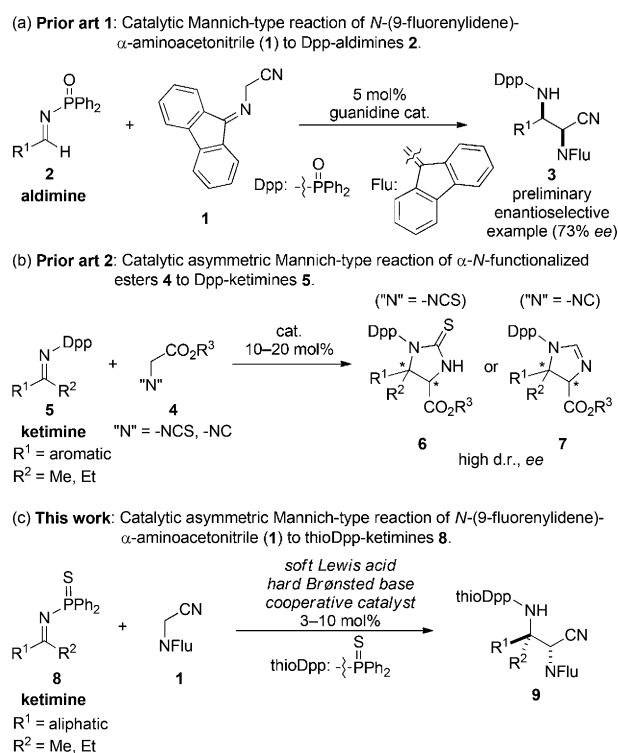


Catalytic Asymmetric Mannich-Type Reaction of *N*-Alkylidene- α -Aminoacetonitrile with Ketimines**

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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 1 a).^[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



Scheme 1. Background for this work.

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 1 b).^[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

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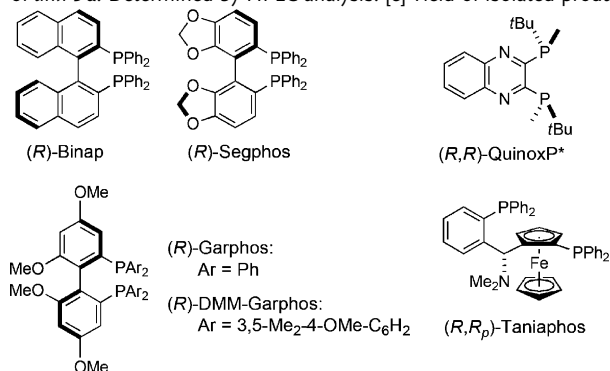
different *N*-protecting groups on the product could be removed selectively.

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 LiOtBu as a Brønsted base resulted in the catalytic asymmetric Mannich-type reaction being promoted in THF at $-60^\circ C$ to give **9a** (Table 1, entries 1–6). Biaryl-type ligands and (*R,R*)-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

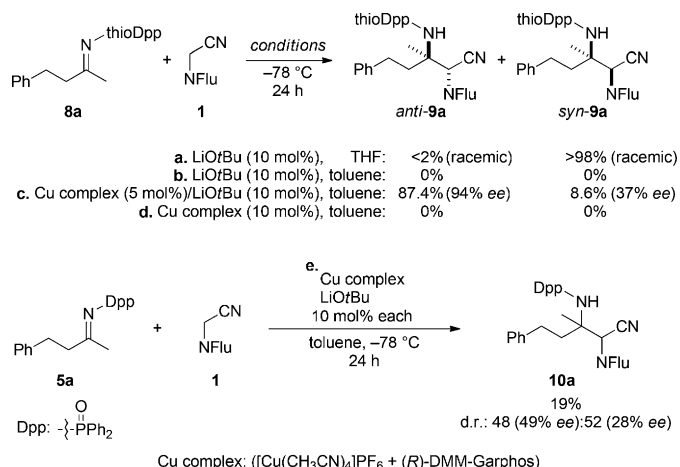
Table 1: Initial screening.^[a]

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

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



reaction temperature to $-78^\circ C$ improved the *anti/syn* ratio and enantioselectivity (entry 7). Decreasing the amount of Cu^I complex (5 mol%) relative to LiOtBu (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 LiOtBu, as confirmed by control experiments outlined in Scheme 2. Unexpectedly, LiOtBu alone catalyzed the Mannich-type reaction of **1** and **8a** in THF at $-78^\circ C$ to



Scheme 2. Control experiments.

give almost exclusively racemic *syn*-**9a** (Scheme 2a). In the presence of excess LiOtBu (entry 8), *anti*-**9a** was mostly produced with high enantioselectivity by the cooperative catalyst, while some fraction of the LiOtBu 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 LiOtBu, 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

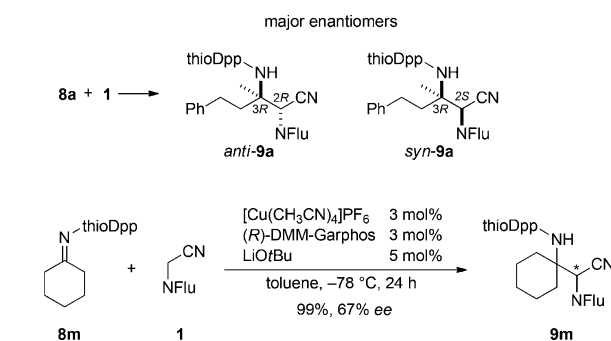
Table 2: Substrate generality.^[a]

$\text{R}^1-\text{N}=\text{C}(\text{thioDpp})-\text{R}^2 + \text{1} \xrightarrow[\text{toluene, } -78^\circ\text{C}]{\begin{smallmatrix} [\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6 & 3 \text{ mol}\% \\ (\text{R})\text{-DMM-Garphos} & 3 \text{ mol}\% \\ \text{LiOtBu} & 5 \text{ mol}\% \end{smallmatrix}} \text{thioDpp}-\text{NH}-\text{C}(\text{CN})-\text{NFlu}$		
1 9a 48 h, 95 % anti/syn = 91:9 93 % ee (anti) 1.09 g scale	2 9b 48 h, 91 % anti/syn = 93:7 94 % ee (anti)	3 9c 72 h, 88 % anti/syn = 90:10 91 % ee (anti)
4 9d 48 h, 97 % anti/syn = 95:5 95 % ee (anti)	5 9e 48 h, 96 % anti/syn = 91:9 90 % ee (anti)	6 9f 72 h, 92 % anti/syn = 90:10 90 % ee (anti)
7 9g 72 h, 97 % anti/syn = 83:17 88 % ee (anti)	8 9h 72 h, 88 % anti/syn = 88:12 91 % ee (anti)	9 9i 72 h, 95 % anti/syn = 92:8 92 % ee (anti)
10 9j 48 h, 99 % anti/syn = 85:15 87 % ee (anti)	11^[b] 9k 72 h, 85 % anti/syn = 83:17 84 % ee (anti)	12^[c] 9l 72 h, 61 % anti/syn = 77:23 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 ¹H NMR spectroscopic analysis of the crude mixture. The ee value was determined using HPLC analysis. [b] 6 mol % of [Cu(CH₃CN)₄]PF₆/(R)-DMM-Garphos and 10 mol % LiOtBu were used. [c] The reaction was conducted at -60 °C. 10 mol % of [Cu(CH₃CN)₄]PF₆/(R,R_p)-Taniaphos and 30 mol % LiOtBu were used to give the enantiomeric product.

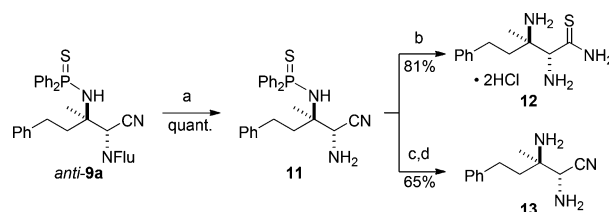
(entries 2–4). Unsaturated bonds, including internal alkynes, were compatible (entries 5–7). Oxygen functionalities, for example, a benzyl ether and an ester group did not have a negative impact on the catalytic efficiency (entries 8 and 9). Xanthine and nitrile functionalities, which can potentially 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 enantio-


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

selectivity 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.

The 9-fluorenylimine moiety of the product was selectively hydrolyzed by 1N 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


Scheme 4. Transformation of the product. a) 1N HCl(aq), THF, RT, 5 h, quant. b) 12N HCl(aq)/MeOH (1:4), 40 °C, 5 days, 81 %. c) 12N HCl(aq)/MeOH (1:4), 30–35 % H₂O₂ aq., RT, 0.5 h. d) 12N HCl(aq)/THF (1:1), 40 °C, 3 days; then 2N NH₃(aq), 65 % (2 steps).

subsequent decomposition. Gentle warming (40 °C) in 12N 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 H₂O₂, and subsequent chemoselective hydrolysis of the Dpp amide with 12N HCl(aq)/THF (1:1) at 40 °C proceeded with the nitrile group intact, thereby affording diamino nitrile **13**.

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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