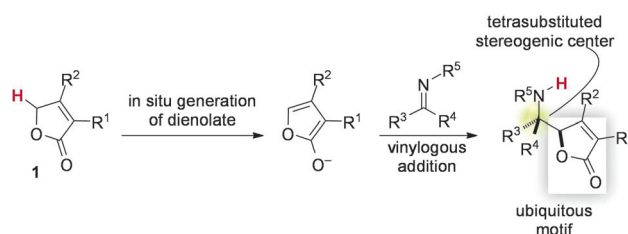


Direct Catalytic Asymmetric Vinylogous Mannich-Type Reaction of γ -Butenolides with Ketimines**

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The construction of tetrasubstituted stereogenic centers through C–C-bond-forming reactions in a catalytic and enantioselective fashion has been studied intensively.^[1] In particular, transformations that entail in situ catalytic generation of active nucleophiles allow for atom-economical access to this class of chemical entities.^[2] γ -Butenolides **1** are an emerging class of pronucleophiles in direct catalytic asymmetric C–C-bond-forming reactions, because: 1) they bear relatively acidic protons that facilitate the generation of the corresponding dienolates, which engage in the subsequent vinylogous nucleophilic addition;^[3–7] and 2) a rich chemical library containing the γ -butenolide motif is found in naturally occurring compounds (Scheme 1).^[8] Despite its rapidly grow-

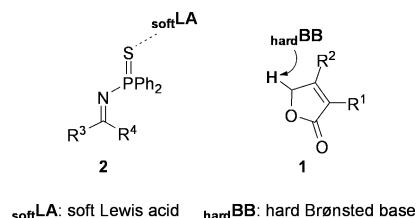


Scheme 1. Direct use of γ -butenolides **1** as pronucleophiles in the vinylogous Mannich-type reaction of ketimines under proton-transfer conditions.

ing utility as a useful pronucleophile under proton-transfer conditions, **1** has not been used in direct catalytic asymmetric vinylogous Mannich-type reactions with ketimines to produce α -tetrasubstituted amines.^[9–12] To date, the catalytic asymmetric vinylogous Mannich-type reaction of ketimines has

only been addressed in an indirect manner utilizing 2-siloxyfuran as the preformed vinylogous enolate and electrophilically activated α -acyloxy ketimines.^[13] Although recent advances in this field allowed the direct catalytic asymmetric Mannich-type reaction of ketimines, electrophilically activated ketimines, e.g., α -carbonyl or α -CF₃ ketimines, were generally used,^[14] and only limited examples using ketimines without an electron-withdrawing group have been reported.^[15] These circumstances and the synthetic utility of γ -butenolides led us to develop the direct catalytic asymmetric vinylogous Mannich-type reaction of γ -butenolide **1** with non-activated ketimines under proton-transfer conditions.

We reasoned that the specific activation mode of ketimines is crucial to achieve this elusive reaction. Recently, we reported that *N*-thiophosphinoyl (–P(S)Ph₂) ketimines **2** were activated in situ with the aid of a soft Lewis acid as catalyst through soft–soft interaction, allowing for direct C–C bond formation with terminal alkynes.^[16,17] In this context, a cooperative catalytic system containing a soft Lewis acid and a hard Brønsted base is a viable strategy,^[18] in which the latter would promote the catalytic generation of dienolates from γ -butenolides **1** (Scheme 2). We initiated our study to identify



Scheme 2. Cooperative activation of ketimine electrophile **2** and γ -butenolide pronucleophile **1**.

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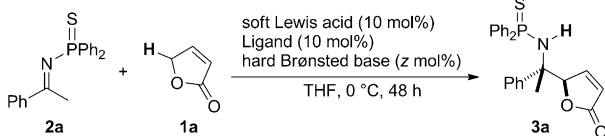
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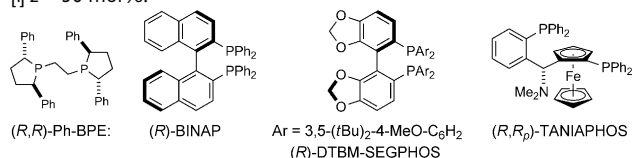
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feasible combinations of a soft Lewis acid and a hard Brønsted base by using γ -crotonolactone (**1a**) and *N*-thiophosphinoyl ketimine **2a** derived from acetophenone (Table 1). With a binary catalyst (10 mol %) comprised of [Cu(CH₃CN₄)PF₆]/(*R,R*)-Ph-BPE and Li(OC₆H₄-*p*-OMe),^[19] the vinylogous Mannich-type reaction of ketimine **2a** proceeded to give the diastereomerically pure product **3a** in moderate yield and high enantioselectivity (Table 1, entry 1). Axially chiral bisphosphine ligands such as (*R*)-BINAP and (*R*)-DTBM-SEGPHOS afforded lower enantioselectivity (Table 1, entries 2,3). Among the chiral ligands screened, (*R,R*)-TANIAPHOS^[20] outperformed in terms of both conversion and enantioselectivity (Table 1, entry 4).^[21] When taking into account the relatively high acidity of **1a**, amine bases would be a reasonable option for the Brønsted base in

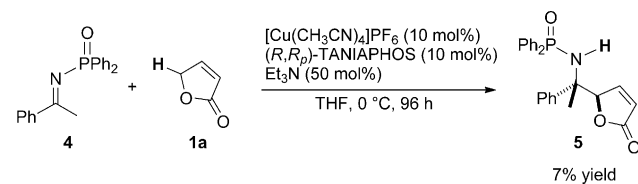
Table 1: Initial screening of the direct catalytic Mannich-type reaction of **1a** and **2a**.^[a]

						
Entry	Soft ^[b] Lewis acid	Ligand	Hard Brønsted base	Yield [%] ^[d]	d.r. ^[d]	ee [%] ^[e]
1	CuPF ₆	(R,R)-Ph-BPE	LiOAr ^[c]	44	> 20:1	93
2	CuPF ₆	(R)-BINAP	LiOAr ^[c]	51	> 20:1	78 ^[h]
3	CuPF ₆	(R)-DTBM-SEGPHOS	LiOAr ^[c]	69	> 20:1	84 ^[h]
4	CuPF ₆	(R,R _p)-TANIAPHOS	LiOAr ^[c]	71	> 20:1	98
5	CuPF ₆	(R,R _p)-TANIAPHOS	iPr ₂ N ⁺ Et	17	> 20:1	98
6	CuPF ₆	(R,R _p)-TANIAPHOS	Cy ₂ NMe	46	> 20:1	99
7	CuPF ₆	(R,R _p)-TANIAPHOS	Et ₃ N	50	> 20:1	99
8	CuPF ₆	(R,R _p)-TANIAPHOS	Et ₃ N ^[i]	87 ^[g]	> 20:1	99
9	AgPF ₆	(R,R _p)-TANIAPHOS	Et ₃ N ^[i]	33	> 20:1	95
10 ^[f]	CuPF ₆	(R,R _p)-TANIAPHOS	—	0	—	—
11 ^[f]	—	—	Et ₃ N ^[i]	0	—	—

[a] **1a**: 0.3 mmol, **2a**: 0.1 mmol, 0.2 M. z = 10 mol %, unless otherwise noted. [b] Acetonitrile complex [Cu(CH₃CN)₄]PF₆ was used. [c] Ar = C₆H₄-p-OMe. [d] Determined by ¹H NMR spectroscopy. [e] Determined by HPLC using a chiral stationary phase. [f] Reaction time was 96 h. [g] Yield of isolated product. [h] *ent*-**3a** was obtained in major. [i] z = 50 mol %.



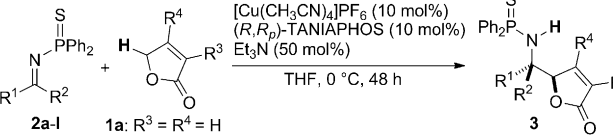
a cooperative catalytic system. Examination of the reaction using amine bases led us to identify Et₃N as a preferred base (Table 1, entries 5–7).^[22] Intensive efforts to enhance the catalytic efficiency by changing other reaction parameters or the use of additives resulted in failure, and inexpensive Et₃N (50 mol %) afforded **3a** in 87% yield and with 99% *ee* (Table 1, entry 8). The catalyst containing silver instead of copper as a soft Lewis acid could promote the reaction, although inferior conversion and enantioselectivity were observed (Table 1, entry 9). No reaction took place in the absence of the soft Lewis acid or the hard Brønsted base even after 96 h, thus confirming that their cooperative function is critical to promote the reaction (Table 1, entries 10,11). The reaction of oxygen analogue *N*-phosphinoyl ketimine **4** barely proceeded under the optimized reaction conditions, thereby proving that the S···Cu interaction was pivotal in activating the *N*-thiophosphinoyl ketimine **2a** (Scheme 3).



Scheme 3. Application of optimized reaction conditions to *N*-phosphinoyl ketimine **4**.

The substrate scope of the direct catalytic asymmetric vinylogous Mannich-type reaction is summarized in Table 2. Uniformly high diastereo- and enantioselectivities were observed with a range of *N*-thiophosphinoyl ketimines **2**. Ketimines derived from *para*-halogenated acetophenones exhibited high reactivity to give the corresponding products in high yield (Table 2, entries 2–4). Catalyst loading could be reduced to 5 mol % in the reaction of a ketimine bearing a CF₃ group without any detrimental effect on the reaction efficiency (Table 2, entry 5). The reaction reached completion with 1.5 equivalents of **1a** (Table 2, entry 5). Substitution at the *ortho*- or *meta*-positions of the aromatic ring of ketimines

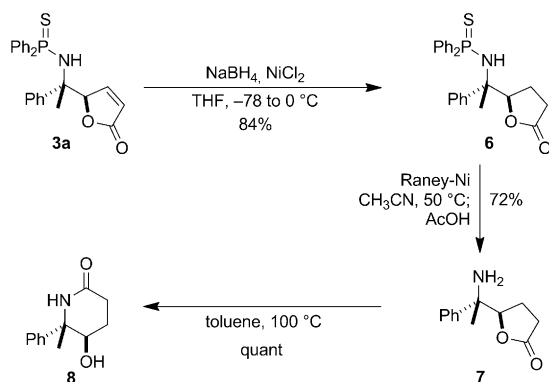
Table 2: Direct catalytic Mannich-type reaction of γ -butenolide **1** and *N*-thiophosphinoyl ketimines **2**.^[a]

		
2a-I	1a : R ³ = R ⁴ = H 1b : R ³ = Me, R ⁴ = H 1c : R ³ = H, R ⁴ = Me	3
1.		3a : 87%, 99% <i>ee</i> d.r. >20:1
2.		3b : 92%, 99% <i>ee</i> d.r. >20:1
3.		3c : 84%, 99% <i>ee</i> d.r. >20:1
4.		3d : 91%, 99% <i>ee</i> d.r. >20:1
5.		5 mol% cat. ^[b] 1.5 equiv of 1a : 83%, 98% <i>ee</i> 89%, 98% <i>ee</i> d.r. >20:1, 72 h d.r. >20:1
6.		3f : 88%, 98% <i>ee</i> d.r. >20:1
7.		3g : 88%, 98% <i>ee</i> d.r. >20:1
8.		3h : 80%, 98% <i>ee</i> d.r. >20:1
9.		3i : 73%, 99% <i>ee</i> d.r. >20:1
10.		3j : 70%, 98% <i>ee</i> d.r. >20:1, 96 h
11.		3k : 63%, 99% <i>ee</i> d.r. >20:1
12.		3l : 52%, 97% <i>ee</i> d.r. >20:1
13.		3m : 61%, 98% <i>ee</i> d.r. >20:1, 96 h
14.		3n : 55%, 99% <i>ee</i> d.r. >20:1

[a] **1**: 0.3 mmol, **2**: 0.1 mmol, 0.2 M. Yields of isolated products are presented. The diastereomeric ratio (d.r.) was determined by ¹H NMR analysis. *ee* values were determined by HPLC using a chiral stationary phase. [b] [Cu(CH₃CN)₄]PF₆ (5 mol %), (R,R_p)-TANIAPHOS (5 mol %), and Et₃N (25 mol %) were used. Reaction was conducted using 1 g of ketimine.

did not interfere with stereoselectivity (Table 2, entries 6, 7). A marginal loss in reactivity was detected with ketimines bearing electron-donating substituents (Table 2, entries 8, 9). Notably, excellent stereoselectivity was observed with more challenging ketimine substrates, e.g., ketimines derived from ethyl ketone and aliphatic ketones; albeit they were isolated with reduced yields (Table 2, entries 10–12). Methyl-substituted γ -crotonolactones **1b,c** were also applicable in the present catalytic system (Table 2, entries 13, 14).

A transformation of the Mannich adduct is outlined in Scheme 4. 1,4-Reduction of an α,β -unsaturated lactone moiety was effected with $\text{NiCl}_2/\text{NaBH}_4$ to give the saturated



Scheme 4. Transformation of Mannich adduct **3a**.

product **6**.^[23] Treatment of **6** with Raney-Ni, followed by the addition of AcOH, cleaved the N–P bond to give amine **7**. Heating of **7** in toluene led to the thermodynamically more-stable six-membered lactam **8** in quantitative yield.

In summary, a direct catalytic asymmetric vinylogous Mannich-type reaction of ketimines has been developed. Activation of the *N*-thiophosphinoyl group by a soft Lewis acid was key to achieve the enantioselective addition of the dienolate generated in situ to otherwise unreactive ketimine substrates. Application of this catalytic protocol to the enantioselective synthesis of biologically significant compounds is currently underway.

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