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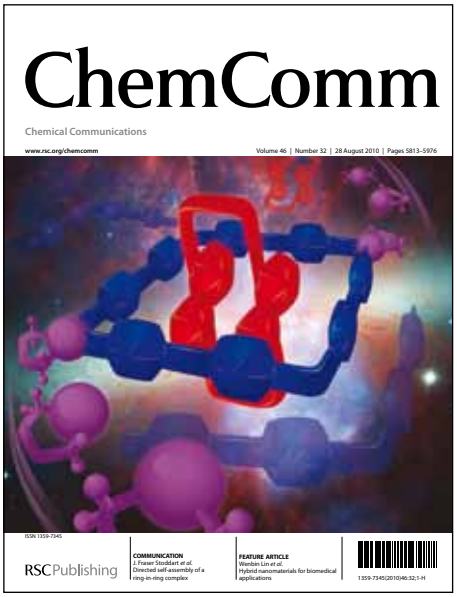

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ARTICLE TYPE

An Efficient Organocatalytic Enantioselective Michael Addition of Aryl Methyl Ketones with 2-Furanone: Highly Functionalized Chiral 3,4-Substituted Lactones

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The efficient asymmetric Michael addition reactions of aryl methyl ketones to 2-furanone were catalyzed by a simple and commercially available chiral 1,2-diphenyl-1,2-ethanediamine and p-TSA·H_2O as cocatalyst with good yields (up to 95%) and excellent enantioselectivities (up to >99% ee). A bi-functional catalytic mechanism for the reaction was proposed.

The γ-butyrolactone skeleton is present in more than 13 000 natural products, some of which show significant biological activities such as antibiotic and anti-tumor properties.[1] During the past decades, different asymmetric approaches for these compounds have been intensively studied[2] and several natural product and synthetic compound representatives are shown in Figure 1.[3] Clearly, direct Michael addition reactions of ketones to 2-furanone derivatives satisfy the principles of atom economy to prepare these compounds. However, as far as we know, no direct Michael addition reactions of aromatic ketones to 2-furanones have been reported. This might be due to the low reactivity of aromatic ketones and the stability of furanones, which undergo decomposition under basic conditions.[4] Usually highly active reagents and metal catalysts are used for the addition to 2-furanones, such as vinylboranes[5a], lithium enolates[5b], malonic esters[5c] and alkyl free radicals[5d]. In the very few reports on the adducts of aromatic ketones and 2-furanones, highly active zinc enolates[5e,5f] tranformed from ketones, were employed as nuclephiles to 2-furanones. Thus it is challenging and highly desirable to develop the direct Michael addition reactions of simple ketones to 2-furanones under mild reaction conditions.

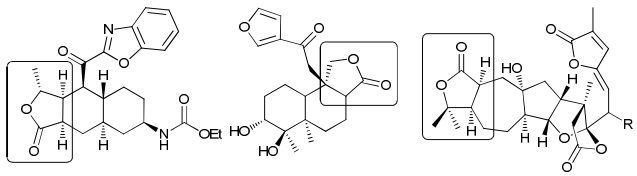


Fig. 1 Representative natural and synthetic compounds with highly substituted chiral γ-butyrolactones.

In the past decade, organocatalysis has undergone a major development in constructing various enantiomerically enriched compounds.[6] In particular, amine catalysts, especially secondary amines (L-Proline and its derivatives) have proven to be extraordinarily successful in the activation of aldehydes or ketones *via* enamine/iminium mechanism.[6a,6b] However, direct construction of a chiral center at the α-position of an aryl ketone still has been rarely reported in enamine catalysis. Primary amine-thioureas seem more effective in the activation of aryl methyl ketones, but the Michael acceptors were mainly limited to highly active substrates, such as β-nitroolefins,[7a-7c] nitrodiene.[7d,7e] Our previous discovery showed 1,2-primary diamine was not only very effective in the activation of aryl/alkyl ketones,[8] α,β-unsaturated ketones and 2-(*5H*)-furanones by enamine/iminium but also 1,3-bifunctional substrates by hydrogen bonds.[8c] In this context, it is promising that Michael addition reactions of aryl methyl ketones to 2-furanone could be catalyzed by a suitable amine catalyst.

After extensive screening, fortunately, we found the reaction of acetonephenone **2a** to 2-furanone **1a** was very successful with 97% yield at room temperature catalyzed by ethylenediamine and acetic acid (Table 1, entry 1). 2-Furanone **1a** represented a large number of natural products with 5,5-disubstituted butyrolactones in the structure.[9] To demonstrate the asymmetric transformation, chiral primary 1,2-diamines and acid additives were screened as catalysts. Acyclic (*1S,2S*)-(-)-1,2-diphenyl-1,2-ethanediamine showed much better enantiocontrol (Table 1, entry 3) than 1,2-diaminocyclohexanes, which showed greater catalytic activity with a 85% yield (Table 1, entry 2). However, secondary amine catalysts L-Proline (**D**) and dipeptide (**E**) did not show any catalytic activity (Table 1 entries 4 and 5).

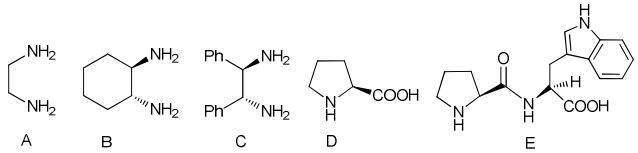
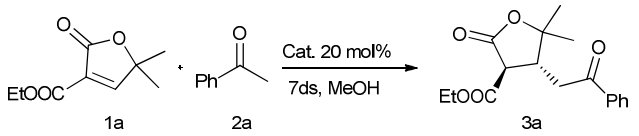


Fig. 2 Catalysts screened for the asymmetric Michael Addition between furanone **1a** and acetophenone **2a.**

J. Wang[8a] disclosed that the additives also showed significant impact on the catalytic manner, such as 1,2-diamine catalyzed Michael addition reactions would be stopped by adding 2 equivalents of strong acid (Table 1, entry 8). We next turned to study the additive effect and found that our previously used weak acid additives AcOH and PhCOOH only gave moderate enantioselectivities (Table 1, entries 3 and 6), while stronger acid CF_3COOH gave quite satisfactory enantiocontrol (up to 95% ee)

with a lower yield (Table 1 entry 7). Much to our surprise, by reducing the amount of strong acid to 1 equivalent of the diamine catalyst, the reaction proceeded quite well with 96% ee and 53% yield at r.t. (Table 1, entry 9). What's more, the product yield could be greatly improved (85% yield) without much loss of enantioselectivity when heated to 50℃ (Table 1 entry 10). And the dr values could be easily improved to nearly 99:1 after being recrystallized once (See Supporting Information).

Table 1 Screening of catalysts for direct Michael reactions of 2-furanone **1a** with acetophenone **2a**



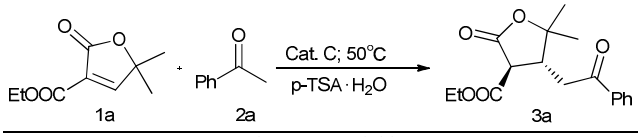
1a 2a 3a

entry	cat.	additive[a]	temp. (℃)	yield (%)[b]	dr anti/syn[c]	ee (%)[d]
1	A	AcOH	r.t.	97	12.3/1	-
2	B	AcOH	r.t.	85	13.0/1	-36
3	C	AcOH	r.t.	54	11.1/1	75
4	D	None	r.t	n.r.	-	-
5	E	None	r.t	n.r.	-	-
6	C	PhCOOH	r.t.	63	8.8/1	75
7	C	CF_3COOH	r.t	37	12.4/1	95
8	C	PTSA·H_2O	r.t.	trace	-	-
9	C	PTSA·H_2O	r.t.	53	13.6/1	96
10	C	PTSA·H_2O	50	85	8.5/1	91

[a]Additive loading is 40 mol% (entries 1-3 and 6-8); for entries 9 and 10, additive loading is 20mol%. [b] Isolated yield of the corresponding product; [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC.

Further screening of the solvent (Table 2, entries 1-4) indicated that *i*-PrOH gave the highest enantioselectivity with a relatively lower yield (Table 2, entry 2). In some cases, we observed that precipitates appeared after we added the catalysts and the substrates into *i*-PrOH, which was separated and identified as the enamine salt formed by diamine monosalt and acetophenone (See ESI-MS results of the intermediates in supporting information). This further proved that primary amines and suitable acid could be efficient catalysts to activate aromatic ketones.

Table 2 Screening of solvents and catalyst loading for direct Michael reactions of furanone **1a** with acetonephenone **2a**



1a 2a 3a

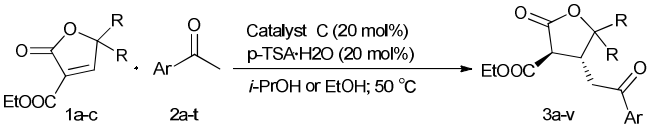
entry	Cat. C (mol%)	solvent	yield (%)[a]	Dr anti/syn[b]	ee (%)[c]
1	20	EtOH	82	14.5/1	95
2	20	*i*-PrOH	66	13.0/1	97
3	20	DMF	65	12.1/1	91
4	20	DMSO	74	13.2/1	90
5[d]	20	*i*-PrOH	82	13.2/1	97
6[d]	10	*i*-PrOH	75	12.8/1	92
7[d]	5	*i*-PrOH	61	10.7/1	91

[a] Isolated yields of the corresponding products. [b] Determined by ^{1}H NMR of crude products. [c] Determined by chiral-phase HPLC. [d] **1a**:**2a**=1:1.2 (0.5mmol:0.6mmol), unless otherwise noted **1a**:**2a**=1:5 (0.5mmol:2.5mmol)

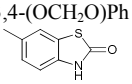
We also attempted to reduce the catalyst loading to 10 mol% and 5 mol%, but the product yield and ee value were sacrificed (Table 2, entries 6 and 7). Hence, 20 mol% of (*1S*,*2S*)-(-)-1,2-diphenyl-1,2-ethanediamine (**C**) and p-TSA·H_2O as cocatalyst at 50℃ in *i*-PrOH were accepted as the optimal conditions.

With the optimal conditions in hand, structural diversity of aryl methyl ketones was then examined. As demonstrated in table 3, this catalytic system was amenable to a very broad range of aromatic ketones. Notably, electron-neutral, electron-poor and electron-rich acetophenones were all easily transformed with good yields and high levels of enantiocontrol (Table 3, entries 1-9, up to 99% ee). More importantly, hetero-aromatic methyl ketones did not show a deleterious impact on the reaction performance (Table 3, entries 10, 11, 15, 19, 20). For some substrates (Table 3, entries 3, 4, 7, 10, 14, 15), the solubility of their intermediates (enamine salts) in *i*-PrOH are not so good, which led to the decrease of the reaction rate. However, the reactions could be smoothly carried out in EtOH at a higher temperature (70 ℃) with quite satisfactory yields and enantioselectivities. Then we examined the reactivity of furanones with bulkier substituents in γ-position. Both furanone **1b** and **1c** showed great product yields and ee% values (Table 3, entries 21 and 22).

Table 3 Substrate scope of diamine catalyzed Michael Addition of 2-furanone **1a-c** with acetyl-ketone **2a-t**



1a-c 2a-t 3a-v

entry	R, R	Ar	solvent	yield (%)[a]	dr (anti/syn)[b]	ee (%)[c]
1	Me, Me	Ph	*i*-PrOH	82(**3a**)	13.2/1	97
2	Me, Me	4-FPh	*i*-PrOH	62(**3b**)	9.1/1	97
3[d]	Me, Me	4-ClPh	Ethanol	90(**3c**)	9.7/1	94
4[d]	Me, Me	4-BrPh	Ethanol	63(**3d**)	9.0/1	97
5	Me, Me	4-NO_2Ph	*i*-PrOH	56(**3e**)	8.1/1	>99
6	Me, Me	4-MePh	*i*-PrOH	85(**3f**)	9.5/1	82
7[d]	Me, Me	3-ClPh	Ethanol	69(**3g**)	8.1/1	82
8	Me, Me	3-NO_2Ph	*i*-PrOH	74(**3h**)	8.8/1	92
9	Me, Me	3-MeOPh	*i*-PrOH	87(**3i**)	11.8/1	92
10[d]	Me, Me	3-pyridine	Ethanol	71(**3j**)	9.0/1	94
11	Me, Me	2-furan	*i*-PrOH	91(**3k**)	12.2/1	79
12	Me, Me	3-AcNHPh	*i*-PrOH	64(**3l**)	11.4/1	93
13	Me, Me	3-MePh	*i*-PrOH	94(**3m**)	11.4/1	95
14[d]	Me, Me	3-FPh	Ethanol	69(**3n**)	9.0/1	94
15[d]	Me, Me	2-thiophene	Ethanol	74(**3o**)	9.5/1	92
16	Me, Me	4-AcNHPh	*i*-PrOH	94(**3p**)	10.6/1	96
17	Me, Me	3,4,5-$(MeO)_3$Ph	*i*-PrOH	95(**3q**)	7.2/1	94
18	Me, Me	3,4-(OCH_2O)Ph	*i*-PrOH	78(**3r**)	8.0/1	87
19	Me, Me		*i*-PrOH	94(**3s**)	12.7/1	98
20	Me, Me	3-Quinoline	*i*-PrOH	54(**3t**)	8.1/1	93
21	Et, Et	Ph	EtOH	73(**3u**)	10.8/1	93
22		Ph	EtOH	92(**3v**)	14.8/1	93

[a] Isolated yields of corresponding products. [b] Determined by ^{1}H NMR of crude products. [c] Determined by chiral-phase HPLC. [d] Reaction temperature was 70℃ (it was 50℃ unless otherwise noted).

The absolute configuration was confirmed to be (3S,4R) by the X-ray structure of **3d** (Figure 3). The great outcome achieved by 1:1 of diamine and strong acid prompted us to propose a distinct catalytic mechanism from those formerly raised by our group.[8a,8b] Based on ESI-MS results of the intermediates (see supporting information $[M_1+1]^+ = 315$; $[M_2-1]^- = 171$), we deduced that an

in-situ formed monosalt actually acted as a bifunctional catalyst. One of the primary amine groups activated acetophenone by the enamine intermediate, and the other primary amine salt of *p*-TSA formed hydrogen bonds with the 1,3-diester groups, which could form both transition states **TS1** and **TS2** (Figure. 4). It is clearly that **TS2** is sterically unfavorable and **TS1** is more feasible leading to the product with (3S,4R) configuration.

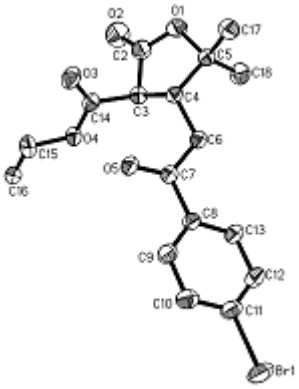


Fig. 3 X-ray structure of **3d.**

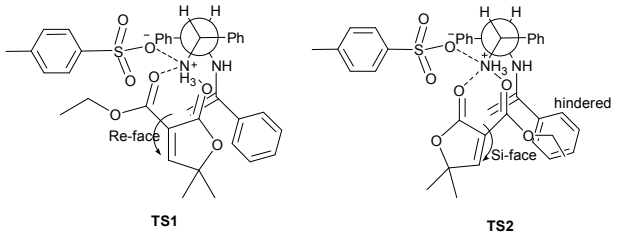


Fig.4 Proposed transitional states.

Conclusions

In summary, we have developed the efficient direct asymmetric Michael addition reactions of aryl methyl ketones with 2-furanones catalyzed by a simple and commercially available (*1S*,*2S*)-(-)-1,2-diphenyl-1,2-ethanediamine and PTSA·H_2O as cocatalyst. A broad range of aromatic ketones were transformed with good yields (up to 95% yield) and excellent enantioselectivities (up to 99% ee). This reaction provides alternative access to synthetically and biologically interesting highly substituted chiral *γ*-Lactones. We fully expect this new method could be further applied to a broader substrate scope, leading to a variety of biologically interesting molecules useful in medicinal chemistry. The bioactivity studies of chiral *γ*-Lactones are currently underway in our group.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Detailed experimental procedures and spectral data for compounds **3a** to **3v**; single crystal for **3d** was recrystallized from EtOH and Water. Crytal data for **3d**: [a]Crystal data for 3d: $C_{17}H_{19}BrO_5$, M = 383.24, orthorhombic, a = 6.941(3) Å b = 11.055(4) Å c = 22.261(8) Å α = 90.00°, β = 90.00°, γ = 90.00°, V = 1708.1(11) Å^3, T = 295(2) K, space group $P212121$, Z = 4, μ(CuKα) = 3.480 mm^{-1}, 15439 reflections measured, 3330 independent reflections (R_{int} = 0.0619). The final R_1 values were 0.0347 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.0863 ($I > 2\sigma(I)$). The final R_1 values were 0.0378 (all data). The final $wR(F^2)$ values were 0.0894 (all data). Flack parameter = -0.008(19).

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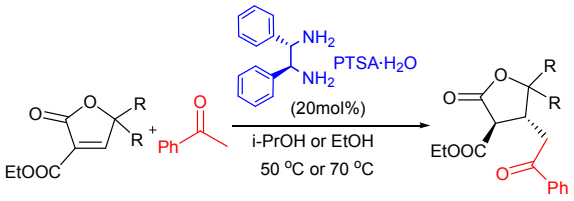

The first direct organocatalytic Michael addition between 2-furanone and aryl-ketones was catalyzed by vicinal primary diamine salts with good product yields (up to 95%), entioselectivities (up to 99%), and diastereoselectivities (*anti:syn* 7.2:1 to 13.2:1).