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Michael Addition–Lactonization of Arylacetyl Phosphonate to β,γ-Unsaturated α-Keto Esters for the Synthesis of Chiral *syn*-3,4-Dihydropyranones and 5,6-Dihydropyranones

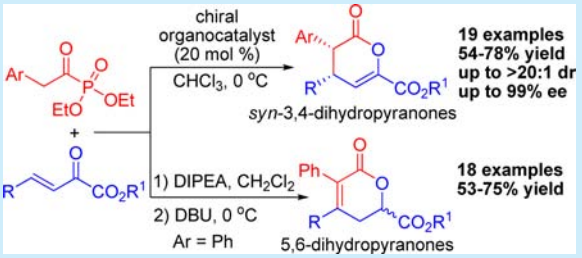
Ming-Liang Zhang,[†,§] Zhi-Jun Wu,[‡] Jian-Qiang Zhao,[†,§] Yuan Luo,[†,§] Xiao-Ying Xu,[*,†] Xiao-Mei Zhang,[†] and Wei-Cheng Yuan[*,†]

[†]National Engineering Research Center of Chiral Drugs, Chengdu Institute of Organic Chemistry and [‡]Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China

[§]University of Chinese Academy of Sciences, Beijing 100049, China

Supporting Information

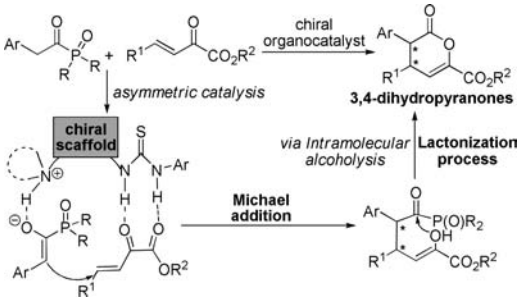
ABSTRACT: Catalytic asymmetric Michael addition–lactonization of arylacetyl phosphonates to β,γ-unsaturated α-keto esters by a chiral bifunctional thiourea–tertiary amine was established. Using the developed protocol, a range of optically pure *syn*-3,4-dihydropyranones were generated in good yields with good to excellent stereoselectivities (up to >20:1 dr and 99% ee). Meanwhile, when stoichiometric diisopropylethylamine and 1,8-diazabicyclo[5.4.0]-undec-7-ene were used as the base for the same reaction, a series of 5,6-dihydropyranones could be obtained in moderate to good yields (53–75% yield).



Dihydropyranones are ubiquitous structural motifs in numerous natural or synthetic biologically active compounds,[1] and they also serve as versatile and important intermediates for the construction of some useful oxygen-containing heterocycles.[2] The importance of dihydropyranones has stimulated considerable interest from organic chemists and has encouraged the development of various strategies for their stereoselective preparation.[3] Among the different types of dihydropyranones, chiral 3,4-dihydropyranone units are common and widely found in a variety of compounds with important biological profiles. Myriad elegant catalytic approaches have been established for the consturction of enantiopure 3,4-dihydropyranones with considerable efficiency.[4] The majority of these strategies afford the 3,4-dihydropyranone products in an *anti*-configuration. In this context, exploring new efficient and highly enantioselective approaches to access dihydropyranones, especially those of *syn*-3,4-dihydropyranones,[5] is a substantial challenge and highly desirable.

We previously reported that arylacetyl phosphonates could react with nitroalkenes via organocatalysis for the synthesis of chiral α-substituted carboxylic ester.[6] In fact, before our work, it had been proved that arylacetyl phosphonates could serve as nucleophiles for the asymmetric Michael addition reaction,[7] while the α-ketophosphonate group therein could be readily converted into ester or amide group via the corresponding alcoholysis or aminolysis.[8] On the other hand, β,γ-unsaturated α-keto esters could be used as versatile reaction components for various asymmetric tandem reactions due to the fine reactivities and the facile conversions of the α-carbonyl and the ester groups.[9] Enlightened by these elegant studies,[6−9] we speculated that the reaction of arylacetyl phosphonates and β,γ-unsaturated α-keto esters should occur via a Michael addition and a sequential lactonization process (Scheme 1). As part of our ongoing interest in the exploration of practical asymmetric organocatalysis,[10] herein we present the first catalytic asymmetric Michael addition-lactonization of arylacetyl phosphonates to β,γ-unsaturated α-keto esters with a chiral bifunctional thiourea-tertiary amine catalyst.[11] This methodology permits the production of optically pure *syn*-3,4-dihydropyranones in good yields with good to excellent

Scheme 1. Strategy for the Reaction of Arylacetyl Phosphonates and β,γ-Unsaturated α-Keto Esters To Access 3,4-Dihydropyranones



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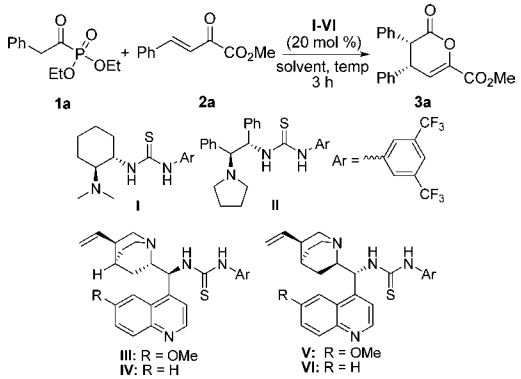
stereoselectivities (up to >20:1 dr and 99% ee) (Scheme 1). We also further demonstrate that the same reaction can generate 5,6-dihydropyranones with the stoichiometric organic bases.

We initiated our investigation with the reaction of arylacetyl phosphonate[12] **1a** and β,γ-unsaturated α-keto ester **2a** in the presence of chiral bifunctional thiourea−tertiary amine catalyst **I** in chloroform at 0 °C. The reaction could proceed to completion within 3 h and furnish the expected Michael addition−lactonization product **3a** in 47% yield with >20:1 dr and 96% ee (Table 1, entry 1). We next evaluated some other

Table 1. Optimization of the Reaction Conditions[a]



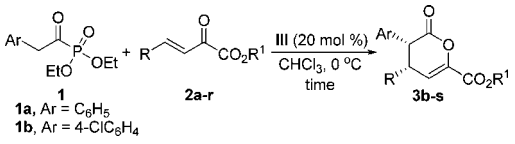
entry	catalyst	solvent	temp (°C)	yield[b] (%)	dr[c]	ee[c] (%)
1	I	$CHCl_3$	0	47	>20:1	96
2	II	$CHCl_3$	0	59	>20:1	92
3	III	$CHCl_3$	0	77	>20:1	96
4	IV	$CHCl_3$	0	26	>20:1	94
5	V	$CHCl_3$	0	24	>20:1	91
6	VI	$CHCl_3$	0	26	>20:1	92
7	III	DCM	0	51	>20:1	96
8	III	Et_2O	0	66	>20:1	97
9	III	toluene	0	44	6:1	98
10	III	EtOAc	0	43	13:1	96
11	III	$CHCl_3$	25	62	10:1	93
12	III	$CHCl_3$	−20	71	>20:1	96
13	III	$CHCl_3$	−30	70	>20:1	93
14	III	$CHCl_3$	0	67	>20:1	96[d]
15	III	$CHCl_3$	0	trace	nd	nd[e]

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.3 mmol), **2a** (0.2 mmol), and 20 mol % catalyst in 2.0 mL of solvent. [b]Isolated yield. Due to the easy degradation of the product upon the isolation by chromatography, the isolate operation should be done as quickly as possible and by using neutral silica gel for column chromatography. [c]Determined by chiral HPLC analysis. [d]10 mol % of catalyst was used. [e]5 mol % of catalyst was used. nd = not determined.

chiral bifunctional thiourea−tertiary amine catalysts **II**−**VI**, derived from 1,2-diphenylethylene−diamine and cinchona alkaloids (Table 1, entries 2−6). It was observed that catalyst **III** was the most effective candidate in light of the reactivity and diastereo- and enantiocontrol (Table 1, entry 3). Next, the screening of the solvents revealed that $CHCl_3$ was better than other solvents (Table 1, entry 3 vs entries 7−10). Variation of the reaction temperature had no significant improvement on the stereoselectivity (Table 1, entries 11−13). After the catalyst loading was lowered from 20 to 10 mol %, the reaction gave **3a** in 67% yield and without any effect on the diastereo- and enantioselectivity (Table 1, entry 14). However, when the catalyst **III** was further decreased to 5 mol %, the reaction provided **3a** only in a trace amount (Table 1, entry 15).

With the optimal reaction conditions in hand, the substrate scope of the reaction was investigated. The β,γ-unsaturated α-keto ester substrate **2b** containing an electron-donating substituent on the phenyl ring was well tolerated and gave **3b** in 54% yield with 19:1 dr and 99% ee (Table 2, entry 1).

Table 2. Substrate Scope of the Catalytic Asymmetric Michael Addition−Lactonization of Arylacetyl Phosphonate and β,γ-Unsaturated α-Keto Esters[a]



entry	R/R^1/2	time (h)	3/yield[b] (%)	dr[c]	ee[c] (%)
1	3-$MeOC_6H_4$/Me/**2b**	5	**3b**/54	19:1	99
2	3-FC_6H_4/Me/**2c**	2	**3c**/77	7:1	96
3	4-FC_6H_4/Me/**2d**	1	**3d**/77	16:1	99
4	2-ClC_6H_4/Me/**2e**	2	**3e**/78	>20:1	99
5	3-ClC_6H_4/Me/**2f**	2	**3f**/63	6:1	95
6	4-ClC_6H_4/Me/**2g**	2	**3g**/72	16:1	99
7	3-BrC_6H_4/Me/**2h**	1	**3h**/67	6:1	94
8	4-BrC_6H_4/Me/**2i**	1	**3i**/65	13:1	98
9	1-naphthyl/Me/**2j**	3	**3j**/75	>20:1[d]	98
10	2-furyl/Me/**2k**	5	**3k**/59	>20:1[d]	93
11	2-thienyl/Me/**2l**	3	**3l**/63	3:1	94
12	4-$MeOC_6H_4$/Et/**2m**	5	**3m**/57	>20:1	93
13	4-MeC_6H_4/Et/**2n**	4	**3n**/61	13:1	95
14	4-FC_6H_4/Et/**2o**	1	**3o**/60	>20:1	96
15	3-ClC_6H_4/Et/**2p**	2	**3p**/77	6:1	97
16	4-ClC_6H_4/Et/**2q**	2	**3q**/71	19:1	94
17	n-C_3H_7/Et/**2r**	3	**3r**/70	>20:1	99
18[e]	Ph/Me/**2a**	2	**3s**/67	>20:1[d]	92

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.3 mmol), **2** (0.2 mmol), and 20 mol % of **III** in 2.0 mL of $CHCl_3$ at 0 °C for the specified time. [b]Isolated yield. Because of the easy degradation of the products during the isolation by column chromatography, the isolated operation should be done as quickly as possible and by using neutral silica gel. [c]Determined by chiral HPLC analysis. [d]dr value was determined by ^1H NMR analysis. [e]The reaction of **1b** and **2a**.

Meanwhile, this protocol also allowed the substitution of various electron-withdrawing substituents at different positions on the phenyl ring, smoothly delivering the expected *syn*-3,4-dihydropyranones **3c**−**i** within 1−2 h in good yields with 6:1 to >20:1 dr and excellent ee values (Table 2, entries 2−8). In addition, reaction of **2j**, which contains sterically hindered 1-naphthyl, proceeded well to give product **3j** in 75% yield with >20:1 dr and 98% ee (Table 2, entry 9). Nevertheless, heteroaromatic ring substituted **2k** and **2l** also proved to be amenable to this developed protocol, and the corresponding products **3k** and **3l** were obtained with the acceptable results (Table 2, entries 10 and 11). On the other hand, the ester moiety of β,γ-unsaturated α-keto esters could be varied from methyl to ethyl ester as shown in substrates **2m**−**r**. When electron-donating (Table 2, entries 12−13) or electron-withdrawing (Table 2, entries 14−16) groups are incorporated into the phenyl ring within the β,γ-unsaturated α-keto ester, these cases could furnish the desired chiral *syn*-3,4-dihydropyranones **3m**−**q** in good yields with high to excellent dr (up to

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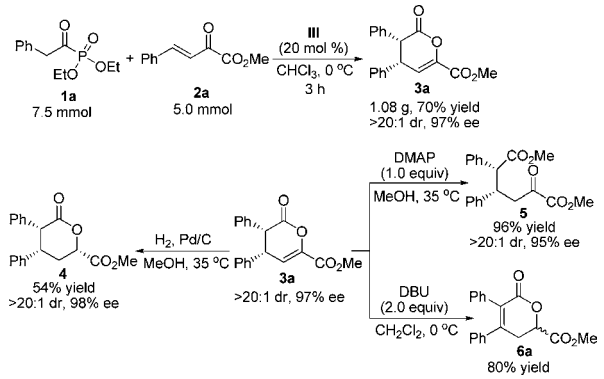
>20:1) and ee (93−97%). These outcomes demonstrated that the ester moiety had almost no impact on the reactivity and stereocontrol. An aliphatic substrate could also be applied in the catalytic system, as shown by the formation of product **3r** in 70% yield with excellent dr and ee values (Table 2, entry 17). Ultimately, 4-chlorophenylacetyl phosphonate **1b** could also react with **2a** to give **3s** in 67% yield, >20:1 dr, and 92% ee (Table 2, entry 18). The absolute configuration of the major isomer **3h** was determined to be (C3*R*,C4*S*) by single-crystal X-ray analysis.[13] The configurations of the other products in Table 2 were assumed by analogy.

To exemplify the synthetic utility of the protocol outlined above, the reaction was scaled up to 5 mmol for **2a**, which is 25 times larger than the scale of the model reaction in Table 1. The preparative-scale reaction proceeded well and afforded **3a** without compromising diastereo- and enantioselecitvity, although a slightly decreased yield was observed (Scheme 2).

Scheme 2. Preparative-Scale Experiment and the Transformations of 3a into other Compounds

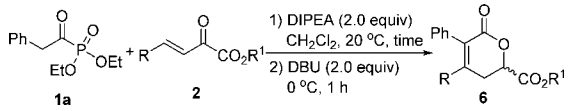


Product **3a** was then further transformed into other chiral compounds.[14] As shown in Scheme 2, the C=C bond in **3a** could be readily hydrogenated by using palladium−carbon catalyst in methanol, generating **4** in 54% yield without loss in the diastereo- and enantioselectivity. Additionally, the alcoholysis of **3a** by using DMAP in MeOH led to the ring opening, giving the chain compound **5** in 96% yield with excellent dr and ee values. Meanwhile, treatment of **3a** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in CH_2Cl_2 caused the migration of the double bond, delivering the isomeric 5,6-dihydropyranone **6a** in 80% yield.

Inspired by the transformation of 3,4-dihydropyranone **3a** to 5,6-dihydropyranone **6** with DBU as the base (Scheme 2), we attempted to directly prepare 5,6-dihydropyranone compounds, which are a class of important δ-lactones serving as versatile intermediates for organic synthesis,[15] using arylacetyl phosphonate **1a** and β,γ-unsaturated α-keto esters under suitable conditions. Unfortunately, if we directly used DBU as base for the reacton of **1a** and **2a**, it was found that the reaction became very complex and without any major product. However, after systematic screening for the influence factors on the reaction, a set of optimized conditions were determined,[16] which can be delineated as performing the reaction in CH_2Cl_2 with 2.0 equiv of diisopropylethylamine as base at 20 °C for a certain reaction time, and then followed by direct addition of 2.0 equiv of DBU into the reaction mixture and then stirring for 1 h at 0 °C.

With a working protocol in place, the generality of the direct preparation of 5,6-dihydropyranones from arylacetyl phosphonate and different β,γ-unsaturated α-keto esters was next exemplified (Table 3). The model reaction could complete in 3

Table 3. Substrate Scope of the Reaction of Arylacetyl Phosphonate and β,γ-Unsaturated α-Keto Esters for the Synthesis of 5,6-Dihydropyranones[a]



entry	R/R^1	time (h)	6	yield[b] (%)
1	Ph/Me (**2a**)	3	**6a**	69
2	4-MeOC_6H_4/Me (**2s**)	5	**6b**	62
3	3-FC_6H_4/Me (**2c**)	1	**6c**	61
4	4-FC_6H_4/Me (**2d**)	1	**6d**	63
5	2-ClC_6H_4/Me (**2e**)	1	**6e**	68
6	3-ClC_6H_4/Me (**2f**)	1	**6f**	59
7	4-ClC_6H_4/Me (**2g**)	2	**6g**	60
8	3-BrC_6H_4/Me (**2h**)	3	**6h**	53
9	4-BrC_6H_4/Me (**2i**)	2	**6i**	59
10	3-$NO_2C_6H_4$/Me (**2t**)	3	**6j**	59
11	1-naphthyl/Me (**2j**)	1	**6k**	75
12	2-furyl/Me (**2k**)	1	**6l**	57
13	2-thienyl/Me (**2l**)	1	**6m**	61
14	4-MeOC_6H_4/Et (**2m**)	6	**6n**	57
15	4-MeC_6H_4/Et (**2n**)	3	**6o**	57
16	4-FC_6H_4/Et (**2o**)	1	**6p**	63
17	3-ClC_6H_4/Et (**2p**)	2	**6q**	60
18	4-ClC_6H_4/Et (**2q**)	1	**6r**	73

[a]The reactions were carried out with **1a** (0.4 mmol), **2** (0.2 mmol), and ^{i}Pr$_2$NEt (0.4 mmol) in 2.0 mL of CH_2Cl_2 at 20 °C for the specified reaction time, and then the temperature was decreased to 0 °C followed by addition of DBU (0.4 mmol) into the reaction mixture and constant stirring for 1 h. [b]Isolated yield.

h and give the desired product **6a** in 69% yield (entry 1). Nevertheless, this protocol allows the substitution of the γ-aryl unit with electron-donating and -withdrawing groups as well as γ-heteroaryl substitutents within the β,γ-unsaturated α-keto methyl esters, providing 5,6-dihydropyranones **6b−m** with yields ranging from 53% to 75% (entries 2−13). Moreover, variation of the ester group also is readily tolerated in this process; regardless of the electron-donating or -withdrawing substituents incorporated on the γ-phenyl ring of the β,γ-unsaturated α-keto ethyl esters, these reactions proceeded efficiently and generated their respective products **6n−r** with moderate yields (57−73% yield, entries 14−18). X-ray crystallography of the product **6r** was achieved, which unambiguously confirmed the structures the obtained 5,6-dihydropyranone compounds.[13]

In conclusion, we have developed an asymmetric Michael addition−lactonization of arylacetyl phosphonates to β,γ-unsaturated α-keto esters by using a chiral bifunctional thiourea−tertiary amine catalyst. With the developed protocol, a range of optically pure *syn*-3,4-dihydropyranones could be smoothly generated in good yields with good to excellent stereoselectivities (up to >20:1 dr and 99% ee). This process represents a new paradigm for preparing the highly enantioenriched *syn*-3,4-dihydropyranone derivatives. Meanwhile, when stoichiometric diisopropylethylamine and DBU are used as bases for the same reaction of arylacetyl phosphonate and β,γ-unsaturated α-keto esters, a series of 5,6-dihydropyr-

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anones can be directly constructed in moderate to good yields (53−75% yield). Studies are ongoing within this laboratory to discover the potential synthetic applications of the developed methodology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02558.

Experimental details, characterization data for new compounds, and X-ray crystal structures (PDF)
X-ray data for compound **3h** (CIF)
X-ray data for compound **6r** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xuxy@cioc.ac.cn.
*E-mail: yuanwc@cioc.ac.cn.

Notes

The authors declare no competing financial interest.

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