Literature Report VII

Phosphine-Catalyzed Activation of Alkylidenecyclopropanes: Rearrangement to Form Polysubstituted Furans and Dienones

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Wu, J.; Tang, Y.; Xu, S. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 6284 He, X.; Tang, Y.; Wang, J.; Xu, S. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 10698





² Phosphine-Catalyzed Activation of Vinylcyclopropanes

³ Phosphine-Catalyzed Activation of Alkylidenecyclopropanes



CV of Silong Xu



Xu, S.

Research:

- Phosphine-mediated transformations
- Lewis base catalysis for cyclopropane ring opening
- C-H activation via transition metal catalysis
- Total synthesis of complex bioactive natural products

Education:

- **2000–2004** B.S., Hunan Normal University
- **2004–2006** Teacher, No. 1 Middle School of Hengnan
- **2006–2012** M.S. & Ph.D., Nankai University (Zhengjie He)
- 2012–2014 Postdoc. & Lecturer, Xi'an Jiaotong University
- 2014–Now Associate Professor, Xi'an Jiaotong University

Phosphine Activations: Key Zwitterion Intermediates and Reactions



Lu, Y. et al. Acc. Chem. Res. 2016, 49, 1369

Allenoate ([3+2] annulation)



Lu, X. et al. J. Org. Chem. 1995, 60, 2906



Marinetti, A. et al. J. Org. Chem. 2013, 78, 1488



Allenoate (y-Addition)



β'-Acetoxy allenoate ([4+1] annulation)



MBH Carbonate ([3+2] annulation)



Zhang, C. et al. Angew. Chem. Int. Ed. 2003, 42, 1035



Wang, L. et al. Org. Lett. 2015, 17, 872



Vinyl ketone ([4+2] annulation)



Activation of Vinylcyclopropanes



Xu, S. et al. Angew. Chem. Int. Ed. 2018, 57, 6284

Investigation of the conditions



Entry ^[a]	Catalyst	Solvent	T [ºC]	t [h]	Yield [%] ^[b]
1	PPh_3	toluene	110	24	10
2	P(PMP) ₃	toluene	110	24	39
3	P(p-tolyl) ₃	toluene	110	24	62
4	P ^t Bu ₃	toluene	110	24	61
5	PCp ₃	toluene	110	24	69
6	P ⁿ Bu ₃	toluene	110	24	85
7	None	toluene	110	48	trace
8	K ₂ CO ₃	toluene	110	48	trace
9 [c]	DABCO	toluene	110	24	14
10	P ⁿ Bu₃	acetonitrile	reflux	24	77

[a] Under N₂ and indicated temperature, to a solution of **1a** (0.5 mmol) in the solvent (5.0 mL) was added the catalyst (20 mol%). [b] Isolated yield. [c] Dihydrofuran **2a'** was obtained in 37% yield. [d] 1.0 equiv of H₂O was added. [e] Under strictly anhydrous conditions. [f] 2.5 mol% of PⁿBu₃ was used. [g] 50 mol% PⁿBu₃ loading. [h] 1.0 equiv of PⁿBu₃ was adopted.

Investigation of the conditions



Entry ^[a]	Catalyst	Solvent	T [ºC]	t [h]	Yield [%] ^[b]
11	P ⁿ Bu ₃	DMSO	110	24	30
12	P ⁿ Bu ₃	acetone	reflux	24	51
13	P ⁿ Bu ₃	DCM	reflux	24	trace
14	P ⁿ Bu ₃	THF	reflux	24	trace
15	P ⁿ Bu ₃	toluene	60	24	trace
16 ^[d]	P ⁿ Bu ₃	toluene	110	24	82
17 ^[e]	P ⁿ Bu ₃	toluene	110	24	69
18 ^[f]	P ⁿ Bu ₃	toluene	110	24	72
19 ^[g]	P ⁿ Bu ₃	toluene	110	24	71
20 ^[h]	P ⁿ Bu ₃	toluene	110	36	22

[a] Under N₂ and indicated temperature, to a solution of **1a** (0.5 mmol) in the solvent (5.0 mL) was added the PⁿBu₃ (20 mol%). [b] Isolated yield. [c] Dihydrofuran **2a'** was obtained in 37% yield. [d] 1.0 equiv of H₂O was added. [e] Under strictly anhydrous conditions. [f] 2.5 mol% of PⁿBu₃ was used. [g] 50 mol% PⁿBu₃ loading. [h] 1.0 equiv of PⁿBu₃ was adopted.

Investigation on Substrate Scope



[a] Conditions: under N₂ and at 110 °C, the reaction was carried out with P^nBu_3 (20 mol%) in toluene for 24-36 h, except that for **2g** and **2h**, DABCO (50 mol%) was used as the catalyst, and for **2i-s**, P^tBu_3 (50 mol%) was employed as the catalyst and PhCI or DMSO as the solvent.

A proposed catalytic cycle



Deuterium-labeling investigations



³¹P tracking



Activation of Alkylidenecyclopropanes



Electron-deficient ACPs:



Li, Y. et al. Angew. Chem. Int. Ed. 2019, 58, 10698

Investigation of the conditions



Entry ^[a]	Catalyst	Solvent	T [ºC]	Yield [%] ^[b]
1	PPh ₃	DMSO	120	78
2	P ⁿ Bu ₃	DMSO	120	34
3	PCy ₃	DMSO	120	58
4	DPPE	DMSO	120	56
5	$P(4-CF_{3}C_{6}H_{4})_{3}$	DMSO	120	53
6	$P(4-MeC_6H_4)_3$	DMSO	120	76
7	$P(4-MeOC_6H_4)_3$	DMSO	120	81
8	P(2-furyl) ₃	DMSO	120	68
9	DABCO	DMSO	120	54 ^[c]
10	$P(4-MeOC_6H_4)_3$	DMF	120	62

[a] Typical procedure: under N_2 , the catalyst (20 mol%) was added to a solution of **1a** (0.1 mmol) in the specified solvent (2.0 mL) in a Schlenk tube (25 mL), and the mixture was heated for 24 h. [b] Yield of isolated product. [c] Dihydrofuran **2a**' was obtained. [d] 10 mol% catalyst loading.

Investigation of the conditions



Entry ^[a]	Catalyst	Solvent	T [ºC]	Yield [%] ^[b]
11	$P(4-MeOC_6H_4)_3$	PhCl	120	54
12	$P(4-MeOC_6H_4)_3$	1,4-dioxane	120	56
13	$P(4-MeOC_6H_4)_3$	DCM	reflux	20
14	$P(4-MeOC_6H_4)_3$	EtOH	reflux	trace
15	$P(4-MeOC_6H_4)_3$	THF	reflux	trace
16	$P(4-MeOC_6H_4)_3$	DMSO	120	47
17	P(4-MeOC ₆ H ₄) ₃	DMSO	100	60

[a] Typical procedure: under N_2 , the catalyst (20 mol%) was added to a solution of **1a** (0.1 mmol) in the specified solvent (2.0 mL) in a Schlenk tube (25 mL), and the mixture was heated for 24 h. [b] Yield of isolated product. [c] Dihydrofuran **2a'** was obtained. [d] 10 mol% catalyst loading.

Synthesis of 2,3,4-trisubstituted furans



Entry ^[a]	R ¹	R ²	R ³	2	Yield [%] ^[b]
1	Bn	CO ₂ Et	Ме	2a	81
2	Bn	COMe	Ме	2b	72
3	Bn	SO ₂ Ph	Ме	2c	81
4	Bn	CO ₂ Me	Et	2d	85
5	Bn	CO ₂ Et	<i>ⁿ</i> Pr	2e	76
6	Bn	CO ₂ ^t Bu	Ме	2f	55
7	Bn	CO ₂ Et	Ph	2g	69
8	Bn	CO ₂ Et	3-CIC ₆ H ₄	2h	55
9	Bn	CO ₂ Et	$4-CIC_6H_4$	2 i	58
10	4-MeOC ₆ H ₄ CH ₂	CO ₂ Et	Ме	2 j	83
11	$n-C_{10}H_{21}$	CO ₂ Et	Ме	2k	81
[a] Typical	procedure: under N ₂ and a	t 120 °C, to a solutio	n of 1 (0.1 mmol) in DMSO	(2.0 mL) was added	P(4-MeOC ₆ H ₄) ₃

(20 mol%), and the mixture was stirred for 24 h. [b] Yield of isolated product.

Synthesis of 1,2,4-trisubstituted dienones



Entry ^[a]	R ¹	R ²	R ³	3	Yield [%] ^[b]	E/Z ^[c]
1	Ph	Ph	Me	3a	81	10:1
2	n-C ₉ H₁9	Ph	Me	3b	72	>20:1
3	Ph	Ph	Ph	3c	81	>20:1
4	Ph	$4-\text{MeC}_6\text{H}_4$	Me	3d	85	10:1
5	Ph	$3-MeC_6H_4$	Me	3e	76	>20:1
6	Ph	$4-FC_6H_4$	Me	3f	55	8.4:1
7	Ph	$4-CIC_6H_4$	Me	3g	69	6:1
8	Ph	3-CIC ₆ H ₄	Me	3h	55	15:1
9	Ph	$4-BrC_6H_4$	Me	3i	58	6:1

[a] Typical procedure: under N₂ and at 120 °C, to a solution of **1-2** (0.1 mmol) in DCE (2.0 mL) was added PBu₃ (20 mol%), and the mixture was stirred for 24 h. [b] Yield of isolated product. [c] E/Z ratio of tetrasubstituted alkenes is determined by NOESY and ¹H NMR; disubstituted alkenes show exclusively E geometry.

Synthesis of fully substituted furans



Entry ^[a]	R ¹	R ²	R ³	4	Yield [%] ^[b]	4/2 ^[c]
1	Ph	Ph	Ме	4a	86	10:1
2	$4-CIC_6H_4$	Ph	Me	4b	85	8:1
3	$2-CIC_6H_4$	Ph	Ме	4c	89	15:1
4	3-CIC ₆ H ₄	Ph	Me	4d	65	7:1
5	$4-\text{MeC}_6\text{H}_4$	Ph	Me	4e	87	10:1
6	4- ^t BuC ₆ H ₄	Ph	Ме	4f	61	10:1
7	$4-MeOC_6H_4$	Ph	Me	4g	88	10:1
8	$4-FC_6H_4$	Ph	Ме	4h	55	>20:1
9	$4-BrC_6H_4$	Ph	Me	4i	85	>20:1
10	Ph	Ph	Ph	4 j	61	>20:1
11	Ph	4-FC ₆ H ₄	Me	4k	64	>20:1
[a] Typical p (20 mol%), a	rocedure: under N_2 and the mixture was	and at 120 °C, to a stirred for 24 h. [b]	solution of 1-3 (0.1 m Yield of isolated prod	mol) in DMSO (2.0 uct. [c] Determined	mL) was added P(4-I by NMR assay.	MeOC ₆ H ₄) ₃

Synthesis of fully substituted furans



Entry ^[a]	R ¹	R ²	R ³	4	Yield [%] ^[b]	4/2 ^[c]
12	Ph	$4-BrC_6H_4$	Ме	41	64	>20:1
13	Ph	$4-CIC_6H_4$	Ме	4m	55	>20:1
14	Ph	3-CIC ₆ H ₄	Ме	4n	51	>20:1
15	Ph	$4-\text{MeC}_6\text{H}_4$	Ме	40	69	>20:1
16	Ph	$3-\text{MeC}_6\text{H}_4$	Ме	4p	89	10:1

[a] Typical procedure: under N₂ and at 120 °C, to a solution of **1-3** (0.1 mmol) in DMSO (2.0 mL) was added P(4-MeOC₆H₄)₃ (20 mol%), and the mixture was stirred for 24 h. [b] Yield of isolated product. [c] Determined by NMR assay.

Proposed mechanism



³¹P tracking





Summary

Phosphine-Catalyzed Activation of Vinylcyclopropanes



Phosphine-Catalyzed Activation of Alkylidenecyclopropanes



Alkylidenecyclopropanes (ACPs) are a type of extremely versatile yet readily available building blocks in organic synthesis. By virtue of significant ring strain, a plethora of ring-opening reactions of ACPs have been developed for the construction of various molecular architectures. To date, the reactivity of ACPs has been predominantly unlocked by transition-metal catalysis, Lewis acid catalysis, radical-induced reactions, and thermally induced cyclizations. However, to the best of our knowledge, the organocatalytic activation of ACPs has not been reported.

The Last Paragraph

In summary, a phosphine-catalyzed ring opening of electrondeficient alkylidenecyclopropanes (ACPs) has been developed. The resulting allylic phosphonium intermediate resembles the well-studied phosphine-allene adducts and shows significant promise for new reaction discovery. Specifically, three types of substrate-dependent phosphine-catalyzed rearrangements of alkylidenecyclopropylketons were developed for the synthesis of tri- and tetrasubstituted furans, and trisubstituted dienones in good yields. This organocatalytic activation of ACPs stands in contrast with previous transition-metal-catalyzed counterparts and thus enriches the synthetic potential of ACPs.

In addition, this reaction broadens the scope of phosphine catalysis by introducing a new subset of reactive substrates. Future studies will focus on exploiting the intermolecular reactivity of the intermediate B.

Baldwin's Rules (From Han Wang)



- •环中原子个数一般为3-8
- •以exo和endo表示闭环时断键位置,exo-环外,endo-环内
- •以tet、trig和dig表示亲电碳的杂化方式,tet-sp³,trig-sp²,

dig-sp.

	3		4	4	Į	5		6		7
	exo	endo	ехо	endo	exo	endo	exo	endo	exo	endo
Tet										
Trig										
dig										