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Phosphine-Catalyzed Intramolecular Cyclizations of α-Nitroethylallenoates Forming (*Z*)-Furanone Oximes

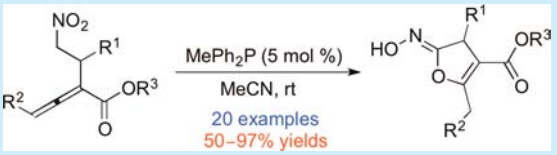
Qing-Fa Zhou,[†,‡] Kui Zhang,[‡] Lingchao Cai,[‡] and Ohyun Kwon*[,‡]

[†]State Key Laboratory of Natural Medicines, Department of Organic Chemistry, China Pharmaceutical University, Nanjing, 210009, P. R. China

[‡]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

Supporting Information

ABSTRACT: A novel and efficient phosphine-catalyzed intramolecular cyclization of α-nitroethylallenic esters is reported. This process appears to be practical for the stereoselective syntheses of (*Z*)-furan-2(3*H*)-one oxime derivatives in excellent yields. Mechanistically, the reaction involves a phosphine-catalyzed Michael addition of an alkylideneazinate and rearrangement of the cyclic nitronate to the α-nitrosodihydrofuran.



Nucleophilic phosphine catalysis has recently flourished because of its high versatility, operational ease, and low cost. In this context, nucleophilic phosphine-catalyzed cyclizations have become extremely multifaceted synthetic methodologies for preparing various carbocycles and heterocycles.[1] Some notable examples include the intramolecular Morita–Baylis–Hillman (MBH) reaction,[2] the intramolecular Rauhut–Currier reaction,[3] and various annulations based on allenes,[4] MBH alcohol derivatives,[5] and alkynes.[6] In addition to these cyclization reactions, methods have also been developed for the syntheses of oxygen-, sulfur-, and nitrogen-containing heterocycles through double-Michael, γ-umpolung–Michael, and intramolecular γ-umpolung additions of 2,3-butadienoates and 2-butynoates.[7]

Based on these earlier studies, we hypothesized that 2-(2′-nitroethyl)allenic esters **1** would undergo intramolecular γ-umpolung additions in the presence of phosphine catalysts to yield highly substituted cyclopentenes **A** (Figure 1).[8a] We could not, however, exclude the possibility of forming cyclic nitronates **B** through intramolecular Michael addition of the oxygen anion of the alkylideneazinate intermediate.[8b] To our surprise, compounds **1** produced, instead, five-membered cyclic *N*-hydroxyimidic acid esters **2** as novel products in high yields under the influence of a tertiary phosphine catalyst. Methods for the synthesis of cyclic *N*-hydroxyimidic acid esters are scarce, with the only known processes being oxidative ring closure of γ- or δ-hydroxyl oximes,[9] rearrangement of nitronates,[10] organoselenium-induced cyclization of β,γ-unsaturated hydroxamic acids,[11] and tandem reactions of β-nitrostyrenes with 1,3-dicarbonyl compounds.[12] Because of their potential biological activities,[9b] herein we report a novel approach toward five-membered cyclic *N*-hydroxyimidic acid esters **2** through highly effective phosphine-catalyzed cyclizations of 2-(2′-nitroethyl)allenic esters **1**. This transformation, which occurs through a mechanistically intriguing cascade process, appears to be a practical and operationally simple method for preparing five-membered cyclic *N*-hydroxyimidic acid esters under extremely mild conditions.

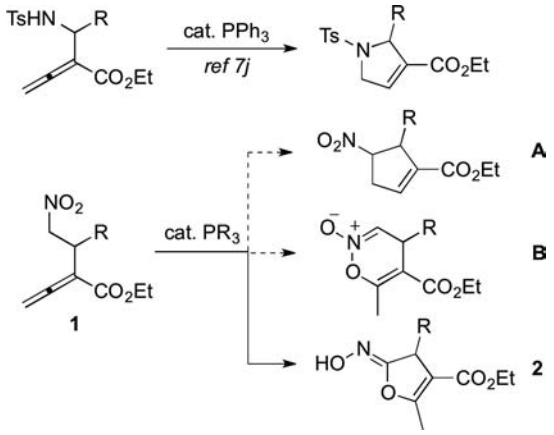


Figure 1. Phosphine-catalyzed intramolecular cyclizations based on γ-umpolung and Michael additions.

To prepare the requisite α-(nitroethyl)allenic esters **1** for this study, a series of phosphoranes **4** were formed through Michael additions of carbethoxymethylenetriphenylphosphorane to nitroalkenes **3** (Scheme 1). Treatment of the stabilized ylides **4** with AcCl and Et_3N produced the allenoates **1** for the subsequent phosphine catalysis reactions.[13]

With these α-(nitroethyl)allenic esters **1** in hand, ethyl 2-(2-nitro-1-phenylethyl)buta-2,3-dienoate (**1a**) was selected for the initial trial reaction with 20 mol % Ph_3P as the catalyst in CH_2Cl_2 at room temperature (Table 1). To our delight, the cyclic *N*-hydroxyimidic acid ester **2a** was obtained with a synthetically useful level of efficiency (entry 1). To improve the product yield, various solvents were examined (entries 2–5). MeCN proved to be the most efficient reaction medium,

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Scheme 1. Synthesis of α-(Nitroethyl)allenic Esters 1

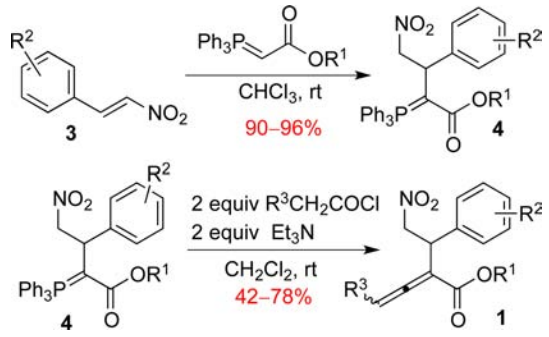
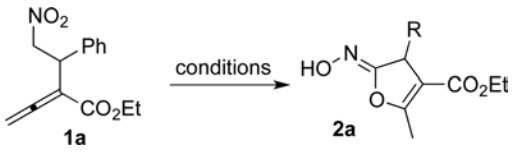


Table 1. Optimization of Reaction Conditions[a]



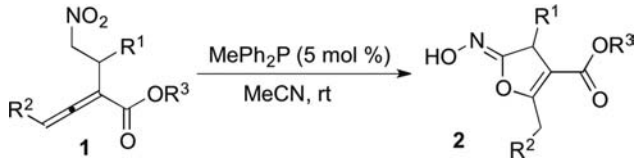
entry	catalyst (mol %)	temp	solvent	time	yield (%)[b]
1	Ph_3P (20)	rt	CH_2Cl_2	24 h	71
2	Ph_3P (20)	rt	THF	24 h	0
3	Ph_3P (20)	rt	toluene	24 h	trace
4	Ph_3P (20)	rt	Et_2O	2 h	0
5	Ph_3P (20)	rt	MeCN	1 h	95
6	$MePh_2P$ (20)	rt	MeCN	10 min	92
7	Me_2PhP (20)	rt	MeCN	10 min	86
8	Me_3P (20)	rt	MeCN	6 min	81
9	Bu_3P (20)	rt	MeCN	30 min	92
10	Bn_3P (20)	rt	MeCN	24 h	0
11	$P(OEt)_3$ (20)	rt	MeCN	24 h	0
12	$P(OEt)_3$ (20)	reflux	MeCN	24 h	0
13	$MePh_2P$ (10)	rt	MeCN	30 min	96
14	$MePh_2P$ (5)	rt	MeCN	40 min	96
15	$MePh_2P$ (1)	rt	MeCN	24 h	84
16	$MePh_2P$ (1)	reflux	MeCN	40 min	77
17	$MePh_2P$ (0.1)	rt	MeCN	24 h	trace
18	$MePh_2P$ (0.1)	reflux	MeCN	24 h	trace
19	none	rt	MeCN	24 h	0

[a]Reaction of **1a** (0.1 mmol) was performed in the listed solvent (1 mL). [b]Isolated yield.

providing the cyclic *N*-hydroxyimidic acid ester **2a** in 95% isolated yield after 1 h (entry 5). Subsequently, the potential of several commonly used phosphines as catalysts was probed in MeCN (entries 6–12). $MePh_2P$ at 10 mol % was the best catalyst in terms of product yield and reaction time (entry 13). Me_2PhP, Me_3P, and Bu_3P also facilitated the cyclization of **1a**, while, surprisingly, Bn_3P was ineffective (entries 6–10). $P(OEt)_3$ did not catalyze this reaction, even when performed under reflux (entries 11 and 12). Additionally, the loading of $MePh_2P$ could be lowered to 5 mol % without impacting the product yield, although a slightly longer reaction time was required (entry 14). Notably, 1 mol % of catalyst was also sufficient for this reaction, offering the product in 77% yield within 40 min under reflux (entries 15 and 16). Only a trace amount of the product formed when using 0.1 mol % of catalyst, even at elevated temperature (entries 17 and 18). Notably, the loading of phosphine catalysts in nucleophilic phosphine-catalyzed reactions is typically greater than 10 mol %, so this reaction is a rare example in which 1 mol % of a phosphine catalyst can effectively promote such a reaction. No product was obtained when the reaction was performed in the absence of a phosphine (entry 19).

With the optimal conditions in hand, several 2-(2-nitro-1-arylethyl)buta-2,3-dienoate esters **1** were converted to their corresponding five-membered cyclic *N*-hydroxyimidic acid esters **2** (Table 2). The yields for these cycloisomerizations

Table 2. Synthesis of Cyclic *N*-Hydroxyimidic Acid Esters[a]



entry	R^1	R^2	R^3	time (min)	product	yield (%)[b]
1	Ph	H	Et	40	**2a**	96
2	4-MeC_6H_4	H	Et	20	**2b**	96
3	4-$MeSC_6H_4$	H	Et	40	**2c**	94
4	4-$MeOC_6H_4$	H	Et	15	**2d**	97
5	4-BrC_6H_4	H	Et	30	**2e**	87
6	4-ClC_6H_4	H	Et	20	**2f**	93
7	4-FC_6H_4	H	Et	30	**2g**	94
8	4-PhC_6H_4	H	Et	20	**2h**	91
9	3-$MeOC_6H_4$	H	Et	40	**2i**	93
10	3-BrC_6H_4	H	Et	30	**2j**	95
11	3-ClC_6H_4	H	Et	30	**2k**	88
12	3-FC_6H_2	H	Et	35	**2l**	96
13	4-(AcO)-3,5-$(MeO)_2C_6H_2$	H	Et	180	**2m**	50
14	4-(AcO)-3,5-$(MeO)_2C_6H_2$	H	Et	50	**2m**	79[c]
15	2-naphthyl	H	Et	30	**2n**	94
16	5-Me-2-furyl	H	Et	20	**2o**	86
17	2-thienyl	H	Et	40	**2p**	73
18[d]	Ph	Me	Et	720	–	–
19	Ph	H	Me	35	**2q**	93
20	Ph	H	Bn	40	**2r**	88
21	Ph	H	*t*-Bu	40	**2s**	92

[a]All reactions were performed using a β′-nitroalkylallenic ester **1** (0.1 mmol) and $MePh_2P$ (5 mol %) in MeCN at room temperature. [b]Isolated yield. [c]10 mol % of $MePh_2P$ was used. [d]No product was formed.

were generally very high. Both meta- and para-substituted phenyl moieties, possessing either electron-donating or -withdrawing substituents, were well tolerated (entries 1–12). For example, α-(2-nitro-1-arylethyl)allenic esters presenting *p*- and *m*-methoxyphenyl groups underwent their reactions smoothly, providing the desired products **2d** and **2i** in 97% and 93% yields, respectively (entries 4 and 9). Importantly, halogen substituents (F, Cl, Br) remained intact under the reaction conditions, providing a handle for subsequent transformations through various coupling protocols (entries 5–7 and 10–12).

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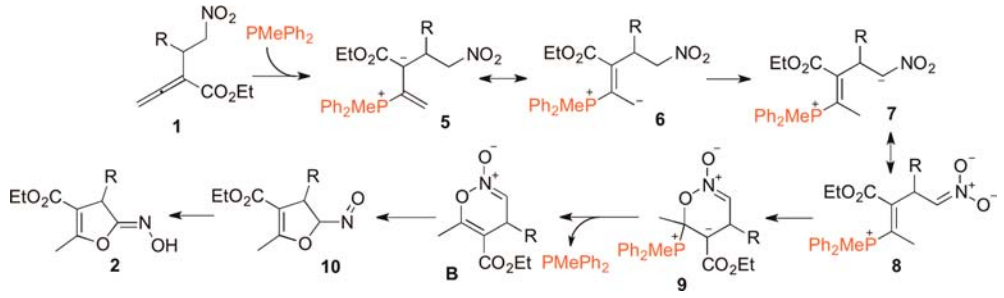
Scheme 2. Mechanism of Phosphine-Catalyzed Formation of *N*-Hydroxyimidic Acid Esters 2



The yield was low when the aryl group was trisubstituted (entry 13), but it improved when using a higher catalyst loading (10 mol %; entry 14). The reaction was equally effective at producing the corresponding product in good yield when a 2-naphthyl group was present (entry 15). Gratifyingly, the benzene ring of the substrates **1** could be replaced by heteroaryl groups, providing the furyl- and thienyl-substituted five-membered cyclic *N*-hydroxyimidic acid esters **2o** and **2p** in 86% and 73% yields, respectively (entries 16 and 17). γ-Substituted allenoates did not participate in this process (entry 18), presumably because the steric bulk lowered the electrophilicity. Variation of the ester group had no obvious effect on the reaction, with the cyclized products again obtained in high yield (entries 19−21). The structures of the products were confirmed through X-ray crystallographic analysis of compound **2m** (Figure 2).[14]

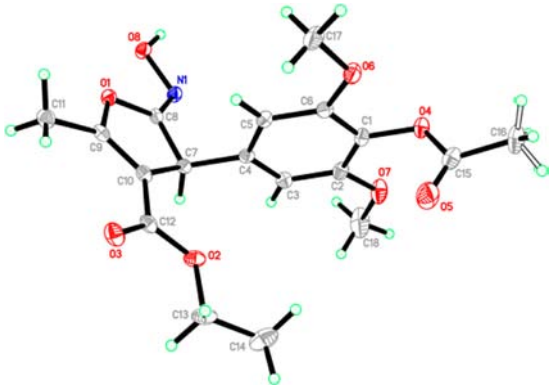


Figure 2. ORTEP representation of the solid state structure of **2m**.

Scheme 2 presents a proposed mechanism to account for the formation of the cyclic *N*-hydroxyimidic acid esters **2**. Conjugate addition of the phosphine to the α-(nitroethyl)-allenic ester **1** leads to the formation of the zwitterionic intermediates **5**↔**6**. 1,5-Proton transfer of the intermediate **6** yields the α-nitro anion **7**, the alternative resonance form (the alkylideneazinate **8**) of which undergoes cyclization to form the nitronate **9**. β-Elimination of the phosphine from the zwitterionic intermediate **9** produces the cyclic nitronate **B**, which rearranges to produce the 2-nitrosodihydrofuran intermediate **10**,[10] with tautomerization giving the five-membered cyclic *N*-hydroxyimidic acid ester **2**.

In conclusion, we have observed the unprecedented chemoselective phosphine-catalyzed intramolecular cyclization of α-nitroethylallenic esters to five-membered cyclic *N*-hydroxyimidic acid esters. This catalytic process, performed under mild and seemingly general conditions, provides access to five-membered cyclic *N*-hydroxyimidic acid esters in high yields. This transformation is a rare example of the rearrangement of cyclic nitronates to furanone oximes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01299.

Crystallographic data for compound **2m** (CIF)
Experimental procedures and characterization data for the starting materials **1** and the products **2** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ohyun@chem.ucla.edu.

Notes

The authors declare no competing financial interest.

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(14) CCDC 1004071 contains the supplementary crystallographic data for compound **2m**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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