

Phosphine-Catalyzed Tandem Reaction
of Allenates with Nitroalkenes

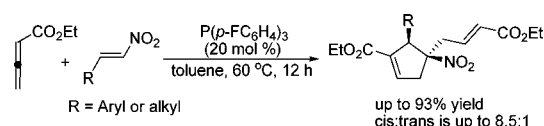
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ABSTRACT



A $P(p\text{-FC}_6\text{H}_4)_3$ -catalyzed tandem reaction between ethyl 2,3-butadienoate and nitroalkenes has been developed, which involves a [3 + 2] cycloaddition and a subsequent umpolung addition. The asymmetric version of this tandem reaction has also been investigated by using chiral phosphines.

Recently, the phosphine-catalyzed cycloaddition reactions of allenates with electron-deficient olefins or imines have received considerable research interest¹ since Lu's pioneering reports on [3 + 2] cycloaddition reactions² between allenates and imines or electron-deficient olefins catalyzed by tertiary phosphines, because it is a highly attractive synthetic method for preparing a variety of carbocycles and heterocycles from readily available starting materials. Moreover, the synthetic utility of these cycloaddition reactions has been largely demonstrated by the preparation of biologically active natural products and pharmaceutically interesting sub-

stances.^{3–5} With the aim of developing new phosphine-catalyzed cycloaddition reactions of allenates, much effort has been devoted to investigate the [3 + 2] cycloaddition reactions of allenates with different kinds of electron-deficient olefins, such as enones and arylmethylidenemalonitriles. However, nitroalkenes have been seldom used in this [3 + 2] cycloaddition reaction. As far as we know, there is only one example of intramolecular cycloaddition of nitrostyrenyl derivative **I** reported by Kwon in 2007 (Scheme 1).⁶ In this reaction, using PPh_3 as the catalyst in tetrahydrofuran (THF) produced the desired annulation product **II** in moderate yield (48%), accompanied by a minor product **III** (12%). Interestingly, the reaction of the nitrostyrenyl derivative **I** catalyzed with PPh_3 in benzene provided the nitronate **III** as the major product in 58% yield along

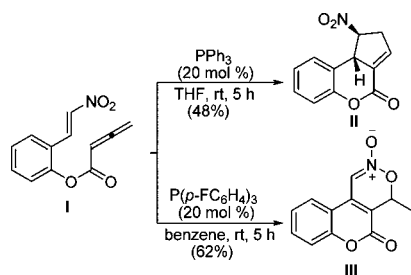
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Scheme 1. Intramolecular Cycloaddition of Nitrostyrenyl Derivative I



with a 14% yield of the cyclopentene adduct **II**. The corresponding reaction catalyzed by the less-nucleophilic tris(*p*-fluorophenyl)phosphine furnished cycloadduct **III** in a slightly improved yield (62%) along with adduct **II** in 19% yield.

It aroused our enthusiasm to study the intermolecular reaction of allenates and nitroalkenes catalyzed by phosphine. Surprisingly, we found a tandem reaction of formal [3 + 2] cycloaddition and a subsequent umpolung addition^{2a} using allenates and nitroalkenes. Herein, we wish to report the details of this novel tandem reaction of allenates with nitroalkenes.

Initially, the reaction of ethyl 2,3-butadienoate with β -nitrostyrene **1a** was conducted in the presence of PPh₃ and THF, affording an unexpected new product **2a** (cis:trans = 3.0:1) in 36% yield (Table 1, entry 1). Through a series of analytical measurements, compound **2a** was identified as a tandem reaction product of formal [3 + 2] cycloaddition and a subsequent umpolung addition between ethyl 2,3-butadienoate and β -nitrostyrene **1a**.

The potential of several commonly used phosphines as catalysts has been assessed for the tandem reaction of ethyl 2,3-butadienoate with β -nitrostyrene **1a**. The results are summarized in Table 1. Stronger nucleophilic phosphines such as methyldiphenylphosphine (PPh₂Me), dimethyl(phenyl)phosphine (PPhMe₂), and tributylphosphine (PBU₃) could not catalyze this reaction (Table 1, entries 2, 3, and 4). This result implied that the nucleophilicities of phosphines had significant influence on the reaction outcome, thus, we

Table 1. Catalyst and Solvent Screening for the Tandem Reaction of Ethyl 2,3-Butadienoate with β -Nitrostyrene **1a**

entry ^a	solvent	cat.	yield (%) ^b	cis:trans ^c
1	THF	PPh ₃	36	3.0:1
2	THF	PPh ₂ Me	trace	
3	THF	PPhMe ₂	trace	
4	THF	PBU ₃	trace	
5	THF	P(<i>p</i> -MeC ₆ H ₄) ₃	21	3.1:1
6	THF	P(<i>p</i> -MeOC ₆ H ₄) ₃	trace	
7	THF	P(<i>p</i> -FC ₆ H ₄) ₃	70	3.0:1
8	toluene	P(<i>p</i> -FC ₆ H ₄) ₃	80	3.1:1
9	DCM	P(<i>p</i> -FC ₆ H ₄) ₃	40	3.1:1
10	CH ₃ CN	P(<i>p</i> -FC ₆ H ₄) ₃	trace	
11	dioxane	P(<i>p</i> -FC ₆ H ₄) ₃	78	3.1:1
12 ^d	toluene	P(<i>p</i> -FC ₆ H ₄) ₃	90	3.9:1
13 ^d	dioxane	P(<i>p</i> -FC ₆ H ₄) ₃	80	5.5:1
14 ^d	THF	P(<i>p</i> -FC ₆ H ₄) ₃	80	4.7:1
15 ^e	toluene	P(<i>p</i> -FC ₆ H ₄) ₃	67	2.7:1
16 ^f	toluene	P(<i>p</i> -FC ₆ H ₄) ₃	80	3.0:1
17 ^{d,g}	toluene	P(<i>p</i> -FC ₆ H ₄) ₃	76	3.4:1
18 ^{d,h}	toluene	P(<i>p</i> -FC ₆ H ₄) ₃	73	2.5:1

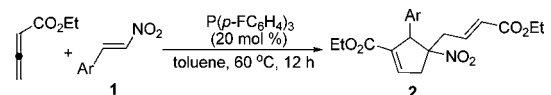
^a All reactions were carried out with **1a** (0.1 mmol) and ethyl 2,3-butadienoate (0.4 mmol). ^b Isolated yields. ^c Determined by ¹H NMR spectrum. ^d At 60 °C. ^e At 100 °C. ^f At 80 °C. ^g 10 mol % of cat. was used. ^h 5 mol % of cat. was used.

subsequently explored the influence of nucleophilicities of phosphines further. Three triphenylphosphines with substituents of different electronic property on the benzene rings were tested as catalysts in this reaction. We found that increasing the nucleophilicities of phosphines led to the decreased yield of **2a**. The least nucleophilic phosphine tris(4-fluorophenyl)phosphine (P(*p*-FC₆H₄)₃) could catalyze the reaction to give product **2a** in the highest yield (70%) along with similar diastereoselectivities among these three phosphines (Table 1, entries 5, 6, and 7). The solvent effects were examined by using P(*p*-FC₆H₄)₃ as the catalyst. Toluene and 1,4-dioxane were the optimal solvents to give **2a** in 80% yield and 78% yield, respectively (Table 1, entries 8 and 11), and the reaction could not occur in acetonitrile (Table 1, entry 10). Temperature effect was next examined with toluene, 1,4-dioxane, and THF as the solvents (Table 1, entries 12, 13, and 14). At 60 °C in toluene, **2a** could be produced in highest yield (90%) along with moderate diastereoselectivity (3.9:1). Increasing the temperature or reducing the employed amount of catalyst, both the yields and diastereoselectivities declined markedly (Table 1, entries 15–18).

Having identified the optimal reaction conditions, we next set out to examine the scope and limitations of this reaction using various nitroalkenes **1** with different substituents on the benzene rings, and the results are summarized in Table 2. As shown in Table 2, whether an electron-withdrawing or electron-donating group at ortho-, meta- or para-position of the benzene ring of nitroalkenes **1** or (*E*)-2-(2-nitrovinyl-

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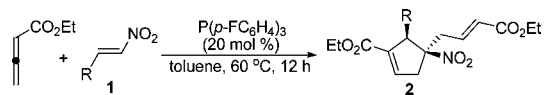
Table 2. Scope of the P(*p*-FC₆H₄)₃-Catalyzed Tandem Reactions of Nitroalkenes **1** with Ethyl 2,3-Butadienoate

entry ^a	Ar	yield (%) ^b	cis:trans ^c
1	<i>p</i> -MeOC ₆ H ₄ , 1b	2b , 80 (60)	3.0:1
2	<i>p</i> -MeC ₆ H ₄ , 1c	2c , 86 (65)	3.1:1
3	<i>p</i> -BrC ₆ H ₄ , 1d	2d , 74 (56)	3.1:1
4	<i>m</i> -NO ₂ C ₆ H ₄ , 1e	2e , 48 (41)	5.9:1
5	<i>m</i> -MeOC ₆ H ₄ , 1f	2f , 63 (47)	3.0:1
6	<i>m</i> -BrC ₆ H ₄ , 1g	2g , 75 (63)	5.4:1
7	<i>o</i> -BrC ₆ H ₄ , 1h	2h , 83 (70)	5.3:1
8	<i>o</i> -ClC ₆ H ₄ , 1i	2i , 93 (77)	4.8:1
9	<i>o</i> -NO ₂ C ₆ H ₄ , 1j	2j , 59 (53)	8.5:1
10	<i>o</i> -CF ₃ C ₆ H ₄ , 1k	2k , 83 (69)	5.1:1
11 ^d	2-furyl, 1l	2l , 56	
12	1-naphthyl, 1m	2m , 75 (46)	1.6:1

^a All reactions were carried out with **1** (0.2 mmol) and ethyl 2,3-butadienoate (0.8 mmol) in the presence of P(*p*-FC₆H₄)₃ in toluene (2.0 mL) at 60 °C. ^b Yields are determined by ¹H NMR spectrum and in parentheses are isolated yields of the *cis* isomer. ^c Determined by ¹H NMR spectrum. ^d It is hard to determine the yield and dr value of **2l** because the proton signals overlap in their ¹H NMR spectra and only the yield of the *cis* isomer was given.

furan **1l** and (*E*)-1-(2-nitrovinyl)naphthalene **1m** were employed, the reactions proceeded smoothly to give **2** in moderate to good yields along with moderate to good diastereoselectivities (Table 2, entries 1–12). When the benzene rings of nitroalkenes **1** had a strongly electron-withdrawing group, such as the NO₂ group, the yields of **2** were lower. The relative configuration of *cis*-**2a** has been determined by its NOESY spectrum (Supporting Information) and the relative configurations of other products **2** were determined by comparing the ¹H NMR spectroscopic data with those of *cis*-**2a**. All of the major diastereoisomers *cis*-**2** could be cleanly isolated from the reaction mixtures (the yields in parentheses). Due to the existence of some byproducts in this reaction, it is difficult to isolate all of the *trans*-isomers of **2** by flash column chromatography. Only *trans* isomers of compounds **2a**, **2b**, **2c**, **2d**, and **2m** were successfully isolated and their ¹H NMR and ¹³C NMR spectroscopic and analytic data were available in the Supporting Information.

Nitroalkenes bearing a wide variety of alkyl groups could also undergo this tandem reaction, giving the corresponding products in moderate yields (Table 3). To the best of our knowledge, reports about the [3 + 2] cycloaddition of allenates with electron-deficient olefins or imines bearing alkyl groups are rare. When the alkyl group was a sterically hindered substituent, such as *i*Pr and cyclohexyl group, the corresponding products in this reaction were obtained in lower yields (Table 3, entries 4 and 7). The diastereoselectivities were not shown in Table 3 and just the isolated yields of the major diastereoisomers were given, because the proton signals in the ¹H NMR spectra of these crude products

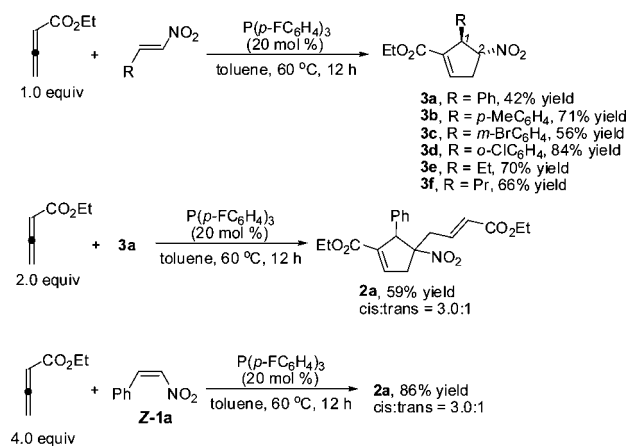
Table 3. Scope of the P(*p*-FC₆H₄)₃-Catalyzed Tandem Reactions of Alkyl Nitroalkenes **1** with Ethyl 2,3-Butadienoate

entry ^a	R	yield (%) ^b
1	Et, 1n	<i>cis</i> - 2n , 48
2	Pr, 1o	<i>cis</i> - 2o , 49
3	Bu, 1p	<i>cis</i> - 2p , 40
4	<i>i</i> Pr, 1q	<i>cis</i> - 2q , 28
5	<i>t</i> Bu, 1r	<i>cis</i> - 2r , 50
6	PhCH ₂ CH ₂ , 1s	<i>cis</i> - 2s , 69
7	cyclohexyl, 1t	<i>cis</i> - 2t , 38

^a All reactions were carried out with **1** (0.2 mmol) and ethyl 2,3-butadienoate (0.8 mmol) in the presence of P(*p*-FC₆H₄)₃ in toluene (2.0 mL) at 60 °C. ^b Isolated yields.

overlapped and it was difficult to determine the diastereomeric ratios in these reactions.

To clarify the reaction pathway, we did some control experiments to further investigate this reaction mechanism (Scheme 2). We found that β -nitrostyrene **1a** could react with

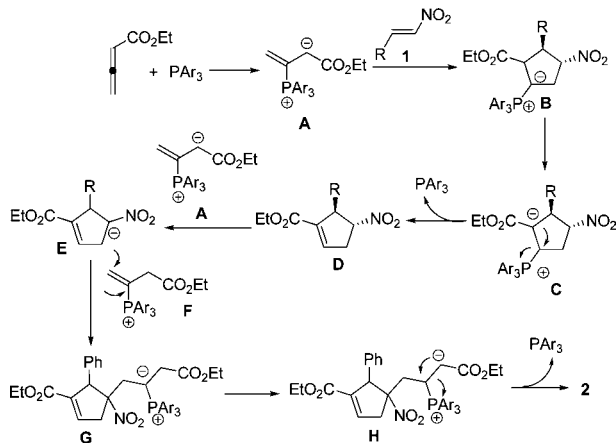
Scheme 2. Control Experiments

1.0 equiv of ethyl 2,3-butadienoate to give the normal [3 + 2] cycloaddition product **3a** in only 42% yield with the *trans* configuration under the same conditions. The *trans*-configuration of **3a** has been determined by its ¹H NMR spectroscopic data. The coupling constant between H¹ and H² is nearly zero (*J* = 1.2 Hz), suggesting that the dihedral angle of H¹ and H² is nearly 90°. Some other nitroalkenes have also been employed in this kind of [3 + 2] cycloaddition and the normal [3 + 2] cycloaddition products could be obtained in moderate yields (Scheme 2). Moreover, **2a** could be obtained in 59% yield through the reaction of **3a** with ethyl 2,3-butadienoate and the ratio of the diastereoisomers was similar to the product attained from the direct reaction of β -nitrostyrene **1a** with 4.0 equiv of ethyl 2,3-butadienoate.

Changing the configuration of the double bond of β -nitrostyrene from *E*-isomer to *Z*-isomer gave similar result as those of *E*-1a.

On the basis of above results and previous literature,² a plausible mechanism for the P(*p*-FC₆H₄)₃-catalyzed tandem reactions between ethyl 2,3-butadienoate and nitroalkenes **1** is proposed in Scheme 3. The Lewis base P(*p*-FC₆H₄)₃ as a

Scheme 3. A Plausible Reaction Mechanism



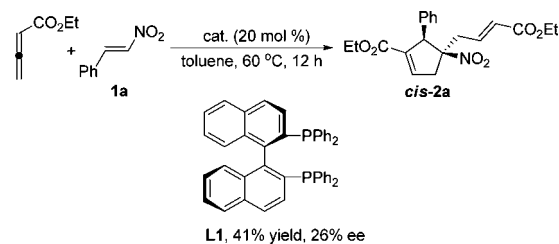
nucleophile reacts with ethyl 2,3-butadienoate to produce the zwitterionic intermediate **A**, which subsequently generates the intermediate **B** through cycloaddition with nitroalkene **1**. **B** is transformed to intermediate **C** through a proton transfer. The elimination of P(*p*-FC₆H₄)₃ from **C** affords intermediate product **D** and regenerates P(*p*-FC₆H₄)₃. Meanwhile, intermediate **A** can deprotonate the intermediate product **D** to generate intermediates **E** and **F** which undergo a subsequent umpolung addition to afford intermediate **G**. **G** will undergo a hydrogen shift to form intermediate **H**. Then, the elimination of P(*p*-FC₆H₄)₃ furnishes product **2** and regenerates the catalyst.

We further investigated the asymmetric version of this new tandem reaction using several commonly used chiral phosphines.⁷ Using (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (Binap) **L1** as the catalyst, *cis*-**2a** could be obtained in

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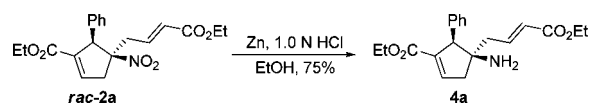
41% yield along with 26% ee (Scheme 4) and others are not efficient catalysts for this reaction. In terms of product

Scheme 4. Asymmetric Version of This Tandem Reaction



transformation, the NO₂ group of product *rac*-**2a** could be conveniently reduced to NH₂ (Scheme 5).

Scheme 5. Transformation of the Product *rac*-**2a**



In conclusion, we have developed a novel P(*p*-FC₆H₄)₃-catalyzed tandem reaction between ethyl 2,3-butadienoate and nitroalkenes, which involves a [3 + 2] cycloaddition and a subsequent umpolung addition. This tandem reaction started from readily available materials under mild reaction conditions to afford highly functionalized cyclopentene derivatives, which offers a new approach potentially used for the synthesis of cyclopentanoid natural products. The asymmetric version of this tandem reaction was also investigated using chiral phosphines, though the results are dissatisfactory. Efforts are in progress to elucidate further mechanistic details of these reactions and to explore their asymmetric versions.

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Supporting Information Available: Procedural and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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