

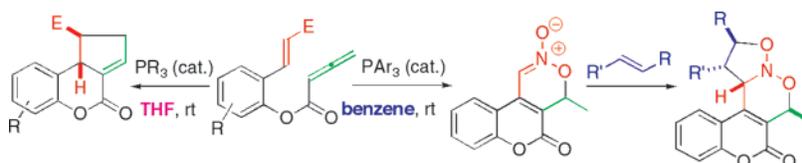
Phosphine-Catalyzed Synthesis of
Highly Functionalized Coumarins

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ABSTRACT



2-Styrenyl allenates are converted into cyclopentene-fused dihydrocoumarins through phosphine-catalyzed regio- and diastereoselective [3 + 2] cycloadditions. Remarkably, changing the solvent from THF to benzene promotes the conversion of the 2-(2-nitrostyrenyl) allenate into a tricyclic nitronate through a previously undocumented mode of phosphine catalysis. This nitronate was subjected to efficient face-, regio-, and exo-selective 1,3-dipolar cycloadditions to provide tetracyclic coumarin derivatives.

Coumarins are heterocycles that are frequently encountered in natural products¹ and used widely in medicinal compounds (e.g., warfarin).² Functionalized coumarins also find applications in perfumery,³ as fluorescent materials,⁴ and as dyes in laser technology.⁵ Not surprisingly, considerable effort has been exerted toward the synthesis of coumarins through the use of Perkin, Pechmann, Wittig, Reformatsky, Claisen, and Knoevenagel reactions.⁶ These traditional methods, however, generally require harsh reaction conditions, often resulting in low product yields. More recently, transition-metal-catalyzed reactions have been reported for the synthesis of

coumarins,⁷ but these examples have been limited to products possessing simple substituents. As part of a program geared toward the design and development of nucleophilic phosphine catalysis for the synthesis of a diverse array of small organic molecules, here we report the expeditious intramolecular phosphine-catalyzed transformation of 2-styrenyl allenates into highly functionalized coumarins.⁸

Phosphine-catalyzed annulation of activated alkenes and alkynes is a highly attractive synthetic method for preparing a variety of carbocycles and heterocycles from readily available starting materials.^{9,10} In particular, much effort has been devoted to the [3 + 2] cycloaddition of allenates with

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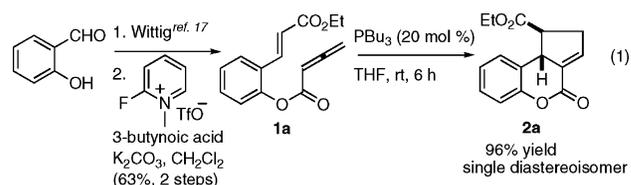
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α,β -unsaturated carbonyl compounds to form cyclopentenes,¹¹ e.g., this process has been applied to natural product synthesis¹² and an enantioselective variant of the reaction has been developed;¹³ in addition, thorough mechanistic studies have been reported by Yu and co-workers and by us.¹⁴ Unfortunately, unlike the [3 + 2] cycloadditions of allenates with imines to form dihydropyrroles,¹⁵ intermolecular annulations between allenates and alkenes generally suffer from the formation of a mixture of regioisomeric cyclopentenes. For example, Lu's original report indicated that the [3 + 2] annulation between ethyl allenate and methyl acrylate furnished a 4:1 mixture of regioisomeric cyclopentenes, favoring α -addition of the phosphonium dienolate intermediate to the acrylate in a Michael-type manner.^{11a} In contrast, in Fu's asymmetric phosphine catalysis of allenenes with β -substituted enones to form cyclopentenes, the preference for α -addition of the allenates to activated (non- β -substituted) alkenes was reversed to γ -addition.^{13c}

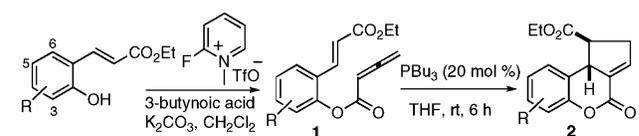
For many C–C bond-forming processes, exclusive regioselectivity is achieved when the reactions are performed intramolecularly.¹⁶ We sought to apply this principle to an intramolecular variant of the allene/alkene [3 + 2] cycloaddition of substrate **1a** (eq 1). Compound **1a** was synthesized from salicylaldehyde through a Wittig reaction¹⁷ followed by coupling with 3-butynoic acid under the influence of Mukaiyama's reagent;^{18,19} presumably, the initial 3-butynoate product isomerized to the allenate under the coupling



reaction conditions.²⁰ Treatment of **1a** with 20 mol % of tributylphosphine in THF at room temperature for 6 h produced **2a** in 96% isolated yield as a single diastereoisomer.²¹ Thus, this catalytic reaction provided a tricyclic dihydrocoumarin structure directly from a cinnamyl allenate through a regioselective annulation process.

This reaction proved to be effective for transforming various other commercially available salicylaldehyde derivatives into cyclopentene-fused dihydrocoumarins (Table 1).

Table 1. Syntheses of Cyclopentene-Fused Dihydrocoumarins **2a**



entry	R (1)	yield (%) ^b	product (2)	yield ^c (%)
1	H (1a)	72	2a	96
2	3-methyl (1b)	64	2b	98
3	3-methoxy (1c)	77	2c	74
4	4-methoxy (1d)	71	2d	94
5	5-methoxy (1e)	73	2e	70
6	5-fluoro (1f)	45	2f	91
7	5-bromo (1g)	38	2g	93
8	5-nitro (1h)	45	2h	9 ^d

^a See the Supporting Information for details. ^b Isolated yield for the formation of **1**. ^c Isolated yield for the formation of **2**. ^d The allenate hydrolyzed to form the 2-hydroxycinnamate; the resulting phenol was added to the starting cinnamyl allenate at the β -carbon atom in 81% yield.

Both electron-withdrawing and -donating substituents on the benzene ring were compatible with the reaction conditions (entries 1–7). A substrate containing a nitro substituent provided the lowest product yield (entry 8); this result is consistent with our previous findings for [4 + 2] allenolate/arylimine annulations.^{8a}

Next, we turned our attention to establishing the role played by the activating substituent on the alkene moiety. Although 2-(2-phenylsulfonyl)styrenyl allenolate **1i** readily

(19) Use of the common (peptide) coupling reagents [DCC, TCT, Hf-(IV) salts, HBTU, HATU, and PyBroP] failed to provide the allenolate product. Presumably, the product allenolate is susceptible to nucleophilic attack by either a base present in the reaction medium or the byproducts derived from the coupling reagents. See the Supporting Information for details regarding the isolation and characterization of the product of *N*-hydroxybenzotriazole addition to the allenolate when using HBTU.

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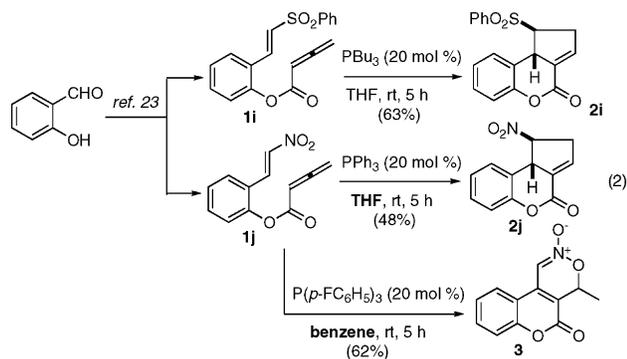
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underwent the annulation reaction to produce the tricyclic coumarin derivative **2i** in 63% yield (eq 2),²² the nitrostyrenyl derivative **1j** did not provide the desired annulation product when subjected to the optimized reaction conditions (20 mol % PBU₃, THF, rt). Catalysis using the less-nucleophilic PPh₃ produced the desired annulation product in moderate yield (48%), accompanied by a minor product **3** (12%). In an attempt to further improve the yield of the [3 + 2] annulation product, we examined the use of some other common organic solvents. Surprisingly, the reaction of the nitrostyrenyl derivative **1j** with PPh₃ in benzene provided the nitronate **3** as the major product in 58% yield, in addition to a 14% yield of the cyclopentene adduct **2j**.²³ The corresponding reaction catalyzed by the even-less-nucleophilic tris(*p*-fluorophenyl)-phosphine furnished **3** in a slightly improved yield (62%; 19% **2j**).



Having synthesized this nitronate, we tested its synthetic utility in 1,3-dipolar cycloadditions to form highly functionalized coumarin derivatives (Table 2). Nitronates are versatile 1,3-dipoles that undergo reactions with neutral, electron-rich, and electron-poor dipolarophiles.²⁴ Indeed, when we treated nitronate **3** with allyl bromide, we obtained the tetracyclic coumarin derivatives **4a** and **5a** in 97% isolated yield as a 7:1 mixture of *exo* and *endo* products (entry 1). The connectivity and relative stereochemistry of the nitroso acetals **4a** and **5a**, as well as **4d**, were confirmed through X-ray crystallographic analysis.²⁵ This reaction exhibited exclusive facial and regioselectivity as well as good *exo* selectivity. Both electron-rich and -poor alkenes underwent [3 + 2] cycloadditions with **3** in excellent yields (93–94%)

(22) NOE analyses confirmed the *trans* stereochemistry of the [3 + 2] annulation product. See the Supporting Information for details.

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(25) Crystallographic data for **4a**, **5a**, and **4d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary numbers CCDC 602367–602369. These data can be obtained online free of charge (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Table 2. 1,3-Dipolar Cycloadditions of Nitronate **3**^a

entry	dipolarophile	major product	yield (%) ^b	4/5
1			97	7:1
2			93	9:1
3			94	11:1
4			95	9:1
5			83	10:1
6		N/A	0 ^c	N/A
7		N/A	NR ^d	N/A

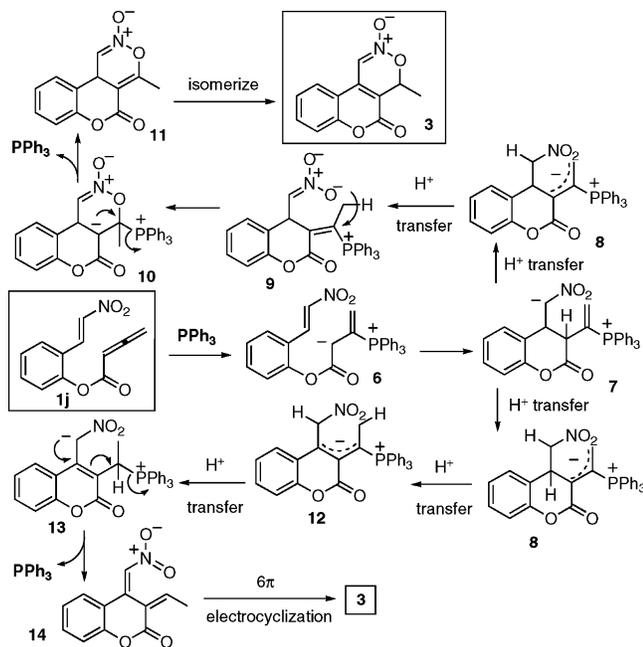
^aSee the Supporting Information for details. ^bIsolated yield. ^cComplex mixture of products. ^dMostly recovered starting material.

with high *exo* selectivity (*exo/endo* = 9–11:1; entries 2 and 3). *Trans*-disubstituted alkenes were viable substrates (entries 4 and 5), but *cis*-disubstituted alkenes were recalcitrant to the reaction (entries 6 and 7). In all the examples, the carbon atom bearing the activating substituent formed a bond to the oxygen atom of the nitronate 1,3-dipole. The product nitroso acetals possess up to four stereogenic centers and are replete with functional groups. Their Raney nickel-catalyzed N–O bond cleavages producing corresponding amino alcohols and their application to the syntheses of alkaloid natural products are well documented.²⁶

Scheme 1 provides two possible mechanisms that account for the formation of nitronate **3**. We excluded the possibility

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Scheme 1. Proposed Mechanisms for the Formation of Nitronate **3**



of a Diels–Alder reaction occurring between the nitroalkene and the allene based on our observation that the reaction did not proceed in the absence of a phosphine.²⁷ Attempts to facilitate the Diels–Alder reaction under thermal or Lewis acid catalysis conditions resulted only in recovery of the starting material. Accordingly, we propose mechanisms involving phosphine as a catalyst. Nucleophilic addition of triphenylphosphine to allenolate **1j** produces the zwitterionic intermediate **6**. Intramolecular Michael addition of the allylic anion to the nitroalkene in **6** leads to the cyclized intermediate **7**. Proton transfer of the most acidic proton, i.e., the one positioned α to the carbonyl group, yields the allylic anion **8**. 1,5-Proton transfer in **8** furnishes **9**, which undergoes 6-endo cyclization to form **10**. Expulsion of the phosphine from **10** produces the nitronate **11**, which can isomerize to the nitronate **3**. In the other scenario, 1,4-proton transfer in

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8 yields **12**. A subsequent 1,4-proton transfer in **12** provides **13**, which generates the nitrodiene **14** upon expulsion of triphenylphosphine. Finally, 6π electrocyclic ring closure of nitrodiene **14** provides the nitronate **3**. To the best of our knowledge, the literature lacks examples of the proposed 6π electrocyclization. The closest precedent is a $6-\pi$ -electron 5-atom electrocyclization of nitrosostyrenes to benzonitrates found in an indole synthesis from nitrobenzenes via reductive cyclization.²⁸

In summary, we have discovered two diverting reaction modalities for the nucleophilic phosphine-mediated reactions of 2-styrenyl allenates. Tertiary phosphines in THF facilitated intramolecular [3 + 2] annulation to provide cyclopentene-fused dihydrocoumarins in excellent to good yields with exclusive diastereoselectivity. The reaction of 2-(2-nitrostyrenyl)allenolate **1j** with triphenylphosphine in benzene, on the other hand, led to the formation of the tricyclic nitronate **3** through an unprecedented mode of catalysis. We have demonstrated the synthetic potential of this nitronate through its 1,3-dipolar cycloadditions with a number of dipolarophiles. The reactions described herein are simple and efficient approaches toward the syntheses of structurally complex coumarins and add to the number of recently discovered phosphine-catalyzed annulation reactions of allenolate precursors. Our future efforts will focus on intramolecular phosphine catalysis of other allenates derived from salicylaldehydes and their application to the synthesis of coumarin-containing natural products.

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Supporting Information Available: Representative experimental procedures and spectral data for all new compounds. Crystallographic data for compounds **4a**, **4d**, and **5a** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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