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A convenient new method to construct 1-alkynyl cyclopropanol and its synthetic application to prepare trisubstituted dienones

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Abstract

A new synthetic route was developed via the nucleophilic addition of lithium alkynylide to 1-arylsulfonyl cyclopropanol 1 to afford 1-alkynyl cyclopropanol, which then reacted with aryl iodide to construct trisubstituted cross-conjugated dienones through a palladiumcatalyzed process, where the key steps included the regioselective carbopalladation of arylpalladium(II) intermediate across the triple bond of 1-alkynyl cyclopropanol and the ring opening of the cyclopropyl group. © 2008 Elsevier Ltd. All rights reserved.

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The development of cyclopropanol chemistry in the past decades has been quite fruitful. These compounds occupied their own niche in synthetic practice as useful intermediates in organic synthesis,^{1–7} and as substances possessing important kinds of biological and pharmaceutical activities.^{8–10} Among a great variety of cyclopropanol derivatives, 1-alkynyl substituted cyclopropanols are of great interest due to the combination of highly reactive triple bond and three-membered ring in one molecule.

Scheme 1 gives an overview of the existing routes to construct such compounds and some of its synthetic applications. The classical route to prepare these compounds is the Simmon-Smith reaction (Route A, Scheme 1) of the alkynyl enol ether 4,¹¹ in which the tedious preparation of the ether reactant is a disadvantage. Another route is the reaction of arylacetylenic magnesium bromides with iodomagnesium 1-ethoxycyclopropylate **3** (Route B, Scheme 1),¹² where long reaction time under a reflux condition is needed.

In this Letter, a new synthetic route is developed via the nucleophilic addition of lithium alkynylide to 1-arylsulfon-

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Scheme 1. Synthetic routes to construct 1-alkynyl cyclopropanol and some of its synthetic applications.

yl cyclopropanol 1 to construct 1-alkynyl cyclopropanol, followed by a reaction with aryl iodide through a palladium-catalyzed process to give trisubstituted cross-conjugated dienones. Unlike the well-known chemistry of alkynyl cyclopropanol's ring expansion to form a four-(Route D, Scheme 1)¹³ or a five-(Route C, Scheme 1)¹¹ membered ring, there has been no precedent, to the best



Scheme 2. The coupling reaction of **1**, phenylacetylene, and disubstituted amine.

of our knowledge, for its rearrangement to construct trisubstituted dienone derivatives.

In the previous studies, we documented well the synthesis of 1-arylsulfonyl cyclopropanol 1,¹⁴ and its application in preparing 1-alkynyl cyclopropylamine (Scheme 2). Compound 1 acts as a cyclopropanone surrogate based on the equilibrium between 1 and cyclopropanone, upon loss of a benzenesulfinic acid. As the continued work of the previous study, herein we describe the reactions of compound 1 with different metal alkynylides in order to study the reactivity of compound 1 and extend its synthetic utilities.

The reaction of compound **1a** and phenylacetylene was chosen as the model system for our initial investigation. In preliminary studies, compound **1a** underwent reaction with lithium phenyl ethynilide at low temperature, providing 1-phenylethynyl cyclopropanol **2a** in high yield (Scheme 3). In contrast, phenyl ethynyl magnesium bromide afforded the desired product only in 35% yield, whereas the zinc alkynilide gave no product at all.

As shown in Table 1, a range of 1-alkynyl cyclopropanols were readily obtained from the reaction of cyclopropanone equivalent 1a with the corresponding lithium alkynilide.¹⁵ Both aromatic and aliphatic terminal alkynes were able to undergo the nucleophilic addition to provide the desired alkynyl cyclopropanols. Electron-rich aromatic (Table 1, entries 3 and 5) and heteroaromatic alkynes (Table 1, entry 9) displayed relatively high reactivity and gave higher conversion. However, aryl alkynes (Table 1, entries 6 and 7) substituted with electron-withdrawing groups, such as chloro and bromo, exhibited relatively low reactivity. The reaction of electron deficient 2-pyridinyl ethyne (Table 1, entry 8) afforded the product in the lowest yield. Aliphatic alkynes such as 3-phenyl-1-propyne and *n*hexyne also worked effectively in this reaction (Table 1, entries 11 and 12). When 1-toluene sulfonyl cyclopropanol



Scheme 3. The reaction of **1a** with metal phenyl ethynilide. Reagents and conditions: unless noted, all reactions were carried out under N_2 with 1 equiv of **1a**, 2 equiv of phenyl acetylene and 2.2 equiv of base in THF. ^a*n*-BuLi, -30 °C; ^bEtMgBr, -30 °C; ^cEt₂Zn, 0 °C.

Table 1				
The reaction of	f 1	with	lithium	alkynili



^a Reaction conditions: unless noted, all reactions were carried out under a nitrogen atmosphere using 1 equiv of **1a**, 2.6 equiv of alkyne and 2.5 equiv of *n*-BuLi at -30 °C for 3 h.

^c Isolated yield.

1b, instead of **1a**, was employed as an electrophile in this reaction, the corresponding products were also obtained in similar yields (Table 1, entries 2 and 4).

We then explored the reaction of 1-phenylethynyl cyclopropanol **2a** with iodobenzene by heating a mixture of **2a** (1 equiv), iodobenzene (2 equiv), $Pd(OAc)_2$ (5 mol %), PPh₃ (10 mol %), NaOAc (2 equiv), and *n*-Bu₄NCl (1 equiv) in 5 mL of DMF for 6.5 h at 80 °C, compound 1,1,5-triphenylpenta-1,4-dien-3-one **7a** was obtained in 30% yield (Table 1, entry 1).¹⁶ The effect of different

^b 1-(Toluenesulfonyl) cyclopropanol **1b** as a substrate.

Table 2

The reaction of 2a, iodobenzene catalyzed by Pd(0)^a



Entry	6 (equiv)	Base/additive	Temperature (°C/time)	Yield ^b (%)
1	2 equiv	NaOAc (2 equiv)/"Bu ₄ NCl (1 equiv)	80/6.5 h	30
2	-	NaOAc (2 equiv)	80/3 h	54
3		Na_2CO_3 (2 equiv)	80/12 h	35
4		Cs_2CO_3 (2 equiv)	80/1 h	0
5		NaHCO ₃ (2 equiv)	80/2 h	18
6		K_2CO_3 (2 equiv)	80/40 min	56
7		Et_3N (2.8 equiv)	80/12 h	0
8		No	80/12 h	12 ^c
9		K_2CO_3 (1 equiv)	80/1 h	47
10		K_2CO_3 (4 equiv)	80/30 min	31
11		K_2CO_3 (2 equiv)	40/6 h	33
12		K_2CO_3 (2 equiv)	60/3 h	44
13		K_2CO_3 (2 equiv)	100/20 min	70
14		K_2CO_3 (2 equiv)	120/16 min	45
15	2.5 equiv	K_2CO_3 (2 equiv)	100/30 min	53

^a Unless noted, all the reactions were carried out at 0.2 mmol scale with 1 equiv of 2a, 2–2.5 equiv of iodobenzene in DMF (4 mL).

^b Isolated yields.

^c A ring-opening product was obtained.¹⁷

reaction conditions on the yield of the dienone product was investigated. Other palladium catalysts and phosphine ligands, such as $Pd(OAc)_2/dppe$, $Pd(Ph_3P)_4$, or $Pd(OAc)_2/PCy_3$, were found to be inactive in this transformation. Removal of the chloride source (*n*-Bu₄NCl) reduced the reaction time and improved the yield somewhat (Table 2, entry 2).

The choice of a base is critical to the reaction. In basescreening experiments, K_2CO_3 was found to be superior to other bases, which gave 56% yield of the desired dienone in 40 min (Table 2, entry 6). Na₂CO₃ and NaHCO₃ showed low activity in the reaction (Table 2, entries 3 and 5); Cs₂CO₃ and organic base, such as Et₃N, and pyridine afforded no product (Table 2, entries 4 and 7). Without any base, a ring-opening product was obtained in low yield (12% yield) (Table 2, entry 8).¹⁷ The amount of the base was then examined. When 1 equiv K₂CO₃ was employed, **7a** was obtained in 47% yield (Table 2, entry 9). Increasing the amount of K₂CO₃ to 4 equiv was proved fruitless (Table 2, entry 10).

Optimization of reaction temperature and the amount of Pd(0) catalyst identified a set of best conditions (**2a** (1 equiv), iodobenzene (2 equiv), Pd(OAc)₂ (5 mol %), PPh₃ (10 mol %), K₂CO₃ (2 equiv), in 4 mL of DMF for 20 min at 100 °C, Table 2, entry 13) to give the desired product in 70% yield. Increasing the amount of iodobenzene (2.5 equiv) slightly lowered the yield (Table 2, entry 15).

With this standard procedure in hand, we explored the scope and limitations of the reaction by examining other alkynyl cyclopropanols, and different substituted aryl iodides.¹⁸ As shown in Table 3, the reaction of iodobenzene, and electron-rich phenyl iodide with conjugated 1-alkynyl cyclopropanols such as **2a**, **2b**, or **2c** gave positive results (Table 3, entries 1–6). Among these, the best yield was obtained in the reaction of 4-methyl phenyl iodide with **2b** (Table 3, entry 5). However, coupling of nonconjugated 1-(4-phenylbut-1-ynyl) cyclopropanol **2h** with iodobenzene provided **7g** in a relative low yield (Table 3, entry 7).

In consideration of the two double bonds existing in these trisubstituted dienone derivatives, it was notable that only one isomer was obtained in the reaction. The examination of the two alkene's configuration was based on their spectral data. E configuration of the first double bond (C1-C2), which is on the right side to the carbonyl group, as exemplified in compound 7g (Scheme 4), can be readily determined from the high coupling constant of the two protons attached to it $(J_{H1-H2} = 16 \text{ Hz})$. ¹H-¹H Noesy spectrum of compound 7g was then studied to investigate the configuration of its second double bond (C4-C5). There was a strong NOE correlation that existed between the protons on C(4) and C(6) at chemical shifts 6.74 and 3.42 ppm, indicating that these protons were in a 'syn' relationship (on the same side of the alkene). Thus, the bis-alkenes system in dienone 7g was proved to be (1E, 4Z)-configuration, from which the exact structures of all the other dienone derivatives can be deduced.

A plausible mechanism for this reaction was provided (Scheme 5). The arylpalladium(II) intermediate, generated by oxidative addition of the aryl iodide to a palladium(0) species, undertook a regioselective carbopalladation across the triple bond of compound 2 to give alkenyl palladium

Table 3 Coupling reaction of 1-alkynyl cyclopropanol **2**, Aryl iodide catalyzed by $Pd(0)^{a}$



^a Unless noted, all the reactions were carried out at 0.2 mmol scale with 1 equiv of 1-alkynyl cyclopropanol **2**, 2 equiv of aryl iodide, 5 mol % of Pd(OAc)₂, 10 mol % of PPh₃, and 2 equiv of K_2CO_3 in 4 mL DMF at 100 °C.

- ^b Isolated yields.
- ^c Reaction temperature is 60 °C.
- ^d Reaction temperature is 80 °C.

intermediate **A**. Upon ring opening of the cyclopropyl group and β -hydrogen elimination, intermediate **A** was transformed into the disubstituted dienone **D**, which then



Scheme 4. Determination of the configuration of the two alkenes in compound 7g.



Scheme 5. A plausible mechanism for the palladium induced reaction of compound 2 with aryl iodide.

reacted with another arylpalladium(II) species in Heck condition to afford the final product. The complexation of Pd(II) with the alkene bond in intermediates **B** and **C**, as illustrated in Scheme 5, led to the formation of a '*syn*' relationship between H(4) and group R.

In summary, a novel synthetic route was developed via the nucleophilic addition of lithium alkynylide to 1-arylsulfonyl cyclopropanol 1 to afford a range of 1-alkynyl cyclopropanols, which was then used to react with aryl iodide to construct trisubstituted cross-conjugated dienones through a palladium-catalyzed process. Further study on the applications of compound 1 either as a cyclopropanone equivalent or as a new synthetic subunit is in progress.

Acknowledgments

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- 15. General procedure for the reaction of 1a with lithium alkynilide: To a solution of 1 mmol arylacetylene in THF (10 mL) was added 1.1 mmol of *n*-butyl lithium (0.69 mL, 1.6 M) via a syringe. The reaction mixture was maintained at $-30 \,^{\circ}$ C for 30 min, and then a solution of 1-(benzenesulfonyl) cyclopropanol 1a (99 mg, 0.5 mmol) in THF (5 ml) was added dropwise. 2 h later, 10 ml saturated NH₄Cl was added slowly to stop the reaction. After the usual workup and removal of solvents, flash chromatograph over SiO₂ gave the desired 1-(arylethynyl)cyclopropanol (PE/EA = 30/1). The spectral data of 1-(phenylethynyl) cyclopropanol 2a: Obtained as a colorless solid in 87% yield ($R_{\rm f} = 0.25$, PE/AcOEt = 20/1). ¹H NMR (CDCl₃, Me₄Si) δ 1.07–1.11 (m, 2H), 1.17–1.22 (m, 2H), 2.76 (br s, 1H), 7.28–7.31 (m, 3H), 7.40–7.43 (m, 2H). ¹³C NMR (CDCl₃) δ 17.7, 46.0, 82.4, 90.8, 122.8, 128.2, 128.3, 131.6. MS *m/z* (%) 158 (M⁺, 25), 129 (100), 115 (27), 103 (11), 78 (28), 55 (21).
- The initial reaction condition was adopted from Tian, Q.; Larock, R. C. Org. Lett. 2000, 2, 3329.

17. The product in this condition is



18. General procedure for Pd(0) catalyzed reaction of 1-alkynyl cyclopropanol 2, Aryl iodide to provide trisubstituted dienone derivatives: Aryl iodide (0.4 mmol, 2 equiv), 1-alkynyl cyclopropanol 2 (0.2 mmol, 1 equiv), Pd(OAc)₂ (5 mol %), PPh₃ (10 mol %), K₂CO₃ (2 equiv), and 4 mL of DMF were placed in a 20 mL reaction vial, which was heated in an oil bath at a given temperature with TLC monitoring. After the reaction was completed, the reaction mixture was cooled, diluted with EtOAc, washed with saturated NH₄Cl, dried over anhydrous Na₂SO₄, and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography (PE/EA = 40/1). The spectral data of (E)-1,1,5-triphenylpenta-1,4-dien-3-one 7a: Obtained as a vellow solid in 70% yield ($R_f = 0.2$, PE/AcOEt = 30/1). ¹H NMR $(CDCl_3, Me_4Si) \delta 6.42 (d, J = 16 Hz, 1H), 6.77 (s, 1H), 7.25-7.31 (m, 100)$ 7H), 7.37–7.41 (m, 8H), 7.50 (d, J = 16 Hz, 1H). ¹³C NMR (CDCl₃) δ 126.5, 127.5, 128.1, 128.3, 128.4, 128.5, 128.6, 128.7, 128.9, 129.4, 130.0, 130.2, 135.0, 139.1, 141.1, 141.8, 154.2, 191.4. MS m/z (%) 310 $(M^+, 75), 309 (M^+-1, 100), 191 (16), 178 (31), 165 (6), 152 (8), 131$ (13), 103 (22), 77 (24), 51 (10). HRMS (EI) calcd for C₂₃H₁₈O: 310.1358; found: 310.1352.