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# $BF_3$·$Et_2O$-Catalyzed Direct Carbon−Carbon Bond Formation of α-EWG Ketene-(*S*,*S*)-Acetals and Alcohols and Synthesis of Unsymmetrical Biaryls

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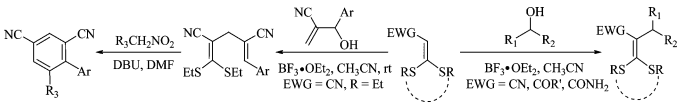
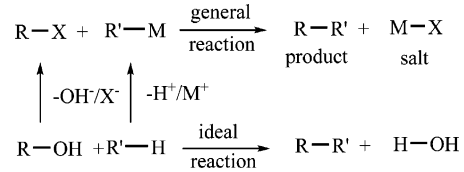



A highly efficient $BF_3$·$OEt_2$-catalyzed formal dehydration C−C coupling reaction between readily available α-EWG ketene-(*S*,*S*)-acetals and various alcohols via direct substitution of the hydroxy group in alcohols has been developed. On the basis of this C−C coupling reaction, a series of alkylated α-EWG ketene-(*S*,*S*)-acetals and functionalized 1,4-pentanedienes were prepared in high to excellent yields and the unsymmetrical biaryls were synthesized in good yields from the generated 1,4-pentanedienes and nitroalkanes through a one-pot annulation−aromatization process.

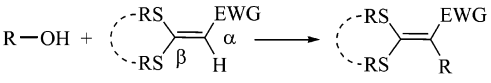
## Introduction

The carbon−carbon bond forming reaction is one of the most fundamental reactions for the construction of the molecular framework in organic chemistry.[1] From the standpoint of atom efficiency,[2] the direct substitution of a hydroxy group in an alcohol (ROH)[3] by a carbon nucleophile (R′H) via a formal dehydration process is an attractive salt-free method because there is no requirement for the transformation of nucleophiles and alcohols to the corresponding reactive organometallic compounds (R′M) and halides or a related species (RX) (Scheme 1).[4a] In recent years, increasing attention has been given to the direct C−C bond forming reactions between ROH and R′H. Among those reported, the C−C coupling reactions between allylic or benzylic alcohols and active methylenes,[4] indoles,[4a,5]

**SCHEME 1**




**SCHEME 2**




**1**

or alkoxylketones[4a] have proven successful. In this context, expanding the scope of the substrates for this type of cross-coupling reaction to a wide range of carbon nucleophiles and alcohols is very important.[3−5]

In our interest in the synthetic applications of the α-EWG ketene-(*S*,*S*)-acetals (**1**) (Scheme 2, EWG = electron withdrawing group),[6,7] we recently showed that the α-carbon atom of α-acetyl/cyano ketene-(*S*,*S*)-acetals can add to aldehydes or ketones in the presence of a Lewis acid, affording the corresponding double Baylis−Hillman (BH) adducts.[8] Thus, as part of our continuing research to understand the nucleophilicity of **1**, alcohols were chosen as carbon electrophiles (Scheme 2).

(1) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992. (b) Scolastico, C., Nocotra, F., Eds. *Current Trends in Organic Synthesis*; Plenum: New York, 1999.

(2) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233.

(3) For reviews, see: (a) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (b) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647.

(4) (a) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793. (b) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968. (c) Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823. (d) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2605. (e) Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4085. (f) Manabe, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 3241.

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(6) For reviews, see: (a) Kolb, M. *Synthesis* **1990**, 171. (b) Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029. (c) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423.

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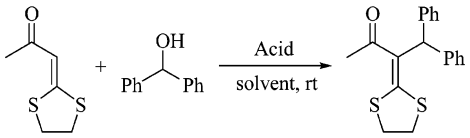
**TABLE 1. Acid-Catalyzed C−C Coupling Reactions of 1a with Benzhydryl Alcohol (2a)[a]**




**1a** **2a** **3aa**

| entry | acid (equiv) | solvent | time (min) | yield[b] (%) |
|---|---|---|---|---|
| 1 | $BF_3{\cdot}OEt_2$ (2.5) | $CH_3CN$ | 5 | 99 |
| 2 | $BF_3{\cdot}OEt_2$ (1.0) | $CH_3CN$ | 5 | 76[c] |
| 3 | $BF_3{\cdot}OEt_2$ (1.0) | $CH_3CN$ | 12 | 99 |
| 4 | $BF_3{\cdot}OEt_2$ (0.5) | $CH_3CN$ | 12 | 60[d] |
| 5 | $BF_3{\cdot}OEt_2$ (0.5) | $CH_3CN$ | 120 | 96 |
| 6 | $BF_3{\cdot}OEt_2$ (0.1) | $CH_3CN$ | 720 | 95 |
| 7 | no acid | $CH_3CN$ | 120 | 0[e] |
| 8 | $AlCl_3$ (1.0) | $CH_3CN$ | 120 | 94 |
| 9 | $FeCl_3$ (1.0) | $CH_3CN$ | 120 | 95 |
| 10 | $H_2SO_4$ (1.0) | $CH_3CN$ | 15 | 95 |
| 11 | $H_2SO_4$ (0.1) | $CH_3CN$ | 300[f] | 84 |
| 12 | $BF_3{\cdot}OEt_2$ (1.0) | $CH_2Cl_2$ | 40 | 87 |
| 13 | $BF_3{\cdot}OEt_2$ (1.0) | THF | 120 | 40[g] |

[a] All reactions were carried out in a solvent (5 mL) with **1a** (1.0 mmol) and **2a** (1.0 mmol) at room temperature. [b] Isolated yield. [c] 22% of **1a** was recovered. [d] 40% of **1a** was recovered. [e] **1a** and **2a** were recovered. [f] The yield could not be further increased with longer reaction time. [g] 55% of **1a** was recovered.

Although the substitution reaction of ketene-(*S*,*S*)-acetals with allylic ethers as carbon electrophiles by the promotion of trityl chloride−tin(II) chloride or a trimethylsilyl chloride−tin(II) chloride catalyst system had been reported,[9] the C−C coupling reaction between ketene-(*S*,*S*)-acetals and alcohols had not been investigated. In the present work, the preliminary results of $BF_3{\cdot}OEt_2$-catalyzed direct C−C bond formation reactions between α-EWG ketene-(*S*,*S*)-acetals (**1**) and various alcohols, including benzhydryl alcohol, phenylmethanols, phenylethanols, and allylic alcohols, and BH adducts[10] together with their synthetic applications are described.

## Results and Discussion

The reaction was first carried out by introducing $BF_3{\cdot}OEt_2$ to a mixture of 1-(1,3-dithiolan-2-ylidene)propan-2-one (**1a**) and benzhydryl alcohol (**2a**) (1:1 ratio) in acetonitrile. A quantitative yield of a direct substitution product, 3-(1,3-dithiolan-2-ylidene)-4,4-diphenylbutan-2-one (**3aa**), was obtained in no more than 12 min at room temperature (Table 1, entries 1 and 3). When a catalytic amount of $BF_3{\cdot}OEt_2$ was used, excellent yields of **3aa** could also be obtained by increasing the reaction time (Table 1, entries 5 and 6). Other Lewis acids, such as $AlCl_3$ and $FeCl_3$, appeared to be effective, although a prolonged reaction time was required to achieve a comparable level of product formation (Table 1, entries 8 and 9). All the reactions between **1a** and benzhydryl alcohol (**2a**) afforded **3aa** in the tested solvents (tetrahydrofuran, dichloromethane, and acetonitrile; Table 1, entries 10 and 11), and acetonitrile was shown to be the best solvent in the case of reaction time and yield. Therefore, the best results were obtained using an equal amount of $BF_3{\cdot}OEt_2$ as the catalyst in acetonitrile (Table 1, entry 3). It should be noted that an equal amount of the general protic acid $H_2SO_4$ is as efficient as $BF_3{\cdot}OEt_2$ for the reaction between **1a** and benzhydryl alcohol (**2a**) to provide 95% yield of **3aa** within 15 min (Table 1, entry 10). However, the yield of **3aa** was reduced to 84% (Table 1, entry 11) employing a catalytic amount of $H_2SO_4$ (0.1 equiv). Furthermore, when a relatively less reactive alcohol, for example, 1-(4-methoxyphenyl)ethanol (**2b**), was used to react with **1a**, only a 64% yield of **3ab** (Table 2, entry 1) was obtained with concentrated $H_2SO_4$ as a catalyst. Comparatively, catalyzed by $BF_3{\cdot}OEt_2$, the reaction between **2b** and **1a** provided an 88% yield of **3ab** (Table 2, entry 1).

To examine the scope of the C−C coupling reaction, different types of alcohols (**2**) were selected to react with 1-(1,3-dithiolan-2-ylidene)propan-2-one (**1a**) under the optimized conditions (Table 1, entry 3). Remarkably, as for the reaction of phenylethanol (**2b**) with **1a** (Table 2, entry 1), the reactions between the selected phenylethanol (**2c**) or phenylmethanols (**2e**−**2g)** (with electron donating groups on the benzene ring) and **1a** afforded the desired alkylated α-acetyl ketene-(*S*,*S*)-acetals (**3ac**) and (**3ae**−**3ag**) in high to excellent yields (Table 2, entries 2, 4−6). Phenylethanol (**2d**) with an electron withdrawing chloro group on the benzene ring gave **3ad** in 65% isolated yield under the reflux temperature of acetonitrile for 3 days (Table 2, entry 3). When (*E*)-1,3-diphenylprop-2-en-1-ol (**2h**) was taken as the alcohol component, **3ah** was also obtained in 95% yield (Table 2, entry 7). In addition, the selected allylic alcohols, for instance, cinnamyl alcohol (**2i**) and 2-methyl-3-(*p*-tolyl)prop-2-en-1-ol (**2j**), gave the desired product **3ai** and **3aj** in excellent yields with high regioselectivity (Table 2, entries 8 and 9). However, under the above identical conditions, some less reactive simple aliphatic alcohols, such as ethanol (**2k**) and *tert*-butyl alcohol (**2l**), did not react with **1a** and the substrate **1a** was recovered after 10 h (Table 2, entries 10 and 11).

All the results described above indicate that α-acetyl ketene-(*S*,*S*)-acetal (**1a**) could be used as an efficient carbon nucleophile for the $BF_3{\cdot}OEt_2$-catalyzed direct dehydrative alkylation of benzhydryl, benzylic, and allylic alcohols. Therefore, the scope of the C−C coupling reaction toward a variety of α-EWG ketene-(*S*,*S*)-acetals was then examined. Accordingly, various α-EWG ketene-(*S*,*S*)-acetals (**1**)[7,8] were prepared to react with benzhydryl alcohol (**2a**) under conditions identical to those above. Fortunately, regardless of the different types of electron withdrawing groups in the α-position of α-EWG ketene-(*S*,*S*)-acetals (**1**), all of the ketene cyclic-(*S*,*S*)-acetals (**1b**−**1g**) were successfully reacted with **2a** to give the corresponding alkylated

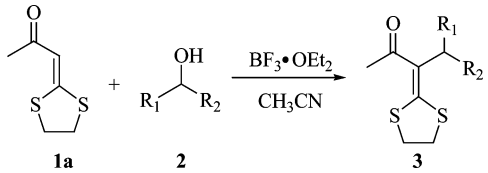
(7) Selected examples: (a) Kang, J.; Liang, F.; Sun, S.; Liu, Q.; Bi, X. *Org. Lett.* **2006**, *8*, 2547. (b) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578. (c) Dong, D.; Ouyang, Y.; Yu, H.; Liu, Q.; Liu, J.; Wang, M.; Zhu, J. *J. Org. Chem* **2005**, *70*, 4535. (d) Zhao, Y.; Liu, Q.; Zhang, J.; Liu, Z. *J. Org. Chem.* **2005**, *70*, 6913. (e) Dong, D.; Bi, X.; Liu, Q.; Cong, F. *Chem. Comm.* **2005**, 3580. (f) Zhao, L.; Liang, F.; Bi, X.; Sun, S.; Liu, Q. *J. Org. Chem.* **2006**, *71*, 1094.

(8) (a) Yin, Y.; Wang, M.; Liu, Q.; Hu, J.; Sun, S.; Kang, J. *Tetrahedron Lett.* **2005**, *46*, 4399. (b) Pan, W.; Dong, D.; Sun, S.; Liu, Q. *Synlett* **2006**, 1090. (c) Zhang, Q.; Liu, Y.; Wang, M.; Liu, Q.; Hu, J.; Yin, Y. *Synthesis* **2006**, 3009. Similar reactions of trimethylsilylketene bis(ethylthio)acetal with aldehydes or amines were reported by Toru Minami and co-workers; see: (d) Okauchi, T.; Tanaka, T.; Minami, T. *J. Org. Chem.* **2001**, *66*, 3924. (e) Yahiro, S.; Shibata, K.; Saito, T.; Okauchi, T.; Minami, T. *J. Org. Chem.* **2003**, *68*, 4947.

(9) Mukaiyama, T.; Sugumi, H.; Uchiro, H.; Kobayashi, S. *Chem. Lett.* **1988**, *8*, 1291.

(10) The Baylis−Hillman (BH) adduct is a kind of important allylic alcohol containing at least three functional groups, i.e., hydroxy, alkene, and electron withdrawing groups obtained from Baylis−Hillman reaction (the C−C coupling reaction of an activated alkene and a carbon nucleophile). For reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Drewes, S. E.; Ross, G. H. P. *Tetrahedron* **1988**, *44*, 4653. (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron*, **1996**, *52*, 8001. (d) Kataoka, T.; Kinoshita, H. *Eur. J. Org. Chem*, **2005**, 45.

**TABLE 2. $BF_3$·$OEt_2$-Catalyzed C−C Coupling Reactions of 1a with Alcohols (2)[a]**

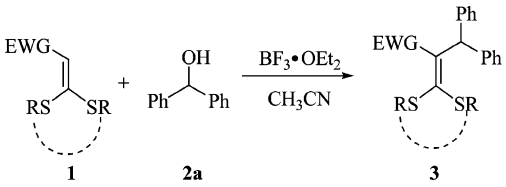



**1a** **2** **3**

| | | alcohol | | | | |
|---|---|---|---|---|---|---|
| entry | **2** | $R_1$ | $R_2$ | time (h) | product **3** | yield[b] (%) |
| 1 | **2b** | 4-$MeOC_6H_4$ | Me | 3.0 /2.0[c] | **3ab** | 88/64[c] |
| 2 | **2c** | Ph | Me | 3.5 | **3ac** | 83 |
| 3 | **2d** | 4-$ClC_6H_4$ | Me | 72 | **3ad** | 65[d] |
| 4 | **2e** | 3,4-$CH_2O_2C_6H_3$ | H | 3.0 | **3ae** | 91 |
| 5 | **2f** | 4-$MeOC_6H_4$ | H | 5.0 | **3af** | 86 |
| 6 | **2g** | 4-$Me_2NC_6H_4$ | H | 4.0 | **3ag** | 90 |
| 7 | **2h** | Ph | PhCH=CH | 1.0 | **3ah** | 95 |
| 8 | **2i** | PhCH=CH | H | 10.0 | **3ai** | 88[d] |
| 9 | **2j** | 4-$MeC_6H_4CH$=$C(CH_3)$ | H | 7.0 | **3aj** | 90 |
| 10 | **2k** | Me | H | 10.0 | **3ak** | 0[e] |
| 11 | **2l** | *t*-BuOH | | 10.0 | **3al** | 0[e] |

[a] The reactions were carried out in acetonitrile (5 mL) with **1a** (1.0 mmol), **2** (1.0 mmol), and $BF_3$·$OEt_2$ (1.0 mmol) at room temperature unless otherwise stated. [b] Isolated yield. [c] With concentrated $H_2SO_4$ (1.0 mmol) as catalyst. [d] Under the reflux temperature. [e] The starting materials were recovered even with alcohol itself as the solvent.

**TABLE 3. $BF_3$·$OEt_2$-Catalyzed C−C Coupling Reactions of α-EWG Ketene-(*S*,*S*)-Acetals (1) with Benzhydryl Alcohol (2a)[a]**




**1** **2a** **3**

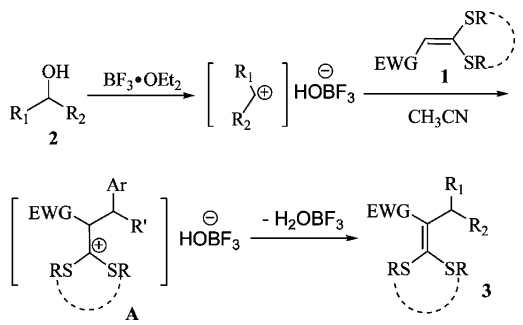
| | | α-EWG ketene-(*S*,*S*)-acetal | | | | |
|---|---|---|---|---|---|---|
| entry | **1** | EWG | R | time (h) | product **3** | yield[b] (%) |
| 1 | **1b** | $CH_3CO$ | $-CH_2CH_2CH_2-$ | 1.5 | **3ba** | 87 |
| 2 | **1c** | $H_2NCO$ | $-CH_2CH_2-$ | 5.0 | **3ca** | 90 |
| 3 | **1d** | CN | $-CH_2CH_2-$ | 0.2 | **3da** | 99 |
| 4 | **1e** | 4-Me−$C_6H_4CH$=CHCO | $-CH_2CH_2-$ | 0.5 | **3ea** | 99 |
| 5 | **1f** | 4-Cl−$C_6H_4CH$=CHCO | $-CH_2CH_2-$ | 1.0 | **3fa** | 98 |
| 6 | **1g** | PhCH=CHCO | $-CH_2CH_2-$ | 0.7 | **3ga** | 99 |
| 7 | **1h** | CN | Me | 2.0 | **3ha** | 88 |
| 8 | **1i** | CN | Et | 4.0 | **3ia** | 89 |

[a] The reactions were carried out in acetonitrile (5 mL) with **1** (1.0 mmol), **2a** (1.0 mmol), and $BF_3$·$OEt_2$ (1.0 mmol) at room temperature. [b] Isolated yield.

ketene cyclic-(*S*,*S*)-acetals (**3ba**−**3ga**) in excellent yields (Table 3, entries 1−6). However, for α-EWG ketene acyclic-(*S*,*S*)-acetals, only 3,3-bis(methylthio)acrylonitrile (**1h**) and 3,3-bis(ethylthio)acrylonitrile (**1i**) could efficiently undergo this reaction to afford **3ha** and **3ia** (Table 3, entries 7 and 8), which are consistent with our previous findings that α-acetyl ketene acyclic-(*S*,*S*)-acetals are inert toward aldehydes[8a] and α-cyanoketene-(*S*,*S*)-acetals are more reactive than α-acetyl ketene-(*S*,*S*)-acetals toward carbonyl electrophiles.[8c]

On the basis of all of the above results, together with the related work in the literature,[4c,11] a possible mechanism for this C−C coupling reaction is proposed in Scheme 3. The hydroxyl group in an alcohol (**2**) is activated by $BF_3$·$OEt_2$ to generate a carbocation, which is then trapped by an α-EWG ketene-(*S*,*S*)-acetal (**1**) to give the more stable carbocation intermediate **A** stabilized by the adjacent two alkylthio groups. Finally, the release of a $BF_3$ from **A** provides the desired alkylated α-EWG ketene-(*S*,*S*)-acetal (**3**).

**SCHEME 3. Proposed Mechanism of the C−C Coupling of 1 and 2**

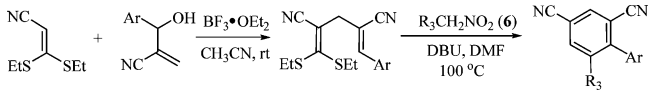



**2** **A**

Due to the high reactivity of 3,3-bis(ethylthio)acrylonitrile (**1i**) (Table 3, entry 8), as mentioned above, we turned our

(11) De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 8345.

**TABLE 4. Preparation of 1,4-Pentanedienes (5) and Their Annulation−Aromatization Reactions with Nitroalkanes (6)**



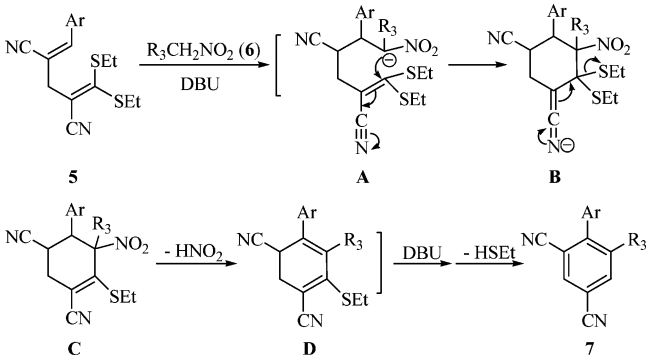

1i 4 5 7

| | BH adduct | | | nitroalkane | | |
|---|---|---|---|---|---|---|
| entry | **4** | Ar | **5**/time (h)/yield[a] (%) | **6** | $R_3$ | **7**/time (h)/yield[a] (%) |
| 1 | **4a** | 4-$MeOC_6H_4$ | **5a**/2.0/85 | **6a** | Me | **7aa**/1.0/60 |
| 2 | **4a** | 4-$MeOC_6H_4$ | **5a**/2.0/85 | **6b** | Et | **7ab**/1.0/45 |
| 3 | **4a** | 4-$MeOC_6H_4$ | **5a**/2.0/85 | **6c** | COOEt | **7ac**/2.0/48 |
| 4 | **4b** | 3,4-$O_2CH_2C_6H_3$ | **5b**/2.0/84 | **6a** | Me | **7ba**/1.0/64 |
| 5 | **4c** | 4-$EtOC_6H_4$ | **5c**/3.0/78 | **6a** | Me | **7ca**/1.0/52 |

[a] Isolated yield.

attention to the reactions of **1i** with BH adducts with the aim to construct the C−C bonds and develop their synthetic potential. The reaction between **1i** and the BH adduct **4a**[10] was investigated as a typical example. Under the above optimized conditions (Table 1, entry 3), the reaction of **4a** with **1i** gave the C−C coupling product, 2-(bisethyl(ethylthio)methylene)-4-(4-methoxybenzylidene)pentanedinitrile (**5a**), in 85% isolated yield with high regioselectivity on the basis of the $^1$H NMR spectrum (Table 4, entry 1). Similar reactions of **1i** with the BH adducts **4b** and **4c** led to the corresponding 1,4-pentanedienes (**5b** and **5c**) (Table 4, entries 4 and 5) in 84% and 78% isolated yields, respectively. Very recently, although Darses and co-workers reported that, in the presence of a rhodium catalyst, BH adducts can react directly with potassium trifluoro(organo)borates[12a] or arylboronic acids[12b] to afford trisubstituted alkenes, most of the transformations of BH adducts required the activation of their hydroxy groups in the form of acetates or carbonates.[13] So far, to the best of our knowledge, the C−C coupling reactions between the BH adducts **4** and **1i** present the first direct substitution reaction between an active alkene (as the carbon nucleophile) and a BH adduct, although Friedel−Crafts reactions of a BH adduct with an aromatic hydrocabon have been described.[14] It should also be noted that the 1,4-diene framework constitutes an important structural unit in many molecules of biological and synthetic importance.[15] Obviously, the direct C−C coupling reaction provides a facile route to the substituted 1,4-pentanedienes (**5**). More importantly, on the basis of our previous work for the synthesis of highly functionalized phenols via the [5C+1C] annulation strategy (the generated 1,4-dienes (**5**) possess the promising structural features as five-carbon 1,5-bielectrophilic species),[7b] the application of 1,4-dienes (**5**) to construct aromatic compounds was next examined by exploring the annulation reactions of **5** with nitroalkanes. In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the one-pot annulation−aromatization reaction between **5a** and nitroethane (**6a**) did occur to afford the unsymmetrical biaryls (**7aa**) (Table 4, entry 1) in 60% isolated yield in DMF at 100 °C within 1 h. Accordingly, the unsymmetrical biaryls (**7ab**−**7ca**) (Table 4, entries 2−5) were obtained in good yields by reacting (**5a**−**5c**) with nitroalkanes (**6a**−**6c**). Because biphenyl derivatives are generally prepared via metal-catalyzed cross-coupling reactions,[16] the above annulation reaction describes a very simple alternative route to the unsymmetrical biaryls starting directly from BH adducts.[17]

**SCHEME 4. Possible Mechanism for the Formation of Unsymmetric Biaryls**




On the basis of our previous work[7b] and the above experimental results, a possible mechanism for the annulation−aromatization is proposed in Scheme 4. In the annulation step, intermediate **C** could be formed via a sequence involving the intermolecular Michael, intramolecular Michael−$S_NV$ from reactions of 1,4-pentanedienes (**5**) and nitroalkanes (**6**). The following aromatization step for unsymmetrical biaryls (**7**) involved the elimination of a nitrous acid molecule from intermediate **C** and, finally, the elimination of the second ethanethiol molecule in the presence of DBU. Interestingly, in the annulation−aromatization process, the third unsaturated degree of aromatization is attained through the elimination of the second alkylthio group. Unlike our previous report of the

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(17) Although the construction of polysubstituted benzenes from BH adducts via a [4+2] annulation strategy had been developed, however, the activation process of the hydroxy group in BH adducts were required and four-step reactions were needed; see: Lee, M. J.; Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 1355.

[5C+1C] annulation,[7b,18] in which one alkylthio group would remain in the target aromatic compounds, this one-pot annulation−aromatization sequence involved the novel elimination of the two alkylthio groups connected to one terminal alkene carbon atom in 1,4-pentanedienes (**5**). The synthetic applications of 1,4-pentanedienes (**5**) for the construction of various heteroaromatic compounds[19] are in progress.

## Conclusion

In summary, a new acid-catalyzed direct C−C coupling reaction via the substitution of the hydroxyl group in various alcohols by readily available α-EWG ketene-(*S*,*S*)-acetals (**1**) was developed, in which the reaction between the α-cyanoketene acyclic-(*S*,*S*)-acetal (**1i**) and the BH adduct **4** realized the first direct substitution reaction between an active alkene (as the carbon nucleophile) and a BH adduct. Some advantages, such as being a salt-free and energy-saving process, requiring very mild reaction conditions, affording high yields, and the broad range of alcohols able to be employed, made this direct C−C coupling method attractive. On the basis of this reaction, a series of alkylated α-EWG ketene-(*S*,*S*)-acetals, functionalized 1,4-pentanedienes, and unsymmetrical biaryls were efficiently prepared. Further applications are currently under way in our laboratory.

## Experimental Section

**General Procedure for the Preparation of 3 (with 3aa as an Example).** To a stirred solution of 1-(1,3-dithiolan-2-ylidene)-propan-2-one (**1a**) (160 mg, 1.0 mmol) and benzhydryl alcohol (**2a**) (182 mg, 1.0 mmol) in $CH_3CN$ (5 mL) in a round-bottom flask was added $BF_3{\cdot}OEt_2$ (0.12 mL, 1.0 mmol) at room temperature. The reaction system was stirred for 12 min (monitored by TLC) before cold saturated $NaHCO_3$ solution (10 mL) was added. A white solid was precipitated, filtrated off, and dried in vacuum to obtained compound **3aa** (323 mg, 99%): mp 147−149 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.87 (s, 3H), 3.25−3.32 (m, 4H), 5.86 (s, 1H), 7.20 (d, $J$ = 7.5 Hz, 4H), 7.27 (t, $J$ = 6.5 Hz, 2H), 7.33 (t, $J$ = 7.0 Hz, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 29.2, 36.3, 38.6, 54.4, 126.7, 127.2, 128.4, 129.2, 140.9, 164.3, 195.7; MS calcd *m*/*z* 326.1, found 327.1 [(M + 1)]$^+$; IR (KBr) 3055, 1629, 1462, 1242, 705 cm$^{-1}$. Anal. Calcd for $C_{19}H_{18}OS_2$: C, 69.90; H, 5.56. Found: C, 69.81; H, 5.61.

**General Procedure for the Preparation of 5 (with 5a as an Example).** To a well-stirred solution of 3,3-bis(ethylthio)acrylonitrile (**1i**) (865 mg, 5.0 mmol) and the Baylis−Hillman adduct **4a** (945 mg, 5.0 mmol) in 10 mL of acetonitrile was added $BF_3{\cdot}OEt_2$ (0.63 mL, 5.0 mmol) dropwise. The reaction system was stirred for 2.0 h and monitored by TLC, and the above mixture was quenched by the addition of a saturated aqueous $NaHCO_3$ solution. The mixture was then extracted with dichloromethane (20 mL × 3) and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure, and the residue was purified by shot flash silica gel column chromatography to give compound **5a** (1460 mg, 85%) as a colorless crystal (eluent: diethyl ether/petroleum ether = 1/6): mp 66−68 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.30 (t, $J$ = 7.5 Hz, 3H), 1.36 (t, $J$ = 7.5 Hz, 3H), 2.95−3.01 (m, 4H), 3.65 (s, 2H), 3.85 (s, 3H), 6.93 (d, $J$ = 8.5 Hz, 2H), 6.98 (s, 1H), 7.74 (d, $J$ = 8.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 15.1, 15.5, 29.6, 30.0, 39.4, 55.7, 102.8, 113.7, 114.5, 117.8, 118.7, 126.1, 131.1, 145.8, 157.1, 161.6; IR (KBr) 2920, 2206, 1605, 1511, 1261 cm$^{-1}$; MS calcd *m*/*z* 344.1, found 345.1 [(M + 1)]$^+$. Anal. Calcd for $C_{18}H_{20}N_2OS_2$: C, 62.76; H, 5.85; N, 8.13. Found: C, 62.81; H, 5.97; N, 8.22.

**General Procedure for the Preparation of 7 (with 7aa as an Example).** To a well-stirred solution of **5a** (172 mg, 0.5 mmol) and nitroethane (**6a**) (150 mg, 2.0 mmol) in 2 mL of *N*,*N*-dimethylformamide (DMF) was added 1,8-diazabicyclo(5.4.0)-undec-7-ene (DBU) (0.30 mL, 2.0 mmol) dropwise. The reaction mixture was stirred for 1.0 h at 100 °C and monitored by TLC. The above mixture was poured into ice−water and quenched with hydrogen chloride to a pH value of 7−8. The mixture was then extracted with dichloromethane (10 mL × 3) and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography to give the product **7aa** (75 mg, 60%) as a yellow solid (eluent: diethyl ether/petroleum ether = 1/25): mp 114−116 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 2.26 (s, 3H), 3.88 (s, 3H), 7.04 (d, $J$ = 8.0 Hz, 2H), 7.21 (d, $J$ = 8.0 Hz, 2H), 7.75 (s, 1H), 7.86 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 20.9, 55.6, 112.2, 114.6, 115.2, 116.9, 117.2, 128.1, 130.2, 133.9, 137.3, 140.1, 149.8, 160.5; IR (KBr) 2975, 2802, 2234, 1610, 1458, 1248 cm$^{-1}$; MS calcd *m*/*z* 248.1, found 249.1 [(M + 1)]$^+$. Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found C, 77.29; H, 4.98; N, 11.45.

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**Supporting Information Available:** Experimental details and full characterization data, copies of $^1$H and $^{13}$C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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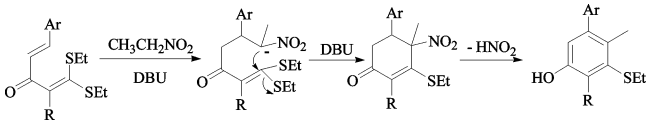
(18) The proposed mechanism in our previous report of annulation (also see ref 7b):




(19) The synthesis of cyclic molecules using BH adducts, including quinolines, quinolines *N*-oxides, naphthalenes, indolizines, benzenes, pyridines, and 2,4-diaminopyrimidines, etc; see: (a) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627. (b) Lee, M. J.; Lee, K. Y.; Park, D. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 3128.