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COMMUNICATION

A Bromine-Radical Mediated Three-Component Reaction Comprising Allenes, Electron-Deficient Alkenes and Allyl Bromides: Facile Synthesis of 2-Bromo-1,7-Dienes

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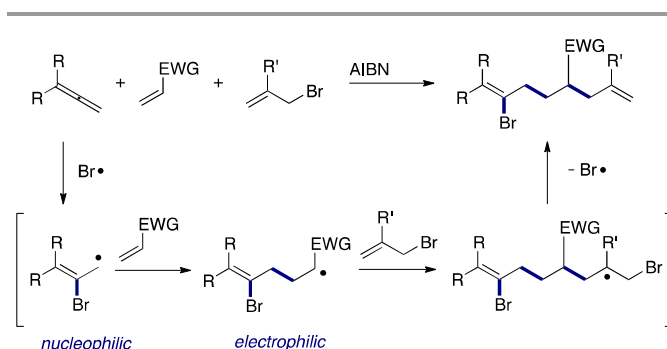
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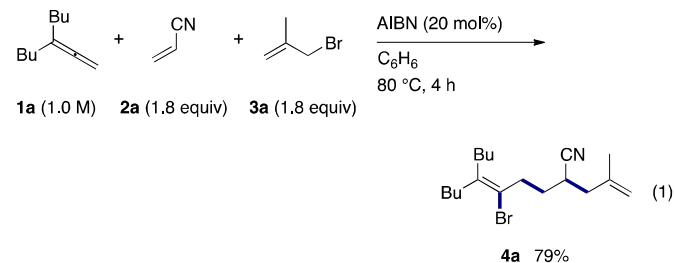
A bromine-radical mediated three-component coupling reaction was effectively achieved by the use of allenenes, electron-deficient alkenes, and allyl bromides and led to the synthesis of 2-bromo-1,7-dienes in good to high yields. This protocol was extended to the three-component process using alkylidenecyclopropane, which gave 2-bromo-1,8-diene along with alkylidenecyclopentane.

Dienes are ubiquitous in nature but also useful as building blocks in organic synthesis. Recently, we reported radical bromoallylation of alkynes, allenenes and alkylidenecyclopropanes, which led to bromo-substituted 1,4-, 1,5-, and 1,6-dienes, respectively.¹ In these reactions, the bromine radical serves as a radical chain carrier^{2,3,4} that is incorporated into product dienes as a vinyl bromine moiety, which can be further functionalized by cross-coupling reactions and radical reactions. To extend the bromoallylation strategy to the synthesis of 1,7-dienes, a three-component process comprising allenenes, alkenes and allyl bromides seems attractive (Scheme 1). Key allyl radicals are expected to gravitate to the more electron-poor alkenes rather than allyl bromides, which would lead the reaction in a given sequence.⁵ For a related three-component reaction leading to 1,7-diene, to our knowledge, only one example is known. In 1988, Mizuno, Otsuji and coworkers reported the synthesis of 1,7-diene by a radical three-component reaction comprising allyl iodide, benzylidenemalononitrile, and allyltributyltin.^{6,7} Herein we report a novel three-component coupling reaction which can access a wide variety of 2-bromo-1,7-dienes.



Scheme 1 A Three-Component Radical Strategy for the Synthesis of 1,7-Dienes

Under Ar atmosphere, a benzene solution containing 3-butyl-1,2-heptadiene (**1a**, 1.0 M), acrylonitrile (**2a**, 1.8 equiv), β -methylallyl bromide (**3a**, 1.8 equiv) and AIBN (2,2'-azobisisobutyronitrile, 20 mol%) was heated at 80 °C for 4 hours. After silica gel chromatography, 5-bromo-6-butyl-2-(2-methylallyl)-5-decenenitrile (**4a**) was obtained in a 79% yield (eq 1). In this reaction, a small amount of 5-bromo-6-butyl-2-methyl-1,5-decadiene was formed as a byproduct, which originated from **1a** and **3a**.



Next, we examined the generality of the present three-component coupling reaction for a variety of allenenes **1**, electron-deficient alkenes **2**

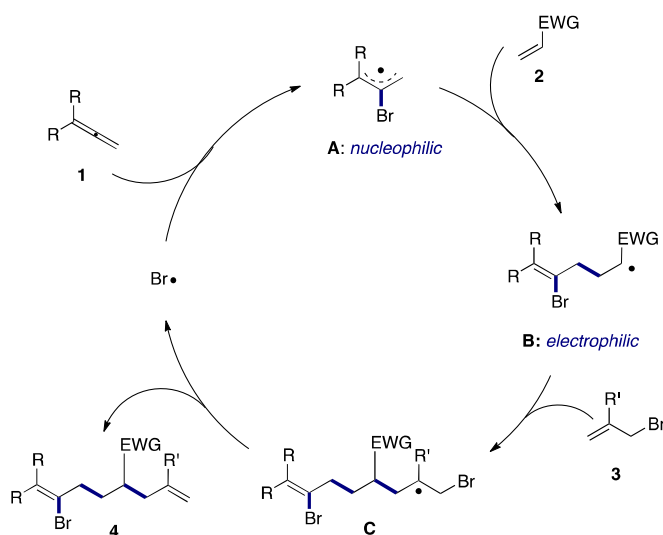
and allyl bromides **3** (Table 1). Ethyl acrylate (**2b**) and methyl vinyl ketone (**2c**) exhibited modest reactivity in a reaction with **1a** and **3a**, and as a result, four equivalents of **2b** and **2c** were used to obtain good yields of product **4b** and **4c** (entries 2 and 3). Other electron-deficient alkenes, such as diethyl 2-methylenemalonate (**2d**), acrolein (**2e**) and benzylidenemalononitrile (**2f**) were all reactive enough with 1.8 equiv, giving the corresponding 2-bromo-1,7-dienes **4d-e** and **4k** in excellent yields (entries 4,5 and 11). Other allyl bromides such as α -bromomethylstyrene (**3b**), 3-bromo-2-chloropropene (**3c**), 2,3-dibromopropene (**3d**) and allyl bromide (**3e**) also worked well. For instance, **3b** reacted with **1a** and **2d** to give the expected three-component coupling product **4f** in an 84% yield (entry 6). The reaction of 3-bromo-2-chloropropene (**3c**) with **1a** and **2d** gave **4g** in a modest yield (entry 7). The reaction of 2,3-dibromopropene (**3d**) with **1a** and **2e** also proceeded well to give **4h** in an 83% yield (entry 8). In these cases, two types of carbon-halogen bonds were incorporated into the product structure. The reactivity of simple allyl bromide (**3e**) was quite low,⁸ however, the use of 10 equivalents of **3e** to allene **1a** gave the desired 1,7-diene **4i** in an 83% yield (entry 9). A wide variety of allenes can participate in the present three-component coupling reaction. Vinylidenecyclohexane (**1b**) afforded an 88% yield of 1,7-diene **4j** (entry 10). 1,2-Nonadiene (**2c**) reacted with **2f** and **3a** efficiently to give **4k** in an 82% yield. Cyclohexylallene (**1d**) underwent a three-component coupling reaction with **2d** and **3a** to give **4l** in an 82% yield (entry 11 and 12). Product **4k** and **4l** were obtained as *E/Z* mixtures favoring the *Z* isomer (entries 11 and 12). The reaction of 1,2-cyclononadiene (**1e**) also worked well to produce the corresponding product **4m** in an 80% yield (entry 13). The reaction of 1,1,3-trisubstituted allene **1f** with **2d** and **3a** also proceeded well to give 1,7-diene **4n** (entry 14).

Table 1 Substrate Scope of Three-Component Reaction^a

| entry | 1 | 2 | 3 | 4 | yield (%) ^b |
|----------------|---|---|---|---|---------------------------------------|
| | | | | | |
| 1 | | | | | 79 |
| 2 ^c | | | | | 57 |
| 3 ^c | | | | | 72 |
| 4 | | | | | 76 |
| 5 | | | | | 78 |
| 6 | | | | | 84 |
| 7 | | | | | 56 |
| 8 | | | | | 83 |
| 9 ^d | | | | | 83 |
| 10 | | | | | 88 |
| 11 | | | | | 82 <i>E/Z</i> = 14/86 ^e |
| 12 | | | | | 82 <i>E/Z</i> = 28/72 ^e |
| 13 | | | | | 80 |
| 14 | | | | | 60 |

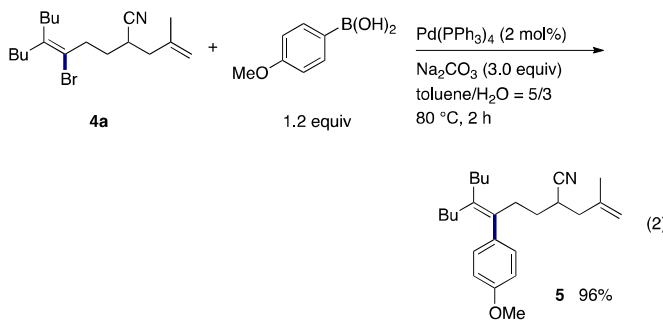
^a Conditions: **1** (1.0 mmol), **2** (1.8 mmol), **3** (1.8 mmol), AIBN (0.2 mmol), C₆H₆ (1.0 mL) 80 °C, 4 h under an argon atmosphere. ^b Isolated yield after flash column chromatography on SiO₂ and preparative HPLC. ^c **2b** or **2c** (4.0 equiv) ^d **3e** (10.0 equiv) ^e *E/Z* ratio was determined by ¹H-NMR analysis of the crude reaction mixture.

Polarity-matched radical chain mechanism can account for the present three-component coupling reaction, which is illustrated in Scheme 2. Initially, cyanopropyl radical formed by the thermal decomposition of AIBN adds to allyl bromide **3** to generate a bromine radical, which attacks the central carbon of allene **1** to give an allyl radical **A**.⁹ Allyl radical **A**, with a nucleophilic character, first reacts with electron-deficient alkene **2**, which leads to electrophilic radical **B**. Then, radical **B** adds to relatively electron-rich allyl bromide **3** to produce intermediate radical **C**, which follows β-fission to give 2-bromo-1,7-diene **4** and regenerate the bromine radical, sustaining the chain.



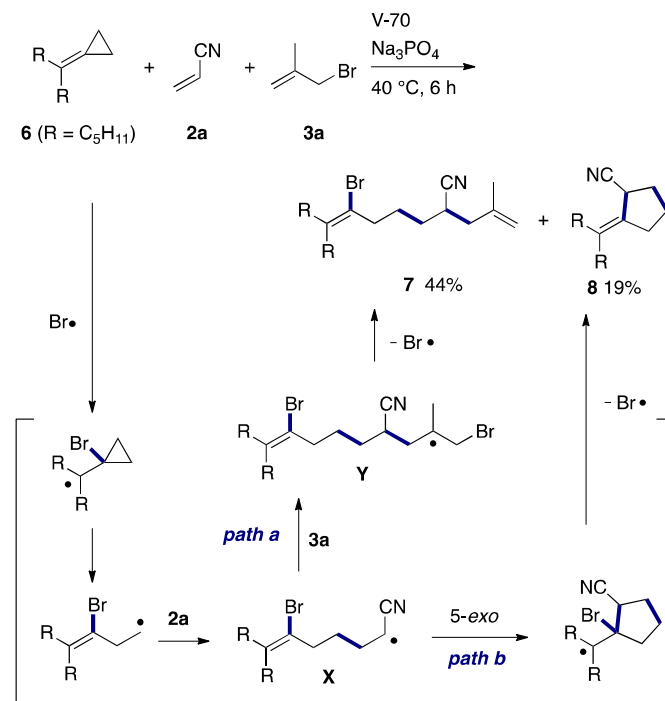
Scheme 2 Polarity-Matched Radical Reaction Mechanism

Since all these 1,7-dienes have a vinyl bromide moiety, conversion to dienes having a tetra-substituted C-C double bond is feasible. For instance, we examined a Suzuki-Miyaura cross-coupling reaction of **4a** with 4-methoxyphenylboronic acid,¹⁰ which worked quite well to give diene **5** in a 96% yield (eq 2).



We then thought that if alkyldenecyclopropane **6** was used as a substrate, the similar three-component coupling reaction with acrylonitrile (**2a**) and β-methallyl bromide (**3a**) would give 2-bromo-1,8-diene **7**. Indeed, when a solution of 6-undecanyldenecyclopropane

(**6**), acrylonitrile (**2a**) and β-methallyl bromide (**3a**) and Na₃PO₄ with V-70 (2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile)) was heated at 40 °C for 6 h, 1,8-diene **7** was obtained in a 44% yield together with a 19% yield of methylenecyclopentane **8**, which is derived from **6** and **2a**. This result can be explained by the initial formation of a cyclopropylcarbinyl radical by the regioselective addition of a bromine radical to alkyldenecyclopropane and its rapid ring-opening to give a homoallyl radical,¹¹ which then underwent consecutive additions to **2a** and **3a**. β-Fission of the resultant radical **Y** produced 2-bromo-1,8-diene **7** and bromine radical (path a). On the other hand, radical **X** can also undergo 5-exo cyclization/β-fission to give methylenecyclopentane **8** (path b).¹²



Scheme 3 Bromine-Radical-Mediated Three-Component Process Leading to 1,8-Diene

In conclusion, we have developed a general, concise, one-pot method to access 2-bromo-substituted 1,7-dienes by a radical three-component reaction between allenes, electron-deficient alkenes and allyl bromides. Alkyldenecyclopropanes can also be employed in this reaction, which lead to 2-bromo-substituted 1,8-dienes. Thus, bromine-radical mediated C-C bond forming reactions permit the design of multi-component processes based on polarity-matching and can provide useful synthetic access to tetrasubstituted and functionalized alkenes.

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Notes and references

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- ¹ (a) T. Kippo, T. Fukuyama and I. Ryu, *Org. Lett.* 2010, **12**, 4006; (b) T. Kippo, T. Fukuyama and I. Ryu, *Org. Lett.* 2011, **13**, 3864; (c) T. Kippo, K. Hamaoka and I. Ryu, *J. Am. Chem. Soc.* 2013, **135**, 632.
- ² (a) M. S. Kharasch and M. Sage, *J. Org. Chem.* 1949, **14**, 79; (b) M. S. Kharasch and G. Büchi, *J. Org. Chem.* 1949, **14**, 84.
- ³ (a) J. M. Tanko and M. Sadeghipour, *Angew. Chem., Int. Ed.* 1999, **38**, 159; (b) J. A. Struss, M. Sadeghipour and J. M. Tanko, *Tetrahedron Lett.* 2009, **50**, 2119.
- ⁴ (a) D. P. Curran, J. Xu and E. Lazzarini, *J. Am. Chem. Soc.* 1995, **117**, 6603; (b) D. P. Curran, J. Xu and E. Lazzarini, *J. Chem. Soc., Perkin Trans. 1* 1995, 3049.
- ⁵ For reviews on radical multicomponent reactions; see: (a) M. Tojino, and I. Ryu, In *Multicomponent Reactions*; J. Zhu and H. Bienayme, ed. Wiley-VCH: Weinheim, 2005; (b) A. Fusano and I. Ryu, In *Science of Synthesis: Multicomponent Reactions 2*; T. J. J. Muller, ed. Georg Thieme Verlag KG, Germany, 2014; (c) E. Godineau and Y. Landais, *Chem. Eur. J.* 2009, **15**, 3044. (d) I. Ryu, N. Sonoda and D. P. Curran, *Chem. Rev.* 1996, **96**, 177.
- ⁶ K. Mizuno, M. Ikeda, S. Toda and Y. Otsuji, *J. Am. Chem. Soc.* 1988, **110**, 1288.
- ⁷ For palladium catalyzed three-component coupling reaction of allyl iodide, electron-deficient alkenes and allyltributyltin; see: (a) H. Nakamura, J. -G. Shim and Y. Yamamoto, *J. Am. Chem. Soc.* 1997, **119**, 8113; (b) H. Nakamura, K. Aoyagi, J. -G. Shim and Y. Yamamoto, *J. Am. Chem. Soc.* 2001, **123**, 372; (c) N. Solin, S. Narayan and K. J. Szabó, *J. Org. Chem.* 2001, **66**, 1686.
- ⁸ (a) M. Walbiner, J. Q. Wu and H. Fischer, *Helv. Chim. Acta* 1995, **78**, 910; (b) T. Zytowski and H. Fischer, *J. Am. Chem. Soc.* 1997, **119**, 12869; (c) H. Fischer and L. Radom, *Angew. Chem., Int. Ed.* 2001, **40**, 1340; (d) H. Fischer and L. Radom, *Macromol. Symp.* 2002, **182**, 1.
- ⁹ For radical addition to allenes; see: J. Hartung and T. Kopf, In *Modern Allene Chemistry*; N. Krause and A. S. K. Hashmi, ed. Wiley-VCH: Weinheim, 2004.
- ¹⁰ N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.* 1979, 3437.
- ¹¹ (a) B. Maillard, D. Forrest and K. U. Ingold, *J. Am. Chem. Soc.* 1976, **98**, 7024; (b) M. Newcomb and A. G. Glenn, *J. Am. Chem. Soc.* 1989, **111**, 275; (c) R. Hollis, L. Hughes, V. W. Bowry and K. U. Ingold, *J. Org. Chem.* 1992, **57**, 4284; (d) J. H. Horner, N. Tanaka and M. Newcomb, *J. Am. Chem. Soc.* 1998, **120**, 10379.
- ¹² For thiyl radical mediated [3+2] cycloaddition of methylenecyclopropanes with alkenes, see: (a) D. A. Singleton and K. M. Church, *J. Org. Chem.* 1990, **55**, 4780; (b) D. A. Singleton, C. C. Huval, K. M. Church and E. S. Priestley, *Tetrahedron Lett.* 1991, **32**, 5765; (c) C. C. Huval, K. M. Church and D. A. Singleton, *Synlett* 1994, 273. (d) C. C. Huval and D. A. Singleton, *J. Org. Chem.* 1994, **59**, 2020.