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Regioselective Radical Bromoallylation of Allenes Leading to 2-Bromo-Substituted 1,5-Dienes

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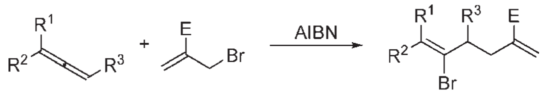
ABSTRACT

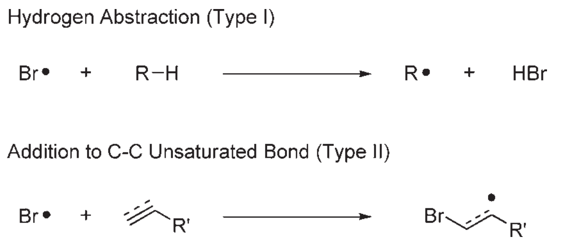


E = H, CO_2Me, CN

The regioselective radical bromoallylation of allenes proceeded efficiently in the presence of AIBN as a radical initiator to give 2-bromo-substituted 1,5-dienes in excellent yields. The addition of a bromine radical took place regioselectively onto the central carbon of allenes generating a stable allyl radical, which underwent addition/β-fragmentation reactions with allylbromides. The products could be further functionalized by Pd-catalyzed coupling reactions.

It has long been known that bromine radicals abstract hydrogen to form alkyl radicals (Scheme 1, Type I) as represented by traditional Wohl–Ziegler bromination, giving benzylic and allylic bromides as products.[1,2] Another well-known behavior of bromine radicals is addition to unsaturated C–C bonds to generate renewed radicals (Scheme 1, Type II), which is exemplified by the anti-Markovnikov addition of HBr to alkenes and alkynes.[3] These potential radical reactions have rarely been associated with the subsequent C–C bond forming reactions, but a breakthrough was reported by Tanko and co-workers, wherein the hydrogen abstraction of alkyl aromatics by a bromine radical was sequenced by the addition to 2-phenylallyl bromide to cause benzylic allylation to give homoallyl aromatics.[4]

Scheme 1. Two Types of Behavior of Bromine Radicals towards Hydrocarbons



If the Type II reaction is successfully sequenced by the subsequent C–C bond forming reaction, a bromine is incorporated into the product structure, which can function as an additional reactive site for further reactions. Since a variety of transformations are available for vinylic bromide moieties, such as metal catalyzed cross-coupling reactions and carbonylation, we became interested in a free-radical-mediated bromoallylation reaction of alkynes with allylbromides and reported that the reaction gave

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[1] (a) Huyser, E. S. *Free-Radical Chain Reaction*; Wiley&Sons: New York, 1970. (b) Kochi, J. K. *Free Radicals*; Wiley&Sons: New York, 1973; Vols.1 and 2.

[2] (a) Wohl, A. *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 51. (b) Wohl, A.; Jaschinowski, K. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 476. (c) Ziegler, K.; Spath, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Justus Liebigs Ann. Chem.* **1942**, *551*, 80. (d) Djerassi, C. *Chem. Rev.* **1948**, *43*, 271. (e) Horner, L.; Winkelmann, E. H. *Angew. Chem.* **1959**, *71*, 349.

[3] For a review on hydrobromination of unsaturated hydrocarbons in radical processes, see: Adams, R.; Blatt, A. H.; Boekelheide, V.; Cairns, T. L.; Cope, A. C.; Curtin, D. Y.; Niemann, C. *Org. React.* **1963**, *13*, 154. Also see a recent study: Matsubara, H.; Tsukida, M.; Ishihara, D.; Kuniyoshi, K.; Ryu, I. *Synlett* **2010**, *13*, 2014.

[4] (a) Tanko, J. M.; Sadeghipour, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 159. (b) Struss, J. A.; Sadeghipour, M.; Tanko, J. M. *Tetrahedron Lett.* **2009**, *50*, 2119.

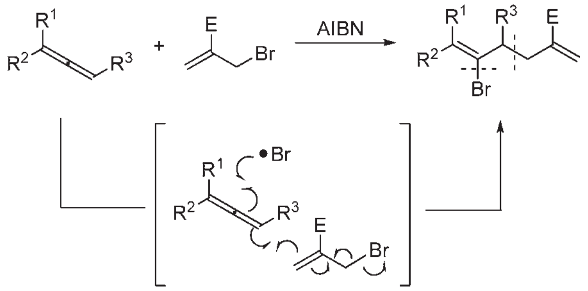
[5] Kippo, T.; Fukuyama., T.; Ryu, I. *Org. Lett.* **2010**, *12*, 4006.

10.1021/ol201395p

good yields of 1-bromo-2-substituted 1,4-dienes.[5] Whereas the regioselectivity of the reaction originated from the less-hindered site addition of bromine radicals to alkynes; it is known that, in the free-radical addition of HBr to allenes, bromine radicals selectively add to the allene center carbon to give stable 2-bromo-substituted allyl radicals.[6,7] If the resulting allyl radicals would add to allylbromides, 2-bromo-substituted 1,5-dienes would be formed (Scheme 2).

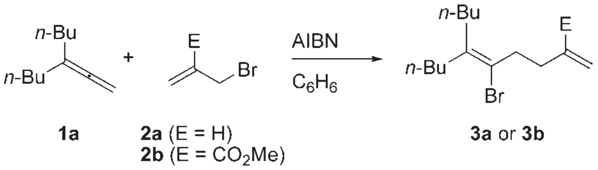
Herein we report the free-radical-mediated addition of allylbromides to allenes proceeds regioselectively to give excellent yields of the desired 2-bromo-substituted 1,5-dienes (Scheme 2). The obtained bromo-dienes could then be successfully converted to substituted alkenes and carbonyl compounds via the subsequent manipulation of vinyl-bromine bonds by Pd-catalyzed reactions.

Scheme 2. Regioselective Radical Bromoallylation of Allenes



In the present study, 5-ethenylidenenonane (**1a**) was selected as a test allene substrate for the control experiments (Table 1). Thus, when a mixture of allene **1a** (1 mmol), allylbromide **2a** (2 mmol), and AIBN (30 mol %) was stirred for 6 h at 80 °C under an argon atmosphere, no anticipated bromoallylated product was obtained (Table 1, entry 1). On the other hand, with the use of a large excess of **2a** (58 equiv), the desired reaction proceeded to give 5-bromo-1,5-diene (**3a**) in 86% yield (entry 2). This reaction was completely regioselective with no other isomers detected. In the hope of accelerating the C–C bond-forming step, methyl 2-(bromomethyl)acrylate (**2b**) was tested, in which a methoxycarbonyl group was introduced into the β-position of allylbromide. This proved to markedly increase bromoallylation even with 2 equiv, which gave the expected 2-bromo-substituted diene **3b** in 72% yield (entry 3). A shorter reaction time (1 h) sufficed to complete the reaction (entry 4). A higher concentration of the solution and a lesser amount of AIBN improved the yield to 84% (Table 1, entries 6 and 7).

Table 1. Regioselective Radical Bromoallylation Reaction of 5-Ethenylidenenonane (**1a**) and Allylbromides **2**[a]



entry	**2** (equiv)	C_6H_6 (M)	time (h)	yield[b] (%)
1	**2a** (2)	0.1	6	0
2	**2a** (58)	–	6	86
3	**2b** (2)	0.1	6	72
4	**2b** (2)	0.1	1	66
5	**2b** (1)	0.1	1	40
6	**2b** (1.5)	1.0	1	61
7[c]	**2b** (2)	1.0	1	84

[a] Conditions: **1a** (1.0 mmol), AIBN (30 mol %), 80 °C under an argon atmosphere. [b] Isolated yield based on **1a**. [c] 20 mol % of AIBN was used.

Having identified the optimal reaction conditions with **2b**, a variety of allenes were examined in order to investigate the scope of the reaction, and the results are shown in Table 2. Monosubstituted allenes such as cyclohexylallene (**1b**) and phenylallene (**1c**), underwent bromoallylation with **2b** efficiently to give excellent yields of the corresponding addition products **3c** and **3d** (entries 2 and 3). The reaction using an electron-deficient allene **1d** with an ethoxycarbonyl substituent also worked well with the identical regioselectivity (entry 4). Products were generally obtained as an *E*/*Z* mixture. However, in this case, only the *E*-form of **3e** was obtained. The reaction using 2-(bromomethyl)acrylonitrile (**2c**) with vinylidenecyclohexane (**1e**) was also successful, which gave the corresponding bromoallylated product **3f** in 88% yield (entry 5). A variety of geminally disubstituted allenes **1f**–**1j** reacted with **2b** smoothly to form the corresponding bromo-dienes **3g**–**3k** in excellent yields (entries 6–10). Functional groups, such as OTIPS, NPhth, and CO_2Et, were tolerated in the present radical bromoallylation reaction. The bromoallylation of 1,3-disubstituted allenes also worked well. For example, similar reactions of allene **1k** or **1l** with **2** gave the corresponding products in 87% and 77% yields, respectively (entries 11 and 12).

A proposed reaction mechanism for the present radical bromoallylation of allenes is shown in Scheme 3. Thus, initiating cyanopropyl radicals are formed by the thermal decomposition of AIBN, which add to **2** to generate bromine radicals. The bromine radicals regioselectively add to the allene center carbon to form allyl radicals, and then an addition to allylbromide **2** takes place in an S_H2' manner to produce the desired 2-bromo-substituted 1,5-dienes and regenerate the bromine radicals, thus achieving

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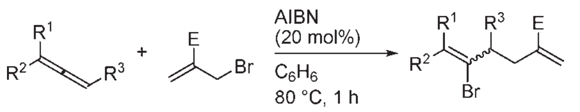
(6) (a) Taylor, D. R. *Chem. Rev.* **1967**, *67*, 317. (b) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805. (c) Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2. (d) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (e) Ma, S. *Aldrichmica Acta* **2007**, *40*, 91.

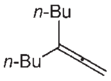
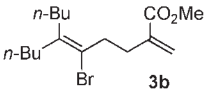
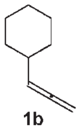
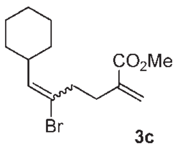
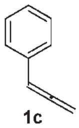
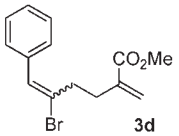
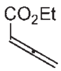
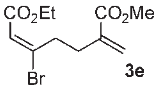
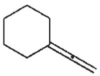
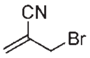
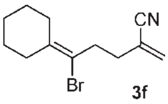
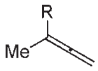
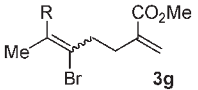
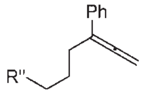
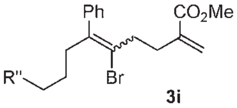
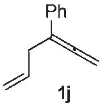
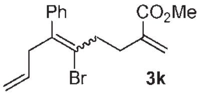
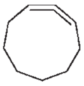
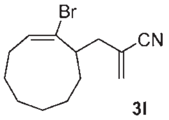
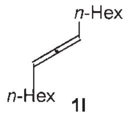
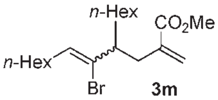
(7) For radical hydrobromination of allenes, see: (a) Kovachic, D.; Leitch, L. C. *Can. J. Chem.* **1961**, *39*, 363. (b) Griesbaum, K.; Oswald, A. A.; Hall, D. N. *J. Org. Chem.* **1964**, *29*, 2404. (c) Abell, P. I.; Anderson, R. S. *Tetrahedron Lett.* **1964**, *5*, 3727. (d) Tien, R. Y.; Abell, P. I. *J. Org. Chem.* **1970**, *35*, 956. (e) Moorthy, S. N.; Singh, A.; Devaprabhakara, D. *J. Org. Chem.* **1975**, *40*, 3452.

(8) For ditin/hν induced radical addition of alkyl halides to allyl chlorides, see: Huval, C. C.; Singleton, D. A. *Tetrahedron Lett.* **1993**, *34*, 3041.

Table 2. Scope of Bromoallylation Reaction of Various Allenes[a]

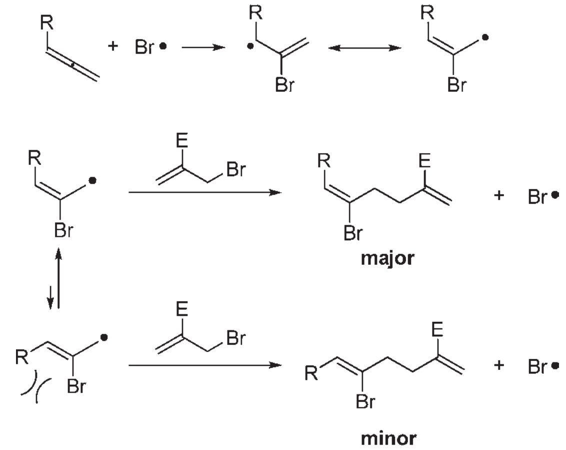


1 (1.0 M) **2** (2.0 equiv) **3**

entry	1	2	3	yield (%)[b]	E/Z[c]
1	 **1a**	**2b**	 **3b**	84	-
2	 **1b**	**2b**	 **3c**	93	77/23
3	 **1c**	**2b**	 **3d**	95	66/34
4	 **1d**	**2b**	 **3e**	99	100/0
5	 **1e**	 **2c**	 **3f**	88	-
6	 **1f** (R = *n*-Hex)	**2b**	 **3g**	86	54/46
7	**1g** (R = Ph)		**3h**	83	80/20
8	 **1h** (R'' = OTIPS)	**2b**	 **3i**	80	82/18
9	**1i** (R'' = NPhth)		**3j**	85	86/14
10	 **1j**	**2b**	 **3k**	94	79/21
11	 **1k**	**2c**	 **3l**	87	-
12	 **1l**	**2b**	 **3m**	77	86/14

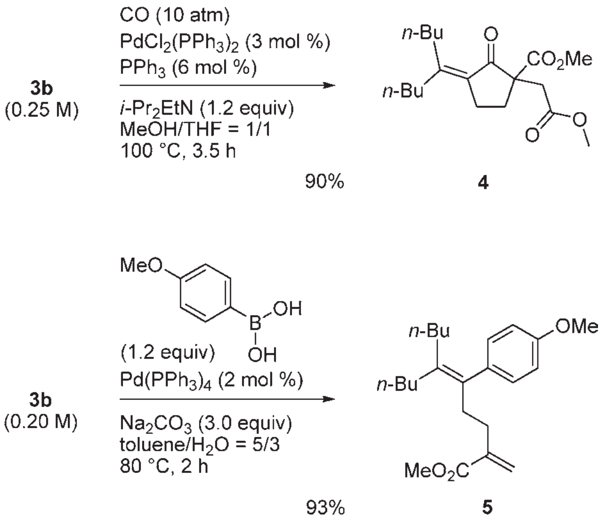
[a] Conditions: allenes **1** (1.0 mmol), allylbromides **2** (2.0 mmol), AIBN (0.2 mmol), 80 °C, 1 h under an argon atmosphere. [b] Isolated yield after flash column chromatography on silica gel and/or preparative HPLC based on **1**. [c] Determined by ^{1}H NMR of the crude reaction mixture.

Scheme 3. Proposed Chain Reaction Mechanism



a radical chain mechanism.[8,9] The preference of *E*-isomers over *Z*-isomers may be explained by assuming steric repulsion of the substituents on the allene and bromine in the allyl radicals.

Scheme 4. Pd-Catalyzed Reaction of **3b**



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(9) In principle the same product can be obtained if an allyl radical adds to the allene terminus and the resultng vinyl radical abstracts bromine from an allyl bromide. This mechanism seems inconsistent with the fact that **2b** is more reactive than **2a**, but the contamination of this chain reaction is not fully ruled out. For the concept of "orthogonal chains" (two different chains that can give the same products), see: Curran, D. P.; Xu, J.; Lazzarini, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 3049.

(10) (a) Camps, F.; Coll, J.; Llebaria, A.; Moretó, J. M. *Tetrahedron Lett.* **1988**, *29*, 5811. (b) Llebaria, A.; Camps, F.; Moretó, J. M. *Tetrahedron* **1993**, *49*, 1283. (c) Kosugi, M.; Sakaya, T.; Ogawa, S.; Migita, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3058. (d) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4317. (e) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4321.

(11) For one-pot methods, see: (a) Bazin, M.-A.; Jouanne, M.; El-Kashef, H.; Rault, S. *Synlett* **2009**, *17*, 2789. (b) Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Tetrahedron* **2005**, *61*, 4043. (c) Kutsumura, N.; Niwa, K.; Saito, T. *Org. Lett.* **2010**, *12*, 3316.

The products **3**, derived from the radical bromoallylation of allenes, bear internal vinyl bromide moieties, which could undergo a variety of metal-catalyzed reactions.[10,11] Indeed, the cyclocarbonylation reaction of **3b** took place smoothly to give methylene cyclopentanone derivative **4** in 90% yield (Scheme 4).[12] The Suzuki–Miyaura coupling reaction of **3b** with arylboronic acid also proceeded efficiently to yield tetrasubstituted alkene **5** in 93% yield.[13]

In summary, the regioselective radical bromoallylation of allenes **1** with allylbromides **2** proceeded smoothly to lead to 5-bromo-substituted 1,5-dienes **3** in high yields. The introduction of an electron-withdrawing group to the β-position of allylbromides accelerated the addition reaction. These bromine radical-mediated C–C bond forming reactions should have many applications in organic synthesis.

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Supporting Information Available. The experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Negishi, E.; Ma, S.; Amanfu, J.; Copéret, C.; Miller, J. A.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5919.

(13) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437.