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5-((3-BROMOALLYL)SULFONYL)-1*H*-TETRAZOLES FOR BROMODIENE SYNTHESIS[†]

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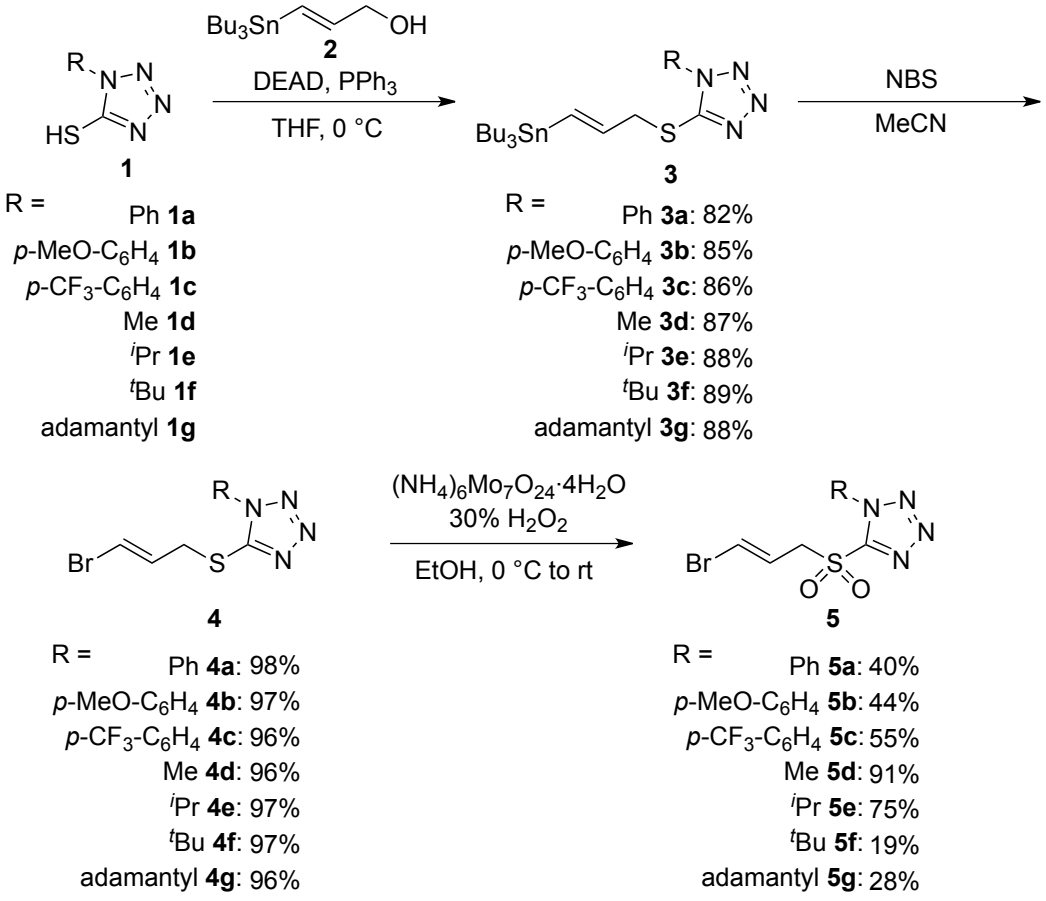
[†] Dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday

Abstract – Reagents for one-step construction of conjugated bromodienes from aldehydes are described. Various 1-alkyl- and 1-aryl-tetrazoyl bromoallylic sulfones were synthesized and evaluated in bromodiene synthesis. 1-Alkyl-tetrazoyl sulfones selectively afforded (1*E*,3*Z*)-bromodienes, while 1-aryl-tetrazoyl sulfones resulted in low selectivity.

Conjugated bromodienes are useful building blocks in organic synthesis.[1] Transition metal-catalyzed cross-coupling reactions with bromodienes provide reliable stereoselective access to conjugated polyenes. In addition, several marine natural products bear a conjugated bromodiene unit.[2] Consequently, various reagents and synthetic protocols to provide bromodienes are reported,[3-10] such as stereoselective reduction/hydrogenolysis of *gem*-dibromoalkenes,[3] bromo-decarboxylation of α,β,γ,δ-unsaturated carboxylic acids,[4] cross-coupling reaction of 1,2-dihaloethylene with alkenylmetal reagents,[5] bromomethylenation of α,β-unsaturated aldehydes,[6] ring-opening reaction of halocyclobutenes,[7] and others.[8-10] These reactions are synthetically useful, but at least two steps are generally required because the carbon elongation process and transformation into bromodienes are often performed separately. For example, Takai olefination followed by cross-coupling,[8] and Seyferth–Gilbert homologation followed by hydrostannylation and NBS treatment,[9] were performed to access bromodienes from aldehydes. In terms of step-economy,[11] a one-step direct introduction of the bromodiene unit starting from aldehydes is ideal, especially when the starting aldehydes are precious intermediates in multi-step synthesis. To address this issue, Yamada and coworkers utilized diethyl 3-bromo-2-propenylphosphonate in their synthesis of

aglycon of aurisides A and B.[12] The reactivity of the Honor–Wadsworth–Emmons reagent, however, was moderate and bromodiene was obtained in low yield. For our ongoing synthetic studies on related marine natural products, we required a new reactive reagent to efficiently provide the bromodiene unit. Here we describe our studies to elucidate the utility of 1-alkyl- and 1-aryl-tetrazoyl bromoallylic sulfones in bromodiene synthesis via Julia olefination. The substituent at the tetrazole ring affected both the *E*/*Z* selectivity and reactivity.

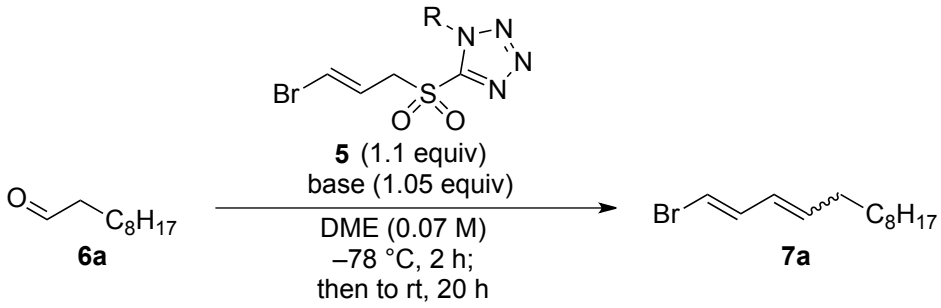
Because tetrazoyl allylic sulfones are reported to be highly reactive Julia reagents for introducing diene units,[13] we envisioned the use of a bromoallylic variant in this study. We first synthesized various 1-aryl- and 1-alkyl-tetrazoyl bromoallylic sulfones to explore substituent effects on the reactivity and selectivity (Scheme 1). Mercaptotetrazoles **1**[14] reacted with alcohol **2** under Mitsunobu conditions[15] to afford stannylsulfide **3** in 82%-89% yield. The tributylstannyl group was almost quantitatively transformed into bromosulfide **4** by treatment with NBS, and oxidation of bromosulfide **4** was accomplished by ammonium molybdate and hydrogen peroxide[16] to give bromoallylic sulfones **5**. Oxidation of **4f** and **4g** with a bulky substituent, either a *t*-butyl or adamantyl group, resulted in low yield, while sterically less hindered **4e** gave bromoallylic sulfone **5e** in 75% yield.



Scheme 1. Synthesis of bromoallylic sulfones

With various bromoallylic sulfones **5** in hand, we compared the reactivity and *E*/*Z* selectivity in a model reaction with decanal (**6a**). 1-Phenyltetrazoyl sulfone **5a** gave bromodiene **7a** in 72% yield with (1*E*,3*E*)/(1*E*,3*Z*) = 52:48 selectivity (Table 1, entry 1). Although Julia-Kocieński olefination using 1-phenyltetrazoyl sulfones without an allylic unit generally affords alkenes with high *E*-stereoselectivity,[17] bromoallylic sulfone **5a** resulted in poor regioselectivity. The observed moderate *E*/*Z* selectivity with 1-aryl-tetrazoyl bromoallylic sulfones is similar to that observed in other allylic sulfones.[13] Aryl-sulfone **5b** and **5c** were used to investigate the electronic effects, but neither **5b** nor **5c** improved the *E*/*Z*-selectivity (entries 2, 3). Trials to improve *E*-selectivity using **5b** failed. For example, the reaction using **5b** in either DMF or DME/HMPA resulted in mixtures of all possible isomers with moderate yield.[18] In contrast to 1-aryl-tetrazoyl sulfones **5a**-**5c**, 1-alkyl-substituted sulfones **5d**-**5g** afforded bromodiene **7a** with good *Z*-selectivity (entries 4-7). Sterically hindered **5f** with a *t*-butyl group and **5g** with an adamantyl group showed perfect *Z*-selectivity (*E*/*Z* = 2:>98), while bromodiene **7a** was obtained in low yield (entry 6, 18%; entry 7, 25%). 1-*i*Pr-tetrazoyl sulfone **5e** exhibited good

Table 1. Optimization of reaction conditions

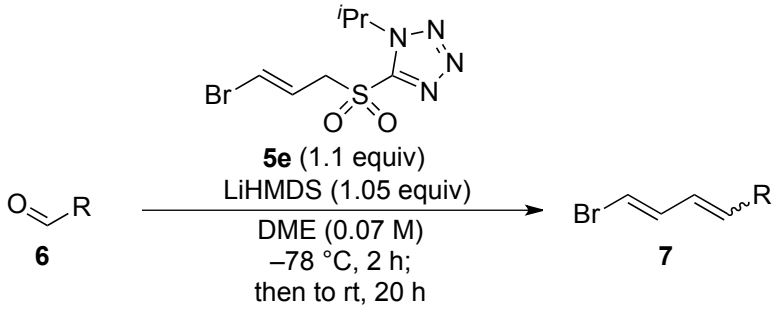


entry	R , **5**	base	% yield[a]	(1*E*,3*E*)/(1*E*,3*Z*)[b]
1	Ph **5a**	LiHMDS	72	52:48
2	*p*-MeO-C_6H_4 **5b**	LiHMDS	78	58:42
3	*p*-CF_3-C_6H_4 **5c**	LiHMDS	71	54:46
4	Me **5d**	LiHMDS	59	11:89
5	^{i}Pr **5e**	LiHMDS	65	6:94
6	^{t}Bu **5f**	LiHMDS	18	2:>98
7	adamantyl **5g**	LiHMDS	25	2:>98
8	^{i}Pr **5e**	NaHMDS	39	17:83
9	^{i}Pr **5e**	KHMDS	5	38:62

[a]Isolated yield. [b]Determined by ^{1}H NMR analysis.

reactivity as well as high *Z*-selectivity (entry 5, 65% yield, *E*/*Z* = 6:94). Other bases, such as NaHMDS and KHMDS, resulted in lower yield and selectivity, and LiHMDS gave the best results (entry 5 vs entries 8 and 9). The observed base effects were different from those of the related allylic sulfones without a bromide unit,[13a,13c] while good *Z*-selectivity using **5e**-**5g** is similar to that in previous studies.[13a] Scope and limitations of aldehydes are summarized in Table 2. In the previous report of Julia olefination using allylic 1-phenyltetrazoyl sulfones without a bromide unit,[13c] α-branched aldehydes furnished conjugated dienes *E*-selectively. With sulfone **5e**, however, moderate *Z*-selectivity was observed with α-branched aldehydes **6c** and **6d**. Aryl aldehyde **6e** also gave bromodiene **7e** with good *Z*-selectivity, albeit in low yield.

Table 2. Substrate scope of aldehydes



entry	aldehyde **6**: R		% yield of **7**[a]	(1*E*,3*E*)/(1*E*,3*Z*)[b]
1	**6a**	C_8H_{17}	**7a** 65	6:94
2	**6b**	Ph	**7b** 57	6:94
3	**6c**		**7c** 77	16:84
4	**6d**		**7d** 39	21:79
5	**6e**	Cl	**7e** 25	7:93

[a]Isolated yield. [b]Determined by ^{1}H NMR analysis.

In summary, we synthesized a series of 1-alkyl- and 1-aryl-tetrazoyl bromoallylic sulfones and evaluated their *E*/*Z*-selectivity and reactivity. While 1-aryl-tetrazoyl sulfones gave bromodiene with modest *E*/*Z*-selectivity, 1-alkyl-tetrazoyl bromoallylic sulfones selectively provided (1*E*,3*Z*)-bromodienes.

Tuning of steric bulkiness was important, and 1-*i*Pr-tetrazoyl sulfone exhibited good reactivity as well as high *Z*-selectivity. The reagent would be useful for the synthesis of natural products bearing the (1*E*,3*Z*)-bromodiene unit.[2a,2f] Application of these reagents in a total synthesis is ongoing and will be reported in due course.

EXPERIMENTAL

General. Melting points were determined on a Yamato melting point apparatus model MP-21 and were uncorrected. Infrared (IR) spectra were recorded on JASCO FT/IR-5300 spectrophotometer and absorbance bands are reported in wavenumber (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra and fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on JEOL JNM-ECP 400 (400 MHz), JEOL JNM-ECS 400 (400 MHz), JEOL JNM-ECX 400P (400 MHz), JEOL JNM-ECA 500 (500 MHz) spectrometers with tetramethylsilane in $CDCl_3$ (δ_H 0.00), hexafluorobenzene in $CDCl_3$ (δ_F –164.9), chloroform-d_1 (δ_H 7.26, δ_C 77.0) or DMSO-d_6 (δ_H 2.50, δ_C 39.5) as an internal standard. Coupling constants (*J*) are reported in hertz (Hz). Abbreviations of multiplicity are as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sext, sextet; sept, septet; m, multiplet; br, broad. Data are presented as follows: chemical shift, multiplicity, coupling constants, integration and assignment. ESI (electrospray ionization) mass spectra were measured with Thermo Scientific Exactive spectrometer and EI (electro ionization) mass spectra were measured with JNM-T100GCV spectrometer. Flash column chromatography was carried out on Kanto silica gel 60 N (40–50 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates. Visualization was accomplished with ultraviolet light and anisaldehyde, followed by heating. Reagents and solvents were purified by standard means or used as received unless otherwise noted. The numbering of bromodienes is assigned from terminal brominated carbon atom.

General Procedure for Julia Olefination

To a stirred solution of isopropylsulfone **5e** (0.33 mmol) in DME (1.3 mL) was added LiHMDS (0.315 mL, 0.315 mmol, 1.0 M THF solution) at –78 °C (dry ice/acetone bath). After stirring for 5 min, aldehyde **6** (0.30 mmol) in DME (1.5 mL) was added to the solution dropwisely and rinsed 2 times with DME (1.0 mL, 0.5 mL). The whole mixture was stirred at this temperature for 2 h, and then warmed to room temperature gradually by removing dry ice and stirred for 20 h. The reaction mixture was quenched with H_2O (2 mL) and the whole mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished crude product, which was purified by flash column chromatography (silica gel, eluent: hexane only) to afford bromodiene.

(1*E*,3*Z*)-1-Bromotrideca-1,3-diene (7a)

18–78% yield ((1*E*,3*E*)/(1*E*,3*Z*) = 52:48–2:>98). Colorless oil; R_f 0.77 (hexane only); IR (neat) 2925, 1574, 1465, 929, 799 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3H, $CH_2CH_2CH_3$), 1.27 (m, 12H, twelve of $CHCH_2(CH_2)_7CH_3$), 1.35–1.41 (m, 2H, two of $CHCH_2(CH_2)_7CH_3$), 2.13 (td, *J* = 7.5, 1.2 Hz, 2H, $CHCH_2CH_2$), 5.49 (dt, *J* = 10.9, 7.5 Hz, 1H, $CHCHCH_2$), 5.90 (dd, *J* = 11.2, 10.9 Hz, 1H, $CHCHCHCH_2$), 6.27 (d, *J* = 13.8 Hz, 1H, $BrCHCH$), 6.99 (ddd, *J* = 13.8, 11.2, 1.2 Hz, 1H, $BrCHCHCH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 27.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 108.6 (CH), 125.6 (CH), 133.2 (CH), 133.9 (CH); EI-HRMS *m*/*z* calcd for $C_{13}H_{23}Br$ $(M)^+$ 258.09831, found 258.09938. ^{1}H NMR and ^{13}C NMR spectra of pure (1*E*,3*Z*)-isomer obtained from the reaction with adamantyl sulfone **5g** are provided in Supporting Information.

((1*E*,3*Z*)-1-Bromohexa-1,3-dien-6-yl)benzene (7b)

57% yield ((1*E*,3*E*)/(1*E*,3*Z*) = 6:94). Colorless oil; R_f 0.38 (hexane only); IR (neat) 3062, 3042, 2925, 2856, 1573, 1496, 1453, 929, 800, 745, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (dtd, *J* = 7.6, 7.4, 1.2 Hz, 2H, $CHCH_2CH_2Ar$), 2.72 (t, *J* = 7.4 Hz, 2H, CH_2CH_2Ar), 5.53 (dt, *J* = 10.8, 7.6 Hz, 0.94H, $CHCHCH_2$ of (1*E*,3*Z*)-isomer), 5.77 (dt, *J* = 15.1, 7.0 Hz, 0.06H, $CHCHCH_2$ of (1*E*,3*E*)-isomer), 5.90–6.03 (m, 1H, $CHCHCHCH_2$), 6.20 (d, *J* = 13.4 Hz, 0.06H, $BrCHCHCH$ of (1*E*,3*E*)-isomer), 6.23 (d, *J* = 13.4 Hz, 0.94H, $BrCHCHCH$ of (1*E*,3*Z*)-isomer), 6.68 (dd, *J* = 13.4, 10.6 Hz, 0.06H, $BrCHCHCH$ of (1*E*,3*E*)-isomer), 6.95 (ddd, *J* = 13.4, 11.6, 1.2 Hz, 0.94H, $BrCHCHCH$ of (1*E*,3*Z*)-isomer); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.6 (CH_2 of (1*E*,3*Z*)-isomer), 34.3 (CH_2 of (1*E*,3*E*)-isomer), 35.3 (CH_2 of (1*E*,3*E*)-isomer), 35.5 (CH_2 of (1*E*,3*Z*)-isomer), 106.6 (CH of (1*E*,3*E*)-isomer), 109.2 (CH of (1*E*,3*Z*)-isomer), 125.9 (CH of (1*E*,3*E*)-isomer), 126.0 (CH of (1*E*,3*E*)-isomer), 126.3 (CH of (1*E*,3*Z*)-isomer), 128.1 (CH of (1*E*,3*E*)-isomer), 128.3 (CH of (1*E*,3*Z*)-isomer), 128.4 (CH of (1*E*,3*Z*)-isomer), 128.6 (CH of (1*E*,3*E*)-isomer), 132.2 (CH of (1*E*,3*Z*)-isomer), 132.9 (CH of (1*E*,3*Z*)-isomer), 135.1 (CH of (1*E*,3*E*)-isomer), 137.5 (CH of (1*E*,3*E*)-isomer), 141.2 (C of (1*E*,3*Z*)-isomer), 141.3 (C of (1*E*,3*E*)-isomer); EI-HRMS *m*/*z* calcd for $C_{12}H_{13}Br$ $(M)^+$ 236.02006, found 236.01997.

((1*E*,3*Z*)-1-Bromobuta-1,3-dien-4-yl)cyclohexane (7c)

77% yield ((1*E*,3*E*)/(1*E*,3*Z*) = 16:84). Colorless oil; R_f 0.76 (hexane only); IR (neat) 2925, 2849, 1574, 1447, 930, 801, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05–1.13 (m, 2H, one of C2'-CH_2 and one of C6'-CH_2), 1.15–1.22 (m, 1H, one of C4'-CH_2), 1.27–1.35 (m, 3H, one of C3'-CH_2, one of C4'-CH_2 and one of C5'-CH_2), 1.62–1.75 (m, 4H, one of C2'-CH_2, one of C3'-CH_2, one of C5'-CH_2 and one of C6'-CH_2),

1.95–2.01 (m, 0.16H, C1'-C*H* of (1*E*,3*E*)-isomer), 2.34–2.42 (m, 0.84H, C1'-C*H* of (1*E*,3*Z*)-isomer), 5.34 (dd, *J* = 10.9, 10.3 Hz, 0.84H, CHC*H*Cy of (1*E*,3*Z*)-isomer), 5.68 (dd, *J* = 15.5, 6.9 Hz, 0.16H, CHC*H*Cy of (1*E*,3*E*)-isomer), 5.80 (dd, *J* = 11.8, 10.9 Hz, 0.84H, CHC*H*CHCy of (1*E*,3*Z*)-isomer), 5.92 (dd, *J* = 15.5, 10.9 Hz, 0.16H, CHC*H*CHCy of (1*E*,3*E*)-isomer), 6.18 (d, *J* = 13.5 Hz, 0.16H, BrC*H*CH of (1*E*,3*E*)-isomer), 6.27 (d, *J* = 12.6 Hz, 0.84H, BrC*H*CH of (1*E*,3*Z*)-isomer), 6.66 (dd, *J* = 13.5, 10.9 Hz, 0.16H, BrCHC*H*CH of (1*E*,3*E*)-isomer), 7.00 (dd, *J* = 12.6, 11.8 Hz, 0.84H, BrCHC*H*CH of (1*E*,3*Z*)-isomer); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.7 (CH_2), 25.8 (CH_2), 26.0 (CH_2 of (1*E*,3*E*)-isomer), 32.5 (CH_2 of (1*E*,3*E*)-isomer), 33.0 (CH_2 of (1*E*,3*Z*)-isomer), 37.0 (CH of (1*E*,3*Z*)-isomer), 40.7 (CH of (1*E*,3*E*)-isomer), 106.0 (CH of (1*E*,3*E*)-isomer), 108.5 (CH of (1*E*,3*Z*)-isomer), 123.8 (CH of (1*E*,3*Z*)-isomer), 125.0 (CH of (1*E*,3*E*)-isomer), 133.4 (CH of (1*E*,3*Z*)-isomer), 137.7 (CH of (1*E*,3*E*)-isomer), 139.5 (CH of (1*E*,3*Z*)-isomer), 142.1 (CH of (1*E*,3*E*)-isomer); EI-HRMS *m*/*z* calcd for $C_{10}H_{15}Br$ $(M)^+$ 214.03571, found 214.03490.

(1*E*,3*Z*)-1-Bromo-5,5-dimethylhexa-1,3-diene (7d)

39% yield ((1*E*,3*E*)/(1*E*,3*Z*) = 21:79). Colorless oil; R_f 0.74 (hexane only); IR (neat) 2959, 2927, 1363, 1211, 980, 929, 770 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 1.9H, C(CH_3)$_3$ of (1*E*,3*E*)-isomer), 1.21 (s, 7.1H, C(CH_3)$_3$ of (1*E*,3*Z*)-isomer), 5.48 (d, *J* = 12.0 Hz, 0.79H, CHC*H*C of (1*E*,3*Z*)-isomer), 5.75–5.81 (m, 1H, CHC*H*CHC of (1*E*,3*Z*)-isomer and CHC*H*C of (1*E*,3*E*)-isomer), 5.93 (dd, *J* = 15.5, 10.3 Hz, 0.21H, CHC*H*CHC of (1*E*,3*E*)-isomer), 6.23–6.28 (m, 1H, BrC*H*CH), 6.71 (dd, *J* = 13.2, 10.3 Hz, 0.21H, BrCHC*H*CH of (1*E*,3*E*)-isomer), 7.27 (ddd, *J* = 13.2, 12.0, 1.2 Hz, 0.79H, BrCHC*H*CH of (1*E*,3*Z*)-isomer); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.2 (CH_3 of (1*E*,3*E*)-isomer), 31.3 (CH_3 of (1*E*,3*Z*)-isomer), 106.0 (CH of (1*E*,3*E*)-isomer), 109.2 (CH of (1*E*,3*Z*)-isomer), 122.6 (CH of (1*E*,3*E*)-isomer), 123.8 (CH of (1*E*,3*Z*)-isomer), 133.4 (CH of (1*E*,3*Z*)-isomer), 138.0 (CH of (1*E*,3*E*)-isomer), 142.9 (CH of (1*E*,3*Z*)-isomer), 147.2 (CH of (1*E*,3*E*)-isomer); EI-HRMS *m*/*z* calcd for $C_8H_{13}Br$ $(M)^+$ 188.02006, found 188.01924.

1-((1*E*,3*Z*)-1-Bromobuta-1,3-dien-4-yl)-4-chlorobenzene (7e)

25% yield ((1*E*,3*E*)/(1*E*,3*Z*) = 7:93). Colorless oil; R_f 0.53 (hexane only); IR (neat) 1490, 1093, 934, 848, 798 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (dd, *J* = 11.5, 11.5 Hz, 0.93H, CHC*H*CHAr of (1*E*,3*Z*)-isomer), 6.25–6.47 (m, 1H, CHC*H*Ar), 6.51–6.54 (m, 1H, BrC*H*CH), 6.64 (dd, *J* = 15.5, 10.9 Hz, 0.07H, CHC*H*CHAr of (1*E*,3*E*)-isomer), 6.86 (dd, *J* = 13.2, 10.9 Hz, 0.07H, BrCHC*H*CH of (1*E*,3*E*)-isomer), 7.14 (ddd, *J* = 13.7, 12.0, 1.2 Hz, 0.93H, BrCHC*H*CH of (1*E*,3*Z*)-isomer), 7.21–7.24 (m, 2H, Ar*H*), 7.90–7.35 (m, 2H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 109.6 (CH of (1*E*,3*E*)-isomer), 112.4

(CH of (1*E*,3*Z*)-isomer), 126.6 (CH of (1*E*,3*E*)-isomer), 127.5 (CH of (1*E*,3*Z*)-isomer), 127.6 (CH of (1*E*,3*E*)-isomer), 128.6 (CH of (1*E*,3*Z*)-isomer), 128.9 (CH of (1*E*,3*E*)-isomer), 129.5 (CH of (1*E*,3*Z*)-isomer), 130.1 (CH of (1*E*,3*Z*)-isomer), 131.9 (CH of (1*E*,3*Z*)-isomer), 133.3 (C of (1*E*,3*Z*)-isomer), 133.5 (CH of (1*E*,3*Z*)-isomer), 135.1 (CH of (1*E*,3*Z*)-isomer), 137.4 (C of (1*E*,3*E*)-isomer); EI-HRMS *m/z* calcd for $C_{10}H_8BrCl$ $(M)^+$ 241.94979, found 241.94923.

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