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Intermolecular Diels–Alder Cycloaddition/Cross-Coupling Sequences of 2-Bromo-1,3-butadienes

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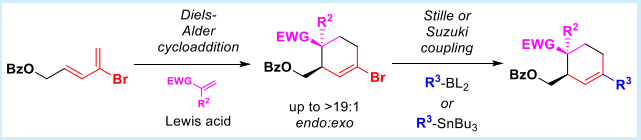
ABSTRACT: 2-Bromo-1,3-butadienes are demonstrated to be effective substrates for tandem Diels–Alder/transition metal cross-coupling reaction sequences. Intermolecular cycloaddition of a 2-bromo-1,3-diene with activated dienophiles proceeded under Lewis acid catalysis in generally high yields with good to excellent *endo* diastereoselectivity. The resulting vinyl bromide cycloadducts underwent subsequent Stille and Suzuki cross-couplings under standard conditions in good yields. Both the Diels–Alder and cross-coupling steps were highly tolerant of a range of functionalities and protecting groups. The use of the bromine substituent as both a cycloaddition directing group and cross-coupling nucleofuge avoids extra steps required to install and remove the more commonly used silyl enol ethers and enol sulfonates for each transformation and gives full control of the alkene regiochemistry throughout the reaction sequence. The 2-bromo-1,3-dienes were conveniently prepared in three steps from readily available aldehydes and established as hydrolytically stable and practical synthetic intermediates.



Diels–Alder cycloaddition[1] is a powerful synthetic tool for the stereoselective construction of complex structures.[2] Despite this utility, it is less employed in applied fields such as medicinal chemistry than the high stereocontrol and increase in molecular complexity might suggest.[3] This may be due to the variables involved, including reaction component selection, orbital electronics, catalyst, and potential for later transformations. As a result, identification of cycloaddition partners demonstrating predictable and reliable reactivity remains an ongoing challenge. Additionally, Diels–Alder strategies incorporating a second reliable synthetic step in a tandem sequence are an area of current interest,[4] especially for access to complex and diverse molecular scaffolds to drive drug discovery.[5] Transition-metal-catalyzed cross-couplings have emerged as suitable partners for these sequences in tandem with the Diels–Alder reaction. The challenge in their synthetic application involves identification of suitable diene substituents that satisfy the reactivity and regioselectivity requirements for both the cycloaddition and cross-coupling steps (Scheme 1). A number of 2-substituted 1,3-butadiene systems have been investigated for their utility in tandem Diels–Alder/cross-coupling sequences, most notably including preparatively useful examples based on boron[6,7] and silicon[8,9] and some less-investigated examples such as iodonium salts and organoindium species.[10] The 2-substituted 1,3-butadiene substrate class are of particular importance as they enable full control of the alkene position through the tandem sequence without the additional steps or alkene regioisomers potentially encountered with the use of more activated dienes (e.g., 2-silyloxy-1,3-butadienes) that involve the intermediacy of a ketone and subsequent conversion to an enol sulfonate cross-coupling partner.

In principle, 2-halogenated 1,3-butadienes are viable substrates for tandem Diels–Alder/cross-coupling sequences; vinyl halides are standard substrates for transition-metal-catalyzed cross-coupling, and some Diels–Alder reactions of halogenated dienes are known. The latter include examples involving 2-chloro-1,3-butadienes[11] or chloro- or iodo-substituted heterocyclic dienes.[12] Cycloadditions of brominated 1,3-butadienes are more widely reported, often in the context of brominated heterocyclic dienes[13] or the intramolecular Diels–Alder (IMDA) reactions of brominated trienes toward natural product frameworks.[14] In some cases the bromine substituent plays a pivotal role in directing the cycloaddition stereoselectivity.[14f,15a] *Inter*molecular examples of Diels–Alder reactions of linear 2- or 3-bromo-1,3-butadienes appear to be very rare in the literature (Scheme 1A).[15] Furthermore, to our knowledge only one example of a 2-bromo-1,3-butadiene Diels–Alder/cross-coupling sequence has been reported, and this example involved a heterocyclic diene rather than a linear diene (Scheme 1B).[16] In the course of our own studies, it appeared that a tandem Diels–Alder/cross-coupling sequence would advantageously simplify the approach required for the synthesis of several natural product

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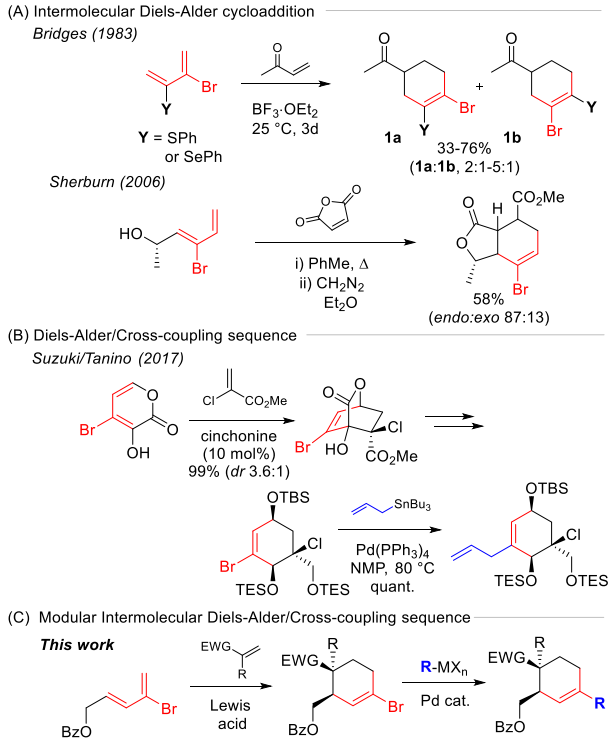
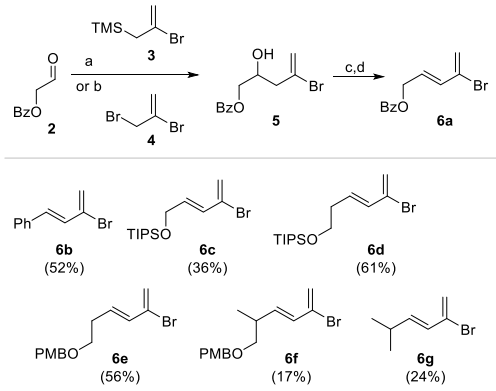
Scheme 1. 2-Bromodienes: Cycloaddition/Cross-Coupling



frameworks. Although the use of 2-substituted butadiene systems based on boron or silicon had merit, their stability toward standard transformations, including aqueous base, was uncertain. After consideration of the above literature, we were encouraged to investigate 2-bromo-1,3-butadiene systems (Scheme 1C). A variety of methods have been employed for the preparation of 2- and 3-bromo-1,3-butadienes, including Wittig olefination of α-bromoaldehydes,[17] vinyl halide formation from α,β-unsaturated ketones,[18] ring opening of dibromocyclopropanes,[19] Suzuki coupling of dibromoalkenes prepared via Corey–Fuchs-type sequences,[14f] and bromination/rearrangement of *N*-allylhydrazones.[20] Approaches based on halogenation–elimination of α-allenic systems (boronic esters,[21] alcohols,[22] and acetates[23]) have also been reported. In our view, however, none of these methods appeared to be optimal for a robust modular approach.

Identification of a general route to 2-bromo-1,3-butadienes began with Lewis acid-catalyzed addition of bromoallylsilane **3**[24] to aldehyde **2**,[25] affording homoallylic alcohol **5** in high yield (Scheme 2). Alcohol **5** was also available via addition of significantly less expensive 2,3-dibromopropene (**4**)[26] to aldehyde **2** using the tin-mediated method described by Otera,[27] which proved to be reliable on a multigram scale. Mesylation/elimination proceeded readily to give bromodiene **6a** in excellent yield exclusively as the *E* isomer (J = 14.7 Hz). Diene **6a** was stable toward long-term storage at 4 °C as a 0.2 M solution in dichloromethane, although some polymerization of the isolated compound was observed upon storage without solvent. To demonstrate that the chemistry was generally applicable for the synthesis of 2-bromo-1,3-butadienes, additional compounds **6b–g** were prepared, including those with OTIPS (**6c**, **6d**) and OPMB (**6e**, **6f**) groups and the Roche ester-derived diene **6f**. All of these compounds proved similarly stable as **6a**, with the exception of **6b**, which was observed to decompose upon isolation as previously reported.[18] Diene **6a**

Scheme 2. Synthesis of 2-Bromo-1,3-butadienes 6a–g[a]



[a]Reagents and conditions: (a) $TiCl_4$, **3**, CH_2Cl_2, −78 °C, 10 h, 84%; (b) **4**, Sn, HBr, Et_2O/H_2O (1:1), rt, 3 h, 79%; (c) MsCl, Et_3N, DMAP, CH_2Cl_2, 3 h; (d) DBU, PhMe, 75 °C, 3 h, 97% (over two steps). Yields for **6b–g** over two steps from the corresponding aldehydes are shown. See the Supporting Information for details.

was then taken forward to probe the feasibility of the cycloaddition.

Initial attempts to effect the Diels–Alder reaction of bromodiene **6a** and acrolein in the presence of boron trifluoride etherate or copper(II) triflate in dichloromethane gave no reaction (Scheme 3). In contrast, the use of tin tetrachloride gave the separable cycloaddition adducts *cis/endo*-**7a** and *trans/exo*-**7b** in 78% yield (*dr* 2:1). The major product was assigned as *cis/endo* on the basis of a NOESY correlation between the indicated *cis* ring protons in **7a** that was not observed in the *trans/exo* isomer **7b**. A series of related dienophiles including methacrolein, methyl acrylate, methyl vinyl ketone, and acrylonitrile were also found to afford the corresponding cycloadducts **8–11** in good yields. Boron trifluoride etherate proved to be the most generally effective Lewis acid for the transformation, although the diastereoselectivity, reaction conditions, and reaction times varied slightly according to the substrates (see the Supporting Information for additional details). In general, the *cis/endo* isomers were observed to predominate, although the relative amount of the thermodynamically favored *trans/exo* isomer[28] formed was found to increase significantly at higher reaction temperatures. Additional reactions of 2-bromodiene **6a** with the dienophile generated in situ from Meldrum's acid and formaldehyde or with benzoquinone also delivered the corresponding cycloadducts **12** and **13** in high yields.

Further structural confirmation of the cycloadduct relative stereochemistry was obtained from an X-ray structure of *cis/endo* isomer **11**. In addition, benzoyl deprotection of cycloadduct **9** (*dr* 1.3:1) delivered separable cyclized *cis/endo* lactone **14** and noncyclized *trans/exo* alcohol **15** in 37% and 31% yield, respectively (Scheme 4). Diels–Alder reaction of 5-hydroxy-2-bromo-1,3-diene **16** and methyl acrylate directly afforded a mixture of the same products, *endo*-lactone **14** (84%) and *exo*-alcohol **15** (10%) (*dr* 8.4:1), in nearly quantitative combined yield.

All of the cycloadditions were found to proceed with complete selectivity for a single regioisomer. Inspection of a representation of the calculated HOMO for 2-bromodiene **6a** (Scheme 5) revealed a larger orbital coefficient localized on C1 of the diene π system.[29] Interestingly, the presence of the

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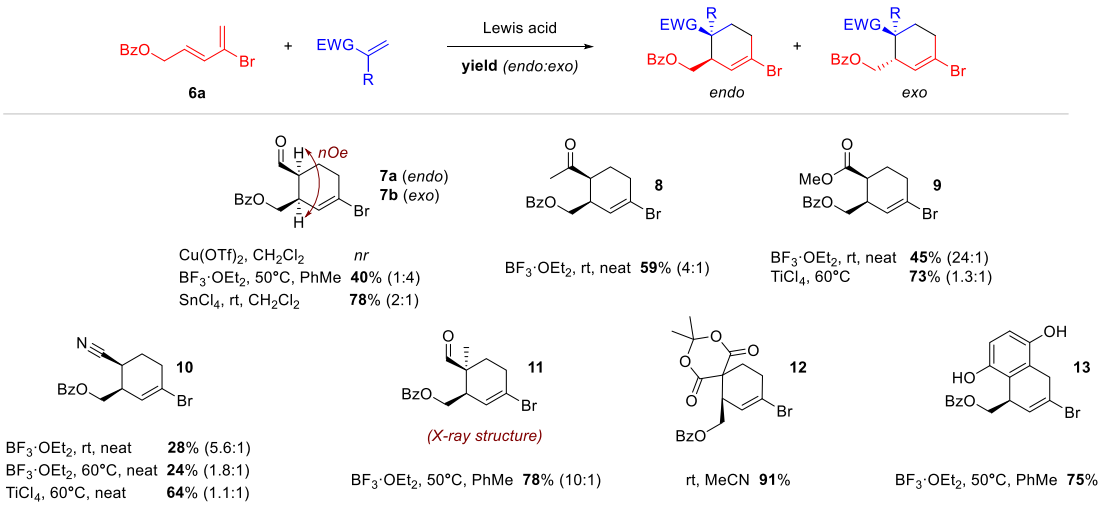
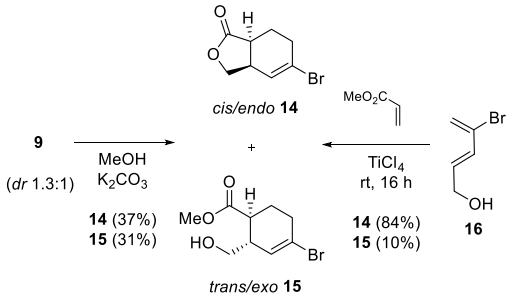
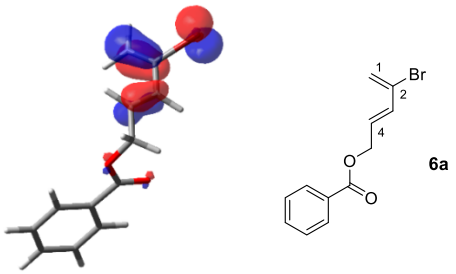
Scheme 3. Diels–Alder Cycloadditions of 2-Bromo-1,3-butadiene 6a



Scheme 4. Direct Lactonization to *cis*/*endo*-14



Scheme 5. Representation of the HOMO of 2-Bromodiene 6a

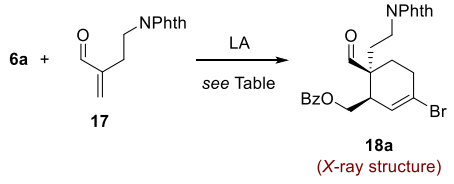


bromine substituent appears to twist the diene slightly out of coplanarity.

To further probe the scope of the 2-bromobutadiene Diels–Alder cycloaddition, the reaction of **6a** and *N*-phthalimido enal **17**[30] was also investigated (Table 1). This system has potential utility for the synthesis of natural product frameworks, including the pro-apoptotic and HIV-1-active spirocyclic imine algal metabolite portimine.[31] In this case, although the use of boron trifluoride etherate afforded the *endo* cycloadduct **18a** in moderate yield with reasonable stereoselectivity, titanium tetrachloride proved to be more successful, giving **18a** in high yield as essentially a single diastereoisomer after a brief optimization. The *endo* relative stereochemistry of **18a** was unambiguously confirmed by X-ray crystallography.

With 2-bromobutadiene systems established as useful substrates for regio- and stereoselective intermolecular Diels–Alder reactions, the ability of the resulting cycloadducts

Table 1. Diels–Alder Cycloaddition of 2-Bromodiene 6a and *N*-Phthalimido Enal 17



entry	LA	temp. (°C)	solvent	time (h)	*dr*[a]	yield (%)
1	$BF_3{\cdot}OEt_2$	−78	CH_2Cl_2	3	n.d.	trace
2	$BF_3{\cdot}OEt_2$	0	CH_2Cl_2	3	10:1	42
3	$BF_3{\cdot}OEt_2$	50	PhMe	3	5:1	47
4	**$TiCl_4$**	**−78**	**CH_2Cl_2**	**18**	**≥19:1**	**81**
5	**$TiCl_4$**	**0**	**CH_2Cl_2**	**18**	**≥19:1**	**88**
6	$TiCl_4$	50	PhMe	10	5:1	67

[a]*endo*:*exo*; n.d. = not determined.

to undergo transition-metal-catalyzed cross-coupling was next confirmed (Scheme 6, top). As expected, cyclohexenyl bromide **11a** was smoothly transformed into the expected vinyl derivative **19** under standard Stille coupling conditions in 86% yield. The Suzuki coupling of **7a** with phenylboronic acid also proceeded uneventfully, affording **20** in good yield without loss of stereochemical integrity.

The synthetic utility of the vinyl bromide handle for elaboration of complex natural product intermediates was exemplified by further transformations of the *N*-phthalimido cycloadduct **18a** (Scheme 6, bottom). Deprotection of the amine group with hydrazine hydrate led to the direct formation of spirocyclic aldimine **21**, which then underwent subsequent Stille coupling with either vinyl- or allyltributylstannane to afford olefins **22** and **23** in 53% and 59% yield, respectively. Alternatively, conversion of the aldehyde function of *N*-phthalimido cycloadduct **18a** to give the corresponding alkyne **24** using the Seyferth–Gilbert reagent (**25**) could also be carried out in excellent yield. Uneventful removal of the *N*-phthalimide protecting group was then followed by gold-catalyzed intramolecular hydroamination[32] to give spirocyclic ketimine **26**. Finally, Stille coupling again proceeded readily under standard conditions to install the exocyclic vinyl group of **27**. These synthetic sequences illustrate the compatibility of

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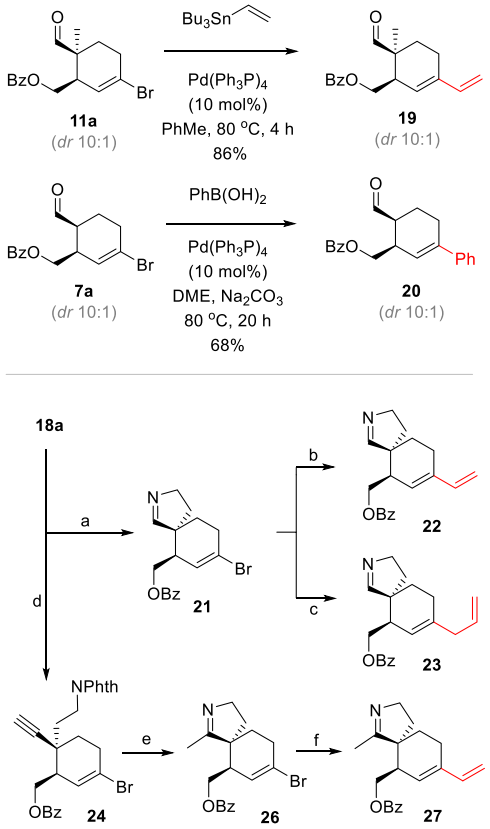
Scheme 6. Elaboration and Cross-Coupling of Diels–Alder Cycloadducts[a]



[a]Reagents and conditions: (a) $H_2NNH_2{\cdot}H_2O$, MeOH, reflux, 2 h, 56%; (b) vinyltributylstannane, $Pd_2(dba)_3$, CsF, $[tBu_3PH]BF_4$, DMF, 100 °C, 18 h, 53%; (c) allyltributylstannane, $Pd_2(dba)_3$, CsF, $[tBu_3PH]BF_4$, DMF, 100 °C, 18 h, 59%; (d) dimethyl (diazomethyl)-phosphonate (**25**), NaHMDS, THF, −78 °C, 0.5 h, 87%; (e) (i) $H_2NNH_2{\cdot}H_2O$, MeOH, reflux, 2 h; (ii) $Au(PPh_3)Cl$, $AgSbF_6$, Et_3N, MeCN, 95 °C, 0.5 h, 86% over two steps; (f) vinyltributylstannane, $Pd_2(dba)_3$, CsF, $[tBu_3PH]BF_4$, DMF, 100 °C, 18 h, 68%.

the vinyl bromide cycloadducts with a wide range of reaction conditions and the tolerance of the cross-coupling step for a diverse selection of sensitive functionalities, including ester, aldehyde, and imine groups.

In summary, 2-bromo-1,3-butadiene systems have been demonstrated to be highly effective substrates for tandem Diels–Alder/cross-coupling reaction sequences. Intermolecular cycloaddition of 2-bromodienes with a variety of activated dienophiles was shown to proceed in generally high yields with good to excellent *endo* diastereoselectivity. The resulting vinyl bromide cycloadducts readily underwent subsequent Stille and Suzuki cross-couplings under standard conditions. Importantly, both the Diels–Alder and cross-coupling steps were highly tolerant of a range of functionalities and protecting groups, which should enable the application of this methodology in diverse synthetic contexts. The use of the bromine substituent as both a directing group for cycloaddition and a nucleofuge for cross-coupling avoids extra steps required to install more commonly used silyl enol ethers and enol sulfonates for each transformation and gives full control of the alkene regiochemistry throughout the reaction sequence. The 2-bromo-1,3-dienes themselves were conveniently prepared in three steps from readily available aldehydes and established as hydrolytically stable and practical synthetic intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04567.

Experimental procedures, characterization data, and NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1972112 and 1972898 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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