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# Modular Synthesis of *N*-Vinyl Benzotriazoles

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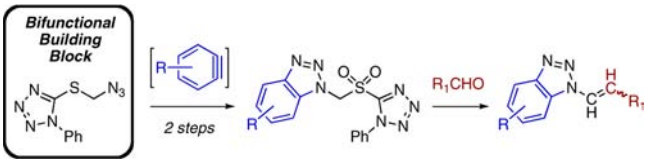
## ABSTRACT




**A modular approach to *N*1-vinyl benzotriazoles by azide–aryne cycloadditions and Julia–Kocienski reactions is described. Reactions of azidomethyl phenyl-1*H*-tetrazol-5-yl (PT) sulfide with arynes gave methyl(PT-sulfanyl)-substituted benzotriazoles in 68–89% yields. Oxidation of the sulfides to the sulfones gave the benzotriazole-substituted Julia–Kocienski reagents. Olefination reactions of aldehydes and a ketone with reagents derived from benzyne, 2,3-naphthyne, and 4,5-dimethoxybenzyne precursors proceeded to give various *N*1-vinyl benzotriazole derivatives. Olefination stereoselectivities are tunable for electron-rich aldehydes, but not for electron-deficient aldehydes and alkanals, where they proceed with good to excellent *Z*-stereoselectivity.**

Benzotriazole derivatives are versatile synthetic intermediates that can undergo multiple transformations.[1] Several benzotriazole derivatives were also found to possess biological activity, such as Vorozole that was in clinical testing as an antineoplastic agent.[2a] Other examples include tubulin inhibitors[2b] and compounds with antitubercular,[2c] antimicrobial,[2d] antiproliferative,[2e] and anti-inflammatory[2f] activities (Figure 1).

In light of the high pharmacological importance as well as synthetic utilities of benzotriazoles, we became interested in delineating a highly modular approach to *N*-vinyl benzotriazoles.

Current approaches to *N*-vinyl benzotriazoles are based on reactions of benzotriazole or benzotriazole derivatives, for example, addition of 1-chlorobenzotriazole to alkenes, followed by elimination,[3a,b] or *N*-alkylation of benzotriazole with chloroethanol, followed by bromination and elimination.[4] However, alkylation reactions of benzotriazoles tend to form *N*1 and *N*2 regioisomers.

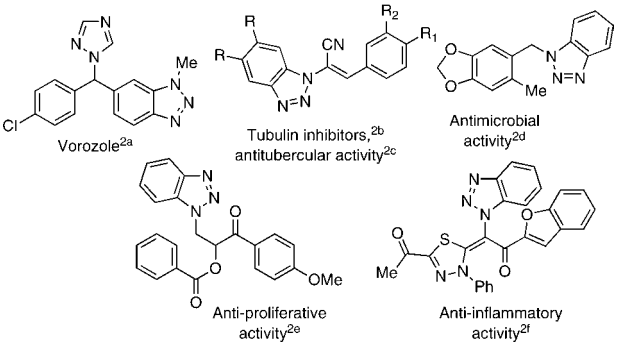



**Figure 1.** Biologically active benzotriazole derivatives.

(1) (a) Katritzky, A. R.; Lan, X. *Chem. Soc. Rev.* **1994**, *23*, 363–373. (b) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409–548. (c) Katritzky, A. R.; Rogovoy, B. V. *Chem.—Eur. J.* **2003**, *9*, 4586–4593. (d) Katritzky, A. R.; Manju, K.; Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, *61*, 2555–2581. (e) Kale, R. R.; Prasad, V.; Mohapatra, P. P.; Tiwari, V. K. *Monatsh. Chem.* **2010**, *141*, 1159–1182.

(2) (a) Goss, P. E. *Breast Cancer Res. Treat.* **1998**, *49*, S59–S69. (b) Carta, A.; Briguglio, I.; Piras, S.; Boatto, G.; La Colla, P.; Loddo, R.; Tolomeo, M.; Grimaudo, S.; Di Cristina, A.; Pipitone, R. M.; Laurini, E.; Paneni, M. S.; Posocco, P.; Fermeglia, M.; Pricl, S. *Eur. J. Med. Chem.* **2011**, *46*, 4151–4167. (c) Sanna, P.; Carta, A.; Nikookar, M. E. R. *Eur. J. Med. Chem.* **2000**, *35*, 535–543. (d) Swamy, S. N.; Basappa; Sarala, G.; Priya, B. S.; Gaonkar, S. L.; Prasad, J. S.; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 999–1004. (e) Zhang, S.-S.; Zhang, H.-Q.; Li, D.; Sun, L.-H.; Ma, C.-P.; Wang, W.; Wan, J.; Qu, B. *Eur. J. Pharmacol.* **2008**, *584*, 144–152. (f) Dawood, K. M.; Abdel-Gawad, H.; Rageb, E. A.; Ellithey, M.; Mohamed, H. A. *Bioorg. Med. Chem.* **2006**, *14*, 3672–3680.

(3) (a) Rees, C. W.; Storr, R. C. *J. Chem. Soc. (C)* **1969**, 1478–1483. (b) Wender, P. A.; Cooper, C. B. *Tetrahedron* **1986**, *42*, 2985–2991.

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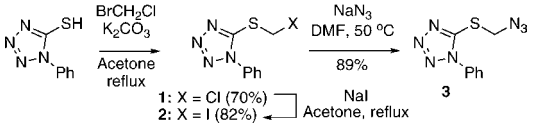
More recent examples involve synthesis of Wittig reagents from 1-(1-chloroalkyl)benzotriazoles followed by olefination,[5a] the Horner–Wadsworth–Emmons approach via diethyl-(1-benzotriazolmethyl)phosphonate,[5b] and a Peterson reaction via desilylative-olefination of 1-[1,1-bis(trimethylsilyl)alkyl]benzotriazoles.[5a,c] Among these various methods, only *a single example* involving the olefination of an enolizable alkanal has been reported in a low 30% yield.[5a]

Alternatively, *N*1-(1-substituted-ethenyl) benzotriazoles were synthesized from *N*1-ethenyl benzotriazole via metalation, followed by reaction with an electrophile.[6] An example of Cu-catalyzed reaction of (*E*)-*β*-bromostyrene with benzotriazole has been reported as well, giving an *E*-olefin, but a mixture of *N*1 (major) and *N*2 regioisomers was formed.[7]

To date, there is no approach to *N*-vinyl benzotriazoles, wherein both the benzotriazole unit as well as the vinyl substituents can be varied in a facile manner. An uncatalyzed azide–aryne [3 + 2] cycloaddition[8] offers efficient access to benzotriazoles, with variable aryl and *N*-substituents. Herein, we report a new and highly modular approach to *N*-vinyl benzotriazoles. Notably, this involves development of a novel bifunctionalizable building block, containing both a Julia–Kocienski[9,10] olefination handle and an azide moiety.

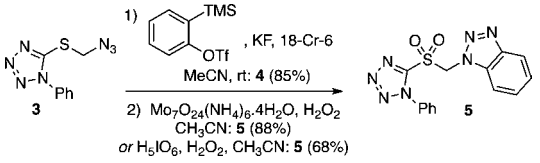
**Scheme 1.** Synthesis of the Azidomethyl PT-Sulfide




Synthesis of the requisite azido derivative with a handle for the Julia–Kocienski olefination is shown in Scheme 1. Our initial substrate, azidomethyl benzothiazolyl sulfide, gave complex reaction mixtures in the reactions with benzyne. This prompted us to focus on the more stable[11] phenyltetrazolyl derivative. Reaction of 1-phenyl-1*H*-tetrazole-5-thiol (PT-thiol) with bromochloromethane gave chloromethyl derivative **1**, which was converted to the more reactive iodo derivative **2**. Reaction of **2** with $NaN_3$ in DMF gave the desired 5-(azidomethylthio)-1-phenyl-1*H*-tetrazole (**3**, Scheme 1). Notably, only **1** needed chromatographic purification, whereas crude **2** and **3** were used in the subsequent steps.

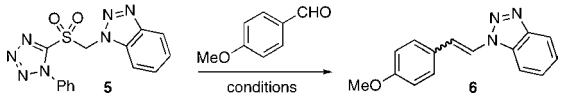
Next, the azide–aryne cycloaddition was utilized to assemble the benzotriazole core. Initially, as a cost-economical approach, the reaction of **3** with benzyne derived from anthranilic acid was evaluated. However, only a complex reaction mixture was obtained. We therefore evaluated the use of *o*-(trimethylsilyl)phenyl triflate.[8] Generation of benzyne from this precursor and reaction with **3** led to the desired benzotriazole derivative **4** in 85% yield after purification (Scheme 2). Oxidation of **4**, using $H_5IO_6/CrO_3$ or $Mo_7O_{24}(NH_4)_6 \cdot 4H_2O/H_2O_2$, gave the Julia–Kocienski reagent **5** (Scheme 2).

**Scheme 2.** Cycloaddition/Oxidation to the Benzotriazole Julia–Kocienski Reagent




Olefination conditions were screened in the reactions of *p*-methoxybenzaldehyde with **5** (Table 1). First, the effect of the base counterion was assessed, and LHMDS gave the highest yield and *E*-selectivity (entries 1–3). Lowering of the reaction temperature reversed the selectivity (entry 4),

**Table 1.** Screening of Olefination Conditions[a]




| entry | base (molar equiv) | solvent | *t* (°C) | rxn time (h) | yield[b] | *E*/*Z* ratio[c] |
|---|---|---|---|---|---|---|
| 1 | NaHMDS (2.4) | THF | 0 | 0.5 | 45% | 60/40 |
| 2 | KHMDS (2.4) | THF | 0 | 0.5 | 66% | 60/40 |
| 3 | LHMDS (2.4) | THF | 0 | 4 | 76% | 79/21 |
| 4 | LHMDS (4.0) | THF | −78 | 32 | –[d] | 28/72 |
| 5 | LHMDS (2.4) | THF | 66[e] | 2 | 81% | 70/30 |
| 6 | LHMDS (3.0) | THF[f] | rt | 5 | 30% | 77/23 |
| 7 | LHMDS (2.4) | DMF/DMPU[g] | −50 | 20 | –[d] | 57/43 |
| 8 | DBU (2.0) | THF | 66[e] | 2 | 47% | 26/74 |

[a] Conditions: sulfone **5** (1 molar equiv), *p*MeO-$C_6H_4$-CHO (1.5 molar equiv). [b] Yields are of isolated and purified products. [c] *E*/*Z* ratio was determined by $^1$H NMR. [d] Reaction was incomplete; **6** was not isolated. [e] At reflux. [f] $MgBr_2 \cdot OEt_2$ additive. [g] DMF/DMPU (1:1 v/v).


(4) Märky, M.; Schmid, H.; Hansen, H.-J. *Helv. Chim. Acta* **1979**, *62*, 2129–2153.

(5) (a) Katritzky, A. R.; Offerman, R. J.; Cabildo, P.; Soleiman, M. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 641–645. (b) Qian, H.; Huang, X. *Synth. Commun.* **2000**, *30*, 1413–1417. (c) Katritzky, A. R.; Lam, J. N. *Heteroatom Chem.* **1990**, *1*, 21–31.

(6) Katritzky, A. R.; Li, J.; Malhotra, N. *Liebigs Ann. Chem.* **1992**, 843–853.

(7) Taillefer, M.; Ouali, A.; Renard, B.; Spindler, J.-F. *Chem.—Eur. J.* **2006**, *12*, 5301–5313.

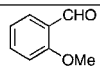
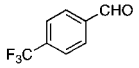
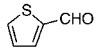
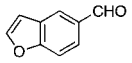
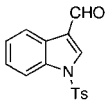
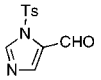
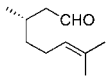
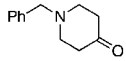
(8) (a) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409–2412. (b) Campbell-Verduyn, L.; Elsinga, P. H.; Mirfeizi, L.; Dierckx, R. A.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 3461–3463.

(9) (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336–357. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856–878.

(10) For reviews on Julia–Kocienski olefination, see: (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585. (b) Plesniak, K.; Zarecki, A.; Wicha, J. *Top. Curr. Chem.* **2007**, *275*, 163–250. (c) Aïssa, C. *Eur. J. Org. Chem.* **2009**, 1831–1844. (d) Blakemore, P. R. Olefination of Carbonyl Compounds by Main-Group Element Mediators. In *Comprehensive Organic Synthesis*, 2nd ed.; Knochel, P., Molander, G., Eds.; Oxford: Elsevier Ltd., 2013, in press. (e) For a review on fluoro Julia–Kocienski olefination, see: Zajc, B.; Kumar, R. *Synthesis* **2010**, 1822–1836.

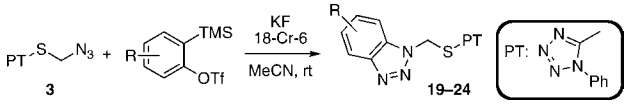
(11) (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28. (b) Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365–366.

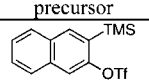
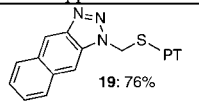
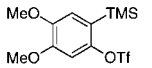
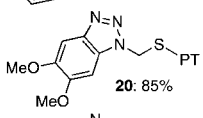
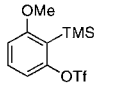
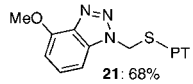
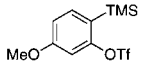
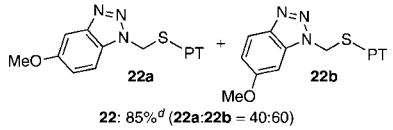
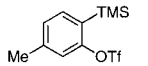
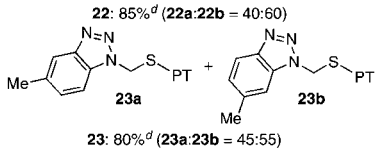
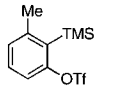
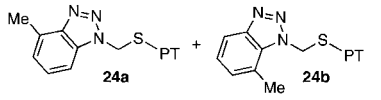
**Table 2.** Synthesis of Vinyl Benzotriazoles[a]

| entry | carbonyl | rxn time | method | product: yield[b] | *E*/*Z* ratio[c] |
|---|---|---|---|---|---|
| 1 |  | 0.5 h | A | **7**: 86% | 93/7 |
| | | 5 h | B | **7**: 57% | 15/85 |
| 2 |  | 0.5 h | A | **8**: 83% | 41/59 |
| | | 5 h | B | **8**: 57% | 11/89 |
| 3 |  | 2 h | A | **9**: 62% | 29/71 |
| 4 |  | 0.5 h | A | **10**: 90% | 40/60 |
| | | 5 h | B | **10**: 47% | 25/75 |
| 5 |  | 1 h | A | **11**: 65% | 64/36 |
| | | 14 h | B | **11**: 60% | 20/80 |
| 6 |  | 3 h | A | **12**: 72% | 71/29 |
| 7 |  | 2 h | A | **13**: 71% | 29/71 |
| 8 |  | 0.5 h | A | **14**: 67% | 4/96 |
| 9 |  | 0.5 h | A | **15**: 73% | 22/78 |
| | | 16 h | B | **15**: 50% | 3/97 |
| 10 |  | 2 h | A | **16**: 53% | 20/80 |
| 11 |  | 1 h | A | **17**: 80% | 16/84 |
| 12 |  | 3 h | A | **18**: 77% | -- |

[a] Conditions: Method A: sulfone **5** (1 molar equiv), carbonyl compound (1.2−1.5 molar equiv), LHMDS (2.4 molar equiv), THF, 0 °C. Method B: sulfone **5** (1 molar equiv), carbonyl compound (1.5 molar equiv), DBU (2.0 molar equiv), THF, reflux. [b] Yields are of isolated and purified products. [c] *E*/*Z* ratio was determined by $^1$H NMR.

**Table 3.** Reactions of **3** with Various Aryne Precursors




| entry | aryne precursor | product yields[a] and isomer ratio where applicable[b] |
|---|---|---|
| 1 |  |  **19**: 76% |
| 2 |  |  **20**: 85% |
| 3[c] |  |  **21**: 68% |
| 4[c] |  |  **22**: 85%[d] (**22a**:**22b** = 40:60) |
| 5[c] |  |  **23**: 80%[d] (**23a**:**23b** = 45:55) |
| 6[c] |  |  **24**: 89%[d] (**24a**:**24b** = 49:51) |

[a] Yields are of isolated and purified products. [b] Determined by $^1$H NMR. [c] Structures of regioisomeric products were determined by NOESY. [d] Combined yield of the two regioisomers.

but the reaction was incomplete after 32 h. A higher yield was obtained with LHMDS at reflux, with a somewhat lower *E*-selectivity (entry 5). Neither $MgBr_2 \cdot OEt_2$ nor DMPU additives improved the *E*-selectivity (entries 6, 7). Condensation also proceeded under mild, DBU mediated conditions, with *Z*-selectivity and in a moderate yield (entry 8).

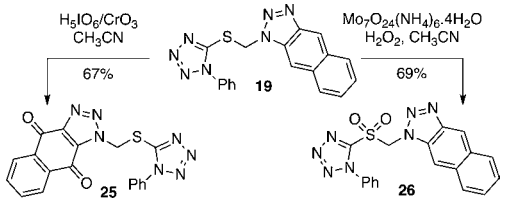
The effect of substrate structure on the yields and stereoselectivities was evaluated in reactions of **5** with a series of aldehydes and a ketone (Table 2). All reactions were performed using Method A (LHMDS, THF, 0 °C). The mild, but lower yielding, *Z*-selective Method B (DBU, THF, reflux) was evaluated against five representative aldehydes. Using Method A, vinyl benzotriazoles were formed in moderate to good yields with a wide range of aldehydes. The *E*-isomer predominated with electron-rich aromatic aldehydes (Table 1, entry 3 and Table 2 entries 1, 5, 6). The exceptions are five-membered heterocycles with the carboxaldehyde in an ortho position to the heteroatom (entries 4, 7). Condensations with electron-deficient aldehydes (entries 2, 3) and alkanals (entries 8−11) proceeded with *Z*-stereoselectivity. Selectivity was highest with *n*-octanal (entry 8), and branching at the α- (entries 9, 10) or *β*-position (entry 11) slightly decreased the selectivity.

A ketone, *N*-benzyl-4-piperidone, reacted as well and gave product **18** in a good 77% yield (entry 12). The bulkier and conjugated acetophenone, on the other hand, did not give good results under these conditions. No further attempts were made to improve the condensation of acetophenone. DBU-mediated reactions were *Z*-selective in all cases tested. As compared to Method A, this is a reversal of selectivity with electron-rich aldehydes (Table 1, entry 8, and Table 2 entries 1, 5) and a substantial improvement in *Z*-selectivity for the electron-deficient aldehyde, thiophene-2-carboxaldehyde, and alkanal (entries 2, 4, 9).

Azidomethyl (phenyl)tetrazolyl sulfide **3** was also reacted with substituted benzynes and 2,3-naphthyne, generated in situ from the corresponding *o*-(trimethylsilyl)aryl triflates. Cycloaddition reactions proceeded in yields of 76−89% (entries 1, 2, 4−6 in Table 3), except for 3-methoxy benzyne, where the yield was lower (68%, entry 3), but here formation of only a single regioisomer was observed. Formation of a single regioisomer in the reaction of 3-methoxy benzyne with benzyl azide has previously been reported.[8]

Sulfides **19**−**21** were oxidized to the Julia−Kocienski reagents. Oxidation of naphthotriazole derivative **19** with $H_5IO_6/CrO_3$ led to the quinone **25**,[12] but not to the sulfone **26** (Scheme 3). On the other hand, use of $Mo_7O_{24}(NH_4)_6 \cdot 4H_2O/H_2O_2$ gave the desired sulfone **26**.

**Scheme 3.** Oxidation of Naphthotriazole Derivative **19**




Similarly, 4-methoxy-substituted benzotriazole derivative **21** gave the corresponding sulfone **27** upon oxidation with $Mo_7O_{24}(NH_4)_6 \cdot 4H_2O/H_2O_2$. 5,6-Dimethoxy-substituted benzotriazole derivative **20** was converted to sulfone **28** via *m*CPBA oxidation (see the Supporting Information (SI) for details).

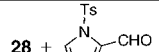
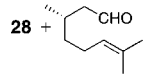
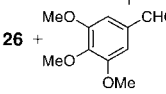
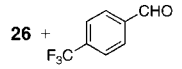
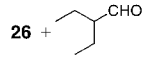
Condensations of sulfones **26** and **28** with aldehydes proceeded smoothly under LHMDS-mediated conditions (Method A) to give *N*-vinyl naphthotriazoles and 5,6-dimethoxybenzotriazoles (Table 4). Since sulfone **26** exhibited poor solubility in THF at 0 °C, it was used as a crude material (entries 3, 6, and 8) or DMF was used as the solvent (entries 4, 7, 9). Product yields were higher in DMF than in THF (entries 4, 7, and 9). The *E*/*Z* selectivity was comparable in THF and DMF for *p*-trifluoromethylbenzaldehyde and was lower in DMF for 2-ethylbutanal. With 3,4,5-trimethoxybenzaldehyde, opposite stereoselectivities were observed in the two solvents. The highest *Z*-selectivity was observed with the use of DBU-mediated conditions (Method B, entry 5); however, the yield was the lowest (compare entries 3, 4, 5).

Possible isomerization of the alkene mixtures was then considered. Exposure of *E*/*Z*-**6** to $I_2$ in $CHCl_3$,[13a] to $(CH_3CN)_2PdCl_2$ in $CH_2Cl_2$,[13b] and to LHMDS in THF at reflux did not cause isomerization. An isomerization attempt using a 450 W medium-pressure Hg lamp in PhH caused decomposition (see the SI).

(12) Oxidation of naphthalene and methyl substituted naphthalenes, phenanthrene, anthracene, and trimethoxy substituted benzene to quinones using $CrO_3/H_5IO_6$ has been reported: Yamazaki, S. *Tetrahedron Lett*. **2001**, *42*, 3355–3357.

(13) (a) Gaukroger, K.; Hadfield, J. A.; Hepworth, L. A.; Lawrence, N. J.; McGown, A. T. *J. Org. Chem*. **2001**, *66*, 8135–8138 and references therein. (b) Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem*. **2002**, *67*, 4627–4629.

**Table 4.** Synthesis of *N*-Vinyl 5,6-Dimethoxy Benzotriazoles and *N*-Vinyl Naphthotriazoles

| entry | sulfone + aldehyde | conditions[a] | product: yield[b] | *E*/*Z* ratio[c] |
|---|---|---|---|---|
| 1 |  | A, THF, 25 min | **29**: 80% | 60/40 |
| 2 |  | A, THF, 25 min | **30**: 69% | 41/59 |
| 3 |  | A, THF, 20 min | **31**: 80% | 65/35[d] |
| 4 | | A, DMF, 40 min | **31**: 93% | 37/63 |
| 5 | | B, THF, 4 h | **31**: 52% | 25/75 |
| 6 |  | A, THF, 20 min | **32**: 56% | 44/56[d] |
| 7 | | A, DMF, 40 min | **32**: 62% | 41/59 |
| 8 |  | A, THF, 25 min | **33**: 54% | 22/78[d] |
| 9 | | A, DMF, 40 min | **33**: 74% | 33/67 |

[a] Conditions: Method A: sulfone (1 molar equiv), carbonyl compound (1.2−2.2 molar equiv, see the SI), LHMDS (2.4 molar equiv), THF or DMF, 0 °C. Method B: sulfone (1 molar equiv), carbonyl compound (1.5 molar equiv), DBU (2.0 molar equiv), THF, reflux. [b] Yields are of isolated and purified products. [c] *E*/*Z* ratio was determined by $^1$H NMR. [d] Due to poor solubility, crude sulfone **26** was used (see the SI).

In summary, a modular and facile approach to *N*1-vinyl benzo-, substituted benzo-, and naphthotriazoles has been reported. The method is highly flexibile for introduction of substituents, at *both the vinyl and the benzotriazolyl moieties*, and circumvents the *N*1/*N*2 regioisomer problem encountered in alkylation reactions. The stereoselectivity of olefinations is tunable for electron-rich aldehydes, whereas reactions with electron-deficient aldehydes and alkanals proceed with good to excellent *Z*-stereoselectivity. Other reactions of bifunctional building block **3** are currently being pursued and will be published in due course.

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**Supporting Information Available.** Experimental details and copies of $^1$H and $^{13}$C NMR spectra. This information is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.