Nucleophilic Aromatic Substitution Reactions of Novel 5-(2-Methoxyphenyl)tetrazole Derivatives with Organolithium Reagents

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Introduction

The tetrazole ring system has attracted considerable attention in recent years, especially among medicinal chemists, as a potential surrogate for *cis*-peptide linkage, carboxylic acids, and others.[2] Driven in particular by the widespread incorporation of tetrazole functionality into angiotensin II antagonist structures, several excellent new synthetic methods have recently been described for the construction, protection, and transformation of this heterocycle.[3]

Ortho-directed lithiation of a suitably *N*-protected 5-(aryl)tetrazole, followed by transmetalation and Pd^0-catalyzed coupling with an aryl halide, is a particularly useful sequence for the preparation of highly functionalized 5-(2-biaryl)tetrazoles;[2g,3m] however, during the course of a research program toward angiotensin II antagonists we required a synthetic route to 5-(2-biaryl)-tetrazoles that would obviate the need for transmetalation and heavy-metal catalysis in the coupling reaction. Aside from the expense and potential concerns associated with the recovery of Pd^0L_4 catalysts from pilot-scale procedures, we observed that it was sometimes difficult to satisfactorily remove trace levels of palladium contamination from the final 5-(2-biaryl)tetrazole products except by inconvenient large-scale chromatographic purification.

Russell and Murray[4] first demonstrated the feasibility of tetrazole-directed nucleophilic aromatic substitution by reaction of *p*-tolylmagnesium bromide with unprotected 5-(2-fluorophenyl)-1*H*-tetrazole in refluxing DME solution to give 5-(4′-methyl[1,1-biphenyl]-2-yl-1*H*-tetrazole in 78% yield. Some apparent limitations of their seminal procedure include (1) use of 3 equiv of the Grignard reagent was recommended, (2) long reaction times in refluxing DME (ca. 16 h at 85 °C) were necessary, probably because of the reduced ability of the electron-rich magnesium tetrazolate group to stabilize a second anionic charge, and (3) within the scope of the Russell and Murray study the nucleofugic group was limited to fluorine since, for example, 5-(2-methoxyphenyl)tetrazole gave very low yields of the desired S_NAr product under their optimal reaction conditions.

The high stability of the tetrazole ring toward organometallic reagents and the well-known propensity of some *N*-substituted tetrazoles to stabilize anionic charge via π-delocalization within the heterocyclic ring[3m] led us to investigate whether a suitably protected tetrazole ring might function as a more efficient and versatile activating group for nucleophilic aromatic substitution reactions. Specifically, we hoped to extend the scope of tetrazole-activated S_NAr processes (1) by enabling the use of easily available organolithium reagents as the nucleophile and reducing the equivalents of organometallic reagent required to achieve acceptable reaction yields, (2) by lowering the effective temperature and/or time required for reaction, and (3) by employing the more commonly accessible methoxy group, in place of fluorine, as the nucleofuge in these reactions. We further hoped to develop a new protecting group strategy for tetrazoles[2g,h] that would facilitate the proposed S_NAr chemistry and subsequently allow for mild deprotection conditions.

Results and Discussion

In a control experiment unprotected 5-(2-methoxyphenyl)-1*H*-tetrazole, **1**, failed to give an S_NAr product with 3 equiv of *n*-BuLi (ether, 0 °C, 1 h; then 23 °C for 14 h); the starting material was recovered from this reaction mixture in quantitative yield. Under identical reaction conditions unprotected 5-(2,3-dimethoxyphenyl)-1*H*-tetrazole, **2**, reacted very slowly with 3 equiv of *n*-BuLi to give 24% of 5-(2-butyl-3-methoxyphenyl)-1*H*-tetrazole along with 70% recovered **2**. Aryltetrazoles **1**−**3**

(1) Roche Bioscience Student Intern, 1997.

(2) (a) Kotoris, C. C.; Chen, M.-J.; Taylor, S. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3275. (b) Bold, G.; Faessler, A.; Capraro, H.-G.; Cozens, R.; Klimkait, T.; Lazdins, J.; Mestan, J.; Poncioni, B.; Roesel, J.; Stover, D.; Tintelnot-Blomly, M.; Acemoglu, F.; Beck, W.; Boss, E.; Eschbach, M.; Huerlimann, T.; Masso, E.; Roussel, S.; Ucci-Stoll, K.; Wyss, D.; Lang, M. *J. Med. Chem.* **1998**, *41*, 3387. (c) Duncia, J. V.; Santella, J. B., Higley, C. A.; Vanatten, M. K.; Weber, P. C.; Alexander, R. S.; Kettner, C. A.; Pruitt, J. R.; Liauw, A. Y.; Quan, M. L.; Knabb, R. M.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 775. (d) Abell, A. D.; Foulds, G. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2475. (e) Lee, D.; Marshall, L. A.; Bolognese, B.; Adams, J. L. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1427. (f) Bavetsias, V.; Jackman, A. L.; Kimbell, R.; Boyle, F. T.; Bisset, G. M. F. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 631. (f) Kees, K. L.; Caggiano, T. J.; Steiner, K. E.; Fitzgerald, J. J.; Kates, M. J.; Christos, T. E.; Kulishoff, J. M.; Moore, R. D.; McCaleb, M. L. *J. Med. Chem.* **1995**, *38*, 617. (f) Ward, P.; Armour, D. R.; Bays, D. E.; Evans, B.; Giblin, G. M. P.; Heron, N.; Hubbard, T.; Liang, K.; Middlemiss, D.; Mordaunt, J.; Naylor, A.; Pegg, N. A.; Vinader, M. V.; Watson, S. P.; Bountra, C.; Evans, D. C. *J. Med. Chem.* **1995**, *38*, 4985. (g) For an excellent review of preparations, reactions, and medicinal chemistry of tetrazoles prior to 1994 see: Wittenberger, S. J. *Org. Prep. Proc. Int.* **1994**, *26*, 499. (h) Alternative *N*(2)-protection for the tetrazole ring includes *tert*-butyl (see, for example: Tilley, J. W.; Danho, W.; Lovey, K.; Wagner, R.; Swistok, J.; Makofske, R.; Michaelewsky, J.; Triscari, J.; Nelson, D.; Weatherford, S. *J. Med. Chem.* **1991**, *34*, 1125) and trityl (see, for example: Shuman, R. F.; King, A. O.; Anderson, R. K. US Patent 5,039,814, Aug 13, 1991). Limitations of the these two protecting groups may include difficulty of removal in the case of *tert*-butyl (HF cleavage) and relatively poor atom economy as well as relatively high sensitivity to acids in the case of trityl.

(3) (a) For a recent review of ring transformations in tetrazole chemistry see: Moderhack, D. *J. Prakt. Chem./Chem.-Ztg.* **1998**, *340*, 687. (b) Kotoris, C. C.; Chen, M.-J.; Taylor, S. D. *J. Org. Chem.* **1998**, *63*, 8052. (c) Chang, K.-H.; Lin, Y.-C. *Chem. Commun.* **1998**, 1441. (d) Bienayme, H.; Bouzid, K. *Tetrahedron Lett.* **1998**, *39*, 2735. (e) Hirose, M.; Kawai, R.; Hayakawa, Y. *Synlett* **1997**, 495. (f) El-Ahl, A.-A. S.; Elmorsy, S. S.; Elbeheery, A. H.; Amer, F. A. *Tetrahedron Lett.* **1997**, *38*, 1257. (g) Yoo, S.-E.; Seo, J.-S.; Yi, K.-K.; Gong, Y.-D. *Tetrahedron Lett.* **1997**, *38*, 1203. (h) Kumar, A.; Narayanan, R.; Shechter, H. *J. Org. Chem.* **1996**, *61*, 4462. (i) Ishmetova, R. I.; Kitaeva, V. G.; Rusinov, G. L.; Beresnev, D. G. *Zh. Org. Khim.* **1995**, *31*, 431. (j) Boivin, J.; Husinec, S.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 11737. (k) Lehnhoff, S.; Ugi, I. *Heterocycles* **1995**, *40*, 801. (l) Satoh, Y.; Marcopulos, N. *Tetrahedron Lett.* **1995**, *36*, 1759. (m) For a review covering metalation reactions of tetrazoles prior to 1995 see: Grimmett, M. R.; Iddon, B. *Heterocycles* **1995**, *41*, 1525.

(4) Russell, R. K.; Murray, W. V. *J. Org. Chem.* **1993**, *58*, 5023.

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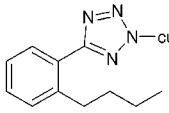
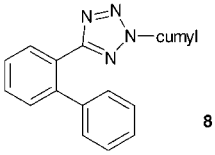
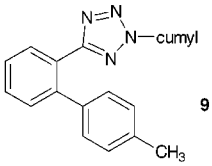
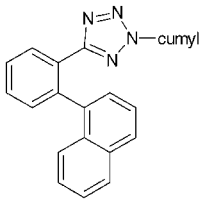
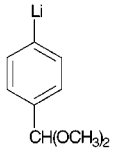
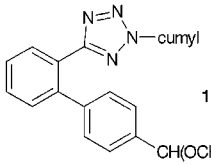
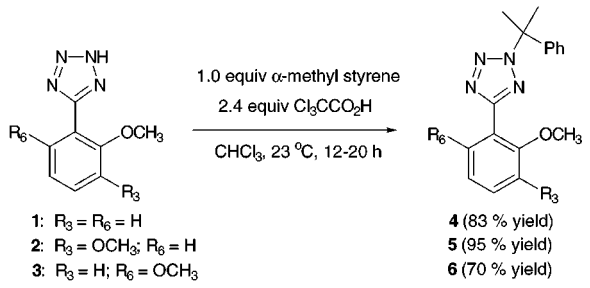
Table 1. Reaction of Organolithiums with *N*(2)-Cumyl-5-(2-methoxyphenyl)tetrazole (4)[a]

entry	5-aryltetrazole[b]	organolithium reagent[c]	reaction time[d]	products (% isolated yield)[e]
1	4	1.3 equiv n-BuLi	4.5 h	 **7** (85 %)
2	4	2.0 equiv PhLi	16 h	 **8** (66 %)
3	4	2.0 equiv p-tolyllithium	8 h	 **9** (47 %)
4	4	2.5 equiv 1-naphthyllithium	13 h	 **10** (80 %)
5	4	2.0 equiv 	12 h	 **11** (90 %)

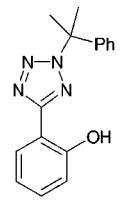
[a] Typical experimental details are given for the preparation and reaction of **4** with *n*-BuLi. [b] Prepared by the method of Sisido et al.[5] [c] *n*-BuLi and PhLi were obtained as hexane solutions from Aldrich Chemical Co. All other organolithium reagents were prepared by standard lithium−halogen exchange methods.[6] [d] All reactions were performed in ether solution at 23 °C. [e] All products were purified by flash chromatography (silica gel).

were efficiently protected with a cumyl group exclusively on N(2) of the tetrazole ring as shown in the following.

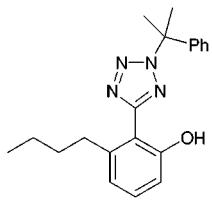


Results of nucleophilic aromatic substitution (S_NAr) reactions of *N*(2)-cumyl-5-(2-methoxyphenyl)tetrazole with representative organolithium reagents are shown in Table 1. Of particular note, 4-(dimethoxymethyl)phenyllithium reacted efficiently with tetrazole **4** to provide a novel construction of biaryl tetrazole intermediate **11** (entry 5, Table 1). Compound **11** has been used previously in a concise synthesis of compound **21**, a convenient precursor to the angiotensin II antagonist **22** (RS-66252).[7]

The S_NAr products summarized in Table 1 were sometimes accompanied by small amounts of phenolic side products in the crude reaction mixtures; however, unless otherwise noted, these were determined by ^1H NMR analysis of the crude reaction mixtures as minor (<5 mol %) impurities and were not isolated. In the case of entry 1 the minor phenolic side products were isolated and identified as 2-cumyl-5-(2 hydroxyphenyl)tetrazole, **12** (2%), and 2-cumyl-5-(2-*n*-butyl-6-hydroxyphenyl)-tetrazole, **13** (2%).[8]



12



13

On the other hand, when a highly sterically congested organometallic reagent, 1-lithio-2-methylnaphthalene (2.4

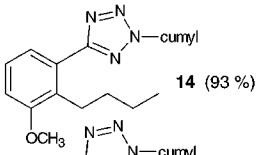
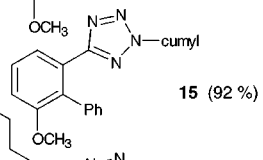
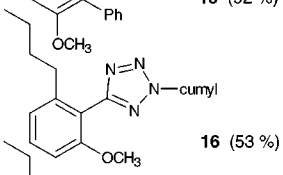
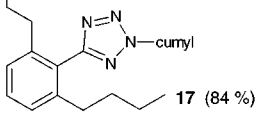
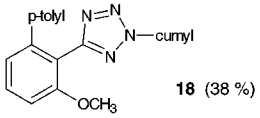
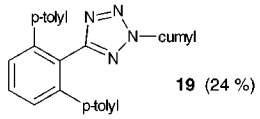
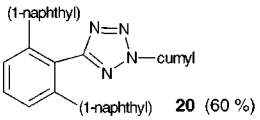
(5) Sisido, K.; Nabika, K.; Isida, T.; Kozima, S. *J. Organomet. Chem.* **1971**, *33*, 337.

(6) Schlosser, M. Organoalkalai Reagents. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Wiley & Sons: Chichester, West Sussex, England, 1994.

(7) Fisher, L. E.; Flippin, L. A.; Martin, M. G. US Patent 5,468,867, 1995.

(8) Compound **12** is presumably formed by nucleophilic displacement of an aryloxide anion by attack of *n*-butyllithium directly on the *O*-methyl group of **4**. The origin of compound **13** is less clear; however, it may plausibly arise from S_NAr attack on the benzenoid C(6) position of **4**, followed by net loss of methane. A limited investigation has precluded the formation of **13** from further reactions of *n*-butyllithium with either compound **12** or compound **7** under the S_NAr reaction conditions.

Table 2. Reaction of Organolithiums with *N*(2)-Cuyl-5-(2,*n*-dimethoxyphenyl)tetrazoles

entry	5-aryltetrazole[a]	organolithium reagent[b]	reaction time[c]	products (% isolated yield)[d]
1	**5**	1.3 equiv n-BuLi	4 h	 **14** (93 %)
2	**5**	2.0 equiv PhLi	16 h	 **15** (92 %)
3	**6**	1.3 equiv n-BuLi	16 h	 **16** (53 %)
4	**6**	3.0 equiv n-BuLi	3 h	 **17** (84 %)
5	**6**	4.0 equiv p-tolyllithium	10 h	 **18** (38 %)  **19** (24 %)
6	**6**	5.0 equiv 1-naphthyllithium	12 h	 **20** (60 %)

[a] Prepared by the method of Sisido et al.[5] [b] Except for *n*-BuLi and PhLi (Aldrich Chemical Co.), organolithium reagents were prepared by standard lithium−halogen exchange methods.[6] [c] All reactions were performed in ether solution. Entries 1 and 2 were conducted at 0 °C, all others at 23 °C. [d] All products were purified by flash chromatography (silica gel).

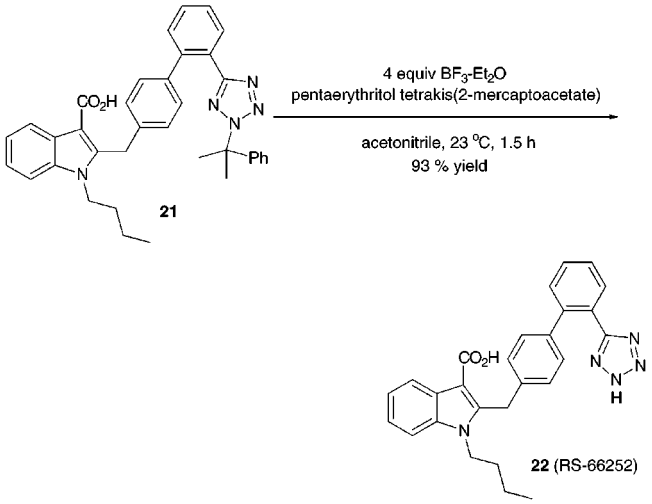
equiv), was allowed to react with **4** for 48 h under standard reaction conditions, the major products were phenol **12** (42% yield) and the deprotected tetrazole **1** (37% yield). No S_NAr product derived from 1-lithio-2-methylnaphthalene was detected in this reaction mixture; however, a trace amount (3.5% yield) of an S_NAr product corresponding to an unknown isomer of lithiated methylnaphthalene was isolated, corresponding to a similar level of an isomeric impurity in the commercial 1-bromo-2-methylnaphthalene used to prepare our organolithium reagent. Both phenolic side products, **12** and **13**, were subsequently prepared by independent routes for structure authentication (see the Experimental Section). Grignard reagents could be used for nucleophilic aromatic substitution of the methoxy group of tetrazole **4**; however, *n*-BuMgCl in ether solution was a less effective nucleophile than the corresponding organolithium reagent in a limited set of examples for which we obtained comparable data. As a typical example, reaction of 1.5 equiv of *n*-BuMgCl with **4** in refluxing ether (34 °C) for 16 h did not lead to complete consumption of the starting material; however, tetrazole **7** was isolated in 49% yield from this reaction mixture (cf. entry 1, Table 1).

Several additional examples of S_NAr reactions with organolithium reagents using *N*(2)-cumyl-5-(2,3-dimethoxyphenyl)tetrazole, **5**, and *N*(2)-cumyl-5-(2,6-dimethoxyphenyl)tetrazole, **6**, are summarized in Table 2. To our knowledge, the *N*-cumyl group was unkown as protection for the tetrazole ring system prior to these investigations; however, it appears to be exceptionally convenient and versatile for this employment. No premature loss of this protecting group was detected under the strongly basic reaction conditions summarized in Table 1 (except in the prolonged reaction between 1-lithio-2-methylnaphthalene and **4** as noted above); however, deprotection of the *N*-cumyltetrazole products could be accomplished in good yield by at least two complementary procedures. For example, transfer hydrogenolysis (3 equiv of potassium formate/catalytic 10% Pd−C/ethanol, reflux, 1 h) using a model system, 2-cumyl-5-phenyltetrazole, gave 5-phenyltetrazole in quantitative yield. Alternatively, treatment of cumyl-protected tetrazole **21** with 4 equiv of BF_3 etherate/1.1 equiv of pentaerythritol tetrakis(2-mercaptoacetate)[9]/CH_3CN, 23 °C, 1.5 h, gave the highly functionalized tetrazole **22** (RS-66252) in 93% yield.

Conclusion

The results of the present study demonstrate that 5-(aryl)tetrazoles protected with an *N*-cumyl group react with a variety of common organolithium reagents to give facile nucleophilic aromatic substitution of either one or two nucleofugic methoxy groups situated ortho to the

(9) Several commonly available monothiol reagents (4.4 equiv), including mercaptoacetic acid and thiophenol, were effective replacements for pentaerythritol tetrakis(2-mercaptoacetate).



tetrazole ring. The employment of tetrazole protection during these reactions provides for milder and more versatile reaction conditions, as well as a generally more economical use of the organometallic reagent, than was previously described[4] for the S_NAr substitution of 5-(2-fluorophenyl)-1*H*-tetrazole. Finally, we have shown that the *N*(2)-cumyl-protected tetrazole ring is generally stable under strongly basic reaction conditions, although it can be removed efficiently by hydrogenolysis or by treatment with boron trifluoride etherate in the presence of a carbocation scavenger. Thus, *N*-cumylation/decumylation may offer a potentially versatile new protection strategy for the tetrazole moiety.

Experimental Section

General Procedures. Reactions were performed under a nitrogen or argon atmosphere in oven-dried glassware. Solvents were dried with standard drying agents[10] and distilled before use. Melting points are uncorrected. Unless otherwise noted, ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at room temperature using $CDCl_3$ solutions. Column chromatography was performed using 230−400 mesh silica gel.

Synthesis of 5-Aryl-1*H*-tetrazoles.[6] 5-(2,3-Dimethoxyphenyl)-1*H*-tetrazole (2). 2,3-Dimethoxybenzonitrile (4.02 g, 25 mmol) and tri(*n*-butyl)tin azide (10.0 *g*, 30 mmol) were dissolved in 30 mL of xylenes, and the reaction mixture was refluxed for 14 h. The reaction mixture was cooled to 10−15 °C, and anhydrous HCl was vigorously bubbled into the mixture for about 5 min. The resultant white precipitate was collected by vacuum filtration, washed thoroughly with ether, and dried under vacuum to give 3.93 g (76% yield) of tetrazole **2**: mp 129−130 °C dec; ^{1}H NMR δ 7.93 (dd, J = 8.0, 1.6 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.11 (dd, J = 8.0, 1.6 Hz, 1H); ^{13}C NMR δ 152.6, 151.8, 146.6, 125.2, 121.0, 116.7, 115.8, 61.3, 56.1. Anal. Calcd for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.07; H, 4.73; N, 26.88.

5-(2-Methoxyphenyl)-1*H*-tetrazole (1). Using the general procedure 2-methoxybenzonitrile gave tetrazole **1** in 95% yield: mp 155−160 °C dec (lit.[11] mp 159−160 °C).

5-(2,6-Dimethoxyphenyl)-1*H*-tetrazole (3). Using the general procedure as above 2,6-dimethoxybenzonitrile afforded tetrazole **3** in 27% yield: mp 257−258 °C dec, ^{1}H NMR (DMSO-d_6) δ 7.53 (t, J = 8.5 Hz, 1H), 6.83 (d, J = 8.5 Hz, 2H), 3.74 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 158.4, 148.3, 132.9, 104.2, 55.9. Anal. Calcd for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.52; H, 4.84; N, 27.16.

Control Reactions with Unprotected Tetrazoles. Method A. Tetrazole **1** (0.205 g, 1.2 mmol) was suspended in 10 mL of ether at 0 °C. A 2.5 M hexane solution of *n*-BuLi (1.4 mL, 3.5 mmol) was added over 3 min, and the reaction mixture was allowed to warm to 23 °C for 12 h. The reaction mixture was quenched with 1 M HCl and extracted with ethyl acetate to give 0.191 g (93% yield) of recovered **1**.

Method B. Tetrazole **2** (0.195 g, 0.95 mmol) was suspended in 10 mL of ether at 0 °C. A 2.5 M hexane solution of *n*-BuLi (1.2 mL, 3.0 mmol) was added over 3 min, and the reaction mixture was allowed to stand at 23 °C for 13 h. The reaction mixture was quenched with 1 M HCl and purified by column chromatography (95:5 CH_2Cl_2−MeOH) to give 0.137 g (70% yield) of unchanged **2** and 0.053 g (24% yield) of 5-(2-*n*-butyl-3-methoxyphenyl)-1*H*-tetrazole: mp 163−164 °C; ^{1}H NMR ($CDCl_3$−DMSO-d_6) δ 7.29 (t, J = 8.0 Hz), 7.15−7.10 (br d, J = ∼8 Hz, 1H), 6.99 (br dd, J = 8, ∼1 Hz, 1H), 3.87 (s, 3H), 2.84 (m, 2H), 1.44 (m, 2H), 1.27 (sextet, J = 7.2 Hz, 2H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 158.0, 132.2, 126.8, 121.8, 55.7, 32.2, 26.5, 22.8, 13.9; EIMS *m*/*z* (relative intensity) 232 (M+, 50), 203 (20), 175 (100).

***N*(2)-Cumylation of 5-Aryltetrazoles. *N*(2)-Cumyl-5-(2,3-dimethoxyphenyl)tetrazole (5).** Tetrazole **2** (3.63 g, 17.6 mmol) and trichloroacetic acid (6.62 g, 40.4 mmol) were dissolved in 30 mL of $CHCl_3$. α-Methylstyrene (2.08 g, 17.6 mmol) in 5 mL of $CHCl_3$ was added dropwise, and the reaction mixture was allowed to stir at room temperature for 14 h. The crude reaction mixture was diluted with ethyl acetate, and the organic layer was washed with 10% aqueous KOH. The organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (9:1 hexanes−EtOAc) to give 5.43 g (95% yield) of **5** as a colorless oil: ^{1}H NMR δ 7.53 (dd, J = 7.7, 1.5 Hz, 1H), 7.34−7.13 (m, 6H), 7.02 (dd, J = 7.7, 1.5 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.24 (s, 6H); ^{13}C NMR δ 162.5, 153.7, 147.7, 144.0, 128.6, 127.8, 124.8, 124.3, 122.6, 121.9, 114.1, 68.2, 61.3, 56.1, 29.2. Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.52; H, 6.13; N, 17.24.

***N*(2)-Cumyl-5-(2-methoxyphenyl)tetrazole (4).** Using the general procedure tetrazole **1** gave protected tetrazole **4** as a colorless oil in 83% yield. Recrystallization (ether−hexane) gave crystalline **4**: mp 51.0−52.5 °C; ^{1}H NMR δ 7.88 (dd, J = 7.9, 1.8 Hz, 1H), 7.42 (td, J = 7.9, 1.8 Hz, 1H), 7.34−7.01 (m, 7H), 3.90 (s, 3H), 2.22 (s, 6H); ^{13}C NMR δ 163.0, 157.6, 144.1, 131.37, 130.9, 128.6, 127.7, 124.8, 120.7, 117.0, 112.0, 68.2, 56.0, 29.2. Anal. Calcd for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.49; H, 6.14; N, 19.08.

***N*(2)-Cumyl-5-(2,6-dimethoxyphenyl)tetrazole (6).** The general procedure using tetrazole **3** gave *N*(2)-cumyl-protected tetrazole **6** as a crystalline solid in 70% yield: mp 114.5−115.5 °C; ^{1}H NMR δ 7.35 (t, J = 8.4 Hz, 1H), 7.31−7.20 (m, 3H), 7.10−7.05 (m, 2H), 6.61 (d, J = 8.4 Hz, 2H), 3.72 (s, 6H), 2.22 (s, 6H); ^{13}C NMR δ 159.5, 159.3, 144.7, 131.7, 128.5, 127.6, 124.7, 104.9, 68.4, 56.0, 29.3. Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.84; H, 6.21; N, 17.34.

Nucleophilic Aromatic Substitution Reactions of *N*(2)-Cumyl-5-(2-methoxyphenyl)tetrazoles. *N*(2)-Cumyl-5-(2-*n*-butylphenyl)tetrazole (7). To a stirred solution of **4** (0.500 g, 1.7 mmol) in 15 mL of ether at 23 °C was added 884 μL (2.2 mmol) of 2.5 M *n*-BuLi in hexanes over 2 min. After 4.5 h the reaction mixture was quenched with 20 mL of water and extracted with several portions of ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (29:1 hexanes−ethyl acetate) to give 0.471 g (87% yield) of **7** as a colorless oil: ^{1}H NMR δ 8.0−7.95 (m, 1H), 7.39−7.20 (m, 6H), 7.17−7.14 (m, 2H), 2.91 (m, 2H), 2.23 (s, 6H), 1.48 (m, 2H), 1.25 (sextet, J = 7.2 Hz, 2H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 164.9, 144.1, 142.4, 130.6, 129.9, 129.8, 128.6, 127.8, 126.0, 124.7, 68.2, 34.1, 33.6, 29.1, 22.7, 14.0. Anal. Calcd for $C_{20}H_{24}N_4$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.93; H, 7.36; N, 17.69.

***N*(2)-Cumyl-5-([1,1′-biphenyl]-2-yl)tetrazole (8).** The general procedure using 2.0 equiv of PhLi with tetrazole **4** gave compound **8** in 66% yield as a colorless oil: ^{1}H NMR δ 7.87 (dd, J = 7.3, 1.7 Hz, 1H), 7.55−7.12 (m, 13 H), 7.0−6.90 (m, 2H), 2.00 (s, 6H); ^{13}C NMR δ 164.9, 143.7, 142.3, 141.1, 130.6, 130.2, 129.8, 129.3, 128.5, 127.8, 127.7, 127.4, 126.8, 126.7, 124.7, 68.0, 29.0. Anal. Calcd for $C_{22}H_{20}N_4$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.52; H, 5.83; N, 16.24.

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***N*(2)-Cumyl-5-(4′-methyl[1,1′-biphenyl]-2-yl)tetrazole (9).** From compound **4**, with 2.0 equiv of *p*-tolyllithium, tetrazole **9** was obtained in 47% yield as a crystalline solid: mp 99−100 °C; ^{1}H NMR δ 7.84−7.81 (m, 1H), 7.50−7.47 (m, 3H), 7.25−7.22 (m, 3H), 7.03 (apparent s, 4H), 6.97−6.92 (m, 2H), 2.33 (s, 3H), 2.02 (s, 6H); ^{13}C NMR δ 164.8, 143.8, 142.3, 138.1, 136.4, 130.6, 130.3, 129.8, 129.1, 128.5, 128.4, 127.6, 127.2, 126.7, 124.7, 124.6, 68.0, 29.0, 21.2. Anal. Calcd for $C_{23}H_{22}N_4$: C, 77.94; H, 6.26; N, 15.81. Found: C, 77.87; H, 6.24; N, 15.75.

***N*(2)-Cumyl-5-(naphth-1-yl)tetrazole (10).** The general procedure using tetrazole **4** with 2.5 equiv of 1-lithionaphthalene gave tetrazole **10** in 80% yield as a crystalline solid: mp 108−109 °C; ^{1}H NMR δ 8.19−8.15 (m, 1H), 7.81 (td, J = 7.7, 1.4 Hz, 2H), 7.60−7.32 (m, 7H), 7.25−7.06 (m, 4 H), 6.60−6.55 (m, 2H), 1.67 (s, 3H), 1.63 (s, 3H); ^{13}C NMR δ 163.6, 143.4, 140.1, 139.4, 133.3, 132.2, 131.6, 129.8, 129.3, 128.3, 128.0, 127.9, 127.8, 127.5, 127.4, 127.0, 125.9, 125.8, 125.4, 125.2, 124.5, 67.5, 28.8, 28.3. Anal. Calcd for $C_{26}H_{22}N_4$: C, 79.97; H, 5.68; N, 14.35. Found: C, 79.72; H, 5.63; N, 14.26.

***N*(2)-Cumyl-5-(4′-(dimethoxymethyl)[1,1′-biphenyl]-2-yl)-tetrazole (11).** The general procedure using compound **4** with 2.0 equiv of 4-(dimethoxymethyl)phenyllithium gave tetrazole **11** in 90% yield as a colorless oil: ^{1}H NMR δ 7.88 (dd, J = 7.1, 1.3 Hz, 1H), 7.53−7.38 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 7.30−7.24 (m, 3H), 7.17 (d, J = 8.0 Hz, 2H), 6.97−6.93 (m, 2H), 5.38 (s, 1H), 3.31 (s, 3H), 1.99 (s, 6H); ^{13}C NMR δ 164.1, 143.8, 141.9, 141.2, 136.7, 130.7, 130.3, 129.8, 129.1, 128.5, 127.7, 127.5, 126.6, 126.2, 124.7, 103.0, 68.1, 52.6, 29.0; EIMS *m*/*z* (relative intensity) 414 (M^+, 24), 383 (17), 296 (28), 265 (34), 238 (19), 209 (30), 193 (65), 165 (56), 119 (100), 91 (75), 75 (100).

***N*(2)-Cumyl-5-(2-*n*-butyl-3-methoxyphenyl)tetrazole (14).** The general procedure using compound **5** with 1.3 equiv of *n*-BuLi afforded a 93% yield of tetrazole **14** as a colorless oil that crystallized on standing: mp 54−56 °C; ^{1}H NMR δ 7.52 (dd, J = 7.8, 1.1 Hz, 1H), 7.27−7.13 (m, 6H), 6.95 (dd, J = 7.8, 1.1 Hz, 1H), 3.85 (s, 3H), 2.85 (m, 2H), 2.22 (s, 6H), 1.49−1.39 (m, 2H), 1.29−1.17 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 164.9, 158.0, 143.9, 131.6, 128.6, 127.8, 126.5, 124.7, 122.1, 111.8, 67.8, 55.7, 32.2, 29.1, 26.7, 23.1, 14.0; LSIMS−HRMS Calcd for $C_{21}H_{27}N_4O$ (M + H^+) 351.2185, found 351. 2187. Anal. calcd for $C_{21}H_{26}N_4O$: C, 71.97; H, 7.48; N, 15.99. Found: C, 71.68; H, 7.45; N, 16.06.

***N*(2)-Cumyl-5-(6-methoxy-[1,1′-biphenyl]-2-yl)tetrazole (15).** With compound **5** and 2.0 equiv of PhLi the general procedure gave tetrazole **15** in 92% yield as a colorless oil that crystallized on standing: mp 66−68 C; ^{1}H NMR δ 7.50 (dd, J = 7.8, 1.3 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.30−7.20 (m, 6H), 7.15−7.10 (m, 2H), 7.08 (dd, J = 7.8, 1.3 Hz, 1H), 6.90−6.84 (m, 2H), 3.76 (s, 3H), 1.94 (s, 6H); ^{13}C NMR δ 164.3, 157.1, 143.7, 136.5, 131.2, 130.4, 128.7, 128.6, 128.4, 127.6, 124.7, 122.1, 112.4, 67.9, 56.0, 28.9; LSIMS−HRMS calcd for $C_{23}H_{23}N_4O$ (M + H^+) 371.1872, found 371.1875. Anal. Calcd for $C_{23}H_{22}N_4O$: C, 74.57; H, 5.99; N, 15.12. Found: C, 74.14; H, 5.96; N, 14.98.

***N*(2)-Cumyl-5-(2-*n*-butyl-6-methoxyphenyl)tetrazole (16).** Using 1.3 equiv of *n*-butyllithium with tetrazole **6**, the general procedure afforded crude tetrazole **16** contaminated with ∼10 mol % diaddition product. The mixture was separated to give 53% yield of pure **16** as a colorless oil: ^{1}H NMR δ 7.35−7.25 (m, 4H), 7.14−7.08 (m, 2H), 6.88 (br d, J = 8 Hz, 1H), 6.80 (br d, J = 8 Hz, 1H), 3.71 (s, 3H), 2.34 (m, 2H), 2.23 (s, 6H), 1.40−1.30 (m, 2H), 1.12 (sextet, J = 7.2 Hz, 2H), 0.75 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 162.0, 158.9, 145.2, 144.7, 131.1, 129.0, 128.1, 125.0, 122.0, 117.3, 108.9, 68.7, 56.2, 33.7, 29.5, 22.9, 14.2; EIMS *m*/*z* (relative intensity) 350 (M^+, 38), 119 (100); LSIMS−HRMS calcd for $C_{21}H_{27}N_4O$ (M + H^+) 350.2107, found 350.2109.

***N*(2)-Cumyl-5-(2,6-di-(*n*-butyl)phenyl)tetrazole (17).** Using 3.0 equiv of *n*-butyllithium and tetrazole **6**, the general procedure gave tetrazole **17** in 84% yield as a colorless oil: ^{1}H NMR δ 7.35−7.25 (m, 4H), 7.16−7.12 (m, 2H), 7.10 (d, J = 7.7 Hz, 2H), 2.32 (m, 2H), 2.23 (s, 6H), 1.40−1.28 (m, 2H), 1.14 (sextet, J = 7.1 Hz, 2H), 0.76 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 163.8, 144.1, 143.1, 129.6, 128.7, 127.9, 126.9, 126.8, 124.6, 68.2, 33.7, 33.4, 29.1, 22.6, 13.8. Anal. Calcd for $C_{24}H_{32}N_4$: C, 76.56; H, 8.57; N, 14.88. Found: C, 76.54; H, 8.43; N, 14.71.

***N*(2)-Cumyl-5-(3-methoxy-4′-methyl-[1,1′-biphenyl]-2-yl)-tetrazole (18) and *N*(2)-cumyl-5-(4,4″-[1,1′;3′,1″]terphenyl-2′-yl)tetrazole (19).** Tetrazole **6** reacted with 4.0 equiv of *p*-tolyllithium to give a mixture of mono- and diaddition products. The mixture was separated to afford tetrazole **18** in 38% yield as a crystalline solid: mp 138−139 °C; ^{1}H NMR δ 7.46 (t, J = 7.8 Hz, 1H), 7.25−7.16 (m, 3H), 7.04−6.92 (m, 6H), 6.89−6.84 (m, 2H), 3.79 (s, 3H), 2.31 (s, 3H), 2.07 (s, 6H); ^{13}C NMR δ 161.0, 158.1, 144.2, 143.6, 136.8, 135.8, 130.3, 128.6, 128.0, 127.8, 126.9, 124.1, 121.7, 115.8, 109.1, 67.6, 55.4, 28.6, 20.6; EIMS *m*/*z* (relative intensity) 384 (M^+, 50),119 (100); EI-HRMS calcd for $C_{24}H_{24}N_4O$ 384.1950, found 384.1947. Anal. Calcd for $C_{24}H_{24}N_4O$ (0.5 mol of H_2O): C, 73.26; H, 6.40; N, 14.24. Found: C, 73.54; H, 6.21; N, 14.21. Also isolated was tetrazole **19** in 24% yield as a crystalline solid: mp 168−169 °C; ^{1}H NMR (DMSO-d_6) δ 7.68 (t, J = 7.8 Hz, 1H), 7.47 (d, J = 7.8 Hz, 2H), 7.32−7.20 (m, 3H), 7.06 (d, J = 8.0 Hz, 4H), 6.94 (d, J = 8.0 Hz, 4H), 6.80−6.72 (m, 2H), 2.28 (s, 6H), 1.87 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 163.0, 143.7, 142.8, 137.0, 136.2, 130.0, 128.7, 128.6, 128.4, 128.2, 125.2, 124.3, 67.4, 28.8, 20.6; EIMS *m*/*z* (relative intensity) 444 (M^+, 52), 269 (100); EI-HRMS calcd for $C_{30}H_{28}N_4$ 444.2314, found 444.2314. Anal. Calcd for $C_{30}H_{28}N_4$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.68; H, 6.25; N, 12.75.

***N*(2)-Cumyl-5-(2,6-dinaphthalen-1-yl-phenyl)tetrazole (20).** Tetrazole **6** reacted with 5.0 equiv of 1-naphthyllithium to give tetrazole **20** as an apparent 45:55 mixture of slowly interconverting meso and *d*,*l* forms in 60% yield: mp 173.5−174.5 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C) δ 7.80−7.25 (m, 17H), 7.12−7.05 (m, 1H), 7.01−6.92 (m, 2H), 6.20−6.10 (m, 2H), 1.38, 1.36, and 1.34 (singlets in ∼2:1:1 ratio, total integration 6H); ^{1}H NMR (600 MHz, $CDCl_3$, −78 °C) δ 7.9−7.0 (m, 20H), 6.16 (d, J = 7.5 Hz, 2H, 45 mol % mixture), 6.05 (d, J = 7.5 Hz, 2H, 55 mol % mixture), 1.42 (s, 6H, 45 mol % mixture), 1.35 (s, 3H, 55 mol % mixture), 1.17 (s, 3H, 55 mol % mixture); LSIMS *m*/*z* (relative intensity) 517 (M + H^+, 24), 399 (100). Anal. Calcd for $C_{36}H_{28}N_4$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.71; H, 5.44; N, 11.25.

***N*(2)-Cumyl-5-(2-hydroxyphenyl)tetrazole (12). Method A.** Compound **12** (0.0095 g, 2% yield) was isolated from the reaction of **4** with *n*-butyllithium (vide supra).

Method B. Compound **12** was prepared independently as follows: *N*(2)-Cumyl-5-phenyltetrazole (0.200 g, 0.8 mmol) was dissolved in 1 mL of dry THF at −10 °C. A 1.6 M solution of *n*-butyllithium in hexane (520 μL, 0.83 mmol) was added dropwise to give a dark purple reaction mixture. After 45 min at −10 °C, oxygen was bubbled into the reaction mixture through a dispersion tube to give a light yellow solution. Sodium borohydride (0.03 g, 0.8 mmol) was added, and the reaction mixture was stirred for 1 h, neutralized with dilute HCl, and extracted with ethyl acetate to give a 1.5:1 mixture of starting material and compound **12**. Chromatographic separation of the mixture afforded 55 mg of pure **12** as a crystalline solid: mp 70.5−71.0 °C; ^{1}H NMR 9.76 (s, 1H), 8.06 (dd, J = 7.8, 1.7 Hz, 1H), 7.39−7.25 (m, 4H), 7.17−7.12 (m, 2H), 7.07 (dd, J = 8.4, 1.0 Hz, 1H), 6.97 (td, J = 8.4, 1.0 Hz, 1H), 2.24 (s, 6H); ^{13}C NMR δ 163.8, 156.4, 143.1, 136.2, 132.1, 128.8, 128.1, 127.5, 124.7, 119.9, 117.5, 111.3, 69.0, 29.1; EIMS *m*/*z* (relative intensity) 280 (M^+, 8), 119 (100). Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 69.03; H, 5.78; N, 19.70.

***N*(2)-Cumyl-5-(2-*n*-butyl-6-hydroxyphenyl)tetrazole (13). Method A.** Compound **13** (0.0131 g, 2% yield) was isolated from the reaction of **4** with *n*-butyllithium (vide supra).

Method B. Compound **13** was prepared independently as follows: Tetrazole **16** (0.196 g, 0.56 mmol) and sodium thiomethoxide (0.235 g, 3.4 mmol) were added to 3 mL of dry DMF. The solution was allowed to reflux for 1 h, cooled to room temperature, diluted with water, and extracted with ether. The crude extract was purified by column chromatography to give 32 mg (17% yield) of tetrazole **13** as a light yellow oil: ^{1}H NMR δ 7.40−7.15 (m, 6H), 6.93 (dd, J = 8.3, 1.3 Hz, 1H), 6.80 (dd, J = 7.6, 1.3 Hz, 1H), 3.01 (m, 2H), 2.24 (s, 6H), 1.50−1.47 (m, 2H), 1.26 (sextet, J = 7.1 Hz, 2H), 0.80 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 163.7, 157.9, 143.9, 143.3, 131.2, 128.7, 128.1, 124.7, 124.6, 122.3, 115.3, 110.2, 68.9, 35.5, 33.4, 29.0, 22.9, 14.0; LSIMS−HRMS calcd for $C_{20}H_{25}N_4O$ (M + H^+) 337.2028, found 337.2026.

Deprotection of *N*(2)-Cumyltetrazoles. Method A. *N*(2)-Cumyl-5-phenyltetrazole (0.2892 g, 1.1 mmol), potassium formate (0.50 g, 6 mmol), and 20% Pd/C (0.1 g) were added to 5 mL of absolute ethanol, and the mixture was heated to reflux for 4 h. The reaction mixture was cooled to room temperature,

filtered through Celite, and concentrated to give a residue. The residue was triturated with water to remove excess potassium formate and dried in a vacuum oven to give 0.166 g (quantitative yield) of 5-phenyl-1*H*-tetrazole.

Method B. Cumyl-protected tetrazole **21**[7] (8.0 g, 14.1 mmol) and 2-ethyl-2-(hydroxymethyl)-1,3-propanediol tris(2-mercaptoacetate) (4.84 mL, 15.5 mmol) were mixed in 120 mL of dry acetonitrile. Freshly distilled boron trifluoride etherate (6.92 mL, 56 mmol) was added dropwise to the stirred solution at 23 °C. After 1.5 h at 23 °C the reaction mixture was quenched with 180 mL of 1 M NaOH, and washed with 40 mL of ethyl acetate. The basic aqueous layer was neutralized with 3 M aqueous HCl to give a crystalline product. The solid was collected by vacuum filtration, triturated with 3 × 30 mL of methanol, and dried under vacuum to give 5.9 g (93% yield) of tetrazole **22**: mp 228−230 °C dec; ^{1}H NMR (DMSO-d_6) δ 12.22 (s, 1H), 8.09−8.06 (m, 1H), 7.68−7.45 (m, 5H), 7.23−7.14 (m, 4H), 7.02 (d, J = 8.2 Hz, 2H), 4.70 (s, 2H), 4.07 (br t, J = 7.2 Hz, 2H), 1.35−1.15 (m, 4H), 0.77 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 167.0, 146.0, 141.6, 137.8, 137.6, 136.0, 131.4, 131.0, 129.3, 128.4, 128.0, 126.8, 122.4, 121.6, 110.7, 104.7, 43.2, 31.4, 30.2, 19.8, 13.9. Anal. Calcd for $C_{27}H_{25}N_5O_2$: C, 71.82; H, 5.58; N, 15.51. Found: C, 71.64; H, 5.62; N, 15.39.

Supporting Information Available: Copies of ^{1}H and ^{13}NMR spectra of 5-(2-*n*-butyl-3-methoxyphenyl)-1*H*-tetrazole and compounds **2**−**19**, **21**, and **22** and copies of 300 and 600 MHz ^{1}H NMR spectra of compound **20** at several temperatures. This material is available free of charge via the Internet at http://ppubs.acs.org.

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