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Ambient-Temperature Cobalt-Catalyzed Cycloaddition Strategies to Aromatic Boronic Esters

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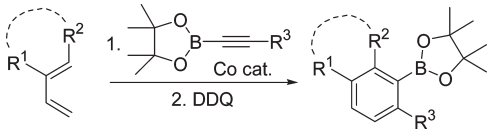
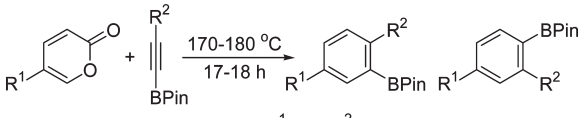


The room-temperature cobalt-catalyzed [4 + 2] cycloaddition of alkynylboronates and 1,3-dienes provides a convenient and general method for the synthesis of benzene-based aromatic boronic esters. Two complementary aromatization strategies involving in situ elimination and DDQ oxidation were explored, with the latter finding more generality. Finally, the potential of this technique to generate highly functionalized biaryls has been demonstrated via the synthesis of chiral (racemic) DMAP catalysts.

Aromatic boronic acid derivatives are among the most widely used synthetic intermediates in organic chemistry.[1] Their synthesis has traditionally involved the employment of aryl halides and related species via the intermediacy of a main group organometallic reagent[2] or, more recently, by the exploitation of Pd catalysis.[3] Additionally, an alternative approach whereby a C−H bond is transformed directly to a C−B bond has emerged and has proved to be particularly effective for the synthesis of heteroaromatic compounds.[4]

Benzannulation approaches to aromatic boronic acid derivatives hold some significant potential as they provide the opportunity to construct complex and heavily substituted systems from relatively simple starting materials. In this context, the inverse-electron-demand [4 + 2] cycloaddition of cyclopentadienones and 2-pyrones provides such compounds in good overall yield and with modest to high levels of regiocontrol.[5] The latter method has proved to be of more general utility, although it requires activated 1,3-diene substrates. Some typical examples are outlined in Scheme 1. While this strategy permits the formation of highly functionalized aromatic boronic acid derivatives in a single step, the process requires elevated temperatures and long reaction times.

SCHEME 1



R^1 = H; R^2 = $SiMe_3$; 86%
R^1 = H; R^2 = Ph; 0%
R^1 = CO_2Me; R^2 = $SiMe_3$; 100% (1:1)
R^1 = CO_2Me; R^2 = Ph; 75% (14:1)

In an effort to uncover more efficient and less demanding conditions for benzannulation reactions, catalytic benzannulation techniques have begun to find prominence. In the context of alkynylboronate reactions, Yamamoto has demonstrated the use of the boronate moiety as a temporary tether to control the regioselectivity of Ru-catalyzed [2 + 2 + 2] cyclotrimerization reactions.[6] An intriguing alternative to this process is the cobalt-catalyzed [4 + 2] cycloaddition of nonactivated 1,3-dienes with alkynylboronates.[7] This process gives rise to 1,4-dienylboronic esters in high yield and with excellent levels of regiocontrol. As outlined in Scheme 2, we were interested in the potential of these 1,4-dienylboronic esters to function as precursors to the aromatic analogues. Specifically, we envisaged that chemoselective oxidation of the hydrocarbon ring (instead of the oxidatively labile C−B bond) would provide the desired compounds.[8] Should this approach prove to be unwieldy, we anticipated that 1,3-dienes bearing a nucleofuge at C-1 would provide access to the correct ring oxidation level after a simple elimination reaction.[9,10] We report herein our investigations toward this end and the realization of a general and mild method for the synthesis of aromatic boronic esters bearing substitution patterns not readily accessible by traditional strategies.

(1) *Boronic Acids*; Hall, D.G., Ed.; Wiley-VCH: Weinheim, 2005.
(2) Vaultier, M.; Carboni, B. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 11, p 191.
(3) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458. (c) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164.
(4) For recent examples, see: (a) Harrison, P.; Morris, J.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2009**, *11*, 3586. (b) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058. (c) Jo, T. S.; Kim, S. H.; Shin, J.; Bae, C. *J. Am. Chem. Soc.* **2009**, *131*, 1656.
(5) (a) Moore, J. E.; York, M.; Harrity, J. P. A. *Synlett* **2005**, 860. (b) Delaney, P. M.; Moore, J. E.; Harrity, J. P. A. *Chem. Commun.* **2006**, 3323. (c) Delaney, P. M.; Browne, D. L.; Adams, H.; Plant, A.; Harrity, J. P. A. *Tetrahedron* **2008**, *64*, 866.
(6) (a) Yamamoto, Y.; Ishii, J.-i.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712. (b) Yamamoto, Y.; Ishii, J.-i.; Nishiyama, H.; Itoh, K. *Tetrahedron* **2005**, *61*, 11501.
(7) (a) Hilt, G.; Smolko, K. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 2795. (b) Hilt, G.; Hess, W.; Schmidt *Eur. J. Org. Chem.* **2005**, 2526. (c) Hilt, G.; Lüers, S.; Smolko, K. I. *Org. Lett.* **2005**, *7*, 251.
(8) A single example of DDQ oxidation of 1,4-dienylboronic esters was reported by Hilt.[7b]
(9) For an early demonstration of this strategy for the synthesis of aromatic compounds by Diels−Alder reactions, see: Dowd, P.; Weber, W. *J. Org. Chem.* **1982**, *47*, 4774.
(10) For cobalt-catalyzed cycloaddition of 1-alkoxydienes toward aromatic products, see: Hilt, G.; Smolko, K. I.; Lotsch, B. V. *Synlett* **2002**, 1081.

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SCHEME 2

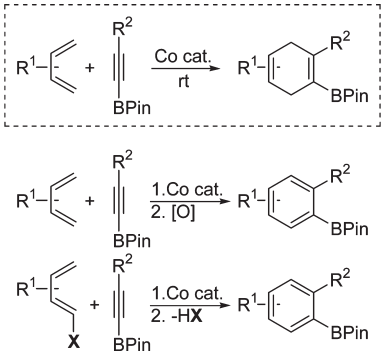
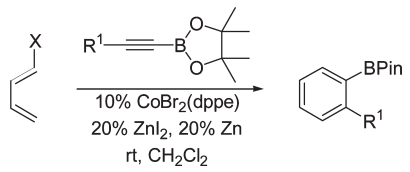
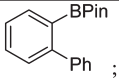
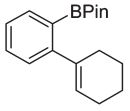
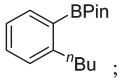
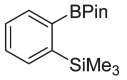


TABLE 1. Scope of the Cycloaddition−Elimination Strategy



entry	X	R^1	product	yield
1	$OSiMe_3$; **1**	Ph; **4**	 ; **8**	59%
2	OPh; **2**	Ph; **4**	**8**	54%
3	SPh; **3**	Ph; **4**	**8**	88%
4	$OSiMe_3$; **1**	 ; **5**	 ; **9**	61%
5	OPh; **2**	**5**	**9**	51%
6	SPh; **3**	**5**	**9**	78%
7	$OSiMe_3$; **1**	^{n}Bu; **6**	 ; **10**	65%
8	OPh; **2**	^{n}Bu; **6**	**10**	68%
9	SPh; **3**	^{n}Bu; **6**	**10**	81%
10	SPh; **3**	$SiMe_3$; **7**	 ; **11**	54%

We began our studies by exploring the cycloaddition−elimination strategy and prepared a selection of 1,3-dienes bearing various potential leaving groups at C-1. Specifically, we prepared a silyl enol ether, an aryl enol ether, and a thiophenol-based enol ether. After some preliminary optimization studies, we found that a catalyst solution generated from 10 mol % of $CoBr_2$(dppe) and 20 mol % of Zn metal and ZnI_2 provided clean and consistent conversion of each 1,3-diene to the corresponding aromatic boronic ester at room temperature. Moreover, we were pleased to find that the corresponding leaving groups (silanol, phenol, and thiophenol) did not interfere with the active catalyst, nor did they appear to promote significant deboronation of the alkyne substrates. This latter point is noteworthy given the facile hydrolysis of the alkyne carbon−boron bond by protic species.[11] As depicted in Table 1, the phenyl-substituted alkynylboronate **4** was converted into **8** in good to high yield with all three dienes, although the thiophenol-based substrate **3** proved to be the most efficient (entries 1−3). The same trend was noted when the cyclohexenyl- and *n*-butyl-substituted alkynes **5** and **6** were used (entries 4−9), and so the studies were completed by carrying out the cycloaddition of trimethylsilyl-substituted alkyne **7** with **3** alone to provide **11** (entry 10). An important issue that relates to the 1,3-diene substrates in all cases is that they are prone to polymerization during storage and under the reaction conditions. Indeed, we suspect that the consistently better yields obtained in the case of **3** as compared to **1** and **2** may be due to the relative stability of this particular substrate.

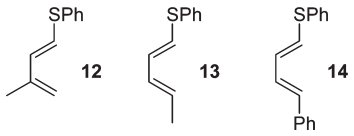


FIGURE 1. Unreactive thioenol ether substrates.

With these preliminary observations in hand, we decided to extend this chemistry to include more heavily substituted dienes as a means to obtaining more functionalized aromatics and as a vehicle for studying cycloaddition regioselectivity. To our disappointment, 1,3-dienes **12**−**14** were found to be inert to cycloaddition or produced complex reaction mixtures (Figure 1).

While the cycloaddition−elimination concept proved to be quite effective for the synthesis of 1,2-disubstituted aromatic boronic esters, the limitations associated with more heavily substituted congeners prompted us to explore the cycloaddition−oxidation pathway in the hope that a more general protocol could be uncovered. Accordingly, we explored the cobalt-catalyzed reaction of a range of commercial or readily prepared 1,3-dienes and subjected the crude cycloadducts to oxidation; our results are shown in Table 2. Pleasingly, simple *ortho*-substituted benzene boronic esters could be readily generated in good yield following a cobalt-catalyzed cycloaddition−DDQ oxidation protocol (entries 1−3). More importantly, and in contrast to the cycloaddition−elimination approach, more heavily substituted products were also found to be accessible by this protocol. Isoprene **16** provided 1,3,4-trisubstituted products **20**−**23** in excellent yield and with complete regiocontrol (entries 4−7), and the method was equally effective for the formation of 1,2,3,4-tetrasubstituted products **24**−**27** (entries 8−11). Finally, we employed 1-phenylbuta-1,3-diene **19** for the synthesis of 1,2,3-trisubstituted aromatic systems. Previous studies on internal alkynes had shown that the cobalt-catalyzed cycloaddition of 1-substituted 1,3-dienes proceeded with variable regioselectivity.[12] In the event, the corresponding 1,2,3-trisubstituted product **28** was generated in good yield and with useful levels of regiocontrol (entry 12).[13]

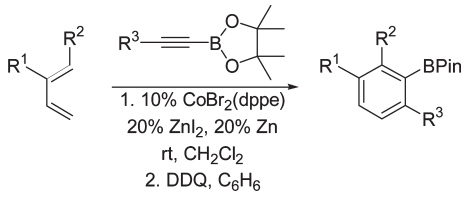
The present methodology makes hindered aromatic compounds that are amenable to further elaboration (e.g., **24**−**28**),

(11) Brown, H. C.; Bhat, N. G.; Srebnik *Tetrahedron Lett*. **1988**, *29*, 2631.

(12) Hilt, G.; Danz, M. *Synthesis* **2008**, 2257.

(13) The regiochemistry of compounds **21**, **22**, **25**, and **26** was assigned by NOE spectroscopy; the regiochemistry of compound **28** was made by chemical derivatization of the minor regioisomer (see the Supporting Information). The regiochemistry of the remaining unsymmetrical compounds was assigned by inference.

TABLE 2. Scope of the Cycloaddition−oxidation Strategy

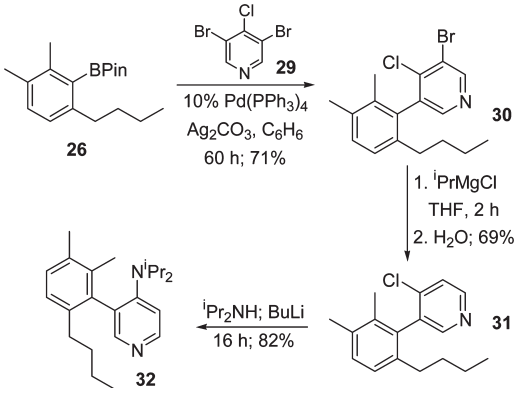


entry	1,3-diene	R^3	product	yield[a]
1	; **15**	Ph; **4**	BPin, Ph ; **8**	68%
2	**15**	; **5**	BPin ; **9**	64%
3	**15**	^{n}Bu; **6**	BPin, ^{n}Bu ; **10**	67%
4	; **16**	Ph; **4**	BPin, Ph ; **20**	84%; (>95:5)
5	**16**	; **5**	BPin ; **21**	77%; (>95:5)
6	**16**	$SiMe_3$; **7**	BPin, $SiMe_3$; **22**	70%; (>95:5)
7	**16**	^{n}Bu; **6**	BPin, ^{n}Bu ; **23**	80%; (>95:5)
8	; **17**	Ph; **4**	BPin, Ph ; **24**	74%; (>95:5)
9	**17**	; **5**	BPin ; **25**	76%; (>95:5)
10	**17**	^{n}Bu; **6**	BPin, ^{n}Bu ; **26**	73%; (>95:5)
11	; **18**	^{n}Bu; **6**	^{t}Bu, BPin, ^{n}Bu ; **27**	71%; (>95:5)
12	; **19**	^{n}Bu; **6**	Ph, BPin, ^{n}Bu ; **28**	77%; (85:15)

[a]Values in parentheses are cycloaddition regioselectivities.[13]

and we anticipate that this method could constitute a valuable technique for the synthesis of axially chiral catalysts and ligands. Indeed, one of the most exciting applications of

SCHEME 3



hindered aromatic compounds in recent times has been their application as chiral organocatalysts. Specifically, a large family of chiral 4-aminopyridines have emerged that have shown significant potential in the kinetic resolution of chiral secondary alcohols.[14] Among this family of catalysts, Spivey and co-workers have investigated an elegant class of DMAP equivalents that incorporate an atropisomeric axis as the key element of chirality.[15] We envisaged that the methodology developed in this program could represent a flexible and modular strategy for the synthesis of such catalysts. Accordingly, and as depicted in Scheme 3, cross-coupling of 3,5-dibromo-4-chloropyridine **29** with boronic ester **26** provided hindered biaryl **30**. Subsequent reduction of the remaining bromide and nucleophilic aromatic substitution of chloride **31** with LDA resulted in the synthesis of hindered DMAP analogue **32**. The concise synthesis of functionalized boronic esters such as **26** outlined herein, together with the robustness of the Spivey route for the synthesis of these atropisomeric biaryl pyridines, suggests that this approach could provide a powerful method for the discovery of new asymmetric kinetic resolution catalysts.

In conclusion, we have demonstrated that benzene boronic acids bearing a range of substitution patterns can be accessed by a Co-catalyzed [4 + 2] cycloaddition of alkynylboronates via cycloaddition−elimination and cycloaddition oxidation strategies. This method provides a powerful means for the generation of heavily substituted aromatic products under ambient conditions, and the potential for this chemistry to provide new chiral biaryl catalysts and ligands is underway and will be reported in due course.

Experimental Section

Representative Procedure for the Cycloaddition−Elimination Strategy. 2-(2-Cyclohexenylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9). A flame-dried Schlenk tube was charged with [$CoBr_2$(dppe)] (62 mg, 0.1 mmol, 10 mol %), zinc iodide (63 mg, 0.2 mmol, 20 mol %), and powdered zinc (13 mg, 0.2 mmol, 20 mol %) in anhydrous dichloromethane (1 mL) under an argon atmosphere. After addition of diene **3** (162 mg, 1 mmol) and cyclohexynylalkynylboronate (232 mg, 1 mmol), the reaction

(14) For a review, see: Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436.

(15) (a) Spivey, A. C.; Arseniyadis, S.; Fekner, T.; Maddaford, A.; Leese, D. P. *Tetrahedron* **2006**, *62*, 295. (b) Spivey, A. C.; Leese, D. P.; Zhu, F.; Davey, S. G.; Jarvest, R. L. *Tetrahedron* **2004**, *60*, 4513. (c) Spivey, A. C.; Zhu, F.; Mitchell, M. B.; Davey, S. G.; Jarvest, R. L. *J. Org. Chem.* **2003**, *68*, 7379. (d) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154.

mixture was stirred at ambient temperature for 16 h. The mixture was filtered through a pad of silica gel and the solvent removed in vacuo. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5), provided the desired compound as a clear oil (222 mg, 78%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (12H, s), 1.65−1.83 (4H, m), 2.15−2.19 (2H, m), 2.35−2.38 (2H, m), 5.55−5.58 (1H, m), 7.19−7−27 (2H, m), 7.33−7.40 (1H, m), 7.63−7.66 (1H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 22.1, 23.2, 24.8, 25.7, 30.6, 83.5, 125.2, 125.7, 127.1, 129.8, 134.3, 140.9, 150.7; FTIR (film) 2978 (s), 2926 (s), 1596 (w), 1392 (s), 1145 (s) cm^{-1}; HRMS (EI) m/z $[MH]^+$ calcd for $C_{18}H_{26}BO_2$ 285.2021, found 285.2026.

Representative Procedure for the Cycloaddition−Oxidation Strategy. 2-(2-*n*-Butylphenyl)4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10). A flame-dried Schlenk tube was charged with [$CoBr_2$(dppe)] (62 mg, 0.1 mmol, 10 mol %), zinc iodide (63 mg, 0.2 mmol, 20 mol %), and powdered zinc (13 mg, 0.2 mmol, 20 mol %) in anhydrous dichloromethane (1 mL) under an argon atmosphere. After addition of butadiene (54 mg, 1 mmol) and *n*-butylalkynylboronate (208 mg, 1 mmol), the reaction mixture was stirred at ambient temperature for 4 h. The mixture was filtered through a pad of silica gel and the solvent removed in vacuo. The crude mixture was dissolved in benzene (10 mL), and DDQ (250 mg, 1.1 mmol) was added. The mixture was stirred for 1 h. A basic solution (10% NaOH/10% $Na_2S_2O_3$, 20 mL) was introduced, and the aqueous layer was extracted with diethyl ether (3×20 mL). The resulting organic layer was washed with brine and dried over $MgSO_4$. After evaporarion in vacuo, the crude product was purified by flash chromatography over silica gel eluting with pentane/EtOAc (95/5) to provide the desired compound as a clear oil (174 mg, 67%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.5 Hz), 1.39 (12H, s), 1.39−1.47 (2H, m), 1.56−1.60 (2H, m), 2.90−2.94 (2H, m), 7.20−7−23 (2H, m), 7.36−7.40 (1H, m), 7.80−7.83 (1H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0, 22.8, 24.9, 35.6, 35.7, 83.3, 124.8, 129.2, 130.8, 136.0, 150.2; FTIR (film) 3051 (w), 2977 (s), 2871 (m), 1600 (s), 1442 (s), 1146 (s) cm^{-1}; HRMS (EI) m/z $[MH]^+$ calcd for $C_{16}H_{26}BO_2$ 261.2037, found 261.2026.

3 Bromo-5-(6-*n*-butyl-2,3-dimethylphenyl)-4-chloropyridine (30). To a solution of **26** (196 mg, 0.68 mmol) and 3,5-dibromo-4-chloropyridine (148 mg, 0.54 mmol) in benzene (7 mL) were added silver(I) carbonate (375 mg, 1.36 mmol) and $Pd(PPh_3)_4$ (79 mg, 0.05 mmol, 10 mol %), and the resulting mixture was heated at reflux for 60 h. The reaction mixture was filtered, the organic layer washed with water and brine, dried over $MgSO_4$, and the solvent removed in vacuo. The crude mixture was purified by flash chromatography (pentane/CH_2Cl_2 25/75) to give **30** as a pale yellow oil (135 mg, 71%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.79 (3H, t, J = 7.5 Hz), 1.15−1.25 (2H, m), 1.33−1.43 (2H, m), 1.91 (3H, s), 2.11−2.19 (1H, m), 2.25−2.31 (1H, m), 2.33 (3H, s), 7.11 (1H, d, J = 8.0 Hz), 7.23 (1H, d, J = 8.0 Hz), 8.31 (1H, s), 8.79 (1H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2, 17.2, 20.7, 22.8, 33.3, 33.6, 122.1, 126.8, 130.8, 134.7, 134.8, 135.2, 138.2, 138.9, 144.2, 150.3, 151.7; FTIR (film) 2955 (s), 2929 (s), 2863 (m), 1558 (w), 1425 (m), 1389 (s), 749 (s) cm^{-1}; HRMS (EI) m/z $[M]^+$ calcd for $C_{17}H_{19}{}^{79}Br^{35}ClN$ 351.0401, found 351.0389.

3 (6-*n*-Butyl-2,3-dimethylphenyl)-4-chloropyridine (31). To a solution of **30** (41 mg, 0.12 mmol) in THF (1 mL) was added dropwise at room temperature a solution of ^{i}PrMgCl (2 M, 90 μL, 0.17 mmol) in THF. After being stirred at room temperature for 2 h, the reaction mixture was quenched with water and extracted with dichloromethane, and the extracts were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc 5/1) to give **31** as a clear oil (26 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (3H, t, J = 7.5 Hz), 1.14−1.23 (2H, m), 1.32−1.42 (2H, m), 1.91 (3H, s), 2.13−2.21 (1H, m), 2.26−2.33 (1H, m), 2.33 (3H, s), 7.10 (1H, d, J = 8.0 Hz), 7.21 (1H, d, J = 8.0 Hz), 7.48 (1H, d, J = 5.5 Hz), 8.41 (1H, s), 8.54 (1H, d, J = 5.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.8, 16.8, 20.3, 22.4, 32.9, 33.3, 124.3, 126.3, 130.1, 134.2, 134.4, 135.0, 136.2, 138.9, 144.0, 149.2, 151.8; FTIR (film) 2958 (s), 2928 (s), 2861 (m), 1581 (w), 1456 (m), 1260 (m), 1194 (w), 750 (s) cm^{-1}; HRMS (EI) m/z $[MH]^+$ calcd for $C_{17}H_{20}{}^{35}ClN$ 273.1271, found 273.1284.

3 (6-*n*-Butyl-2,3-dimethylphenyl)-*N*,*N*-diisopropylpyridin-4-amine (32). To a solution of **31** (15 mg, 0.05 mmol) in THF (0.5 mL) was added diisopropylamine (48 mg, 0.5 mmol). A freshly prepared solution of LDA in THF (2.1 M, 55 μL, 0.11 mmol) was then added at room temperature via syringe. The mixture was heated to reflux for 16 h. The reaction mixture was cooled to rt, and then the solvent was removed in vacuo. The residue was extracted from water with dichloromethane, the organic layer dried over $MgSO_4$, and solvent removed in vacuo. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc 2/1) to give **32** as a yellow oil (11 mg, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (3H, t, J = 7.5 Hz), 1.15−1.30 (14H, m), 1.36−1.44 (2H, m), 1.98 (3H, s), 2.32−2.35 (5H, m), 3.76−3.87 (2H, m), 6.98−6.99 (1H, m), 7.07 (1H, d, J = 8.0 Hz), 7.15 (1H, d, J = 8.0 Hz), 7.83 (1H, d, J = 1.5 Hz), 8.26 (1H, d, J = 3.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.8, 17.4, 20.4, 21.1, 21.4, 22.6, 33.4, 33.7, 47.7, 126.2, 126.4, 129.2, 134.1, 135.0, 136.3, 138.3, 138.9, 139.3, 139.6, 143.7; FTIR (film) 2965 (s), 2930 (s), 2871 (m), 1582 (w), 1456 (s), 1368 (m), 1195(s), 817 (w) cm^{-1}; HRMS (EI) m/z $[M]^+$ calcd for $C_{23}H_{34}N_2$ 338.2711, found 338.2722.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.