JOC*Note*

Stereoselective Synthesis of 3,3-Diarylacrylonitriles as Tubulin Polymerization Inhibitors

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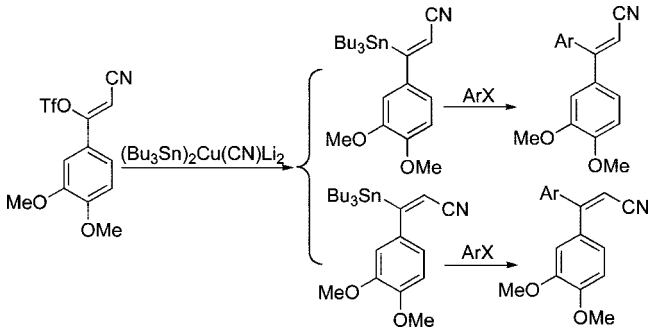

A series of 3,3-diarylacrylonitriles were synthesized stereoselectively as tubulin polymerization inhibitors for potential use in cancer chemotherapy. This synthetic route features stannylcupration and palladium-catalyzed Stille cross-coupling chemistry, allowing both *E* and *Z* isomers of 3,3-diarylacrylonitriles to be prepared in a very short sequence of reactions.

Microtubules, made of heterodimeric α- and *β*-tubulin subunits with highly dynamic behavior,[1] are fundamental components of cellular structure. They participate in a wide variety of critical cellular functions, such as motility, division, shape maintenance, and intracellular transport.[2] Drugs that interfere with microtubule/tubulin dynamic equilibrium have antimitotic activity. These drugs modulate microtubule assembly either by inhibition of tubulin polymerization or by blocking microtubule disassembly. On the basis of their mechanisms of action, these drugs are classified as tubulin polymerization inhibitors or microtuble stabilizers.[3] Some common tubulin polymerization inhibiting anticancer drugs derived from natural sources include colchicine (Figure 1), the cryptophycins, vincristine, combretastatin A4, and vinblastine. Well-known microtubule stabilizing anticancer drugs include paclitaxel (Taxol), docetaxel (Taxotere), discodermolide, the epothilones, the eleutherobins, and laulimalide.[4] These small molecules bind to different sites on tubulin and thereby exert diverse effects on microtubule dynamics. However, all of these compounds have limitations resulting from high toxicity, poor oral bioavailability, difficulty of synthesis or isolation from natural sources, and drug resistance.[5] Therefore, there is current interest in the development of new synthetic compounds with both improved oral bioavailability and lower toxicity. Recently, researchers at Celgene Corp. reported a novel synthetic tubulin polymerization inhibitor, the 3,3-diarylacrylonitrile CC-5079 (Figure 1), for potential use in cancer chemotherpy.[6]

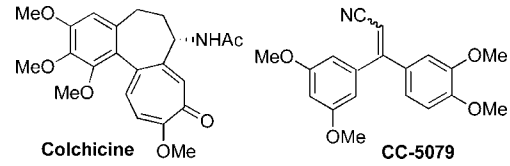

FIGURE 1. Colchicine and synthetic tubulin polymerization inhibitor CC-5079.

3,3-Diarylacrylonitriles bind to tubulin at the colchicine-binding site.[6] In the Celgene study, compound **CC-5079** was tested for biological activity as a mixture of *E* and *Z* isomers. Methods that would allow the synthesis of the *E* and *Z* isomers are needed so that either one can be prepared in stereochemically pure form, thus eliminating the need for the difficult and time-consuming separation of the final products. To explore the structure−activity relationships associated with 3,3-diarylacrylonitrile tubulin polymerization inhibitors, a set of compounds derived from the general structures (*E*)-**1** and (*Z*)-**1** were considered (Figure 2), and a versatile synthesis that would allow the incorporation of a variety of substituents was therefore needed. This led to the decision to explore the Stille cross-coupling reaction as a possible solution of this problem (Figure 2).[7]

The target compounds (*E*)-**1** and (*Z*)-**1** can be disconnected retrosynthetically into the aromatic halides or the triflate **4** and

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(1) Jordan, M. A. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *1*, 1–17.
(2) Downing, K. H.; Nogales, E. *Curr. Opin. Cell Biol.* **1998**, *10*, 16–22.
(3) (a) Li, Q.; Sham, H. L. *Exp. Opin. Ther. Pat.* **2002**, *12*, 1662–1702. (b) Prinz, H. *Exp. Rev. Anticancer Ther.* **2002**, *2*, 695–708. (c) Beckers, T.; Mahboobi, S. *Drugs Future* **2003**, *28*, 767–785.
(4) Kavallaris, M.; Verills, N. M.; Hill, B. T. *Drug Resist. Updates* **2001**, *4*, 392–401.
(5) Wood, K. W.; Cornwell, W. D.; Jackson, J. R. *Curr. Opin. Pharmacol.* **2001**, *1*, 370–377.
(6) Zhang, L. H.; Wu, L.; Raymon, H. K.; Chen, R. S.; Corral, L.; Shirley, M. A.; Narla, R. K.; Gamez, J.; Muller, G. W.; Stirling, D. I.; Bartlett, J. B.; Schafer, P. H.; Payvandi, F. *Cancer Res.* **2006**, *66*, 951–959.
(7) Merkushev, E. B. *Synthesis* **1998**, 923–937.

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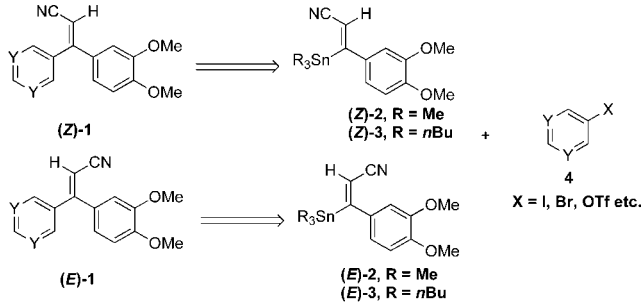
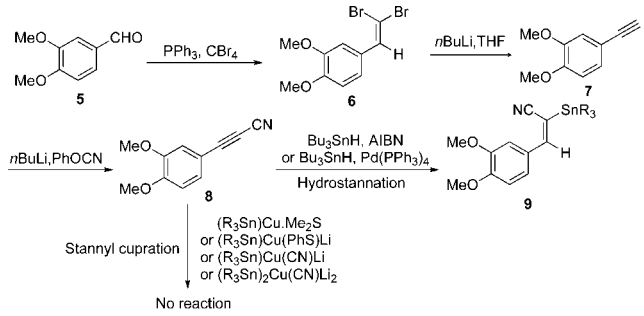


FIGURE 2. Retrosynthetic analysis of 3,3-diarylacrylonitriles **1**.

the possible vinylstannane intermediates **2** or **3** (either *E* or *Z* isomers). Intermediates of general structure **4** are commercially available or can be prepared easily by halogenation of aromatic rings[7] or triflation of substituted phenols.[8]

There are many efficient methods for the synthesis of vinylstannanes reported in the literature.[9] For example, vinylstannanes can be prepared by hydrostannation of alkynes either under radical conditions[10] or catalyzed by transition metal complexes like $Pd(PPh_3)_4$.[11] However, when propiolonitrile **8** was treated with Bu_3SnH under either of these two conditions, only the undesired vinylstannane intermediate **9** with the incorrect regiochemistry was obtained (Scheme 1).

SCHEME 1. Failed Hydrostannation or Stannyl Cupration Attempts for the Synthesis of Vinylstannanes 2 or 3



Therefore, these unsuccessful attempts to generate compounds **2** or **3** led us to consider another well-developed method for the preparation of vinylstannanes: stannylcupration of alkynes.[12] Stannylcuprates are known to react in a Michael fashion with 2-ynoates to afford 3-trialkylstannyl-2-enoates.[13] Although there is no literature precedent, we attempted to extend this chemistry to the direct stannylcupration of propionitrile **8** to afford 3-(trialkylstannyl)acrylonitriles **2** or **3**. Despite several attempts, stannylcupration of propionitrile **8** failed to produce vinylstannane intermediates **2** or **3**.

Stannylcuprates are also known to undergo substitution reactions with 3-iodo-2-enones,[14] enol triflates of cyclic β-ketoesters,[15] and 2-enoates containing good leaving groups (such as Cl or I) at the β-position.[16] These substitution reactions are believed to proceed through a conjugate addition−elimination pathway or by direct substitution. Based on this precedent, conjugated enol triflate (*Z*)-**11** was synthesized in two steps, and its structure was determined by X-ray crystallography (Figure 3). Compound (*Z*)-**11** was then converted to (*Z*)-**3** and (*E*)-**3**. The optimal conditions we found for this reaction used $(Bu_3Sn)_2Cu(CN)Li_2$ at −50 °C for 10 min (entry 7 in Table 1).

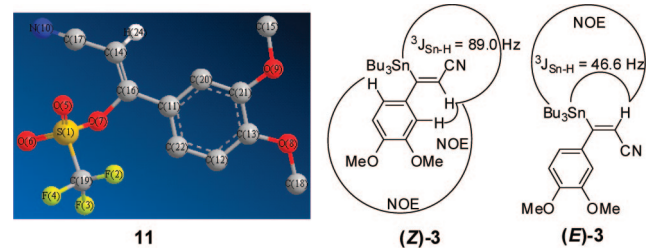
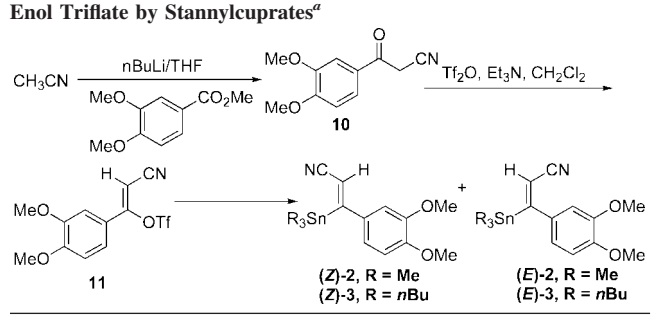


FIGURE 3. X-ray structure of **11** and stereochemical assignment for vinylstannane for intermediates **3**.

TABLE 1. Syntheses of 2 or 3 via Substitution of Conjugated Enol Triflate by Stannylcuprates[a]



entry	reagent	temp (°C)	time (min)	product (% yield)	*E*/*Z*
1	Bu_3SnCu	−50	10	**3** (0)	N/A
2	$Bu_3SnCu(PhS)Li$	−78	10	**3** (0)	N/A
3	$Bu_3SnCu(PhS)Li$	−50	10	**3** (0)	N/A
4	$Bu_3SnCu(CN)Li$	−78	10	**3** (0)	N/A
5	$Bu_3SnCu(CN)Li$	−50	10	**3** (0)	N/A
6	$(Bu_3Sn)_2Cu(CN)Li_2$	−78	30	**3** (<5)	1:1
7	$(Bu_3Sn)_2Cu(CN)Li_2$	−50	10	**3** (80)[c]	3:2
8	$(Bu_3Sn)_2Cu(CN)Li_2$	−20	10	**3** (35)	4.6:1
9	$(Me_3Sn)_2Cu(CN)Li_2$[b]	−20	10	**2** (0)	N/A
10	$Me_3SnCu(PhS)Li$[b]	−20	10	**2** (0)	N/A
11	$(Me_3Sn)_2Cu(PhS)Li_2$[b]	−20	10	**2** (0)	N/A

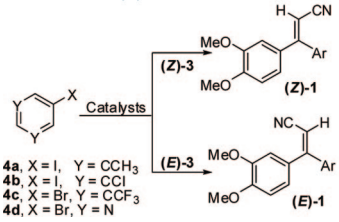
[a] All reactions were carried out with 1 mmol of **11** and 1.1 mmol of stannylcuprates in THF. [b] 5.0 mmol of stannylcuprates was used. [c] This reaction was done on 10 mmol scale.

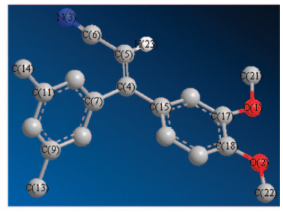
(8) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85–126.
(9) Davies, A. G. *Organotin Chemistry*, 2nd ed.; Wiley-VCH Verlag Gmbh & Co German KGaA:. Weinheim, Germany, 2004; Chapter 8, pp 114.
(10) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581–5583.
(11) (a) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257–3282. (b) Ferri, F.; Alami, M. *Tetrahedron Lett.* **1996**, *37*, 7971–7974.
(12) (a) Fleming, I. *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, UK, 1994; Chapter 12, p 257. (b) Piers, E.; Rogers, C. *Encylopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; Vol. 7, pp 5328. (c) Piers, E.; Rogers, C. *Encylopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; Vol. 7, p 5024. (d) Piers, E.; Rogers, C. *Encylopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; Vol. 5, p 3157. (e) Piers, E.; Rogers, C. *Encylopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; Vol. 3, p 1965.
(13) (a) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263–4264. (b) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1981**, *22*, 4905–4908. (c) Piers, E.; Chong, J. M. *J. Org. Chem.* **1982**, *47*, 1602–1604. (d) Cox, S. D.; Wudl, F. *Organometallics* **1983**, *2*, 184–185. (e) Piers, E.; Tillyer, R. D. *J. Org. Chem.* **1988**, *53*, 5366–5369.
(14) Piers, E.; Morton, H. E.; Chong, J. M. *Can. J. Chem.* **1987**, *65*, 78–87.
(15) (a) Lipshutz, B. H.; Sharma, S.; Reuter, D. C. *Tetrahedron Lett.* **1990**, *31*, 7253–7256. (b) Piers, E.; Tse, H. L. A. *Can. J. Chem.* **1993**, *71*, 983–994. (c) Houpis, I. N.; DiMichele, L.; Molina, A. *Synlett* **1993**, *5*, 365–366. (d) Piers, E.; McEachern, E. J.; Romero, M. A.; Gladstone, P. L. *Can. J. Chem.* **1997**, *75*, 694–701. (e) Piers, E.; Boehringer, E. M.; Yee, J. G. K. *J. Org. Chem.* **1998**, *63*, 8642–8643. (f) Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett.* **1988**, *29*, 4795–4798.
(16) (a) Seitz, D. E.; Lee, S.-H. *Tetrahedron Lett.* **1981**, *22*, 4909–4912. (b) Imanieh, H.; MacLeod, D.; Quayle, P.; Zhao, Y.; Davis, G. M. *Tetrahedron Lett.* **1992**, *33*, 405–408.

No desired product was detected with other stannylcuprates tried, rather elimination product **8** was obtained. Compound **8** is most likely formed due to the competing elimination reaction with the cuprates acting as a base.

The geometric configurations of the vinylstannanes (*E*)-**3** and (*Z*)-**3** were determined by their NMR coupling constants between the α-olefinic proton and the tin atom (^{117}Sn, ^{119}Sn) of the Bu_3Sn group (Figure 3). It is well-known that when a trialkylstannyl group and a proton are vicinal on a C=C double bond, the $^3J_{Sn-H}$ values are much larger when the moieties are trans than when they are cis.[17] As shown below in Figure 3, the $^3J_{Sn-H}$ values of (*E*)-**3** and (*Z*)-**3** are 46.4 and 89.0 Hz, respectively. According to selective transient 1D NOE studies, there is a significant ^{1}H NOE between the vinyl proton and the aromatic protons in (*Z*)-**3**, while there is a significant ^{1}H NOE between the vinyl proton and the methylene protons in the Bu_3Sn group in (*E*)-**3** (Figure 3). These corroborating observations provide strong evidence for the assignment of stereochemistry for both (*E*)-**3** and (*Z*)-**3**.

TABLE 2. Stille Coupling Reaction of Vinylstannane 3 and X-ray Structure of (*Z*)-1a





entry	3	ArX	conditions[a]	prod (% yield)
1	*Z*	**4a**	$Pd(PPh_3)_4$, CuI, CSF, rt	(*Z*)-**1a** (0)
2	*Z*	**4a**	$Pd(PPh_3)_4$, CuI, CSF, 60 °C	(*Z*)-**1a** (0)
3	*Z*	**4a**	$Pd_2(dba)_3$, $AsPh_3$, CuI, CSF, 60 °C	(*Z*)-**1a** (0)
4	*Z*	**4a**	$Pd_2(dba)_3$, $AsPh_3$, CSF, 60 °C	(*Z*)-**1a** (45)
5	*Z*	**4a**	Pd(dppf), CSF, 60 °C	(*Z*)-**1a** (85)
6	*E*	**4a**	Pd(dppf), CSF, 60 °C	(*E*)-**1a** (81)
7	*Z*	**4b**	Pd(dppf), CSF, 60 °C	(*Z*)-**1b** (76)
8	*E*	**4b**	Pd(dppf), CSF, 60 °C	(*E*)-**1b** (70)
9	*Z*	**4c**	Pd(dppf), CSF, 60 °C	(*Z*)-**1c** (73)
10	*E*	**4c**	Pd(dppf), CSF, 60 °C	(*E*)-**1c** (65)
11	*Z*	**4d**	Pd(dppf), CSF, 60 °C	(*Z*)-**1d** (0)
12	*Z*	**4d**	$Pd_2(dba)_3$, $PtBu_3$, CSF, 60 °C	(*Z*)-**1d** (68)
13	*E*	**4d**	$Pd_2(dba)_3$, $PtBu_3$, CSF, 60 °C	(*E*)-**1d** (71)

[a] All reactions were done in a sealed tube with anhydrous DMF, which was degassed with argon.

Vinylstannanes (*E*)-**3** and (*Z*)-**3** were then coupled with a variety of aryl and heteroaromatic halides under Stille cross-coupling conditions (Table 2). Several catalytic systems were studied, and we found that Pd(dppf) as the catalyst with CsF as promoter in DMF worked best with aryl iodides and activated aryl bromides.[18] For unactivated (hetero)aryl bromides, the $Pd_2(dba)_3$/$PtBu_3$/CsF catalytic system was optimal.[19] For aryl iodides (entries 5−8) and activated aryl bromide (entries 9 and 10), the Stille reactions were completed at 60 °C in 4 and 6 h, respectively. For the unactivated aryl bromide (entries 12 and 13), the reactions were completed at 60 °C in 24 h. All of the Stille reactions were stereospecific. None of the undesired isomers were detected.

The final compounds **1** were tested for inhibition of tubulin assembly and inhibition of colchicine binding to tubulin, as well as for their inhibitory properties against three cell lines: MDA-MB-231, LLC, and HUVEC. The biological results are shown in Table 3. Most of the compounds **1** had good activity against tubulin polymerization, especially (*Z*)-**1a** and (*Z*)-**1b**. The (*Z*)-**1** isomers are generally more potent inhibitors of tubulin polymerization. Likewise, the same stereochemical trend holds for the in vitro cytotoxicity and endothelial cell proliferation assays.

A computer modeling study was performed to find a possible binding model of 3,3-diarylacrylonitriles with tubulin. The X-ray structure of the colchicine−tubulin complex (PDB code: 1SA0) was downloaded and the structure of colchicine was deleted.[22] Then (*Z*)-**1a** was docked into the empty colchicine cavity by using GOLD software (BST, v3.0, 2005). The postdocking energy minimization was performed by using the MMFF94s force field and MMFF94 charges within Sybyl 7.3. The resulting structure is displayed in Figure 4. According to the model, the 1,2-dimethoxyphenyl group occupies the cavity that is distal to the GTP. This puts the nitrile of (*Z*)-**1a** in proximity of the Tyr224 phenol, with formation of a hydrogen bond in (*Z*)-**1a**.

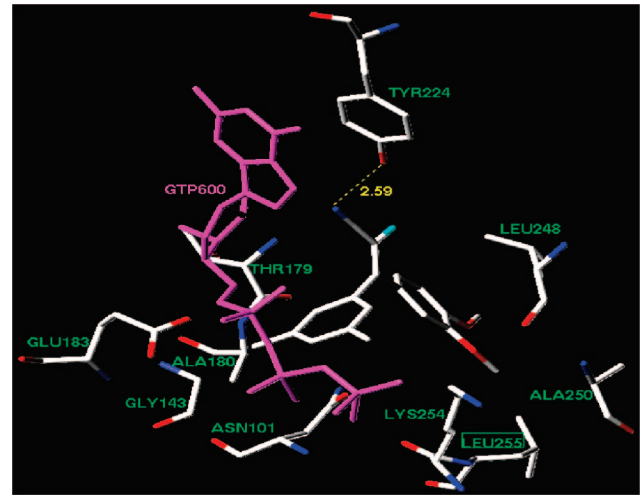


FIGURE 4. Hypothetical model for the binding of (*Z*)-**1a** to tubulin.

In summary, a series of 3,3-diarylacrylonitriles were synthesized stereoselectively. This synthetic route utilizes a stannylcuprate-mediated substitution of a conjugated enol triflate followed by a Stille cross-coupling reaction. The biological studies demonstrated that 3,3-diarylacrylonitriles are effective tubulin polymerization inhibitors and are good inhibitors of endothelial cell proliferation and cytotoxic agents with the *Z* isomers being more potent than corresponding *E* isomers.

Experimental Section

Syntheses of (*Z*)-3-(3,4-Dimethoxyphenyl)-3-(tributylstannyl)acrylonitrile ((*Z*)-3) and (*E*)-3-(3,4-Dimethoxyphenyl)-3-(tributylstannyl)acrylonitrile ((*E*)-3). Bu_3SnH (3.51 mL, 13.2 mmol)

(17) Leusink, A. J.; Budding, H. A.; Marsamn, J. W. *J. Organomet. Chem.* **1967**, *9*, 285–294.
(18) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132–1136.
(19) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.
(20) Hamel, E. *Cell Biochem. Biophys.* **2003**, *38*, 1–21.
(21) Verdier-Pinard, P.; Lai, J.-Y.; Yoo, H.-D.; Yu, J.; Marquez, B.; Nagle, D. G.; Nambu, M.; White, J. D.; Falck, J. R.; Gerwick, W. H.; Day, B. W.; Hamel, E. *Mol. Pharmacol.* **1998**, *53*, 62–76.
(22) (a) Ravelli, R. B. G.; Gigant, B.; Curml, P. A.; Jourdain, I.; Lachkar, S.; Sobel, A. *Nature* **2004**, *428*, 198–202. (b) Gigant, B.; Curmi, P. A.; Martin-Barbey, C.; Charbaut, E.; Lachkar, S.; Lebeau, L. *Cell* **2000**, *102*, 809–816. (c) Lowe, J.; Li, H.; Downing, K. H.; Nogales, E. *J. Mol. Biol.* **2001**, *313*, 1045–1057.

TABLE 3. Cytotoxicities and antitubulin activities of 3,3-Diarylacrylonitriles 1

	cytotoxicity (IC_{50} in nM)[a]				
compd	MDA-MB-231	LLC	HUVEC	inhibition of tubulin assembly (IC_{50}, μM) ± SD[b]	inhibition of colchicine binding (% ± SD)
(*Z*)-**1a**	17.6	22.1	17.3	1.6[c,d]	78 ± 0.1
(*E*)-**1a**	680	595	320	4.2 ± 0.3	40 ± 4
(*Z*)-**1b**	18.0	15.5	8.66	1.0[d]	86 ± 3
(*E*)-**1b**	1750	2320	1760	5.8 ± 0.5	27 ± 6
(*Z*)-**1c**	79.1	73.6	82.4	6.5 ± 0.4	23 ± 7
(*E*)-**1c**	70000	97100	151000		
(*Z*)-**1d**	>100000	>10000	>10000		
(*E*)-**1d**	186000	118000	164000		
CSA4				1.2 ± 0.1	98 ± 0.3

[a] The cytotoxicity IC_{50} values are the concentrations corresponding to 50% growth inhibition. [b] Tubulin concentration was 1.0 mg/mL (10 μM). Assay performed as described previously.[20] [c] Tubulin concentration was 1.0 μM, [^{3}H]colchicine and inhibitor concentrations, 5.0 μM. Assay performed as described previously.[21] [d] Same value obtained in all experiments.

was added to LDA (15.6 mmol, 8.67 mL, 1.80 M solution) in anhydrous THF (100 mL) under argon at −60 to −78 °C. The reaction mixture was stirred for 20 min. CuCN (592 mg, 6.60 mmol) was added and the solution was slowly warmed to −50 °C. The solid CuCN dissolved, resulting in a green-yellow solution. Compound **11** (2.03 g, 6.0 mmol) in THF (50 mL) was added dropwise and the color of the solution changed to red-orange. After 10 min of further stirring, the reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc and washed with H_2O and brine. The organic solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash column chromatography on SiO_2 eluting with pure dichloromethane afforded the desired products (*Z*)-**3** (0.92 g, less polar which came out of column first) and (*E*)-**3** (1.38 g, more polar which came out of column last) both as pale yellow oils in a yield of 80%.

Compound (*Z*)-**3**: IR (film) 2954, 2922, 2207, 1511, 1462, 1259, 1140, 1026, 804 cm^{-1}; EIMS *m*/*z* (rel intensity) 479 (M^+, 14), 422 (100), 366 (30), 308 (50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, J = 8.3 Hz, 1 H), 6.67 (dd, J = 2.2, 8.6 Hz, 1 H), 6.62 (d, J = 2.2 Hz, 1 H), 6.02 (s, $^3J_{Sn-H}$ = 89 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 1.59−1.45 (m, 6 H), 1.38−1.25 (m, 6 H), 1.17 (t, J = 8.2 Hz, 6 H), 0.87 (t, J = 7.2 Hz, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 149.5, 149.0, 137.2, 119.2, 119.1, 111.2, 109.3, 108.4, 56.1, 56.0, 29.1, 27.3 (J_{Sn-C} = 30.2 Hz), 13.8, 11.6. Anal. Calcd for $C_{23}H_{37}NO_2Sn$: C, 57.76; H, 7.80; N, 2.93. Found: C, 57.90; H, 7.79; N, 2.92.

Compound (*E*)-**3**: IR (film) 2955, 2928, 2870, 2851, 2205, 1597, 1509, 1463, 1410, 1259, 1140, 1073, 1026, 863, 799, 762, 667 cm^{-1}; EIMS *m*/*z* (rel intensity) 479 (M^+, 15), 422 (100), 366 (33), 308 (50), 188 (95); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, J = 8.3 Hz, 1 H), 6.86 (d, J = 2.0 Hz, 1 H), 6.81 (dd, J = 2.0, 8.3 Hz, 1 H), 5.54 (s, $^3J_{Sn-H}$ = 46.6 Hz, 1 H), 3.91 (s, 6 H), 1.54−1.40 (m, 6 H), 1.35−1.24 (m, 6 H), 1.02 (t, J = 8.1 Hz, 6 H), 0.87 (t, J = 7.3 Hz, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 149.2, 148.9, 134.8, 119.8, 116.7, 111.2, 109.7, 104.3, 56.0, 28.9 (J_{Sn-C} = 10.0 Hz), 27.3 (J_{Sn-C} = 29.0 Hz), 13.7, 11.0. Anal. Calcd for $C_{23}H_{37}NO_2Sn$: C, 57.76; H, 7.80; N, 2.93. Found: C, 57.94; H, 7.78; N, 2.95.

General Procedure for the Synthesis of 3,3-Diarylacrylonitriles by the Stille Cross-Coupling Reaction of (*Z*)-3 or (*E*)-3 with Aromatic Iodides or Bromides. A mixture of (*Z*)-3-(3,4-dimethoxyphenyl)-3-(tributylstannyl)acrylonitrile ((*Z*)-**3**) or (*E*)-3-(3,4-dimethoxyphenyl)-3-(tributylstannyl)-acrylonitrile ((*E*)-**3**) (0.1 mmol, 1.0 equiv), aryl halide (1.20 equiv), cesium fluoride (2.20 equiv), and Pd(dppf) (5.0 mol%) or $Pd_2(dba)_3$ (2.5 mol%) and $PtBu_3$ (5.0 mol%) in anhydrous DMF (1.0 mL, degassed by freeze−pump−thaw−pump method) was stirred in the dark under argon at 60 °C for the indicated time. The reaction mixture was then cooled to room temperature and filtered through a short column of silica gel (5 g), and the column was washed with ethyl acetate. The solvent was removed under reduced pressure and purified by column chromatography on SiO_2 eluting with EtOAc−hexanes.

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Supporting Information Available: Experimental procedures, NMR spectra for all compounds, the selective transient 1D NOE for **3**, and the X-ray coordinates for **11** and (*Z*)-**1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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