

# Cyclohexylcarbonitriles: Diastereoselective Arylations with TMPZnCl·LiCl

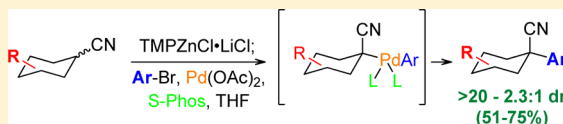
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## Supporting Information

**ABSTRACT:** Deprotonating substituted cyclohexanecarbonitriles with TMPZnCl·LiCl affords zincated nitriles that diastereoselectively couple with aryl bromides in the presence of catalytic Pd(OAc)<sub>2</sub> and S-Phos. Steric and electronic effects influence the diastereoselectivity; 4-*t*-butyl-, 4-TBSO-, and 2-Me-cyclohexanecarbonitriles exert virtually complete diastereocontrol whereas modest diastereoselectivity is observed with 4-*i*-Pr-, 4-Me-, and 3-Me-cyclohexanecarbonitriles. The unusual diastereoselectivity trends should prove useful for synthesizing substituted cyclohexanecarbonitrile-containing pharmaceuticals.



Substituted arylacetonitriles are prevalent motifs embedded within diverse pharmaceuticals (Figure 1).<sup>1</sup> Typically the

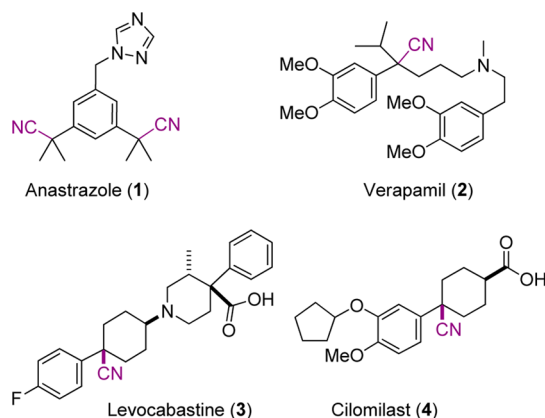


Figure 1. Arylacetonitrile pharmaceuticals.

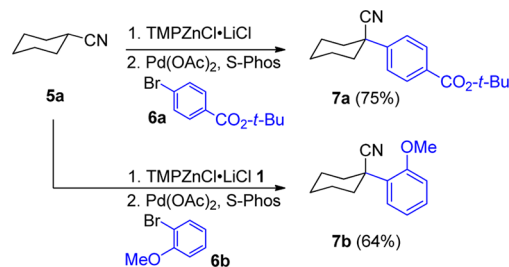
nitrile-bearing carbon is fully substituted, as in the blockbuster drug anastrozole (1)<sup>2</sup> and the well-studied antiarrhythmic agent verapamil (2).<sup>3</sup> Conspicuous among nitrile-containing pharmaceuticals is the aryl-substituted cyclohexanecarbonitrile pharmacophore as contained within the second-generation H<sub>1</sub>-receptor antagonist levocabastine (3)<sup>4</sup> and the antiasthmatic cilomilast (4).<sup>5</sup> Cilomilast (4) and related arylacetonitriles are being pursued as inhibitors of phosphodiesterase 4.<sup>6</sup>

Several excellent methods access aryl-substituted nitriles through Pd-catalyzed  $\alpha$ -arylation.<sup>7</sup> Typically palladated nitriles are accessed by metalation-transmetalation sequences,<sup>8</sup> decarboxylation,<sup>9</sup> or cleavage of silylketenimines,<sup>7c</sup> followed by coupling with an aryl halide and a catalyst-ligand combination.<sup>10</sup> Among these approaches, tetramethylpiperidine (TMP)

bases<sup>11</sup> in combination with palladium catalysts are particularly efficacious for the direct arylation of aliphatic nitriles.

As a prelude to developing a diastereoselective cross coupling of cyclohexanecarbonitriles, cyclohexanecarbonitrile (5a) was deprotonated with the powerful base TMPZnCl·LiCl<sup>12</sup> and coupled with aryl halides (Scheme 1). During optimization with

## Scheme 1. $\alpha$ -Arylation of Cyclohexanecarbonitrile (5)



Pd(OAc)<sub>2</sub> and S-Phos,<sup>13</sup> 4-iodobenzonitrile was found to afford significant amounts of [1,1'-biphenyl]-4,4'-dicarbonitrile whereas the corresponding bromide did not. The optimized procedure involves deprotonating cyclohexanecarbonitriles with TMPZnCl·LiCl for 20 min followed by the addition of S-Phos, Pd(OAc)<sub>2</sub>, and aryl bromide and then heating to 50 °C. Under the optimized conditions, 5a couples with the electron deficient *t*-butyl 4-bromobenzoate (6a) to afford nitrile 7a and with the hindered, electron-rich 1-bromo-2-methoxybenzene (6b) to form 7b (Scheme 1). The coupling conditions tolerate the presence of the *t*-butyl ester, although the corresponding ethyl ester suffers competitive attack from the metalated nitrile.

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Table 1. Diastereoselective Cyclohexanecarbonitrile Coupling

entry	nitrile	ArBr	quaternary nitrile	yield (dr)
1		6c		75% (>20:1) <sup>a</sup>
2		6d		60% (8.4:1) <sup>b</sup>
3		6c		72% (>20:1) <sup>a</sup>
4		6c		71% (>20:1) <sup>a</sup>
5		6c		72% (2.3:1) <sup>b</sup>
6		6c		68% (3.5:1) <sup>c</sup>
7		6d		68% (4.8:1) <sup>c</sup>
8		6c		70% (6.2:1) <sup>c</sup>
9		6c		51% (>20:1) <sup>a</sup>

<sup>a</sup>No diastereomers were detected. <sup>b</sup>Ratio determined by <sup>1</sup>H NMR Spectroscopy. <sup>c</sup>Ratio determined by GC.

Controlling the arylation diastereoselectivity in cross couplings of *substituted* cyclic nitriles is a significant challenge.<sup>14</sup> Related arylations of substituted cyclohexanones<sup>15</sup> and cyclohexylcarboxylate-derived enolates<sup>16</sup> exhibit stereoselectivities in which electronic effects of the substituent and the aryl halide exert unusual diastereoselectivity trends that sometimes do not correlate with the substituents' steric demand.<sup>17</sup>

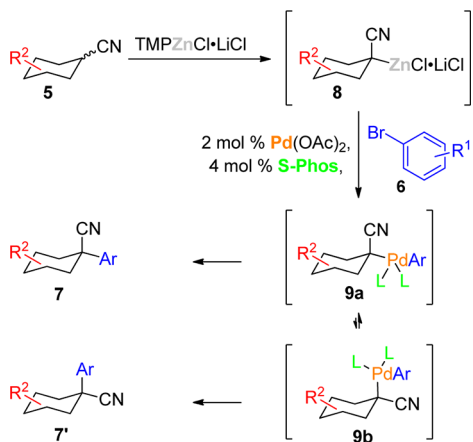
Coupling a range of cyclohexanecarbonitriles **5**<sup>18</sup> with 4-bromobenzonitrile (**6c**) and 1-bromo-4-methoxybenzene (**6d**) as representative electron deficient and electron rich aryl bromides, respectively, provides insight into the diastereoselective arylation of substituted cyclohexanecarbonitriles (Table 1). 4-*t*-Butylcyclohexanecarbonitrile (**5b**) was employed as a conformationally constrained prototype because extensive alkylations provide stereoselectivity trends relating the hybrid-

ization of the nucleophilic carbon to the alkylation ratio.<sup>19</sup> The arylation of 4-*t*-butylcyclohexanecarbonitrile (**5b**) with electron deficient **6c** is greater than 20:1 (**7c**, Table 1, entry 1) but is diminished to 8.4:1 with the more electron rich aromatic **6d** (**7d**, Table 1, entry 2).<sup>20</sup> In comparable couplings with 4-bromobenzonitrile (**6c**), the steroidal nitrile **7e** and the silyloxy nitrile **7f** are formed with essentially complete stereoselectivity (Table 1, entries 3 and 4, respectively) whereas an analogous arylation with 4-isopropylcyclohexanecarbonitrile (**5e**) proceeds with reduced diastereoselectivity (2.3:1 for **7g**, Table 1, entry 5).<sup>21</sup>

Coupling 4-methyl-cyclohexanecarbonitrile (**5f**) and 3-methyl-cyclohexanecarbonitrile (**5g**) with electron rich and electron deficient aryl bromides installs quaternary centers with diastereoselectivities in the range of 3.5–6.2:1 (Table 1, entries 6–8). The diastereoselectivity is only modestly influenced by the electronic character of the aryl bromide (compare entry 1 with entry 2 and entry 6 with entry 7) whereas the nature and position of the substituent has a dramatic effect. Moving the methyl group progressively closer to the nitrile-bearing carbon increases the diastereoselectivity (Table 1, compare entry 6, **7h**, with entries 8 and 9, **7j** and **7k**, respectively), and is highest for 2-methyl-cyclohexanecarbonitrile (**5h**) which forms **7k** bearing adjacent tertiary and quaternary centers (Table 1, entry 9).

Mechanistically, the reaction most likely proceeds through zincation,<sup>11</sup> transmetalation to palladium, and reductive elimination (Scheme 2).<sup>7</sup> Deprotonating **5** with

Scheme 2. Metalated Nitrile Coupling Mechanism



TMPZnCl·LiCl affords a C-zincated nitrile<sup>22</sup> that likely equilibrates through a conducted tour C → N → C metal migration sequence<sup>23</sup> to **8** with zinc in the equatorial orientation.<sup>24</sup> Transmetalation of the zincated nitrile **8** with an arylpalladium bromide would afford the C-palladated nitrile **9** with subsequent reductive elimination affording nitrile **7**.<sup>25</sup> Variations in the diastereomeric ratio for the same carbonitrile with different aryl bromides (Table 1, entries 1–2 and 6–7) implies that an equilibrium exists between axial and equatorial C-palladated nitriles **9a** and **9b**. A similar electronic influence on the equilibrium between **9a** and **9b** is implied from the distinctly different diastereomeric ratios of the *t*-butyl- and isopropylcyclohexane carbonitriles (Table 1, compare entries 1 and 5) which typically exert similar conformational restriction.<sup>26</sup> An electronic influence from the remote 4-*t*-butyl substituent decreases the *s* character at the metalated carbon, because of a bond angle distortion at C-4,<sup>27</sup> causing a

diastereoselectivity difference not present in the corresponding isopropyl and methyl analogs **5e** and **5f**, respectively. Consistent with the relayed electronic influence from the remote C-4 substituent is the virtually exclusive diastereocontrol for the 4-OTBS cyclohexanecarbonitrile (**5d**) which has a significantly smaller steric demand than either a *t*-butyl or *i*-Pr substituent (0.7, 4.2, and 2.2 kcal mol<sup>-1</sup> for OTBS, *t*-Bu, and *i*-Pr groups, respectively)<sup>26</sup> and yet couples with virtually complete diastereoselectivity.

The coupling of 2-methylcyclohexanecarbonitrile (**5h**) is highly diastereoselective (Table 1, entry 9). Presumably the C-palladated nitrile<sup>25</sup> **9** (R<sup>2</sup> = Me) exerts a strong preference for conformer **9a** where the small nitrile and vicinal methyl groups are gauche to avoid steric compression between a gauche methyl group and the sterically demanding palladium-SPhos complex (cf. **9b**).

Deprotonating cyclohexanecarbonitriles with TMPZnCl·LiCl and coupling with aryl bromides diastereoselectively affords substituted cyclohexanecarbonitriles. The diastereoselectivity trends are unusual in exhibiting a strong electronic dependence on the nature of the aryl bromide and the substituents on the cyclohexane ring. 4-*t*-Butyl-, 4-TBSO-, and 2-Me substituents exert virtually complete stereocontrol whereas 4-*i*-Pr-, 4-Me, and 3-Me substituents are significantly less selective. Collectively these alkylations are the first diastereoselective arylations of cyclic nitriles and establish unusual stereoelectronic effects that should prove useful in synthesizing cyclohexanecarbonitrile-containing pharmaceuticals.

## EXPERIMENTAL SECTION

**General Procedure for the Conversion of Ketones to Nitriles.** Modifying a known procedure,<sup>18</sup> solid *t*-BuOK (1.2 equiv) was added to a vigorously stirred, THF solution (0.1 M) of the ketone (1 equiv). After 20 min solid toluenesulfonylmethyl isocyanide (TosMIC, 1.2 equiv) was added. After 4 h, a saturated, aqueous NH<sub>4</sub>Cl solution was added, the phases were separated, and the aqueous phase was extracted with Et<sub>2</sub>O (3X). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and purified by silica gel (230–400 mesh) chromatography to afford analytically pure material.

### 4-((*tert*-Butyldimethylsilyloxy)cyclohexanecarbonitrile (**5d**).

Two portions of solid NaBH<sub>4</sub> (360 mg, 9.51 mmol) were added to a 0 °C, methanolic solution (20 mL) of 4-oxocyclohexanecarbonitrile<sup>28</sup> (585 mg, 4.75 mmol). After 30 min the ice bath was removed and after 1 h the solvent was under reduced pressure. The concentrate dissolved in EtOAc (100 mL), extracted with water (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and then the solvent was evaporated under reduced pressure. The crude hydroxynitrile 270.7 mg (2.16 mmol) was dissolved in DMF (5 mL) and then TBSCl (244.8 mg, 1.62 mmol) and imidazole (229.4 mg, 3.36 mmol) were added. After 16 h a solution of aqueous, saturated NH<sub>4</sub>Cl (20 mL) was added, the phases were separated, and the aqueous phase extracted with ether (100 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent was evaporated under reduced pressure, and the crude silyl ether nitrile was purified by column chromatography (hexanes) to afford 318.3 mg (82% yield) of **5d** as a mixture of diastereomers:<sup>29</sup> IR (neat) 2239 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.81–3.74 (m, 1H), 2.63 (m, 1H), 2.09–1.99 (m, 2H), 1.89–1.76 (m, 1H), 1.72–1.52 (m, 4H), 1.49–1.33 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 122.32, 122.25, 67.45, 66.69, 32.12, 27.13, 25.71, 17.99, -4.87; HRMS (ESI-TOF) *m/z* calcd for C<sub>13</sub>H<sub>25</sub>NOSiNa (M + Na) 262.1603; found 262.1615.

**4-Isopropylcyclohexanecarbonitrile (**5e**).** Performing the general cyanation procedure with 4-isopropylcyclohexanone (1.00 g, 7.13 mmol), *t*-BuOK (0.96 g, 8.56 mmol), and TosMIC (1.67 g, 8.55 mmol) gave the crude nitrile that was purified by column chromatography (95:5, hexanes/EtOAc) to afford 0.865 g (80%

yield) of **5e** as an oily mixture of diastereomers:<sup>30</sup> IR (neat) 2230  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.94–2.90 (m, 1H), 2.33 (tt,  $J = 4.0, 12.5$  Hz, 1H), 2.15–2.10 (m, 2H), 2.10–1.98 (m, 2H), 1.81–1.76 (m, 2H), 1.58–1.52 (m, 2H), 1.50–1.33 (m, 4H), 1.12–1.02 (m, 2H), 1.02–0.95 (m, 2H), 0.89 (d,  $J = 7.0$  Hz, 6H), 0.85 (d,  $J = 6.5$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  122.84, 122.16, 43.22, 42.54, 32.39, 29.99, 28.51, 28.29, 27.14, 25.60, 19.60, 19.50; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{10}\text{H}_{17}\text{NNa}$  ( $M + \text{Na}$ ) 174.1259; found 174.1246.

**4-Methylcyclohexanecarbonitrile (5f).** Performing the general cyanation procedure with 4-methylcyclohexanone (1.00 g, 7.13 mmol), *t*-BuOK (1.20 g, 10.7 mmol), and TosMIC (2.09 g, 10.7 mmol) gave the crude nitrile that was purified by column chromatography (95:5, hexanes/EtOAc) to afford 0.829 g (75% yield) of **5f** as an oily mixture of diastereomers:<sup>31</sup>  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.99–2.94 (m, 1H), 2.43 (tt,  $J = 4.0, 12.4$  Hz, 1H), 2.09–2.04 (m, 3H), 1.91–1.86 (m, 3H), 1.84–1.75 (m, 3H), 1.75–1.64 (m, 3H), 1.48–1.32 (m, 4H), 1.32–1.15 (m, 4H), 0.93 (d,  $J = 6.8$  Hz, 3H), 0.92 (d,  $J = 6.4$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  122.74, 122.45, 37.89, 36.41, 34.01, 33.65, 31.78, 29.54, 28.28, 28.25, 27.20, 25.02, 22.17, 22.13, 21.82; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_8\text{H}_{10}\text{NNa}$  ( $M - 3\text{H} + \text{Na}$ ) 143.0694; found 143.0702.

**3-Methylcyclohexanecarbonitrile (5g).** Performing the reaction according to the general cyanation procedure using 3-methylcyclohexanone (1.00 g, 7.13 mmol), *t*-BuOK (1.20 g, 10.69 mmol), and TosMIC (2.09 g, 10.70 mmol) gave the crude nitrile that was purified by column chromatography (85:15, pentane/ether) to afford 0.847 g (77% yield) of the nitrile **5g** as an oily mixture of diastereomers:<sup>32</sup>  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.98–2.94 (m, 1H), 2.43 (tt,  $J = 3.6, 12.4$  Hz, 1H), 2.11–2.00 (m, 3H), 1.95–1.87 (m, 2H), 1.85–1.75 (m, 3H), 1.74–1.65 (m, 4H), 1.50–1.40 (m, 2H), 1.30–1.14 (m, 4H), 0.93 (d,  $J = 6.8$  Hz, 3H), 0.92 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  122.73, 122.41, 37.92, 36.43, 36.43, 34.02, 33.66, 31.79, 29.56, 28.52, 28.27, 25.03, 22.15, 21.79; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_8\text{H}_{14}\text{N}$  ( $M + \text{H}$ ) 124.1126; found 124.1096.

**2-Methylcyclohexanecarbonitrile (5h).** Performing the reaction according to the general cyanation procedure using 2-methylcyclohexanone (2.03 g, 18.10 mmol), *t*-BuOK (2.48 g, 22.10 mmol), and TosMIC (4.42 g, 22.64 mmol) gave the crude nitrile that was purified by column chromatography (85:15, pentane/ether) to afford 1.86 g (83% yield) of the nitrile **5h** as an oily mixture of diastereomers exhibiting spectral properties identical to that exhibited by previously isolated material:<sup>33</sup>  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.83–2.79 (m, 1H), 2.12–1.98 (m, 3H), 1.79–1.53 (m, 11H), 1.36–1.15 (m, 4H), 1.12 (d,  $J = 6.4$  Hz), 1.08 (d,  $J = 6.4$  Hz), 1.04–0.90 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  122.28, 120.66, 36.18, 35.29, 34.65, 33.82, 33.50, 30.65, 29.98, 28.70, 25.11, 25.03, 24.88, 21.93, 20.79, 20.07.

**General Coupling Procedure.** A THF solution of  $\text{TMPZnCl}\cdot\text{LiCl}$  (1.5 equiv) was added, dropwise, to a THF solution (2 mL) of the nitrile in a 25 mL Schlenk-tube. After 20 min, complete deprotonation was checked by removing an aliquot and treating with allyl bromide and a catalytic amount  $\text{CuCN}\cdot 2\text{LiCl}$  solution (1 M in THF).<sup>35</sup> Upon complete metalation, SPhos (4 mol %),  $^{13}\text{Pd}(\text{OAc})_2$  (2 mol %) and the electrophile (0.6 equiv) were added and then the reaction mixture was placed in an oil bath at 50 °C. Reaction progress was checked by GC analysis of aliquots quenched with a solution of  $\text{NH}_4\text{Cl}$ . Upon completion, saturated, aqueous  $\text{NH}_4\text{Cl}$  was added, the phases were separated, and the aqueous phase was extracted with ether. The combined organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), the solvent was evaporated under reduced pressure, and the crude nitrile was then purified by silica gel flash chromatography or radial chromatography.

***tert*-Butyl 4-(1-cyanocyclohexyl)benzoate (7a).** Performing the general coupling procedure with cyclohexanecarbonitrile (**5a**, 91.9 mg, 0.842 mmol),  $\text{TMPZnCl}\cdot\text{LiCl}$  (1.30 M, 0.81 mL, 1.26 mmol), SPhos (10.6 mg, 4 mol %),  $\text{Pd}(\text{OAc})_2$  (2.9 mg, 2 mol %) and *t*-butyl 4-bromobenzoate (166.4 mg, 0.647 mmol) and purification of the crude nitrile by column chromatography (95:5, pentane/ether) afforded 128.1 mg (75% yield) of **7a** as a white solid (mp 93–96 °C): IR (neat) 2235, 1706  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.00 (d,  $J = 8.8$  Hz, 2H), 7.55 (d,  $J = 8.8$  Hz, 2H), 2.18–2.13 (m, 2H), 1.93–1.73 (m, 6H), 1.59 (s, 9H), 1.35–1.24 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):

$\delta$  165.09, 145.68, 131.61, 129.69, 125.48, 122.14, 81.22, 44.53, 37.20, 28.14, 24.86, 23.46; HRMS (ESI-TOF)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{23}\text{NO}_2$  ( $M^+$ ) 285.1728; found 285.1702.

**1-(2-Methoxyphenyl)cyclohexanecarbonitrile (7b).** Performing the general coupling procedure with cyclohexanecarbonitrile (**5a**, 91.9 mg, 0.81 mmol),  $\text{TMPZnCl}\cdot\text{LiCl}$  (1.30 M, 0.81 mL, 1.26 mmol), SPhos (10.6 mg, 4 mol %),  $\text{Pd}(\text{OAc})_2$  (2.9 mg, 2 mol %) and 2-bromoanisole (0.80 mL, 0.647 mmol) and purification of the crude nitrile by column chromatography (95:5, pentane/ether) afforded 88.5 mg (64% yield) of **7b**<sup>36</sup> as an oil: IR (neat) 2229  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.31 (m, 2H), 6.99–6.95 (m, 2H), 3.93 (s, 3H), 2.40 (br d,  $J = 1.2$  Hz, 2H), 1.89–1.77 (m, 6H), 1.30–1.27 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  157.57, 129.14, 129.07, 125.94, 122.50, 120.80, 112.18, 55.57, 40.82, 34.55, 25.31, 23.34.

**4-((1*S*,4*S*)-4-(*tert*-Butyl)-1-cyanocyclohexyl)benzonitrile (7c).** Performing the general coupling procedure with 4-(*tert*-butyl)cyclohexanecarbonitrile (**5b**, 122 mg, 0.738 mmol),<sup>19</sup>  $\text{TMPZnCl}\cdot\text{LiCl}$  (1.25 M, 0.89 mL, 1.11 mmol), SPhos (9.3 mg, 4 mol %),  $\text{Pd}(\text{OAc})_2$  (2.6 mg, 2 mol %) and 4-bromobenzonitrile (103.4 mg, 0.568 mmol) and purification of the crude nitrile by column chromatography (95:5, pentane/ether) afforded 113.5 mg (75% yield) of (**1*S*,4*S*)-7c**: IR (neat) 2230  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (d,  $J = 8.8$  Hz, 2H), 7.62 (d,  $J = 8.8$  Hz, 2H), 2.26–2.19 (m, 2H), 2.00–1.93 (m, 2H), 1.81 (tt,  $J = 3.2, 12.8$  Hz, 2H), 1.68–1.57 (m, 2H), 1.13 (tt,  $J = 3.2, 12.0$  Hz, 1H), 0.94 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  146.33, 132.72, 126.58, 121.55, 118.22, 112.02, 47.00, 44.73, 37.56, 32.45, 27.44, 24.54; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{22}\text{N}_2$  ( $M^+$ ) 266.1783; found 266.1763.

**(1*S*,4*S*)-4-(*tert*-Butyl)-1-(4-methoxyphenyl)cyclohexanecarbonitrile (7d).** Performing the general coupling procedure with 4-(*tert*-butyl)cyclohexanecarbonitrile<sup>19</sup> (**5b**, 138 mg, 0.758 mmol),  $\text{TMPZnCl}\cdot\text{LiCl}$  (1.25 M, 1.00 mL, 1.25 mmol), SPhos (10.5 mg, 4 mol %),  $\text{Pd}(\text{OAc})_2$  (2.9 mg, 2 mol %) and 4-bromoanisole (0.08 mL, 0.637 mmol) gave the crude nitrile that was purified by column chromatography (97:3, pentane/ether) to afford 103.6 mg (60% yield) of (**1*S*,4*S*)-7d** as an oily mixture of diastereomers (8.4:1 ratio) that were separated by preparative HPLC. For (**1*S*,4*S*)-7d**: IR (neat) 2239  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (d,  $J = 9.2$  Hz, 2H), 6.91 (d,  $J = 8.8$  Hz, 2H), 3.82 (s, 3H), 2.22 (br d,  $J = 10.8$  Hz, 2H), 1.93 (br d,  $J = 12.8$  Hz, 2H), 1.75 (dt,  $J = 2.8, 12.8$  Hz, 2H), 1.66–1.54 (m, 2H), 1.10 (tt,  $J = 3.2, 12$  Hz, 1H), 0.93 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.99, 133.37, 126.67, 122.92, 114.10, 55.3247.10, 43.46, 37.89, 32.42, 27.49, 24.70; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{25}\text{NONa}$  ( $M + \text{Na}$ ) 294.1834; found 294.1811. For (**1*R*,4*S*)-7d**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 (d,  $J = 9.2$  Hz, 2H), 6.93 (d,  $J = 8.8$  Hz, 2H), 3.84 (s, 3H), 2.75–2.67 (m, 2H), 2.13–2.03 (m, 2H), 1.72–1.63 (m, 2H), 1.17–1.05 (m, 2H), 0.93–0.85 (m, 1H), 0.77 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.85, 128.89, 128.42, 152.50, 114.35, 55.27, 47.21, 37.27, 35.27, 32.36, 27.27, 21.98; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{25}\text{NONa}$  ( $M + \text{Na}$ ) 294.1834; found 294.1832.

**(3*S*,5*R*,8*S*,9*R*,10*R*,13*S*,14*R*,17*S*)-3-(4-Cyanophenyl)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1H-cyclopenta[*a*]phenanthrene-3-carbonitrile (7e).** Performing the general coupling procedure with (**5*R*,8*S*,9*R*,10*R*,13*S*,14*R*,17*S*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadeca-hydro-1H-cyclopenta[*a*]phenanthrene-3-carbonitrile<sup>18</sup> (61.6 mg, 0.155 mmol),  $\text{TMPZnCl}\cdot\text{LiCl}$  (2.0 M, 0.77 mL, mmol), SPhos (4.0 mg, 4 mol %),  $\text{Pd}(\text{OAc})_2$  (1.2 mg, 2 mol %) and 4-bromobenzonitrile (29.1 mg, 0.160 mmol) gave the crude nitrile that was purified by column chromatography (hexanes) to afford 92.7 mg (72% yield) of **7e**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (d,  $J = 8.0$  Hz, 2H), 7.62 (d,  $J = 8.0$  Hz, 2H), 2.05–0.97 (m, H), 0.91 (d,  $J = 8.0$  Hz, 3H), 0.88 (s, 3H), 0.89  $\times$  2 (d,  $J = 8.0$  Hz, 3H), 0.67 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  146.32, 132.73, 126.59, 122.19, 118.27, 111.93, 56.25, 56.13, 53.65, 45.28, 43.42, 42.54, 39.78, 39.48, 38.81, 36.11, 35.79, 35.58, 35.44, 35.37, 32.93, 31.52, 28.19, 28.00, 27.99, 24.13, 23.81, 22.83, 22.55, 20.95, 18.64, 12.20, 12.07. HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{35}\text{H}_{50}\text{N}_2\text{Na}$  ( $M + \text{Na}$ ) 521.3872; found 521.3836.**



**4-((1SR, 4SR)-4-((tert-Butyldimethylsilyloxy)-1-cyanocyclohexyl)benzonitrile (7f).** Performing the general coupling procedure with 4-((tert-butylidimethylsilyloxy)-cyclohexanecarbonitrile (**5d**, 109.4 mg, 0.457 mmol), TMPZnCl-LiCl (0.86M, 0.89 mL, 0.685 mmol), SPhos (7.5 mg, 4 mol %), Pd(OAc)<sub>2</sub> (2.1 mg, 2 mol %) and 4-bromobenzonitrile (55.3 mg, 0.304 mmol) gave the crude nitrile that was purified by radial chromatography (92:8, hexanes/EtOAc) to afford 73.5 mg (71% yield) of (**1SR,4SR**)-**7f**: IR (neat) 2232 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.70 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 3.70–3.62 (m, 1H), 2.21–2.15 (m, 2H), 2.05–1.99 (m, 2H), 1.68–1.57 (m, 2H), 1.97–1.92 (m, 1H), 1.91–1.82 (m, 3H), 0.91 (s, 9H), 0.09 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 145.49, 132.76, 126.60, 121.23, 118.12, 112.18, 69.51, 43.68, 35.59, 32.83, 25.76, 18.07, -4.63; HRMS (ESI-TOF) *m/z* calcd for C<sub>20</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>SiNa (M + Na) 363.1869; found 363.1852.

**4-((1SR,4SR)-1-Cyano-4-isopropylcyclohexyl)benzonitrile (7g).** Performing the general coupling procedure with 4-isopropylcyclohexanecarbonitrile (**5e**, 103.8 mg, 0.686 mmol), TMPZnCl-LiCl (1.04M, 1.00 mL, 1.04 mmol), SPhos (11.3 mg, 4 mol %), Pd(OAc)<sub>2</sub> (3.1 mg, 2 mol %) and 4-bromobenzonitrile (123.6 mg, 0.679 mmol) gave the crude nitrile that was purified by column chromatography (95:5, pentane/ether) to afford 123.7 mg (72% yield) of **7g** as an oily mixture of diastereomers (2.3:1 ratio): IR (neat) 2230 cm<sup>-1</sup>; HRMS (ESI-TOF) *m/z* calcd for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>Na (M + Na) 275.1524; found 275.1501. For (**1SR,4SR**)-**7g**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.69 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 2.24–2.16 (m, 2H), 1.94–1.87 (m, 2H), 1.79 (dt, *J* = 3.5, 13.5 Hz, 2H), 1.64–1.52 (m, 3H), 1.21–1.11 (m, 1H), 0.94 (d, *J* = 7 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 146.311, 132.70, 126.56, 118.23, 111.94, 44.78, 42.82, 37.24, 32.42, 26.74, 19.73. For (**1RS,4SR**)-**7g**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.04–1.98 (m, 2H), 1.89–1.84 (m, 2H), 1.35–1.30 (m, 1H), 0.89 (d, *J* = 6.5, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 146.38, 132.75, 127.19, 118.20, 111.98, 44.78, 42.82, 37.24, 32.89, 24.92.

**4-((1SR,4SR)-1-Cyano-4-methylcyclohexyl)benzonitrile (7h).** Performing the general coupling procedure with 4-methylcyclohexanecarbonitrile (**5f**, 90.0 mg, 0.731 mmol), TMPZnCl-LiCl (1.25 M, 0.88 mL, 1.10 mmol), SPhos (9.2 mg, 4 mol %), Pd(OAc)<sub>2</sub> (2.5 mg, 2 mol %) and 4-bromobenzonitrile (102.3 mg, 0.679 mmol) gave the crude nitrile that was purified by column chromatography (90:10, pentane/ether) to afford 85.8 mg (68% yield) of **7h** as a mixture of diastereomers (3.5:1 ratio): IR (neat) 2231 cm<sup>-1</sup>; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 146.28, 132.67, 126.91, 126.55, 121.54, 118.16, 111.97, 111.95, 44.39, 37.13, 31.81, 31.52, 28.82, 21.95, 21.86; HRMS (ESI-TOF) *m/z* calcd for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>Na (M + Na) 247.1211; found 247.1206. For (**1SR,4SR**)-**7h**: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.69 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 2H), 2.17–2.13 (m, 2H), 1.90–1.85 (m, 2H), 1.81 (dt, *J* = 3.6, 13.2 Hz, 2H), 1.03 (d, *J* = 6.0 Hz, 3H). For (**1RS,4SR**)-**7h**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.06–1.95 (m, 2H), 1.01 (d, *J* = 6.6, 3H).

**(1SR,4SR)-1-(4-Methoxyphenyl)-4-methylcyclohexanecarbonitrile (7i).** Performing the general coupling procedure with 4-methylcyclohexanecarbonitrile (**5f**, 68.0 mg, 0.552 mmol), TMPZnCl-LiCl (1.25M, 0.67 mL, 0.838 mmol), SPhos (7.9 mg, 4 mol %), Pd(OAc)<sub>2</sub> (2.2 mg, 2 mol %) and 4-bromoanisole (0.06 mL, 0.478 mmol) gave the crude nitrile that was purified by radial chromatography (95:5, hexanes/EtOAc) to afford 79.8 mg (68% yield) of **7i** as a mixture of diastereomers (4.8:1 ratio): <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 158.98, 158.96, 133.44, 133.36, 127.70, 127.16, 126.68, 123.57, 122.96, 114.19, 114.10, 55.31, 43.16, 37.50, 32.13, 31.70, 29.06, 22.06; HRMS (ESI-TOF) *m/z* calcd for C<sub>15</sub>H<sub>19</sub>NOK (M + K) 268.1098; found 268.1106. For (**1SR,4SR**)-**7i**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 2.62–2.30 (m, 2H), 1.86–1.79 (m, 4H), 1.57–1.47 (m, 2H), 1.46–1.39 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 3H). For (**1RS,4SR**)-**7i**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.82 (s, 3H), 2.00–1.95 (m, 2H), 0.98 (d, *J* = 6.8, 3H).

**4-((1SR,3SR)-1-Cyano-3-methylcyclohexyl)benzonitrile (7j).** Performing the general coupling procedure with 3-methylcyclohexanecarbonitrile (**5g**, 176 mg, 1.428 mmol), TMPZnCl-LiCl (1.25 M, 1.72 mL, 2.15 mmol), SPhos (18.1 mg, 4 mol %), Pd(OAc)<sub>2</sub> (4.9 mg,

2 mol %) and 4-bromobenzonitrile (198.9 mg, 1.093 mmol) gave the crude nitrile that was purified by column chromatography (90:10, pentane/ether) to afford 171 mg (70% yield) of **7j** as a mixture of diastereomers (6.2:1 ratio). For (**1SR,3SR**)-**7j**: IR (neat) 2230 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 2H), 2.15–2.07 (m, 2H), 2.04–1.94 (m, 1H), 1.93–1.85 (m, 3H), 1.67 (dt, *J* = 4.2, 12.6 Hz), 1.39 (dd, *J* = 12.0, 12.6 Hz, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.05–0.98 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 146.29, 132.64, 126.48, 121.70, 118.14, 111.89, 44.97, 36.68, 36.61, 33.47, 29.87, 23.32, 21.89; HRMS (ESI-TOF) *m/z* calcd for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub> (M<sup>+</sup>) 224.1313; found 224.1312. For (**1RS,3SR**)-**7j**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.54–2.42 (m, 2H), 1.71–1.61 (m, 1H), 1.45–1.30 (m, 1H), 1.21–1.11 (m, 1H), 1.00 (d, *J* = 6.3 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 143.65, 132.79, 127.94, 123.8, 112.01, 42.60, 39.19, 34.69, 33.11, 27.26, 21.52, 20.57; HRMS (ESI-TOF) *m/z* calcd for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub> (M<sup>+</sup>) 224.1313; found 224.1312.

**4-((1RS,2SR)-1-Cyano-2-methylcyclohexyl)benzonitrile (7k).** Performing the general coupling procedure with 2-methylcyclohexanecarbonitrile (**5h**, 165.0 mg, 1.34 mmol), TMPZnCl-LiCl (1.40 M, 1.44 mL, 2.02 mmol), SPhos (5.0 mg, 4 mol %), Pd(OAc)<sub>2</sub> (17.0 mg, 2 mol %) and 4-bromobenzonitrile (187.7 mg, 1.031 mmol), except performing the deprotonation at 50 °C for 12 h, gave the crude nitrile that was purified by column chromatography (90:10, pentane/ether) to afford 117.6 mg (51% yield) of (**1RS, 2SR**)-**7k**: IR (neat) 2230 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 2.08–1.77 (m, 6H), 1.62–1.52 (m, 2H), 1.44–1.38 (m, 1H), 0.79 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 145.45, 132.68, 126.85, 119.79, 118.25, 111.80, 51.77, 40.12, 39.12, 31.81, 25.44, 23.41, 17.72; HRMS (ESI-TOF) *m/z* calcd for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>Na (M + Na) 247.1206; found 247.1200.

## ■ ASSOCIATED CONTENT

### ☞ Supporting Information

<sup>1</sup>H NMR, and <sup>13</sup>C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

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## ■ REFERENCES

- (1) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.
- (2) Milani, M.; Jha, G.; Potter, D. A. *Clin. Med. Ther.* **2009**, *1*, 141.
- (3) Cooper-DeHoff, R. M.; Handberg, E. M.; Mancina, G.; Zhou, Q.; Champion, A.; Legler, U. F.; Pepine, C. J. *Expert Rev. Cardiovasc. Ther.* **2009**, *7*, 1329.
- (4) Noble, S.; McTavish, D. *Drugs* **1995**, *50*, 1032.
- (5) Rennard, S.; Knobil, K.; Rabe, K. F.; Morris, A.; Schachter, N.; Locantore, N.; Canonica, W. G.; Zhu, Y.; Barnhart, F. *Drugs* **2008**, *68*, 3.
- (6) Christensen, S. B.; Guider, A.; Forster, C. J.; Gleason, J. G.; Bender, P. E.; Karpinski, J. M.; DeWolf, W. E., Jr.; Barnette, M. S.; Underwood, D. C.; Griswold, D. E.; Cieslinski, L. B.; Burman, M.; Bochnowicz, S.; Osborne, R. R.; Manning, C. D.; Grous, M.; Hillegas, L. M.; Bartus, J. O.; Ryan, M. D.; Eggleston, D. S.; Haltiwanger, R. C.; Torphy, T. J. *J. Med. Chem.* **1998**, *41*, 821.

(7) For reviews see: (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 646. (c) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

(8) (a) Todorovic, N.; Awuah, E.; Albu, S.; Ozimok, C.; Capretta, A. *Org. Lett.* **2011**, *13*, 6180. (b) Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming, F. F.; Knochel, P. *Org. Lett.* **2011**, *13*, 1690.

(9) (a) Recio, A., III; Heinzman, J. D.; Tunge, J. A. *Chem. Commun.* **2012**, *48*, 142. (b) Yeung, P. Y.; Chung, K. H.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 2912. (c) Shang, R.; Ji, D.-S.; Chu, L.; Fu, Y.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4470.

(10) See also: (a) Velcicky, J.; Soicke, A.; Steiner, R.; Schmalz, H.-G. *J. Am. Chem. Soc.* **2011**, *133*, 6948. (b) He, A.; Falck, J. R. *J. Am. Chem. Soc.* **2010**, *132*, 2524.

(11) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794.

(12) (a) Bresser, T.; Mosrin, M.; Monzon, G.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4686. (b) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837.

(13) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(14) Thaler, T.; Haag, B.; Gavryushin, A.; Schober, K.; Hartmann, E.; Gschwind, R. M.; Zipse, H.; Mayer, P.; Knochel, P. *Nat. Chem.* **2010**, *2*, 125.

(15) Aggarwal, V. K.; Olofsson, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5516.

(16) Bercot, E. A.; Caille, S.; Bostick, T. M.; Ranganathan, K.; Jensen, R.; Faul, M. M. *Org. Lett.* **2008**, *10*, 5251.

(17) (a) Nagao, Y.; Goto, M.; Ochiai, M.; Shiro, M. *Chem. Lett.* **1990**, 1503. (b) Baldry, K. W.; Gordon, M. H.; Hafter, R.; Robinson, M. J. T. *Tetrahedron* **1976**, *32*, 2589.

(18) Oldenziel, O. H.; van Leusen, D.; van Leusen, A. M. *J. Org. Chem.* **1977**, *42*, 3114.

(19) Fleming, F. F.; Gudipati, S.; Zhang, Z.; Liu, W.; Steward, O. W. *J. Org. Chem.* **2005**, *70*, 3845.

(20) Configurational assignments were based on NOESY correlations, provided in the Supporting Information, or based on the diagnostic  $^{13}\text{C}$  NMR chemical shift of the nitrile group: Fleming, F. F.; Wei, G. *J. Org. Chem.* **2009**, *74*, 3551.

(21) Repeated couplings demonstrated excellent reproducibility of the diastereomeric ratio.

(22) (a) Brombacher, H.; Vahrenkamp, H. *Inorg. Chem.* **2004**, *43*, 6054. (b) Orsini, F. *Synthesis* **1985**, 500. (c) Goasdoue, N.; Gaudemar, M. *J. Organomet. Chem.* **1972**, *39*, 17.

(23) (a) Patwardhan, N. N.; Gao, M.; Carlier, P. R. *Chem.—Eur. J.* **2011**, *17*, 12250. (b) Carlier, P. R. *Chirality* **2003**, *15*, 340.

(24) Nitriles have an exceedingly small steric demand, a mere 0.2 kcal mol $^{-1}$ , and while the corresponding A value for an alkylzinc has not been determined, alkylations of zincated nitriles are consistent with the steric demand of the organozinc being greater: Fleming, F. F.; Liu, W. *Eur. J. Org. Chem.* **2009**, 699.

(25) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398.

(26) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 686–754.

(27) Hawkes, G. E.; Utley, J. H. P. *J. Chem. Soc., Perkin Trans. II* **1973**, 128.

(28) Tremblay, M. WO Patent 2007013848 A1 20070201, 2007.

(29) Plettenburg, O.; Lorenz, K.; Weston, J.; Loehn, M.; Kleemann, H.-W.; Duclos, O.; Jeannot, F. WO Patent 2009156100 A1 20091230, 2009.

(30) Reid, J. R.; Dufresne, R. F.; Chapman, J. J. *Org. Synth.* **1997**, *74*, 217.

(31) Yokohama, S.; Miwa, T.; Aibara, S.; Fujiwara, H.; Matsumoto, H.; Nakayama, K.; Iwamoto, T.; Mori, M.; Moroi, R.; Tsukada, W.; Isoda, S. *Chem. Pharm. Bull.* **1992**, *40*, 2391.

(32) Mousseron, M.; Winternitz, F.; Jullien, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1948**, 79.

(33) Okimoto, M.; Chiba, T. *J. Org. Chem.* **1990**, *55*, 1070.

(34) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837.

(35) Complete consumption of the nitrile was monitored by GCMS.

(36) Higginbottom, M.; Kesten, S. R.; Lewthwaite, R. A.; Pritchard, M. C.; Rawson, D. J.; Schelkun, R. M.; Yuen, P.-W. WO Patent WO 2003092670 A1 20031113, 2003.

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