Synthesis of Higher Helicenes via Olefin Metathesis and C–H Activation

Julie Côté, Shawn K. Collins*

Département de Chimie, Université de Montréal, C. P. 6128, Succursale Centre-ville, Montréal H3C 3J7, QC, Canada
Fax +1(514)3437586; E-mail: shawn.collins@umontreal.ca

Received 27 October 2008; revised 16 December 2008

Abstract: Functionalized heterohelicenes were prepared using sequential olefin metathesis and direct arylation reactions. Functionalization via C–H activation always occurs at the least hindered position of the [5]helicene carbon skeleton. Attempts at blocking the least hindered positions to force arylation at the interior of the helicene skeleton result in decomposition of the starting material. Installation of larger aromatic groups via arylation can form helicenes albeit with limited solubility in common organic solvents.

Key words: helicene, olefin metathesis, C–H activation, heterohelicene, arylation

Helicenes continue to be a subject of interest due to their conjugated structures and optoelectronic properties.[1] These can vary considerably by changing the length of the helix or through the addition or subtraction of substituents. Thus, scientific advancements are often directly linked to the availability of synthetic methods for making new well-defined molecular architectures.[2] Although new strategies for helicene construction continue to be developed,[2–4] methods to functionalize the termini of carbohelicenes, particularly those which extend an already existing helical skeleton, are rare. Only the photocyclization of stilbenes, chemistry extensively popularized by Martin and co-workers over 30 years ago,[3] and more recently, the Diels–Alder reaction with benzoquinones,[4] exists to extend the frameworks of small [4]- and [5]carbohelicenes. The installation of additional benzene rings into the helicene skeleton requires the construction of new carbon–carbon bonds. Considering the advances in cross-coupling technology, it is surprising that this synthetic challenge has not been revisited. Herein we wish to report the application of olefin metathesis and the investigation of a direct arylation protocol for the preparation of functionalized heterohelicenes.

We have recently developed two complimentary olefin metathesis protocols for the formation of various [5]helicenes, and the higher [6]- and [7]helicenes.[5] In an effort to construct functionalized helicenes,[6] we sought to apply methods traditionally used for the formation of biaryls for the functionalization of the termini of a substituted [5]helicene **1** (Figure 1). We were intrigued by the possibility of applying a direct arylation reaction for this purpose, as no prior activation of C1 or C3 in **1** would be required.[7]

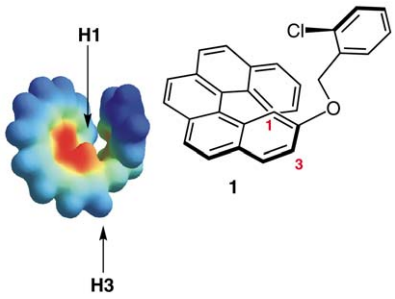


Figure 1 Electron density map of a substituted helicene **1**

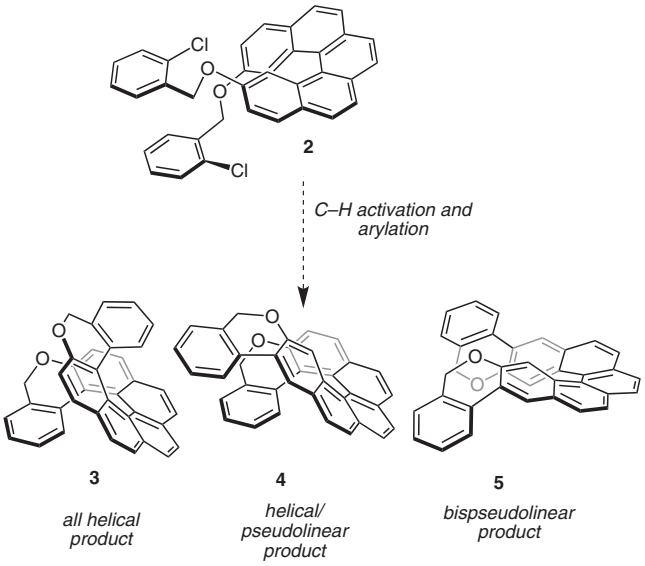


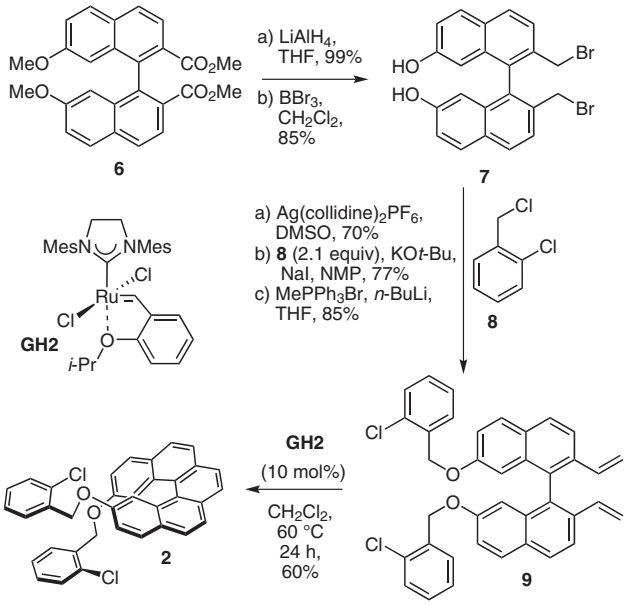
Figure 2 Possible products of arylation using the symmetric helicene **2**

Extension of the carbon skeleton of [5]helicene in a helical fashion would require the installation of a new carbon–carbon bond at its most sterically hindered position (C1 of helicene **1**, Figure 1).[8] Molecular modeling revealed that helicene **1**, appended with a 2-chlorobenzyloxy group in the 2-position shows a distinct distribution of electron density whereby the protons in the interior of the helicene are richer in electron density, making the proton at position 3 the most acidic. This points to both an electronic and steric preference for cyclization at the exterior of the helical structure. To investigate the stereochemical course of direct arylations on [5]helicenes, we prepared the C_2 symmetric helicene **2**. If the direct arylation reaction is efficient, then three different products could be expected: the helical product **3** would result from both

SYNTHESIS 2009, No. 9, pp 1499–1505
Advanced online publication: 25.03.2009
DOI: 10.1055/s-0028-1088165; Art ID: M06508SS

arylations occurring at the interior of the [5]helicene framework, while the bispseudolinear product **5** would result from both arylations at the exterior and the mixed product **4** would result from one coupling each at the interior and exterior of the core [5]helicene (Figure 2).

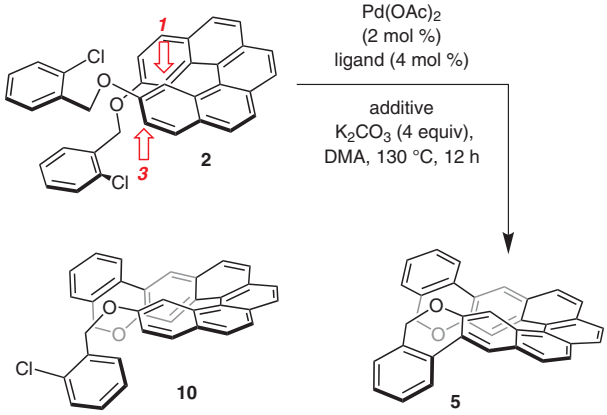
Helicene **2** was prepared from the diester **6** (Scheme 1). Reduction with lithium aluminum hydride provided a diol which was treated with boron tribromide to effect deprotection of the methoxy groups and transformation of the primary alcohols into the corresponding bromides, affording the dibromide **7** in approximately 85% isolated yield over two steps. Oxidation using a bis(collidine)silver(I) salt,[9] alkylation with 2-chlorobenzyl chloride (**8**) and Wittig reaction provided the divinyl compound **9**. Ring-closing metathesis of **9** mediated by Grubbs–Hoveyda 2nd Generation catalyst **GH2** afforded helicene **2** in 60% yield. With the C_2-symmetric helicene **2** in hand, we next investigated various direct arylation conditions to investigate whether arylation at the most hindered positions of the helicene skeleton was possible.



Scheme 1 Synthesis of helicene **2**

Although, all attempts to affect direct arylation at C1 of the [5]helicene skeleton of **2** failed, we were able to effectively develop a procedure to functionalize the termini of [5]helicene **2** at C3 (Table 1). The direct arylation of **2** was initially studied using ligands that had been reported by Fagnou and co-workers as being effective for intramolecular direct arylation.[10] The biaryl ligand S-Phos showed little reactivity towards helicene **2** (Table 1, entry 1), but DavePhos did produce 5% isolated yield of **10** and a 13% yield of the C_2-symmetric helicene **5** (entry 2). X-ray crystal structure analysis was used to confirm the identity of the products formed via arylation (Figure 3). The phosphine salt di-*tert*-butylmethylphosphine tetrafluoroborate showed much better reactivity, producing 20% of **5** and 31% isolated yield of the monocoupled

Table 1 Direct Arylation of Helicene **2**[a]



Entry	Ligand	Additive	Yield (%)	
			5	**10**
1	S-Phos	none	–	–
2	DavePhos	none	13	5
3	$PMe(t\text{-}Bu)_2HBF_4$	none	20	31
4	PCy_3HBF_4	none	11	50
5	PCy_3HBF_4	KF	13	44
6	PCy_3HBF_4	PivOH	41	20
7	PCy_3HBF_4	BzOH	40	11
8[b]	PCy_3HBF_4	none	95	–

[a] DMA = *N*,*N*-dimethylacetamide.
[b] Catalyst and ligand loadings were increased to $Pd(OAc)_2$ (10 mol%) and Cy_3PHBF_4 (20 mol%).

product **10** (entry 3). Similar reactivity was also observed with tricyclohexylphosphine tetrafluoroborate as ligand (entry 4).[11] Consequently, we examined the effect of various additives using this ligand. If a chloride anion remains bound as a ligand to palladium, it was believed that substituting it for a less bulky fluoride anion might affect the selectivities. Unfortunately, the addition of potassium fluoride resulted in little change in reactivity or selectivity (entry 5). Fagnou and co-workers have reported that pivalic acid can have a dramatic effect on reactivities in direct arylations, effectively replacing the halide ligands on the palladium center.[12] Indeed, upon addition of 10% of pivalic acid to the reaction mixture the yield of the product **5** increased to 41% (entry 6). Substituting pivalic acid for benzoic acid had a no effect and ratios were almost identical. Finally, by simply increasing the catalyst and ligand loading, we are able to isolate high yields (95%) of the arylated helicene **5** (entry 8).[13] The reluctance of **2** to undergo arylation at the interior of the helicene skeleton is not surprising. Although electronics may play a role, it is likely that the factor determining the site of arylation is mainly steric in nature.[14] During the course of our work, Kamikawa and co-workers reported on the formation of

[5]- and [6]helicenes via C–H activation.[15] However, they disclosed that all attempts at forming the more sterically encumbered [7]helicene skeletons failed. Our results agree with those of Kamikawa, in that arylation at the interior of the [5]helicene skeleton to form a [7]- or [9]helicene was not possible.

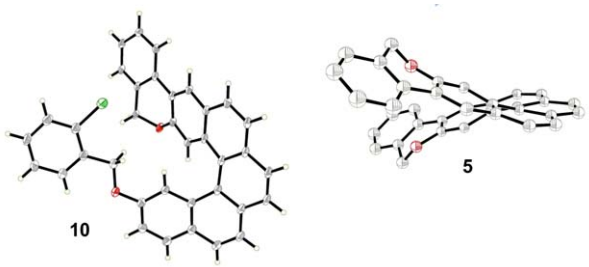
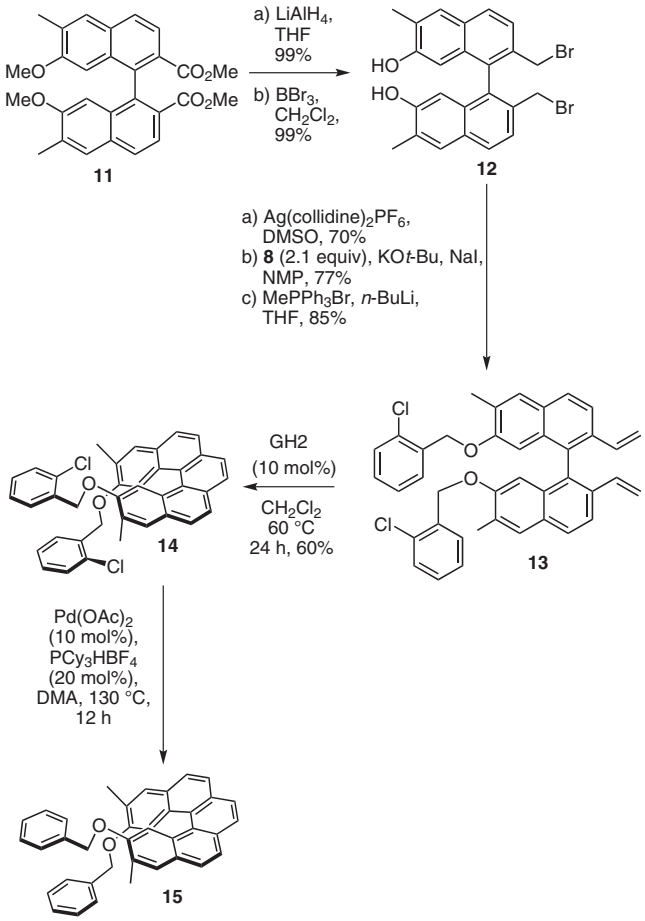


Figure 3 X-ray crystal structures of **10** and **5**[16]

In an effort to force the formation of helical products such as **3**, we decided to construct a new [5]helicene precursor where the hydrogen atoms at C3 and C12 positions would be blocked with methyl groups. The dimethyl[5]helicene **14** was prepared using the same methodology as **2** starting from the diester **11** (Scheme 2). Reduction with lithium aluminum hydride provided a diol, which was treated with boron tribromide to effect deprotection of the methoxy groups and transformation of the primary alcohols into the corresponding bromides, affording the dibromide **12** in quantitative yield. Once again, a series of oxidation, alkylation, and Wittig reactions afforded the desired divinyl compound **13**. Ring-closing metathesis of **13** mediated by Grubbs–Hoveyda 2nd generation catalyst **GH2** afforded **14** in 60% yield. Unfortunately, when [5]helicene **14** was treated under forcing conditions [10 mol% $Pd(OAc)_2$, 20 mol% PCy_3HBF_4] no cyclization to the desired helical product was observed. A complex mixture was formed and no insertion into the methyl groups was observed.[17] Analysis of the mixture by mass spectrometry revealed the dehalogenated product **15** as one of the constituents. In addition, products resulting from benzyl cleavage and/or monodehalogenation could also be identified.

Despite the fact that no arylation could be conducted at the interior of the [5]helicene skeleton, the arylation conditions developed still provided a convenient access to functionalized helicenes with extended skeletons. To further probe the scope of the tandem olefin metathesis/arylation strategy, we attempted to prepare heterohelicenes **19** and **24a**. The arylation to form **19** would be of interest as it is difficult to access nitro- or amine-containing helicenes via photocyclization. The arylation of heterohelicene **24a** would represent an extension of six cycles to the [5]helicene core.

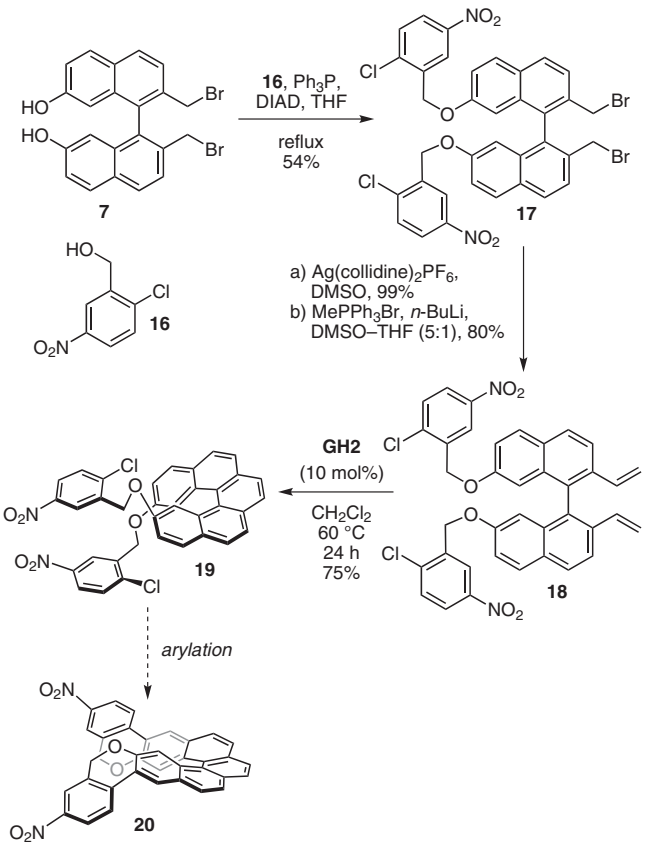
The nitro-containing styrene **18** was prepared from the dibromide **7** using an analogous protocol as described in Schemes 1 and 2. Alkylation of **7** using the established protocol utilizing potassium *tert*-butoxide failed and a Mitsunobu protocol using alcohol **16** was used to provide



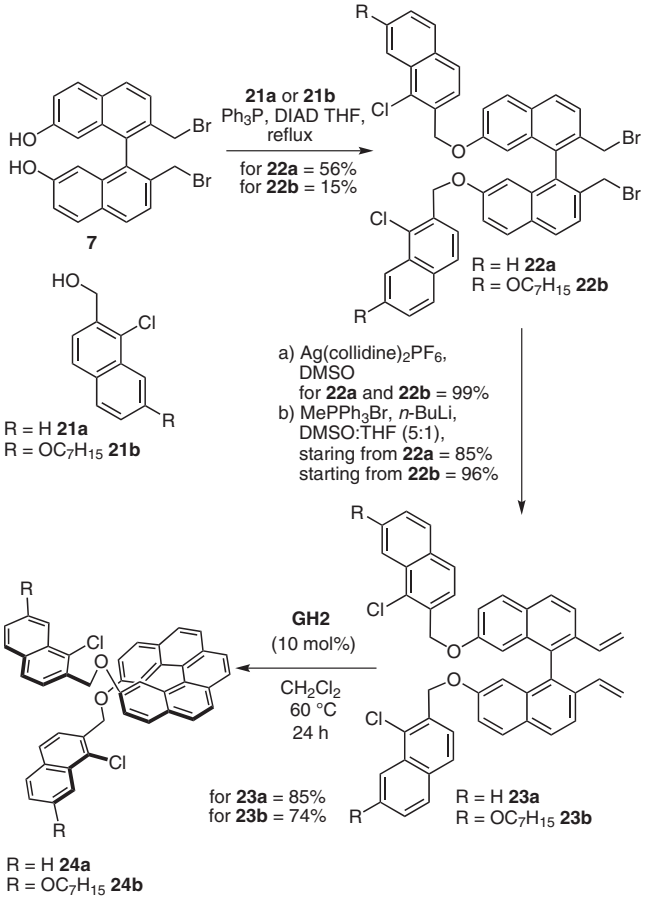
Scheme 2 Synthesis of helicene **14** and attempted arylation

the bromide **17** in 54% yield (Scheme 3). The bromide **17** was converted into the corresponding styrene via oxidation with bis(collidine)silver(I) hexafluorophosphate and subsequent Wittig olefination (99% and 80% isolated yields, respectively). The aldehyde intermediate was unstable and also poorly soluble in tetrahydrofuran. As such, the addition of dimethyl sulfoxide to the reaction mixture was necessary to improve conversion and the overall yield (80%). The ring-closing olefin metathesis protocol was found to be tolerant of the nitro functionality present and **19** was formed in 75% isolated yield. Although the metathesis reaction was tolerant of the nitro functionality, the subsequent arylation was not. This is surprising as intramolecular arylation of nitro-containing substrates has been previously reported.[11a] The arylation of **19** seemed to form a soup of products. Analysis of the crude reaction mixture by mass spectrometry suggests the presence of the product **20**. However, despite repeated attempts, the product **20** could never be cleanly isolated. In addition to the problem of separating various products with similar polarities, the products of the arylation tend to co-elute with each other and with residual tricyclohexylphosphine, even in various solvent systems.

We also attempted to perform arylation with aromatic groups such as substituted naphthalenes, which would result in the formation of larger helically chiral systems



Scheme 3 Synthesis and arylation of helicene **19**



Scheme 4 Synthesis and arylation of helicenes **24a** and **24b**

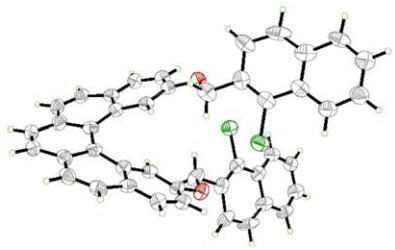
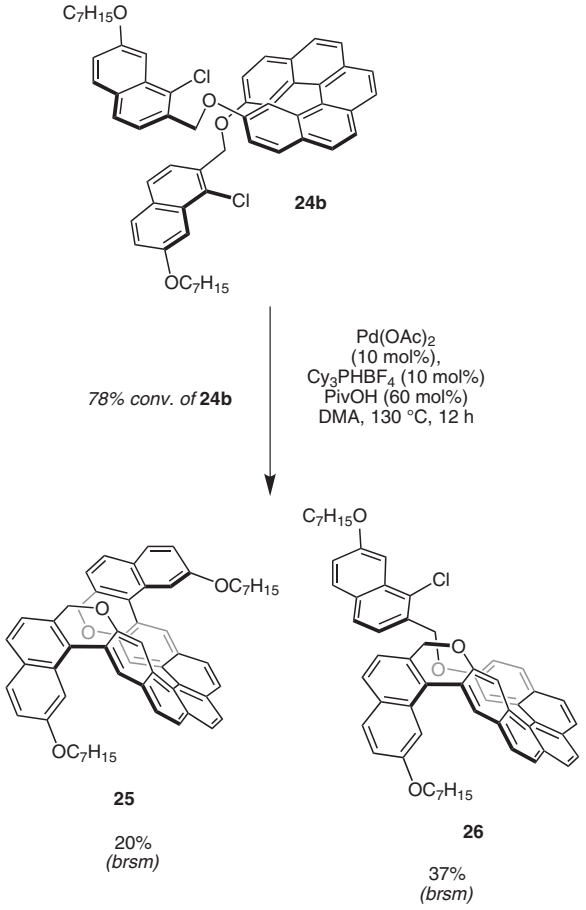


Figure 4 X-ray crystal structure **24a**[16]

(Scheme 4). Our initial investigations began with Mitsunobu alkylation of **7** using the naphthyl alcohol **21a**. Treatment of **7** with alcohol **21a** and diisopropyl azodicarboxylate in tetrahydrofuran at room temperature resulted in no conversion. However, when the reaction was heated to reflux the corresponding dibromide **22a** was isolated in modest yield (56%). The dibromide **22a** could be then be oxidized with bis(collidine)silver(I) hexafluorophosphate (99% yield) and the corresponding dialdehyde subjected to Wittig olefination using the dimethyl sulfoxide–tetrahydrofuran solvent mixture (85% yield) to afford the divinyl product **23a**. Treatment of **23a** with the Grubbs–Hoveyda 2nd generation catalyst resulted in 100% conversion of the starting material; however, isolation of the helicene **24a** was complicated by its poor solubility in common organic solvents and the tendency to co-elute during column purification with residual tricyclohexylphosphine. As such, an X-ray crystal structure analysis was performed to confirm the structure (Figure 4). Subsequent arylation of the crude helicene **24a** was also found to be difficult, probably due to its purity.

We then attempted to improve the solubility of **24a** through the installation of an alkyl chain on the naphthyl group. Following an analogous synthetic route as was used for helicene **24a**, the starting material **7** was alkylated with naphthyl alcohol **21b** in the presence of diisopropyl azodicarboxylate in tetrahydrofuran at reflux to afford the dibromide **22b** in poor isolated yield (15%). The following oxidation and olefination occurred in good yields (99% and 96% yields, respectively). The divinyl product **23b** was then treated with the Grubbs–Hoveyda 2nd generation catalyst resulting in 100% conversion of the starting material, and the helicene **24b** was isolated in 74% yield without the problematic solubility profile that plagued the isolation of **24a**. When the arylation of **24b** was carried out under the optimized conditions, the pseudolinear product **25**, and the product arising from a monocoupling **26** were identified by mass spectrometry (Scheme 5). However, the purification of products was continually problematic due to co-elution with residual quantities of tricyclohexylphosphine. Reducing the amount of phosphine to 10 mol% and adding 60 mol% of pivalic acid reduced the conversion to 76%, but **25** and **26** could be isolated with only ~5% of tricyclohexylphosphine observable by ^{1}H NMR. Based upon recovered



Scheme 5 Arylation of helicene **24b**

starting material, **25** was isolated in 20% yield and **26** in 37% yield.

In summary, arylation of disubstituted [5]helicenes affords products resulting from reaction at the C1 and C14 positions, such as extended helicenes **5** and **25**. No arylation at the C2 and C11 positions was observed. The regiochemistry of the arylation was confirmed by X-ray crystallographic analysis. Furthermore, blocking of the C2 and C13 positions by methyl groups could not induce cyclization at the most hindered positions at the interior of the helicene skeleton. This demonstrates that despite the recent advances in arylation technology, the activation of hindered C–H bonds such as those at the interior of helicene skeletons is not yet possible. New C–H activation protocols that exhibit highly selective reactions based on electronic preferences, despite steric biases, will need to be developed. Synthetic methods that are highly reactive but do not require phosphine ligands might be preferable for large aromatic systems. Elongated aromatic ribbon-like structures such **5**, **25**, and **26** may be of interest in materials science applications, where helical aromatics can assemble into nanofibers in columnar arrangements for liquid crystals applications[18] or as molecular glues.[19] Although new synthetic methodologies have allowed access to new heterohelicene structures, it is important to point out that the synthesis of macromolecular extended higher helicenes remains a significant synthetic challenge.

All chemical products were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. NMR spectra were taken in deuterated $CDCl_3$ using Bruker AV-300, AMX 300 and AMX 400 instruments unless otherwise noted. HRMS was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization.

2,13-Bis(2-chlorobenzyloxy)[5]helicene (2); Typical Procedure for Olefin Metathesis Reactions

In a dry sealed tube was added *rac*-7,7′-bis(2-chlorobenzyloxy)-2,2′-divinyl-1,1′-binaphthyl (**9**, 59 mg, 0.1 mmol, 1.0 equiv). Anhyd CH_2Cl_2 (1 mL) was added followed by the Grubbs–Hoveyda 2nd generation catalyst (6.27 mg, 10 mol%) and the mixture was stirred at 60 °C for 24 h. Silica gel was directly added to the mixture and the solvent was evaporated under vacuum. The resulting solid was purified by flash column chromatograph (silica gel, hexanes–EtOAc, 30:1) to afford pure *rac*-**2** as an off-white solid; yield: 34.1 mg (60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 1.5 Hz, 2 H), 7.94 (d, *J* = 3.0 Hz, 2 H), 7.91 (d, *J* = 3.0 Hz, 2 H), 7.89 (d, *J* = 3.0 Hz, 2 H), 7.80 (d, *J* = 6.0 Hz, 2 H), 7.44–7.41 (m, 2 H), 7.32–7.27 (m, 4 H), 7.20–7.15 (m, 4 H), 4.97 (d, *J* = 12 Hz, 2 H), 4.85 (d, *J* = 12 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.4, 122.3, 120.8, 120.7, 119.4, 117.8, 117.6, 117.3, 116.4, 115.9, 115.5, 115.3, 114.9, 113.1, 107.4, 101.1, 61.0, 29.6.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{36}H_{24}Cl_2O_2Na$: 581.1045; found: 581.1043.

2,13-Bis(2-chlorobenzyloxy)-3,12-dimethyl[5]helicene (14)

Yield: 69.4 mg (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 2 H), 7.85–7.83 (m, 4 H), 7.78 (s, 2 H), 7.76 (d, *J* = 3.8 Hz, 2 H), 7.44–7.42 (m, 2 H), 7.28–7.24 (m, 2 H), 7.19–7.13 (m, 4 H), 4.87 (d, *J* = 12.6 Hz, 2 H), 4.68 (d, *J* = 12.6 Hz, 2 H), 2.51 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.8, 134.4, 132.3, 131.8, 129.3, 128.9, 128.8, 128.3, 128.2, 127.7, 127.5, 126.6, 126.3, 126.1, 125.8, 123.9, 109.3, 66.2, 16.5.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{38}H_{29}Cl_2O_2$: 587.1539; found: 587.1528.

2,13-Bis(2-chloro-5-nitrobenzyloxy)[5]helicene (19)

Yield: 101 mg (75%).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 2.8 Hz, 2 H), 8.035 (dd, *J* = 8.7, 2.7 Hz, 2 H), 7.98 (d, *J* = 9.1 Hz, 2 H), 7.94 (d, *J* = 8.4 Hz, 2 H), 7.92–7.91 (m, 4 H), 7.85 (d, *J* = 7.7 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.35 (dd, *J* = 8.7, 2.5 Hz, 2 H), 4.90 (d, *J* = 14.0 Hz, 2 H), 4.80 (d, *J* = 14.0 Hz, 2 H).

^{13}C NMR (175 MHz, $CDCl_3$): δ = 154.7, 146.6, 138.8, 136.6, 132.8, 131.0, 130.2, 130.0, 128.4, 127.6, 127.1, 126.1, 124.9, 123.6, 123.0, 118.2, 110.9, 65.9.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{23}Cl_2N_2O_6$: 649.0928; found: 649.0953.

2,13-Bis[(1-chloro-2-naphthyl)methoxy][5]helicene (24a)

Yield: 61.5 mg (85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.4 Hz, 2 H), 7.92 (d, *J* = 8.4 Hz, 2 H), 7.83–7.78 (m, 6 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 7.50–7.39 (m, 8 H), 7.16 (dd, *J* = 8.6, 2.2 Hz, 2 H), 5.08 (d, *J* = 13.2 Hz, 2 H), 4.96 (d, *J* = 13.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 133.7, 132.4, 131.8, 131.0, 130.5, 129.4, 129.3, 127.9, 127.8, 127.2, 127.0, 126.9, 126.8, 126.4, 126.0, 125.0, 124.1, 124.0, 117.9, 110.9, 67.1.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{44}H_{29}O_2Cl_2$: 659.1532; found: 659.1539.

2,13-Bis{[1-chloro-7-(heptyloxy)-2-naphthyl]methoxy}[5]helicene (24b)

Yield: 38 mg (74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 2.2 Hz, 2 H), 7.94–7.89 (m, 6 H), 7.79 (d, *J* = 8.5 Hz, 2 H), 7.63 (d, *J* = 9.0 Hz, 2 H), 7.50–7.44 (m, 4 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.27–7.23 (m, 2 H), 7.16 (dd, *J* = 8.9, 2.5 Hz, 2 H), 5.19(d, *J* = 12.9 Hz, 2 H), 5.07 (d, *J* = 13.0 Hz, 2 H), 4.14–4.12 (m, 4 H), 1.91–1.86 (m, 4 H), 1.60–1.54 (m, 4 H), 1.44–1.37 (m, 12 H), 0.96–0.89 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.9, 155.3, 132.1, 131.7, 129.3, 129.2, 129.1, 128.9, 127.6, 127.0, 126.6, 126.3, 126.2, 124.0, 122.5, 119.3, 119.2, 117.7, 110.9, 103.0, 102.9, 67.8, 67.3, 31.5, 28.9, 28.8, 25.8, 22.3, 13.8.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{58}H_{57}O_4Cl_2$: 887.3628; found: 887.3610.

5,10-Dihydro[5]heliceno[2,3-*c*:13,12-*c*]bis(2-benzopyran) (5); Typical Procedure

In a glovebox, to a dry sealed tube was added $Pd(OAc)_2$ (1.24 mg, 0.005 mmol, 10 mol%), PCy_3HBF_4 (4.05 mg, 0.01 mmol, 20 mol%), and K_2CO_3 (30.4 mg, 0.22 mmol, 4 equiv). A soln of *rac*-2,13-bis(2-chlorobenzyloxy)[5]helicene (**2**, 25.8 mg, 0.046 mmol, 1 equiv) in anhyd DMA was added to the sealed tube. The sealed tube was removed from the glovebox and the mixture was stirred at 130 °C for 12 h. Silica gel was directly added to the mixture and the solvent was evaporated under vacuum. The resulting solid was purified by flash column chromatograph (silica gel, hexanes–EtOAc, 30:1) to afford pure **5** as an off-white solid; yield: 22 mg (95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (s, 2 H), 8.14 (s, 2 H), 8.00 (d, *J* = 8.1 Hz, 2 H), 7.93 (d, *J* = 8.6 Hz, 2 H), 7.83 (s, 2 H), 7.76 (d, *J* = 8.5 Hz, 2 H), 7.50 (td, *J* = 7.8, 1.5 Hz, 2 H), 7.36 (td, *J* = 7.5, 0.9 Hz, 2 H), 7.18 (d, *J* = 7.5 Hz, 2 H), 5.16 (d, *J* = 13.4 Hz, 2 H), 4.99 (d, *J* = 13.2 Hz, 2 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 151.5, 133.0, 130.9, 128.8, 128.6, 128.4, 127.9, 126.8, 126.4, 125.9, 125.1, 124.6, 124.0, 123.5, 123.3, 121.2, 115.9, 68.9.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{23}O_2$: 487.1693; found: 487.1684.

16-(2-Chlorobenzyloxy)-12*H*-[5]heliceno[2,3-*c*][2]benzopyran (10)

Yield: 12 mg (50%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 8.07 (d, *J* = 3.6 Hz, 2 H), 7.96–7.80 (m, 6 H), 7.77 (d, *J* = 2.1 Hz, 1 H), 7.74 (d, *J* = 1.8 Hz, 1 H), 7.48–7.39 (m, 2 H), 7.35–7.30 (m, 1 H), 7.27 (d, *J* = 2.4 Hz, 1 H), 7.16–7.06 (m, 4 H), 5.12 (d, *J* = 13.5 Hz, 1 H), 5.0 (d, *J* = 10.8 Hz, 2 H), 4.89 (d, *J* = 12.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =155.3, 151.5, 134.3, 132.4, 132.3, 132.2, 131.3, 131.0, 129.7, 129.1, 128.8, 128.7, 128.5, 128.3, 128.2, 128.1, 127.8, 127.6, 127.3, 127.0, 126.9, 126.8, 126.4, 126.3, 124.7, 124.6, 124.4, 124.0, 122.9, 122.4, 122.2, 118.0, 115.4, 110.7, 68.2, 66.7.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calculated for $C_{36}H_{23}ClO_2Na$: 545.1278; found: 545.1274.

2,17-Bis(heptyloxy)-7,12-dihydro[5]heliceno[2,3-*a*:13,12-*a*]bis(naphtho[2,1-*c*]pyran) (25)

Following the typical procedure for **5**, but PivOH (60 mol%) was added.

Yield: 14 mg (20% based on recovered **24b**).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.61 (s, 2 H), 8.35 (s, 2 H), 7.94 (d, *J* = 5.0 Hz, 2 H), 7.89 (s, 2 H), 7.84 (d, *J* = 5.0 Hz, 2 H), 7.82 (d, *J* = 5.0 Hz, 2 H), 7.73 (d, *J* = 10.0 Hz, 2 H), 7.26–7.24 (m, 4 H), 7.12 (d, *J* = 10.0 Hz, 2 H), 5.09 (d, *J* = 15.0 Hz, 2 H), 4.89 (d, *J* = 15.0 Hz, 2 H), 4.30–4.22 (m, 4 H), 1.98–1.93 (m, 4 H), 1.61–1.57 (m, 4 H), 1.38–1.35 (m, 12 H), 0.94–0.90 (m, 6 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 158.5, 153.6, 134.6, 132.8, 131.2, 130.8, 130.4, 129.8, 128.8, 128.2, 127.6, 127.5, 126.8, 126.7, 125.7, 125.2, 124.5, 120.2, 118.7, 116.0, 104.8, 70.1, 68.3, 31.9, 29.8, 29.3, 26.2, 22.7, 14.2.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{58}H_{54}O_4Na$: 837.3914; found: 837.3949.

18-{[1-Chloro-7-(heptyloxy)-2-naphthyl]methoxy}-9-(heptyloxy)-14*H*-[5]heliceno[2,3-*b*]naphtho[2,1-*d*]pyran (26)

Following the typical procedure for **5**, but PivOH (60 mol%) was added.

Yield: 26 mg (37% based on recovered **24b**).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (s, 1 H), 8.24 (d, *J* = 8.0 Hz, 2 H), 7.94–7.88 (m, 6 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.47 (m, 4 H), 7.34 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.26–7.23 (m, 2 H), 7.11 (d, *J* = 8.0 Hz, 1 H), 7.06 (d, *J* = 4.0 Hz, 1 H), 7.00 (dd, *J* = 8.8, 2.4 Hz, 1 H), 5.24 (d, *J* = 12.0 Hz, 1 H), 5.17 (d, *J* = 12.0 Hz, 1 H), 5.06 (d, *J* = 16.0 Hz, 1 H), 4.89 (d, *J* = 12.0 Hz, 1 H), 4.24–4.18 (m, 1 H), 4.10–4.04 (m, 1 H), 3.93–3.88 (m, 2 H), 1.93–1.88 (m, 2 H), 1.85–1.80 (m, 2 H), 1.57–1.49 (m, 4 H), 1.39–1.37 (m, 6 H), 1.30–1.26 (m, 6 H), 0.95–0.92 (m, 3 H), 0.88–0.85 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.5, 158.0, 156.0, 153.4, 134.6, 132.9, 132.8, 132.7, 131.8, 131.6, 131.1, 130.9, 130.4, 129.9, 129.6, 129.3, 129.0, 128.8, 128.2, 128.1, 127.7, 127.6, 127.4, 127.3, 127.4, 126.8, 126.6, 126.5, 126.4, 125.7, 125.2, 124.4, 124.3, 122.4, 120.3, 119.4, 118.6, 118.5, 116.4, 111.4, 105.0, 102.8, 70.0, 68.2, 68.0, 67.9, 31.9, 31.8, 29.7, 29.4, 29.3, 29.2, 26.2, 26.1, 22.7, 22.6, 14.2, 14.1.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{58}H_{55}O_4ClNa$: 873.3681; found: 873.3682.

Acknowledgment

We thank NSERC (Canada), FQRNT (Québec), CFI (Canada), Boehringer Ingelheim (Canada) Ltd., Merck Frosst Centre for Therapeutic Research and the Université de Montréal for generous financial support. The authors thank Prof. A. Schmitzer for the molecular modeling of helicene **1**, Martin Vachon for the X-ray analysis of compound **5** and Francine Bélanger-Gareipy for the X-ray analysis of compounds **10** and **24a**.

References

(1) (a) Schmuck, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 2448. (b) Hopf, H. *Classics in Hydrocarbon Chemistry*; Wiley-VCH: Weinheim, **2000**, 321–330. (c) Vögtle, F. *Fascinating Molecules in Organic Chemistry*; Wiley: New York, **1992**, 156–180. (d) Meurer, K. P.; Vögtle, F. *Top. Curr. Chem.* **1985**, *127*, 1. (e) For some examples of optical or electronic properties of helicenes see: Martin, R. H. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 649. (f) Hu, Y.; Wex, B.; Perkovic, M. W.; Neckers, D. C. *Tetrahedron* **2008**, *64*, 2251. (g) Katz, T. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 1921. (h) For examples of medicinal properties see: Grimme, S.; Harren, L.; Sobanski, A.; Vögtle, F. *Eur. J. Org. Chem.* **1998**, 1491. (i) Honzawa, S.; Okubo, H.; Anzai, S.; Yamaguchi, M.; Tsumoto, K.; Kumagai, I. *Bioorg. Med. Chem.* **2002**, *10*, 3213. (j) Xu, Y.; Zhang, X. Y.; Sugiyama, H.; Umano, T.; Osuga, H.; Tanaka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6566.

(2) For a recent review of helicene synthesis see: (a) For other recent examples see: Urbano, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3986. (b) Harrowven, D. C.; Guy, I. L.; Nanson, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 2242. (c) Dubois, F.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 5039. (d) Zhang, Y.; Petersen, J. L.; Wang, K. K. *Tetrahedron* **2008**, *64*, 1285. (e) Rajca, A.; Rajca, S.; Pink, M.; Miyasaka, M. *Synlett* **2007**, 1799. (f) Ichikawa, J.; Yokota, M.; Kudo, T.; Umezaki, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 4870.

(3) (a) Kagan, H.; Moradpour, A.; Nicoud, J. F.; Balavoine, G.; Martin, R. H.; Cosyn, J. P. *Tetrahedron Lett.* **1971**, *12*, 2479. (b) Martin, R. H.; Baes, M. *Tetrahedron* **1975**, *31*, 2135. (c) Moradpour, A.; Kagan, H.; Baes, M.; Morren, G.; Martin, R. H. *Tetrahedron* **1975**, *31*, 2139. (d) Martin, R. H.; Morren, G.; Schurter, J. J. *Tetrahedron Lett.* **1969**, *10*, 3683.

(4) (a) Carreno, M. C.; Gonzalez-Lopez, M.; Urbano, A. *Chem. Commun.* **2005**, 611. (b) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A. *Chem.–Eur. J.* **2003**, *9*, 4118. (c) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A. *J. Am. Chem. Soc.* **2001**, *123*, 7929. (d) Paruch, K.; Vyklicky, L.; Katz, T. J. *Org. Synth.* **2003**, *80*, 233. (e) Paruch, K.; Vyklicky, L.; David, Z.; Katz, T. J.; Incarvito, C.; Zakharov, L.; Rheingold, A. L. *J. Org. Chem.* **2003**, *68*, 8539. (f) Willmore, N. D.; Liu, L.; Katz, T. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1093. (g) Carreno, M. C.; Enriquez, A.; Garcia-Cerrada, S.; Sanz-Cuesta, M. J.; Urbano, A.; Maseras, F.; Nonell-Canals, A. *Chem.–Eur. J.* **2008**, *14*, 603.

(5) For the use of [2+2+2] cycloadditions to access helicenes see: (a) Míšek, J.; Teplý, F.; Stará, I. G.; Tichý, M.; Šaman, D.; Císařová, I.; Vojtíšek, P.; Starý, I. *Angew. Chem. Int. Ed.* **2008**, *47*, 3188. (b) Stará, I. G.; Starý, I.; Kollárovic, A.; Teplý, F.; Vyskočil, ; Šaman, D. *Tetrahedron Lett.* **1999**, *40*, 1993. (c) Teplý, F.; Stará, I. G.; Starý, I.; Kollárovic, A.; Šaman, D.; Rulíšek, L.; Fiedler, P. *J. Am. Chem. Soc.* **2002**, *124*, 9175. (d) Sehnal, P.; Krausova, Z.; Teply, F.; Stara, I. G.; Stary, I.; Rulisek, L.; Saman, D.; Cisarova, I. *J. Org. Chem.* **2008**, *73*, 2074. (e) Stary, I.; Stara, I. G.; Alexandrova, Z.; Sehnal, P.; Teply, F.; Saman, D.; Rulisek, L. *Pure Appl. Chem.* **2006**, *78*, 495. (f) Stara, I. G.; Alexandrova, Z.; Teply, F.; Sehnal, P.; Stary, I.; Saman, D.; Budesinsky, M.; Cvacka, J. *Org. Lett.* **2005**, *7*, 2547. (g) Tanaka, K.; Kamisawa, A.; Suda, T.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc.* **2007**, *129*, 12078.

(6) Collins, S. K.; Grandbois, A.; Vachon, M. P.; Côté, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2923.

(7) For other recent examples of the asymmetric synthesis of heterohelicenes see: (a) Rajca, A.; Miyasaka, M.; Pink, M.; Wang, H.; Rajca, S. *J. Am. Chem. Soc.* **2004**, *126*, 15211. (b) Nakano, K.; Hidehira, Y.; Takahashi, K.; Hiyama, T.; Nozaki, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 7136. (c) Lamanna, G.; Faggi, C.; Gasparrini, F.; Ciogli, A.; Villani, C.; Stephens, P. J.; Devlin, F. J.; Menichetti, S. *Chem.–Eur. J.* **2008**, *14*, 5747.

(8) For some recent reviews/highlights in arylation see: (a) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (d) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748. (e) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (f) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904.

(9) For a recent example of helicenes with aryl groups at the interior positions see: Hu, Y.; Wex, B.; Perkovic, M. W.; Neckers, D. C. *Tetrahedron* **2008**, *64*, 2251.

(10) For another example of the use of similar silver(I) salts see: Jung, M. E.; Nichols, C. J. *J. Org. Chem.* **1998**, *63*, 347.

(11) (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, *7*, 1857.

(12) Attempts to invert the sequence and perform arylation on **9** prior to metathesis gave only complex product mixtures.

(13) (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Oezdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156.

(14) The analogous bromide and iodide of **2** also gave **5** as the major product.

(15) Kamikawa, K.; Takemoto, I.; Takemoto, S.; Matsuzaka, H. *J. Org. Chem.* **2007**, *72*, 7406.

(16) X-ray crystal structure data have been deposited at the Cambridge Crystallographic Data Centre under reference numbers CCDC-723431 (**5**), CCDC-723433 (**10**), and CCDC-723432 (**24a**). These data can be obtained free of charge at www.ccdc.com.ac.uk or from CCDC, 12, Union Road, Cambridge CB2 1EK, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk.

(17) For examples of arylation reactions that could proceed at either Csp^2 or Csp^3 centers see: (a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (b) Mousseau, J. J.; Larivee, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641.

(18) Lee, E.; Huang, Z.; Ryu, J.-H.; Lee, M. *Chem.–Eur. J.* **2008**, *14*, 6957.

(19) Lee, E.; Kim, J.-K.; Lee, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 6375.