Helicene Synthesis

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Preparation of Helicenes through Olefin Metathesis**

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The last decade has seen the interest in helicenes and helical-type molecules undergo a significant renaissance. Although the [*n*]helicenes were long considered academic curiosities,[1] their helically chiral, conjugated structures afford fascinating optical[2] and electronic properties,[3] thus recently finding application in the field of medicinal chemistry.[4] Consequently, methods for the preparation of helicenes have advanced in tandem.[5] The need for more highly substituted and structurally varied helicenes has led to the development of new methods as replacements of the classical synthesis by the photocyclization of stilbenes.[6] These methods include successive Diels–Alder reactions,[7] cyclotrimerizations of

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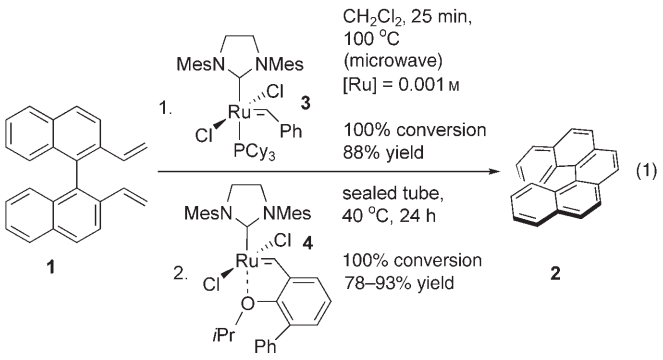
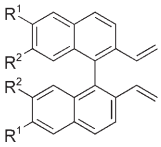
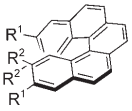
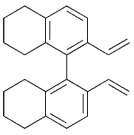
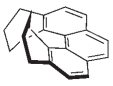
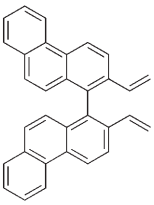
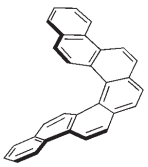
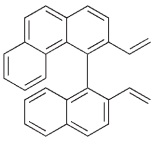
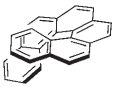
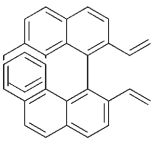
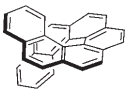
acetylenes,[8] carbenoid couplings,[9] Pd-mediated techniques,[10] and radical cyclizations.[11] In general, each of the above methods is used to form a benzene ring within the helicene framework. Herein, we describe a preparation of helicenes using olefin metathesis for the formation of a benzene ring. It is quite surprising that despite the power of ring-closing olefin metathesis to prepare a variety of cyclic structures, so few examples have been documented for the formation of benzenes, undoubtedly one of the most important cycles in all of organic chemistry. Only three examples have been reported, all in the last two years.[12,13,14] Notably, King and co-workers clearly demonstrated by density functional theory calculations that the formation of an aromatic ring through olefin metathesis should act as a thermodynamic sink and an exergonic reaction is predicted by -28 kcal mol^{-1}.[13] However, there is no precedent that indicates whether olefin metathesis will be feasible to form the strained [5]helicene structure, although the normally competing reverse ring-opening reaction will not be possible. An added benefit of our strategy is the use of 1,1′-binaphthyls as precursors. The modification and alteration of this skeleton has been extensively studied with regards to the preparation of chiral ligands.[15] A short series of elementary transformations would prepare the 1,1′-binaphthyl framework for transformation into the helicene motif by a ring-closing metathesis reaction.[16]



(1)

2,2′-Binaphthol was first converted into its corresponding divinyl precursor **1**.[17] Following extensive optimization,[18] two optimal protocols for the conversion of **1** into [5]helicene were identified [Eq. (1); Mes = mesityl, Cy = cyclohexyl]. The first utilizes catalyst **3** and resulted in a reproducible yield of 88% of the isolated product, [5]helicene, after 25 min in CH_2Cl_2 at 100 °C under microwave irradiation.[19] Although this protocol is extremely rapid, we sought to decrease the reaction temperature. Consequently, a second protocol was developed using catalyst **4**, whereby yields of 78–93% of the isolated [5]helicene could be obtained at 40 °C in a sealed-tube vessel.

Table 1: Preparation of helicenes by olefin metathesis.[a]

Entry	Precursor		Helicene		Cat.	*t*	Conversion [%][b]	Yield [%][c]
1		**5**		**6**	**3**	25 min	100	(90)
	$R^1 = p$-tol, $R^2 = H$,		$R^1 = p$-tol, $R^2 = H$,		**4**	24 h	55	87 (52)
2	$R^1 = H$, $R^2 = OMe$,	**7**	$R^1 = H$, $R^2 = OMe$,	**8**	**3**	120 min	95	57
					4	24 h	40	55 (25)
3	$R^1 = H$, $R^2 = OBn$,	**9**	$R^1 = H$, $R^2 = OBn$,	**10**	**3**	25 min	100	(61)
					4	24 h	41	49 (22)
4		**11**		**12**	**3**	140 min	100	(80)
					4	24 h	50	(45)
5		**13**		**14**	**3**	25 min	100	(75)
					4	24 h	45	55 (31)
6		**15**		**16**	**3**	60 min	100	(80)
					4	24 h	100	(70)
7		**17**		**18**	**3**	60 min	100	(81)
					4	24 h	100	(80)

[a] The reaction conditions: for catalyst **2**: [Ru] = 0.001 M in CH_2Cl_2, sealed tube, microwave heating in 5-min pulses at 100 °C, 10 mol% catalyst; for catalyst **5**: sealed tube, [Ru] = 0.001 M in PhH at 40 °C, 10 mol% catalyst. [b] Conversion measured by ^{1}H NMR spectroscopic analysis. [c] Yields calculated based on ^{1}H NMR spectroscopic analysis; yields of the isolated products were determined by flash column chromatography on silica gel and are indicated in brackets.

Following these studies, the two protocols outlined above were chosen for further examination (Table 1). Subsequently, the 6,6′-di-*p*-tolyl derivative **5** (using binaphthyl numbering) underwent smooth conversion into the corresponding helicene **6** when subjected to the microwave heating protocol (entry 1). A conversion of 100% was observed with ^{1}H NMR

spectroscopic analysis and a yield of 90% of the isolated product **6** was obtained in just 25 min. Heating with catalyst **4** at 40°C for 24 h provided a yield of 52% of the isolated product (55% conversion; entry 1). These results for the two metathesis protocols are quite general in that the microwave protocol tends to give excellent conversions and yields, whereas the protocol which employs **4** at 40°C is gentler, albeit giving generally lower yields. Substituents at the 7,7′-positions of the binaphthyl skeleton also had little affect on the outcome of the ring-closing event (entries 2 and 3). The ring closure of dimethyl ether **7** was performed on the largest scale possible (which was limited because of the volume of the microwave vessel; scale: ≈350 mg of **7**; entry 2). The microwave could reach a maximum temperature of 120°C on this scale. Following irradiation for 120 min, **7** underwent 95% conversion, and 57% yield of the isolated helicene **8** was obtained. Treatment of **7** with **4** at 40°C in a sealed tube resulted in a conversion of 40% and a similar yield of 22% for the isolated product **8** (55% yield based on the recovered starting material). The dibenzyl ether **9** also provided a conversion of 100% after 25 min under microwave heating conditions (entry 3). However, some benzyl deprotection was observed and a yield of 61% was obtained for the isolated product **10**. The milder cyclization using **4** resulted in only 41% conversion, but cleavage of the benzyl group was not observed and the yield of the isolated product **10** (22% vs 49% yield based on the recovered starting material) was nearly identical to that observed for the methoxy derivative **8**. To improve the efficiency of the reaction, the microwave protocol was repeated, but catalyst **3** was replaced with **4**. As expected 100% conversion was observed after 25 min; however, some cleavage of the benzyl group was again observed, although the yield of the isolated product was slightly higher than the previous run with **3** (68 vs 61%).

Substituents at the 8,8′-positions were expected to be problematic, as they result in increased ring strain in the helicene products. Consequently, the first substrate investigated possessed the smallest substituent possible, an extra hydrogen atom (entry 4). 5,5′-6,6′-7,7′-8,8′-Octahydro-1,1′-bi-2-naphthol was transformed into **11** and subjected to microwave irradiation with **3**; although 100% conversion of **11** was obtained, 140 minutes were required for complete conversion. Surprisingly, 50% conversion (45% yield of the isolated product) was obtained with catalyst **4**, thus prompting a second trial with **4** under microwave irradiation. Gratifyingly, 75% conversion was obtained after only 25 min, and the saturated helicene **12** was isolated in 68% yield (86% yield based on recovered **11**).

Higher helicenes were also accessible using the above protocols. The first attempt involved the conversion of 2-phenanthrol into the corresponding divinyl precursor **13** through the same series of transformations used for **1** (entry 5).[15] The resulting helicene **14** was expected to form readily under conditions optimized for [5]helicene. Indeed, following microwave irradiation for 25 min in the presence **3**, 100% conversion of **13** was observed and 75% yield of the helicene product **14** was obtained. Strangely, heating **13** in a sealed tube with **4** gave a conversion of 45% and a yield of 55% (based on the recovered starting material) for **14**.

Subsequent experiments sought to further investigate the effect of the substituents which would result in increased strain in the helicene products. Consequently, the [6]helicene precursor **15** underwent smooth conversion (100%) to the corresponding [6]helicene **16** after 60 min under microwave irradiation, which was isolated in 80% yield (entry 6). Treatment with catalyst **4** at 40°C in a sealed tube resulted in 100% conversion and 70% yield of the isolated product. Similar results were obtained for the preparation of [7]helicene (entry 7). For example, substrate **17** required 60 min of microwave irradiation with **2** to undergo complete conversion into **18** (81% yield of isolated product). Milder conditions with catalyst **4** also resulted in 100% conversion and 80% yield of isolated [7]helicene.

In summary, we have developed a novel synthesis of substituted [5]helicenes and [6]- and [7]helicenes through ring-closing olefin metathesis. Conditions have been optimized using two separate protocols: catalyst **3**/CH_2Cl_2 under microwave irradiation or catalyst **4**/PhH at 40°C, when a sensitive functionality may be present. A highlight of this method is the facile formation of various substituted [5]helicenes and [6]- and [7]helicenes from the readily modifiable 1,1′-binaphthyls. For example, substituted [6]helicenes could be formed from mixed oxidative couplings between 3-phenanthrol and various 2-naphthols. This ease of functionalization suggests that these methods should be of significant interest in the fields of materials science and medicinal chemistry. These studies reinforce that olefin metathesis catalysts can be remarkably effective in generating strained molecular architectures and emphasize that ring-closing olefin metathesis can be a powerful route to the preparation of aromatic compounds. In contrast to other methods for helicene formation which utilize reactive radical or carbene intermediates, these olefin-metathesis conditions are gentle and the possibility of an asymmetric route to helicenes through a kinetic-resolution route is currently being pursued.

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[17] Binaphthol ditriflate is carboxymethylated using an established protocol; see: M. Seki, S.-I. Yamada, T. Kuroda, R. Imashiro, T. Shimizu, *Synthesis* **2000**, 1677 – 1680; subsequent reduction (lithium aluminum hydride, Et_2O), oxidation (pyridinium chlorochromate, CH_2Cl_2), and the Wittig reaction (*t*BuOK, $CH_2{=}PPh_3$, THF) yields the divinyl precursor.
[18] See the Supporting Information for the experimental procedures and further details concerning catalyst optimization.
[19] Higher temperatures can be used, but did not affect the rate or yield of [5]helicene significantly.

