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# Enantioselective Synthesis of [7]Helicene: Dramatic Effects of Olefin Additives and Aromatic Solvents in Asymmetric Olefin Metathesis

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**Abstract:** The asymmetric synthesis of [7]helicene was accomplished in good *ee* (80%) by kinetic resolution by means of asymmetric olefin metathesis. Three key factors contributed to the success of the kinetic resolution: the use of new Ru-based olefin metathesis catalysts bearing $C_1$-symmetric N-heterocyclic carbene ligands, simple olefins as additives to control the nature of the propagating alkylidene and hexafluorobenzene as a solvent.

**Keywords:** asymmetric synthesis · catalysis · helicenes · kinetic resolution · olefin metathesis

## Introduction

Helicenes continue to be topics of intense interest as their helically chiral structures have interesting potential optical, electronic and medicinal properties.[1] Despite the relatively high level of interest in these structures, the synthetic methods available for their preparation remain relatively underdeveloped.[2] All new synthetic methods that are developed must construct the strained carbon skeletons that result from the *ortho*-fused aromatic rings.[3] Consequently, the asymmetric synthesis of helicenes is also challenging. New methods for the asymmetric preparation of heterohelicenes have appeared and usually involve the enantioselective formation of a carbon-heteroatom bond.[4] The synthetic challenge associated with an asymmetric synthesis of carbohelicenes is associated with enantioselectively inducing helicity while forming a carbon–carbon bond. Herein, we report a novel catalytic and enantioselective synthetic protocol for the formation of [7]helicene by kinetic resolution by means of asymmetric ring-closing metathesis (ARCM) that exploits the use of olefin additives.

Enantioenriched carbohelicenes can be obtained by resolution on chiral stationary phases; however, the development of a practical asymmetric synthesis of enantioenriched all-carbon helicenes remains of interest.[5] The first attempt to prepare enantioenriched all-carbon helicenes was reported by Martin, Kagan and co-workers more than 30 years ago.[5a] Unfortunately, enantioinduction by photocyclisation using circularly polarised light failed to afford significant levels of enantioexcess. In the past decade, an efficient method to access enantiopure helicenes was developed that employs an asymmetric Diels–Alder reaction of quinones bearing enantioenriched sulfoxides as chiral auxiliaries.[6] In the late 90s, Starý and co-workers reported the first catalytic and asymmetric approach to helicenes consisting of an imaginative [2+2+2] cyclotrimerisation of alkynes that yielded tetrahydro[6]helicenes with moderate levels of *ee* (42–48% *ee*).[7] Although the racemic tetrahydrohelicenes prepared in this manner could be subsequently oxidised to the corresponding [6]helicene, elevated temperatures were required and no mention of whether the enantioenriched tetrahydrohelicenes retained their enantiomeric excess was reported. In 2007, Tanaka and co-workers revisited this cyclotrimerisation approach and prepared oxygen-containing dihydroheterohelicenes and some related helically chiral molecules by using a cationic $Rh^I$/modified BINAP complex.[8b]

Our laboratories have been developing new protocols to access strained molecules by olefin metathesis. In 2006, our group published a new synthetic route to various substituted [5]helicenes as well as [6]- and [7]helicene by using ring-closing olefin metathesis (Scheme 1).[8] Two separate olefin metathesis protocols were developed that utilised either Grubbs 2nd-generation catalyst **5** in $CH_2Cl_2$ at 100°C under microwave irradiation or Blechert's catalyst **6** at 40°C in a sealed tube vessel. Under the optimised conditions employing microwave irradiation, [6]helicene could be prepared with excellent conversion (100%) and isolated yield (80%). [7]Helicene could also be prepared and similar yields were

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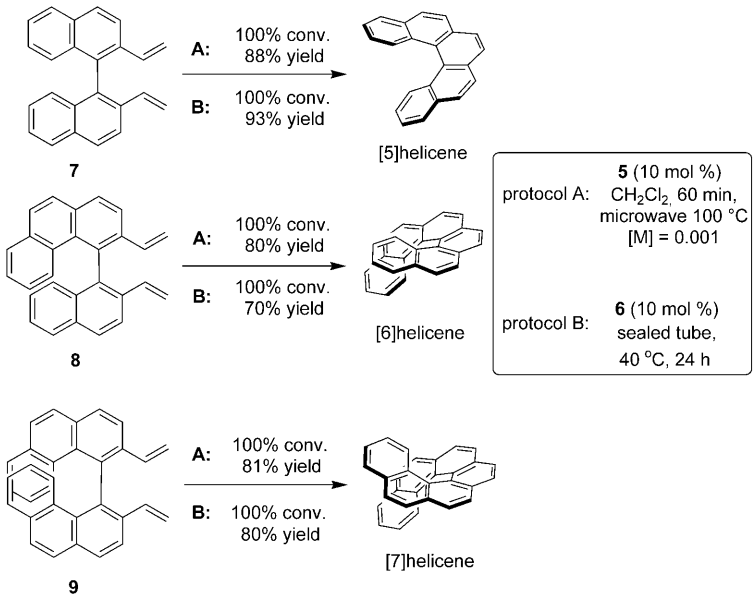
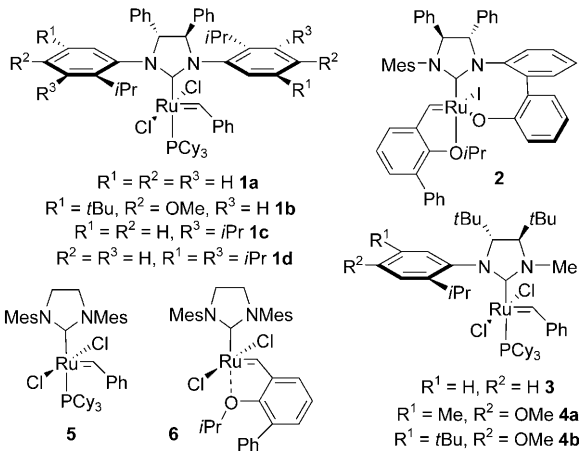



Scheme 1. Olefin metathesis as a route to [5]-, [6]- and [7]helicene.



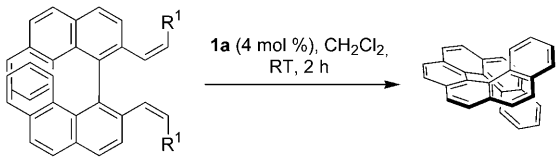

obtained by using either of the optimised synthetic protocols (81 and 80% isolated yield).

An obvious advantage to using olefin metathesis to form these structures was the possibility of using a mild transition-metal complex controlled process to effect an asymmetric synthesis of helicenes. Asymmetric olefin metathesis represents a novel and potentially powerful method for the formation of enantiomerically enriched helicenes as it constructs carbon–carbon bonds under relatively mild reaction conditions.[9] To date, chiral Ru-based olefin metathesis catalysts **1** have been developed that can afford both enantioenriched cyclic or acyclic products through asymmetric ring-closing desymmetrisation and asymmetric cross metathesis.[10] Both catalysts **1** and **2** have been shown to be effective for tandem asymmetric ring opening/cross metathesis processes (AROM/CM).[11] In cases for which catalysts **1** and **2** were not highly selective for ARCM, modification of the alkene structure or the use of halide additives helped to increase enantioselection.[10a,b,11] Recently, Hoveyda and Giudici reported a novel method of increasing enantioselection in the AROM/CM of cyclopropenes with catalyst **2** that uses enoate or ynoate motifs as directing groups.[12]

## Results and Discussion

We were concerned that the elevated temperatures associated with the previously developed olefin metathesis protocols could be detrimental to inducing significant levels of enantioexcess. As such, we investigated the rate of ring-closing metathesis of **7** and **9** at room temperature by using catalyst **5**. We found that **9** would undergo complete ring closure to afford [7]helicene in approximately 4 h. This is in stark contrast to the formation of [5]helicene from **7**, in which only traces of helicene can be observed under identical conditions after two weeks. While the origin of the increased rate of ring closure of **9** versus **7** are still under study, the fact that the ring-closing metathesis reaction of **9** could be conducted at room temperature with catalyst **5** implied that catalysts **1a–d** would likely be potential catalysts for the study of a kinetic resolution to form [7]helicene. Consequently, our initial investigations into a novel catalytic and enantioselective synthesis of [7]helicene began with treating the divinyl precursor **9** with catalyst **1a**.

Upon treatment of the divinyl precursor **9** with catalyst **1a**, good conversions to [7]helicene were obtained; however, only a 6% *ee* was observed [Eq. (1)].




(1)

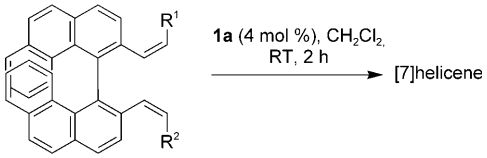
In an effort to boost the enantioselectivity of the process, we turned to substrate modification. In ARCM reactions, the substitution pattern of the olefins in the substrates often plays a large role in determining the overall enantioselectivity of the process.[10a,13a] Consequently, we prepared the divinyl precursor **10**. A significant increase in enantioselectivity

was observed (6→56–60% *ee*); however, low conversions were obtained (11–13%). Analysis of the reaction mixture revealed that the olefins of starting material **10** had completely isomerised to the *trans* configuration. All attempts to coerce this *trans* isomer to undergo ring closure, which included excessive heating in a microwave reactor, failed.[13]

In an effort to boost enantioselection and avoid problematic isomerisation, we continued to study the effects of modifying the substrate structure and we prepared a series of substituted divinyl precursors (Table 1). The propenyl deriv-

Table 1. Kinetic resolution to afford [7]helicene.[a]



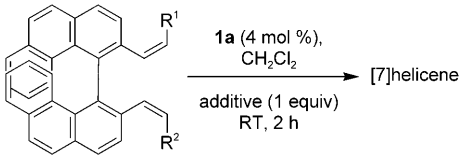

| Di-vinyl[a] | $R^1$ | $R^{2[b]}$ | *ee* [%] (conf.)[b] | conv. [%][c] |
|---|---|---|---|---|
| **9** | H | H | 6 (*P*) | 46 |
| **11** | H | Me | 22 (*P*) | 15 |
| **12** | H | Et | 30 (*P*) | 4 |
| **13** | H | Ph | 17 (*M*) | 21 |
| **14** | Ph | Ph | – | NR |
| **15** | *i*Pr | *i*Pr | – | NR |
| **16** |  |  | 17 (*M*) | 53 |

[a] Reaction concentration [M] = 0.012. [b] Enantiomeric excesses were determined by chiral HPLC: see the Supporting Information for chromatograms. [c] Determined by the $^1$H NMR spectrum of the crude reaction mixture, see the Supporting Information. NR = no reaction.

ative **11**, butenyl derivative **12** or styrenyl derivative **13** afforded higher *ee* values (17–30% *ee*) than had been previously obtained with **9** (6% *ee*). Unfortunately, once again, the level of conversion remained problematic and increasing the reaction time had no beneficial effect. Then, we evaluated symmetric divinyl precursors, such as **14** and **15**; however, these substrates were not reactive. We also evaluated the precursor **16** containing relay ring-closing metathesis side chains.[14] While the conversions could then be improved, the stereoselectivity of the process had once again dropped (17–25% *ee*) below that obtained with substrate **10** (56–60% *ee*).

Thwarted by our efforts to use substrate modification to improve the selectivities and conversions, we next turned our attention to the use of halide additives. When **1a** is treated with NaI in THF, an exchange of the chloride ligands in **1a** for iodides is observed. The use of NaI, in particular, as an additive has been well documented; in desymmetrisation reactions significant increases (>50% *ee*) in enantioselectivity have been observed.[10a,b] When **9** was treated with catalyst **1a** in $CH_2Cl_2$ with either NaBr or NaI as the additive, only minimal increases in enantioselectivity were observed (Table 2). In addition, performing the kinetic resolution of **10** by using **1a** in $CH_2Cl_2$ in the presence of

Table 2. Kinetic resolution to afford [7]helicene by using halide additives.[a]




| Di-vinyl | Additive[b] | *ee* [%] (conf.)[b] | conv. [%][c] |
|---|---|---|---|
| **9** | none | 6 (*P*) | 46 |
| | NaBr | 8 (*P*) | 30 |
| | NaI | 14 (*P*) | 48 |
| **10** | none | 56–60 (*P*) | 11–13 |
| | NaBr | 61 (*P*) | <5 |
| | NaI | 61 (*P*) | <5 |
| **16** | NaI | 22 (*M*) | 10[d] |

[a] Reaction concentration [M] = 0.012. [b] Enantiomeric excesses were determined by chiral HPLC: see the Supporting Information for chromatograms. [c] Determined by the $^1$H NMR spectrum of the crude reaction mixture: see the Supporting Information. [d] Reaction conducted in THF. NR = no reaction.

NaI resulted in even lower levels of conversion to the desired helicene and only isomerisation was observed. The reaction of the relay side chain containing substrate **16** with NaI as an additive also failed to produce significant increases in selectivity and a noticeable drop in conversion was once again observed.

We began to suspect that the enantiodetermining step in the catalytic cycle may be the first metathesis sequence that leads to the binding of the substrate to the catalyst. Hence, we believed that the nature of the propagating carbene would play an influential role, as is the case in asymmetric cross metathesis (ACM) processes, in which control over unwanted dimerisation pathways is essential.[10c] In the kinetic resolution of **9**, a Ru–methylidene is the expected propagating species. With substrate **10**, a Ru–ethylidene would be the propagating species and would likely be responsible for the observed isomerisation. We envisioned controlling the nature of the propagating carbene in our kinetic resolution to form helicenes through the addition of achiral olefins to the reaction mixture. Following ring closure, the resulting carbene would react primarily with the terminal olefin of the additive instead of the sterically encumbered divinyl substrate **9**. This is in contrast to ACM, in which the carbene is eventually incorporated into the product.

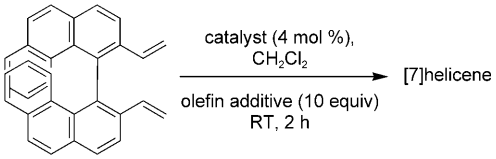
Potential olefin additives must not engage in a productive cross-metathesis reaction with the substrate. As none of the metathesis reactions described in Tables 1 and 2 ever produced a cross-metathesis product between the substrates, such as **9**, and the residual styrene produced from the precatalyst during the first catalytic cycle, styrenes emerged as potential additive candidates. Vinyl cyclohexane was also selected due to its steric similarity to styrene. We also investigated 1-hexene and 4-methylpentene as additives, as they would afford propagating alkylidenes structurally similar to the ethylidene that afforded a good *ee* with catalyst **1a** and substrate **10** [Eq. (1)]. In addition to testing the catalyst **1a**, we also screened several new chiral Ru-based catalysts (**3**,

**4a** and **4b**) developed in our group that have displayed improved reactivity profiles and enantioselectivities in desymmetrisation reactions.[15]

When 10 equivalents of 1-hexene were added to substrate **9** in the presence of catalyst **1a**, a small increase in enantioselectivity from 6 to 12% *ee* was observed (Table 3). Larger quantities of additive (>25 equiv) resulted in significantly lower conversions and longer reaction times and lower quantities (<5 equiv) provided little effect on the *ee* of the process. By using catalyst **3** with substrate **9**, the *ee* increased from 7 to 35% *ee* when using 1-hexene as an additive. Interestingly, the addition of the olefin additive resulted in the *M* isomer being favored over the *P* isomer. When 1-hexene was used as an additive in the kinetic resolution with catalyst **4a**, a 30% *ee* was obtained in which the product had been obtained as a racemic mixture in the absence of additive. The greatest increase in enantioselectivity came from using catalyst **4b**, in which the *ee* increased from 10 to 48% when 1-hexene was added to the reaction mixture. Upon identifying catalyst **4b** as the optimal catalyst, we screened other additive types. The use of 4-methylpentene gave similar results as were obtained with 1-hexene. In terms of both *ee* and conversion, vinylcyclohexane was observed to provide modest *ee* (53%) and good conversion (43%). Excess styrene as an additive resulted in a 55% *ee*, but the reaction was sluggish and only a 25% conversion was obtained after 2 h. More exotic olefin additives, such as a vinyl boronate, were ineffective.

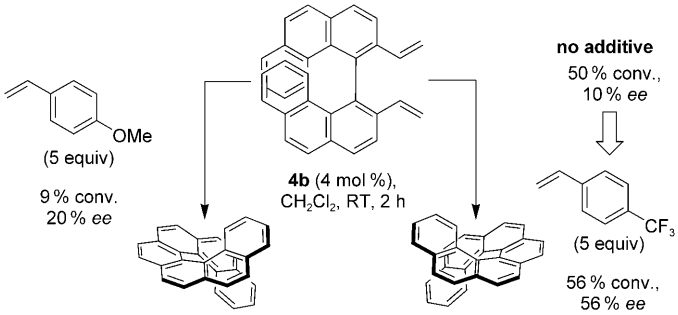
Table 3. Additive effects on kinetic resolution.[a]




| Cat.[a] | Additive | *ee* [%] (conf.)[b] | conv. [%][c] |
|---|---|---|---|
| **1a** | none | 6 (*P*) | 46 |
| | 1-hexene | 12 (*P*) | 30 |
| **3** | none | 7 (*P*) | 55 |
| | 1-hexene | 35 (*M*) | 55 |
| **4a** | none | *rac* | 48 |
| | 1-hexene | 30 (*M*) | 54 |
| **4b** | none | 10 (*M*) | 50 |
| | 1-hexene | 48 (*M*) | 40 |
| | vinylcyclohexane | 53 (*M*) | 43[d] |
| | styrene | 55 (*M*) | 25 |
| | 2-methylstyrene | 26 (*M*) | 45 |
| | 3-methylstyrene | 55 (*M*) | 12 |
| | 1,2-divinylbenzene | – | – |
| | *p*-$CF_3$-styrene | 56 (*M*) | 56 |
| | *p*-methoxysytrene | 20 (*P*) | 9 |
| | vinyl boranic acid | – | – |
| | pinacolic ester | – | – |
| | 4-methylpentene | 44 (*M*) | 54 |

[a] Reactions at [M] = 0.012. [b] Enantiomeric excesses were determined by chiral HPLC: see the Supporting Information for chromatograms. [c] Determined by the $^1$H NMR spectrum of the crude reaction mixture: see the Supporting Information. [d] The starting material **5** was obtained in 51 *ee*. *rac* = racemic.

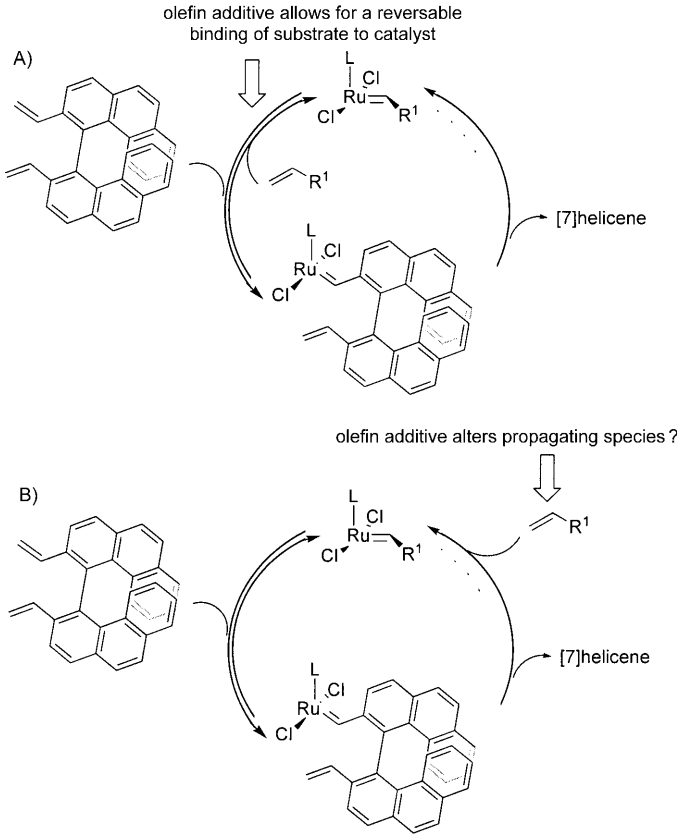
We also tested various styrene derivatives as additives to probe subtle steric and electronic effects (Scheme 2). As such, 4-methoxystyrene caused a significant inhibition of the reaction as the conversion dropped to 9% and *ee* decreased to 20%. However, replacement of the MeO group with an electron-withdrawing $CF_3$ group restored the high conversions and pushed the *ee* to 56%. Interestingly, the switch in the electronic properties caused a switch in the enantiomeric preference: 4-methoxystyrene afforded the *P* enantiomer, whereas 4-trifluoromethylstyrene preferred the *M* enantiomer. The influence of the steric properties of the additives on the kinetic resolution was also investigated. The use of *o*-methylstyrene caused the *ee* to decrease relative to styrene (55→26% *ee*), whereas *m*-methylstyrene provided similar *ee* values and conversions relative to styrene. We were also intrigued as to whether a "bidentate" additive could be applied. Unfortunately, when **9** was treated with catalyst **4b** and allyl methacrylate as an additive, the kinetic resolution afforded low conversions (<5%).[16] We also investigated 1,2-divinylbenzene as an additive. Grubbs and co-workers recently reported that X-ray crystal structures obtained for the reaction of 1,2-divinylbenzene with Grubbs 2nd-generation catalyst revealed that one of the vinyl groups was bound in a "side-on" fashion.[17] Given that a similar mode of binding was proposed by Hoveyda for catalyst **2** with allyl methacrylate, we investigated 1,2-divinylbenzene as an additive. Unfortunately, the use of 1,2-divinylbenzene results in a complete inhibition of the reaction and no RCM is observed, even under forcing conditions.




Scheme 2. Choice of additive provides access to either stereoisomer of [7]helicene.

The olefin additives could play two roles. The first possibility is that the olefin additive acts to enable reversible binding of the substrate to catalyst (Scheme 3A). In the absence of simple olefins in solution, once the catalyst has bound to substrate, the reverse reaction is likely slow. The reverse reaction would require a cross metathesis with another olefin in solution, either from another molecule of the starting material **9** or residual styrene formed from the first catalytic cycle of the precatalyst itself.[18] Therefore, the olefin additive may act to facilitate this reverse reaction and, therefore, aid in the enantioselection of the catalyst.[19]

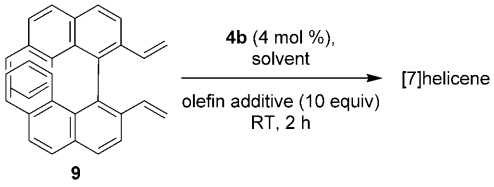



Scheme 3. Possible dual role of olefin additives in the kinetic resolution to form [7]helicene.

The second possible role is to alter the propagating carbene species in the catalytic cycle (Scheme 3B). Not only would this likely increase the stability of the propagating species and hence conversions, but it is also likely to exert an influence on the *ee* of the overall process. This is similar to what was observed by Hoveyda and Giudici.[4] We believe this mechanism is likely due to the results obtained with the electronically different styrene additives. It is obvious that these olefins play a large role in enantioselection as modification of the electronic characteristics of the styrene change the preference for either the *P* or *M* isomer. In the enantioselective AROM/CM processes reported by Hoveyda and Giudici enantioselection is believed to be augmented through coordination of the ynoate or enoate moiety with the Ru catalyst resulting in diastereomeric carbenes. In the AROM/CM process, the ynoate or enoate groups are eventually incorporated in the final product. The achiral olefins presented herein are used solely as inexpensive additives that are not incorporated into the metathesis products.

Following the optimisation of the olefin additive, we tried to fine-tune the enantioselectivity of the kinetic resolution protocol by examining different solvents (Table 4). We chose to examine the effects of aromatic solvents based upon two key factors: It has been reported that aromatic solvents can interact with the N-aryl groups of the N-heterocyclic carbene ligands in Ru-based olefin metathesis catalysts,[20] and the large π-surface of **9** could potentially interact with aromatic solvents. By using catalyst **4b** and switching from $CH_2Cl_2$ to benzene as the solvent produced a modest increase in *ee* (53→65% *ee*), and a further increase was observed when using trifluorotoluene (65% *ee* in PhH→70% *ee* in $PhCF_3$). The conversions also begin to decrease due to the lesser solubility of **9**. The use of hexafluorobenzene allowed for the highest *ee* of [7]helicene achieved to date (80% *ee*, 38% conv.), which was surprising since **9** appears to be sparingly soluble in $C_6F_6$. Trying to obtain a homogeneous solution by conducting the reaction in a 1:1 mixture of $CH_2Cl_2$ and $C_6F_6$ resulted in a decrease in *ee* and conversion. Despite the poor solubility, the solvent effect is apparent even in the absence of olefin additive, as the *ee* obtained was 33% (compared to 10% in $CH_2Cl_2$). These results suggest that the additive and solvent effects work in tandem to afford the observed enantioselectivity. While it is clear that the solvent plays an important role in the preparation of [7]helicene, it is unclear if this is due to interactions with the N-aryl group of the catalyst. The N-aryl group of catalyst **4b** is highly substituted and in a sterically crowded environment, which likely makes π–π interactions with the solvent difficult. Considering the large π-surface of substrate **9**, it is more likely that the solvent is interacting with the substrate.

Table 4. Solvent effects on kinetic resolution.[a]




| Substrate[a] | Additive | Solvent | *ee* [%] (conf.)[b] | conv. [%][c] |
|---|---|---|---|---|
| **9** | vinylcyclohexane | $CH_2Cl_2$ | 53 (*M*) | 43 |
| | vinylcyclohexane | PhH | 65 (*M*) | 32 |
| | vinylcyclohexane | trifluorotoluene | 70 (*M*) | 15 |
| | vinylcyclohexane | $C_6F_6$ | 80 (*M*) | 38 |
| | vinylcyclohexane | $C_6F_6/CH_2Cl_2$ | 60 (*M*) | 26 |
| | none | $C_6F_6$ | 33 (*M*) | <5 |

[a] Reactions at [M] = 0.012. [b] Enantiomeric excesses were determined by chiral HPLC: see the Supporting Information for chromatograms. [c] Determined by the $^1$H NMR spectrum of the crude reaction mixture, see the Supporting Information.

## Conclusion

We have reported that the combination of simple achiral olefins can be used as additives and hexafluorobenzene can be used as a solvent to improve asymmetric olefin metathesis reactions. As a result, hexafluorobenzene has been applied in a novel protocol for the synthesis of enantioenriched [7]helicene. The kinetic resolution reported herein is noteworthy in that 1) it illustrates that control of the propagating alkylidene can be an effective method for improving

enantioselection in ARCM processes and can at times be more effective than the use of halide additives that can result in lower catalyst reactivity, 2) it represents a rare example of an asymmetric and catalytic preparation of [7]helicene, 3) it is the first reported application of asymmetric olefin metathesis towards helically chiral molecules, and 4) demonstrates the importance of solvent in olefin metathesis reactions. This work also highlights the effectiveness of chiral Ru-based olefin metathesis catalysts bearing $C_1$-symmetric NHC ligands. The mild reaction conditions suggest that this method could be used for the preparation of heterohelicenes for both materials and medicinal applications. Further catalyst development, investigation of the use of chiral olefins and solvent effects in ARCM,[19] and asymmetric preparation of heterohelicenes are currently underway in our laboratories.

## Experimental Section

All experimental procedures and characterisation data for all new compounds can be found in the Supporting Information. A general procedure for the kinetic resolution to form [7]helicene by using olefin additives is as follows: 3,3′-Divinyl-4,4′-biphenanthryl (**5**; 10 mg, 0.025 mmol), and vinylcyclohexane (27 mg, 10 equiv, 0.25 mmol) were added in a glove box to a flame-dried sealed tube and the mixture was suspended in hexafluorobenzene (1 mL). A stock solution of ruthenium catalyst **4b** (1 mL of a 1.0 mg mL$^{-1}$ solution in hexafluorobenzene, 0.05 equiv, 0.0013 mmol) was then added, the tube is sealed, and the reaction mixture was stirred at RT for 2 h. The reaction mixture was then filtered through a silica pad ($CH_2Cl_2$) and the solvent was evaporated under vacuum. Conversions were measured directly by $^1$H NMR spectroscopy and enantiomeric excesses were measured by chiral HPLC (ChiralCel OD (0.46 cm × 25 cm): 90% hexanes, 10% *i*PrOH, 1 mL min$^{-1}$, 23 °C, 10 min runtime, $t_R$ = 5.34 (*M*) and 6.57 min (*P*). The [7]helicene and residual **5** can also be purified on a preparative scale by HPLC with a Chiralcel OD preparative column.

## Acknowledgements

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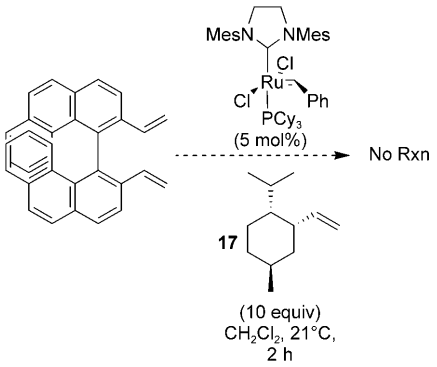


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