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Asymmetric synthesis of an atropisomeric β-carboline via regioselective intermolecular Rh(I)-catalyzed [2 + 2 + 2] cyclotrimerization

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ABSTRACT

The rational design of atropisomeric small molecules is becoming increasingly common in chemical synthesis as a result of the unique advantages this property provides in drug discovery, asymmetric catalysis, and chiroptical activity. In this study, we designed a synthesis of a configurationally stable β-carboline in six steps. Our synthesis made use of an innovative Grignard addition/elimination reaction that formed an yne-ynamide precursor that then reacted with ethyl cyanoformate in a rhodium(I)-catalyzed [2 + 2 + 2] cyclotrimerization reaction to give the atropisomeric β-carboline in excellent yield, good enantioselectivity, and excellent regioselectivity. Extensive optimization of this transformation is described. Racemization kinetics experiments were also conducted on the individual atropisomers and their absolute configurations were determined by circular dichroism.

Introduction

The stereochemistry of small molecules is a critical determinant of their physical and biological properties. Therefore, exquisite control over the spatial arrangement of atoms and groups in small molecules is important for the design of functional probes [1–3]. While organic chemists typically use sp^3-carbon stereocenters to impart distinct three-dimensionality, point chirality is just one source of chirality in organic chemistry. Axial chirality occurs when defined stereochemical arrangements of atoms or groups exist because of hindered rotation about an axis. In particular, atropisomerism occurs when molecules have a σ bond that cannot undergo a full 360° of rotation due to one or more high energy transition states. This property can introduce challenges during chemical synthesis due to its inherent dynamism [4–7], but it can also be exploited if chirality is configurationally stable over a range of temperatures and experimental conditions [8–9]. For example, specific enantiomeric atropisomers have the potential to bind more strongly to macromolecular targets, could be used as ligands in asymmetric transition metal catalysis, or have interesting spectral or physical properties [10].

In recent years, our group has worked on the synthesis and biological activity of β-carbolines, in particular those molecules that have an aryl- or heteroaryl group attached to the 1-position of the ring that could make them atropisomeric/proatropisomeric (Fig. 1) [11–13]. We have successfully shown that configurationally stable β-carbolines can be prepared by a racemic Suzuki cross coupling strategy, followed by resolution of the resulting atropisomers via chiral HPLC [14]. Since this approach poses a long-term bottleneck to progress in this area, we became interested in creating non-interconverting β-carboline atropisomers asymmetrically, for which no such techniques currently exist.

Towards this end, we hypothesized that the metal-catalyzed [2 + 2 + 2] cyclotrimerization reaction would be an atom economical way to construct the β-carboline fragment. A large volume of research in this area exists for the synthesis of axially chiral biaryls, with Rh(I), Co(I), Ir(I), and Ru(II) catalysis being the most common [15–20]. Less common are methods for 2-pyridyl-containing heterobiaryls, but Tanaka's use of Rh(I) cationic salts in the presence of a chiral bisphosphine ligand for the synthesis of atropisomeric 3-aryl pyridines serves as precedent [21]. In order to synthesize axially chiral β-carbolines via this method, the ret-

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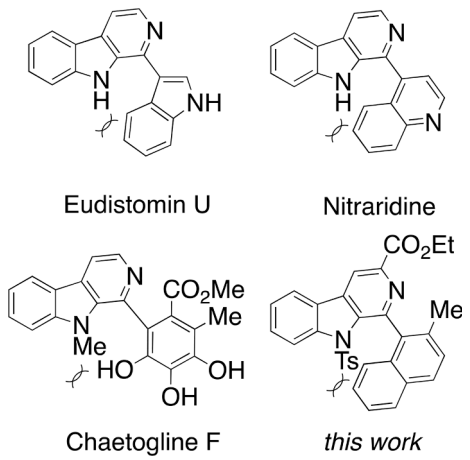


Fig. 1. Examples of atropisomeric β-carbolines.

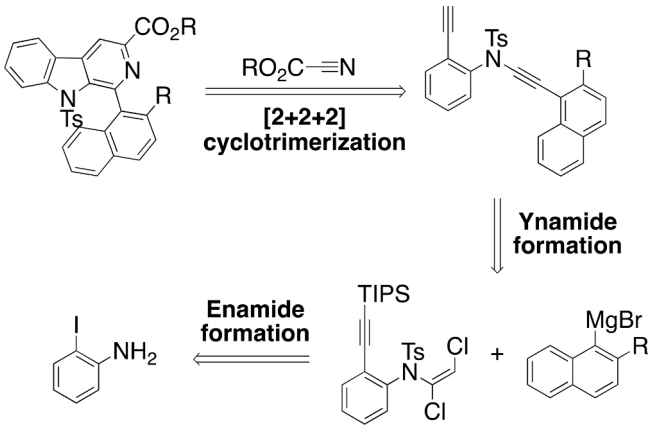


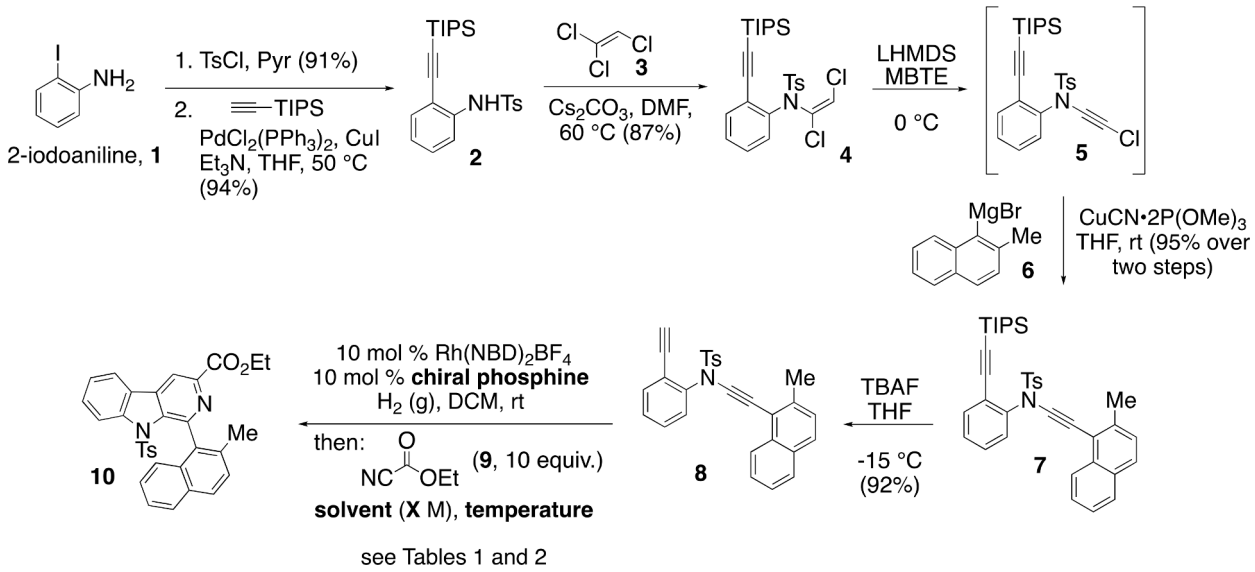
Fig. 2. Retrosynthetic strategy for the synthesis of atropisomeric β-carbolines.

rosynthetic strategy outlined in Fig. 2 was taken. This approach would require the asymmetric reaction between an yne-ynamide and an exogenous nitrile in the last step with exquisite regioselectivity. Formation of the yne-ynamide would come from a Grignard addition/elimination to an alkynyl chloride generated *in situ* from the corresponding dichloroenamide, which can be made in three steps from 2 to iodoaniline. In this Letter, we report a proof-of-principle study into the feasibility of this approach.

Results and discussion

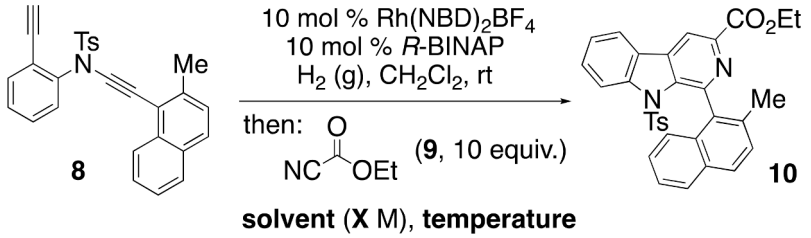
Our synthetic strategy is outlined in Scheme 1, which provides access to the 1-aryl- β-carboline **10** in six steps. First, 2-iodoaniline **1** was protected as the *p*-toluenesulfonamide for three reasons: 1) it can be easily removed from indole rings under mild conditions and still be configurationally stable, 2) we needed a handle to facilitate N—C bond formation (*vida infra*), and 3) we hypothesized that it would produce favorable noncovalent interactions during the [2 + 2 + 2] cyclotrimerization reaction that would favor the synthesis of a single enantiomer. The *p*-toluenesulfonamide was then converted to the protected alkyne via a Sonogashira coupling with triisopropylsilylacetylene (a trimethylsilyl protecting group was unstable to the subsequent conditions). Efforts to couple sulfonamide **2** directly to an alkynyl bromide using the conditions of Hsung [22] led to formation of an alkyne homodimer and hydrolysis of the N—S bond. Alternatively, we chose to approach formation of the yne-ynamide functional group using an umpolung strategy pioneered by Anderson [23]. Formation of the dichloroenamide **4** proceeded in excellent yield. Treatment of **4** with lithium bis(trimethylsilyl)amide (LHMDS) afforded an alkynyl chloride **5** which underwent fast conversion to the yne-ynamide **7** in excellent yield upon addition of the commercially available Grignard reagent **6** and a copper salt. Removal of the triisopropylsilyl group gave the terminal yne-ynamide **8**, which was then subjected to the conditions of Tanaka [21] in the presence of 10 equivalents of ethyl cyanoformate **9** to afford β-carboline **10** with no detection of the γ-carboline regioisomer, as confirmed by HMBC (see electronic supporting information for full details). This precise control over regioselectivity is consistent with the observations of Witulski for other aryl-substituted yne-yneamides [24].

Formation of the atropisomeric β-carboline **10** proceeds in two



Scheme 1. Synthesis of an atropisomeric 1-aryl- β-carboline.

Table 1
Optimization of the [2 + 2 + 2] Cyclotrimerization.



Entry	Solvent	Concentration of **8** (M)	Temperature (°C)	NMR Yield (%)[a]
1	CH_2Cl_2	0.2	40	59[b,c]
2	Toluene	0.2	40	43
3	$CHCl_3$	0.2	40	25
4	MeCN	0.2	40	7
5	Acetone	0.2	40	18
6	1,4-Dioxane	0.2	40	12
7	THF	0.2	40	17
8	CH_2Cl_2	0.1	40	88[c]
9	CH_2Cl_2	0.025	40	50
10	CH_2Cl_2	0.05	40	57
11	CH_2Cl_2	0.1	4	15
12	CH_2Cl_2	0.1	25	50
13	CH_2Cl_2	0.1	60	99

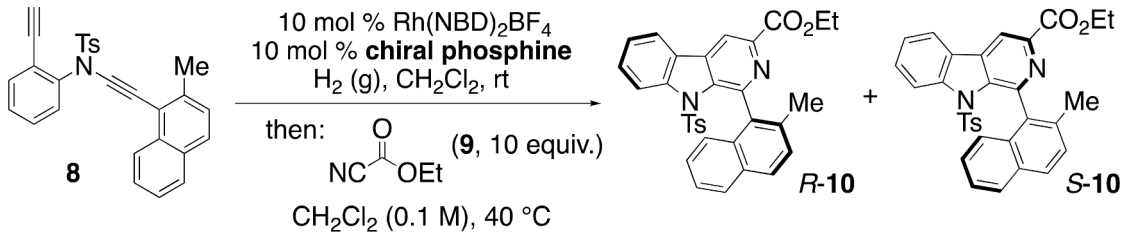
[a] Using trimethoxybenzene as internal standard; [b]Average of two experiments; [c]Isolated yield.

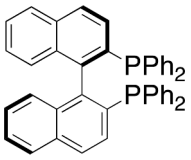
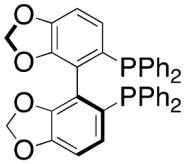
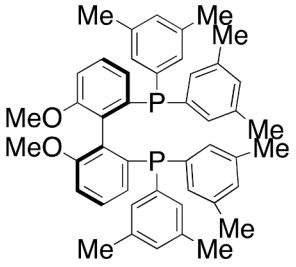
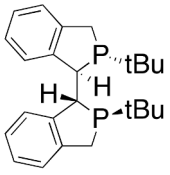
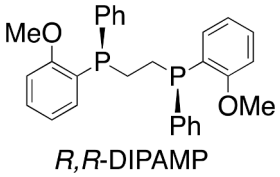
stages: 1) hydrogenation of the diene ligand and complexation of the chiral bisphosphine ligand at room temperature in dichloromethane, and 2) cyclotrimerization with ethyl cyanoformate. Our initial attempts with the cationic $Rh(COD)_2BF_4$ complex resulted in poor and inconsistent yields, which we found was due to the slow hydrogenation of the cyclooctadiene ligand. We found that switching to $Rh(NBD)_2BF_4$ resulted in a more rapid hydrogenation that could facilitate coordination of the bisphosphine ligand and allow the reaction to proceed [25]. The optimization of two other parameters for the [2 + 2 + 2] cyclotrimerization step is shown in Table 1. We used *R*-BINAP as the model ligand given its effectiveness in other [2 + 2 + 2] cyclotrimerization reactions. First, we performed a solvent screen in six other solvents. While dichloromethane was the best solvent for this reaction (entry 1), we also saw modest yields with toluene (entry 2). Strongly coordinating solvents such as acetonitrile, acetone, 1,4-dioxane, and tetrahydrofuran resulted in poor yields (entries 4–7). The concentration of the substrate had a dramatic effect on the outcome of the reaction. A two-fold reduction in the concentration increased the yield to 88 % (entry 8), but lower yields were observed upon further dilution (entries 9–10). Finally, we examined the effect of temperature on the yield of the reaction (entries 11–13). Lower temperatures resulted in poor yields, but higher temperatures were tolerated well. Ultimately, we settled on 40 °C as the optimal temperature for the development of an asymmetric variant of this reaction.

Next, we screened eleven different chiral bisphosphines from several known classes of ligands (Table 2). The model ligand *R*-BINAP gave good enantioselectivity (entry 1). Modest yields but low enantioselectivities were observed for the biaryl ligands *S*-SEGPHOS and *R*-Xyl-MeOBIPHEP (entries 2–3). Ligands with aliphatic, ferrocenyl, or spirocyclic backbones gave either poor yields or poor enantioselectivities (entries 4–8). No product formation was observed using *R*,*R*-QuinoxP and *R*-Josiphos as ligands (entries 9–10). Finally, H_8-BINAP produced the desired β-carboline in excellent yield and with the highest enantioselectivity of the ligands tested. Modest improvements to the enantioselectivity were observed using toluene as reaction solvent, with only a small decrease in isolated yield. Unfortunately, lowering the catalyst/ligand loading to 5 mol % resulted in a deterioration of both the yield and enantioselectivity, further indicating the sensitivity of this transformation to the reaction conditions. Together, these results indicate that bisphosphine ligands with binaphthyl-like backbones are a privileged ligand class in this reaction. While these enantioselectivities are a good starting point, further optimization is needed.

Scheme 2 shows a possible model for the observed regio- and enantioselectivities. We propose that diyne **8** undergoes complexation with a chiral rhodium-bisphosphine complex to give intermediate **11**. Rotation around the C—C bond prior to formation of the rhodacyclopentadiene gives rise to two different atropisomers, **12a** and **12b**. Insertion of methyl cyanoformate would generate two different azarhodacycles, **13a**/**13b** and **14a**/**14b**, which would eventually become a β-carboline (**a** series) or γ-carboline (**b** series), respectively. We hypothesize that **13b** and **14b** are disfavored due to steric occlusion between the ethyl ester and the aryl substituent. Thus, reductive elimination of **13a** and **14a** would result in exclusive formation of the β-carboline regioisomers *R*-**10** and *S*-**10**, respectively. We hypothesize that the modest enantioselectivities we observe derive from the fact that the steric strain in **12a** between the methyl group and the chiral phosphine backbone is only marginally worse than the same occlusion with the naphthalene ring in **12b**. Another possibility is that the insertion of methyl cyanoformate to form azarhodacycles **13** and **14** generates a seven-membered ring with greater flexibility for C—C bond rotation. We hypothesize that higher enantioselectivities could be observed using different substituents at the 2-position of the naphthalene ring or by replacing the phenyl groups of the bisphosphine with alkyl groups that might provide greater discriminating ability between the two atropisomers. Thus, while the 2-methylnaphthyl substituent has been a good model system to demonstrate the feasibility of our approach, more work is needed to expand the scope and understand the factors influencing asymmetric induction.

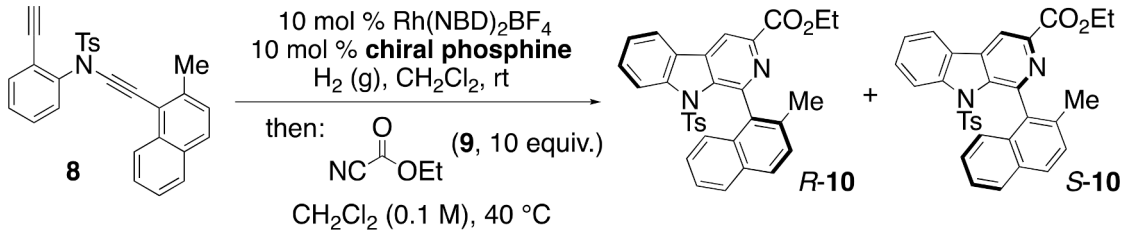
Table 2
Chiral bisphosphine screening.

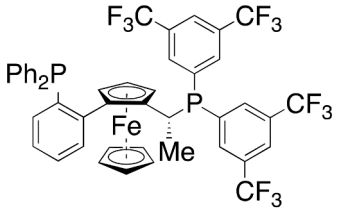
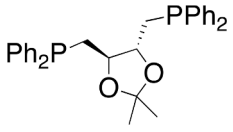
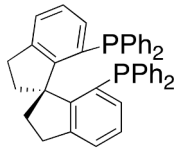
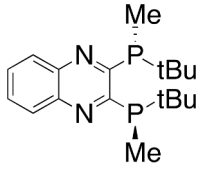
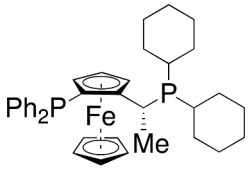
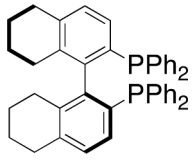


Entry	Ligand	Isolated Yield (%)	Enantiomeric ratio (*R*:*S*)
1	 *R*-BINAP	98	27:73
2	 *S*-SEGPHOS	75	62:39
3	 *R*-3,5-Xyl-MeOBIPHEP	48	44:56
4	 *1R,1'R,2S,2'S*-DuanPhos	56	22:78
5	 *R,R*-DIPAMP	72	39:61

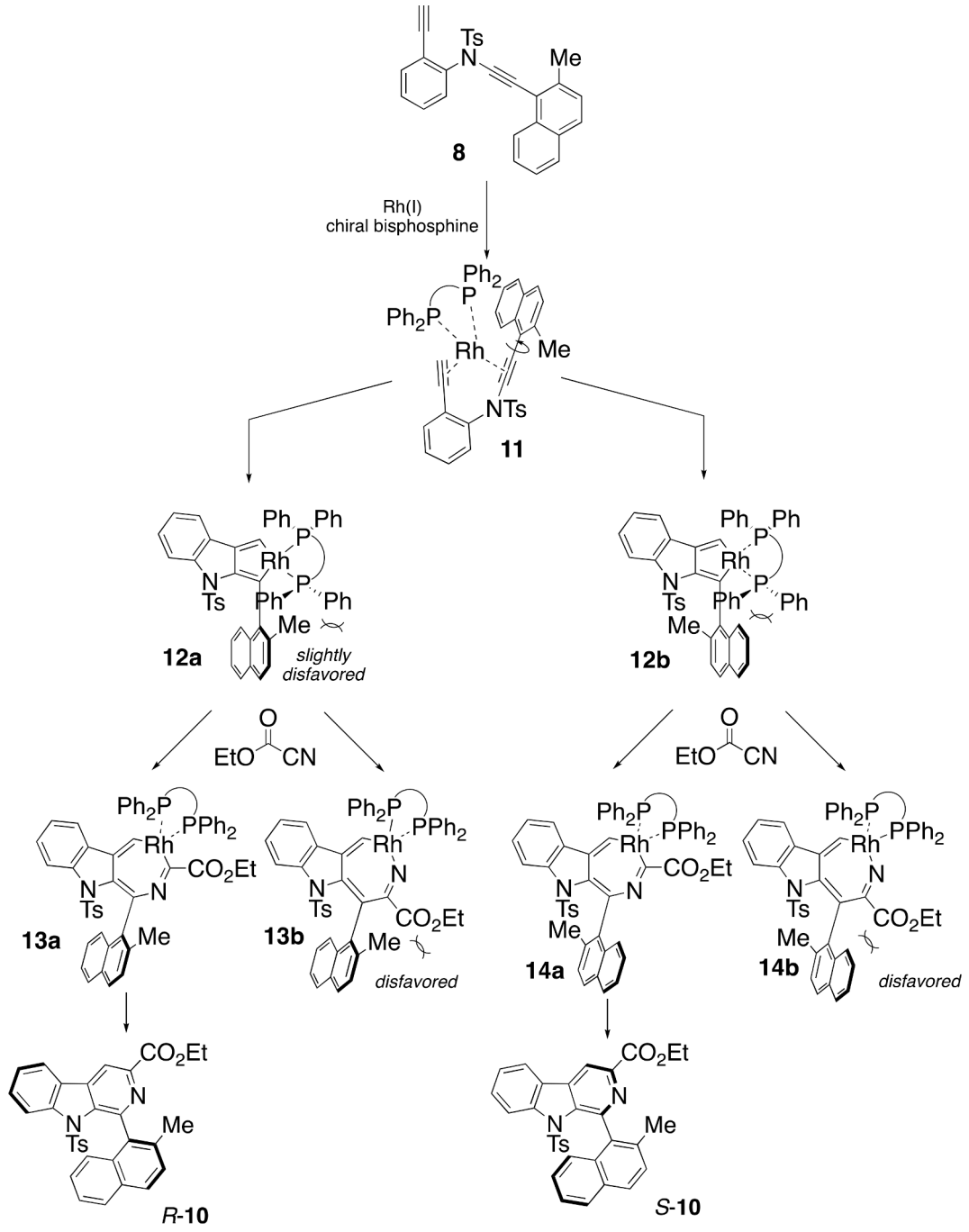
(*continued on next page*)

Table 2 (*continued*)



Entry	Ligand	Isolated Yield (%)	Enantiomeric ratio (*R*:*S*)
6	 *R*-Walphos	41	79:21
7	 *R*,*R*-DIOP	17	47:53
8	 *S*-SDP	35	23:77
9	 *R*,*R*-QuinoxP	0	N/A
10	 *R*-Josiphos	0	N/A
11	 *S*-H_8-BINAP	99 (91)[a,b] (24)[c]	79:21 (19.5:80.5)[a,b] (32:68)[c]

[a] Reaction performed in toluene; [b]Reaction performed with *R*-H_8-BINAP; [c]Reaction performed in toluene with 5 mol % catalyst and 5 mol % ligand.



Scheme 2. Proposed model of regio- and enantioselectivity.

Finally, we studied the physicochemical properties of the atropisomeric β-carboline **10**. Racemization kinetics were performed on the individual enantiomers that were isolated by chiral HPLC. The barrier to rotation was determined to be 31.5 kcal/mol, consistent with other configurationally stable β-carboline atropisomers [14]. The presence of a *p*-toluenesulfonyl protecting group reduced the barrier to rotation significantly compared to our recent report of a methyl group at the indole nitrogen. This can presumably be attributed to the longer N—S bond and the larger tetrahedral sulfur atom providing greater conformational flexibility in the transition state.

Conclusions

In summary, we described herein the first asymmetric synthesis of an atropisomeric 1-aryl- β-carboline. Our approach made use of a novel two-step Grignard addition/elimination and rhodium(I)-catalyzed [2 + 2 + 2] cyclotrimerization sequence to establish the axis of chirality. Extensive optimization of the latter reaction was performed that demonstrates the sensitivity of the transformation to the reaction conditions in the model substrate. Efforts to increase the substrate scope, improve the enantioselectivity, and understand the asymmetric induction are ongoing.

CRediT authorship contribution statement

Riley R. Hughes: Writing – review & editing, Investigation. **Lorenzo D. Battistoni:** Writing – review & editing, Investigation. **Matthew J. Ciesla:** Investigation. **Te'jandrio Bolton:** Investigation. **Patrick M. Asher:** Investigation. **Giancarlo Irizarry:** Investigation. **Alma de Jesus Antonio Martinez:** Investigation. **Kristen M. Baker:** Writing – review & editing, Supervision, Investigation. **Seann P. Mulcahy:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2024.155187.

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