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Advanced Synthesis & Catalysis

A Scalable Synthesis of Chiral Himbert Diene Ligands for Asymmetric Catalysis

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Dedicated to the memory of David A. Evans.

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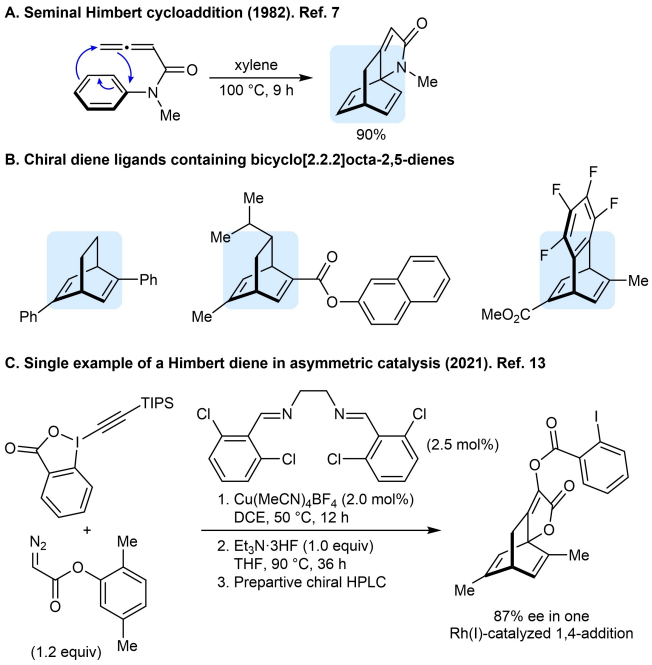
Abstract: Chiral dienes are important ligands in asymmetric catalysis but they are less accessible than other commonly used ligands such as chiral bisphosphines. Here, we show that intramolecular [4+2] cycloaddition of a simply attained chiral allenecarboxanilide readily affords pseudoenantiomeric bicyclo[2.2.2]octa-2,5-dienes containing an alkenyl bromide, which can be readily functionalized to give diverse chiral diene ligands. The synthesis is straightforward and easily conducted on multigram scales. These ligands exhibit high performance in nine types of enantioselective Rh(I)-catalyzed 1,4-addition or 1,2-addition reactions.

Keywords: asymmetric catalysis; chiral dienes; enantioselectivity; rhodium

Introduction

Chiral dienes are important ligands in asymmetric catalysis, which often exhibit higher catalytic activities than other, more commonly used ligands such as chiral bisphosphines.[1] A wide variety of chiral dienes have been designed and synthesized,[1] some of which exhibit high catalytic activity and enantioselectivities across several types of reactions. However, synthetic routes to these important ligands can often be lengthy. In addition, preparation of chiral dienes as single enantiomers often requires separation by preparative chiral HPLC,[2] enzymatic kinetic resolution,[1c,3] resolution of the corresponding rhodium complexes with chiral auxiliaries (rather than the chiral dienes themselves),[4] (catalytic) asymmetric reactions,[5] or the use of chiral pool starting materials that can give unequal access to both enantiomeric (or pseudoenantiomeric) series.[6] Although these issues do not prevent productive investigation of chiral dienes in asymmetric catalysis, and there are examples where they can be accessed on scale,[5c] the effort required to prepare them is a significant barrier to their wider adoption. It likely also contributes to the fact that few chiral dienes are commercially available, which further inhibits their evaluation and application. Therefore, the development of more efficient and practical synthetic routes to chiral dienes, such that more ligands become widely available, would be of significant value.

In 1982, Himbert and Henn reported the intramolecular Diels-Alder reaction of an allenecarboxanilide that results in dearomatization of the benzene ring (Scheme 1A).[7] Since then, several groups have



Scheme 1. Synthesis of bicyclo[2.2.2]octa-2,5-dienes by intramolecular [4+2] cycloaddition and their presence in chiral diene ligands.

described variants of this process[8] and its mechanism has been investigated computationally.[10b,c,15]

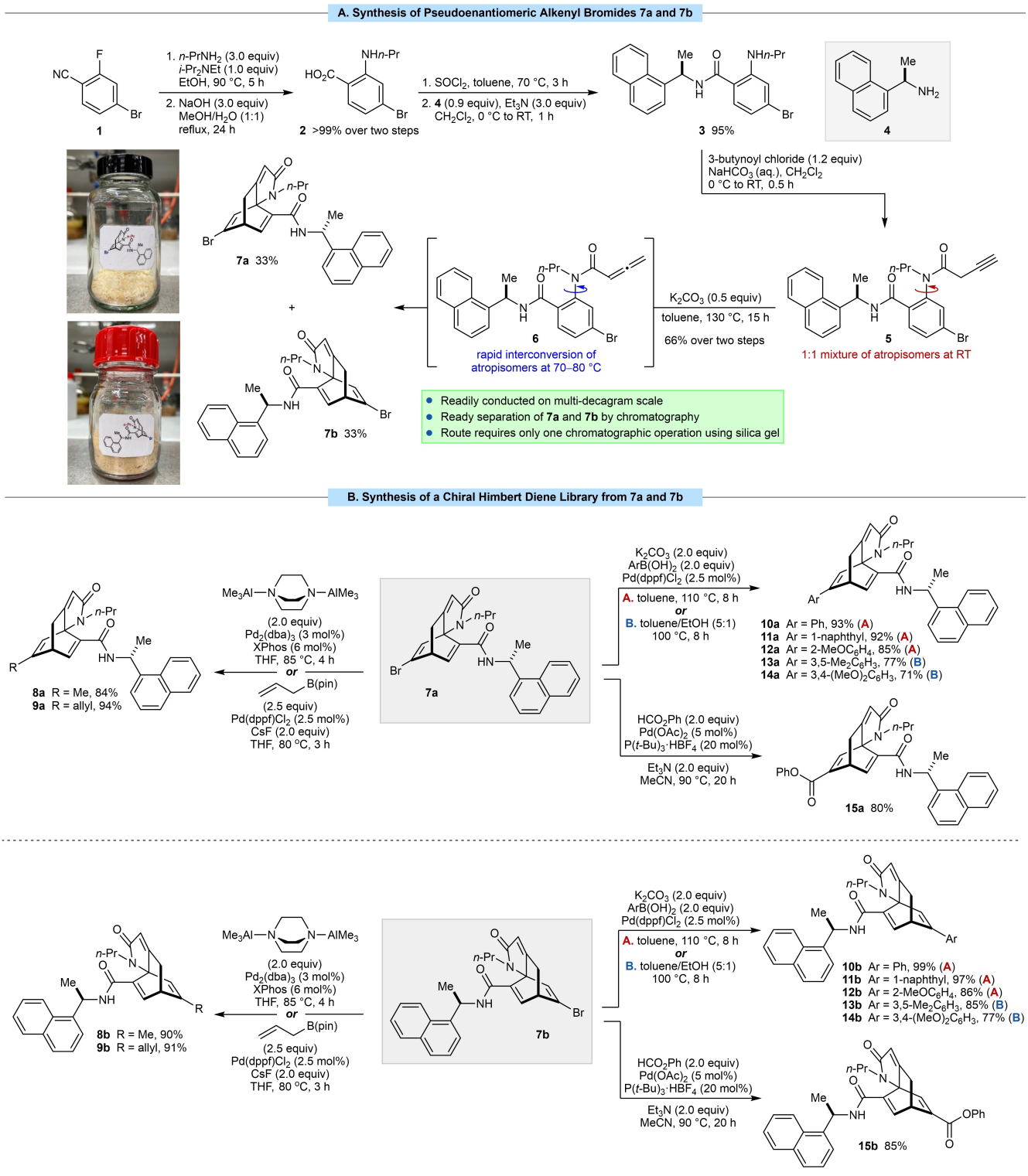
These reactions give bicyclo[2.2.2]octa-2,5-dienes, which are the core structures of many chiral diene ligands (Scheme 1B).[1] We proposed that this cycloaddition could be harnessed in efficient syntheses of chiral dienes. Here, we describe the successful application of this strategy to the preparation of new ligands **7a**–**15a** and **7b**–**15b** that we refer to as "Himbert dienes". The synthetic route is easily scaled to produce pseudoenantiomeric alkenyl bromides **7a** and **7b** in multigram quantities, which can be employed to readily prepare libraries of diverse ligands (Scheme 2). We also demonstrate the general applicability of these ligands in nine types of highly enantioselective Rh(I)-catalyzed 1,4-addition or 1,2-addition reactions.

During our investigations, Waser and co-workers reported a single application of a chiral Himbert diene in asymmetric catalysis (Scheme 1C).[13] The racemic ligand was prepared by the copper-catalyzed oxyalkynylation of an α-diazoester, followed by the desilylation of the triisopropylalkyne, which leads to the *in situ* formation of an allene and intramolecular [4+2] cycloaddition. Preparative chiral HPLC gave access to a small quantity of the enantiopure chiral Himbert diene, which was used in the enantioselective Rh(I)-catalyzed 1,4-addition of $PhB(OH)_2$ to 2-cyclohexenone to give the product in 87% ee.[13] Although this example serves as an important proof-of-concept, there is certainly scope for a more practical access to chiral Himbert dienes and a more comprehensive demonstration of their utility in asymmetric catalysis; issues that are directly addressed herein.

Results and Discussion

Our synthetic route to new chiral Himbert diene ligands was designed with two main objectives in mind. First, straightforward access to both (pseudo)enantiomeric series was required, the separation of which would ideally be achieved using crystallization or standard column chromatography, rather than more specialized techniques such as preparative chiral HPLC. We therefore decided to incorporate a chiral auxiliary into the [4+2] cycloaddition precursor to give diastereomeric cycloaddition products that would potentially by readily separated. A similar strategy was reported by Nishimura, Nagaosa, and Hayashi, although unsatisfactory yields were obtained.[16] Second, the [4+2] cycloaddition products should contain a functional handle that can be used to install diverse new substituents into the ligand framework, thus enabling fine-tuning of catalytic performance when required. For this purpose, we selected an alkenyl bromide, which can be readily functionalized through cross-coupling reactions.

Our synthesis of new chiral Himbert dienes is shown in Scheme 2. First, an S_NAr reaction of commercial 4-bromo-2-fluorobenzonitrile (**1**) with *n*-propylamine, followed by hydrolysis of the cyano group, gave aniline **2** in >99% yield over two steps. Next, **2** was converted into an acid chloride with $SOCl_2$, which was reacted with our chosen chiral auxiliary, commercial (*R*)-1-(1-naphthyl)ethylamine (**4**) (the enantiomer of which is also commercially available) to give amide **2** in 95% yield without the need for purification (Scheme 2A). In principle, attachment of the chiral auxiliary could have been achieved by replacing *n*-propylamine with (*R*)-1-(1-naphthyl)ethylamine (**4**) in the first step, in an S_NAr reaction with nitrile **1** or a suitable equivalent. However, connecting the chiral auxiliary through one of the alkenyl positions of the chiral diene framework, where the effect of its stereogenic center would be better expressed, would likely lead to greater differences in the physical properties of the final diastereomeric ligands, thus increasing the chances of separating them through crystallization or column chromatography. Acylation of the anilino group in **3** with 3-butynoyl chloride gave terminal alkyne **5**, which at room temperature exists as a 1:1 mixture of inseparable atropisomers about the *N*–*C*(aryl) axis. Following the method described by Vanderwal and coworkers,[10a] heating **5** to 130 °C in the presence of K_2CO_3 (0.5 equiv.) led to isomerization to the corresponding allenamide **6**, which underwent the key

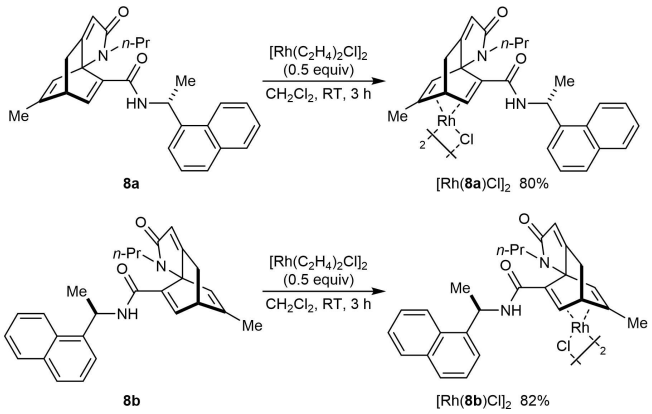


Scheme 2. Synthesis of new chiral Himbert dienes.

intramolecular [4+2] cycloaddition *in situ* to give a 1:1 mixture of the pseudoenantiomeric alkenyl bromides **7a** and **7b**. This mixture was readily purified by standard column chromatography to give **7a** and **7b** as pale yellow solids, each in 33% yield.[17] A variable temperature ^{1}H NMR experiment conducted in DMSO-D_6 on a sample of allenamide **6** that was prepared separately revealed that rapid interconversion of the two atropisomers of **6** occurs at 70–80 °C, before [4+2] cycloaddition starts to take place at 120–130 °C (see

Supporting Information for details). The synthetic route requires only one standard chromatographic operation using silica gel and is readily scaled to produce multigram quantities of **7a** and **7b**.[18]

The alkenyl bromides in the pseudoenantiomers **7a** and **7b** are useful functional handles for the preparation of diverse chiral diene ligands (Scheme 2B). For example, Pd-catalyzed methylation or allylation of **7a** and **7b** were accomplished using DABAL-Me_3[19] or allyl pinacolboronate, respectively, to give the corresponding products **8a**, **10a**, **8b**, and **10b** in high yields. In addition, Suzuki coupling reactions of **7a** and **7b** with a range of arylboronic acids gave dienes **10a**–**14a** and **10a**–**14b** in good to high yields. In addition, Pd-catalyzed carbonylation of **7a** and **7b** was readily accomplished using phenyl formate in the presence of $Pd(OAc)_2$ (5 mol%), $P(t\text{-}Bu)_3 \cdot HBF_4$ (20 mol%), and Et_3N (2.0 equiv.) in MeCN at 90 °C to give **15a** and **15b** in good yields.[20]

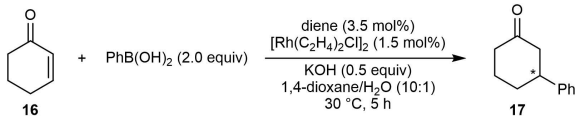


Scheme 3. Synthesis of rhodium(I) complexes of **8a** and **8b**.

With a range of chiral Himbert dienes in hand, we investigated the ability of representative ligands to form coordination complexes with metals. Reaction of **8a** with $[Rh(C_2H_4)_2Cl]_2$ in CH_2Cl_2 at room temperature for 3 h produced the dimeric Rh(I)–diene complex $[Rh(\mathbf{8a})Cl]_2$ in 80% yield (Scheme 3). In a similar manner, $[Rh(\mathbf{8b})Cl]_2$ was prepared in 82% yield. Interestingly, crystallization of $[Rh(\mathbf{8a})Cl]_2$ and $[Rh(\mathbf{8b})Cl]_2$ gave material that X-ray crystallography revealed to be coordination polymers, in which each rhodium atom is bound to a chiral Himbert diene, a chlorine atom, and a lactam carbonyl group (see the Supporting Information for details).[17]

Next, the efficacy of our new chiral Himbert dienes in enantioselective catalysis was investigated in the Rh(I)-catalyzed addition of $PhB(OH)_2$ to 2-cyclohexenone (**16**) (Table 1).[21,22] As the most well-studied reaction using chiral diene ligands,[22a] this reaction allows the benchmarking of our new Himbert dienes against known ligands. These reactions were conducted by heating a mixture of **16**, $PhB(OH)_2$ (2.0 equiv.), $[Rh(C_2H_4)_2Cl]_2$ (1.5 mol%), Himbert diene (3.5 mol%), and KOH (0.5 equiv.) in a 10:1 mixture of 1,4-dioxane and H_2O at 30 °C for 5 h. In almost all cases (entries 2–8 and 11–17), **17** was obtained in excellent yields and high enantioselectivities (≥97% ee), with the exception being the reactions using the alkenyl bromides **7a** and **7b** (entries 1 and 10) and phenyl-ester-substituted dienes **15a** and **15b** (entries 9 and 18), which gave somewhat inferior results. Comparison of the results using ligands **7a**–**15a** (entries 1–9) with their diastereomeric counterparts **7b**–**15b** (entries 10–18) showed that there was only a marginal matched/mismatched effect of the individual stereochemical elements within the ligands in favor of **7b**–**15b**, which gave slightly higher enantioselectivities. Although care should be

Table 1. Evaluation of Himbert dienes in the enantioselective Rh(I)-catalyzed addition of $PhB(OH)_2$ to 2-cyclohexenone.[a]



Entry	Diene	Yield [%][b]	ee [%][c]	Entry	Diene	Yield [%][b]	ee [%][c]
1	**7a**	51	98 (*R*)	10	**7b**	67	99 (*S*)
2	**8a**	99	97 (*R*)	11	**8b**	96	>99 (*S*)
3	**9a**	97	99 (*R*)	12	**9b**	86	>99 (*S*)
4	**10a**	98	>99 (*R*)	13	**10b**	98	>99 (*S*)
5	**11a**	>99	98 (*R*)	14	**11b**	98	>99 (*S*)
6	**12a**	>99	>99 (*R*)	15	**12b**	96	>99 (*S*)
7	**13a**	98	99 (*R*)	16	**13b**	94	>99 (*S*)
8	**14a**	97	99 (*R*)	17	**14b**	>99	>99 (*S*)
9	**15a**	54	93 (*R*)	18	**15b**	54	98 (*S*)

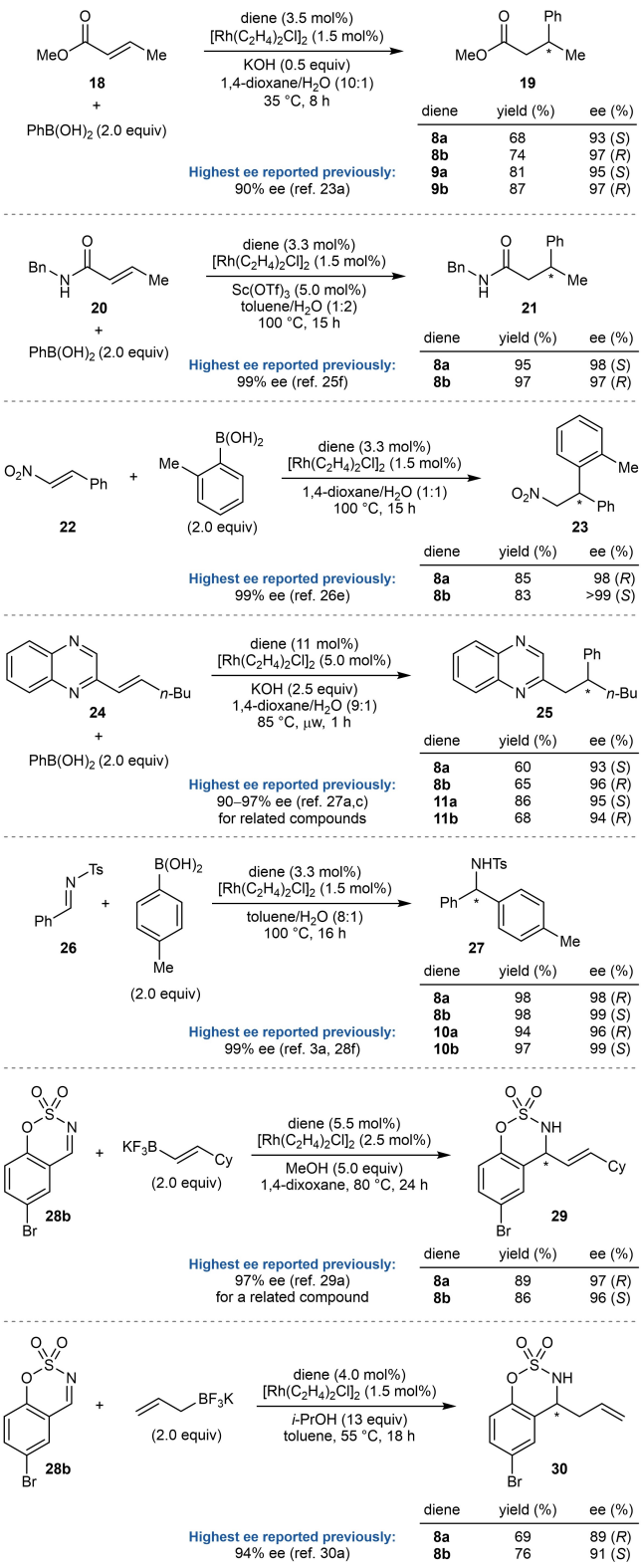
[a] Reactions were conducted with 0.30 mmol of **15** in 1,4-dioxane (1 mL) and H_2O (0.1 mL).
[b] Yield of isolated **16**.
[c] Determined HPLC analysis on a chiral stationary phase.

exercised when comparing these results with those reported previously because of the wide range of reaction conditions (including catalyst loadings) that have been employed, analysis of the literature[1a,22a] demonstrates that ligands **8a**–**14a** and **8b**–**14b** certainly compete with the very best-performing chiral dienes that have been reported for this reaction.

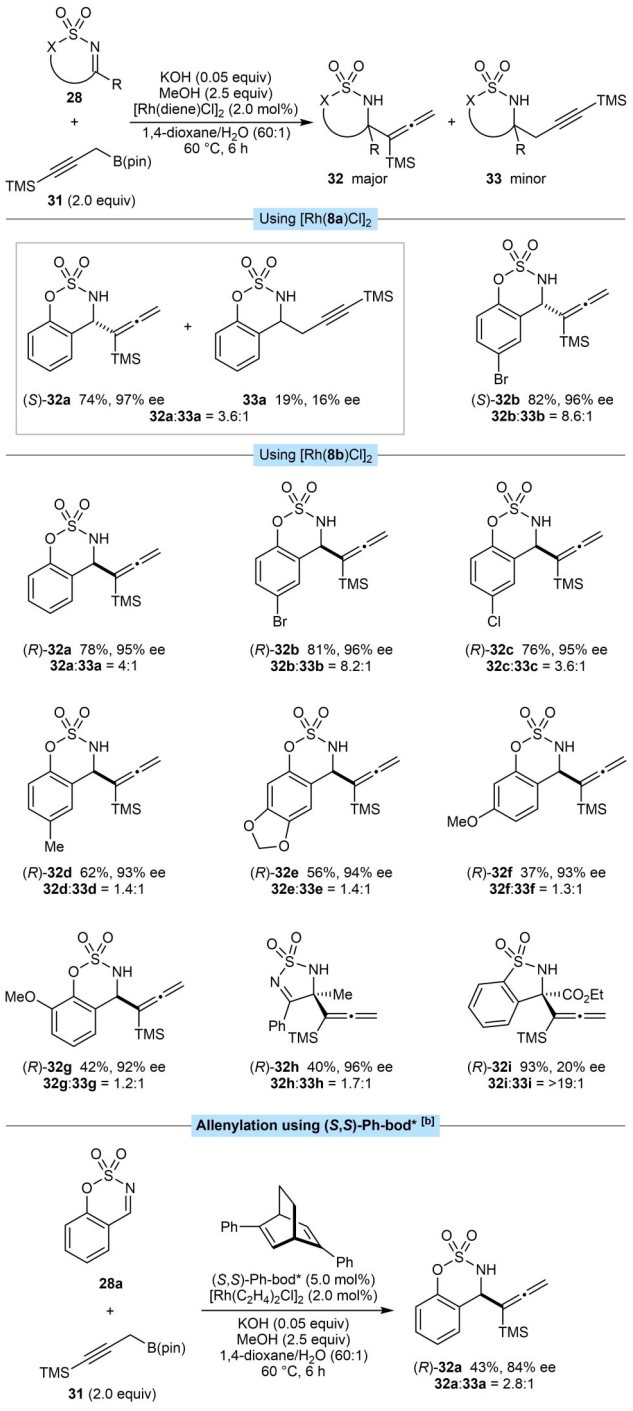
Next, the performance of representative chiral Himbert dienes was explored in a more challenging range of enantioselective Rh(I)-catalyzed nucleophilic additions of organoboron reagents (Scheme 4). First, we examined the 1,4-addition of $PhB(OH)_2$ to methyl crotonate (**18**). Good results were obtained using ligands **8a** and **8b**, but the allyl-substituted ligands **9a** and **9b** were superior, giving **19** in higher yields and 95% and 97% ee, respectively. These enantioselectivities are higher than those reported previously for all other processes catalyzed by either Rh(I)[6b,23] or Pd(II).[24] With dienes **8a** and **8b**, good results were also observed in enantioselective 1,4-additions of arylboronic acids to unsaturated amide **20**[25] using $Sc(OTf)_3$ as an additive,[25f] nitroalkene **22**,[26] and 2-alkenylquinoxaline **24**,[27] which gave the corresponding products **21**, **23**, and **25** in reasonable to good yields and high enantioselectivities (93–>99% ee). In the case of alkenylquinoxaline **24**, the 1-naphthyl-substituted Himbert dienes **11a** and **11b** gave comparable results to dienes **8a** and **8b**. Comparison of these results with the highest enantioselectivities reported previously for products **19** (90% ee[23a]), **21** (99% ee[25f]), **23** (99% ee[26e]), and products similar to **25** (90–97% ee[27a,c]) demonstrates the new chiral Himbert dienes are competitive with existing best-in-class chiral ligands for asymmetric Rh(I)-catalyzed 1,4-arylations.

Chiral Himbert dienes are also effective in enantioselective Rh(I)-catalyzed 1,2-additions to imines (Scheme 4). For example, 4-methylphenylboronic acid reacted with *N*-tosylimine **26** to give **27** in high enantioselectivities using dienes **8a**, **8b**, **10a**, or **10b**.[28] With dienes **8a** and **8b**, nucleophilic additions of a potassium alkenyltrifluoroborate[29] and potassium allyltrifluoroborate[30] to cyclic imine **28b**, respectively, were successful to give products **29** and **30** in 89–97% ee. Again, comparison of these results with the highest enantioselectivities reported previously for product **27** (99% ee[3a,28f]), a product similar to **29** (chloride instead of bromide; 97% ee[29a]), and product **30** (94% ee[30a]) indicates the new ligands are competitive with existing best-in-class chiral dienes for asymmetric Rh(I)-catalyzed 1,2-additions of organoboron reagents.

We next investigated the catalytic enantioselective allenylation of imines[31] using a trimethylsilyl-substituted propargylboron reagent **31** (Scheme 5). Although previous studies have shown chiral copper[31c] and rhodium[31d] catalysts to be successful in this type of reaction, chiral dienes have not, to our knowledge,



Scheme 4. Rh(I)-catalyzed additions of organoboron reagents. Yields are of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.



[a] Reactions were conducted with 0.25 mmol of **28**. The stated yields are of isolated allenylation products **32**. The ratios of **32** to **33** were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. Except for **33a**, propargylation products **33** were not isolated. The absolute configuration of **33a** was not determined. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.
[b] Conducted with 0.15 mmol of **28a**.

Scheme 5. Enantioselective allenylation of cyclic imines.[a]

been reported as the chiral ligands. We found that 2.0 mol% of chiral rhodium complexes [Rh(**8a**)Cl]$_2$ or [Rh(**8b**)Cl]$_2$ catalyzed the addition of propargyl boronate **31** to a variety of cyclic imines **28** in the presence of KOH (0.05 equiv.) and MeOH (2.5 equiv.) in 1,4-dioxane/H_2O (60:1) at 60 °C for 6 h. Benzoxathiazine-2,2-dioxides with a range of substituents (including bromo, chloro, methyl, dioxole, or methoxy) at various positions reacted successfully to give allenylation products **32a**–**32g** in 37–82% yield and 92–97% ee. [Rh(**8b**)Cl]$_2$ also catalyzed the addition of **31** to cyclic ketimines such as a 1,2,5-thiadiazolidine-1,1-dioxide and a benzoisothiazole 1,1-dioxide to give (*R*)-**32h** and (*R*)-**32i**, respectively, although the enantiomeric excess of (*R*)-**32i** was only 20% ee. Except for the reaction forming (*R*)-**32i**, all these allenylation reactions also gave appreciable quantities of propargylation products **33** as minor components. However, these were readily separated from the allenylation products **32** by chromatography and were generally not isolated. In the reaction producing (*S*)-**32a** (95% ee), the propargylation product **33a** was also isolated in 19% yield but interestingly, with a much lower enantiomeric excess (16% ee). The allenylation of **28a** with **31** was also conducted using (*S,S*)–Ph-bod*, a commercially available (but expensive) chiral diene that has been shown to be highly effective in a range of enantioselective Rh(I)-catalyzed reactions,[1a,28b] including 1,2-additions to imines.[28b] This reaction gave (*R*)-**32a** in 43% yield and 84% ee, with an allenylation to propargylation ratio of 2.8:1, which shows that chiral Himbert dienes **8a** and **8b** provide better results than (*S,S*)–Ph-bod* in this transformation.

Conclusion

In summary, we have shown that chiral Himbert dienes easily prepared by the intramolecular [4+2] cycloaddition of an allenecarboxamide are excellent chiral ligands for a range of enantioselective Rh(I)-catalyzed reactions, including hitherto undescribed allenylations of cyclic imines. Although many different types of chiral diene ligands have been reported previously, some of which exhibit high catalytic activity and enantioselectivities across several types of reactions,[1] there are several features of these new chiral Himbert dienes that make them advantageous: (i) their synthesis can be conducted straightforwardly on multigram scales without recourse to more specialized techniques such as enzymatic resolution, preparative chiral HPLC, or the use of catalytic asymmetric reactions; (ii) both pseudoenantiomeric series of the ligands can be readily accessed, which is not always the case for known chiral dienes that are prepared from chiral pool starting materials, and (iii) the synthesis proceeds through intermediates that can be modified at the final stage by cross-coupling to give diverse chiral dienes for fine-

tuning of catalytic performance, which may be important for particularly challenging transformations. Although several existing chiral dienes possess one or more of these attributes, we believe the extent to which all three features are manifested in these new chiral Himbert dienes should make them particularly attractive candidates for evaluation. We therefore hope that these new chiral dienes will become more widely available to enable their greater adoption in asymmetric catalysis, which may facilitate the discovery of additional useful new transformations.

Experimental Section

4-Bromo-2-(propylamino)benzonitrile. A solution of 4-bromo-2-fluorobenzonitrile (**1**, 20.0 g, 100 mmol), *n*-propylamine (24.6 mL, 300 mmol), and *N*,*N*-diisopropylethylamine (17.0 mL, 100 mmol) in EtOH (20 mL) was heated at 90 °C for 6 h. The reaction was cooled at room temperature and transferred to a separating funnel. H_2O (50 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to leave *4-bromo-2-(propylamino)benzonitrile* (24.0 g) as off-white solid that was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (1H, d, J = 8.2 Hz, Ar**H**), 6.81 (1H, d, J = 1.7 Hz, Ar**H**), 6.78 (1H, dd, J = 8.3, 1.7 Hz, Ar**H**), 4.60 (1H, s, N**H**), 3.14 (2H, td, J = 7.1, 5.3 Hz, NC**H**$_2$), 1.69 (2H, sext, J = 7.3 Hz, C**H**$_2$CH$_3$), 1.02 (3H, t, J = 7.4 Hz, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1 (C), 133.8 (CH), 129.6 (C), 119.6 (CH), 117.5 (C), 113.8 (CH), 94.5 (C), 45.2 (CH_2), 22.3 (CH_2), 11.6 (CH_3).

4-Bromo-2-(propylamino)benzoic acid (2). The crude material from above reaction was dissolved in MeOH:H_2O (1:1, 200 mL) and NaOH (20.0 g, 5.0 equiv.) was added. The mixture was heated at 100 °C for 24 h, cooled to room temperature, transferred to a beaker, and dissolved in H_2O (1 L). The solution was then slowly acidified to ~pH 4 with concentrated aqueous HCl. The resulting precipitate was collected by filtration, and dried in an oven to afford *acid* **2** (25.6 g, 99% over two steps from **1**) as a white powder that was used without further purification. m.p. 170–172 °C (Et_2O/petrol); IR 3359 (OH), 2955, 2861, 1663 (C=O), 1567, 1504, 1241, 1153, 893, 756 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-D_6) δ 12.82 (1H, br s, O**H**), 7.94 (1H, s, N**H**), 7.68 (1H, d, J = 8.5 Hz, Ar**H**), 6.86 (1H, d, J = 1.9 Hz, Ar**H**), 6.68 (1H, dd, J = 8.5, 1.9 Hz, Ar**H**), 3.12 (2H, t, J = 7.0 Hz, NC**H**$_2$), 1.59 (2H, sext, J = 7.2 Hz, C**H**$_2$CH$_3$), 0.94 (3H, t, J = 7.4 Hz, C**H**$_3$); ^{13}C NMR (101 MHz, DMSO-D_6) δ 169.6 (C), 151.7 (C), 133.5 (CH), 128.7 (C), 116.8 (CH), 113.4 (CH), 109.0 (C), 43.7 (CH_2), 21.7 (CH_2), 11.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{10}H_{11}BrNO_2]^-$ $[M-H]^-$: 255.9979, found 255.9979.

(*R*)-4-Bromo-*N*-[1-(naphthalen-1-yl)ethyl]-2-(propylamino)benzamide (3). A solution of acid **2** (25.8 g, 100 mmol) (obtained by combining material from several runs of the hydrolysis of **S1** into **2**) and thionyl chloride (21.8 mL, 300 mmol) in toluene (200 mL) was heated at 70 °C for 3 h, cooled to room temperature and the solvent and volatile residues were removed under reduced pressure. The resulting crude acid chloride was dissolved in CH_2Cl_2 (20 mL) and the solution was slowly added to a solution of (*R*)-1-(naphthalen-1-yl)ethan-1-amine (**4**, 15.41 g, 90.0 mmol), Et_3N (41.8 mL, 300 mmol) in CH_2Cl_2 (150 mL) at 0–5 °C. The mixture was stirred at room temperature for 1 h and the transferred to a separating funnel. The mixture was washed with H_2O (100 mL) followed by brine (100 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in the minimum amount of CH_2Cl_2 before petrol was added to induce precipitation. More petrol was added until no more precipitation was observed. The precipitate was collected by filtration and dried to leave *amide* **3** (34.99 g, 95%) as a colorless solid that was used without further purification. R_f = 0.44 (10% EtOAc in petrol); m.p. 134–136 °C (EtOAc/petrol); $[\alpha]_D^{25}$ +52.0 (*c* 1.00, $CHCl_3$); IR 3370, 3303, 2957, 1621 (C=O), 1566, 1504, 1263, 1235, 1152, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, dd, J = 7.9, 1.7 Hz, Ar**H**), 7.92–7.85 (1H, m, Ar**H**), 7.82 (1H, d, J = 8.1 Hz, Ar**H**), 7.69 (1H, br s, ArN**H**), 7.59–7.41 (4H, m, Ar**H**), 7.05 (1H, d, J = 8.3 Hz, Ar**H**), 6.79 (1H, d, J = 1.9 Hz, Ar**H**), 6.57 (1H, dd, J = 8.4, 1.9 Hz, Ar**H**), 6.24 (1H, d, J = 7.8 Hz, CHN**H**), 6.07–5.97 (1H, m, NHC**H**), 3.08 (2H, t, J = 7.0 Hz, NC**H**$_2$), 1.74 (3H, d, J = 6.8 Hz, CHC**H**$_3$), 1.68 (2H, sext, J = 7.3 Hz, C**H**$_2$CH$_3$), 1.02 (3H, t, J = 7.4 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3 (C), 151.0 (C), 138.3 (C), 134.2 (C), 131.2 (C), 129.0 (CH), 128.64 (CH), 128.61 (CH), 127.7 (C), 126.8 (CH), 126.0 (CH), 125.4 (CH), 123.4 (CH), 122.7 (CH), 117.2 (CH), 114.4 (CH), 113.6 (C), 45.1 (CH), 45.0 (CH_2), 22.4 (CH_2), 21.0 (CH_3), 11.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{24}BrN_2O]^+$ $[M+H]^+$: 411.1067, found 411.1064.

(*R*)-4-Bromo-*N*-[1-(naphthalen-1-yl)ethyl]-2-(*N*-propylbut-3-ynamido)benzamide (5). An oven-dried round bottom flask was charged with but-3-ynoic acid (8.93 g, 106.3 mmol) and CH_2Cl_2 (80 mL) under argon. The solution was cooled to 0–5 °C, oxalyl chloride (8.75 mL, 102 mmol) and DMF (0.2 mL) were added, and the mixture was stirred at room temperature for 2.5 h. The resulting acid chloride solution was transferred *via* syringe [using CH_2Cl_2 (2 × 15 mL) to rinse] to a cooled (0–5 °C) biphasic mixture of amide **3** (34.96 g, 85.0 mmol) in CH_2Cl_2 (80 mL) and saturated aqueous $NaHCO_3$ solution (80 mL), and reaction mixture was then stirred at room temperature for 30 min. The organic layer was separated, dried (Na_2SO_4), and concentrated *in vacuo* to leave *alkyne* **5** as an off-white foam (41.01 g) as a 1:1 mixture of atropisomers that was used without further purification. Purification of a small sample of a previous batch by column chromatography (petrol to 50% EtOAc in petrol) gave a white solid. R_f = 0.49 (40% EtOAc in petrol); m.p. 185–187 °C (EtOAc/cyclohexane); IR 3304, 3223, 2970, 1643 (C=O), 1625 (C=O), 1585, 1566, 1524, 1508, 800, 777 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-D_6) δ 9.17 (1H, d, J = 7.8 Hz, Ar**H**), 9.11 (1H, d, J = 8.0 Hz, Ar**H**), 8.20–8.13 (2H, m, Ar**H**), 7.99–7.92 (2H, m, Ar**H**), 7.85 (2H, dd, J = 8.2, 3.0 Hz, Ar**H**), 7.76–7.70 (2H, m, Ar**H**), 7.65 (1H, d, J = 2.0 Hz, Ar**H**), 7.63–7.46 (10H, m, Ar**H** and N**H**), 7.41 (1H, d, J = 8.1 Hz, Ar**H**), 5.87–5.79 (2H, m, NHC**H**), 3.76–3.68 (1H, m, NC**H**$_2$), 3.66–3.59 (1H, m, NC**H**$_2$), 3.32 (1H, d, J = 1.8 Hz, ≡C**H**) 3.25–3.14 (1H, m, NC**H**$_2$), 3.08–3.06 (1H, m, ≡C**H**), 3.06–3.02 (2H, m, C**H**$_2$C≡), 2.93–2.83 (3H, m, C**H**$_2$C≡ and NC**H**$_2$), 1.57 (3H, d, J = 6.9 Hz, CHC**H**$_3$), 1.53 (3H, d, J = 6.9 Hz, CHC**H**$_3$), 1.48–1.37 (2H, m, C**H**$_2$CH$_3$), 1.33–1.25 (1H, m, C**H**$_2$CH$_3$), 1.24–1.17 (1H, m, C**H**$_2$CH$_3$), 0.83 (3H, t, J =

7.4 Hz, CH_2CH_3), 0.65 (3H, t, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR (101 MHz, DMSO-D_6) δ 166.1 (C), 165.8 (C), 165.3 (C), 165.0 (C), 140.4 (C), 140.2 (C), 139.7 (C), 139.4 (C), 135.1 (C), 134.6 (C), 133.37 (C), 133.34 (C), 133.3 (2 CH), 131.6 (CH), 131.5 (CH), 130.7 (CH), 130.34 (CH), 130.31 (C), 130.2 (C), 128.69 (CH), 128.65 (CH), 127.43 (CH), 127.36 (CH), 126.33 (CH), 126.29 (CH), 125.7 (CH), 125.62 (CH), 125.56 (CH), 125.3 (CH), 123.04 (CH), 122.96 (C), 122.91 (CH), 122.85 (C), 122.7 (CH), 122.4 (CH), 78.3 (2 C), 73.62 (CH), 73.58 (CH), 50.41 (CH_2), 50.38 (CH_2), 44.61 (CH), 44.58 (CH), 26.4 (CH_2), 26.2 (CH_2), 21.4 (CH_3), 21.3 (CH_3), 20.4 (CH_2), 20.3 (CH_2), 11.2 (CH_3), 10.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{26}BrN_2O_2]^+$ $[M+H]^+$: 477.1172, found 477.1166.

[4+2] Cycloaddition to give 7a and 7b: An oven-dried round bottom flask was charged with the crude material from previous reaction, K_2CO_3 (5.87 g, 42.5 mmol), and toluene (800 mL), and the mixture was heated at 130 °C for 15 h. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved $CHCl_3$ (400 mL) and the solution was washed with H_2O (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc in petrol to EtOAc) using a 9 cm diameter column (height of silica bed *ca.* 25 cm) gave *diene* **7a** (13.38 g, 33%) as a pale yellow solid and *diene* **7b** (13.46 g, 33%) as a pale yellow solid.

(5*S*)-9-Bromo-*N*-[(*R*)-1-(naphthalen-1-yl)ethyl]-2-oxo-1-propyl-1,2,4,5-tetrahydro-5,7a–ethenoindole-7-carboxamide (7a). R_f = 0.58 (EtOAc); m.p. 186–188 °C (EtOAc/cyclohexane); $[\alpha]_D^{25}$ +60.0 (*c* 1.02, $CHCl_3$); IR 3275, 3047, 2967, 1672 (C=O), 1649 (C=O), 1586, 1525, 1342, 779, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (1H, d, J = 8.3 Hz, Ar**H**), 7.86 (1H, d, J = 8.0 Hz, Ar**H**), 7.81 (1H, d, J = 7.4 Hz, Ar**H**), 7.58–7.43 (4H, m, Ar**H**), 6.89 (1H, d, J = 6.5 Hz, =C**H**CH), 6.31 (1H, d, J = 2.2 Hz, =C**H**C), 6.05–5.93 (1H, m, NHC**H**), 5.87 (1H, br s, N**H**), 5.83 (1H, s, C**H**C=O), 4.04–3.97 (1H, m, CH_2C**H**), 3.17–3.05 (1H, m, NC**H**$_2$), 2.90–2.78 (1H, m, NC**H**$_2$), 2.56 (1H, d, J = 16.7 Hz, =CC**H**$_2$), 2.35 (1H, d, J = 16.7 Hz, =CC**H**$_2$), 1.66 (3H, d, J = 6.7 Hz, CHC**H**$_3$), 1.64–1.55 (1H, m, C**H**$_2$CH$_3$), 1.50–1.33 (1H, m, C**H**$_2$CH$_3$), 0.61 (3H, t, J = 7.4 Hz, CH_2C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C), 162.7 (C), 158.0 (C), 138.8 (C), 137.5 (CH), 137.4 (C), 134.0 (C), 131.2 (C), 129.5 (CH), 129.0 (CH), 128.8 (CH), 126.9 (CH), 126.1 (CH), 125.5 (CH), 124.3 (C), 123.3 (CH), 122.9 (CH), 116.6 (CH), 76.8 (C), 48.2 (CH), 45.2 (CH_2), 44.5 (CH), 29.6 (CH_2), 21.6 (CH_2), 20.3 (CH_3), 11.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{26}BrN_2O_2]^+$ $[M+H]^+$: 477.1172, found 477.1166.

(5*R*)-9-Bromo-*N*-[(*R*)-1-(naphthalen-1-yl)ethyl]-2-oxo-1-propyl-1,2,4,5-tetrahydro-5,7a-ethenoindole-7-carboxamide (7b). R_f = 0.39 (EtOAc); m.p. 185–187 °C (EtOAc/cyclohexane); $[\alpha]_D^{25}$ −48.0 (*c* 1.02, $CHCl_3$); IR 3276, 3046, 2969, 1672 (C=O), 1648 (C=O), 1585, 1524, 1359, 779, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, d, J = 8.3 Hz, Ar**H**), 7.86 (1H, dd, J = 7.8, 1.7 Hz, Ar**H**), 7.79 (1H, dd, J = 6.7, 2.7 Hz, Ar**H**), 7.57–7.47 (2H, m, Ar**H**), 7.47–7.39 (2H, m, Ar**H**), 6.75 (1H, d, J = 6.5 Hz, =C**H**CH), 6.37 (1H, d, J = 2.2 Hz, =C**H**C), 6.00–5.90 (1H, m, NHC**H**), 5.84 (1H, s, C**H**C=O), 5.81 (1H, d, J = 8.7 Hz, N**H**), 4.01 (1H, dd, J = 6.4, 2.7 Hz, CH_2C**H**), 3.84 (1H, ddd, J = 14.2, 11.0, 5.6 Hz, NC**H**$_2$), 3.24 (1H, ddd, J = 14.2, 10.8, 5.2 Hz, NC**H**$_2$), 2.55 (1H, d, J = 16.7 Hz, =CC**H**$_2$), 2.33 (1H, d, J = 16.7 Hz, =CC**H**$_2$), 1.96–1.78 (1H, m, C**H**$_2$CH$_3$), 1.72–1.59 (1H, m, C**H**$_2$CH$_3$), 1.66 (3H, d, J = 6.7 Hz, CHC**H**$_3$), 0.93 (3H, t, J = 7.4 Hz, CH_2C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C), 163.3 (C), 157.7 (C), 139.5 (C), 137.8 (C), 135.9 (CH), 134.1 (C), 131.1 (C), 129.6 (CH), 129.0 (CH), 128.7 (CH), 126.8 (CH), 126.1 (CH), 125.4 (CH), 124.1 (C), 123.3 (CH), 122.8 (CH), 116.7 (CH), 77.0 (C), 48.2 (CH), 45.4 (CH_2), 44.7 (CH), 29.7 (CH_2), 22.2 (CH_2), 20.8 (CH_3), 11.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{26}BrN_2O_2]^+$ $[M+H]^+$: 477.1172, found 477.1173.

(5*S*)-9-Methyl-*N*-[(*R*)-1-(naphthalen-1-yl)ethyl]-2-oxo-1-propyl-1,2,4,5-tetrahydro-5,7a-ethenoindole-7-carboxamide (8a). To a solution of alkenyl bromide **7a** (477 mg, 1.00 mmol), $Pd_2(dba)_3$ (27.5 mg, 0.03 mmol) and XPhos (28.6 mg, 0.06 mmol) in THF (5.0 mL) was added a solution of DABAL-Me_3 (512 mg, 2.00 mmol) in THF (3 mL). The mixture was heated at 85 °C for 4 h, cooled to room temperature and quenched carefully with 1 M aqueous HCl solution (10 mL). The mixture was extracted with EtOAc (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc in petrol to EtOAc) gave *diene* **8a** (347 mg, 84%) as an amorphous off-white solid that was not able to be recrystallized. R_f = 0.41 (EtOAc); $[\alpha]_D^{25}$ +48.0 (*c* 1.00, $CHCl_3$); IR 3255, 3044, 2964, 1654 (C=O), 1596, 1524, 1444, 1342, 799, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, d, J = 8.4 Hz, Ar**H**), 7.86 (1H, d, J = 9.5 Hz, Ar**H**), 7.82 (1H, dd, J = 7.2, 2.2 Hz, Ar**H**), 7.58–7.44 (4H, m, Ar**H**), 7.01 (1H, d, J = 6.4 Hz, =C**H**CH), 6.09–5.97 (1H, m, NHC**H**), 5.81 (1H, d, J = 8.7 Hz, N**H**), 5.77 (2H, s, =C**H**C and C**H**C=O), 3.76–3.68 (1H, m, CH_2C**H**), 2.88 (1H, ddd, J = 14.0, 11.5, 5.3 Hz, NC**H**$_2$), 2.71 (1H, ddd, J = 14.1, 11.4, 5.1 Hz, NC**H**$_2$), 2.35 (1H, d, J = 16.0, =CC**H**$_2$), 2.29 (1H, d, J = 16.0, =CC**H**$_2$), 1.83 (3H, d, J = 1.6 Hz, CC**H**$_3$), 1.64 (3H, d, J = 6.7 Hz, CHC**H**$_3$), 1.62–1.51 (1H, m, C**H**$_2$CH$_3$), 1.42–1.25 (1H, m, C**H**$_2$CH$_3$), 0.48 (3H, t, J = 7.4 Hz, CH_2C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (C), 163.1 (C), 161.1 (C), 144.3 (C), 139.7 (CH), 138.9 (C), 137.7 (C), 134.0 (C), 131.4 (C), 129.0 (CH), 128.7 (CH), 126.9 (CH), 126.1 (CH), 125.6 (CH), 123.5 (CH), 123.2 (CH), 123.0 (CH), 115.2 (CH), 75.7 (C), 45.2 (CH_2), 44.2 (CH), 44.0 (CH), 29.5 (CH_2), 21.4 (CH_2), 20.4 (CH_3), 19.5 (CH_3), 11.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{29}N_2O_2]^+$ $[M+H]^+$: 413.2224, found 413.2224.

(5*R*)-9-Methyl-*N*-[(*R*)-1-(naphthalen-1-yl)ethyl]-2-oxo-1-propyl-1,2,4,5-tetrahydro-5,7a-ethenoindole-7-carboxamide (8b). To a solution of alkenyl bromide **7b** (477 mg, 1.00 mmol), $Pd_2(dba)_3$ (27.5 mg, 0.03 mmol) and XPhos (28.6 mg, 0.06 mmol) in THF (5.0 mL) was added a solution of DABAL-Me_3 (512 mg, 2.00 mmol) in THF (3 mL). The mixture was heated at 85 °C for 4 h, cooled to room temperature and quenched carefully with 1 M aqueous HCl solution (10 mL). The mixture was extracted with EtOAc (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc in petrol to EtOAc) gave *diene* **8b** (371 mg, 90%) as an off-white solid. R_f = 0.25 (EtOAc); m.p. 143–145 °C (EtOAc/cyclohexane); $[\alpha]_D^{25}$ −64.0 (*c* 1.01, $CHCl_3$); IR 3259, 3046, 2965, 1652 (C=O), 1595, 1514, 1442,

1341, 797, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, d, J = 8.4 Hz, Ar**H**), 7.85 (1H, d, J = 7.9 Hz, Ar**H**), 7.78 (1H, dd, J = 5.6, 3.8 Hz, Ar**H**), 7.57–7.45 (2H, m, Ar**H**), 7.46–7.37 (2H, m, Ar**H**), 6.79 (1H, d, J = 6.4 Hz, =C**H**CH), 6.01–5.90 (1H, m, NHC**H**), 5.87 (1H, s, =C**H**C), 5.78 (1H, s, C**H**C=O), 5.73 (1H, d, J = 8.3 Hz, N**H**), 3.86 (1H, ddd, J = 14.0, 11.0, 5.6 Hz, NC$\mathbf{H}_2$), 3.73–3.65 (1H, m, CH_2C**H**), 3.32 (1H, ddd, J = 14.0, 10.8, 5.1 Hz, NC$\mathbf{H}_2$), 2.32 (1H, d, J = 16.7 Hz, =C$\mathbf{H}_2$), 2.26 (1H, d, J = 16.7 Hz, =CC$\mathbf{H}_2$), 1.99–1.89 (1H, m, C$\mathbf{H}_2$$CH_3$), 1.85 (3H, d, J = 1.7 Hz, CC$\mathbf{H}_3$), 1.78–1.68 (1H, m, C$\mathbf{H}_2$$CH_3$), 1.66 (3H, d, J = 6.8 Hz, CHC$\mathbf{H}_3$), 0.96 (3H, t, J = 7.4 Hz, CH_2C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (C), 164.0 (C), 160.7 (C), 144.2 (C), 139.7 (C), 138.1 (C), 137.6 (CH), 134.0 (C), 131.1 (C), 129.0 (CH), 128.5 (CH), 126.7 (CH), 126.0 (CH), 125.5 (CH), 123.4 (CH), 123.2 (CH), 122.7 (CH), 115.2 (CH), 75.9 (C), 45.5 (CH_2), 44.7 (CH), 43.9 (CH), 29.6 (CH_2), 22.2 (CH_2), 21.1 (CH_3), 19.6 (CH_3), 11.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{29}N_2O_2]^+$ $[M+H]^+$: 413.2224, found 413.2223.

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Conflict of Interest

A patent application (GB2215535.2) associated with this work was submitted on behalf of the University of Nottingham on 20th October 2022.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article and at: https://doi.org/10.17639/nott.7269.

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[18] For example, we have carried out the route straightforwardly starting from 20.0 g (100 mmol) batches of nitrile **1**. From 25.8 g (100 mmol) of acid **2**, we have prepared 13.4 g and 13.5 g of alkenyl bromides **7a** and **7b**, respectively, in one run. We anticipate scaling up further is feasible.
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RESEARCH ARTICLE

A Scalable Synthesis of Chiral Himbert Diene Ligands for Asymmetric Catalysis

Adv. Synth. Catal. **2023**, *365*, 1 – 12

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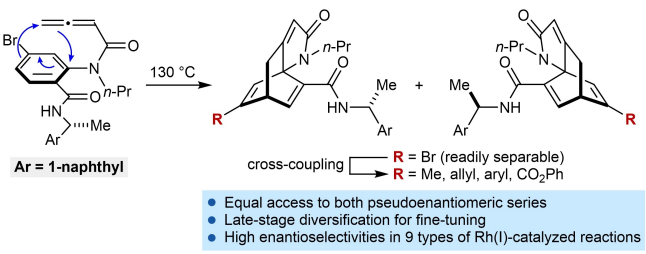

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