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A Rhodium(I)-Xylyl-BINAP Catalyzed Asymmetric Ynamide-[2 + 2 + 2] Cycloaddition in the Synthesis of Optically Enriched *N,O*-Biaryls

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Abstract

A rhodium(I)-xylyl-BINAP catalyzed asymmetric [2 + 2 + 2] cycloaddition of achiral conjugated aryl ynamides with various diynes is described here. This asymmetric cycloaddition provides a series of structurally interesting chiral *N,O*-biaryls with excellent enantioselectivity along with a modest diastereoselectivity with respect to both C-C and C-N axial chirality.

Keywords

Aryl ynamides; asymmetric [2 + 2 + 2] cycloaddition; chiral *N*; *O*-biaryls; rhodium(I) catalyst and *(S)*-xylyl-BINAP; C-N axial chirality; and double asymmetric induction of non-point stereocenters

1. Introduction

In the last 15 years, ynamides have captured much interest from the synthetic community. An immense amount of efforts has led to a number of elegant synthetic methodologies to be developed adopting ynamides as a *de novo* functional group,[1–4] and culminated in several total syntheses employing ynamides as a versatile building block.[5,6] Among these efforts [Figure 1], both Witulski's work on [2 + 2 + 2] cycloadditions of ynamides in the synthesis of indoles and carbazoles,7›8 and Rainier's formal [2 + 2 + 2] cycloaddition9 inspired us10›11 to develop a new approach toward chiral *N,O*-biaryls through a [2 + 2 + 2] cycloaddition of conjugated aryl ynamides with diynes.[12–]14 This concept was envisioned at the heel of our success in the synthesis of conjugated aryl ynamides via Sonogashira cross-coupling.15 During our pursuit, Tanaka16›[17] beautifully demonstrated the feasibility of an asymmetric [2 + 2 + 2] cycloaddition of ynamides in the synthesis of anilides with an axially chiral C-N bond.[18–]20

Because our diastereoselective ynamide-[2 + 2 + 2] cycloaddition only resulted in modest selectivity through the use of chiral aryl ynamide **1** [Scheme 1],[10] we began contemplating the possibility of pursuing an asymmetric cycloaddition employing achiral aryl ynamides **3** and a suitable chiral rhodium(I) complex.[11] If successful, asymmetry could be induced at both axially chiral C-C biaryl bond [in blue] and C-N anilide bond [in red] in cycloadducts **5**, thereby constituting a rare example of double asymmetric induction of non-point stereocenters by a

single catalyst.12,20–22 Moreover, the coordinating ability of the achiral amido-carbonyl group could play a role in the asymmetric induction, thereby rendering this design an achiral-template directed asymmetric catalysis.[23] We report here our development of an asymmetric ynamide-[2 + 2 + 2] cycloaddition.

2. Results and Discussions

2.1. Establishing the Feasibility

In our earlier work, we were intrigued by the observation that while we could not improve the diastereoselectivity in our $RhCl(Ph_3P)_3$-catalyzed [2 + 2 + 2] cycloadditions of chiral ynamide **1**, we could readily diminish the ratio from 4:1 by using an external phosphine ligand such as BINAP [Scheme 2]. To account for the modest diastereoselectivity, we had proposed *pro-**M***- and *pro-**P***-TS models, which consist of the key bidentate coordination [in green] of Rh(III) from both the oxazolidinone carbonyl oxygen and the anisol oxygen atom. We concluded that neither really possesses a distinct advantage over the other except with *pro-**P***-TS suffering from a remote steric interaction [red arrows] between the cyclopentyl and the phenyl group on the oxazolidinone ring. Based on these same models, the above finding suggests that an external chiral ligand [in blue] exerts a stronger influence on this cycloaddition than the stereocenter on the chiral ynamide, thereby implying the possibility of an asymmetric cycloaddition manifold employing achiral ynamides.

Toward this goal, we synthesized achiral conjugated aryl ynamides **6** and **7**[24–26] containing a sulfonamide and an acyclic amide, respectively, as shown in Scheme 3. However, to our disappointment, after screening several catalytic systems, we were unable to even find the desired cycloaddition products **8** and **9** let alone analyzing possible enantioselectivity. Recognizing that ynamides with the amido group cyclic in nature may be better suited for the cycloaddition, we proceeded to prepare aryl ynamide **10a** containing the 2-oxazolidinone ring [Scheme 4].

After screening again conditions such as $Rh(PPh_3)_3Cl/AgSbF_6$, $[Rh(CO)_2Cl]_2$, $[Rh(cod)Cl]_2/AgSbF_6$, and $[Rh(cod)_2]BF_4$ activated with H_2, we found that the usage of 10 mol% $[Rh(cod)_2]BF_4$ and 10 mol% *(S)*-xylyl-BINAP at 85 °C in $ClCH_2CH_2Cl$ with 4Å MS provided the best outcome when reacting **10a** with diyne **11**. While the resulting diastereomeric *N,O*-biaryls **12-*M,p*** and **12-*P,p***[27] were separable by TLC, they rapidly inter-converted to the enantiomer of each other: **12-*M,p*** led to **12-*M,m*** with **12-*P,p*** yielding **12-*P,m*** via C-N bond rotation [in red]. Even after a clean and facile separation on a silica gel column, NMR analysis revealed that the two diastereomers of **12** have already scrambled likely during the removal of the solvent under reduced pressure even without heating. Thus, this complication prevented us from meaningfully determining *dr* and *ee*.

Ultimately, cycloadditions of achiral conjugated aryl ynamides **10b** and **10c** allowed us to analyze possible enantioselectivity. As shown in Scheme 5, *N,O*-biaryl atropisomers **14-*M,p*** and **14-*P,p*** were attained in 95% yield from **10b** when reacting with diyne **13a**. Although potential diastereomers of **14** due to restricted C-N bond rotation were detectable in proton NMR, they were not separable physically. Consequently, we were able to cleanly assess the enantiomeric excess using Chiral HPLC.

Furthermore, aryl ynamide **10c** containing the 6-membered 2-oxazinone ring also led to *N,O*-biaryls **15** and **16** when reacting with diynes **13a** and **13b**, respectively. There was even less complication in these two reactions, as only a single diastereomer was detectable in ^1H NMR presumably due to rapid free rotation at the C-N bond. Thus, we were able to concisely calibrate *ee* values for both **15** and **16**, which are lower than that of **14**. It is noteworthy that since BINAP

had given lower *ee* and yield than xylyl-BINAP, and with Tanaka's success using xylyl-BINAP, we did not screen beyond these two chiral bidentate phosphines.

2.2. Syntheses of Chiral *N,O*-Biaryls

Having established an asymmetric protocol, a range of chiral *N,O*-biaryls could be prepared as shown in Figure 1. Reactions of aryl ynamide **10a** with diyne **11** led to the respective diastereomeric *N,O*-biaryl isomers **17** and **18** in good yields. Notably, we observed a diastereoselectivity as high as 8:1 in favor of the isomer **17-*M,p***, which also possesses an enantiomeric excess of 95%, while the minor isomer **18-*P,p*** has a 54% *ee*. The usage of *(R)*-xylyl-BINAP led to chiral *N,O*-biaryls *ent*-**17** and *ent*-**18** but in slightly lower *ee* and *dr*. Moreover, reactions of ynamide **10b** containing the 5-membered 2-oxazolidinone ring led to *N,O*-biaryls generally with higher *ee* for both *[P,p]* and *[M,p]* diastereomers. For example, while diastereomeric isomers **23-*M,p*** and **24-*P,p*** were attained with a *dr* of 6:1, both diastereomers possess 99% *ee*. Finally, while the ratio dropped for diastereomeric *N,O*-biaryls **27** and **28,** as well as for **29** and **30**, which all contain a naphthyl ring, their respective enantioselectivity remained high.

2.3. Assignment of Absolute Configurations

The minor diastereomer **18-*P,p*** is crystalline, and its absolute configuration could be readily resolved through X-ray structure of a single crystal [Figure 3].[28] However, assignments of the major isomer were not as trivial. As shown in Scheme 6, absolute configurations of major isomers **17-*M,p*** containing the 6-membered 2-oxazinone ring, and **23-*M,p*** containing the 5-membered 2-oxazolidinone ring, had to be assigned via X-ray structures of their respective camphor-sulfonyl derivatives **32-*M,p*** and **34-*M,p*** prepared in two steps. X-Ray structures of **32-*M,p*** and **34-*M,p*** are shown in Figure 4. Correlations of aromatic protons on the anisyl ring allow for the assignment of all other isomeric *N,O*-biaryls.

2.4. Synthesis of a Chiral Amino-Biaryl

To demonstrate that these chiral *N,O*-biaryls can be useful in the venue of designing new chiral *N,O*-biaryl ligands, we pursue the follow asymmetric cycloaddition, As shown in Scheme 7, cycloaddition of ynamide **35** containing the 2-oxazolidinone ring with gem-diphenyl substitutions[11,25] with diyne **36** gave cycloadducts **37-*M,p*** and **38-*P,p*** in 1:1 ratio with 82% *ee* for each diastereomer. We took **37-*M,p*** on and removed the achiral 2-oxazolidinone ring via hydrogenations to afford aniline **39-*M***. Although we were unable to clearly discern the final enantiomeric access of **39-*M*** through chiral HPLC, with the C-C bond rotational barrier being 37.7 kcal mol^{-1} [PM3 calculations], we believe there should be very little racemization during the hydrogenation at rt.

2.5. Equilibration Studies

We were fascinated with the unique structural feature of these *de novo N,O*-biaryls. Spartan™ *B3LYP/6-31G** calculations revealed a ΔE of 1.11 Kcal mol^{-1} in favor of the minor isomer **18**, thereby implying that the observed selectivity for **17** is kinetic. In addition, *B3LYP/6-31G** calculations provided E_{act} of 34.0 Kcal mol^{-1} and 94.4 Kcal mol^{-1}, respectively, for the axially chiral C-N and C-C bonds. These calculations would suggest that any thermal equilibrations would first lead to epimerization through the C-N rotation. That is the equilibration between **17-*M,p*** and *ent*-**18-*M,m***, or between **18-*P,p*** and *ent*-**17-*P,m*** [see Scheme 8], should occur faster at lower temperature than that between **17-*M,p*** and **18-*P,p***, or between *ent*-**18-*M,m*** and *ent*-**17-*P,m***. To confirm these assertions, we carried out following equilibration studies.

As shown in Table 1, heating pure biaryl **17-*M,p*** with a 95% *ee* at 85 °C in toluene-d_8 for 24 h [the original reaction temperature] did not result in any epimerization or loss of optical integrity. At 120 °C, epimerization occurred and led to a significant loss of **17-*M,p*** and an increase in the amount of *ent*-**18-*M,m***. However, there was no loss of enantiomeric access [94% *ee*] for both **17-*M,p*** and *ent*-**18-*M,m***, thereby suggesting that at 120 °C, the epimerization was occurring solely through rotation of the axially chiral C-N bond [assuming enantiomers in general possess the same rate of epimerization in first order]. At 165 °C and 200 °C, while **17-*M,p*** continued to epimerize to *ent*-**18-*M,m*** with the ratio gravitating toward 23:77, there was a noticeable loss in the *ee* for both **17-*M,p*** and *ent*-**18-*M,m***. Thus, at these high temperatures, epimerization was taking place through free rotations at both C-N and C-C bonds, which should then lead to racemization.

Equilibrations of pure *ent*-**17-*P,m*** with a 86% *ee* led to a very similar outcome and likewise with equilibrations of **18-*P,p*** even starting at a 52% *ee* [Table 2]. It is noteworthy that all the equilibration studies led to a final resting thermodynamic ratio of 22:78 for **17:18**. This appears to be the thermodynamic ratio, which is consistent with the calculation in which isomer **18** is favored by 1.11 kcal mol^{-1}.

2.6. Mechanistic Considerations

Given the stereochemical outcome, we proposed a mechanistic model that could provide a unified rationale for the observed asymmetric inductions. As shown in Scheme 9, with the rhodio-cyclopentadiene intermediate complexed to *(S)*-xylyl-BINAP, a respective ynamide could approach the metal more favorably as shown in complex-**A1** with the anisole ring sliding into the less hindered space near $\mathbf{Ar^2}$ with a smaller amido group assuming the relatively more crowded space next to $\mathbf{Ar^1}$. This binding orientation would be the opposite in complex-**B1** and would lead to a less favorable fit in the two respective “binding pockets.”

With complex-**A1** in hand, a key bidentate chelation of the Rh metal via both the anisyl OMe and the carbonyl group could occur to assist the complexation of the ynamide unto the metal center. The ensuing cycloaddition, in a stepwise or Diels-Alder manner, would lead to the major diastereomer *[M,p]*. Because the enantiomer of the major isomer would come from complex-**B1**, which is not favored in these reactions, enantiomeric access is high in almost all cases for atropisomer *[M,p]*.

If the bidentate chelation fails due to the slipping of the weaker coordination from the anisole oxygen atom through a C-C rotation, one would obtain complex-**A2**, which would give the observed minor diastereomer *[P,p]* after the cycloaddition. On the other hand, if the C-N bond in **A1** rotates and one loses the stronger coordination from the carbonyl oxygen, complex-**A3** would be present to give corresponding the *[M,m] isomer*, which is the enantiomer of the minor diastereomer. Since the carbonyl oxygen in general possesses better coordinating ability than a phenolic ethereal oxygen, it is reasonable to see much less formation of *[M,m]*, thereby rendering *[P,p]* as the major enantiomer for the minor diastereomer.

Finally, the importance of the carbonyl oxygen in this asymmetric cycloaddition can also further underscored from the fact that 2-oxazolidinone is better chelator than 2-oxazinone. Consequently, ynamides substituted with 2-oxazolidinone gave higher *ee*. Overall, the current mechanistic model provides another excellent example for showcasing the versatility of enantioselective catalysis through an asymmetric template that employs an achiral auxiliary.[23]

3. Conclusion

We have described here a rhodium(I)-xylyl-BINAP catalyzed asymmetric [2 + 2 + 2] cycloaddition of achiral conjugated aryl ynamides with various diynes. This asymmetric cycloaddition represents a rare example of double asymmetric induction of non-point stereocenters by a single catalyst, and provides a series of structurally interesting chiral *N*,*O*-biaryls with excellent enantioselectivity in most cases along with a modest diastereomeric selectivity with respect to both C-C and C-N axial chirality.

4. Experimental Section

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separations were performed using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-300, VI-400, and VI-500 spectrometers using $CDCl_3$ (except where noted) with TMS or residual $CHCl_3$ in the solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Bruker Equinox 55/S FT–IR Spectrophotometer, and relative intensities are expressed qualitatively as s (strong), m (medium), and w (weak). TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and a suitable chemical stain. Low-resolution mass spectra were obtained using an Agilent-1100-HPLC/MSD and can be either APCI or ESI, or an IonSpec HiRes-MALDI FT-Mass Spectrometer. High-resolution mass spectral analyses were performed at University of Wisconsin Mass Spectrometry Laboratories. All spectral data obtained for new compounds are reported.

4.1. A General Procedure for the Asymmetric Ynamide-[2 + 2+ 2] Cycloaddition

To a solution of $[Rh(cod)_2]BF_4$ (10 mol%) and (*S*)-xylyl-BINAP (10 mol%) in anhyd $ClCH_2CH_2Cl$ (5.0 mM) was added 4Å Molecular Sieves in a sealed tube. The mixture was stirred at rt for 10 min before a respective ynamide (1.00 mmol) and diyne (2.00 mmol) were added. The solution was heated to 85°C and followed by LCMS. After the reaction was complete, the solution was cooled to RT and filtered through a short pad of silica gel. Elution with EtOAc/hexanes (1:1) followed by concentration *in vacuo* afforded a crude mixture of diastereomers. Separation and purification of the resulting crude residue via silica gel flash column chromatography (gradient eluent: EtOAc in hexanes) afforded the desired *N*,*O*-biaryl diastereomers. Diastereomeric ratios were found in crude ^1H NMR, and enantiomeric excess of each diastereomer was determined via chiral HPLC [CHIRALCEL OD-H; Size: 250 × 4.6mm (L × I.D.); eluent: iso-propyl alcohol in Hexanes].

4.1.1. Establishing the Feasibility

Chiral Biaryl 12-Major: R_f = 0.52 [20% EtOAc in chloroform]; thick oil; ^1H NMR (500 MHz, $CDCl_3$) δ 1.81 (s, 3H), 1.96 (s, 3H), 2.16 (s, 3H), 3.35 (td, *J* = 8.9, 4.6 Hz, 1H), 3.54–3.59 (m, 2H), 3.61–3.74 (m, 4H), 3.68 (s, 3H), 3.792 (s, 3H), 3.797 (s, 3H), 4.22 (td, *J* = 8.6, 4.6 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.0, 16.4, 20.0, 40.66, 40.68, 46.9, 53.36, 53.43, 55.6, 59.4, 62.9, 107.7, 123.4, 126.8, 128.6, 129.9, 131.1, 133.2, 136.2, 139.3, 139.4, 139.7, 156.6, 156.8, 172.4, 172.8; IR (film) cm^{-1} 2946w, 2354w, 1730s, 1688s, 1461m, 1439m, 1235s, 1183m; mass spectrum (APCI): m/e (% relative intensity) 468 (100) $(M + H)^+$; **12-Minor.** R_f = 0.52 [20% EtOAc in chloroform]; thick oil; ^1H NMR (500 MHz, $CDCl_3$) δ 1.88 (s, 3H), 1.93 (s, 3H), 2.17 (s, 3H), 3.01 (td, *J* = 8.6, 4.7 Hz, 1H), 3.48 (q, *J* = 8.8 Hz, 1H), 3.54–3.75 (m, 5H), 3.67 (m, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 4.18 (td, *J* = 8.7, 4.7 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 7.2 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.0, 16.4, 19.9, 30.0,

40.7, 46.3, 53.4, 55.9, 59.4, 62.3, 108.5, 122.1, 126.3, 126.6, 128.8, 130.06, 130.08, 131.1, 135.6, 139.5, 139.8, 156.4, 157.8, 172.2, 173.0 [missing one carbon due to overlap]; IR (film) cm^{-1} 2896w, 2344w, 1724s, 1679s, 1443m, 1425m, 1245s, 1190m; mass spectrum (APCI): m/e (% relative intensity) 468 (100) $(M + H)^+$; HRMS of the isomeric mixture (ESI, m/e) calcd for $C_{26}H_{30}NO_7$ 468.2017, found 468.2013.

Chiral Biaryl 14-*M*: Rotamers observed on the NMR timescale; R_f = 0.34 [60% EtOAc in hexanes]; pale solid; mp 185–188 °C; $[\alpha]_D^{20}$ = − 16.7 (*c* 2.14, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.73 (s, 3H), 1.25 (s, 3H), 1.26 (s, 3H), 2.07 (s, 3H), 2.17 (s, 3H), 3.66 (d, *J* = 8.4 Hz, 1H), 3.68 (s, 6H), 3.75 (d, *J* = 8.4 Hz, 1H), 3.97 (d, *J* = 8.0 Hz, 1H), 3.99 (d, *J* = 8.0 Hz, 1H), 5.09–5.20 (m, 8H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 6.8 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 7.13 (s, 2H), 7.15 (s, 1H), 7.19 (s, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 21.1, 23.5, 23.8, 24.9, 55.3, 55.6, 62.2, 62.5, 73.5, 73.6, 75.0, 75.3, 107.7, 107.8, 122.69, 122.72, 124.5, 125.0, 125.2, 125.5, 127.9, 128.2, 128.7, 128.9, 133.8, 134.1, 137.4, 137.5, 138.0, 139.76, 139.83, 139.91, 139.95, 157.3, 157.6, 158.4 [missing four carbons due to overlap]; IR (film) cm^{-1} 2935w, 1746s, 1466m, 1389s, 1259s, 1068s, 1029s, 734s; mass spectrum (APCI): m/e (% relative intensity) 354 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{21}H_{23}NO_4$ 353.1622, found 353.1626.; HPLC (80:20 hexane/2-propanol): t_r = major 15.6 min, and minor 12.0 min.

Chiral Biaryl 15-*M*: R_f = 0.10 [50% EtOAc in hexanes]; pale solid; mp 96–100 °C; $[\alpha]_D^{20}$ = − 27.5 (*c* 2.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.58 (broad s, 3H), 0.92–0.96 (broad m, 3H), 2.09 (s, 3H), 3.02–3.09 (broad m, 2H), 3.62–3.70 (broad m, 1H), 3.70 (s, 3H), 3.84–3.87 (broad m, 1H), 5.12 (s, 2H), 5.16 (s, 2H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 7.04 (s, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 22.0, 22.8, 29.2, 31.1, 55.9, 59.9, 73.9, 76.3, 108.0, 122.0, 123.2, 124.7, 127.4, 129.5, 135.6, 139.4, 140.7, 140.9, 141.5, 152.3, 156.8; IR (film) cm^{-1} 2959w, 2927w, 2361w, 2249w, 1735s, 1698s, 1476m, 1356m; mass spectrum (APCI): m/e (% relative intensity) 368 (100) $(M + H)^+$.

Chiral Biaryl 16-*M*: R_f = 0.38 [60% EtOAc in hexanes]; pale solid; mp 74–80 °C; $[\alpha]_D^{20}$ = − 25.3 (*c* 2.16, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (broad s, 3H), 0.98 (broad m, 3H), 2.09 (s, 3H), 2.12 (quintet, *J* = 7.6 Hz, 2H), 2.89–3.08 (broad m, 6H), 3.65 (broad m, 1H), 3.69 (s, 3H), 3.86–3.87 (broad m, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.8, 22.9, 25.8, 29.0, 32.8, 33.0, 55.6, 59.9, 76.4, 107.9, 123.1, 124.6, 127.4, 128.0, 128.5, 133.6, 139.3, 140.5, 144.2, 145.0, 152.7, 156.9; IR (film) cm^{-1} 2959w, 2839w, 1791s, 1473s, 1371m, 1260s, 1200s, 1148m, 1057m; mass spectrum (APCI): m/e (% relative intensity) 366 (100) $(M + H)^+$.

4.1.2. Synthesis Chiral *N,O*-Biaryls

Chiral Biaryl 17-*M,p*: R_f = 0.28 [60% EtOAc in hexanes]; pale solid; mp 111–113 °C; $[\alpha]_D^{20}$ = − 46.7 (*c* 1.0, CH_2Cl_2); ***ent*-17-*P,m***: $[\alpha]_D^{20}$ = + 39.5 (*c* 0.72, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.53 (s, 3H), 1.01 (s, 3H), 1.85 (s, 3H), 1.91 (s, 3H), 2.15 (s, 3H), 2.57 (d, *J* = 11.0 Hz, 1H), 2.82 (dd, *J* = 11.2, 1.2 Hz, 1H), 3.34 (d, *J* = 10.5 Hz, 1H), 3.59 (ABq, Δν = 19.7 Hz, *J* = 17.0 Hz, 2H), 3.65 (ABq, Δν = 18.2 Hz, *J* = 17.0 Hz, 2H), 3.67 (s, 3H), 3.70 (dd, *J* = 10.5, 1.0 Hz, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 16.5, 20.0, 22.4, 23.2, 29.2, 40.7, 40.8, 53.3, 53.4, 55.9, 58.7, 59.4, 75.4, 108.3, 122.0, 126.7, 128.7, 129.6, 131.2, 134.7, 137.7, 137.9, 138.9, 139.2, 151.6, 158.3, 172.2, 173.1; IR (Neat) cm^{-1} 2958w, 2360m, 2342m, 1734m, 1696m, 1433w, 1265s, 1109m, 734s; mass spectrum (APCI): m/e (% relative intensity) 510

(100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{29}H_{35}NO_7$ 510.2487, found 510.2482; HPLC (95:5 hexane/2-propanol): t_r = major 11.4 min, and minor 14.7 min.

Chiral Biaryl 18-*P,p*: R_f = 0.35 [60% EtOAc in hexanes]; pale solid; mp 187–190 °C; $[\alpha]_D^{20}$ = + 5.9 (*c* 2.40, CH_2Cl_2); ***ent*-18-*M,m***: $[\alpha]_D^{20}$ = − 3.2 (*c* 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.51 (s, 3H), 0.95 (s, 3H), 1.78 (s, 3H), 2.01 (s, 3H), 2.15 (s, 3H), 2.92 (d, *J* = 11.6 Hz, 1H), 2.99 (dd, *J* = 11.8, 1.6 Hz, 1H), 3.47 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.65 (ABq, Δν = 71.6 Hz, *J* = 16.8 Hz, 2H), 3.66 (ABq, Δν = 24.1 Hz, *J* = 17.2 Hz, 2H), 3.67 (s, 3H), 3.789 (s, 3H), 3.795 (s, 3H), 3.80 (d, *J* = 10.5 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 16.4, 20.2, 21.9, 23.2, 29.1, 40.7, 40.8, 53.3, 53.4, 55.3, 58.8, 59.4, 76.0, 107.7, 123.5, 126.8, 128.5, 129.2, 131.4, 135.1, 138.0, 138.7, 139.2, 140.5, 152.1, 156.7, 172.4, 172.9; IR (Neat) cm^{-1} 2957w, 2360w, 1734s, 1697s, 1467m, 1427m, 1251s, 1172s, 1061s; mass spectrum (APCI): m/e (% relative intensity) 510 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{29}H_{35}NO_7$ 510.2487, found 510.2494.; HPLC (95:5 hexane/2-propanol): t_r = major 40.9 min, and minor 40.0 min.

19-*M,p*: R_f = 0.34 [60% EtOAc in hexanes]; pale solid; mp 80–83 °C; $[\alpha]_D^{20}$ = − 65.1 (*c* 0.723, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (s, 3H), 1.02 (s, 3H), 1.86 (s, 3H), 1.89–1.92 (m, 1H), 1.94 (s, 3H), 2.00–2.15 (m, 2H), 2.16 (s, 3H), 2.60 (d, *J* = 10.4 Hz, 1H) 2.83–2.94 (m, 4H), 3.35 (d, *J* = 10.0 Hz, 1H), 3.69 (s, 3H), 3.71 (dd, *J* = 6.8, 1.2 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 16.6, 20.0, 22.3, 23.2, 24.4, 29.2, 32.67, 32.70, 55.9, 58.7, 75.4, 108.3, 121.9, 127.2, 128.4, 129.3, 131.0, 133.5, 136.6, 137.9, 143.0, 143.3, 151.7, 158.3; IR (film) cm^{-1} 2949s, 2923s, 2852s, 2362m, 2344m, 1685s, 1469s, 1373m, 1256m; mass spectrum (APCI): m/e (% relative intensity) 394 (100) $(M + H)^+$; HRMS of mixture of **19-*M,p*** and **20-*P,p*** (ESI, m/e) calcd for $C_{25}H_{31}NO_3$ 393.2299, found 393.2303; HPLC (95:5 hexane/2-propanol): t_r = major 26.7 min, and minor 25.5 min.

Chiral Biaryl 20-*P,p*: R_f = 0.48 [60% EtOAc in hexanes]; thick oil; $[\alpha]_D^{20}$ = + 7.5 (*c* 0.185, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.44 (s, 3H), 0.88 (s, 3H), 1.70–1.76 (m, 1H), 1.72 (s, 3H), 1.97 (s, 3H), 2.05 (quintet, *J* = 7.4 Hz, 2H), 2.10 (s, 3H), 2.80–2.95 (m, 4H), 3.50 (dd, *J* = 11.6, 1.8 Hz, 1H), 3.41 (dd, *J* = 10.6, 1.8 Hz, 1H), 3.62 (s, 3H), 3.74 (d, *J* = 10.8 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 16.5, 20.2, 21.9, 23.2, 24.3, 29.0, 29.9, 32.67, 32.75, 55.4, 58.9, 76.0, 107.7, 123.4, 127.3, 128.3, 131.2, 133.8, 137.0, 140.6, 142.9, 143.5, 152.2, 156.7; IR (film) cm^{-1} 2969s, 2918s, 2850s, 2360m, 2340m, 1686s, 1467s, 1378m, 1256m; mass spectrum (APCI): m/e (% relative intensity) 394 (100) $(M + H)^+$; HRMS of mixture of **19-*M,p*** and **20-*P,p*** (ESI, m/e) calcd for $C_{25}H_{31}NO_3$ 393.2299, found 393.2303; HPLC (95:5 hexane/2-propanol): t_r = major 26.7 min, and minor 25.5 min.

Chiral Biaryl 21-*M,p*: R_f = 0.17 [60% EtOAc in hexanes]; pale solid; mp 174–176 °C; $[\alpha]_D^{20}$ = − 71.3 (*c* 1.42, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (s, 3H), 1.03 (s, 3H), 1.83 (s, 3H), 1.95 (s, 3H), 2.14 (s, 3H), 2.62 (d, *J* = 10.4 Hz, 1H), 2.85 (dd, *J* = 11.2, 1.6 Hz, 1H), 3.37 (d, *J* = 10.4, Hz, 1H), 3.69 (s, 3H), 3.72 (dd, *J* = 10.6, 1.4 Hz, 1H) 5.07–5.16 (m, 4H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 16.3, 19.8, 22.3, 23.0, 29.1, 55.8, 58.6, 74.3, 75.4, 108.3, 122.0, 126.0, 127.3, 128.8, 128.9, 135.2, 137.7, 137.99, 138.02, 138.5, 151.5, 158.1 [missing one carbon due to overlap]; IR (film) cm^{-1} 3418w, 2967w, 2360w, 1692s, 1578w, 1468s, 1373m, 1259m, 1175m; mass spectrum (APCI): m/e (% relative intensity) 396 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{24}H_{29}NO_4$ 395.2092, found 395.2093; HPLC (95:5 hexane/2-propanol): t_r = major 27.0 min, and minor 26.5 min.

Chiral Biaryl 22-*P,p*: R_f = 0.26 [60% EtOAc in hexanes]; thick oil; $[\alpha]_D^{20}$ = + 21.4 (*c* 0.075, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.52 (s, 3H), 0.96 (s, 3H), 1.76 (s, 3H), 2.04 (s, 3H), 2.14 (s, 3H), 2.95 (d, *J* = 11.6 Hz, 1H), 3.01 (dd, *J* = 11.6, 1.6 Hz, 1H), 3.50 (dd, *J* = 10.8, 2.0 Hz, 1H), 3.70 (s, 3H), 3.83 (d, *J* = 10.4 Hz, 1H) 5.14–5.19 (m, 4H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 16.3, 20.1, 21.8, 23.2, 29.0, 55.3, 58.7, 74.3, 76.0, 77.4, 107.8, 123.5, 126.2, 127.0, 128.7, 129.1, 135.6, 137.9, 138.4, 138.6, 140.4, 152.0, 156.6; IR (film) cm^{-1} 2969w, 2884w, 2839w, 2360m, 2342m, 1754s, 1699s, 1468s, 1258s; mass spectrum (APCI): m/e (% relative intensity) 396 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{24}H_{29}NO_4$ 395.2092, found 395.2081; HPLC (95:5 hexane/2-propanol): t_r = major 24.3 min, and minor 25.8 min.

Chiral Biaryl 23-*M,p*: R_f = 0.32 [60% EtOAc in hexanes]; pale solid; mp 96–100 °C; $[\alpha]_D^{20}$ = − 6.8 (*c* 1.18, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.45 (s, 3H), 1.14 (s, 3H), 1.88 (s, 3H), 2.00 (s, 3H), 2.14 (s, 3H), 3.61 (s, 2H), 3.65 (ABq, Δν = 17.1 Hz, *J* = 16.8 Hz, 2H), 3.66 (s, 3H), 3.75 (d, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 4.00 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.9, 17.5, 20.2, 24.7, 25.8, 40.9, 41.2, 53.38, 53.40, 55.8, 59.2, 62.0, 77.0, 108.2, 122.1, 127.7, 128.8, 131.79, 131.85, 133.1, 137.0, 139.3, 139.7, 139.8, 157.2, 158.0, 172.2, 173.1; IR (film) cm^{-1} 2972w, 2360w, 1735s, 1434m, 1374m, 1264s, 1061m, 733s; mass spectrum (APCI): m/e (% relative intensity) 496 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{28}H_{33}NO_7$ 496.2330, found 496.2339; HPLC (80:20 hexane/2-propanol): t_r = major 28.2 min, and minor 25.8 min.

Chiral Biaryl 24-*P,p*: R_f = 0.44 [60% EtOAc in hexanes]; thick oil; $[\alpha]_D^{20}$ = + 29.8 (*c* 0.33, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (s, 3H), 1.10 (s, 3H), 1.77 (s, 3H), 2.01 (s, 3H), 2.12 (s, 3H), 3.65 (ABq, Δν = 61.3, *J* = 16.8 Hz, 2H), 3.67 (ABq, Δν = 31.7, *J* = 17.2 Hz, 2H), 3.69 (s, 3H), 3.796 (s, 3H), 3.804 (s, 3H), 3.89 (d, *J* = 8.0 Hz, 1H), 4.05 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 17.0, 20.1, 23.1, 26.1, 40.9, 41.1, 53.3, 53.4, 55.1, 59.1, 61.9, 107.3, 123.2, 127.9, 128.6, 131.1, 131.7, 133.2, 137.0, 139.2, 139.5, 139.8, 157.8, 157.9, 172.4, 172.9, [missing one carbon due to overlap]; IR (film) cm^{-1} 2956w, 2360w, 1735s, 1698s, 1468m, 1433m, 1252s, 1173m; mass spectrum (APCI): m/e (% relative intensity) 496 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{28}H_{33}NO_7$ 496.2330, found 496.2320; HPLC (95:5 hexane/2-propanol): t_r = major 25.5 min, and minor 19.3 min.

Chiral Biaryl 25-*M,p*: R_f = 0.35 [60% EtOAc in hexanes]; pale solid; mp 110–113 °C; $[\alpha]_D^{20}$ = − 4.3 (*c* 3.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.48 (s, 3H), 1.17 (s, 3H), 1.86 (s, 3H), 2.04 (s, 3H), 2.13 (s, 3H), 3.68 (s, 3H), 3.79 (d, *J* = 8.4 Hz, 1H), 4.03 (d, *J* = 8.0 Hz, 1H), 5.07–5.19 (m, 4H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 17.2, 20.1, 24.6, 25.8, 55.8, 61.9, 74.5, 74.6, 108.3, 122.2, 127.0, 129.0, 129.5, 129.6, 133.6, 137.5, 139.0, 139.06, 139.1, 157.1, 157.9 [missing one carbon due to overlap]; IR (film) cm^{-1} 2968w, 2858w, 2369w, 2335w, 1745s, 1582w, 1397m, 1210m; mass spectrum (APCI): m/e (% relative intensity) 382 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{23}H_{27}NO_4$ 381.1935, found 381.1938; HPLC (95:5 hexane/2-propanol): t_r = major 27.0 min, and minor 26.0 min.

Chiral Biaryl 26-*P,p*: R_f = 0.41 [60% EtOAc in hexanes]; thick oil; $[\alpha]_D^{20}$ = + 65.0 (*c* 0.85, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.63 (s, 3H), 1.13 (s, 3H), 1.76 (s, 3H), 2.05 (s, 3H), 2.11 (s, 3H), 3.72 (s, 3H), 3.92 (d, *J* = 8.4 Hz, 1H), 4.07 (d, *J* = 8.0 Hz, 1H), 5.12–5.21 (m, 4H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 16.9, 20.1, 23.1, 26.1, 55.2, 62.0, 74.5, 74.6, 77.7, 107.4, 123.3, 127.3, 128.8, 128.9, 129.6, 133.7, 137.6, 138.5, 139.0, 139.7, 157.80, 157.85; IR (film) cm^{-1} 2956w, 2360w, 1735s, 1698s, 1468m, 1433m, 1252s, 1173m; mass spectrum (APCI): m/e (% relative

intensity) 496 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{23}H_{27}NO_4$ 382.2013, found 382.2013; HPLC (95:5 hexane/2-propanol): t_r = major 24.3 min, and minor 25.8 min.

Chiral Biaryl 27-*M,p*: R_f = 0.17 [10% EtOAc in CH_2Cl_2]; yellow solid; mp 110–114 °C; $[\alpha]_D^{20} = -24.4$ (*c* 1.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.096 (s, 3H), 0.99 (s, 3H), 1.73 (s, 3H), 2.18 (s, 3H), 3.65 (d, *J* = 7.8 Hz, 1H), 3.66 (s, 2H), 3.71 (ABq, Δν = 19.9 Hz, *J* = 17.0 Hz, 2H), 3.81 (s, 3H), 3.82 (s, 6H), 3.94 (d, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.27–7.35 (m, 2H), 7.35 (d, *J* = 9.2 Hz, 1H), 7.79 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 18.0, 24.1, 26.4, 40.9, 41.3, 53.4, 56.4, 59.1, 61.9, 77.0, 77.5, 113.3, 121.3, 123.3, 125.1, 127.0, 128.6, 128.7, 129.8, 131.9, 132.6, 133.9, 134.9, 135.8, 139.8, 140.1, 154.9, 157.3, 172.2, 173.1; IR (film) cm^{-1}: 2930w, 1735s, 1623w, 1595w, 1436m, 1397w, 1371m, 1351m, 1337m, 1272s, 1249s, 1167s, 1060s; mass spectrum (APCI): m/e (% relative intensity) 532 (100) $(M + H)^+$, 474 (7); HRMS (ESI, m/e) calcd for $C_{31}H_{33}NO_7$ 532.2330, found 532.2320; HPLC (95:5 hexane/2-propanol): t_r = major 26.4 min, and minor 25.2 min.

Chiral Biaryl 28-*P,p*: R_f = 0.39 [10% EtOAc in CH_2Cl_2]; yellow solid; mp 245–250 °C; $[\alpha]_D^{20} = -19.6$ (*c* 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (s, 3H), 1.12 (s, 3H), 1.80 (s, 3H), 2.17 (s, 3H), 3.50 (d, *J* = 8.2 Hz, 1H), 3.60–3.80 (m [two ABq], 4H), 3.81 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 3.89 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 9.2 Hz, 1H), 7.28–7.35 (m, 2H), 7.50–7.52 (m, 1H), 7.73–7.75 (m, 1H), 7.88 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 17.2, 23.9, 25.7, 41.0, 41.2, 53.3, 53.4, 55.7, 59.1, 62.0, 77.7, 111.8, 122.2, 124.3, 126.6, 126.9, 127.2, 129.0, 129.9, 131.6, 132.7, 133.3, 133.6, 135.8, 139.5, 139.9, 154.5, 157.2, 172.4, 172.9; IR (film) cm^{-1}: 3003w, 1730s, 1592w, 1512w, 1462w, 1433w, 1397w, 1368w, 1268s, 1246s, 1199m, 1168m, 1062s; mass spectrum (APCI): m/e (% relative intensity) 532 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{31}H_{33}NO_7$ 532.2330, found 532.2327; HPLC (95:5 hexane/2-propanol): t_r = major 20.7 min, and minor 15.7 min.

Chiral Biaryl 29-*M,p*: R_f = 0.25 [60% EtOAc in hexanes]; yellow solid; mp 105–110 °C; $[\alpha]_D^{20} = -40.8$ (*c* 2.055, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.052 (s, 3H), 1.02 (s, 3H), 1.71 (s, 3H), 2.17 (s, 3H), 3.70 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 3.97 (d, *J* = 8.0 Hz, 1H), 5.12–5.25 (m, 4H), 7.26–7.38 (m, 3H), 7.37 (d, *J* = 9.2 Hz, 1H), 7.82 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 17.9, 24.1, 26.4, 56.5, 61.9, 74.5, 74.6, 77.1, 113.3, 120.7, 123.4, 124.9, 127.2, 128.69, 128.73, 129.6, 130.1, 130.5, 134.4, 134.8, 136.4, 139.1, 139.5, 155.0, 157.3; IR (film) cm^{-1}: 2933w, 2839w, 1747s, 1620w, 1593w, 1507w, 1457w, 1416w, 1367m, 1345m, 1296w, 1274m, 1261m; mass spectrum (APCI): m/e (% relative intensity) 418 (100) $(M + H)^+$; HRMS of mixture of **29-*M,p*** and **30-*P,p*** (ESI, m/e) calcd for $C_{26}H_{27}NO_4$ 417.1935, found 417.1928; HPLC (80:20 hexane/2-propanol): t_r = major 17.1 min, and minor 13.2 min.

Chiral Biaryl 30-*P,p*: R_f = 0.42 [60% EtOAc in hexanes]; yellow solid; mp 115–120 °C; $[\alpha]_D^{20} = -57.8$ (*c* 0.79, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (s, 3H), 1.15 (s, 3H), 1.78 (s, 3H), 2.16 (s, 3H), 3.53 (d, *J* = 8.2 Hz, 1H), 3.89 (s, 3H), 3.91 (d, *J* = 8.2 Hz, 1H), 5.15–5.25 (m, 4H), 7.28 (d, *J* = 9.2 Hz, 1H), 7.30–7.38 (m, 2H), 7.52–7.55 (m, 1H), 7.75–7.78 (m, 1H), 7.91 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 17.1, 23.9, 25.7, 55.8, 62.0, 74.57, 74.64, 77.0, 111.8, 121.5, 124.4, 126.3, 127.1, 127.4, 129.0, 129.4, 130.2, 130.6, 133.2, 134.1, 136.4, 138.7, 139.4, 154.5, 157.2; IR (film) cm^{-1}: 2840w, 1743m, 1592w, 1510w, 1462w 1362w, 1345w, 1300w, 1258m, 1244m; mass spectrum (APCI): m/e (% relative intensity) 418 (100) $(M + H)^+$; HRMS of mixture of **29-*M,p*** and **30-*P,p*** (ESI, m/e) calcd for $C_{26}H_{27}NO_4$ 417.1935, found 417.1928; HPLC (80:20 hexane/2-propanol): t_r = major 18.7 min, and minor 15.2 min.

4.1.3. Assignment of Absolute Configurations

Demethylation Procedure: A solution of **17-*M,p*** (30.0 mg, 0.059 mmol) in anhyd CH_2Cl_2 was cooled to −78 °C under an argon atmosphere. To tthis reaction mixture was added BBr_3 (1.0 *M* soln in CH_2Cl_2, 5.0 equiv) carefully dropwise. The reaction mixture was warmed to −25 °C and stirred for 24 h. After the reaction was complete, the solution was quenched with H_2O and the reaction mixture was warmed to RT. The layers were separated and the organic layer extracted with CH_2Cl_2 (2 × equal volume). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure.

The crude product was re-dissolved in anhyd acetone and 2.5 equiv of Me_2SO_4, and anhyd solid $NaHCO_3$ (2.5 equiv) was added under an argon atmosphere. The reaction mixture was stirred at RT for 48 h. After the reaction was complete, the mixture filtered through a short pad of Celite.™ Acetone was removed under reduced pressure and the crude mixture was re-dissolved in EtOAc. The reaction mixture was washed with water followed by sat aq NaCl (equal volume). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude residue by silica gel flash column chromatography [isocratic eluent: 50% EtOAc in hexanes] yielded the desired phenol **31-*M,p*** in 73% yield. **31-*M,p***: R_f = 0.52 [50% EtOAc in hexanes]; white solid; mp 165–168 °C; $[\alpha]_D^{20}$ = + 7.8 (*c* 2.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.50 (s, 3H), 0.96 (s, 3H), 1.84 (s, 3H), 1.94 (s, 3H), 2.16 (s, 3H), 2.69 (dd, *J* = 11.2, 2.0 Hz, 1H), 3.08 (d, *J* = 11.2 Hz, 1H), 3.57–3.71 (m, 5H), 3.79 (s, 3H), 3.80 (s, 3H), 3.94 (d, *J* = 10.8 Hz, 1H), 6.28 (s, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 16.4, 20.2, 21.3, 23.0, 29.1, 40.6, 53.3, 53.4, 58.4, 59.3, 60.6, 76.1, 116.2, 122.5, 125.8, 129.0, 129.2, 132.5, 133.5, 136.7, 137.8, 139.9, 140.3, 154.1, 155.0, 172.0, 172.7 [missing one carbon due to overlap]; IR (film) cm^{-1} 3332s, 2959w, 2889w, 2360w, 2254w, 1734s, 1697s, 1467m, 1402m; mass spectrum (APCI): m/e (% relative intensity) 496 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{28}H_{33}NO_7$ 496.2330, found 496.2318.

Preparation of Camphor Sulfonyl Derivative: A solution of **31-*M, p*** (55.0 mg, 0.11 mmol) in anhyd CH_2Cl_2 was cooled to 0 °C under an argon atmosphere. To the reaction mixture was added (1*S*)-(+)-10-camphorsulfonyl chloride (31.0 mg, 0.122 mmol) followed by catalytic DMAP and Et_3N (0.122 mmol). The reaction was warmed to RT and stirred for 12 h. After the reaction was complete, the solution was quenched with pH 7.0 aqueous buffer and the layers were separated. The organic layer was extracted with CH_2Cl_2 (2 × equal volume), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude residue by silica gel flash column chromatography [isocratic eluent: 40% EtOAc in hexanes] afforded the product **32-*M,p*** in 85% yield. **32-*M,p***: R_f = 0.46 [50% EtOAc in hexanes]; clear crystals; mp 230–233 °C; $[\alpha]_D^{20}$ = − 39.2 (*c* 1.66, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.49 (s, 3H), 0.73 (s, 3H), 0.79 (s, 3H), 0.97 (s, 3H), 1.20–1.28 (m, 1H), 1.36–1.43 (m, 1H), 1.52–1.59 (m, 1H), 1.71–1.80 (m, 1H), 1.80 (d, *J* = 18.4 Hz, 1H), 1.89 (s, 3H), 1.97 (t, *J* = 4.4 Hz, 1H), 2.01 (s, 3H), 2.15 (s, 3H), 2.27 (ddd, *J* = 17.2, 4.4, 3.2 Hz, 1H), 2.47 (d, *J* = 10.8 Hz, 1H), 2.84 (d, *J* = 10.8 Hz, 1H), 3.40 (ABq, Δν = 85.5 Hz, *J* = 15.2 Hz, 2H), 3.49 (d, *J* = 10.0 Hz, 1H), 3.58 (ABq, Δν = 33.3 Hz, *J* = 17.0 Hz, 2H), 3.66 (ABq, Δν = 54.1 Hz, *J* = 16.6 Hz, 2H), 3.78 (d, *J* = 9.2 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.1, 16.7, 19.4, 19.6, 20.0, 22.1, 23.1, 24.0, 27.1, 29.1, 40.7, 42.6, 43.1, 48.3, 49.7, 53.3, 53.4, 58.3, 58.8, 59.0, 75.6, 120.1, 127.9, 129.0, 130.1, 130.8, 132.0, 132.8, 138.3, 138.6, 139.1, 139.8, 147.4, 151.4, 172.2, 172.7, 214.1; IR (film) cm^{-1} 2959w, 2889w, 2360w, 2254w, 1734s, 1697s, 1467m, 1402m; mass spectrum (APCI): m/e (% relative intensity) 709 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{38}H_{47}NO_{10}S$ 710.2994, found 710.3004.

Free Phenol 33-*M,p*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (s, 3H), 1.17 (s, 3H), 1.87 (s, 3H), 1.99 (s, 3H), 2.14 (s, 3H), 3.59–3.72 (m, 3H), 3.81 (s, 3H), 3.81 (s, 3H), 6.05 (s, 1H), 6.79 (d, 1H, *J* = 7.6 Hz), 6.89 (d, *J* = 8.0 Hz), 7.14 (t, *J* = 8.0 Hz, 1H); mass spectrum (APCI): m/e (% relative intensity) 496 (10) $(M+H)^+$, 483 (30), 482 (100); **34-*M,p***. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.47 (s, 3H), 0.75 (s, 3H), 0.84 (s, 3H), 1.11 (s, 3H), 1.40 (ddd, *J* = 4.4, 9.2, 13.6 Hz, 1H), 1.65–1.83 (m, 4H), 1.92 (s, 3H), 1.97 (t, *J* = 4.4 Hz, 1H), 2.11 (s, 3H), 2.15 (s, 3H), 2.30 (ddd, *J* = 2.8, 4.4, 18.4 Hz, 1H), 2.93 (d, *J* =15.2 Hz, 1H), 3.61 (t, *J* =6.4 Hz, 2H), 3.66 (d, *J* = 6.8 Hz, 2H), 3.80 (s, 6H), 4.03 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 9.2 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0,17.5, 19.5, 19.6, 20.3, 24.4, 25.9, 27.1, 40.9, 41.1, 42.6, 43.3, 48.0, 49.6, 53.3, 53.4, 58.4, 58.8, 62.1, 120.8, 128.1, 129.0, 132.2, 132.3, 132.5, 133.5, 135.3, 137.2, 139.5, 140.3, 140.6, 147.3, 153.9, 157.2, 169.4, 172.2, 172.8; IR (neat) cm^{-1} 3474w, 2967m, 2893m, 23841w, 2340w, 1737s, 1686m, 1578w, 1481m, 1433s, 1398m, 1374m, 1355m; mass spectrum (APCI): m/e (% relative intensity) 695 (40) $(M+H)^+$, 694 (100), 481 (20), 480 (90), 422 (20), 231(20); HRMS (ESI, m/e) calcd for $C_{37}H_{45}NNaO_{10}S$, 718.2657, found 718.2643.

4.1.4. Synthesis of a Chiral Amino Biaryl Ligand

Ynamide 35: R_f = 0.58 [50% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.72 (s, 3H), 4.88 (s, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.36–7.41 (m, 6H), 7.41–7.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 53.7, 56.0, 70.4, 71.8, 76.6, 86.0, 108.0, 111.9, 121.8, 127.7, 128.7, 128.9, 139.7, 142.1, 155.3, 160.5 [missing eight carbons due to symmetry and overlap]; IR (film) cm^{-1} 2969w, 2900w, 2839w, 2360w, 2248m, 1777w, 1716s, 1472s; mass spectrum (APCI): m/e (% relative intensity) 384 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{38}H_{47}NO_{10}S$ 383.1516, found 383.1505.

Chiral Biaryl 37-*M,p*: R_f = 0.39 [60% EtOAc in hexanes]; pale solid; mp 103–106 °C; $[\alpha]_D^{20}$ = − 21.6 (*c* 0.98, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.42 (s, 3H), 1.64 (s, 3H), 3.78 (s, 3H), 4.40 (d, *J* = 8.4 Hz, 1H), 4.95 (ABqd, Δν = 29.9, *J* = 12.4, 2.2 Hz, 2H), 5.10 (ABqd, Δν = 37.2, *J* = 12.8, 1.6 Hz, 2H), 5.20 (d, *J* = 8.4 Hz, 1H), 6.19 (d, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 3H), 7.05 (t, *J* = 8.0 Hz, 1H), 7.23–7.27 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 17.03, 20.0, 55.9, 71.2, 74.4, 74.6, 77.0, 107.8, 123.1, 126.5, 126.7, 127.1, 128.07, 128.15, 128.4, 128.6, 128.7, 129.8, 130.9, 135.9, 137.4, 137.9, 138.6, 138.7, 139.2, 144.0, 157.7, 158.0 [missing four carbons due to symmetry]; IR (film) cm^{-1} 3058w, 2840w, 2360w, 1760s, 1579w, 1469m, 1262m, 1069m, 908w; mass spectrum (APCI): m/e (% relative intensity) 506 (100) $(M + H)^+$; HRMS (ESI, m/e) calcd for $C_{33}H_{31}NO_4$ 505.2253, found 505.2250; HPLC (95:5 hexane/2-propanol): t_r = major 27.5 min, and minor 26.4 min.

Chiral Biaryl 38-*P,p*: R_f = 0.62 [60% EtOAc in hexanes]; thick oil; $[\alpha]_D^{20}$ = + 74.5 (*c* 0.98, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.62 (s, 3H), 2.19 (s, 3H), 2.92 (s, 3H), 4.31 (d, *J* = 8.0 Hz, 1H), 4.92 (ABq, Δν = 49.9, *J* = 12.2 Hz, 2H), 5.12 (ABq, Δν = 28.7, *J* = 12.5 Hz, 2H), 5.29 (d, *J* = 3.2 Hz, 1H), 5.31 (d, *J* = 4.0 Hz, 1H), 5.89 (d, *J* = 8.4 Hz, 1H), 6.43 (broad d, *J* = 7.2 Hz, 2H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 6.8 Hz, 1H), 7.01 (dt, *J* = 6.8, 0.8 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.34–7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 16.8, 20.2, 53.9, 71.0, 74.2, 74.5, 77.1, 107.7, 122.7, 125.4, 126.8, 127.0, 127.9, 128.2, 128.5, 128.7, 129.5, 129.9, 135.3, 136.4, 138.2, 138.9, 139.0, 139.2, 145.2, 156.7, 158.9 [missing four carbons due to symmetry and one carbon due to overlap]; IR (film) cm^{-1} 3058w, 2839w, 2360w, 2341w, 1753s, 1598w, 1492m, 1468m, 1301m; mass spectrum (APCI): m/e (% relative intensity) 506 (100) $(M + H)^+$; HRMS (ESI, m/z) calcd for $C_{33}H_{31}NO_4$ 505.2253, found 505.2257; HPLC (95:5 hexane/2-propanol): t_r = major 11.5 min, and minor 16.3 min.

Preparation of Chiral Amino-Biaryl 39-*M*: To a solution of chiral biaryl **37-*M, p*** [13.0 mg, 82% *ee*) in MeOH (3 mL) flushed with argon was added 10 mol% Pd/C (3.0 mg). The reaction mixture was flushed with H_2 gas and then stirred under a balloon of H_2 for 3 d. The resulting mixture was filtered though a short pad of Celite™ and solvent was removed under reduced pressure. The crude product was purified by preparative TLC (1:1 Hex/EtOAc) and 3.0 mg of the desired amino biaryl **39-*M*** was isolated (42% yield). **39-*M***: R_f = 0.55 [10% CH_2Cl_2/EtOAc]; $[\alpha]_D^{23}$ = +25.8° [c 0.0039 CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75 (s, 3H), 1.98 (s, 3H), 2.05 (s, 3H), 3.21–3.56 (bs, 1H), 3.66 (d, 1H, *J* = 3.0 Hz), 3.73 (s, 3H), 5.15 (d, 4H, *J* = 21.5 Hz), 6.87 (d, 1H, *J* = 10.5 Hz), 6.96 (d, *J* = 9.5 Hz), 7.25–7.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 16.5, 19.7, 29.9, 56.1, 74.4, 74.4, 108.8, 112.7, 114.1, 122.5, 123.1, 125.9, 127.5, 127.8, 128.8, 137.6, 139.3, 141.5, 141.7, 157.7; IR (neat) cm^{-1} 2918s, 2849s, 2361m, 2340w, 1732w, 1618w, 1578w, 1467s, 1367m; mass spectrum (APCI): m/e (% relative intensity) 352 (100) $(M+H)^+$, 285 (20), 284 (100).

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24. For a review on synthesis of ynamides, see: Tracey, MR.; Hsung, RP.; Antoline, JA.; Kurtz, KCM.; Shen, L.; Slafer, BW.; Zhang, Y. Science of Synthesis, Houben-Weyl Methods of Molecular Transformations. Steve, M Weinreb, editor. Stuttgart, Germany: Georg Thieme Verlag KG; 2005. Chapter 21.4
25. For synthesis of ynamides through Ullmann-type coupling, see: (a) Zhang Y, Hsung RP, Tracey MR, Kurtz KCM, Vera EL. Org Lett 2004;6:1151. [PubMed: 15040745] (b) Dunetz JR, Danheiser RL. Org Lett 2003;5:4011. [PubMed: 14535766] (c) Frederick MO, Mulder JA, Tracey MR, Hsung RP, Huang J, Kurtz KCM, Shen L, Douglas CJ. J Am Chem Soc 2003;125:2368. [PubMed: 12603105] (d) Zhang X, Zhang Y, Huang J, Hsung RP, Kurtz KCM, Oppenheimer J, Petersen ME, Sagamanova IK, Tracey MR. J Org Chem 2006;71:4170. [PubMed: 16709057] (e) Sagamanova IK, Kurtz KCM, Hsung RP. Organic Syn 2007;84:359. (f) Kohnen AL, Dunetz JR, Danheiser RL. Organic Syn 2007;84:88. (g) Riddell N, Villeneuve K, Tam W. Org Lett 2005;7:3681. [PubMed: 16092849]
26. For a recent oxidative cross-coupling, see: Hamada T, Ye X, Stahl SS. J Am Chem Soc 2008;130:833. [PubMed: 18166058]
27. Throughout the paper, the capital *M* and *P* denote C-C axial chirality while small *m and p* denote C-N-axial chirality and are listed second.
28. CCDC for compounds 32-*M*,*p*, 18-*P*,*p* and 34-*M*,*p* are 665008, 665009 & 722530, respectively. CCDC 665008, 665009 and 722530 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallopgraphic Data Centre viawww.ccdc.cam.ac.uk/data_request.cif.

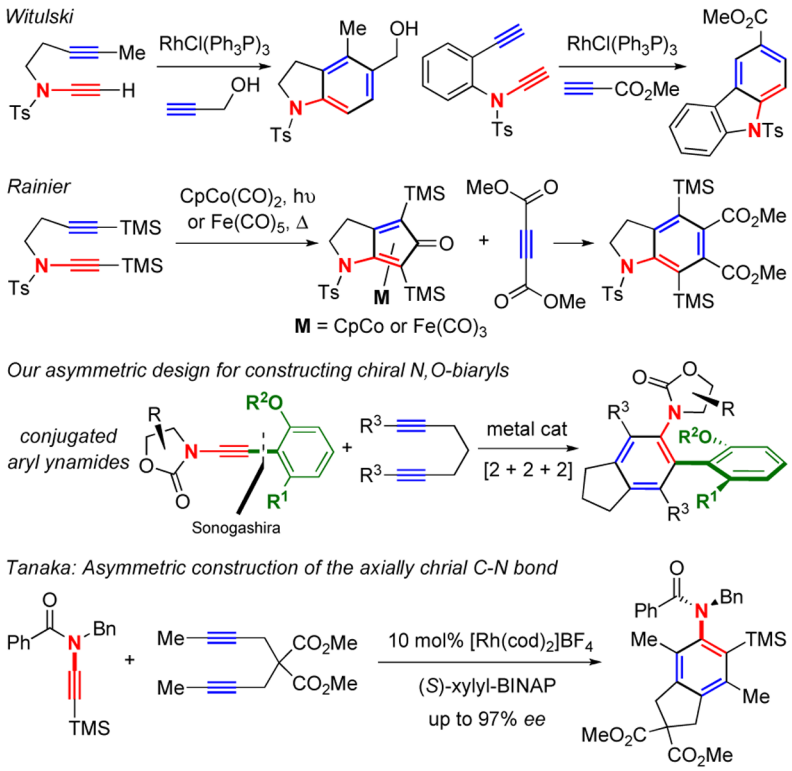


Figure 1.
Ynamide-[2 + 2 + 2] Cycloadditions.

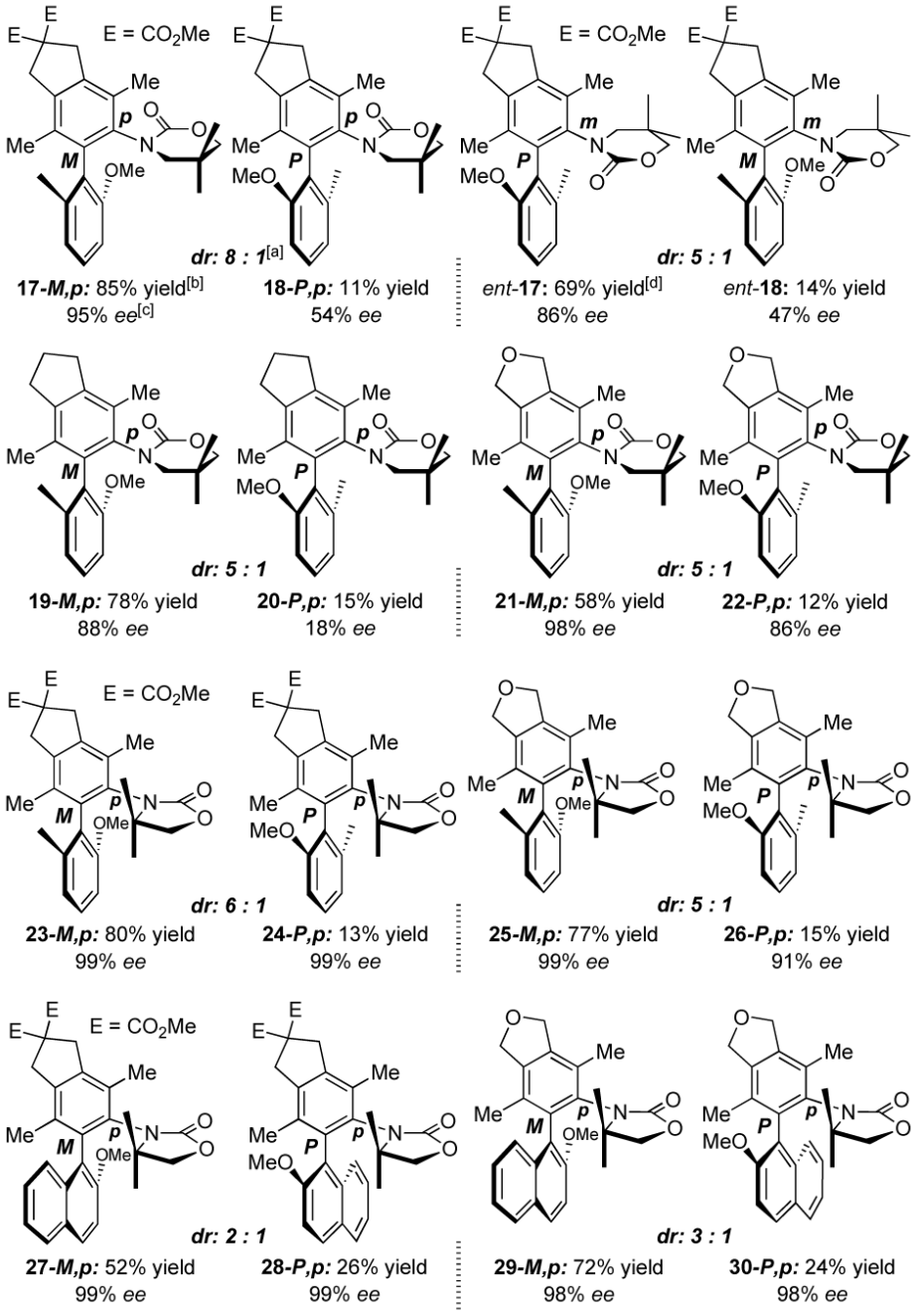


Figure 2. Scope of Asymmetric Ynamide-[2 + 2 + 2] Cycloadditions

[a] The *dr* was determined using $^{1}H/^{13}C$ NMR. **[b]** Isolated yields. **[c]** The *ee* was determined using chiral HPLC [CHIRALCEL OD-H; Size: 250 × 4.6 mm]; eluent: *i*-PrOH in hexanes. **[d]***(R)*-Xylyl-BINAP was used.

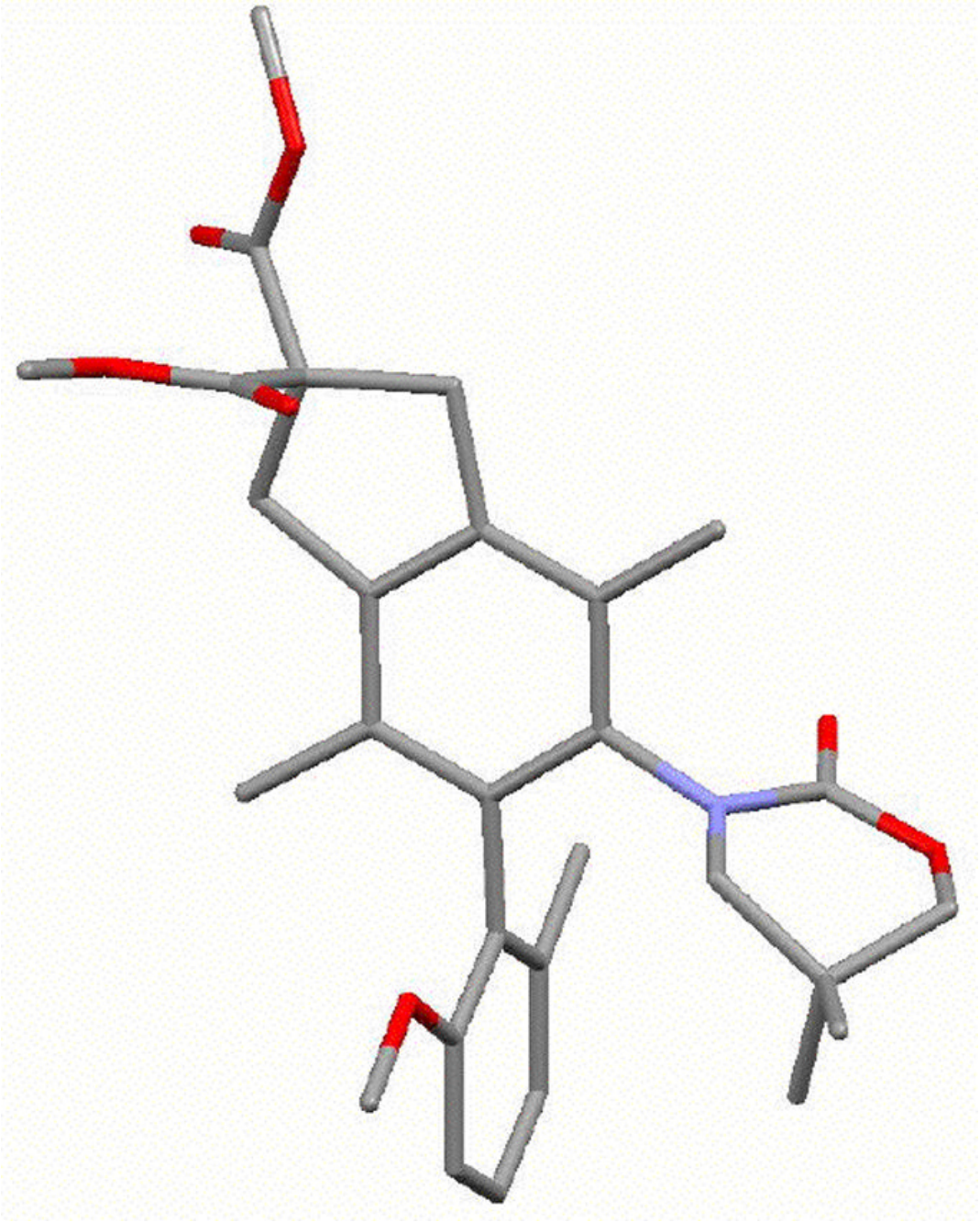


Figure 3.
X-Ray Structures Minor Atropisomer **18-P,p**.

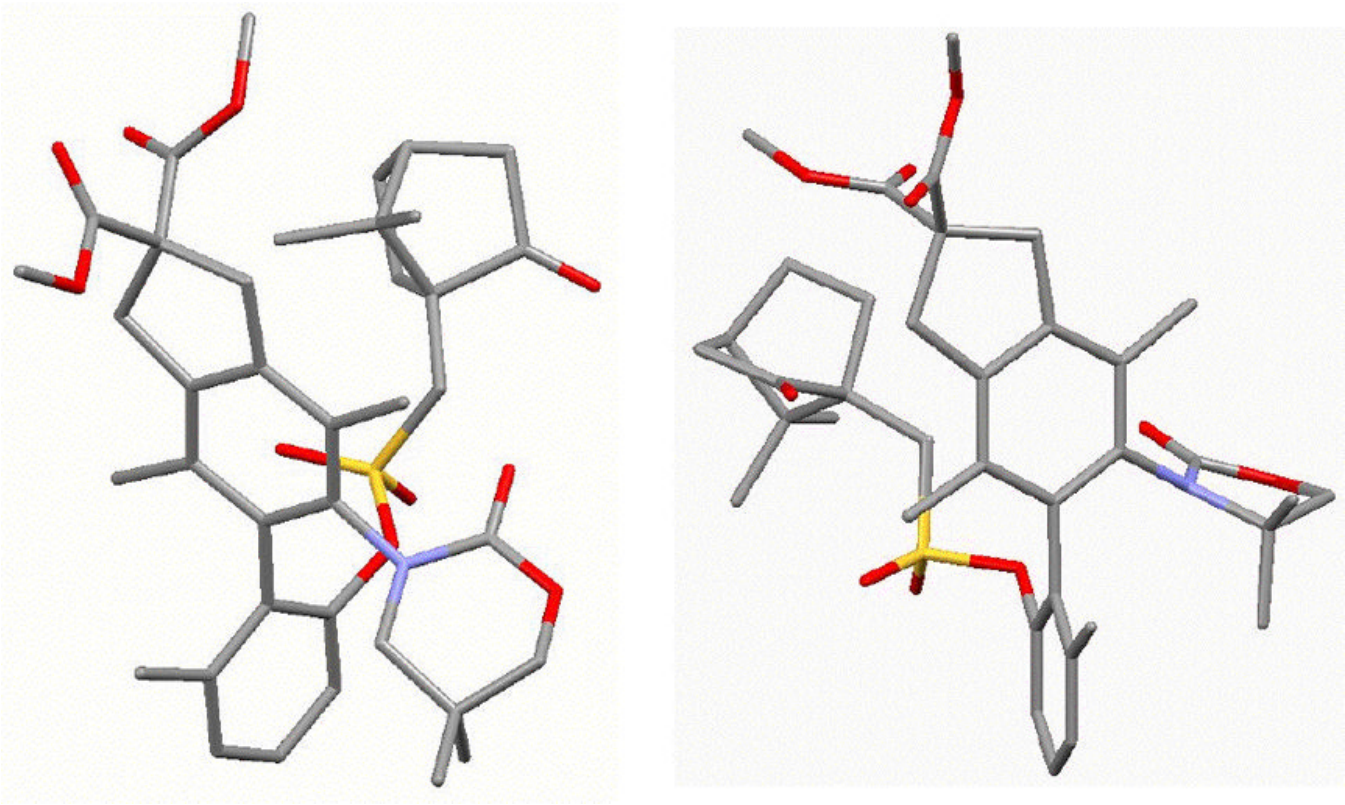
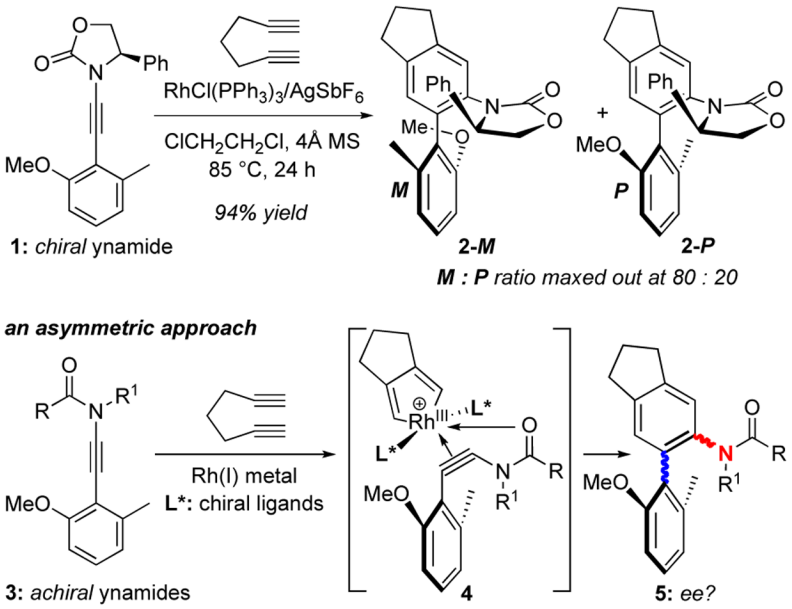
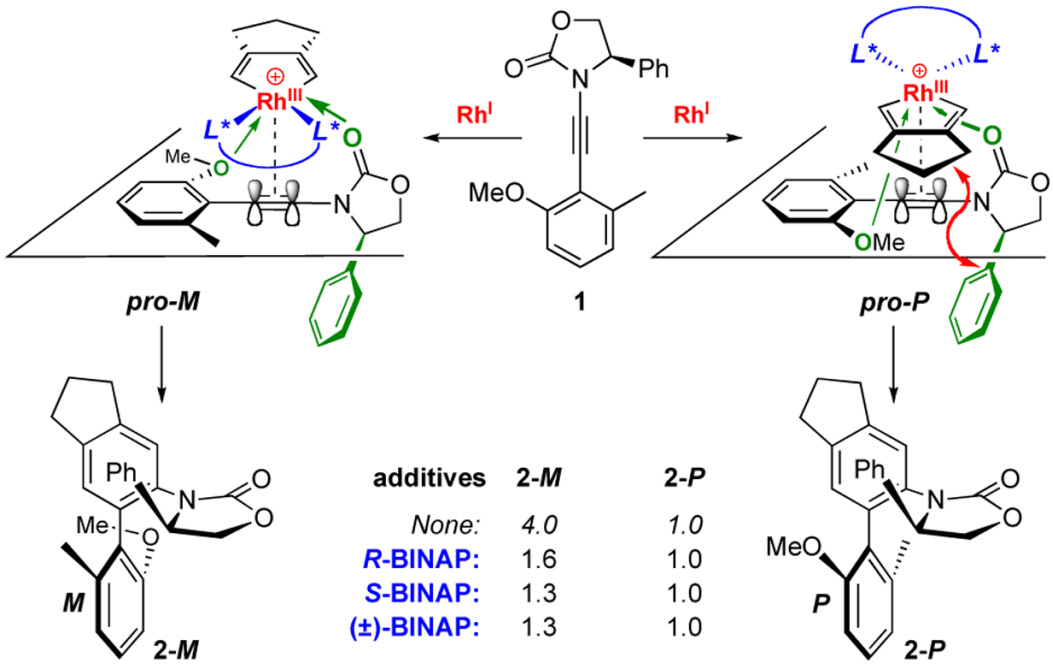


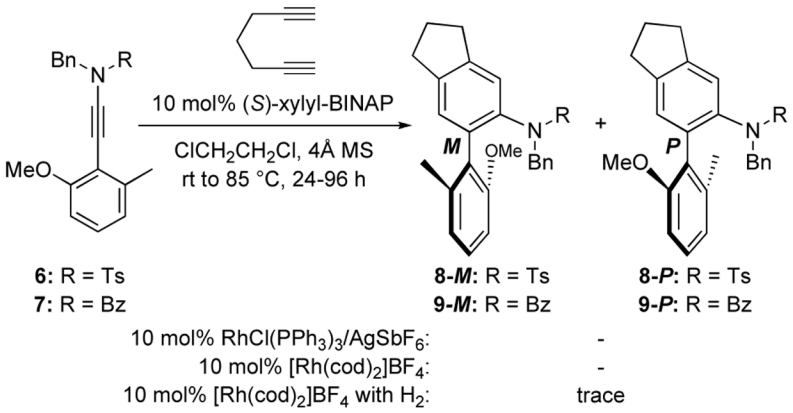
Figure 4.
X-Ray Structures: **18-P,p 32-M,p** [left] and **34-M,p** [right].



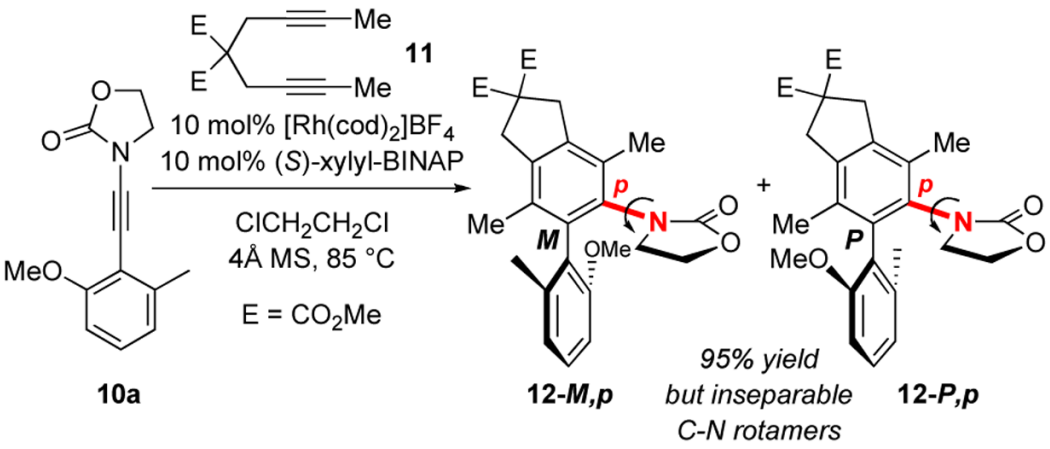
Scheme 1.
An Asymmetric Ynamide-[2 + 2 + 2] Cycloaddition.



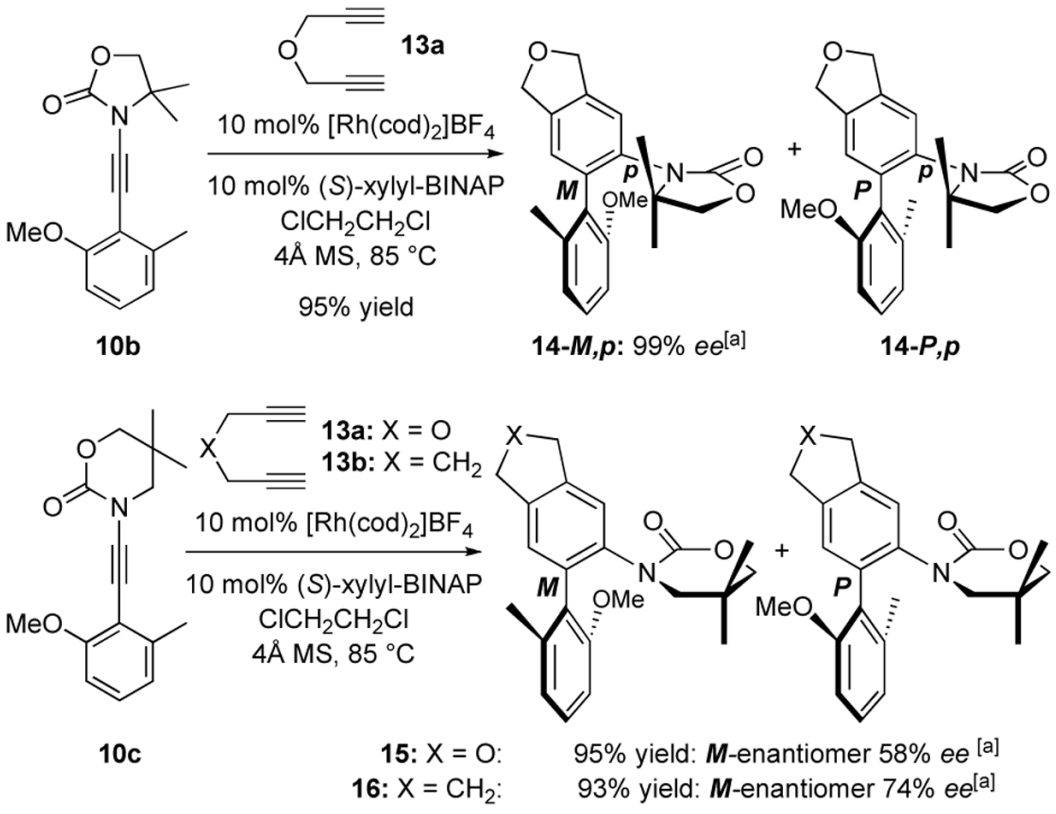
Scheme 2.
Recognition of An External Ligand Controlled Process.



Scheme 3.
Cycloadditions of Ynamides with an Acyclic Amido-Motif.

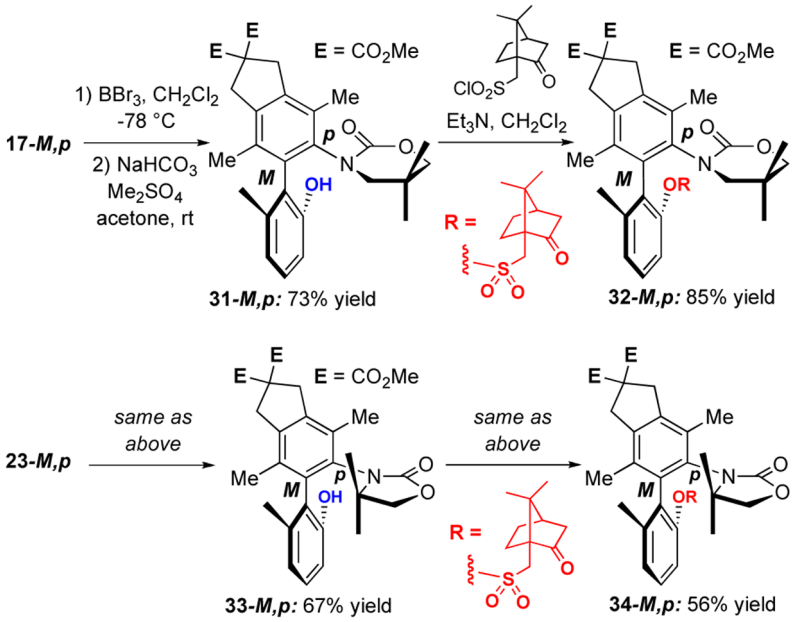


Scheme 4.
Cycloadditions of Ynamides with a Cyclic Amido-Motif.

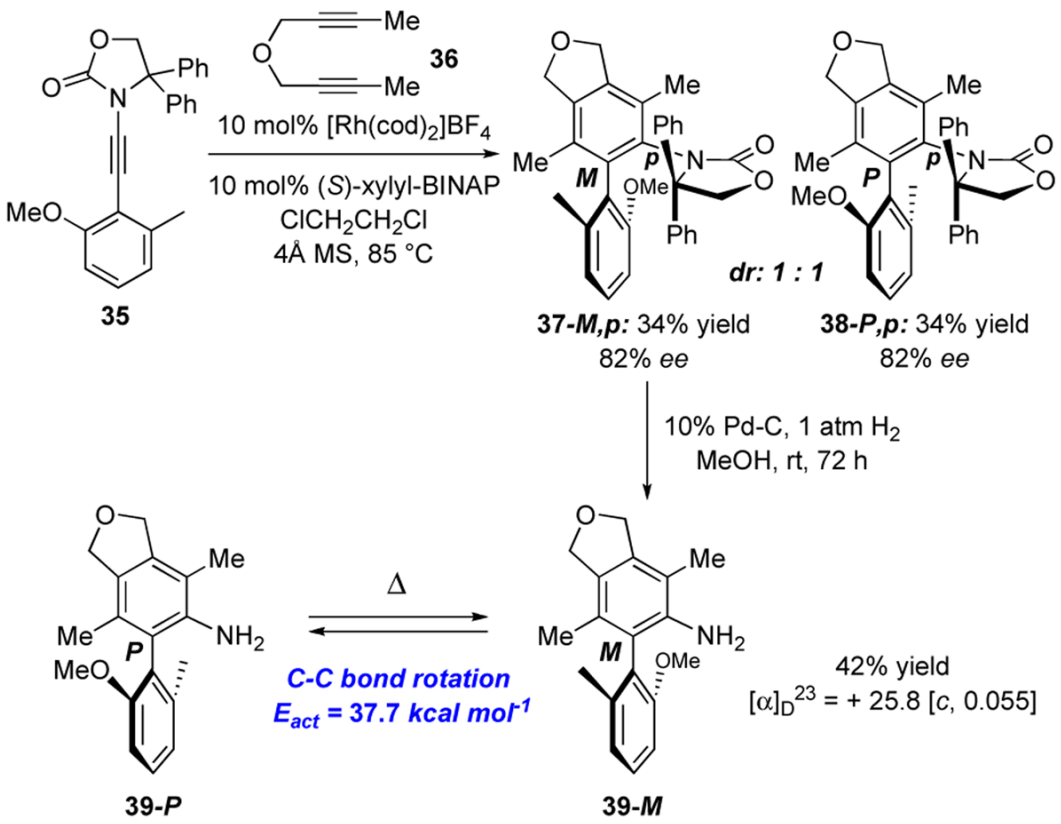


Scheme 5.

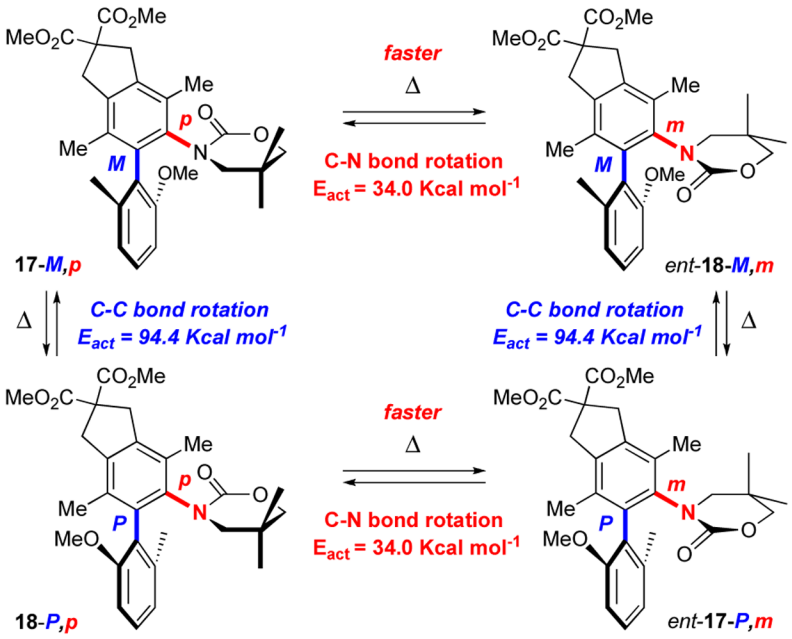
An Asymmetric Ynamide-[2 + 2 + 2] Cycloaddition.
[a] The *ee* was determined using chiral HPLC [CHIRALCEL OD-H; Size: 250 × 4.6mm (L × I.D.); eluent: *i*-PrOH in hexanes].



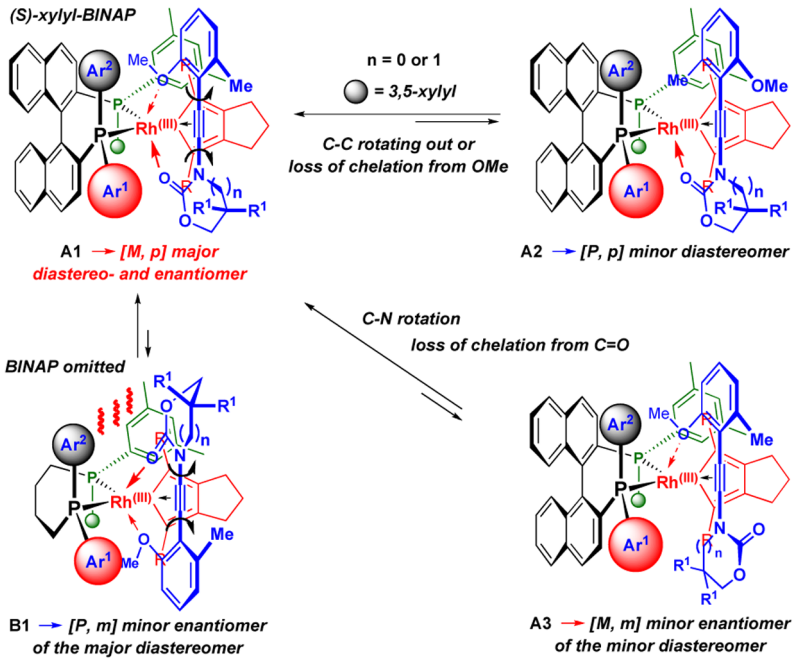
Scheme 6.
Syntheses of **32-M,p** and **34-M,p**.



Scheme 7.
Synthesis of Chiral Amino-Biaryl **38-M.**



Scheme 8.
Thermal Equilibration and Rotational Barriers.



Scheme 9.
A Proposed Asymmetric Model.

Table 1

Heating of Pure **17-M,p** Diastereomer

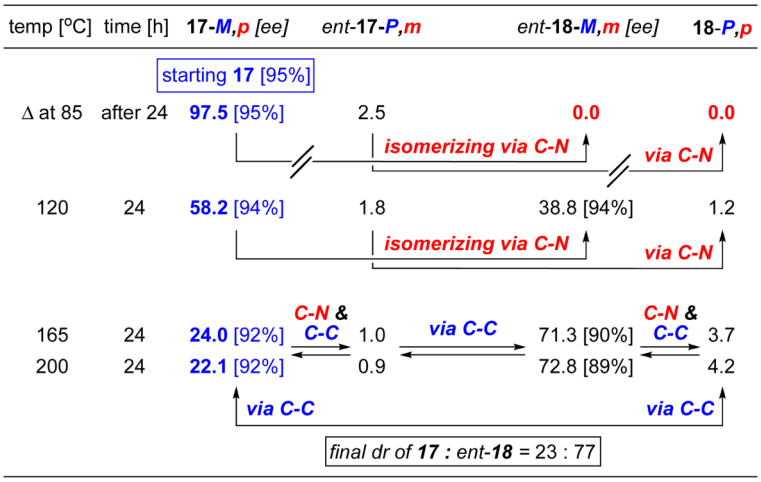


Table 2

Heating of Pure ent-**17-P,m** and **18-P,p** Diastereomers.

temp [°C]	time [h]	**17-*M,p***	*ent*-**17-*P,m*** [ee]	*ent*-**18-*M,m***	**18**-***P,p*** [ee]
			starting ***ent*-17** [86%]		
Δ at 85	after 24	7.0	**93.0** [86%]	**0.0**	**0.0**
				C-N ↑	***C-N*** ↑
120	24	1.8	**24.2** [86%]	5.2	68.8 [86%]
				C-N ↑	***C-N*** ↑
			*free rotations at both **C-N** and **C-C***		
165	24	1.8	**21.2** [84%]	7.7	69.3 [80%]
			*final dr of ent-**17 : 18*** = 23 : 77		
					18 [52%]
			*free rotations at both **C-N** and **C-C***		
Δ at 165	after 24	6.2	15.8 [44%]	20.3	**57.7** [48%]
200	8	6.7	15.3 [39%]	21.8	**56.2** [44%]
			*final dr of ent-**17 : 18*** = 22 : 78		