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Stereochemical Control of Both C–C and C–N Axial Chirality in the Synthesis of Chiral *N,O*-Biaryls

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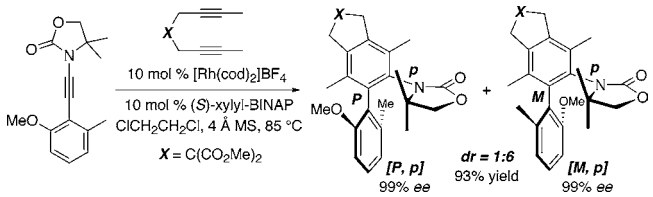
ABSTRACT



A Rh(I)-catalyzed asymmetric [2 + 2 + 2] cycloaddition of achiral ynamides is described here. This work demonstrates a unique concept of stereochemical control of both the C–C and C–N axial chirality and provides an approach to the synthesis of chiral *N,O*-biaryls as well as chiral anilides.

Ynamides have been featured in a diverse array of synthetic methodologies in the recent years.[1,2] Our interest in ynamides[3] and in the synthesis of chiral biaryls[4−6] led us to investigate [2 + 2 + 2] cycloadditions employing ynamides[7] for which the concept had been elegantly demonstrated by Witulski[8] in the synthesis of indoles and carbazoles. In our work,[9] we focused on the biaryl synthesis via a Rh(I)-catalyzed [2 + 2 +2] cycloaddition of diynes with chiral ynamides **1**. Our efforts were overall thwarted, for we could not supersede the modest diastereoselectivity in favor of the *M*-atropisomer **2-*M*** (Scheme 1). However, the failure in achieving high diastereoselectivity through a chiral auxiliary-based approach prompted us to explore asymmetric approaches via external chiral ligands. Recently, Tanaka et al.[10] disclosed their beautiful work on asymmetric [2 + 2 + 2] cycloadditions of ynamides en route to chiral anilides

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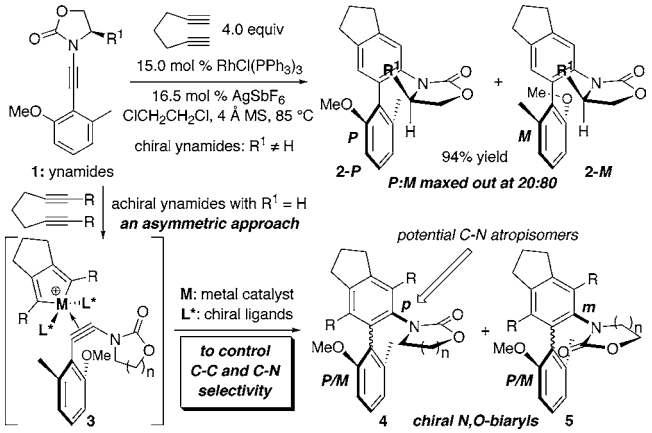
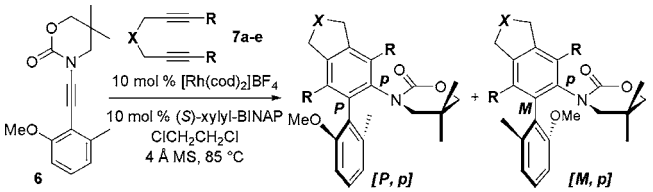
Scheme 1. Asymmetric Ynamide [2 + 2 + 2] Cycloaddition



containing the axial C−N chirality.[11,12] Tanaka's work provided further significance for our ongoing endeavor because we recognized a unique opportunity to control both the C−C and C−N axial chirality via intermediate **3** en route to useful chiral *N*,*O*-biaryls **4** and/or **5**.[4,13] We communicate here an enantio- and diastereoselective [2 + 2 + 2] cycloaddition of ynamides.

We were able to quickly establish a suitable protocol for asymmetric [2 + 2 + 2] cycloadditions of ynamides. As summarized in Table 1, by using optimized conditions[14]

Table 1. Feasibility of an Asymmetric Ynamide-[2 + 2 + 2]



entry	Diynes: **X** = ; **R** =	yield [%][a]	*[P, p]* & *[M, p]*	*dr*[b]	*ee:* ***[P, p]*** [a]	*ee:* ***[M, p]*** [a]
1	**7a**: $C(CO_2Me)_2$; Me	96	**8** & **9**	1:8	54	95
2	**7a**: $C(CO_2Me)_2$; Me	83	***ent*-8** & ***ent*-9**	1:5[c]	47 ***[M, m]***	86 ***[P, m]***
3	**7b**: CH_2; Me	93	**10** & **11**	1:5	18	88
4	**7c**: CH_2; H	93	**12**	--[d]	--	74 ***[M]***
5	**7d**: O; Me	70	**13** & **14**	1:5	86	98
6	**7e**: O; H	95	**15**	--[d]	--	58 ***[M]***

[a] Isolated yields. [b] The dr was determined using $^1H/^{13}C$ NMR, and the ee was determined using chiral HPLC [CHIRALCEL OD-H; Size: 250 × 4.6 mm]; eluent: *i*-PrOH in hexanes. [c] (*R*)-Xylyl-BINAP was used. [d] There are no C−N atropisomers. A single diastereomer was seen in the ^1H NMR with broadening of peaks due to free rotation through C−N bond.

involving 10 mol % of $[Rh(cod)_2]BF_4$ and 10 mol % of (*S*)-xylyl-BINAP in 1,2-dichloroethane at 85 °C, cycloadditions of achiral ynamide **6**,[15] containing a 6-membered 2-oxazinone ring, with diynes **7a**−**e** led to respective desired chiral *N*,*O*-biaryls **8**−**15** in good yields. Notably, we observed a diastereoselectivity of 1:8 in favor of atropisomer **9**, which possesses an enantiomeric excess of 95% (entry 1), while the minor isomer **8** possessed 54% ee. The usage of (*R*)-xylyl-BINAP led to *ent*-**8** and *ent*-**9** but in lower ee and dr (entry 2). Analogous outcomes were obtained when diynes **7b** and **7d** (entries 3 and 5) were employed, although in the latter case the ee was much higher for atropisomer **13**. Reactions of diynes **7c** and **7e** (entries 4 and 6) afforded *N*,*O*-biaryls **12** and **15**, respectively, as a single diastereomer due to free C−N bond rotation.

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(14) We screened various conditions that included the usage of $Rh(PPh_3)_3$-Cl with $AgSbF_6$, $[Rh(cod)Cl]_2$ with $AgSbF_6$, or $[Rh(cod)_2]BF_4$ activated with H_2. They led to lower yields and/or ee's.

(15) See the Supporting Information. General procedure: To a solution of $[Rh(cod)_2]BF_4$ (10 mol %) and (*S*)-xylyl-BINAP (10 mol %) in anhyd 1,2-dichloroethane (5.0 mM) was added 4 Å 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 the crude ^1H NMR, and the enantiomeric excess of each diastereomer was determined via chiral HPLC [CHIRALCEL OD-H; 250 × 4.6 mm (*l* × i.d.); eluent: *i*-PrOH in hexanes].

The absolute stereochemistry of **9** was assigned as *[M,p]*[16] via an X-ray structure (Figure 1) of its camphor−sulfonyl

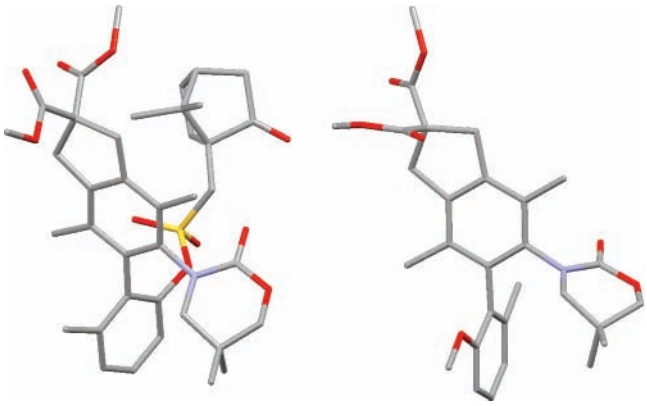
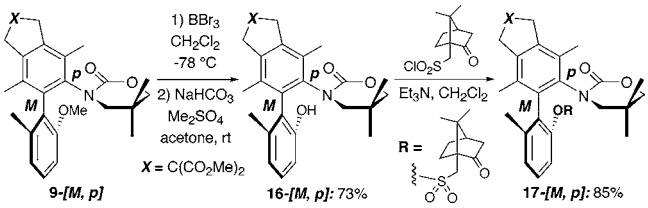


Figure 1. X-ray structures for **17-[*M,p*]** (left) and **8-[*P,p*]** (right).

derivative **17** (Scheme 2). The X-ray structure (Figure 1) resolved the relative stereochemistry in **8** with its absolute

Scheme 2. Synthesis of **17-[*M, p*]**



stereochemistry for the major enantiomer being deduced as *[P,p]* in the epimerization study described below. Correlations of aromatic protons on the anisyl ring allow for the assignment of all other isomeric *N,O*-biaryls.

Given the unique structural feature in these *N,O*-biaryls, we pursued computation and equilibration studies. Spartan B3LYP/6-31G* calculations revealed a $\Delta E = 1.11$ kcal mol^{-1} in favor of biaryl **8**, thereby implying that the selectivity for **9** is kinetic. Equilibration of pure biaryl **9**-*[M,p]* supports such assertion (Table 2). Heating **9** at 85 °C in toluene-d_8 for 24 h (the actual reaction conditions) did not result in any epimerization or loss of optical integrity (entry 1), at temperatures of 120 °C and above, epimerization occurred with ratio gravitating toward 23:77 in favor of *ent*-**8** (entries 2−4).

Interestingly, we observed high ee for the isolated *ent*-**8**, thereby implying that only one of the two axial centers was scrambling. B3LYP/6-31G* calculations suggest that the C−N rotates first and not the C−C bond, as evident with E_{act} being 34.0 kcal mol^{-1} and E_{act} 94.4 kcal mol^{-1}, respectively, for C−N and C−C bonds. Only after extended

(16) 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.

Table 2. Equilibration Studies

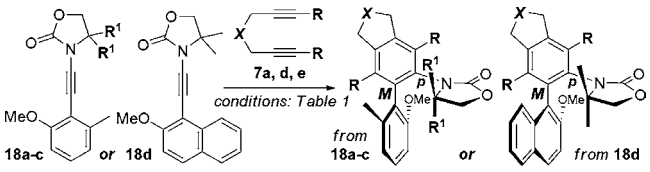
entry	temp [°C]	time [h]	dr[a] of **9** : **8**	ee:[a] **9**-*[M, p]*	*ent*-**8**-*[M, m]*	*ent*-**9**-*[P, m]*	**8**-*[P, p]*
pure **9** [95% *ee*] $\xrightarrow{\Delta}$ *ent*-**8**				C-N: E_{act} = 34.0 Kcal mol^{-1}			
1	85	24	100:0	95	--		
2	120	24	60:40	94	94		
3	165	24	25:75	C-C { 92	90	} E_{act} = 94.4 Kcal mol^{-1}	
4	200	24	23:77	92	89		
pure ent-**9** [86% *ee*] $\xrightarrow{\Delta}$ **8**							
5	85	24	100:0			86	--
6	120	24	26:74			86	86
7	165	24	23:77		C-C	84	80
pure **8** [52% *ee*] $\xrightarrow{\Delta}$ *ent*-**9**							
8	120	21	0:100			--	52
9	165	24	22:78	*slower equilibration*	C-C	44	48
10	200	8	22:78			39	44

[a] The final dr was determined using NMR. The final ee for recovered starting and equilibrated isomers were determined using chiral HPLC.

heating at 165 or 200 °C (Table 2, entries 3 and 4) did we observe some loss of ee, thereby suggesting a concomitant epimerization of the C−C axial chirality. While equilibrations of pure *ent*-**9**-*[P,m]* yielded similar outcome (entries 5−7), equilibrations of **8**-*[P,p]* were found to be relatively slower in leading to *ent*-**9**, but the final ratio of **9**:**8** (entry 10) still reflects the calculated ΔE. These equilibrations studies demonstrate the ability to access all four possible isomers.

We next examined ynamides **18a**−**d**, containing 5-membered 2-oxazolidinones. Ynamide **18a** with a simple 2-oxazolidinone led to biaryls **19** in high yield as separable but rapid interconverting atropisomers,[17] and thus, its stereochemistry was unassigned (Table 3, entry 1). Reactions of

Table 3. Syntheses of Chiral *N,O*-Biaryls



entry	ynamide	R^1	diyne	*X* = ; R = ;	*[P, p]* & *[M, p]*	yield [%][a]	dr[b]	ee: *[P, p]* [b]	*[M, p]*
1	**18a**	H	**7a**	$C(CO_2Me)_2$; Me	**19**	95	--[c]	--	--
2	**18b**	Me	**7e**	O; H	**20**	95	--[d]	--	99 *[M]*
3	**18b**	Me	**7a**	$C(CO_2Me)_2$; Me	**21** & **22**	93	1:6	99	99
4	**18b**	Me	**7d**	O; Me	**23** & **24**	92	1:5	91	99
5	**18d**	--	**7a**	$C(CO_2Me)_2$; Me	**25** & **26**	78	1:2	99	99
6	**18d**	--	**7d**	O; Me	**27** & **28**	96	1:3	98	98
7	**18c**	Ph	**7d**	O; Me	**29** & **30**	68	1:1	82	82

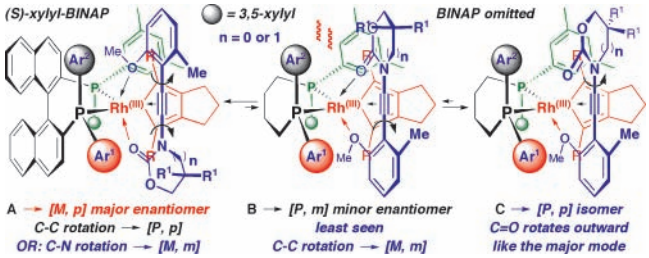
[a] Isolated yields. [b] The dr was determined using ^{1}H/^{13}C NMR, and the ee was determined using chiral HPLC. [c] Biaryl **19** contained separable but interconverting C−N atropisomers. In this case, the dr and ee were not determined. [d] C−N atropisomers were not separable and were seen only on the ^{1}H NMR time scale.

ynamides **18b** and **18d**, containing a *gem*-dimethyl group, provided respective *[P,p]* and *[M,p]* diastereomers with high levels of enantioselectivity (entries 2−6), although diastereoselectivity was better in the former example. Interestingly, the diastereoselectivity tapered off when using ynamides **18c** with a *gem*-diphenyl group substituted 2-oxazolidinone (entry 7).

Given the stereochemical outcome, we proposed a mechanistic model that could lend a unified rationale for the

observed asymmetric inductions. As shown in Scheme 3,

Scheme 3. Unified Mechanistic Model



with the rhodio-cyclopentadiene intermediate complexed to (*S*)-xylyl-BINAP, a respective ynamide could approach the metal as shown in complex **A** with the anisole ring sliding into the less hindered space adjacent to Ar-1 while a smaller amido group assuming the relatively more crowded space next to Ar-2. In this manner, a key bidentate chelation of the Rh metal via both the anisyl OMe and the carbonyl group could occur, and the ensuing cycloaddition would lead to the major *[M,p]*-stereoisomer. If the bidentate chelation fails due to the loss of the coordination through C−C or C−N bond rotation, one would obtain the minor diastereomer *[P,p]* or *[M,m]*. Since the carbonyl oxygen chelates better than a phenolic ethereal oxygen, it is reasonable to observe *[P,p]* as the major enantiomer.

While analyzing complex **A** alone could be sufficient, given the high *M*-selectivity in the absence of C−N atropisomerism and the high enantioselectivity for *[P,p]* (Table 3), we believe the minor isomer is likely derived from complex **C**. If the ynamide would approach the metal in an opposite manner as in **A**, complexes-**B** and **C** are the possible. While complex **B** can contribute to the minor *[P.m]*-enantiomer, the coordination of the carbonyl group could suffer from interaction between Ar-2 and R^1, which would result in the more favorable mono-coordinated shown as complex-**C**. Cycloaddition via complex **C** would then give the *[P,p]*-enantiomer.

This assessment is also consistent with the observation of loss in the dr when R^1 is large such as in entry 7 of Table 3. The preference for the ynamide approach shown in **A** could suffer if the size of the amido is increased, and complex **B** and/or **C** could play a larger role, leading to erosions in both dr and ee. Further work in examining either alternative chiral ligand systems or those related to BINAP should yield further insight to this model when correlated the stereochemical outcome, and we are currently pursuing these studies. 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.[18]

We have described here a Rh(I)-catalyzed asymmetric [2 + 2 + 2] cycloaddition of achiral ynamides to concisely demonstrate the ability to stereochemically control both the C−C and C−N axial chirality. Our work provides a useful synthetic approach to chiral *N*,*O*-biaryls and chiral anilides.

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Supporting Information Available: Experimental and ^{1}H NMR spectral and characterizations for all new compounds as well as X-ray structrural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Upon a clean and facile separation on silica gel flash column chromatography, and after removal of the solvent under reduced pressure without heating, the two atropisomers of **19** have already scrambled based on NMR analysis. This prevented us from obtaining any meaningful ratios.

(18) For elegant examples of achiral template based asymmetric catalysis, see: (a) Sibi, M. P.; Soeta, T. *J. Am. Chem. Soc.* **2007**, *129*, 4522. (b) Sibi, M. P.; Stanley, L. M.; Nie, X.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2007**, *129*, 395. (c) Sibi, M. P.; Manyem, S.; Palencia, H. *J. Am. Chem. Soc.* **2006**, *128*, 13660. (d) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8277. (e) Sibi, M. P.; Zhang, R.; Manyem. S. *J. Am. Chem. Soc.* **2003**, *125*, 9306.