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Rhodium(I)-Catalyzed [2 + 2 + 2] Cycloadditions of Ynamides in the Synthesis of Amide-Substituted Chiral Biaryls

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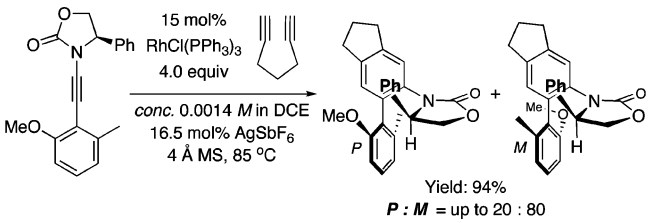

Rhodium(I)-catalyzed [2 + 2 + 2] cycloadditions of sterically encumbered aryl-substituted ynamides with various diynes are described here. These cycloadditions provide the synthesis of an array of new chiral amide-substituted biaryls that can be useful in future chiral ligand designs.

[2 + 2 + 2] Cycloadditions and related annulations represent powerful synthetic methods for constructing aromatic and heteroaromatic systems.[1−3] Ynamides have emerged as a highly versatile organic building block that has been featured in a diverse array of new methodologies.[4−9] These synthetic methods include Witulski's elegant work[10,11] on [2 + 2 + 2] cycloadditions in which the ynamide motif is strategically situated as part of diynes that would lead to the constructions of indoles and carbazoles. Very recently, Tanaka[12] disclosed their beautiful work on asymmetric [2 + 2 + 2] cycloadditions of ynamides en route to anilides containing the axial C−N chirality.[13] However, [2 + 2 + 2] cycloadditions employing chiral ynamides **1** en route to the synthesis of chiral biaryls **3p** and/or **3m**, as shown in Scheme 1, has not been reported. This particular cycloaddition implies a potential chirality transfer from central chirality to axial chirality.[14] Although both *P* and *M* isomers can be obtained, they are equally interesting in that they both possess a potentially useful chiral anilide motif.[13] The major

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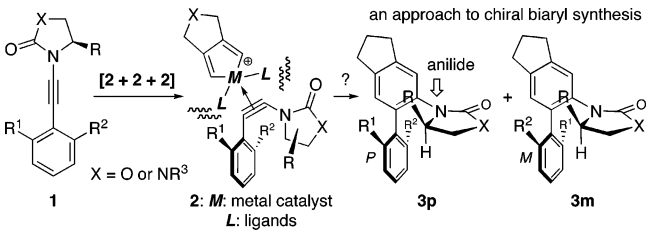
SCHEME 1. [2 + 2 + 2] Cycloadditions of Aryl-Substituted Ynamides



challenge of this endeavor likely resides in the congested nature of chiral aryl-substituted ynamides **1**, which could very well preclude us from establishing its feasibility as an approach for chiral biaryl synthesis. We report here our success with [2 + 2 + 2] cycloadditions of chiral ynamides in the synthesis of amide-substituted chiral biaryls.

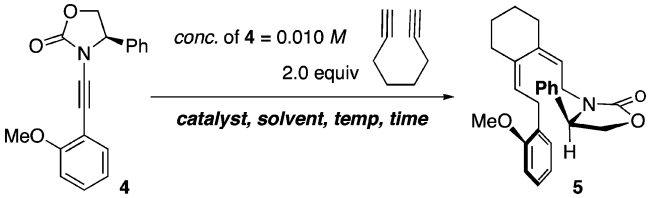
To demonstrate the feasibility, we prepared aryl ynamide **4** containing the Ph-substituted Evans' auxiliary[15] and examined its cycloaddition with 1,7-octadiyne via screening of a series of metal catalysts and solvents. To expedite the screening process, we mostly focused on the conversions without isolating the actual products. These studies are as summarized in Table 1. In short, Wilkinson's catalyst appears to be the best catalyst leading to biaryl **5**[16] in good conversion at 100 °C in 1,2-dichloroethane (entries 7 and 8). Despite the poor yield range [10−40%, which implies that conversion included decomposition of ynamide **5** under the reaction conditions], we were encouraged with the possibility and continued to optimize the reaction conditions via ynamide **6** with a sterically less encumbered Bn group.

As highlighted in Table 2, it was quickly evident that there is a counteranion effect in which the presence of additives such as $AgSbF_6$ at 16.5 mol % could improve the efficiency of the cycloaddition (entries 9 and 10) and the reaction could be carried out at even lower temperature. More importantly, the usage of molecular sieves proved to be very critical in improving the yield (entry 9 versus 10), as the presence of H_2O led to facile demethylation.[17] Although the diastereomeric ratio is only 1:1, vigorous assignments of both biaryls **7p** and **7m** were unambiguously achieved using single-crystal X-ray structures.[16]

Having identified the optimized conditions as shown in entry 10 of Table 2, the [2 + 2 + 2] cycloaddition also proved to be general and was feasible for a range of diynes, leading to both *P* and *M* isomers of biaryls 8−10 in very good yields (Figure 1). It is also noteworthy that all of these *M* and *P* biaryl isomers are readily separable, and thus both antipodes of these chiral birayls are accessible through one reaction.

Having established the feasibility of the [2 + 2 + 2] cycloaddition reaction, we became intrigued with the stereorandomness of the reaction. As shown in Scheme 2, PM3 calculations via Spartan Model revealed a value of 29.5 Kcal mol^{-1} for the biaryl rotational barrier for **7**, and thermal equilibration experiments employing pure **7p** and **7m** would support such a high rotational barrier. Equilibration did not occur until the temperature well surpassed 120 °C, thereby suggesting

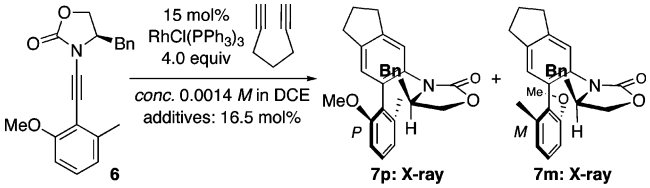
TABLE 1. Screening for a Suitable Metal Catalyst



entry	catalyst [mol %]	solvent	temp [°C]	time [h]	conv [%][a]	yield [%][b,c]
1	Pd_2dba_3 [5]	THF	100	8	52	ND
2	$Pd[PPh_3]_4$ [5]	THF	100	8	13	ND
3	$RuCl_2$ [5]	DCE[c]	100	22	11[d]	ND
4	$CoCp(CO)_2$ [10]	DME[c]	100	8	0	ND
5	$Ni(acac)_2$ [20]	THF	100	22	0	ND
6	$RhCl(PPh_3)_3$ [20]	DCE	100	22	67[d]	ND
7	$RhCl(PPh_3)_3$ [20][e]	DCE	100	22	79−86[d]	15−40
8	$RhCl(PPh_3)_3$ [20][f]	DCE	100	20	100	15−40
9	$RhCl(PPh_3)_3$ [50]	DCE	70	20	41	ND
10	$RhCl(PPh_3)_3$ [10]	DCE	70	20	46	ND
11	$RhCl(PPh_3)_3$ [5]	CH_2Cl_2	70	20	40	ND
12	$RhCl(PPh_3)_3$ [5]	THF	70	20	28	ND
13	$RhCl(PPh_3)_3$ [5]	PhMe	70	20	31	ND

[a] Determined by LCMS. [b] Isolated yields. [c] ND = not determined. DCE = 1,2-dichloroethane. DME = dimethoxyethane. [d] Also observed were HCl addition products (14−20%). [e] 5−10 equiv of diyne. [f] [**4**] = 0.017−0.068 M.

TABLE 2. Additives for Optimizations



entry	additives	temp [°C]	time [h]	conv[a]	yields [%]:[b]	7p	7m
1	None	25	16	13%		ND[c]	ND
2	None	85	3	20		ND	ND
3	AgOTf	25	16	24		ND	ND
4	AgOTf	85	3	68		ND	ND
5	$AgBF_4$	25	16	17		ND	ND
6	$AgPF_6$	25	16	36		ND	ND
7	$AgPF_6$	85	3	81	ratio 1 : 1	10	10
8	$AgSbF_6$	25	16	47		ND	ND
9	$AgSbF_6$	85	3	81		20	20
10	$AgSbF_6$	85[c]	16	100		48	48

[a] Determined by LCMS. [b] Isolated yields. [c] 4 Å MS were used, and concentration of **6** was 0.05 M.

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(16) See Supporting Information.

(17) We found benzofuran formation after demethylation.

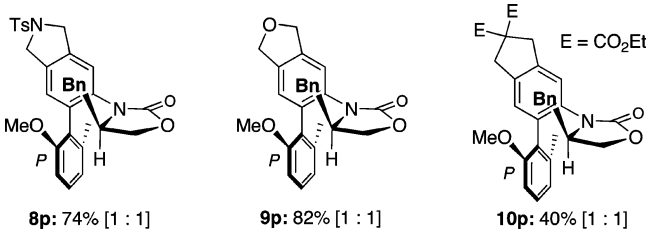
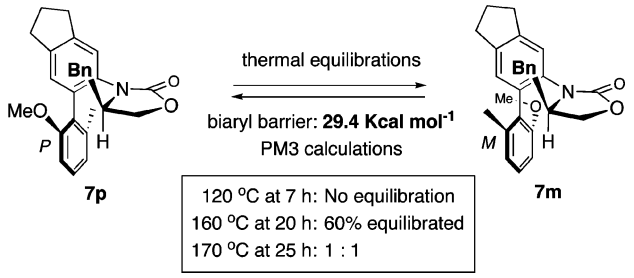


FIGURE 1. Stereodivergent synthesis of chiral biaryls.

SCHEME 2. Thermal Equilibrations of *P*- and *M*-Biaryl Isomers



that the lack of diastereoselectivity is likely not a result of equilibration under the reaction conditions.[18]

The auxiliary appears to have an influence on the diastereoselectivity. As shown in Figure 2, modest selectivity in favor of *M* axial-chirality could be achieved specifically using the Ph-substituted Evans auxiliary (see biaryls **12m**, **16m**, and **18m**) and the Close imidazolidinone-based auxiliary[19] (see **14m**, **17m**, and **19m**), whereas Sibi's auxiliary[20] and Boeckman's *aza*-camphor[21] did not seem to improve the ratio further (see biaryl **13** and **15**). In addition, although sterically much more encumbered ynamides (see biaryls **16**−**19**) or diyne (see biaryl **20**) could still undergo efficient cycloadditions, they did not lead to better ratios. To further confirm our assignment of the *M* isomer as the major isomer for those containing non-Evans auxiliaries without simply resorting to spectra correlations with **7p** and **7m**, we obtained a single-crystal X-ray structure of **17m**.[16]

Mechanistically, there can be two possible transition states in which the rhodio-cyclopentadiene intermediate could approach to coordinate to the ynamide, **21**-*M-1* and **21**-*M-2* [Scheme 3]. While both approaches would lead to the *M*-isomer, the slight advantage of **21**-*M-2* over **21**-*M-1* would be that the rhodium metal could be more readily chelated (in red) to both the methoxy and carbonyl oxygen atoms (in blue). In addition to lack of the bidentate coordination, another slight disadvantage for **21**-*M-1* would be the presence of the Ph ring on the auxiliary, which not only serves to block the bottom face but can also come in contact with rhodio-cyclopentadiene (all in dark green). For the respective TS **21**-*P-1* (not shown) and **21**-*P-2*, they both would suffer from either the lack of bidentate chelation (for **21**-*P-1*) or the aforementioned steric interaction as shown in **21**-*P-2*, although it has bidentate coordination as in **21**-*M-2*.

(18) Similar results were also obtained in the presence of catalysts and additives.

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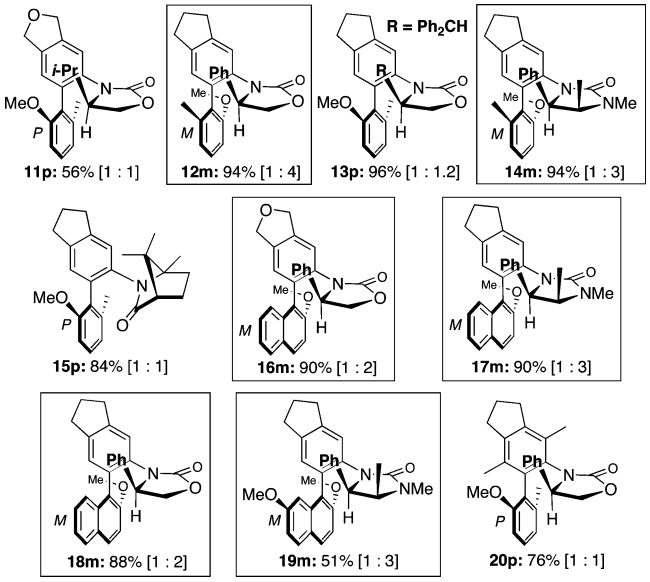
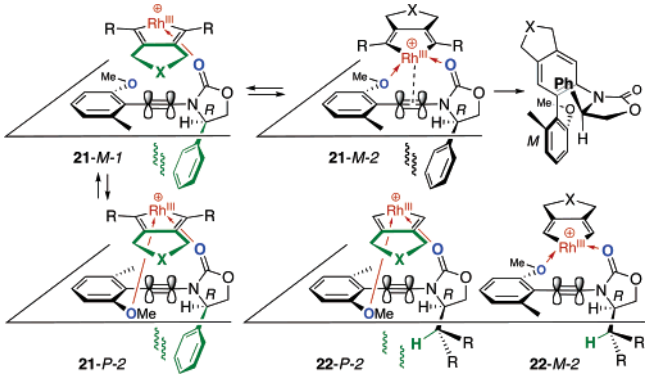


FIGURE 2. Modest *M*-selective [2 + 2 + 2] cycloadditions.

SCHEME 3. Possible Mechanistic Model for *M*-Selectivity



With both having disadvantages, the pathway leading to the *M* isomer would predominate.

We have described here the rhodium(I)-catalyzed [2 + 2 + 2] cycloaddition of sterically encumbered aryl-substituted ynamides with various diynes. The overall diastereoselectivity is modest in favor of the *M* isomer, but these cycloadditions provide a useful synthetic entry to an array of new chiral amide-substituted biaryls.

Experimental Section

General Procedure for [2 + 2 + 2] Cyclotrimerization without Additives. To a solution of ynamide (0.062 mmol) and diyne (0.124 mmol, 2 equiv) in anhydrous 1,2-dichloroethane (6.2 mL) was added $RhCl(PPh_3)_3$ (11.5 mg, 20 mol %). The solution was heated to 85 °C in a sealed tube, followed by LCMS. After the reaction was complete, the solution was cooled to room temperature and filtered through a short pad of silica gel. Removal of solvent in vacuo and purification of the resulting crude residue via silica gel flash column chromatography (gradient eluent 0% to 25% EtOAc in hexanes) afforded the desired biaryl product.

General Procedure for Rhodium(I)-Catalyzed [2 + 2 + 2] Cycloaddition with $AgSbF_6$. To a solution of $RhCl(PPh_3)_3$ (15 mol %) and $AgSbF_6$ (17 mol %) in anhyd dichloroethane (5 mM) was added 4 Å molecular sieves in a sealed tube. The mixture was stirred at room temperature for 1 h before ynamide (1.0 mmol) and diyne (4.0 mmol) were added. The solution was heated to 85

°C and followed by LCMS. After the reaction was complete, the solution was cooled to room temperature and filtered through a short pad of silica gel. CH_2Cl_2 was used as eluent to remove oligomerization of the diyne, and subsequent elution with EtOAc/hexanes (1:1) followed by concentration in vacuo yielded a crude mixture of diastereomers. Separation and purification of the resulting crude residue via silica gel flash column chromatography (gradient eluent % 0 to 50% EtOAc in hexanes) afforded the desired biaryl diastereomers.

Diastereomer 7p: $R_f = 0.40$ (33% EtOAc in hexanes); colorless solid; mp 169−170 °C; $[\alpha]^{20}_D = -16.6$ (*c* 5.5, CH_2Cl_2); IR (thin film) cm^{-1} 2949 (w), 2841 (w), 1754 (s), 1578 (w), 1467 (m), 1414 (m), 1256 (m), 1086 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 (s, 3 H), 2.16 (m, 2 H), 2.49 (dd, J = 13.5, 11.5 Hz, 1 H), 2.92−3.08 (m, 5 H), 3.59 (m, 1 H), 3.70 (t, J = 9.0 Hz, 1 H), 3.76 (s, 3 H), 3.88 (dd, J = 9.0, 4.0 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 6.90 (d, J = 7.5 Hz, 1 H), 6.97 (d, J = 5.5 Hz, 2 H), 7.07 (s, 1 H), 7.18−7.26 (m, 4 H), 7.35 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 25.8, 32.9, 33.0, 38.4, 55.7, 58.2, 66.6, 105.7, 108.1, 123.0, 125.4, 127.0, 127.9, 128.7, 128.9, 129.2, 132.3, 133.2, 136.4, 139.7, 144.9, 156.8, 157.0; mass spectrum (APCI) *m*/*e* (% relative intensity) 414 (100) $(M + H)^+$, 388 (1), 370 (1), 322 (1); *m*/*e* (ESI) calcd for $C_{27}H_{27}N_1O_3Na$ 436.1889, found 436.1886.

Diastereomer 7m: $R_f = 0.30$ (33% EtOAc in hexanes); mp 65−67 °C; $[\alpha]^{20}_D = -84.1$ (*c* 2.0, CH_2Cl_2); IR (thin film) cm^{-1} 2948 (w), 2843 (w), 1759 (s), 1468 (m), 1414 (m), 1260 (m), 1085 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09−2.20 (m, 2 H), 2.25 (s, 3H), 2.50 (dd, J = 13.5, 11.5 Hz, 1H), 2.87 (dd, J = 13.5, 4.0 Hz, 1 H), 2.93 − 3.06 (m, 4 H), 3.34−3.41 (m, 1 H), 3.62 (t, J = 8.5 Hz, 1 H), 3.69 (s, 3 H), 3.87 (dd, J = 8.5, 4.0 Hz, 1 H), 6.78 (d, J = 8.0 Hz, 1 H), 6.92−6.95 (m, 3 H), 7.13 (s, 1 H), 7.15−7.26 (m, 4 H), 7.33 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 25.8, 32.8, 33.0, 38.9, 55.8, 58.0, 66.5, 108.2, 122.8, 125.6, 127.1, 127.5, 127.6, 129.0, 129.2, 132.5, 132.8, 136.0, 137.2, 144.3, 144.9, 156.8, 157.5; mass spectrum (APCI) *m*/*e* (% relative intensity) 414 (100) $(M + H)^+$, 388 (1), 370 (1), 322 (1); *m*/*e* (ESI) calcd for $C_{27}H_{27}N_1O_3Na$ 436.1889, found 436.1888.

Diastereomer 17p: $R_f = 0.44$ (10% EtOAc in dichloromethane); mp 216−219 °C; $[\alpha]^{20}_D = -84.6$ (*c* 1.4, CH_2Cl_2); IR (neat) cm^{-1} 3051 (w), 2930 (w), 2842 (w), 1699 (s), 1593 (w), 1423 (s), 1394 (s), 1209 (s), 1077 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.39 (d, J = 6.8 Hz, 3H), 2.01−2.12 (m, 2H), 2.27 (dq, J = 8.4, 6.6 Hz, 1H), 2.40 (s, 3H), 2.81−2.90 (m, 3H), 2.96−3.04 (m, 1H), 3.77 (d, J = 8.4 Hz, 1H), 3.81 (s, 3H), 6.97 (broad m, 2H), 7.11 (s, 1H), 7.16−7.22 (m, 3H), 7.30−7.37 (m, 3H), 7.41 (d, J = 8.8 Hz, 1H), 7.50 (dd, J = 7.8, 1.0 Hz, 1H), 7.80 (dd, J = 7.6, 1.2 Hz, 1H), 7.92 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 25.7, 29.4, 32.8, 33.1, 56.0, 56.5, 63.1, 113.3, 123.4, 124.0, 125.9, 126.5, 126.7, 127.6, 127.9, 128.31, 128.27, 128.9, 129.6, 130.4, 133.1, 134.7, 137.3, 142.6, 144.6, 153.7, 160.7; mass spectrum (APCI) *m*/*e* (% relative intensity) 463 (100) $(M)^+$, 464 (38) $(M + H)^+$; *m*/*e* (MALDI) calcd for $C_{31}H_{31}N_2O_2$ 463.2386, found 463.2312.

Diastereomer 17m: $R_f = 0.22$ (10% EtOAc in dichloromethane); mp 225−227 °C; $[\alpha]^{20}_D = -77.9$ (*c* 2.4, CH_2Cl_2); IR (neat) cm^{-1}: 3062 (w), 3028 (w), 2930 (w), 2853 (w), 1708 (s), 1595 (w), 1428 (m), 1396 (m), 1262 (s), 1078 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.46 (d, J = 6.4 Hz, 3H), 1.97−2.13 (m, 2H), 2.70 (s, 3H), 2.80−2.87 (m, 3H), 2.93−3.05 (two m, 2H), 3.71 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 6.67 (broad s, 2H), 7.03 (s, 1H), 7.08−7.14 (m, 3H), 7.26−7.30 (m, 1H), 7.33−7.39 (m, 4H), 7.86 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 25.7, 29.5, 32.8, 33.0, 56.3, 56.8, 63.3, 113.5, 122.8, 123.7, 125.5, 126.1, 126.6, 127.8, 127.9, 128.1, 128.2, 128.6, 129.4, 129.5, 131.0, 133.8, 135.7, 137.0, 142.6, 144.5, 154.6, 160.6; mass spectrum (APCI) *m*/*e* (% relative intensity) 463 (100) $(M)^+$, 464 (37) $(M + H)^+$; *m*/*e* (MALDI) calcd for $C_{31}H_{31}N_2O_2$ 463.2386, found 463.2361.

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Supporting Information Available: Experimental procedures, NMR spectra, and characterizations for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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