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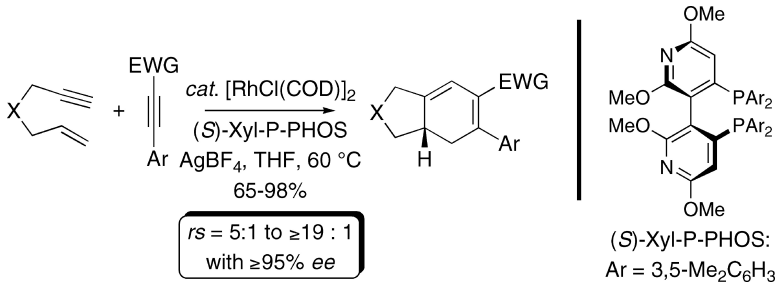

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Regio- and Enantioselective *Inter*molecular Rhodium-Catalyzed [2+2+2] Carbocyclization Reactions of 1,6-Enynes with Methyl Arylpropiolates

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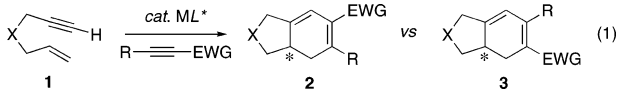
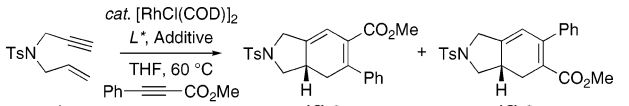
Transition metal-catalyzed [*m*+*n*+*o*] carbocyclization reactions provide powerful methods for the construction of complex polycyclic systems that are generally not accessible through classical pericyclic reactions.[1] Although the *inter*molecular metal-catalyzed [2+2+2] carbocyclization reaction of carbon and heteroatom tethered 1,6-enynes with symmetrical 1,2-disubstituted alkynes has been described, a significant challenge with this process is the ability to regioselectively incorporate unsymmetrical 1,2-disubstituted alkynes.[2−6] Furthermore, despite the myriad of metal-catalyzed carbocyclization reactions, the enantioselective version of the metal-catalyzed [2+2+2] carbocyclization of a 1,6-enyne has not been described. In light of these significant challenges, we sought to develop the combined regio- and enantioselective metal-catalyzed [2+2+2] carbocyclization reaction with unsymmetrical 1,2-disubstituted alkynes and thereby provide a new paradigm for this type of transformation. Herein, we now describe the regio- and enantioselective rhodium-catalyzed [2+2+2] carbocyclization of carbon- and heteroatom-tethered 1,6-enynes **1** with unsymmetrical 1,2-disubstituted alkynes to afford the corresponding bicyclohexadienes **2/3** in excellent yield (eq 1).



Preliminary studies focused on the development of the regio- and enantioselective version of the rhodium-catalyzed [2+2+2] carbocyclization using the 1,6-enyne **1a** as outlined in Table 1. Treatment of **1a** with excess methyl phenylpropiolate and the chiral complex derived from AgOTf-*modified* [RhCl(COD)]$_2$ with (*S*)-BINAP in benzene at 60 °C, furnished the bicyclohexadienes **2**/**3** in 27% yield as a 2:1 mixture of regioisomers (entry 1).[7,8] Although the overall efficiency and regioselectivity were not particularly encouraging, the major isomer **2a** was obtained with high enantioselectivity (86% ee). Previous studies demonstrated that the overall efficiency could be improved dramatically by simply adjusting the nature of the solvent and/or counterion.[5c] In light of this fact, we probed the effect of coordinating solvents and silver salts with progressively weaker coordinating counterions (entries 2−5). Gratifyingly, the ethereal solvent tetrahydrofuran in combination with the tetrafluoroborate counterion proved optimal in terms of efficiency (entry 5), since these conditions completely suppressed the undesired homo-coupling of enyne **1a**. Additional optimization focused on the nature of the chiral phosphine ligand to improve and potentially understand the factors that control regioselectivity. Interestingly, switching to (*S*)-Xyl-BINAP led to significantly improved regioselectivity (entry 5 vs 6). Hence, the more sterically hindered bisphosphine can more effectively discriminate the termini of methyl phenylpropiolate (Ph vs CO_2Me). The more π-acidic (*S*)-DIFLUORPHOS ligand, which has a narrower dihedral angle than (*S*)-Xyl-BINAP, furnished the product with diminished regioselection, albeit with higher enantioselectivity (entry 7).[9] In accord with this observation, the dipyridyl-phosphines CTH-(*S*)-P-PHOS and (*S*)-Xyl-P-PHOS ligands, which possesses a dihedral angle similar to that of (*S*)-DIFLUORPHOS (see Figure 1), afforded excellent enantioselectivity, in which (*S*)-Xyl-P-PHOS provided the optimum ligand in terms of regioselectivity (entry 9).[10] This trend is analogous with the improvement observed for the switch from the (*S*)-BINAP to (*S*)-Xyl-BINAP ligand (entry 5 vs 6), presumably due to similar reasoning.

Table 1. Optimization of *Inter*molecular Rhodium-Catalyzed [2+2+2] Carbocyclization Reaction[a]



entry	solvent	additive	ligand (*L**)	yield (%)[b]	rs (**2a:3a**)[c]	*ee* of **2a** (%)[d,e]
1	PhH	AgOTf	(*S*)-BINAP	27	2:1	86
2	MeCN	"	"	0	–	–
3	THF	"	"	68	3:1	92
4	"	$AgSbF_6$	"	82	3:1	89
5	"	$AgBF_4$	"	95	3:1	92
6	"	"	(*S*)-Xyl-BINAP	93	8:1	88
7	"	"	(*S*)-DIFLUORPHOS	73	4:1	97
8	"	"	(*S*)-P-PHOS	75	5:1	97
9	***THF***	***$AgBF_4$***	***(S)-Xyl-P-PHOS***	***98***	***10:1***	***97***

[a] All reactions were carried out on a 0.25 mmol reaction scale utilizing the chiral complex derived from 5 mol % of [RhCl(COD)]$_2$ and 12 mol % of the bidentate phosphine ligand, further *modified* with 20 mol % of silver salt and methyl phenylpropiolate (3 equiv) under an atmosphere of argon.[11] [b] Isolated yields. [c] Regioselectivity was determined by 400 MHz ^{1}H NMR on the crude reaction mixtures. [d] Enantiomeric excess of the major regioisomer **2a** was determined by chiral HPLC analysis. [e] The regioselectivity and absolute configuration of **(*S*)-2a** were established by NOESY and X-ray crystallography, respectively.

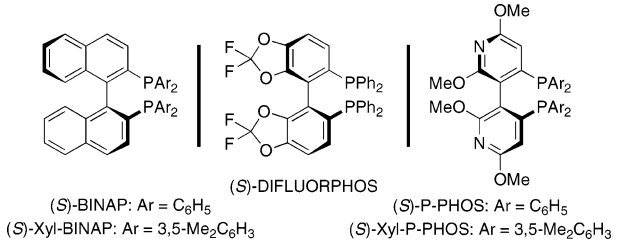


Figure 1. Chiral ligands used in the optimization studies.

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 9) to the various carbon- and heteroatom-tethered 1,6-enynes using an array of methyl *para*-substituted arylpropiolates. Interestingly, the carbocyclization reaction is highly enantioselective regardless of the nature of the enyne tether and/or the aryl substituent, whereas the yield and/or regioselectivity are influenced by these parameters. For example, although all the

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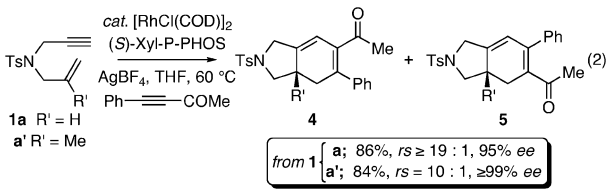
Table 2. Scope of the Regio- and Enantioselective Rhodium-Catalyzed [2+2+2] Carbocyclization Reaction (eq 1; R = *p*-FG-C_6H_4, EWG = CO_2Me)[a]

entry	1,6-enyne **1** X =		alkyne FG =	yield (%)[b]		rs (**2**:**3**)[c]	*ee* of **2** (%)[d]
1	TsN	**a**	H	98	**a**	10:1	97
2	"	"	OMe	84	**b**	14:1	97
3	"	"	Me	95	**c**	11:1	97
4	"	"	F	87	**d**	10:1	97
5	"	"	CF_3	86	**e**	10:1	98
6	$C(CO_2Me)_2$	**b**	H	88	**f**	9:1	≥99
7	"	"	OMe	85	**g**	10:1	98
8	"	"	Me	80	**h**	9:1	95
9	"	"	F	74	**i**	7:1	98
10	"	"	CF_3	65	**j**	5:1	98
11	O	**c**	H	86	**k**	≥19:1	≥99
12	"	"	OMe	95	**l**	≥19:1	98
13	"	"	Me	87	**m**	≥19:1	98
14	"	"	F	75	**n**	17:1	≥99
15	"	"	CF_3	72	**o**	17:1	97

[a] All reactions were carried out on a 0.25 mmol reaction scale. [b] Isolated yields.[11] [c] Ratio of regioisomers was determined by 400 MHz ^{1}H NMR on the crude reaction mixtures. [d] Enantiomeric excess of the major regioisomer was determined by chiral HPLC analysis.[12]

enynes undergo regioselective carbocyclizations, the nature of the tether has a profound influence on the level of regiocontrol (O ≫ NTs > $C(CO_2Me)_2$). Similarly, the overall efficiency and regioselectivity can be directly related to the electronic nature of the aryl substituents. This trend is particularly prominent with carbon tethers (entries 7−10), whereas regioselectivity and efficiency are somewhat affected in the nitrogen (entries 2−5) and oxygen tethers (entries 12−15), respectively. *Overall, this work now provides access to previously unknown enantiomerically enriched bicyclohexadienes that are useful synthons for target-directed synthesis.*

To further demonstrate the scope of this transformation, we elected to examine an alternative electron-withdrawing group within the alkyne. Treatment of the 1,6-enyne **1a** under the optimized reaction conditions with 4-phenyl-3-butyn-2-one furnished the bicyclohexadienes **4a**/**5a** (R′ = H) in 86% yield, with ≥19:1 regioselectivity and 95% *ee* for **4a** (eq 2).[12] Additionally, we



envisioned the application of this methodology to a substituted 1,6-enyne **1a′** (R′ = Me) would facilitate the enantioselective introduction of a quaternary carbon stereogenic center, which would be a particularly attractive feature of this methodology.[13] Gratifyingly, treatment of **1a′** under the optimized carbocyclization conditions with 4-phenyl-3-butyn-2-one furnished the quaternary substituted bicyclic azacycles **4a′**/**5a′** (R′ = Me) in 84% yield, with 10:1 regioselectivity and ≥99% *ee* for **4a′**.[12]

In conclusion, we have developed the first regio- and enantioselective crossed *inter*molecular rhodium-catalyzed [2+2+2] carbocyclization of carbon- and heteroatom-tethered 1,6-enynes with unsymmetrical 1,2-disubstituted alkynes. This study clearly delineates the specific ligand requirements for obtaining excellent regio- and enantioselectivity. Furthermore, the ability to utilize various electron-withdrawing groups, and to introduce quaternary carbon stereogenic centers, provides the level of versatility necessary for its application to target-directed synthesis. Additional studies on the development and application of this novel methodology to the total synthesis of natural products are currently underway.[14]

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Supporting Information Available: Spectral data for **2a**−**o** and **4a**/**a′** and X-ray crystallographic analysis of **(*S*)-2a** (where X = NTs, R = C_6H_5, and EWG = CO_2Me). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The in situ activation of $[RhCl(COD)]_2$ with $AgBF_4$ provides superior results as compared to the $[Rh(COD)_2]BF_4$ precatalyst in terms of chemical yield.

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(11) *Representative Experimental Procedure:* $[RhCl(COD)]_2$ (6.2 mg, 5 mol %) and $AgBF_4$ (9.7 mg, 20 mol %) were suspended in anhydrous THF (1.0 mL) and stirred at room temperature under an atmosphere of argon for *ca.* 10 min. (*S*)-Xyl-P-PHOS (22.7 mg, 12 mol %) in anhydrous THF (3.0 mL) was then added to the yellow suspension, and the mixture was stirred at room temperature for an additional *ca.* 30 min. Methyl phenylpropiolate (120.1 mg, 0.75 mmol) was added in one portion, followed by addition of 1,6-enyne **1a** (62.3 mg, 0.25 mmol) in anhydrous THF (2.0 mL) via syringe pump over *ca.* 2 h at 60 °C, followed by an additional *ca.* 30 min (TLC control). The reaction mixture was allowed to cool to room temperature, and the resultant mixture was filtered through a short pad of silica gel (eluting with 50% ethyl acetate/hexanes) and concentrated *in vacuo* to afford the crude product. Purification by flash chromatography (silica gel, eluting with a 10−30% ethyl acetate/hexanes gradient) afforded the bicyclohexadienes **2a**/**3a** (94.1 mg, 98%) as a white solid, with 10:1 regioselectivity and 97% *ee*.

(12) The absolute configuration was made by analogy with **(*S*)-2a**, which was determined by X-ray crystallography.

(13) For recent reviews on the enantioselective construction of quaternary carbon stereocenters, see: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105 and pertinent references therein.

(14) The application of this methodology to alkyl-substituted alkynes also provides excellent enantioselectivity, albeit with diminished regioselectivity. Hence, conjugated alkynes (where R = aryl or vinyl) are crucial for achieving useful levels of regiocontrol. For example, for **1a**, where EWG = CO_2Me and R = Me (*rs* = 4:1, 97% *ee*, 90%) whereas R = $C(=CH_2)Me$ (*rs* = 10:1, 97% *ee*, 66%).

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