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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. 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. 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-envne 1a as outlined in Table 1. Treatment of **1a** with excess methyl phenylpropiolate and the chiral complex derived from AgOTf-modified [RhCl(COD)]<sub>2</sub> 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).<sup>7,8</sup> 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. <sup>5c</sup> 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 envne1a. 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  $\pi$ 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). In accord with this observation, the dipyridyl-phosphines CTH-(S)-P-PHOS and

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(*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). <sup>10</sup> 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 2 summarizes the application of the optimized reaction conditions (Table 1, entry 9) to the various carbon- and heteroatomtethered 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 enynes undergo regioselective carbocyclizations, the nature of the tether has a profound influence on the level of regiocontrol (O  $\gg$  NTs > C(CO<sub>2</sub>Me)<sub>2</sub>). 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  ${\bf 1a}$  under the optimized reaction conditions with 4-phenyl-3-butyn-2-one furnished the bicyclohexadienes  ${\bf 4a/5a}$  (R' = H) in 86% yield, with  $\geq$  19:1 regioselectivity and 95% ee for  ${\bf 4a}$  (eq 2). 12 Additionally, we envisioned the application of this methodology to a substituted 1,6-enyne  ${\bf 1a}$  '(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  ${\bf 1a}$ ' under the optimized carbocyclization conditions with 4-phenyl-3-butyn-2-one furnished the quaternary substituted bicyclic azacycles  ${\bf 4a}$ '/ ${\bf 5a}$ ' (R' = Me) in 84% yield, with 10:1 regioselectivity and  $\geq$  99% ee for  ${\bf 4a}$ '. 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. <sup>14</sup>

## **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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- 7. The in situ activation of [RhCl(COD)]<sub>2</sub> with AgBF<sub>4</sub> provides superior results as compared to the [Rh (COD)<sub>2</sub>]BF<sub>4</sub> precatalyst in terms of chemical yield.
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- 11. Representative Experimental Procedure: [RhCl(COD)]<sub>2</sub> (6.2 mg, 5 mol %) and AgBF<sub>4</sub> (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.
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- 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<sub>2</sub>Me and R = Me (*rs* = 4:1, 97% *ee*, 90%) whereas R = C([unk]CH<sub>2</sub>)Me (*rs* = 10:1, 97% *ee*, 66%).



**Figure 1.** Chiral ligands used in the optimization studies.



**Table 1**Optimization of *Inter*molecular Rhodium-Catalyzed [2+2+2] Carbocyclization Reaction<sup>a</sup>



entry	solvent	additive	ligand ( $L^*$ )	yield $(\%)^b$	rs (2a:3a) <sup>c</sup>	ee of 2a (%) <sup>d</sup> ,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	${\rm AgBF}_4$	(S)-Xyl-P-PHOS	98	10:1	97	

<sup>&</sup>lt;sup>a</sup>All reactions were carried out on a 0.25 mmol reaction scale utilizing the chiral complex derived from 5 mol % of [RhCl(COD)]<sub>2</sub> 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.<sup>11</sup>

 $<sup>^{\</sup>it b}$ Isolated yields.

 $<sup>^{\</sup>it c}$  Regioselectivity was determined by 400 MHz  $^{1}{\rm H}$  NMR on the crude reaction mixtures.

 $d_{\mbox{\footnotesize Enantiomeric}}$  excess of the major regioisomer  ${\bf 2a}$  was determined by chiral HPLC analysis.

<sup>&</sup>lt;sup>e</sup>The regioselectivity and absolute configuration of (S)-2a were established by NOESY and X-ray crystallography, respectively.

Table 2Scope of the Regio- and Enantioselective Rhodium-Catalyzed [2+2+2] Carbocyclization Reaction (eq 1; R = p-FG-C $_6$ H $_4$ , EWG = CO $_2$ Me) $^a$ 

ee of 2 (%)	rs (2:3) <sup>c</sup>		yield $(\%)^{b}$	alkyne FG =		1,6-enyne 1 X =	entry
97	10:1	a	98	Н	a	TsN	1
97	14:1	b	84	OMe	"	"	2
97	11:1	c	95	Me	"	"	3
97	10:1	d	87	F	"	"	4
98	10:1	e	86	CF <sub>3</sub>	44	"	5
≥99	9:1	f	88	Н	b	$C(CO_2Me)_2$	6
98	10:1	g	85	OMe	"		7
95	9:1	ĥ	80	Me	"	"	8
98	7:1	i	74	F	"	"	9
98	5:1	i	65	CF <sub>3</sub>	"	"	10
≥99	≥19:1	k	86	Н	c	0	11
98	≥19:1	ī	95	OMe	"	"	12
98	≥19:1	m	87	Me	"	"	13
≥99	17:1	n	75	F	"	"	14
97	17:1	0	72	CF <sub>3</sub>	"	"	15

 $<sup>^{\</sup>it a}$  All reactions were carried out on a 0.25 mmol reaction scale.

<sup>&</sup>lt;sup>b</sup>Isolated yields.<sup>11</sup>

 $<sup>^{</sup>c}$ Ratio of regioisomers was determined by 400 MHz  $^{1}$ H NMR on the crude reaction mixtures.

 $<sup>\</sup>ensuremath{^{d}\text{Enantiomeric}}$  excess of the major regioisomer was determined by chiral HPLC analysis.  $^{12}$