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Ligand-Controlled Enantioselective [2 + 2] Cycloaddition of Oxabicyclic Alkenes with Terminal Alkynes Using Chiral Iridium Catalysts

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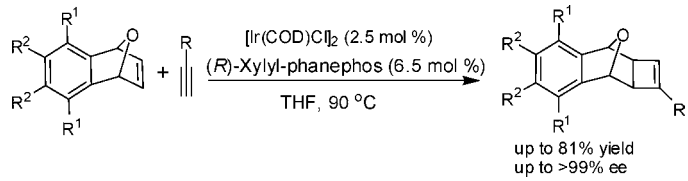
ABSTRACT



The first catalytic asymmetric [2 + 2] cycloaddition of oxabicyclic alkenes and terminal alkynes has been developed. This iridium-catalyzed enantioselective [2 + 2] cycloaddition allows the formation of four stereocenters in a single step with excellent enantioselectivity (94→99% ee).

Due to the unique reactivity of oxabicyclic alkenes, transition-metal-catalyzed reactions of oxabicyclic alkenes have attracted much attention in recent years.[1] Of these reactions, the reactions between oxabicyclic alkenes and terminal alkynes are particularly interesting because of their amazing chemical diversity. In the presence of different catalysts and under the different reaction conditions, nucleophilic ring-opening reaction,[2] cycloaddition,[3] as well as hydroalkynylation[4] can occur selectively. Despite the interesting chemistry, development of the corresponding catalytic asymmetric reactions of oxabicyclic alkenes and terminal alkynes has been elusive. Recently, we developed the first catalytic asymmetric hydroalkynylation of oxabicyclic alkenes with terminal alkynes. The hydroalkynylation products were obtained in the presence of $[Ir(COD)Cl]_2$/(*R*)-SYNPHOS ([(5,6),(5′,6′)-bis(ethylenedioxy)biphenyl-2,2′-diyl]bis(diphenylphosphine)) in up to 77% ee (Scheme 1).[5] This represents the first application of iridium in oxabicyclic alkene chemistry.[6] On the basis of this discovery and the chemical diversity in the reactions of oxabicyclic alkenes and terminal alkynes, we envisioned that the corresponding catalytic asymmetric [2 + 2] cycloaddition reactions of oxabicyclic alkenes and terminal alkyne could be realized by tuning the ligand.

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(1) (a) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48. (b) Rayabarapu, D. K.; Cheng, C. H. *Acc. Chem. Res.* **2007**, *10*, 971.
(2) Rayabarapu, D. K.; Chiou, C.-F.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 1679.
(3) [2 + 2] cycloaddition: (a) Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem.−Eur. J.* **2000**, *6*, 3706. (b) Chao, K. C.; Rayabarapu, D. K.; Wang, C.-C.; Cheng, C.-H. *J. Org. Chem.* **2001**, *66*, 8804[2 + 2 + 2] cycloaddition: (c) Huang, D.-J.; Sambaiah, T.; Cheng, C.-H. *New J. Chem.* **1998**, *22*, 1147. (d) Sambaiah, T.; Huang, D.-J.; Cheng, C.-H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 195.

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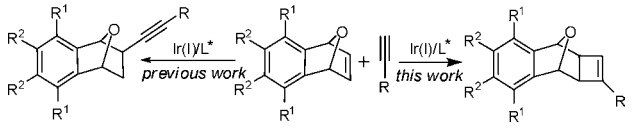
Scheme 1. Irridium-Catalyzed Reactions of Oxabicyclic Alkenes and Terminal Alkynes

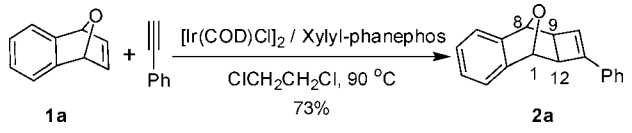


As part of our research interest in developing new catalytic asymmetric reactions,[7] particularly those involving terminal alkynes,[8] and in the oxabicyclic alkene chemistry,[9] we herein describe a new Ir•L* to achieve ligand-controlled catalytic asymmetric [2 + 2] cycloaddition. To the best of our knowledge, this work represents the first catalytic asymmetric [2 + 2] cycloaddition of oxabicyclic alkenes and terminal alkynes.

Transition-metal-catalyzed [2 + 2] cycloaddition of oxabicyclic alkenes with alkynes[10] is of great interest as it serves as one of the most powerful methods for access to fused cyclobutene derivatives which represent a special class of strained compounds of synthetic interest.[11] However, though racemic [2 + 2] cycloadditions of oxabicyclic alkenes with internal alkynes have been studied comprehensively,[12] successful examples of transition-metal-catalyzed [2 + 2] cycloaddition of oxabicyclic alkenes with terminal alkynes are quite limited. To date, there are only two examples[3a,b] dealing with racemic [2 + 2] cycloaddition between oxabicyclic alkenes and terminal alkynes in the literature. Moreover, to the best of our knowledge, there is no report on catalytic asymmetric [2 + 2] cycloaddition of oxabicyclic alkenes with terminal alkynes.[13]

Initially, 7-oxabenzonorbornadiene **1a** was treated with phenylacetylene (2 equiv) in the presence of $[Ir(COD)Cl]_2$ in combination with PHANEPHOS-type achiral ligands in DCE ($ClCH_2CH_2Cl$) at 90 °C (Scheme 2). To our delight,

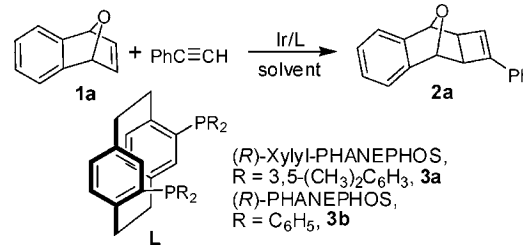
Scheme 2



with the Xylyl-PHANEPHOS ligand, the [2 + 2] cycloaddition product **2a** was obtained in 73% yield. It is interesting to note that with the SYNPHOS ligand hydroalkynylation products were achived in the Ir-catalyzed reactions of oxabicyclic alkenes and terminal alkynes.[5] It was found that only the *exo* isomer was observed in this iridium-catalyzed [2 + 2] cycloaddition. The relative stereochemistry of **2a** was established based on the coupling constants in its proton NMR spectrum: the protons at the 4/6 ring junction appeared as singlets, showing no coupling with the bridgehead protons. The data indicated that the protons at the ring junction occupied the *endo* position.[3a,b,14]

Encouraged by this result, we then investigated the catalytic asymmetric version of this Ir-catalyzed [2 + 2] cycloaddition using the corresponding chiral ligands. As shown in Table 1, the use of (*R*)-Xylyl-PHANEPHOS **3a**

Table 1. Screening of the Reaction Conditions for the Ir-Catalyzed Asymmetric [2 + 2] Cycloaddition of 7-Oxabenzonorbornadiene **1a** with Phenylacetylene[a]



entry	Ir precatalyst	temp (°C)	solvent	**3a**	time (h)	% yield[b]	% ee[c]
1	$[Ir(COD)Cl]_2$	90	DCE	**3a**	20	75	94
2	$[Ir(COD)Cl]_2$	90	DCE	**3b**	20	37	86
3	Ir(I)(COD)(acac)	90	DCE	**3a**	23	58	84
4	$Ir(III)(C_7H_8)_3(acac)$	90	DCE	**3a**	23	trace	N.D.
5	$[Ir(COD)Cl]_2$	70	DCE	**3a**	72	75	94
6	$[Ir(COD)Cl]_2$	50	DCE	**3a**	96	70	94
7	$[Ir(COD)Cl]_2$	90	THF	**3a**	20	**79**	>99[d]
8	$[Ir(COD)Cl]_2$	90	DME	**3a**	20	71	97
9	$[Ir(COD)Cl]_2$	90	toluene	**3a**	20	79	96
10	$[Ir(COD)Cl]_2$	90	MeOH	**3a**	20	80	85
11	$[Ir(COD)Cl]_2$	90	dioxane	**3a**	20	58	95
12	$[Ir(COD)Cl]_2$	90	*i*-PrOH	**3a**	20	81	95

[a] All the reactions were carried out in a 0.3 mmol scale of **1a** using 2 equiv of phenylacetylene in 2 mL of solvent with 5 mol % catalyst. [b] Yields of isolated products. [c] Determined by chiral HPLC using a Chiralcel OD-H. [d] Absolute configuration was not determined.

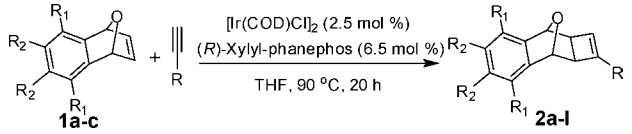
provided the desired [2 + 2] cycloaddition product **2a** in 75% yield and 94% ee (entry 1). The use of (*R*)-PHANEPHOS **3b** resulted in lower yield (37%) and enantioselectivity (86% ee) (entry 2). Then, other iridium complexes in combination with (*R*)-Xylyl-PHANEPHOS **3a** were investigated in this reaction. Ir(I)(COD)(acac) gave lower yield (58%) and enantiomeric excess (84% ee) under the same conditions (entry 3). $Ir(III)(C_7H_8)_3(acac)$ showed poor catalytic activity (entry 4). Thus, $[Ir(COD)Cl]_2$ in combination with (*R*)-Xylyl-PHANEPHOS **3a** was chosen to investigate

(4) Tenaglia, A.; Giordano, L.; Buono, G. *Org. Lett.* **2006**, *8*, 4315.
(5) Fan, B.-M.; Shao, Z.-H.; Li, Y.-M.; Chan, A. S. C. *Adv. Synth. Catal.*, submitted.
(6) For a review, see: Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, 3349.
(7) Shao, Z.-H.; Zhang, H.-B. *Chem. Soc. Rev.* **2009**, *38*, 2745.
(8) (a) Shao, Z.; Wang, J.; Ding, K.; Chan, A. S. C. *Adv. Synth. Catal.* **2007**, *349*, 2375. (b) Shao, Z.; Pu, X.; Li, X.; Fan, B.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2009**, *20*, 225.
(9) Peng, F.; Fan, B.; Shao, Z.; Pu, X.; Li, P.; Zhang, H. *Synthesis* **2008**, 3043.
(10) For a review on transition-metal-catalyzed [2 + 2] cycloaddition reactions between bicyclic alkenes and alkynes, see: Tam, W.; Goodreid, J.; Cockburn, N. *Curr. Org. Synth.* **2009**, *6*, 219.
(11) Halton, B. *Advances in Strained and Interesting Organic Molecules*; JAI Press: Greenwich, CT, 1999; Vol. 8.
(12) (a) Burton, R. R.; Tam, W. *Tetrahedron Lett.* **2006**, *47*, 7185. (b) Burton, R. R.; Tam, W. *J. Org. Chem.* **2007**, *72*, 7333, and references therein.

the temperature effect. The cycloaddition at 70 °C afforded the desired product **2a** in the same yield (75%) and enantioselectivity (94% ee) obtained at 90 °C but with longer reaction time (72 h) (entry 5). Further decreasing the temperature to 50 °C gave a similar yield (70%) and enantioselectivity (94% ee), however, in 96 h (entry 6). Subsequently, several different solvents were screened. All the solvents except MeOH afforded good enantioselectivity (95−99% ee). The cycloaddition in THF furnished the best results (79% yield, >99% ee) (entry 7).

To extend the scope of substrates, a variety of terminal alkynes were investigated under optimized conditions (Table 2). All terminal aromatic alkynes reacted with **1a** smoothly

Table 2. Iridium-Catalyzed Asymmetric [2 + 2] Cycloaddition of 7-Oxabicyclic Alkenes with Terminal Alkynes[a]



entry	R_1, R_2	R	product	% yield[b]	% ee[c]
1	H, H	C_6H_5	**2a**	79	99
2	H, H	4-F−C_6H_4	**2b**	70	97
3	H, H	4-Br−C_6H_4	**2c**	67	97
4	H, H	4-CF_3−C_6H_4	**2d**	61	98
5	H, H	3-CH_3O−C_6H_4	**2e**	69	95
6	H, H	4-CH_3−C_6H_4	**2f**	57	96
7	H, H	4-CF_3O−C_6H_4	**2g**	81	97
8	H, H	3,5-$(CH_3O)_2$−C_6H_3	**2h**	60	98
9	H, H	CH_2CH_2−C_6H_4	**2i**	trace	N.D.
10	H, H	CO_2Me	**2j**	N.R.	−
11	MeO, H	C_6H_5	**2k**	60	98
12	H, Me	C_6H_5	**2l**	63	94

[a] All the reactions were carried out in a 0.3 mmol scale of oxabicyclic alkenes using 2 equiv of terminal alkynes in 2 mL of THF with 5 mol % catalyst at 90 °C. [b] Yields of isolated products. [c] Determined by chiral HPLC using a Chiralcel OD-H or OJ-H column.

to provide the corresponding adducts in excellent enantioselectivities (95% to >99% ee) (entries 1−8, Table 2). It appears that the position and electronic properties of the substituents for aromatic rings of terminal alkynes have little effect on the enantioselectivity. Whether electron-withdrawing (entries 2−4, Table 2), -donating (entries 5−8, Table 2), or -neutral (entry 1, Table 2) groups on aromatic rings were used, the reactions proceeded smoothly to give the desired adducts in excellent enantioselectivity. The [2 + 2] cycloaddition with terminal aliphatic alkynes such as 4-ethylphenylacetylene (R = CH_2CH_2−C_6H_4) led to poor results (entry 9, Table 2). The [2 + 2] cycloaddition reaction with terminal alkynes with electron-withdrawing groups such as methyl propiolate (R = CO_2Me) did not occur (entry 10, Table 2). The [2 + 2] cycloaddition of oxabenzonorbornadienes bearing substituents at various positions with phenylacetylene also provided the corresponding products in excellent enantioselectivity (94−98% ee, entries 11 and 12, Table 2).

In summary, we have developed the first catalytic asymmetric [2 + 2] cycloaddition of oxabicyclic alkenes and terminal alkynes by using $[Ir(COD)Cl]_2$/(*R*)-Xylyl-PHANEPHOS as the catalyst. This ligand-controlled iridium-catalyzed enantioselective [2 + 2] cycloaddition allows the formation of four stereocenters in a single step with excellent enantioselectivity (94→99% ee). Further investigation of the full scope and limitations of this iridium-catalyzed chemodivergence as well as elucidation of the reaction mechanism are in progress and will be reported in due time.

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Supporting Information Available: Representative experimental procedure, compound characterization data, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For chiral auxiliary-directed diastereoselective [2 + 2] cycloaddition with chiral internal alkynes, see: Villeneuve, K.; Tam, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 610. For the first example of enantioselective [2 + 2] cycloaddition of norbornene derivatives with internal alkynes, see: Shibata, T.; Takami, K.; Kawachi, A. *Org. Lett.* **2006**, *8*, 1343. For Rh-catalyzed asymmetric cross-cyclodimerization of oxabenzonorbornadiene and dimethyl 2-butynedioate (an internal alkyne), see: Nishimura, T.; Kawamoto, T.; Sasaki, K.; Tsurumaki, E.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 1492.

(14) (a) Smith, C. D. *J. Am. Chem. Soc.* **1966**, *88*, 4273. (b) Meinwald, J.; Meinwald, Y. C.; Baker, T. N. *J. Am. Chem. Soc.* **1964**, *86*, 4074.