Iridium Complex-Catalyzed Enantioselective Intramolecular [4+2] Cycloaddition of Dieneynes

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Abstract: A catalytic and highly enantioselective intramolecular [4+2] cycloaddition of dieneynes was achieved by use of chiral iridium complex prepared in situ from $[IrCl(cod)]_2$ and BDPP [2,4-bis(diphenylphosphino)pentane]. The reaction proceeded in refluxed *tert*-butyl acetate to give chiral cyclohexa-1,4-dienes in very high enantiomeric excess.

Key words: catalysis, chiral auxiliaries, cycloadditions, Diels–Alder reactions, Iridium

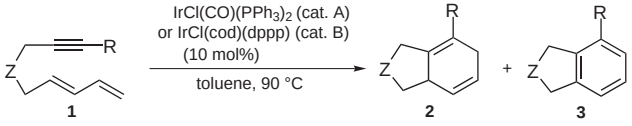
Enantioselective [4+2] cycloaddition is the most reliable and a common protocol for the construction of chiral 6-membered ring systems. In particular, chiral Lewis acid promoted [4+2] cycloaddition (Diels–Alder reaction) is comprehensively examined[1] and development of highly efficient catalysts is still an intriguing topic.[2] The coordination of heteroatoms of activated dienophiles (alkenes) to chiral Lewis acids realized enantioselective Diels–Alder reactions. Therefore functional groups like carbonyl moiety adjacent to alkene play a pivotal role for asymmetric induction. On the other hand, the transition metal complex-catalyzed cycloaddition of unactivated substrates possessing no heteroatoms proceeds smoothly because direct coordination of reaction sites like alkynes, alkenes, and dienes to the transition metal promotes the formation of metallacycle, an intermediate of cycloaddition.[3] Actually, intramolecular [4+2] cycloadditions of dieneynes or trienes catalyzed by transition metal (e.g. Ni,[4] Pd,[5] and Rh[6]) complexes have been reported. Enantioselective [4+2] cycloadditions were also realized by chiral cationic rhodium complexes, which were prepared in situ from Rh(I), chiral phosphine, and Ag(I) salt.[7]

We recently found that iridium-phosphine complexes are efficient catalysts for [2+2+1] cycloadditions (carbonylative alkyne-alkyne[8] and enantioselective carbonylative alkyne-alkene couplings[9]).[10] We report here that an iridium-chiral phosphine complex catalyzes an enantioselective intramolecular [4+2] cycloaddition of dieneynes to give chiral bicyclic products in high enantiomeric excess.

At first, we examined non-asymmetric cycloaddition using Vaska's complex and IrCl(cod)(dppp) which was used in [2+2+1] cycloadditions.[8] We chose dieneynes **1** possessing an unsubstituted diene because most of reported intramolecular [4+2] cycloadditions have used dienes having a methyl substituent on their terminal, which are derived from sorbic alcohol (hexa-2,4-dien-1-ol) except limited examples.[4a,c,6b] Moreover, no enantioselective intramolecular [4+2] cycloadditions have been reported using unsubstituted dienes derived from penta-2,4-dien-1-ol as far as we know.

In the presence of 10 mol% catalyst, the [4+2] cycloaddition of dieneyne **1a** was examined at 90 °C (Table 1). Both iridium complexes provided cyclohexa-1,4-diene **2a** in ca. 70% yield (entries 1 and 2). Other penta-2,4-dienyl propargyl ether **1b**,**c** were also transformed into the corresponding bicyclic products **2b**,**c** (entries 3–6). Along with the formation of **2a**–**c**, aromatized products **3a**–**c** were also generated in each reaction (5–15%). Penta-2,4-dienylpropargylamine **1d** was found to be a good substrate and **2d** was obtained in high yield without the formation of **3d** even for prolonged reaction time (entries 7 and 8).

Table 1. Ir Complex-Catalyzed [4+2] Cycloaddition[a]



Entry	R	Z	1	Catalyst	Time /h	Yield of 2/%	Yield of 3/%
1	C_6H_5	O	**1a**	A	19	71 (**2a**)	4 (**3a**)
2	C_6H_5	O	**1a**	B	11	68 (**2a**)	8 (**3a**)
3	4-$MeOC_6H_4$	O	**1b**	A	30	71 (**2b**)	15 (**3b**)
4	4-$MeOC_6H_4$	O	**1b**	B	15	68 (**2b**)	7 (**3b**)
5	4-ClC_6H_4	O	**1c**	A	23	71 (**2c**)	15 (**3c**)
6	4-ClC_6H_4	O	**1c**	B	10	65 (**2c**)	7 (**3c**)
7	C_6H_5	NTs	**1d**	A	96	70 (**2d**)	-
8	C_6H_5	NTs	**1d**	B	53	80 (**2d**)	-

[a] dppp: 1,3-Bis(diphenylphosphino)propane.

We further studied an enantioselective reaction using chiral iridium complexes (Table 2). Dieneyne **1a** was submitted to [4+2] cycloaddition in the presence of a chiral catalyst which was prepared in situ from $[IrCl(cod)]_2$ and tolBINAP.[9] **2a** was obtained in moderate ee (entry 1).

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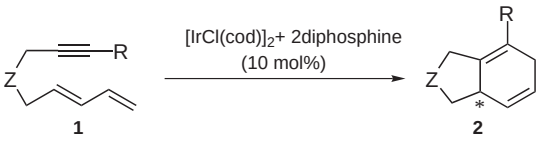
Next, we examined Me-DUPHOS and DIOP, which are efficient chiral ligands for cationic Rh complex-catalyzed enantioselective [4+2] cycloadditions.[7b,c] However, the results were poorer than those of tolBINAP in both yield and ee (entries 2,3). When we chose BDPP as a chiral ligand, dieneyne **1a** was consumed within 2 hours and the ee of obtained **2a** significantly increased to 78% (entry 4). After screening of various solvents, ethyl acetate was proved to be the best one and the ee reached over 90% (entries 4–7). In order to shorten the reaction time, other acetates having higher boiling points were examined as solvent (entries 8–9). As a result, the reaction proceeded smoothly to give **2a** with 95% ee in *tert*-butyl acetate (bp: 96 °C).[11] When $[RhCl(cod)]_2$ was used in place of $[IrCl(cod)]_2$ under the same reaction conditions, **2a** with only 4% ee was obtained in 80%. These results imply that the iridium complex realized the highly enantioselective [4+2] cycloaddition of **1a**. Highly enantiomerically enriched **2b**,**c** were obtained in good yield from **1b**,**c** (entries 10 and 11). Dieneyne **1d** was also transformed into **2d** in very high ee within 1 hour (entry 12).[12]

Table 2. Ir Complex-Catalyzed Enantioselective [4+2] Cycloaddition



1 **2**

Entry	**1**	Diphosphine[a]	Solvent[b]	Time /h	Yield /%	ee /%
1	**1a**	*(S)*-tolBINAP	Toluene	5	63 (**2a**)	68
2	**1a**	(*S*,*S*)-Me-DUPHOS	Toluene	8	36 (**2a**)	60
3	**1a**	(*S*,*S*)-DIOP	Toluene	8	37 (**2a**)	24
4	**1a**	(*S*,*S*)-BDPP	Toluene	2	58 (**2a**)	78
5	**1a**	(*S*,*S*)-BDPP	CH_3CN	15	47 (**2a**)	49
6	**1a**	(*S*,*S*)-BDPP	DME	14	33 (**2a**)	83
7	**1a**	(*S*,*S*)-BDPP	AcOEt	20	60 (**2a**)	92
8	**1a**	(*S*,*S*)-BDPP	AcO-*i*-Pr	5	56 (**2a**)	94
9	**1a**	(*S*,*S*)-BDPP	AcO-*t*-Bu	2	64 (**2a**)	95
10	**1b**	(*S*,*S*)-BDPP	AcO-*t*-Bu	1	73 (**2b**)	98
11	**1c**	(*S*,*S*)-BDPP	AcO-*t*-Bu	1	73 (**2c**)	94
12	**1d**	(*S*,*S*)-BDPP	AcO-*t*-Bu	1	67 (**2d**)	97

[a] tolBINAP: 2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl, Me-DUPHOS: 1,2-Bis(2,5-dimethylphospholano)benzene. DIOP: *O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, BDPP: 2,4-Bis(diphenylphosphino)pentane.
[b] In toluene, the reaction was performed at 90 °C. In other solvents, the reaction was performed under refluxed conditions.

In summary, we developed the first example of iridium complex-catalyzed [4+2] cycloaddition. Highly enantioselective intramolecular reaction of dieneynes with an unsubstituted diene moiety proceeded using an Ir-chiral diphosphine complex to give chiral cyclohexa-1,4-dienes in up to 98% ee.

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(11) A typical experimental procedure is as follows (Table 2, entry 9): Stirring of (*S*,*S*)-BDPP (17.6 mg, 0.04 mmol) and $[IrCl(cod)]_2$ (13.4 mg, 0.02 mmol) in *t*-BuOAc (1 mL) at 40 °C under argon gave a light yellow solution. After addition of a *t*-BuOAc solution (1 mL) of dieneyne **1a** (40.7 mg, 0.205 mmol), the solution was refluxed for 2 h. Solvent was removed under a reduced pressure, then the resulting crude products were purified by thin layer chromatography. Pure **2a** was obtained (26.0 mg, 0.131 mmol, 64% yield) and the ee was determined to be 95% by HPLC analysis using a chiral column.
(12) Aromatized products **3a**–**d** were also generated (entries 9–12).