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Asymmetric Synergy between Chiral Dienes and Diphosphines in Cationic Rh(I)-Catalyzed Intramolecular [4 + 2] Cycloaddition

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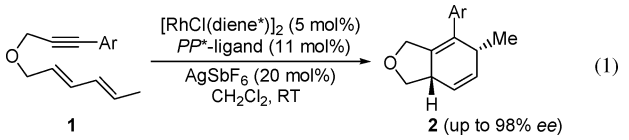
Transition metal-catalyzed Diels−Alder reactions[1] of unactivated dieneynes, such as intramolecular [4 + 2] cycloaddition, are powerful synthetic methods leading to 5,6- or 6,6-fused rings.[2,3] The fused structures thus obtained can be inducted into a variety of natural products whose syntheses are difficult without use of transition metals. Therefore a number of catalyst systems, such as Rh complexes,[2] that perform intramolecular [4 + 2] cycloaddition in excellent yields have been developed in the past 15 years.[3,4] However, the highly enantioselective catalysis is only limited;[5] the chiral Rh catalysts are generally derived from achiral diene−Rh precatalysts and chiral diphosphine ligands, but the effect of the dienes on enantioselectivity has been overlooked. Herein we report a highly efficient catalysis by cationic Rh(I)−chiral diphosphine complexes in the proper combination of *chiral* diene−Rh precatalysts (eq 1). The intramolecular [4 + 2] cycloaddition of dieneyne **1** catalyzed by the chiral diene−Rh(I)−chiral diphosphine complex thus provides significantly increased enantioselectivity than that obtained simply by the Rh(I)−chiral diphosphine complex without involvement of chiral diene.



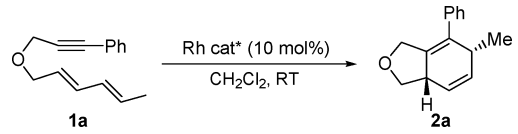
(1)

The reaction of dieneyne **1a** was first attempted by use of a variety of Rh catalyst systems with (*S*,*S*)-BDPP[6] as a chiral diphosphine ligand (Table 1, entries 1−5), which have been found to be effective in the asymmetric ene-type cyclization, including trisubstituted 1,6-enyne substrates.[7] [Rh{(*S*,*S*)-BDPP}(COD)] SbF_6 (COD = 1,5-cyclooctadiene) or the combination of $[Rh(COD)_2]$-SbF_6 with (*S*,*S*)-BDPP was not active presumably because of the competition between COD and the diene substrate **1a** (entries 1 and 2). In contrast, the Rh−NBD (NBD = 2,5-norbornadiene) catalyst was active to give the desired product **2a** in 81% yield (entry 3). The same [Rh{(*S*,*S*)-BDPP}(NBD)]SbF_6 complex was, after hydrogenation under hydrogen (1 atm) to remove NBD, not active enough to catalyze the reaction over 18 h in only 69% yield (entry 4).[5c,7] Intriguingly, the mixture of $[RhCl(COD)]_2$, (*S*,*S*)-BDPP, and $AgSbF_6$[8] gave 89% yield, within 30 min, of the racemic product **2a** (entry 5). A variety of chiral diphosphine ligands (such as DIOP)[9] was thus examined (entries 6−9), and (*R*,*R*)-Me-DUPHOS[10] was the most effective to give **2a** with 13% ee in 99% yield within 5 min (entry 9). In sharp contrast, when $[RhCl(NBD)]_2$ was used instead of $[RhCl(COD)]_2$, the racemic **2a** was obtained (entry 10). These results imply that the dienes, such as COD and NBD, affect enantiodiscrimination between the enantiofaces of substrate **1a**.

Therefore, we investigated the effect of chiral dienes,[11] such as C_1 symmetric dienes **3**−**5**,[11b] in the combination of chiral diphosphine ligands. A remarkable increase in enantioselectivity was observed by using chiral dienes (Table 2). When $[RhCl(\mathbf{3})]_2$ was examined without chiral diphosphine ligand, the product **2a** was obtained in 91% yield within 30 min though with low enantioselectivity (26% ee) (entry 1). The combination of diene **3** with CHIRAPHOS[12] gave a low level of enantioselectivity (entry 2). The use of BINAP[13] and sterically more demanding DM-BINAP even in either enantiomeric form did not influence the sense of enantioselectivity: The same enantiomer product was obtained with a similar level of enantioselectivity (26−30% ee), presumably because the sterically demanding BINAP derivative might be kicked out (entries 1 vs 3−6). However, the combination of $[RhCl(\mathbf{3})]_2$ with (*R*,*R*)-Me-DUPHOS provided an effective catalyst system to afford the product **2a** in high enantioselectivity and yield (entry 7). The use of (*R*,*R*)-Me-DUPHOS gave a higher level of enantioselectivity than that obtained with only chiral diene or the combination of (*R*,*R*)-Me-DUPHOS with *achiral* COD (Table 2, entries 7 vs 1, or Table 1, entry 9). On the other hand, the use of (*S*,*S*)-Me-DUPHOS led to the opposite enantiomer product with lower enantioselectivity (entry 8). Use of monodentate PPh_3 led to the same enantioselectivity as in entry 1 (entry 9).

These results clearly show that both chirality of chiral dienes and Me-DUPHOS work synergistically in the right combination in the enantiodiscriminating step of the intramolecular [4 + 2] cycloaddition; (*R*,*R*)-Me-DUPHOS is the matched pair with the chiral dienes **3**, and hence (*S*,*S*)-Me-DUPHOS is the mismatched

Table 1. Enantioselective [4 + 2] Cycloaddition of **1a** by Rh Catalysts Derived from a Variety of Rh−Diene Precatalysts



entry	Rh cat*	time	yield (%)[c]	ee (%)[d]
1[a]	[Rh(COD$_2$](SbF$_6$)/(*S*,*S*)BDPP	48 h	0	
2	[Rh{(*S*,*S*)-BDPP}(COD)]SbF$_6$	48 h	0	
3	[Rh{(*S*,*S*)-BDPP}(NBD)]SbF$_6$	4 h	81	0
4	[Rh{(*S*,*S*)-BDPP}]SbF$_6$	18 h	69	0
5[b]	[RhCl(COD)]$_2$/(*S*,*S*)-BDPP/AgSbF$_6$	30 min	89	0
6[b]	[RhCl(COD)]$_2$/(*S*,*S*)-CHIRAPHOS/AgSbF$_6$	40 min	87	0
7[b]	[RhCl(COD)]$_2$/(*R*,*R*)-DIOP/AgSbF$_6$	15 min	94	−2[e]
8[b]	[RhCl(COD)]$_2$/(*S*)-BINAP/AgSbF$_6$	20 min	70	9
9[b]	[RhCl(COD)]$_2$/(*R*,*R*)-Me-DUPHOS/AgSbF$_6$	5 min	99	13
10[b]	[RhCl(NBD)]$_2$/(*R*,*R*)Me-DUPHOS/AgSbF$_6$	5 min	88	0

[a] Rh:BDPP = 1:1.1. [b] Rh:ligand:$AgSbF_6$ = 1:1.1:2. [c] Isolated yield. [d] Enantiopurity was determined by chiral GC analysis on a CP-cyclodextrin-β-2,3,6-M-19. [e] Opposite configuration.

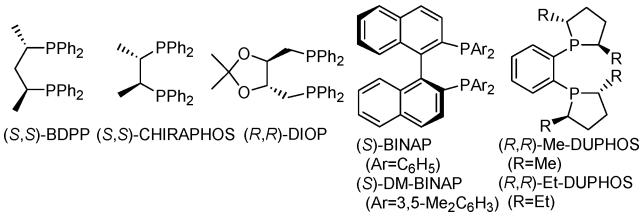


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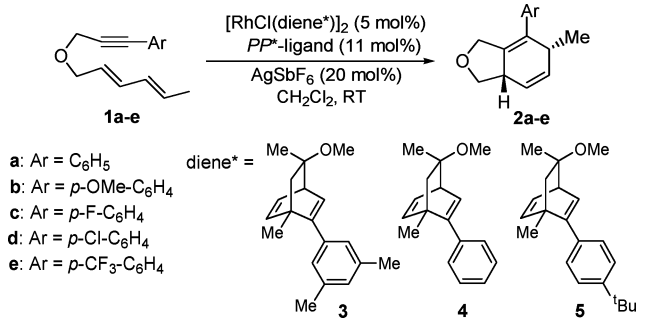
Table 2. Enantioselective [4 + 2] Cycloaddition of **1a**−**e** Catalyzed by Diphosphine−Rh Complexes Bearing Chiral Dienes



entry	substrate	diene*	PP* ligand	time	yield (%)[b]	ee (%)[c]
1	**1a**	**3**		30 min	91	26
2	**1a**	**3**	(*S*,*S*)-CHIRAPHOS	1 h	61	22
3	**1a**	**3**	(*S*)-BINAP	3 h	27	30
4	**1a**	**3**	(*R*)-BINAP	3 h	51	26
5	**1a**	**3**	(*S*)-DM-BINAP	30 min	81	29
6	**1a**	**3**	(*R*)-DM-BINAP	30 min	94	28
7	**1a**	**3**	(*R*,*R*)-Me-DUPHOS	40 min	90	88
8	**1a**	**3**	(*S*,*S*)-Me-DUPHOS	60 min	96	−9[d]
9[a]	**1a**	**3**	PPh_3	30 min	85	26
10	**1a**	**4**	(*R*,*R*)-Me-DUPHOS	2 h	82	91
11	**1a**	**5**	(*R*,*R*)-Me-DUPHOS	50 min	68	87
12	**1b**	**4**	(*R*,*R*)-Me-DUPHOS	2.5 h	51	81
13	**1c**	**3**	(*R*,*R*)-Me-DUPHOS	5 h	91	93
14	**1a**	**3**	(*R*,*R*)-Et-DUPHOS	2 h	99	95
15	**1d**	**3**	(*R*,*R*)-Et-DUPHOS	2 h	89	86
16	**1e**	**3**	(*R*,*R*)-Et-DUPHOS	1.5 h	97	98

[a] Rh:ligand:$AgSbF_6$ = 1:2.2:2. [b] Isolated yield. [c] Enantiopurity was determined by chiral GC analysis on a CP-cyclodextrin-β-2,3,6-M-19. [d] Opposite configuration.

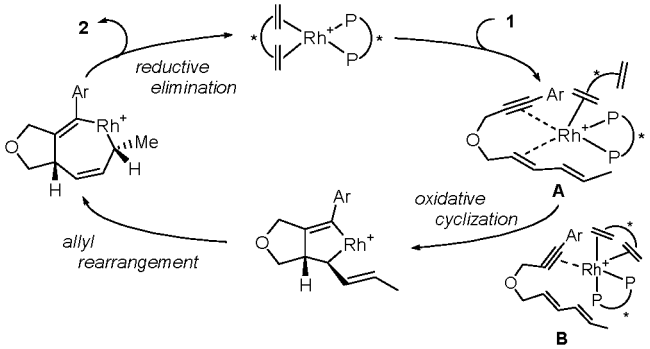


Figure 1. Plausible reaction mechanism.

pair. The enantioselectivity was increased to 91% ee by **4** instead of **3** (entry 10). In the case of **5**, the enantioselectivity slightly decreased (entry 11). A variety of Rh complexes bearing a achiral diene, such as COD or NBD, have been used for catalytic cycloadditions.[3−5,7,8] However, there has been no report on the effect of dienes in detail.

Dieneyne substrates **1b**−**e** with aromatic terminal substituents were further examined under the optimized conditions. The reactions were shown to be effective with both electron-withdrawing and -donating aromatic substituents. Specifically, CF_3 substituents **1e** gave the highest level of enantioselectivity by use of (*R*,*R*)-Et-DUPHOS (97%, 98% ee) (entry 16).

In a plausible mechanism (Figure 1), the substrate-coordinated intermediate **A** forms, and then oxidative cyclization[3a,b,h] of dieneyne substrate **1** affords the metallacyclopentane. Subsequently, allyl rearrangement and, finally, the reductive elimination produces the desired cyclization product **2**. Another possible intermediate **B**, where both chiral diene and diphosphine coordinate to Rh in bidentate fashion, can be eliminated because [Rh{(*S*,*S*)-BDPP}-(COD)]SbF_6 or combination of [$Rh(COD)_2$]SbF_6 with (*S*,*S*)-BDPP is inactive. Therefore, it can be proposed that chiral dienes coordinate to rhodium in monodentate fashion in the enantiodiscriminating step **A**.

In summary, we have succeeded in a highly enantioselective intramolecular [4 + 2] cycloaddition catalyzed by cationic chiral Rh complexes bearing not only chiral phosphine but also chiral diene. This is the first example of asymmetric synergy between chiral dienes and diphosphines. Further studies on the synergy effect on asymmetric catalysis are underway.[14]

Supporting Information Available: Typical experimental procedures and spectral data for **1**, **2**, and [RhCl(diene*)]$_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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