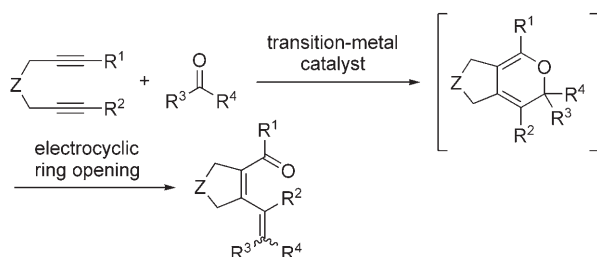


Highly Regio-, Diastereo-, and Enantioselective [2+2+2] Cycloaddition of 1,6-Enynes with Electron-Deficient Ketones Catalyzed by a Cationic Rh^I/H₈-binap Complex**

Ken Tanaka,* Yousuke Otake, Hiromi Sagae, Keiichi Noguchi, and Masao Hirano

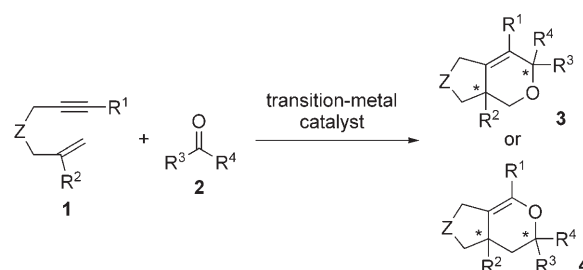
Transition-metal-catalyzed [2+2+2] cycloaddition reactions are efficient methods for the construction of six-membered carbocycles and heterocycles.^[1] For the synthesis of six-membered oxygen heterocycles, [2+2+2] cycloaddition reactions involving carbonyl compounds are potentially attractive. Catalytic [2+2+2] cycloaddition reactions of diynes with carbonyl compounds^[2] in the presence of various transition-metal complexes have been reported, for example, with Ni,^[3] Ru,^[4] and Rh.^[5] However, these reactions frequently failed to produce oxygen heterocycles, and instead dienones were obtained as the major products as a result of electrocyclic ring opening of the initially formed fused α -pyrans (Scheme 1). In



Scheme 1. Transition-metal-catalyzed [2+2+2] cycloaddition of 1,6-diynes with carbonyl compounds.

contrast, a transition-metal-catalyzed [2+2+2] cycloaddition of enynes **1** to ketones **2** would furnish fused dihydropyrans **3** or **4** with two quaternary carbon centers,^[6] bicyclic compounds that would not be converted into ring-opened

products (Scheme 2). Although a Ni⁰/imidazolyldiene-catalyzed reaction of a 1,7-enyne with benzaldehyde has been reported, poor regioselectivity and β -hydride elimination



Scheme 2. Transition-metal-catalyzed [2+2+2] cycloaddition of 1,6-enynes with ketones.

prior to reductive elimination from the corresponding nickelacycle were observed.^[3b,7] Our research group recently reported the reaction of 1,6-diynes with carbonyl compounds to give dienones and *ortho*-functionalized aryl ketones under the catalysis of cationic complexes of Rh^I with modified binap ligands (binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl).^[8,9] Herein, we describe the [2+2+2] cycloaddition of 1,6-enynes with electron-deficient ketones to give fused dihydropyrans with two quaternary carbon centers under the catalysis of a cationic Rh^I/H₈-binap complex, as well as the *ortho* functionalization of aryl ketones with 1,6-enynes in the presence of the same catalyst. Both reactions proceed with excellent regio-, diastereo-, and enantioselectivity.

We first investigated the reaction of the tosylamide-linked 1,6-enyne **1a**, which contains a geminally disubstituted alkene moiety, with ethyl pyruvate (**2a**) in the presence of cationic Rh^I/binap-type bisphosphane complexes (Table 1). The reaction proceeded at 80°C to give the desired fused dihydropyran **3aa** as a single regioisomer and a single diastereomer in excellent yield and with high enantioselectivity in the presence of the catalyst [Rh(cod)₂]BF₄/(*R*)-binap (10 mol %; Table 1, entry 1). The use of the sterically demanding binap-type bisphosphane ligands (*R*)-tol-binap and (*R*)-xyl-binap led to a significant decrease in the yield of **3aa** (Table 1, entries 2 and 3). Although the use of (*R*)-segphos led to an improvement in the enantioselectivity, the yield of **3aa** decreased to 58 % (Table 1, entry 4). Both high yield and high enantioselectivity were observed with the ligand (*R*)-H₈-binap (Table 1, entry 5).

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

Table 1: Screening of ligands for the Rh-catalyzed [2+2+2] cycloaddition of **1a** with ethyl pyruvate (**2a**).

Entry	Ligand	Yield [%] ^[a]	ee [%]
1	(<i>R</i>)-binap	> 99	91
2	(<i>R</i>)-tol-binap ^[b]	22	92
3	(<i>R</i>)-xyl-binap ^[c]	< 10	–
4	(<i>R</i>)-segphos ^[d]	58	96
5	(<i>R</i>)-H ₈ -binap ^[e]	> 99	95

[a] Yield of the isolated product. [b] 2,2'-Bis(di-*p*-tolylphosphanyl)-1,1'-binaphthyl. [c] 2,2'-Bis(di(3,5-xylyl)phosphanyl)-1,1'-binaphthyl. [d] (4,4'-Bi-1,3-benzodioxole)-5,5'-diylbis(diphenylphosphane). [e] 2,2'-Bis(diphenylphosphanyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. cod = 1,5-cyclooctadiene, Ts = *p*-toluenesulfonyl.

We then explored the scope of this process with respect to the two substrates (Table 2). Not only ethyl pyruvate (**2a**; Table 2, entry 1), but also 2,3-butanedione (**2b**; entry 3) and diethyl ketomalonate (**2d**, entry 5), underwent the desired reaction with **1a** to furnish the expected dihydropyran in high yield; however, the reaction of ethyl phenylglyoxylate (**2c**) with **1a** gave the expected dihydropyran **3ac** in low yield (Table 2, entry 4), and acetone (**2e**) failed to react with **1a**

Table 2: Rh⁺/(*R*)-H₈-binap-catalyzed regio-, diastereo-, and enantioselective [2+2+2] cycloaddition of 1,6-enynes **1** with ketones **2**.

Entry	1 (Z, R ¹ , R ²)	2 (R ³ , E)	3	Yield [%] ^[a]	ee [%]
1	1a (NTs, Me, Me)	2a (Me, CO ₂ Et)	(–)- 3aa	> 99	95
2 ^[b,c]	1a (NTs, Me, Me)	2a (Me, CO ₂ Et)	(–)- 3aa	91	> 99
3	1a (NTs, Me, Me)	2b (Me, Ac) ^[d]	(3 <i>R</i> ,6 <i>S</i>)-(–)- 3ab ^[e]	73	98
4	1a (NTs, Me, Me)	2c (Ph, CO ₂ Et)	(+)- 3ac	24	97
5	1a (NTs, Me, Me)	2d (CO ₂ Et, CO ₂ Et)	(–)- 3ad	89	97
6	1a (NTs, Me, Me)	2e (Me, Me) ^[f]	3ae	< 1	–
7	1b (C(CO ₂ Me) ₂ , Ar ^[g] , Me)	2a (Me, CO ₂ Et)	(+)- 3ba	49	98
8	1b (C(CO ₂ Me) ₂ , Ar ^[g] , Me)	2b (Me, Ac) ^[d]	(+)- 3bb	33	92
9 ^[b,c]	1b (C(CO ₂ Me) ₂ , Ar ^[g] , Me)	2a (Me, CO ₂ Et)	(+)- 3ba	82	> 99
10	1c (O, Ph, Me)	2a (Me, CO ₂ Et)	(+)- 3ca	67	> 99
11	1c (O, Ph, Me)	2d (CO ₂ Et, CO ₂ Et)	(+)- 3cd	64	96
12	1d (O, CO ₂ Me, Me)	2a (Me, CO ₂ Et)	(–)- 3da	17	98
13	1d (O, CO ₂ Me, Me)	2d (CO ₂ Et, CO ₂ Et)	(–)- 3dd	61	93
14 ^[b,h]	1e (NTs, Me, H)	2a (Me, CO ₂ Et) ^[d]	(–)- 3ea	25 (30 ^[i])	94
15 ^[b,h]	1e (NTs, Me, H)	2d (CO ₂ Et, CO ₂ Et) ^[d]	3ed	< 1 (70 ^[i])	(–) (52 ^[j])

[a] Yield of the isolated product. [b] Catalyst: 20 mol %. [c] The reaction was carried out at 25 °C in CH₂Cl₂. [d] Compound **2**: 2 equivalents. [e] The absolute configuration of (–)-**3ab** was determined by X-ray crystallographic analysis (Figure 1). [f] Acetone (**2e**) was used as both substrate and solvent. [g] Ar = 4-BrC₆H₄. [h] Ligand: (*R*)-binap. [i] Data for **5ea** (d.r. 2.8:1). [j] The ee value of the major diastereomer. [k] The ee value of the minor diastereomer. [l] Data for **5ed**.

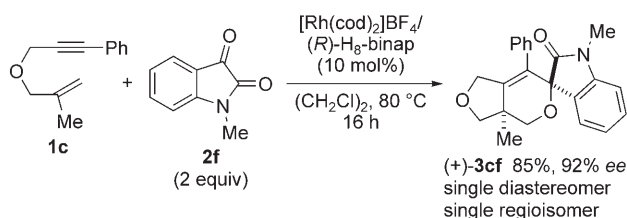
(entry 6).^[10] When the reaction of **1a** with **2a** was carried out at 25 °C with 20 mol % of the Rh catalyst, almost complete enantioselectivity was observed (Table 2, entry 2).

We found that 1,6-enynes with tosylamide (**1a**; Table 2, entries 1–5), malonate (**1b**, entries 7–9), and oxygen (**1c** and **1d**, entries 10–13) linkages could be used in the cycloaddition. With respect to the substituent R¹ at the alkyne terminus, 1,6-enynes substituted not only with methyl (**1a**; Table 2, entries 1–5), but also with phenyl and 4-bromophenyl groups (**1c** and **1b**, entries 7–11), participated in the reaction. In the case of the 4-bromophenyl-substituted 1,6-enyne **1b**, improved yield and enantioselectivity were observed when the reaction was carried out at 25 °C with 20 mol % of the Rh catalyst (Table 2, entry 9). The reaction of the methoxycarbonyl-substituted 1,6-enyne **1d** with **2a** furnished the corresponding dihydropyran **3da** in low yield as a result of the rapid [2+2+2] homocycloaddition of **1d** (Table 2, entry 12); however, when the highly electron deficient ketone **2d** was used, the corresponding dihydropyran **3dd** was obtained in good yield (entry 13). Although the 1,6-enyne **1e** with a monosubstituted alkene moiety reacted with **2a**, the alcohol **5ea** was obtained as the major product along with the expected dihydropyran **3ea** (Table 2, entry 14). Furthermore, the use of diethyl ketomalonate (**2d**) instead of **2a** led to the almost exclusive formation of the alcohol **5ed** (Table 2, entry 15).^[11,12]

We applied this regio-, diastereo-, and enantioselective [2+2+2] cycloaddition to the synthesis of the enantiomerically enriched spirocyclic compound **3cf** by using 1-methylisatin (**2f**) as the carbonyl substrate (Scheme 3).^[13] Importantly, neither the regioisomer **4** nor the other diastereomer was detected in the crude product mixture for this reaction or any of those described in Table 2. The absolute configuration of the dihydropyran product (–)-**3ab** was determined by the anomalous dispersion method (Figure 1).^[14]

Scheme 4 depicts a possible mechanism for the selective formation of the dihydropyran (3*R*,6*S*)-**3ab**: The 1,6-enyne **1a** reacts with the rhodium center of the catalyst to form the rhodacyclopentene **A** as a result of a steric interaction between the Rh-CH₂ moiety and the equatorial P-Ph group of (*R*)-H₈-binap. Subsequently, 2,3-butanedione (**2b**) coordinates to **A** to form complex **B**. The insertion of **2b** followed by the reductive elimination of rhodium then furnishes (3*R*,6*S*)-**3ab**.

Next, we examined the reaction of 1,6-enynes with electron-rich aryl ketones (Table 3). In analogy with



Scheme 3. Synthesis of the enantiomerically enriched spirocyclic compound (+)-3cf.

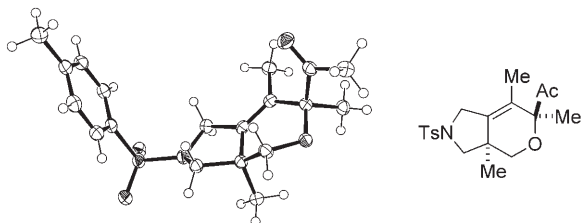
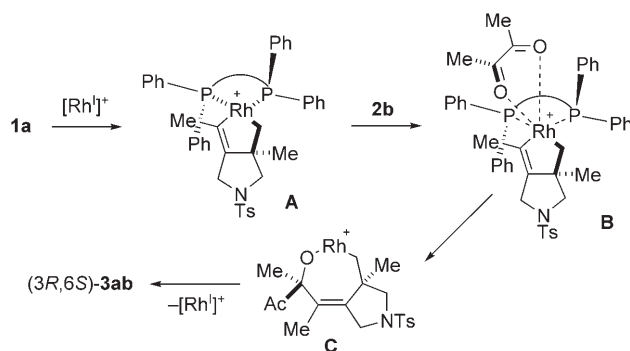


Figure 1. ORTEP drawing of (3R,6S)-(-)-3ab drawn at the 50% probability level.



Scheme 4. Possible mechanism for the selective formation of the dihydropyran (3R,6S)-3ab.

the reactions of 1,6-diynes with electron-rich aryl ketones,^[8a] when the 1,6-enyne **1e** was added over 5 min to a solution of benzophenone (**2g**) and the $[\text{Rh}(\text{cod})_2]\text{BF}_4/(\text{R})\text{-H}_8\text{-binap}$ catalyst (5 mol%) in CH_2Cl_2 at 25 °C, the *ortho*-functionalized aryl ketone **6eg** was isolated in 55% yield (Table 3, entry 1).^[15–17] Although the desired product was obtained in comparable yield when the ligand (*R*)-segphos was used (Table 3, entry 2), the use of (*R*)-binap led to a significantly lower yield of **6eg** (entry 3).^[18] These reactions proceeded with perfect regioselectivity and high enantioselectivity. Acetophenone (**2h**) also participated in the reaction with **1e** (Table 3, entry 4). Although **2i**, in which the *meta* substituent R^3 is an electron-donating group, reacted with **1f** to provide the expected product **6fi** as a single regioisomer (Table 3, entry 5), the presence of an electron-withdrawing group at the *meta* position (in **2j**) led to a complete shutdown of the reaction (entry 6). Furthermore, the 1,6-enyne **1a** with a geminally disubstituted alkene moiety failed to react with **2g**. Instead, **1a** underwent [2+2+2] homocycloaddition (Table 3, entry 7). The absolute configuration of the *ortho*-

Table 3: Rh-catalyzed regio- and enantioselective *ortho* functionalization of aryl ketones **2** with 1,6-enynes **1**.^[a]

Entry	1	2 (R^2 , R^3)	Ligand	6	Yield [%] ^[b]	ee [%]
1	1e	2g (Ph, H)	(<i>R</i>)-H ₈ -binap	(+)- 6eg	55	96
2	1e	2g (Ph, H)	(<i>R</i>)-segphos	(+)- 6eg	59	95
3	1e	2g (Ph, H)	(<i>R</i>)-binap	(+)- 6eg	26	97
4	1e	2h (Me, H)	(<i>R</i>)-H ₈ -binap	(<i>R</i>)-(+)- 6eh ^[c]	34	98
5	1f	2i (Me, OMe)	(<i>R</i>)-H ₈ -binap	(+)- 6fi	34	94
6	1f	2j (Me, CF ₃)	(<i>R</i>)-H ₈ -binap	6fj	< 1	–
7	1a	2g (Ph, H)	(<i>R</i>)-H ₈ -binap	6ag	< 1	–

[a] The enyne **1** was added over a period of 5 min (see the Supporting Information). [b] Yield of the isolated product. [c] The absolute configuration of (+)-**6eh** was determined by X-ray crystallographic analysis (Figure 2).

functionalized aryl ketone (+)-**6eh** was determined by the anomalous dispersion method (Figure 2).^[14]

In conclusion, a cationic $\text{Rh}^{\text{I}}/(\text{R})\text{-H}_8\text{-binap}$ complex catalyzes the [2+2+2] cycloaddition of 1,6-enynes with

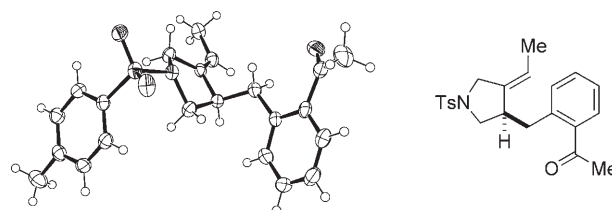


Figure 2. ORTEP drawing of (*R*)-(+)-**6eh** drawn at the 50% probability level.

electron-deficient ketones to give fused dihydropyrans containing two quaternary carbon centers with excellent regio-, diastereo-, and enantioselectivity. Electron-rich aryl ketones react with 1,6-enynes in the presence of the same catalyst to give *ortho*-functionalized aryl ketones with excellent regio- and enantioselectivity. Further studies to expand the scope of the two reactions and elucidate the reaction mechanisms are in progress.

Experimental Section

Representative procedure: (*R*)-H₈-binap (18.9 mg, 0.030 mmol) and $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (12.2 mg, 0.030 mmol) were dissolved in CH_2Cl_2 (2.0 mL) in a Schlenk tube under an argon atmosphere, and the

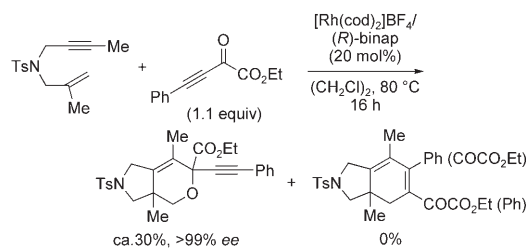
mixture was stirred at room temperature for 5 min. H_2 was introduced into the resulting solution, which was then stirred at room temperature for 0.5 h, concentrated to dryness, and dissolved in $(CH_2Cl)_2$ (0.5 mL). A solution of **1c** (55.9 mg, 0.300 mmol) and **2f** (96.7 mg, 0.600 mmol) in $(CH_2Cl)_2$ (1.5 mL) was added at room temperature, and the resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was then concentrated, and the product was purified by preparative TLC (hexane/ethyl acetate 2:1) to furnish (+)-**3cf** (88.8 mg, 0.256 mmol, 85 %, 92 % ee, single diastereomer) as a pale yellow oil. $[\alpha]_D^{25} = +52.8$ deg $cm^3 g^{-1} dm^{-1}$ ($c = 2.04 \times 10^{-2}$ g cm^{-3} acetone; 92 % ee); 1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.29$ (d, $J = 7.5$ Hz, 1H), 7.20 (t, $J = 7.5$ Hz, 1H), 7.15–6.99 (m, 4H), 6.87–6.75 (m, 2H), 6.57 (d, $J = 7.5$ Hz, 1H), 4.59 (d, $J = 10.5$ Hz, 1H), 4.45 (d, $J = 13.8$ Hz, 1H), 4.09 (d, $J = 13.8$ Hz, 1H), 3.93 (d, $J = 10.5$ Hz, 1H), 3.91 (d, $J = 8.1$ Hz, 1H), 3.62 (d, $J = 8.1$ Hz, 1H), 3.00 (s, 3H), 1.58 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 175.6$, 144.3, 144.1, 135.3, 129.9, 128.7, 128.6, 128.0, 127.5, 127.2, 124.4, 122.9, 108.2, 79.1, 77.0, 69.7, 68.3, 41.4, 25.8, 23.0 ppm; IR (neat): $\tilde{\nu} = 2964$, 1715, 1090, 1052, 705 cm^{-1} ; HRMS (FAB): m/z calcd for $C_{22}H_{21}NO_3$: 380.1532; found: 380.1562 $[M+H]^+$; HPLC (chiralcel OD-H, hexane/iPrOH 90:10, 1.0 mL min^{-1}): t_R (major isomer): 8.5 min, t_R (minor isomer): 12.9 min.

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