Carbocyclization

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Rhodium-Catalyzed Regio- and Enantioselective Intermolecular [4+2] Carbocyclization of 4-Alkynals with *N*,*N*-Dialkyl Acrylamides**

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Transition-metal-catalyzed cycloaddition is a powerful synthetic method for the construction of cyclic frameworks.[1] In particular, [4+2] cycloadditions of dienes or enynes with alkynes or alkenes have been widely examined for the construction of six-membered-ring systems.[2–4] However, [4+2] cycloadditions via cyclic acyl metal intermediates to give six-membered carbonyl compounds are rare.[5] Furthermore, although some transition-metal-catalyzed enantioselective intramolecular [4+2] cycloadditions have been reported,[3] enantioselective intermolecular [4+2] cycloaddition has not been established.

A recent report described the rhodium-catalyzed [4+2] carbocyclization of 4-alkynals with alkynes to afford cyclo-

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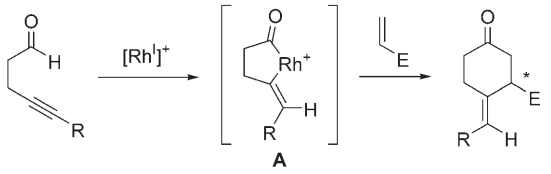
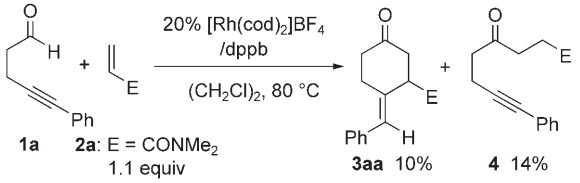
Supporting information for this article (full procedures and characterization data) is available on the WWW under http://www.angewandte.org or from the author.

hexenones via five-membered acyl rhodium intermediates **A**, formed through the intramolecular hydroacylation of alkynes.[6] Murakami et al. also reported that similar five-membered acyl rhodium intermediates, formed by insertion of rhodium between the carbonyl carbon atom and the α-carbon atom of cyclobutanones, undergoes intramolecular reaction with alkenes to afford bicyclic cyclohexanones.[7] Herein we reveal that a cationic rhodium(I) complex of (*R*,*R*)-walphos (*R*,*R*-**7**)[8] catalyzes a highly regio- and enantioselective intermolecular [4+2] carbocyclization of 4-alkynals with *N*,*N*-dialkyl acrylamides to give enantioenriched cyclohexanones(Scheme 1).



Scheme 1. Regio- and enantioselective intermolecular [4+2] carbocyclization of 4-alkynals with alkenes.

We first examined the [4+2] carbocyclization of 5-phenyl-4-pentynal (**1a**) with alkenes. After screening various alkenes and rhodium(I) complexes, we found that the reaction of **1a** with *N*,*N*-dimethylacrylamide (**2a**) in the presence of catalytic [Rh(cod)$_2$]BF$_4$/dppb furnished cyclohexanone **3aa** in low yield along with alkynyl ketone **4** (Scheme 2). On the other hand, the use of dppe as a ligand did not furnished cyclohexanone **3aa** at all.

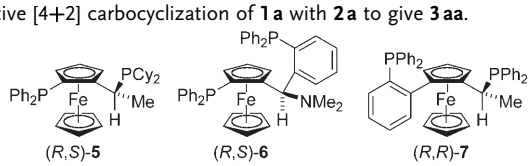


Scheme 2. [4+2] Carbocyclization of 5-phenyl-4-pentynal (**1a**) with *N*,*N*-dimethylacrylamide (**2a**).

The enantioselective [4+2] carbocyclization of **1a** with **2a** was examined with various chiral bidentate phosphine ligands (Table 1), which have large P-M-P natural bite angles to facilitate the reductive elimination step. The study revealed that the use of ligand (*R*,*R*)-**7** dramatically increased the yield and *ee* value of **3aa** (Table 1, entry 5). Although lower yield and *ee* were observed, the reaction can be carried out with a low catalyst loading of 5% (Table 1, entry 7). The reaction did not proceed at all in the presence of (*R*,*R*)-**6**, which bears a coordinating dimethylamino group (Table 1, entry 4).

A series of 5-substituted-4-pentynals **1a**–**f** was subjected to the above optimized reaction conditions (Table 2). The reactions of aryl- (Table 2, entries 1–4), alkenyl- (Table 2, entry 6), and alkyl- (Table 2, entry 7) substituted 4-pentynals with **2a** afforded the corresponding cyclohexanones in good yield with high enantioselectivity. The absolute configuration

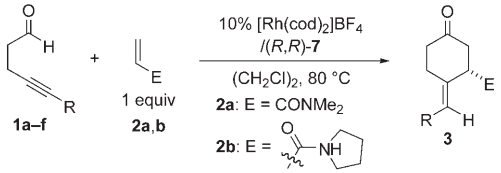
Table 1: Screening of ligands **5**–**7** in the rhodium-catalyzed enantioselective [4+2] carbocyclization of **1a** with **2a** to give **3aa**.



Entry	Ligand	Catalyst [%]	Yield [%]	*ee* [%]
1	(*S*,*S*)-diop	20	10[a]	37
2	(*R*)-Tol-binap	20	9[a]	2
3	(*R*,*S*)-**5**	20	15[a]	20
4	(*R*,*S*)-**6**	20	0[a]	
5	(*R*,*R*)-**7**	20	72[b]	>99
6	(*R*,*R*)-**7**	10	57[b]	>99
7	(*R*,*R*)-**7**	5	52[b]	98

[a] Yield determined by NMR spectroscopy. [b] Yields of isolated products.

Table 2: Rhodium-catalyzed enantioselective [4+2] carbocyclization of 5-substituted-4-pentynals with *N*,*N*-dialkylacrylamides.[a]



Entry	**1** (R)	Alkene	Product	Yield [%][b]	*ee* [%]
1	**a** (Ph)	**2a**	(+)-**3aa**	57	>99
2	**b** (4-MeOC$_6$H$_4$)	**2a**	(+)-**3ba**	58	>99
3	**c** (4-F$_3$CC$_6$H$_4$)	**2a**	(+)-**3ca**	51	94
4	**d** (4-ClC$_6$H$_4$)	**2a**	(+)-(*S*)-**3da**	68	>99
5	**d** (4-ClC$_6$H$_4$)	**2b**	(+)-**3db**	77	>99
6[c]	**e** (1-cyclohexenyl)	**2a**	(+)-**3ea**	50	97
7[c,d]	**f** (*n*Bu)	**2a**	(+)-(*S*)-**3fa**	77	>99

[a] No signals for other regioisomers were observed in the ^{1}H NMR spectra. The *ee* values were determined by chiral HPLC and GC analysis. [b] Yields of isolated products. [c] Catalyst: 20%. [d] Temperature: 40°C.

of (+)-**3da** was determined to be *S* by an anomalous dispersion method (Figure 1),[9] and that of (+)-**3fa** was determined to be *S* by the circular dichroism exciton chirality method.

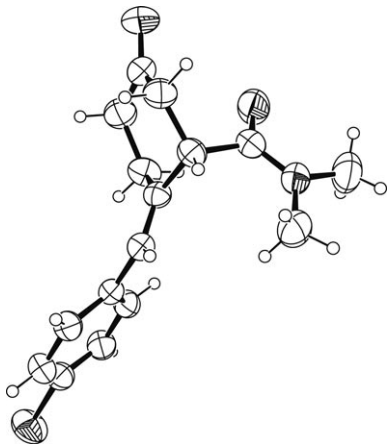
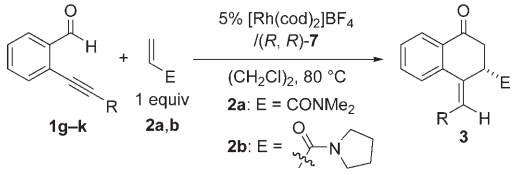


Figure 1. ORTEP diagram of (*S*)-(+)-**3da**. Ellipsoids drawn at the 50% probability level.

The enantioselective [4+2] carbocyclization of 2-alkynyl benzaldehydes **1g–k** with **2a** was investigated next (Table 3). Aryl- (Table 3, entries 1 and 3), alkenyl- (Table 3, entry 4), and alkyl- (Table 3, entries 5 and 6) substituted 2-ethynyl-

Table 3: Rhodium-catalyzed enantioselective [4+2] carbocyclization of 2-alkynylbenzaldehydes with *N*,*N*-dialkylacrylamides.[a]



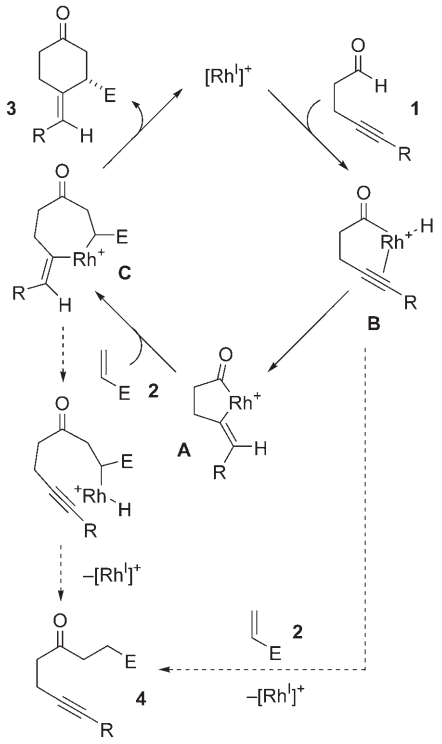
Entry	**1** (R)	Alkene	Product	Yield [%][b]	*ee* [%]
1	**g** (Ph)	**2a**	(+)-**3ga**	80	97
2	**g** (Ph)	**2b**	(+)-**3gb**	80	97
3	**h** (2-ClC_6H_4)	**2a**	(+)-**3ha**	94	90
4	**i** (1-cyclohexenyl)	**2a**	(+)-**3ia**	56	99
5	**j** (*n*Bu)	**2a**	(+)-**3ja**	56	>99
6	**k** (Cl(CH_2)$_3$)	**2a**	(+)-**3ka**	81	97

[a] No signals for other regioisomers were observed in the ^{1}H NMR spectra. The *ee* values were determined by chiral HPLC analysis. [b] Yields of isolated products.

benzaldehydes afforded the corresponding cyclohexanones in good yield with high enantioselectivity. Not only *N*,*N*-dimethylacrylamide (**2a**), but also *N*-acryloylpyrrolidine (**2b**) can be employed (Table 2, entry 5 and Table 3, entry 2).[10] In general, the reactions of 2-alkynylbenzaldehydes **1g–k** are more facile than those of 5-substituted-4-pentynals **1a–f**, which allows a lower catalyst loading. Because the [4+2] carbocyclization of 2-alkynyl benzaldehydes with alkynes did not proceed at all, this successful [4+2] carbocyclization of 2-alkynyl benzaldehydes with *N*,*N*-dialkylacrylamides is noteworthy. Importantly, these [4+2] carbocyclizations of 4-alkynals **1a–k** with **2a**,**b** are highly regioselective and no regioisomers were detected in the crude reaction mixtures.[11]

Scheme 3 shows a plausible mechanism for this carbocyclization. We infer that the rhodium catalyst oxidatively inserts into the aldehyde C–H bond to afford a rhodium acyl hydride **B**. The *cis* addition of the rhodium hydride species to the metal-bound alkyne then provides the five-membered acyl rhodium intermediate **A**.[12] Complexation of the alkene is followed by insertion to form metallacycle **C**. Reductive elimination furnishes the cyclohexanone **3** and regenerates the Rh catalyst. On the other hand, β-hydride elimination from metallacycle **C** can furnish the alkynyl ketone **4**. Alternatively, carbometalation of intermediate **B** with the alkene prior to hydrometalation can also furnish **4**.

In conclusion, we have developed a rhodium-catalyzed regio- and enantioselective intermolecular [4+2] carbocyclization of 4-alkynals with *N*,*N*-dialkylacrylamides. This method serves as an attractive new route to enantioenriched cyclohexanones in view of the one-step access to 4-alkynals from readily available terminal alkynes (1,4-addition to acrolein or Sonogashira coupling with 2-bromobenzaldehyde).



Scheme 3. Plausible mechanism for the rhodium-catalyzed [4+2] carbocyclization of 4-alkynals with *N*,*N*-dialkylacrylamides.

Experimental Section

Representative procedure (Table 3, entry 1): Under an Ar atmosphere, a solution of (*R*,*R*)-**7** (9.9 mg, 0.015 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of [Rh(cod)$_2$]BF_4 (6.6 mg, 0.015 mmol) in CH_2Cl_2 (1.0 mL) at room temperature, and the mixture was stirred for 5 min. H_2 was introduced to the resulting solution in a Schlenk tube. The mixture was stirred at room temperature for 0.5 h, and the resulting solution was concentrated to dryness. Benzaldehyde **1g** (61.9 mg, 0.300 mmol) and **2a** (29.7 mg, 0.300 mmol) were added to the residue by using (CH_2Cl)$_2$ (1.5 mL). The mixture was stirred at 80 °C for 20 h. The resulting solution was concentrated and purified by preparative TLC (hexane/EtOAc 1:4) to furnish (+)-**3ga** (73.3 mg, 0.240 mmol, 80% yield, 97% *ee*) as an orange solid. M.p. 56–58 °C; $[\alpha]_D^{25}$ +201.0° (acetone, *c* 1.534; 97% *ee*); IR (neat): $\tilde{\nu}$ = 2930, 1680, 1630, 1600, 1445, 1400, 1282, 1240, 1142, 772, 758, 730, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.12–8.02 (m, 1H), 7.37–7.28 (m, 1H), 7.27–7.07 (m, 7H), 6.67 (s, 1H), 4.04 (dd, *J* = 6.9 and 4.5 Hz, 1H), 3.25 (dd, *J* = 17.4 and 6.9 Hz, 1H), 3.20 (s, 3H), 2.94 (s, 3H), 2.87 ppm (dd, *J* = 17.4 and 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 196.2, 170.2, 137.5, 136.1, 134.1, 133.2, 132.2, 129.1, 128.9, 128.7, 128.5, 128.3, 127.5, 126.7, 48.7, 43.1, 37.6, 36.0 ppm; HRMS (EI): calcd for $C_{17}H_{13}O$ [*M*–$CONMe_2$]$^+$: 233.0967; found; 233.0984; HPLC: t_R = 18.3 min (major isomer) and 22.7 min (minor isomer) (CHIRALPAK AD, hexane/*i*PrOH 90:10, 1.0 mL min^{-1})

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[10] The use of substituted *N*,*N*-dialkyl acrylamides (*N*,*N*-dimethylmethacrylamide, 1-pyrrolidinylpropenone, *N*-methylmaleimide) did not afford the desired carbocyclization products.

[11] In the case of the reactions of **1a–k** with Rh^{I}–(*R*,*R*)-walphos, no vinyl protons other than those for the desired cyclohexanones **3** were observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. Although we examined a wide variety of phosphine ligands, the other regioisomer derived from **1a** and **2a** was not obtained at all. On the other hand, the other regioisomer derived from **1g** and **2a** was isolated in trace amounts when using Rh^{I+}–dppb. The desired major regioisomer **3ga** and the minor regioisomer can easily be distinguished by the ^{1}H NMR chemical shifts of their vinyl protons (major isomer: $\delta =$ 6.68 ppm (s), minor isomer: $\delta = 6.78$ ppm (d, $J = 1.2$ Hz)).

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