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Asymmetric Three-Component Coupling Reaction of Alkyne, Enone, and Aldehyde Catalyzed by Chiral Phebox Ruthenium Catalysts

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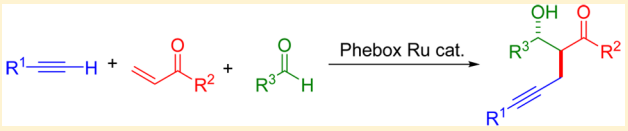
Supporting Information

ABSTRACT: Catalytic asymmetric three-component coupling reactions of terminal alkynes, α,β-unsaturated ketones, and aldehydes were studied. The chiral ruthenium complexes containing bis(oxazolinyl)phenyl ligands were found to serve as efficient catalysts for a tandem reaction based on conjugate addition of terminal alkynes to α,β-unsaturated ketones and subsequent aldol reaction with aldehydes, giving β-hydroxyketone derivatives containing α-propargyl groups in high yields with moderate to good enantioselectivities. This method can produce various functional molecules from commercially available substrates in a one-pot procedure. The absolute configuration of the major product was determined by X-ray analysis. The control experiments suggested that a ruthenium enolate species generated in situ by conjugate addition could be involved as an intermediate for the aldol coupling with an aldehyde.

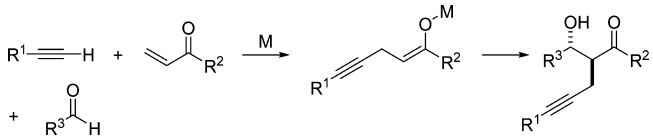


INTRODUCTION

Catalytic multicomponent coupling reactions are an effective synthetic methodology for construction of multifunctional organic molecules and bioactive compounds from simple and ubiquitous precursors.[1] The advantage of this method is that an intermediate can be used in the next step without its isolation. Thus far, successive conjugate addition and aldol reactions have been widely elucidated as an effective strategy for sequence bond forming reactions.[2] Since Cu-catalyzed enantioselective conjugate addition of alkylzinc with α,β-unsaturated carbonyl compounds is a reliable C−C bond formation protocol, the subsequent aldol reaction with a zinc enolate intermediate generated in situ accomplishes a tandem coupling reaction.[3] In this context, the seminal study by Feringa and co-workers showed highly selective Cu catalysts with chiral phosphoramidite ligands for asymmetric three-component coupling reactions of organozinc reagents, α,β-unsaturated carbonyl compounds, and aldehydes.[4] This type of asymmetric tandem coupling reaction triggered by conjugate addition of alkylzinc reagents has been expanded to various one-pot processes to prepare chiral materials.[5] Concurrently, Rh-catalyzed conjugate addition with organoborane reagents has expanded the substrate variation in transition-metal-catalyzed C−C bond formation reactions.[6] For example, Hayashi and co-workers reported a sequence of conjugate arylation of an α,β-unsaturated ketone with an arylborane reagent and aldol reaction of aldehydes with a Rh enolate species generated in situ.[7] Recently, Krische and co-workers developed an intramolecular annulation reaction by using a chiral Rh catalyst.[8]

Catalytic and direct conjugate addition of terminal alkynes to α,β-unsaturated carbonyl compounds using transition-metal catalysts is also a useful and atom-economic C−C bond forming process.[9] Thus, multicomponent coupling via the direct conjugate addition of a terminal alkyne and successive aldol coupling reaction with carbonyl compounds can provide an efficient method for the preparation of complex molecules with various functional groups (Scheme 1). Despite the synthetic potential of this process, to our best knowledge, an efficient process based on direct conjugate alkynylation and aldol reaction has not been reported. In this process, 1,2-addition of alkynes to carbonyl compounds, such as aldehydes, giving propargyl alcohol derivatives is considered to be a major side reaction.[10] In addition, transition metals also catalyze dimerization and trimerization of alkynes that form byproducts, namely, enynes and benzene derivatives, respectively.[11,12] Thus, control of chemoselectivity by metal catalysts is a key to obtain multicomponent coupling products effectively.

Scheme 1. Three-Component Coupling of an Alkyne, Enone, and Aldehyde



Recently, transition-metal complexes with pincer ligands have been extensively studied as efficient catalysts in various reactions.[13] Their stability and unique reactivity are due to their structural feature of having two metallacycles. In particular, chiral NCN pincer complexes have been applied to asymmetric transformations as efficient catalysts.[14] For example, the bis(oxazolinyl)phenyl (phebox) ligands have recently been applied to conjugate reduction,[15] reductive aldol,[16] alkynylation,[17] diborylation,[18] and C−H functionalization.[19] The

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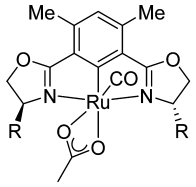
related bis(imidazolinyl)phenyl (phebim) and bis(imidazolidine) (phbidine) ligands have also been employed as efficient chiral NCN ligands for Pt,[20] Pd,[21] and Rh[22] catalysts. Thus, these pincer metal catalysts have the potential to promote new catalytic transformations.



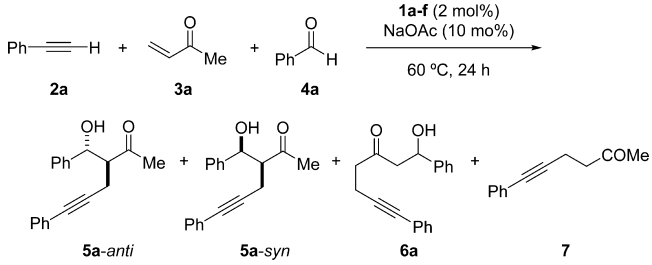
R = Ph (**1a**), *i*-Pr (**1b**), *i*-Bu (**1c**)
Bn (**1d**), Et (**1e**), Me (**1f**)

We previously found that the NCN pincer Ru complex containing the phebox ligand serves as an asymmetric catalyst in the direct alkynylation of aldehydes and α,β-unsaturated carbonyl compounds.[23,24] These reactions are atom-economic transformations for the construction of alkyne derivatives. In the case of conjugate addition, a Ru enolate species could be formed by insertion of a terminal alkyne into an α,β-unsaturated carbonyl compound. Thus, trapping of the Ru enolate intermediate by an electrophile, such as an aldehyde, could be used to construct various functionalized molecules in a one-pot procedure. Here, we report the three-component coupling reaction of aldehydes, alkynes, and enones catalyzed by the phebox-Ru complex **1**.

RESULTS AND DISCUSSION

First, the catalytic reaction of phenylacetylene (**2a**), methylvinylketone (**3a**), and benzaldehyde (**4a**) was conducted in the presence of **1a** (2 mol %). Heating of a mixture of **2a**, **3a**, and **4a** in a 4:3:1 ratio in THF at 60 °C resulted in the formation of coupling products **5a** and **6a** in 44% yield with a high ratio of 94:6 (Table 1, entry 1). In this reaction, the *anti*-isomer of **5a**-*anti* was obtained as the major product with an *anti*/*syn* diastereomeric ratio of 1.3:1 and 47% ee of the *anti*-isomer. A major byproduct was found to be the γ,δ-alkynyl ketone $PhCC(CH_2)_2COMe$ (**7**), which was formed simply by conjugate addition of **2a** with **3a**. The ^1H NMR spectrum indicated that **7** was formed in 37% yield based on the amount of **3a**. In contrast, a propargyl alcohol derivative obtained by 1,2-addition of **2a** with **4a** was not detected, indicating that conjugate addition to an enone was more favorable than 1,2-addition to an aldehyde. The catalytic reaction was affected by solvents and additives. The use of toluene increased the enantioselectivity (entry 2). Interestingly, reactions in ethanol and 2-propanol improved the diastereoselectivity to 2.6−3.3:1 (entries 3 and 4). Furthermore, neat conditions increased the product yield to 68% (entry 5). In this case, the diastereoselectivity decreased compared to those of the reaction in alcohol solutions. This indicated that alcohols influenced the selectivity of the reaction. When the catalytic reaction was conducted in the presence of a catalytic amount of alcohol (20 mol %), both the diastereoselectivity and yield were enhanced without decreasing the enantioselectivity (entries 6 and 7).[25] In these reactions, **7** was also formed as a major byproduct in 59% and 66% yields based on the amount of **3a**. When the reaction was conducted for 12 h, the enantioselectivity was slightly improved despite the lower ratio of **5a**:**6a** (entry 8). It is noted that the catalytic reaction did not proceed in the absence of NaOAc.

Table 1. Enantioselective Three-Component Coupling Reaction of Phenylacetylene (2a), Methylvinylketone (3a), and Benzaldehyde (4a) Catalyzed by (phebox)Ru Catalysts[a]



entry	cat	solvent	yield of **5a** and **6a** (**5a**:**6a**)[b]	ratio of **5a**-*anti*:**5a**-*syn*[c]	% ee[d] **5a**-*anti*/**5a**-*syn*
1	**1a**	THF	44 (96:4)	1.3:1	47/7
2	**1a**	toluene	34 (87:13)	1.3:1	64/12
3	**1a**	ethanol	32 (93:7)	3.3:1	69/20
4	**1a**	2-propanol	36 (>99:1)	2.6:1	68/22
5	**1a**		68 (93:7)	1.3:1	66/19
6[e]	**1a**		77 (93:7)	3.0:1	70/27
7[f]	**1a**		82 (93:7)	2.0:1	69/25
8[e,g]	**1a**		88 (87:13)	1.3:1	79/46
9[e]	**1b**		90 (>99:1)	2.0:1	53/81
10[e]	**1c**		84 (>99:1)	1.3:1	25/60
11[e]	**1d**		85 (>99:1)	1.4:1	45/66
12[e]	**1e**		83 (>99:1)	1.9:1	32/56
13[e]	**1f**		92 (>99:1)	0.9:1	51/46

[a]Reaction conditions: **1** (0.020 mmol), **2a** (1.0 mmol), **3a** (4.0 mmol), **4a** (3 mmol), 60 °C, 24 h. [b]The ratio of **5a**:**6a** was determined by ^1H NMR. [c]Determined by ^1H NMR. [d]Determined by HPLC. [e]Use of ethanol (20 mol %). [f]Use of 2-propanol (20 mol %). [g]Reaction time: 12 h.

Next, the effect of the substituents on the phebox ligands was examined by using **1b**−**f** (entries 9−13). In the case of **1b** with the isopropyl phebox ligand, the enantioselectivity of **5a**-*anti* decreased, but the enantioselectivity of **5a**-*syn* was enhanced to 81% (entry 9). Ru catalysts with isobutyl, benzyl, ethyl, and methyl phebox ligands **1c**−**f** gave good yields and ratios of **5a**:**6a**, but lower enantioselectivity of **5a**-*anti*. Thus, the phenyl substituent was suitable in terms of product selectivity. We also examined other Ru catalysts in this coupling reaction. Although the BINAP-Ru complex $[(R)\text{-BINAP}]Ru(OAc)_2$ and the pybox-Ru complex $[(S,S)\text{-pybox-}i\text{Pr}]RuCl_2(C_2H_4)$ exhibited catalytic activity, they were less effective than the phebox-Ru complexes. This result suggested the importance of the NCN-Ru pincer scaffold. The stereochemistry of **5a** was confirmed by derivatization by hydrogenation to a known compound[26] and X-ray analysis of the related product (vide infra). To the best of our knowledge, this result is the first example of an asymmetric three-component coupling involving direct conjugate addition of a terminal alkyne and aldol reaction with an aldehyde.

Next, the catalytic reaction of other aldehydes and alkynes was examined by using the phebox-Ru complex **1a** (Table 2, entry 1). Reaction with benzaldehyde derivatives containing electron-withdrawing groups at the para position proceeded smoothly to give the desired products **5b**−**f** in 40−82% yields with dr = 1.3−2.1:1 and 53−78% ee of *anti*-products (entries 1−5). In the case of a benzaldehyde derivative containing an electron-donating methoxy group at the para position, the yield was maintained, but a decrease in enantioselectivity was observed (entry 6). Reaction with 2-naphthaldehyde showed

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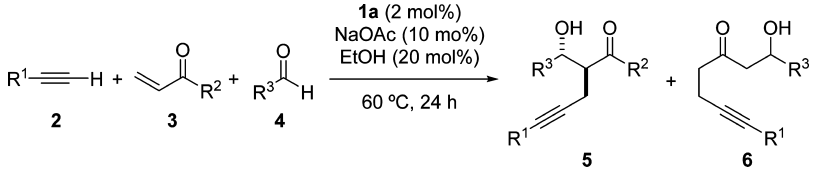
Table 2. Enantioselective Three-Component Coupling Reaction of Alkynes 2, α,β-Unsaturated Ketones 3, and Aldehydes 4 Catalyzed by (phebox)Ru Catalyst 1a[a]



entry	R^1; R^2; R^3 (**5**)	yield of **5** and **6** (**5**:**6**)[b]	ratio of **5**-*anti*:**5**-*syn*[c]	% ee[d] **5**-*anti*/**5**-*syn*
1[e]	Ph; Me; 4-BrC_6H_4 (**5b**)	82 (>99:1)	1.9:1	78/18
2	Ph; Me; 4-ClC_6H_4 (**5c**)	51 (>99:1)	1.3:1	61/9
3	Ph; Me; 4-$NO_2C_6H_4$ (**5d**)	71 (>99:1)	1.2:1	53/3
4[e]	Ph; Me; 4-$CF_3C_6H_4$ (**5e**)	71 (95:5)	1.8:1	70/10
5	Ph; Me; 4-$MeO_2CC_6H_4$ (**5f**)	69 (93:7)	2.1:1	69/12
6	Ph; Me; 4-$MeOC_6H_4$ (**5g**)	52 (86:14)	2.1:1	39/25
7	Ph; Me; 3-BrC_6H_4 (**5h**)	72 (95:5)	1.9:1	60/8
8	Ph; Me; 2-naphthyl (**5i**)	75 (91:9)	3.0:1	64/16
9	Ph; Me; 2-thiophenyl (**5j**)	68 (>99:1)	2.1:1	61/7
10	4-$CF_3C_6H_4$; Me; Ph (**5k**)	87 (>99:1)	1.9:1	52/12
11	4-BrC_6H_4; Me; Ph (**5l**)	51 (>99:1)	1.3:1	65/44
12	4-$MeOC_6H_4$; Me; Ph (**5m**)	40 (95:5)	1.1:1	52/8
13	Ph; *n*-C_5H_{11}; Ph (**5n**)	48 (>99:1)	1.6:1	60/13

[a]Reaction conditions: **1a** (0.020 mmol), **2** (1.0 mmol), **3** (4.0 mmol), **4** (3.0 mmol), 60 °C, 24 h. [b]The ratio of **5a**:**6a** was determined by ^{1}H NMR. [c]Determined by ^{1}H NMR. [d]Determined by HPLC. [e]Reaction time: 12 h.

higher diastereoselectivity than those of other aldehydes (entry 8). A heteroaromatic aldehyde was also used as an electrophile to give the coupling product in 68% yield (entry 9). Substituents on the terminal alkynes affected product yields, with electron-withdrawing groups at an aromatic ring showing higher yields (entries 10−12). This trend was similar to the conjugate addition of alkynes to α,β-unsaturated ketones catalyzed by **1a**.[24] Thus, efficiency of the conjugate addition step and stability of the resulting Ru-enolate species are considered to be significant to obtain products **5** in high yields. As an enone substrate, oct-1-en-3-one was used in the coupling reaction to give the corresponding product **5n** (entry 13). In contrast, phenylvinylketone, 2-hydroxypropan-2-ylvinylketone, and ethyl acrylate were not viable as substrates. Since conjugate addition with those substrates with phenylacetylene was catalyzed by the phebox-Ru complexes,[24] subsequent aldol reaction could not occur probably due to first protonation of a Ru-enolate intermediate prior to the aldol reaction.

The absolute configuration of **5b**-*anti* was determined by X-ray analysis. The crystals of **5b**-*anti* (93% ee) were obtained by crystallization twice from a hexane solution. The ORTEP diagram unambiguously showed the *anti*-conformation (Figure S1). The absolute configurations at the C3 and C4 atoms were determined to be S and R, respectively. The C6−C7 bond length of 1.201(5) Å is that of a typical triple bond.

To obtain insight into the catalytic reaction, we monitored the catalytic reaction by ^{1}H NMR spectroscopy (Figure 1). After 12 h, the concentrations of **5a** and **4a** reached maximum and minimum values, respectively. At this point, methylvinylketone **3a** was synchronously consumed. After that, the concentration of **5a** gradually decreased and that of **4a** increased. At the same time, the concentration of **6a** also reached a maximum value and then decreased over time. These results suggested that **5a** and **6a** underwent a retro-aldol reaction to give **4a** and **7**.

The retro-aldol of the product **5** was checked in the presence and/or absence of the Ru catalyst **1a** and NaOAc. When **5a**-*anti*

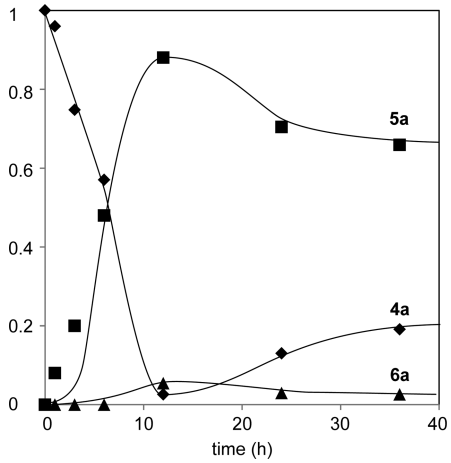


Figure 1. Time conversion curves of the catalytic reaction of **2a** (4 mmol), **3a** (3 mmol), and **4a** (1 mmol) with the Ru catalyst **1a** (2 mol %), NaOAc (10 mol %), and EtOH (20 mol %). The vertical scale was normalized.

in the presence of **1a** (2 mol %) and NaOAc (10 mol %) was heated at 60 °C for 24 h, formation of **4a** and **7** in 21% yield each and recovery of **5a**-*anti* in 58% yield were detected in the ^{1}H NMR spectrum (Scheme 2). This observation indicated the retro-aldol reaction of **5a**-*anti*. The enantiomeric excess of the recovered **5a**-*anti* was unchanged, and the formation of **5a**-*syn* was not detected. Thus, interconversion between **5a**-*anti* and **5a**-*syn* did not proceed under the catalytic conditions. Simultaneously, this reaction produced unidentified byproducts, which led to a decrease in material balance. In contrast, the reaction with **1a** in the absence of NaOAc resulted in the complete recovery of **5a**-*anti*. Furthermore, the use of only NaOAc gave **4a** and **7** in 12% and 23% yields, respectively. We also confirmed that the reaction in the absence of both **1a** and NaOAc did not proceed. These results clearly indicated that the retro-aldol reaction of **5** was catalyzed by NaOAc. In this

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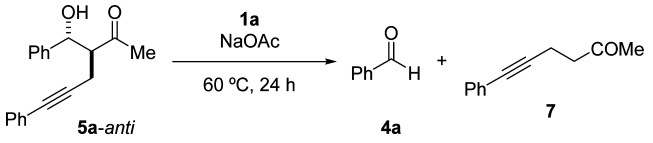
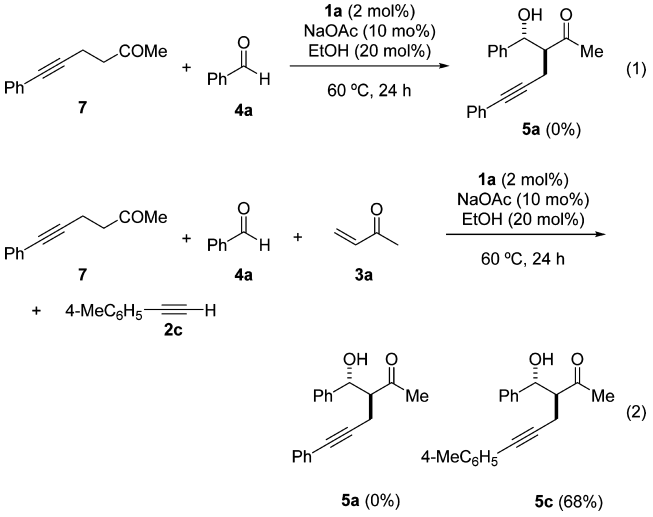
Scheme 2. Retro-Aldol Reaction of 5b-*anti*



1a	NaOAc	5a-*anti*	4a	7
2 mol%	10 mol%	58%	21%	21%
2 mol%	-	>99%	<1%	<1%
-	10 mol%	65%	12%	23%
-	-	>99%	<1%	<1%

Scheme 3. Aldol Reaction of 4a with 7



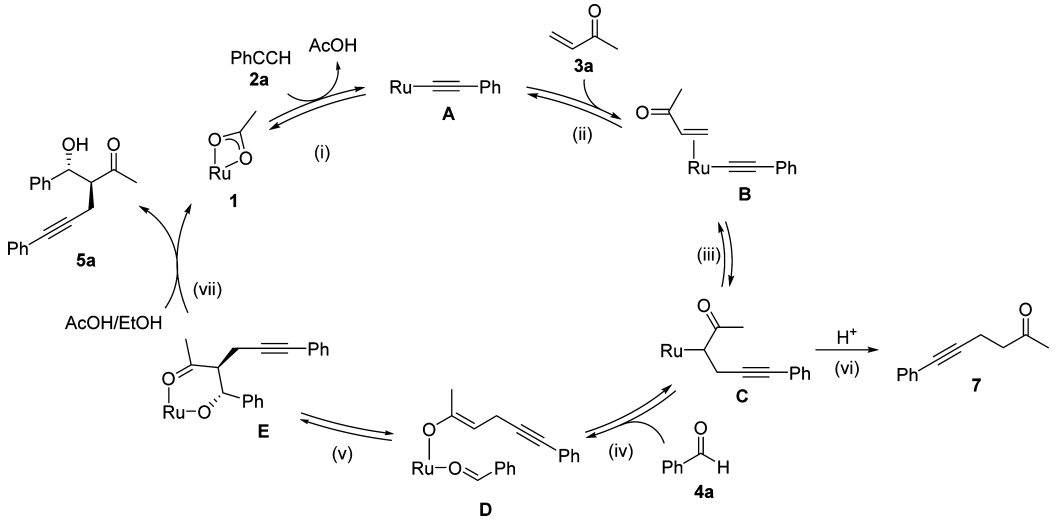
regard, the reaction rate of the retro-aldol reaction of **5** and **6** might affect the ratio of **5**:**6**.

Further control experiments for the aldol reaction were also examined. In the catalytic cycle, the γ-alkynyl ketone **7**, which is produced in situ by the conjugate addition of **2a** with **3a**, is a candidate as an intermediate for the aldol reaction with **4a** giving **5a**.[27] Thus, we monitored the reaction of **7** with **4a** in the presence of **1a** (2 mol %) and NaOAc (10 mol %). However, the formation of the coupling product **5a** was not detected after heating at 60 °C for 24 h [Scheme 3, eq (1)]. To test the effect of the presence of extra alkyne and enone, the reaction of **7** and **4a** in the presence of **2c** and **3a** was also conducted. The NMR spectrum of the crude product showed the formation of compound **5c**, which was formed by coupling of **2c**, **3a**, and **4a** in 68% yield [Scheme 3, eq (2)]. In this reaction, the formation of **5a** was not detected. Judging from these results, the phebox Ru catalyst **1** could not catalyze direct aldol reaction of **7** with **4a** to give the coupling product **5a**. Thus, we concluded that the Ru enolate species generated by conjugate addition of alkynes to α,β-unsaturated carbonyl compounds is the key to the formation of **5a**.

We propose the reaction mechanism shown in Scheme 4. Reaction of an alkyne **2** with a Ru acetate generates a Ru acetylide intermediate **A** (step i). This step is in equilibrium with the protonation of **A**, and NaOAc might play a role to increase the concentration of **A**. Next, the coordination of **3a** forms the intermediate **B**, followed by insertion into the Ru−acetylide bond to give the Ru enolate intermediate **C** (steps ii and iii). In this step, alkynylation to an aldehyde is considered to be much slower than the conjugate addition. Successive isomerization to a Ru-O-enolate and coordination of an aldehyde gives intermediate **D** (step iv), which undergoes C−C bond formation to afford **E** (step v). In contrast, protonation of **C** results in the formation of the conjugate addition product **7** (step vi), which is the major side reaction. Judging from the time conversion curve, the ratio of steps iv and vi is estimated to be ca. 1:3. In the previous report, Rh and Ir enolate intermediates generated by insertion of an α,β-unsaturated carbonyl compound into the M−H bond were believed to trap the aldehyde.[28,29] Hayashi and co-workers suggested that the Rh enolate species generated by insertion of a Rh−Ph bond into cyclohexenone could undergo the subsequent aldol reaction.[7] We propose that a Ru enolate could be a key intermediate for the aldol reaction.[30] At this stage, the aldol reaction proceeds without dissociation of **7** due to the lack of reaction of **7** with the aldehyde catalyzed by **1a**. Further protonation of the resulting intermediate **D** gives **5**, accompanied by **1** (step vii). At the same time, an undesired retro-aldol reaction of **5** is independently catalyzed by NaOAc.

The absolute configuration of **5b**-*anti* was determined to be *S*(α),*R*(β). In this sense, the major *anti*-isomer could be formed

Scheme 4. Proposed Mechanism



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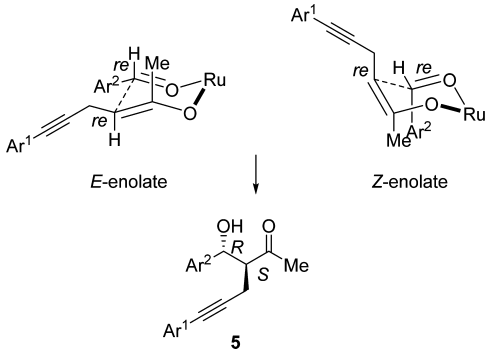
by C−C bond formation between the *re* face of the aldehyde and the *re* face of the enolate in a six-membered cyclic transition state (Scheme 5). At this point, both *E*- and *Z*-

Scheme 5. Proposed Transition State



enolate species could be formed. We assume that the *E*-enolate is the more favorable pathway to the *anti*-isomer than the *Z*-enolate when the six-membered cyclic transition state is involved. Although the additive effect of the alcohol is still unclear, it affects the dissociation step of the product as a proton donor.

In summary, we described a Ru-catalyzed three-component coupling between alkyne, α,β-unsaturated ketone, and aldehyde via direct conjugate alkynylation and successive aldol reaction. This method provides efficient preparation of a variety of new β-hydroxyketone derivatives having α-propargyl groups in high yields and high chemoselectivities. The advantage of this catalytic system is the commercial availability of the substrates. While the enantioselectivity is still moderate, this reaction is a challenging synthetic strategy to construct complex and functionalized organic molecules from ubiquitous starting materials in a one-pot procedure. The stereochemistry of the major *anti*-product was unambiguously confirmed by X-ray diffraction studies. Control experiments implied that the Ru-enolate species, generated by conjugate addition of an alkyne to an enone, served as a key intermediate for the following aldol coupling step.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C spectra were obtained at 25 °C in $CDCl_3$ on a 300 MHz spectrometer. ^{1}H NMR chemical shifts are reported in δ units, in ppm relative to the singlet at 7.26 ppm for $CDCl_3$. ^{13}C NMR spectra are reported in terms of chemical shifts (δ, ppm) relative to the triplet at δ = 77.0 ppm for $CDCl_3$. Infrared spectra were recorded on a Fourier transform IR spectrometer using a KBr pellet. Mass spectra were recorded on a double-focusing mass spectrometer (FAB) and hybrid quadrupole-orbitrap mass spectrometer (ESI). Optical rotation measurements were recorded on a polarimeter in $CHCl_3$. Column chromatography was performed on a neutral silica gel. The phebox-Ru complexes **1a**−**b** were prepared by the reported method.[23,31]

General Procedure of 5. A mixture of **1a** (12 mg, 0.020 mmol), **2** (4.0 mmol), **3** (3.0 mmol), **4** (1.0 mmol), NaOAc (8 mg, 0.1 mmol), and ethanol (8 mg, 0.20 mmol) was stirred at 60 °C for 24 h. After removal of volatile materials under reduced pressure, the residue was purified by column chromatography on silica gel with hexane/ethyl acetate to give **5** and **6** as a diastereomeric mixture. Compounds **5**-*anti* were separated by a recycle LC.

3-[Hydroxy(phenyl)methyl]-6-phenylhex-5-yn-2-one (***5a***). Reaction of ethynylbenzene **2a** (411 mg), but-3-en-2-one **3a** (210 mg), and benzaldehyde **4a** (106 mg) for 12 h yielded a mixture of **5a** and **6a** (244 mg, 88% yield). **5a**-***anti***: yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.42−2.60 (m, 2H), 2.98 (d, J = 4.8 Hz, 1H), 3.14−3.18 (m, 1H), 4.96 (dd, J = 5.0, 7.7 Hz, 1H), 7.25−7.38 (m, 10H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 20.0, 32.4, 57.6, 74.8, 82.9, 85.8, 122.9, 126.1, 127.8, 128.0, 128.04, 128.5 131.3, 141.2, 211.4. IR (KBr): 3448 (ν_{OH}), 2235 (ν_{CC}), 1703 (ν_{CO}) cm^{-1}. $[\alpha]_D^{19}$ = −43.9 (c = 1.0 in $CHCl_3$, 78% ee). HRMS (ESI): m/z calcd for $C_{19}H_{18}O_2$ [M + Na]$^+$, 301.1204; found, 301.1199. **5a**-***syn***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.68−2.91 (m, 3H), 3.16−3.22 (m, 1H), 5.04 (dd, J = 2.6, 5.3 Hz), 7.25−7.37 (m, 10H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 17.6, 32.4, 58.0, 73.3, 82.5, 87.1, 123.0, 125.9, 127.7, 127.8, 128.0, 128.4 131.3, 140.8, 211.1. HPLC (Daicel CHIRALPAK AD-H × 2, hexane:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm): 79% ee (*anti*), 46% ee (*syn*), t_R = 121.5 (*anti, major*), 128.2 (*syn, major*), 132.2 (*anti, minor*), 140.7 (*syn, minor*) min.

3-[(4-Bromophenyl)(hydroxy)methyl]-6-phenylhex-5-yn-2-one (***5b***). Reaction of **2a** (408 mg), **3a** (210 mg), and 4-bromobenzaldehyde **4b** (184 mg) for 24 h yielded a mixture of **5b** and **6b** (264 mg, 88% yield). **5b**-***anti***: yellowish solid, mp: 75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.50 (d, J = 6.6 Hz, 2H), 3.08 (dt, J = 7.5, 6.6 Hz, 1H), 4.92 (d, J = 7.5 Hz, 1H), 7.19−7.33 (m, 7H), 7.44−7.49 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 19.9, 32.2, 57.4, 74.1, 83.2, 85.4, 121.9, 122.7, 127.8, 127.9, 128.1, 131.3 131.5, 140.3, 211.1. IR (KBr): 3411 (ν_{OH}), 1698 (ν_{CO}) cm^{-1}. HRMS (FAB): m/z calcd for $C_{19}H_{17}BrO_2$ [M + Na]$^+$, 379.0310; found, 379.0302. $[\alpha]_D^{23}$ = +7.0 (c = 1.0 in $CHCl_3$, 74% ee). **5b**-***syn***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.63−2.70 (m, 1H), 2.77 (dd, J = 9.3, 17.1 Hz, 1H), 3.02 (br, 1H), 3.10−3.17 (m, 1H), 5.04 (d, J = 5.1 Hz), 7.23−7.36 (m, 7H), 7.47−7.51 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 17.3, 32.3, 57.5, 72.5, 82.7, 86.7, 121.6, 122.9, 127.7, 127.8, 128.1, 131.3 131.4, 139.9, 211.0. HPLC (Daicel CHIRALPAK AD-H, hexane:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm): 78% ee (*anti*), 18% ee (*syn*), t_R = 79.6 (*syn, major*), 90.9 (*anti, major*), 97.1 (*anti, minor*), 120.2 (*syn, minor*) min.

3-((4-Chlorophenyl)(hydroxy)methyl)-6-phenylhex-5-yn-2-one (***5c***). Reaction of **2a** (408 mg), **3a** (210 mg), and 4-chlorobenzaldehyde **4c** (171 mg) for 24 h yielded a mixture of **5c** and **6c** (158 mg, 51% yield). **5c**-***anti***: yellowish solid; mp: 60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.44 (m, 2H), 2.94 (br, 1H), 3.04 (q, J = 7.2 Hz, 1H), 4.89 (d, J = 7.8 Hz, 1H), 7.18−7.29 ppm (m, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 19.9, 32.2, 57.5, 74.0, 83.1, 85.5, 122.7, 127.5, 127.9, 128.1, 128.4, 131.3, 133.6, 139.8, 211.6. IR (KBr): 3467 (ν_{OH}), 1702 (ν_{CO}) cm^{-1}. HRMS (FAB): m/z calcd for $C_{19}H_{17}ClO_2$ [M + Na]$^+$, 335.0815; found, 335.0814. $[\alpha]_D^{23}$ = −4.6 (c = 1.0 in $CHCl_3$, 61% ee). **5c**-***syn***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H), 2.57−2.76 (m, 2H), 2.92 (br, 1H), 3.04−3.09 (q, J = 7.2 Hz, 1H), 4.96 (d, J = 5.4 Hz, 1H), 7.17−7.31 (m, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 17.4, 32.3, 57.7, 72.5, 82.6, 86.8, 122.8, 127.3, 127.8, 128.0, 128.4, 131.2, 133.4, 139.4, 211.0 ppm. HPLC (Daicel CHIRALPAK AD-H, hexane:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm): 61% ee (*anti*), 9% ee (*syn*), t_R = 124.1 (*syn, major*), 131.5 (*anti, major*), 139.4 (*anti, minor*), 165.6 (*syn, minor*) min.

3-[Hydroxy(4-nitrophenyl)methyl]-6-phenylhex-5-yn-2-one (***5d***). Reaction of **2a** (408 mg), **3a** (210 mg), and 4-nitrobenzaldehyde **4d** (151 mg) for 24 h yielded a mixture of **5d** and **6d** (228 mg, 71% yield). **5d**-***anti***: yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.58 (dd, J = 7.2, 17.2 Hz, 1H), 2.68 (dd, J = 5.9, 17.2 Hz, 1H), 3.15 (m, 1H), 5.16 (d, J = 6.9 Hz, 1H), 7.26−7.38 (m, 5H), 7.58 (d, J = 8.8 Hz, 2H), 8.23 (d, J = 8.8 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 20.0, 32.0, 57.1, 73.6, 83.7, 84.9, 122.5, 123.7, 127.0, 128.12, 128.15, 131.3, 147.4, 148.6, 210.8. IR (KBr): 3411 (ν_{OH}), 1703 (ν_{CO}) cm^{-1}. HRMS (FAB): m/z calcd for $C_{19}H_{17}NO_4$ [M + Na]$^+$, 346.1055; found, 346.1047. $[\alpha]_D^{18}$ = −55 (c = 1.0 in $CHCl_3$, 55% ee). **5d**-***syn***: ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, TMS): δ 2.35 (s, 3H), 2.61 (dd, J = 5.3, 17.0 Hz, 1H), 2.78 (dd, J = 9.0, 17.0 Hz, 1H), 3.18 (m, 1H), 5.25 (d, J = 4.2 Hz, 1H), 7.24−7.33 (m, 5H), 7.57 (m, 2H), 8.23 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 20 °C, TMS): δ 17.3, 32.5, 57.4, 72.3, 83.5, 86.6, 123.0, 123.9, 127.2, 128.4, 128.5, 131.6, 147.6, 148.4, 211.3. HPLC (Daicel CHIRALPAK AD-H, hexane:*i*-PrOH = 97:3, 0.5

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mL/min, 254 nm): 55% ee (*anti*), 3% ee (*syn*), t_R = 37.1 (*syn, major*), 40.1 (*anti, minor*), 42.4 (*anti, major*), 49.8 (*syn, minor*) min.

3-{Hydroxyl[4-(trifluoromethyl)phenyl]methyl}-6-phenylhex-5-yn-2-one (**5e**). Reaction of **2a** (408 mg), **3a** (210 mg), and 4-(trifluoromethyl)benzaldehyde **4e** (188 mg) for 12 h yielded a mixture of **5e** and **6e** (252 mg, 73% yield). **5e-*anti***: yellowish solid; mp: 58 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.55 (d, J = 6.8 Hz, 2H), 3.71 (q, J = 6.8 Hz, 1H), 3.44 (br, 1H), 5.05 (dd, J = 3.6, 6.8 Hz), 7.24−7.38 (m, 5H), 7.50 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 19.8, 32.1, 57.3, 74.0, 83.3, 85.3, 124.1 (J_{CF} = 220 Hz), 125.3 (J_{CF} = 3.4 Hz), 126.5, 127.9, 128.0, 128.1, 130.0 (J_{CF} = 33 Hz), 131.3, 145.3, 211.0. IR (KBr): 3508 (ν_{OH}), 1711 (ν_{CO}) cm^{-1}. HRMS (FAB): m/z calcd for $C_{20}H_{17}F_3O_2$ [M + Na]$^+$, 369.1078; found, 369.1069. $[\alpha]_D^{21}$ = −45.3 (c = 1.0 in $CHCl_3$, 62% ee). **5e-*syn***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.53−2.66 (m, 1H), 2.77 (dd, J = 9.0, 17.1 Hz, 1H), 3.10−3.18 (m, 1H), 3.34 (br, 1H), 5.13 (d, J = 4.8 Hz, 1H), 7.21−7.35 (m, 5H), 7.47 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H). HPLC (Daicel CHIRALPAK AD-H × 2, hexane:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm): 70% ee (*anti*), 10% ee (*syn*), t_R = 91.8 (*syn, major*), 115.7 (*anti, minor*), 128.0 (*anti, major*), 138.6 (*syn, minor*) min.

Methyl 4-(2-Acetyl-1-hydroxy-5-phenylpent-4-yn-1-yl)benzoate (**5f**). Reaction of **2a** (408 mg), **3a** (210 mg), and methyl 4-formylbenzoate **4f** (164 mg) for 24 h yielded a mixture of **5f** and **6f** (234 mg, 69% yield). **5f-*anti***: yellowish solid; mp: 60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.57 (d, J = 6.9 Hz, 2H), 3.17 (q, J = 6.9 Hz, 1H), 3.92 (s, 3H), 5.06 (t, J = 6.2 Hz), 7.26−7.38 (m, 5H), 7.46 (d, J = 8.4 Hz, 2H), 8.02−8.05 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, rt): δ 19.9, 32.3, 52.3, 57.3, 72.7, 83.3, 85.4, 122.7, 126.1, 127.9, 129.6, 129.7, 131.3, 146.4, 166.3, 211.2. IR (KBr): 3463 (ν_{OH}), 1703 (ν_{CO}) cm^{-1}. HRMS (FAB): m/z calcd for $C_{21}H_{20}O_4$ [M + Na]$^+$, 359.1259; found, 359.1246. $[\alpha]_D^{26}$ = −39.5 (c = 1.0 in $CHCl_3$, 69% ee). **5f-*syn***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.58−2.68 (m, 1H), 2.79 (dd, J = 9.6, 17.1 Hz, 1H), 3.92 (s, 3H), 5.14 (dd, J = 2.6, 4.7 Hz, 1H), 7.24−7.37 (m, 5H), 7.45 (d, J = 8.1 Hz, 2H), 8.04 (d, J = 8.1 Hz, 2H). HPLC (Daicel CHIRALPAK AD-H, hexane:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm): 70% ee (*anti*), 10% ee (*syn*), t_R = 69.6 (*anti, major*), 75.8 (*syn, major*), 79.4 (*syn, minor*), 85.1 (*anti, minor*) min.

3-(Hydroxy(4-methoxyphenyl)methyl)-6-phenylhex-5-yn-2-one (**5g**). Reaction of **2a** (408 mg), **3a** (210 mg), and 4-methoxybenzaldehyde **4g** (136 mg) for 24 h yielded a mixture of **5g** and **6g** (234 mg, 69% yield). **5g-*anti***: yellowish solid; mp: 112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.42 (dd, J = 5.1, 17.1 Hz, 1H), 2.52 (dd, J = 8.4, 17.1 Hz, 1H), 2.86 (br, 1H), 3.14 (dt, J = 5.1, 8.1 Hz), 3.80 (s, 3H), 4.88 (dd, J = 4.2, 8.1 Hz, 1H), 6.87−6.92 (m, 2H), 7.25−7.36 (m, 7H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 19.9, 32.3, 55.3, 57.8, 74.5, 82.7, 85.9, 113.8, 122.9, 127.3, 127.7, 128.0, 131.2, 133.3, 159.1, 211.4; IR (KBr): 3469 (ν_{OH}), 1699 (ν_{CO}) cm^{-1}; HRMS (FAB): m/z calcd for [$C_{20}H_{20}O_3$ + Na$^+$]: 331.1310; found: 331.1315 [M + Na$^+$]; $[\alpha]_D^{21}$ = −1.4 (c = 1.0 in $CHCl_3$, 39% ee). **5g-*syn***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H), 2.75 (d, J = 6.7 Hz, 2H), 2.83 (br, 1H), 3.16 (q, J = 6.7 Hz, 1H), 3.78 (s, 3H), 4.92 (d, J = 6.7 Hz, 1H), 6.85−6.89 (m, 2H), 7.23−7.34 (m, 7H). HPLC (Daicel CHIRALPAK AY-H, hexane:*i*-PrOH = 95.5:4.5, 1.0 mL/min, 254 nm): 39% ee (*anti*), 25% ee (*syn*), t_R = 59.5 (*syn, major*), 76.2 (*anti, major*), 89.1 (*syn, minor*), 101.6 (*anti, minor*) min.

3-[(3-Bromophenyl)(hydroxy)methyl]-6-phenylhex-5-yn-2-one (**5h**). Reaction of **2a** (408 mg), **3a** (211 mg), and 3-bromobenzaldehyde **4h** (184 mg) for 24 h yielded a mixture of **5h** and **6h** (258 mg, 72% yield). **5h-*anti***: yellowish solid; mp: 88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.51 (d, J = 6.6 Hz, 2H); 3.03 (br, 1H), 3.10 (q, J = 7.0 Hz, 1H), 4.91 (d, J = 7.5 Hz, 1H), 7.17−7.42 (m, 8H), 7.52 (s, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 20.0, 32.3, 57.3, 74.0, 83.2, 85.4, 122.65, 122.71, 124.8, 127.9, 128.1, 129.2, 130.0, 131.0, 131.3, 143.6, 211.1. IR (KBr): 3428 (ν_{OH}), 1703 (ν_{CO}) cm^{-1}. HRMS (FAB): m/z calcd for $C_{19}H_{17}BrO_2$ [M + Na]$^+$, 379.0310; found, 379.0315. $[\alpha]_D^{24}$ = −30.9 (c = 1.0 in $CHCl_3$, 60% ee). **5h-*syn***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.62 (dd, J = 4.8, 17.1 Hz, 1H), 2.76 (dd, J = 9.6, 17.1 Hz, 1H), 3.09−3.15 (m, 1H), 5.03 (d, J = 4.8 Hz, 1H), 7.18−7.42 (m, 8H), 7.52 (s, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 17.2, 32.2, 57.4, 72.3, 82.7, 86.7, 122.6, 122.9, 124.6, 127.8, 128.0, 128.9, 129.9, 130.8, 131.3, 143.1, 211.0. HPLC (Daicel CHIRALCEL OD-H, hexane:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm): 60% ee (*anti*), 8% ee (*syn*), t_R = 64.1 (*anti, minor*), 99.8 (*syn, minor*), 132.1 (*syn, major*), 151.0 (*anti, major*) min.

3-[Hydroxy(naphthalen-2-yl)methyl]-6-phenylhex-5-yn-2-one (**5i**). Reaction of **2a** (408 mg), **3a** (210 mg), and 2-naphthaldehyde **4i** (156 mg) for 24 h yielded a mixture of **5i** and **6i** (245 mg, 75% yield). **5i-*anti***: yellowish solid; mp: 133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.47 (dd, J = 5.1 17.0 Hz, 1H), 2.58 (dd, J = 8.6, 17.0 Hz, 1H), 3.23−3.31 (m, 1H), 5.11 (d, J = 7.8 Hz, 1H), 7.22−7.33 (m, 5H), 7.44−7.49 (m, 3H), 7.78−7.85 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 20.0, 32.4, 57.5, 75.0, 82.8, 85.9, 122.8, 123.6, 125.3, 125.9, 126.1, 127.4, 127.7, 127.8, 128.0, 128.3, 131.2, 132.8, 132.9, 138.5, 211.3. IR (KBr): 3471 (ν_{OH}), 1700 (ν_{CO}) cm^{-1}. HRMS (FAB): m/z calcd for $C_{23}H_{20}O_2$ [M + Na]$^+$, 351.1361; found, 351.1352. $[\alpha]_D^{24}$ = −24.6 (c = 1.0 in $CHCl_3$, 64% ee). **5i-*syn***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.85 (dd, J = 5.0 16.9 Hz, 1H), 2.94 (dd, J = 9.3, 16.9 Hz, 1H), 3.35−3.42 (m, 1H), 5.29 (d, J = 5.1 Hz, 1H), 7.32−7.61 (m, 9H), 7.90−7.95 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 17.5, 32.3, 57.9, 73.4, 82.5, 87.1, 122.8, 123.6, 125.3, 125.9, 126.1, 127.4, 127.7, 127.8, 128.0, 128.3, 131.2, 132.8, 132.9, 138.5, 211.1. HPLC (Daicel CHIRALCEL OD-H, hexane:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm): 64% ee (*anti*), 16% ee (*syn*), t_R = 73.4 (*anti, minor*), 90.3 (*syn, minor*), 103.6 (*anti, major*), 115.8 (*syn, major*) min.

3-[Hydroxy(thiophen-2-yl)methyl]-6-phenylhex-5-yn-2-one (**5j**). Reaction of **2a** (408 mg), **3a** (210 mg), and thiophene-2-carbaldehyde **4j** (112 mg) for 24 h yielded a mixture of **5j** and **6j** (224 mg, 79% yield). **5j-*anti***: yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.53−2.56 (m, 2H), 3.17 (m, 1H), 5.20 (d, J = 7.5 Hz, 1H), 6.93−7.00 (m, 2H), 7.22−7.35 (m, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 20.0, 32.3, 57.8, 71.0, 83.0, 85.5, 122.8, 124.7, 125.2, 126.6, 127.8, 128.0, 131.3, 145.1, 211.1. IR (KBr): 3486 (ν_{OH}), 1706 (ν_{CO}) cm^{-1}. HRMS (FAB): m/z calcd for $C_{17}H_{16}O_2S$ [M + Na]$^+$, 307.0769; found, 307.0754. $[\alpha]_D^{26}$ = −39.3 (c = 1.0 in $CHCl_3$, 61% ee). **5j-*syn***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.79−2.82 (m, 2H), 3.15−3.23 (m, 1H), 5.25−5.27 (m, 1H), 6.93−7.01 (m, 2H), 7.22−7.35 (m, 6H). HPLC (Daicel CHIRALCEL OD-H, hexane:*i*-PrOH = 98:2, 0.5 mL/min, 254 nm): 61% ee (*anti*), 7% ee (*syn*), t_R = 94.0 (*anti, minor*), 133.5 (*syn, major*), 180.0 (*anti, major*), 191.2 (*syn, minor*) min.

3-[Hydroxy(phenyl)methyl]-6-[4-(trifluoromethyl)phenyl]hex-5-yn-2-one (**5k**). Reaction of 1-ethynyl-4-(trifluoromethyl)benzene **2b** (680 mg), **3a** (210 mg), and **4a** (106 mg) for 24 h yielded a mixture of **5k** and **6k** (300 mg, 87% yield). **5k-*anti***: yellowish solid; mp: 65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H), 2.31−2.52 (m, 2H), 2.69 (br, 1H), 3.05−3.13 (m, 1H), 4.83 (dd, J = 4.1, 7.7 Hz, 1H), 7.14−7.44 (m, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 19.8, 32.4, 57.4, 74.9, 81.5, 88.7, 123.7 (J_{CF} = 269 Hz), 125.0 (J_{CF} = 3.5 Hz), 126.1, 126.7, 128.1, 128.5, 129.5 (J_{CF} = 31.9 Hz), 131.5, 141.1, 211.1. IR (KBr): 3430 (ν_{OH}), 2241 (ν_{CC}), 1703 (ν_{CO}) cm^{-1}. HRMS (FAB): m/z calcd for $C_{20}H_{17}F_3O_2$ [M + Na]$^+$, 369.1078; found, 369.1083. $[\alpha]_D^{25}$ = −13.6 (c = 1.0 in $CHCl_3$, 52% ee). **5k-*syn***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.62−2.77 (m, 2H), 2.96−3.06 (m, 1H), 4.85−4.89 (m, 1H), 7.16−7.44 (m, 9H). HPLC (Daicel CHIRALPAK AD-H × 2, hexane:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm): 52% ee (*anti*), 12% ee (*syn*), t_R = 72.1 (*anti, major*), 76.4 (*anti, minor*), 86.2 (*syn, major*), 103.7 (*syn, minor*) min.

6-(4-Bromophenyl)-3-[hydroxy(phenyl)methyl]hex-5-yn-2-one (**5l**). Reaction of 1-bromo-4-ethynylbenzene **2c** (724 mg), **3a** (210 mg), and **4a** (106 mg) for 24 h yielded a mixture of **5l** and **6l** (278 mg, 78% yield). **5l-*anti***: yellowish solid; mp: 110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H), 2.34 (dd, J = 5.1, 17.0 Hz, 1H), 2.45 (dd, J = 8.3, 17.0 Hz, 1H), 3.06 (m, 1H), 4.84 (d, J = 7.5 Hz, 1H), 7.07−7.32 (m, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 19.8, 32.3, 57.5, 74.8, 81.7, 87.2, 121.9, 126.0, 128.0, 128.4, 131.2, 132.7, 141.1, 211.1. IR (KBr): 3388 (ν_{OH}), 1708 (ν_{CO}) cm^{-1}. HRMS (FAB): m/z calcd for $C_{19}H_{17}BrO_2$ [M + Na]$^+$, 379.0310; found, 379.0320. $[\alpha]_D^{26}$ = −27.4 (c = 1.0 in $CHCl_3$, 65% ee). **5l-*syn***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08

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(s, 3H), 2.61 (dd, J = 5.1, 17.0 Hz, 1H), 2.71 (dd, J = 9.3, 17.0 Hz, 1H), 3.08 (m, 1H), 4.93 (d, J = 5.4 Hz, 1H), 7.07−7.33 (m, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 17.6, 32.2, 58.0, 73.3, 81.4, 88.5, 121.9, 125.9, 127.8, 128.4, 131.3, 132.7, 140.8, 210.7. HPLC (Daicel CHIRALPAK AD-H × 2, hexane:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm): 65% ee (*anti*), 44% ee (*syn*), t_R = 182.8 (*anti, major*), 194.7 (*anti, minor*), 201.7 (*syn, major*), 249.6 (*syn, minor*) min.

*3-[Hydroxy(phenyl)methyl]-6-(4-methoxyphenyl)hex-5-yn-2-one (**5m**).* Reaction of 1-ethynyl-4-methoxybenzene **2d** (528 mg), **3a** (210 mg), and **4a** (106 mg) for 24 h yielded a mixture of **5m** and **6m** (123 mg, 40% yield). **5m-*anti***: yellowish solid; mp: 60 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H), 2.36−2.46 (m, 2H), 3.03−3.08 (m, 1H), 3.69 (s, 3H), 4.86 (dd, J = 2.1, 7.5 Hz, 1H), 6.69−6.72 (m, 2H), 7.16−7.27 (m, 7H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 17.6, 32.3, 55.3, 58.1, 73.4, 82.2, 85.5, 113.7, 115.1, 125.9, 127.7, 128.3, 132.6, 140.9, 158.9, 211.2. IR (KBr): 3412 (ν_{OH}), 1702 (ν_{CO}) cm^{-1}. HRMS (FAB): m/z calcd for $C_{20}H_{20}O_3$ $[M + Na]^+$, 331.1310; found, 331.1302. $[\alpha]_D^{23}$ = −29.8 (c = 1.0 in $CHCl_3$, 52% ee). **5m-*syn***: ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.60 (dd, J = 5.3, 17.0 Hz, 1H), 2.69 (dd, J = 6.5, 17.0 Hz, 1H), 3.05−3.11 (m, 1H), 3.70 (s, 3H), 4.93 (d, J = 5.1 Hz, 1H), 6.68−6.73 (m, 2H), 7.15−7.29 (m, 7H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 20.0, 32.4, 55.3, 57.7, 74.8, 82.7, 84.2, 113.7, 115.0, 126.1, 127.9, 128.4, 132.7, 141.3, 159.0, 211.5. HPLC (Daicel CHIRALPAK AD-H × 2, hexane:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm): 52% ee (*anti*), 8% ee (*syn*), t_R = 228.7 (*anti, major*), 248.2 (*anti, minor*), 262.8 (*syn, major*), 311.3 (*syn, minor*) min.

*4-[Hydroxy(phenyl)methyl]-1-phenyldec-1-yn-5-one (**5m**).* Reaction of **2a** (409 mg), oct-1-en-3-one **3b** (378 mg), and **4a** (106 mg) for 24 h yielded a mixture of **5n** and **6n** (334 mg, 48% yield). **5n-*anti***: yellowish oil. ^1H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, J = 6.8 Hz, 3H), 1.10−1.26 (m, 4H), 1.45−1.56 (m, 2H), 2.32−2.64 (m, 4H), 3.07−3.19 (m, 2H), 4.93 (dd, J = 5.4, 6.3 Hz, 1H), 7.23−7.35 (m, 10H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 14.1, 20.3, 22.6, 22.7, 31.3, 45.6, 56.9, 75.0, 82.8, 86.1, 122.9, 125.9, 127.8, 127.9, 128.0, 128.4, 131.3, 141.5, 213.9. IR (KBr): 3467 (ν_{OH}), 1712 (ν_{CO}) cm^{-1}. HRMS (ESI): m/z calcd for $C_{23}H_{26}O_2$ $[M + Na]^+$, 357.1825; found, 357.1821. $[\alpha]_D^{17}$ = −7.7 (c = 0.5 in $CHCl_3$, 60% ee). **5n-*syn***: ^1H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, J = 6.8 Hz, 3H), 1.07−1.28 (m, 4H), 1.40−1.56 (m, 2H), 2.25−2.33 (m, 1H), 2.52−2.86 (m, 3H), 2.98 (brs, 1H), 3.13−3.21 (m, 1H), 4.97 (d, J = 6.0 Hz, 1H), 7.24−7.39 (m, 10H). HPLC (Daicel CHIRALPAK AD-H × 2, hexane:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm): 60% ee (*anti*), 13% ee (*syn*), t_R = 84.5 (*anti, major*), 101.6 (*anti, minor*), 105.2 (*syn, major*), 149.8 (*syn, minor*) min.

Preparation of Bis(oxazolinyl)benzene.[15,31] *[(S,S)-dm-Phebox-iBu]H.* A solution of 4,6-dimethylisophthalic acid (0.97 g, 5.0 mmol) and $SOCl_2$ (3 mL) in toluene (5 mL) was refluxed for 6 h, and then the solvent was removed under reduced pressure. The residue was dissolved in THF, and the solution was slowly added to a THF solution of (*L*)-leucinol (1.17 g, 10 mmol) and triethylamine (20 mL) at 0 °C. The mixture was stirred at room temperature for 2 h. Then, methanesulfonyl chloride (2 mL) was added at 0 °C, and the mixture was stirred at room temperature for 6 h. Then, aqueous potassium carbonate (ca. 7 g/50 mL) was added at 0 °C and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The crude product was purified by column chromatography to give [(*S,S*)-*dm*-Phebox-*i*Bu]H in 29% yield (0.52 g, 1.45 mmol). ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, J = 6.3 Hz, 6H), 0.96 (d, J = 6.6 Hz, 6H), 1.31−1.40 (m, 2H), 1.62−1.71 (m, 2H), 1.77−1.86 (m, 2H), 2.56 (s, 6H), 3.89 (t, J = 7.2 Hz, 2H), 4.26−4.42 (m, 4H), 7.07 (s, 1H), 8.20 (s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 21.8, 22.9, 23.0, 25.7, 45.8, 65.6, 72.2, 124.5, 131.1, 133.9, 140.8, 162.6. Anal. Calcd for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.03; H, 9.34; N, 7.88.

[(S,S)-dm-Phebox-Bn]H. Reaction of 4,6-dimethylisophthalic acid (0.93 g, 4.8 mmol) and (*L*)-phenylalaninol (1.57 g, 10 mmol) gave [(*S,S*)-*dm*-Phebox-Bn]H in 61% yield (1.49 g, 3.5 mmol). ^1H NMR (300 MHz, $CDCl_3$): δ 2.60 (s, 6H), 2.72 (dd, J = 8.6, 13.7 Hz, 2H), 3.21 (dd, J = 5.1, 13.7 Hz, 2H), 4.08 (t, J = 7.8 Hz, 2H), 4.27 (t, J = 9.0 Hz, 2H), 4.55−4.65 (m, 2H), 7.12 (s, 1H), 7.12−7.33 (m, 10H), 8.25 (s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 21.8, 41.9, 68.2, 70.9, 124.3, 126.2, 128.2, 129.0, 131.3, 134.0, 137.7, 141.1, 163.3. Anal. Calcd for $C_{28}H_{28}N_2O_2$: C, 79.22; H, 6.65; N, 6.60. Found: C, 78.92; H, 6.66; N, 6.60.

[(S,S)-dm-Phebox-Et]H. Reaction of 4,6-dimethylisophthalic acid (0.98 g, 5.0 mmol) and (*S*)-2-amino-1-butanol (0.89 g, 10 mmol) gave [(*S,S*)-*dm*-Phebox-Et]H in 88% yield (1.32 g, 4.4 mmol). ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (t, J = 7.4 Hz, 6H), 1.54−1.81 (m, 4H), 2.58 (s, 6H), 3.96−3.99 (m, 2H), 4.22−4.40 (m, 2H), 4.40−4.43 (m, 2H), 7.10 (s, 1H), 8.21 (s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 10.2, 21.7, 28.9, 68.4, 71.2, 124.5, 131.2, 133.9, 140.8, 162.7. Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.67; H, 8.37; N, 9.28.

[(S,S)-dm-Phebox-Me]H. Reaction of 4,6-dimethylisophthalic acid (1.25 g, 6.4 mmol) and (*L*)-lalaninol (0.97 g, 13 mmol) gave [(*S,S*)-*dm*-Phebox-Me]H in 70% yield (1.22 g, 4.5 mmol). ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (d, J = 6.3 Hz, 6H), 2.59 (s, 6H), 3.94 (t, J = 7.1 Hz, 2H), 4.39−4.51 (m, 4H), 7.12 (s, 1H), 8.27 (s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 21.7, 21.8, 62.3, 73.2, 124.4, 131.3, 133.9, 140.8, 162.8. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.46; H, 7.55; N, 10.08.

Preparation of Complexes 1c−f.[23,31] *Complex **1c**.* A 100 mL flask was charged with $RuCl_3{\cdot}3(H_2O)$ (566 mg, 2.2 mmol), [(*S,S*)-*dm*-Phebox-*i*Bu]H (337 mg, 0.95 mmol), and Zn (337 mg). Under an argon atmosphere, ethanol (20 mL) and 1,5-cyclooctadiene (0.6 mL) were added, and the mixture was refluxed for 24 h. After removal of the solvent under reduced pressure, the residue was extracted with toluene and the extract was concentrated. The residue was purified by column chromatography on silica gel with ethyl acetate/hexane (1:3) to give a yellow solid. 2-Propanol (10 mL) was added to a mixture of the solid and NaOAc (380 mg, 4.6 mmol). The mixture was stirred at 60 °C for 12 h, and then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate) to give **1c** in 66% yield (340 mg, 0.63 mmol). ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 1.33−1.42 (m, 2H), 1.54−1.68 (m, 2H), 1.79−2.07 (m, 2H), 1.90 (s, 3H), 2.49 (s, 6H), 3.96−4.16 (m, 2H), 4.27−4.42 (m, 2H), 4.85−4.91 (m, 2H), 6.67 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 19.4. 21.8, 22.2, 22.8, 23.4, 23.9, 24.0, 25.5, 25.6, 43.0, 44.6, 60.0, 63.7, 75.7, 76.2, 126.8, 129.3, 129.4, 139.3, 139.5, 173.5, 173.9, 184.9, 193.3, 197.4. IR (KBr): 1919 (ν_{CO}) cm^{-1}; Anal. Calcd for $C_{25}H_{34}N_2O_5Ru$: C, 55.24; H, 6.30; N, 5.15. Found: C, 55.35; H, 6.35; N, 5.02.

*Complex **1d**.* Reaction of $RuCl_3{\cdot}3(H_2O)$ (546 mg, 2.1 mmol) and [(*S,S*)-*dm*-Phebox-Bn]H (424 mg, 1.0 mmol) gave **1d** in 22% yield (134 mg, 0.22 mmol). ^1H NMR (300 MHz, $CDCl_3$): δ 1.97 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 2.55−2.72 (m, 2H), 3.45−3.66 (m, 2H), 4.20−4.30 (m, 1H), 4.38−4.46 (m, 2H), 4.54−4.71 (m, 3H), 6.61 (s, 1H), 7.20−7.36 (m, 10H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 19.36, 19.40, 24.2, 40.1, 40.8, 63.3, 66.0, 75.0, 75.1, 126.55, 126.62, 127.0, 128.6, 128.9, 136.9, 137.0, 139.9, 140.0, 174.3, 174.8, 185.4, 193.4, 197.9. IR (KBr): 1920 (ν_{CO}) cm^{-1}. Anal. Calcd for $C_{31}H_{30}N_2O_5Ru$: C, 60.87; H, 4.94; N, 4.58. Found: C, 60.59; H, 5.32; N, 4.34.

*Complex **1e**.* Reaction of $RuCl_3{\cdot}3(H_2O)$ (552 mg, 2.1 mmol) and [(*S,S*)-*dm*-Phebox-Et]H (335 mg, 1.1 mmol) gave **1e** in 18% yield (98 mg, 0.20 mmol). ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, J = 6.6 Hz, 3H), 1.02 (t, J = 7.5 Hz, 3H), 1.48−1.67 (m, 3H), 1.90 (s, 3H), 1.90−2.05 (m, 1H), 2.49 (s, 3H), 2.50 (s, 3H), 3.93−4.08 (m, 2H), 4.36 (t, J = 8.9 Hz, 1H), 4.49 (t, J = 8.1 Hz, 1H), 4.77−4.89 (m, 2H), 6.57 (s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 9.7, 9.9, 19.71, 19.74, 24.4, 26.8, 27.6, 63.0, 66.3, 74.95, 75.08, 127.2, 129.59, 129.65, 139.9, 140.0, 174.1, 174.6, 185.4, 193.8, 197.8. Anal. Calcd for $C_{21}H_{26}N_2O_5Ru$: C, 51.74; H, 5.38; N, 5.75. Found: C, 51.47; H, 5.23; N, 5.71.

*Complex **1f**.* Reaction of $RuCl_3{\cdot}3(H_2O)$ (562 mg, 2.1 mmol) and [(*S,S*)-*dm*-Phebox-Me]H (272 mg, 1.0 mmol) gave **1f** in 76% yield (349 mg, 0.76 mmol). ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (d, J = 6.0 Hz, 3H), 1.36 (d, J = 6.6 Hz, 3H), 1.91 (s, 3H), 2.49 (s, 3H), 2.50 (s, 3H), 4.07−4.40 (m, 4H), 4.86−4.95 (m, 2H), 6.58 (s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 19.28, 19.34, 19.7, 20.6, 24.0, 31.1, 57.4, 60.3, 126.8, 129.3, 129.4, 139.4, 139.6, 173.7, 174.2, 185.0, 193.3,

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197.6. IR (KBr): 1917 (ν_{CO}) cm^{-1}. Anal. Calcd for $C_{19}H_{22}N_2O_5Ru$: C, 49.67; H, 4.83; N, 6.10. Found: C, 49.63; H, 4.78; N, 5.83.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00374.

Crystallographic data for **5**-*anti* (CIF)

Spectral data for all compounds, HPLC charts, and crystallographic data (PDF)

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Notes

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