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Enantioselective Synthesis of β-Substituted Cyclic Ketones via Cobalt-Catalyzed Asymmetric Reductive Coupling of Alkynes with Alkenes

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S *Supporting Information*

ABSTRACT: A CoI_2/(*R*)-BINAP, Zn, ZnI_2, H_2O system efficiently catalyzes the intermolecular asymmetric reductive coupling of alkynes with cyclic enones to afford highly regio- and enantioselective β-alkenyl cyclic ketones. A possible mechanism that involves the formation of a cobaltacyclopentene intermediate from the alkyne and cyclic enone is proposed.

Transition-metal-catalyzed asymmetric carbon−carbon bond formation by uniting readily available π components is an atom- and step-economical method in organic synthesis.[1,2] Among such reactions, asymmetric reductive coupling involving alkynes as substrates is a competent method for the synthesis of highly regio-, stereo-, and enantioselective substituted alkenes.[3] Various types of π components, such as aldehyde, imine, epoxide, and ketone, have been employed in the enantioselective coupling with alkynes using nickel,[3a−j] rhodium,[3k−m] and iridium[3n,o] complexes as catalysts. In this context, the asymmetric reductive coupling of alkynes with alkenes remains less explored,[4] despite the fact that its racemic variants have been well-studied by Montgomery's group,[4d−g] Jang and Krische,[4h] Reichard and Micalizio,[4i] and our group.[5a,b] In 1998, Sato and Urabe reported a stoichiometric reaction of titanium alkoxide-mediated diastereoselective cyclization of enynols,[4a] but the catalytic intramolecular asymmetric reductive coupling of 1,6-enynes was demonstrated by Krische and co-workers[4b] using chirally modified cationic rhodium complexes as precatalysts and hydrogen as the reducing agent. Previously, Ikeda's group also reported a related intermolecular three-component asymmetric alkylative coupling reaction of cyclic enones, alkynes, and dimethylzinc in the synthesis of enantioselective β-substituted cyclic ketones using Ni/oxazoline as the catalyst.[4c]

Our continuing interest in the coupling reactions of π components[5a−i] and the related asymmetric syntheses[5j] prompted us to explore a mild, convenient, and atom-economical method for the synthesis of β-substituted cyclic enones with high enantioselectivity. Herein we report that cobalt complexes can catalyze the enantioselective intermolecular reductive coupling of alkynes and cyclic enones with high regio- and stereoselectivity. This reaction provides an excellent complement to the metal-catalyzed enantioselective addition reaction of organometallic reagents to unsaturated carbonyl compounds.

Treatment of diphenylacetylene (**1a**) with 2-cyclohexenone (**2a**) in the presence of CoI_2 (5.0 mol %) as the catalyst, (*R*)-BINAP (5.0 mol %) as the ligand, Zn (1.10 mmol) as the reducing agent, ZnI_2 (0.20 mmol) as the Lewis acid, H_2O (0.80 mmol) as the proton source, and 1,4-dioxane as the solvent at room temperature for 24 h afforded the enantioselective reductive coupling product **3a** in 67% yield with 92% *ee*. The absolute configuration of **3a** was determined to be *S* by comparison of the ^{13}C NMR data for the ketal derivatives prepared from the reaction of (2*R*,3*R*)-butane-2,3-diol with **3a** and a racemic mixture of **3a** (see the Supporting Information).[6] Control experiments revealed that the asymmetric catalytic reaction did not proceed in the absence of either CoI_2/(*R*)-BINAP or Zn and ZnI_2. The reductive coupling product **3a** obtained is highly stereo- and regioselective: the two phenyl groups of the **1a** moiety are cis to each other, and the carbon−carbon bond formed in the product is between the β-carbon of **2a** and an alkyne carbon of **1a**.

To optimize the catalytic conditions, we surveyed various chiral bidentate phosphine ligands using **1a** and **2a** as model substrates in the presence of CoI_2 (5.0 mol %), Zn (1.10 mmol), ZnI_2 (0.20 mmol), and H_2O (0.80 mmol) at room temperature with CH_3CN as the solvent (Table 1). Among them, chiral ligands such as (*R*)-Prophos (**L1**), (*S*,*S*)-Chiraphos (**L2**), and (*S*,*S*)-BDPP (**L3**) afforded the reductive coupling product **3a** in moderate *ee*, whereas with (*R*,*R*)-DIOP (**L4**), both the conversion and enantioselectivity were low. Improved results were observed using (*R*)-BINAP (**L5**) and (*R*)-QUINAP (**L6**), with 81 and 74% *ee*, respectively. The chiral BINAP derivatives (*R*)-H_8-BINAP (**L7**) and (*S*)-Tol-BINAP (**L8**) were also active but provided **3a** in only 63 and 61% *ee*, respectively. The solvent greatly influences the *ee* and yield of the reaction: 1,4-dioxane was found to be the best, affording the product in 67% yield with 92% *ee*, whereas THF, toluene, DCE, DME, EA, and DCM were totally inactive. Other cobalt salts, including $CoBr_2$/(*R*)-BINAP and $CoCl_2$/(*R*)-BINAP, were slightly less active and selective, affording **3a** in 49 and 54% yield with 81 and 87% *ee*, respectively.

To explore the scope of the present enantioselective reductive coupling, the reactions of various alkynes with **2a** were examined under the optimized reaction conditions (Table 2, entries 2−5). Thus, di-*p*-tolylacetylene (**1b**) gave reductive coupling product **3b** in 71% yield and 93% *ee* (entry 2). In a similar manner, di-*p*-chlorophenylacetylene (**1c**) afforded the expected product **3c** in 72% yield with 96% *ee* (entry 3). The *S* configuration of product **3c** was confirmed by single-crystal structure analysis of its oxime derivative (Figure 1; also see the Supporting Information).

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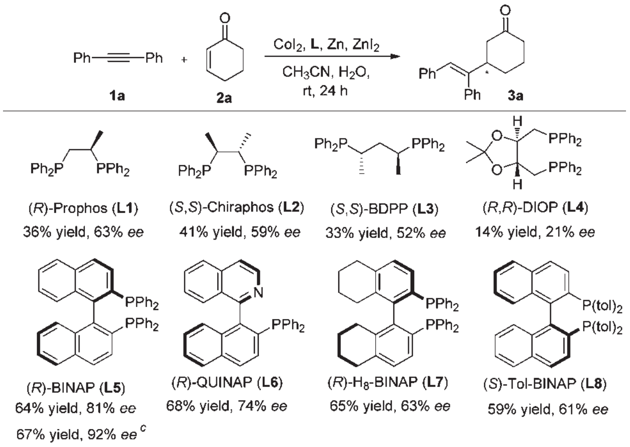
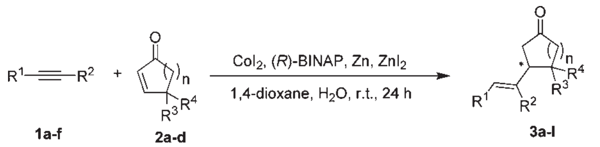
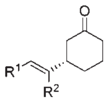
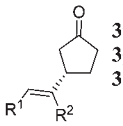
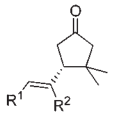
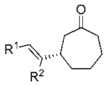
Table 1. Influence of Chiral Ligands[a,b]



[a] Unless otherwise mentioned, each reaction was carried out using **1a** (0.40 mmol) and **2a** (0.60 mmol) in the presence of CoI_2 (5.0 mol %), ligand (L) (5.0 mol %), Zn (1.10 mmol), ZnI_2 (0.20 mmol), and H_2O (0.80 mmol) in CH_3CN (0.80 mL) at rt for 24 h. [b] Isolated yields are shown. [c] The reaction was carried out using 1,4-dioxane as the solvent.

Table 2. Results of Cobalt-Catalyzed Asymmetric Reductive Coupling of Alkynes and Alkenes[a]



entry	1	2	product 3		yield (%)[b]	ee (%)
1	**1a**	**2a**		**3a**: $R^1 = R^2 = Ph$	67	92 (*S*)
2	**1b**	**2a**		**3b**: $R^1 = R^2 = p\text{-}CH_3C_6H_5$	71	93
3	**1c**	**2a**		**3c**: $R^1 = R^2 = p\text{-}ClC_6H_5$	72	96 (*S*)
4	**1d**	**2a**		**3d**: $R^1 = Ph$, $R^2 = Me$	70	90
5	**1e**	**2a**		**3e**: $R^1 = 2$-naphthyl, $R^2 = Me$	58	91
6	**1c**	**2b**		**3f**: $R^1 = R^2 = p\text{-}ClC_6H_5$	81	85
7	**1a**	**2b**		**3g**: $R^1 = R^2 = Ph$	72	90[d]
8	**1f**	**2b**		**3h**: $R^1 = CO_2Et$, $R^2 = Ph$	83	86
9	**1a**	**2c**		**3i**: $R^1 = R^2 = Ph$	63	92
10	**1d**	**2c**		**3j**: $R^1 = Ph$, $R^2 = Me$	67	95
11	**1a**	**2d**		**3k**: $R^1 = R^2 = Ph$	74	96[c]
12	**1d**	**2d**		**3l**: $R^1 = Ph$, $R^2 = Me$	70	85[c,d]

[a] Unless otherwise mentioned, each reaction was carried out using alkyne **1** (0.40 mmol) and alkene **2** (0.60 mmol) in the presence of CoI_2 (5.0 mol %), (*R*)-BINAP (5.0 mol %), Zn (1.10 mmol), ZnI_2 (0.20 mmol), and H_2O (0.80 mmol) in 1,4-dioxane (0.80 mL) at rt for 24 h. [b] Isolated yields. [c] The reaction was carried out using CH_3CN as the solvent. [d] The reaction was carried out using $ZnCl_2$ as the Lewis acid.

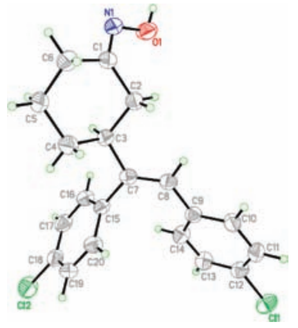
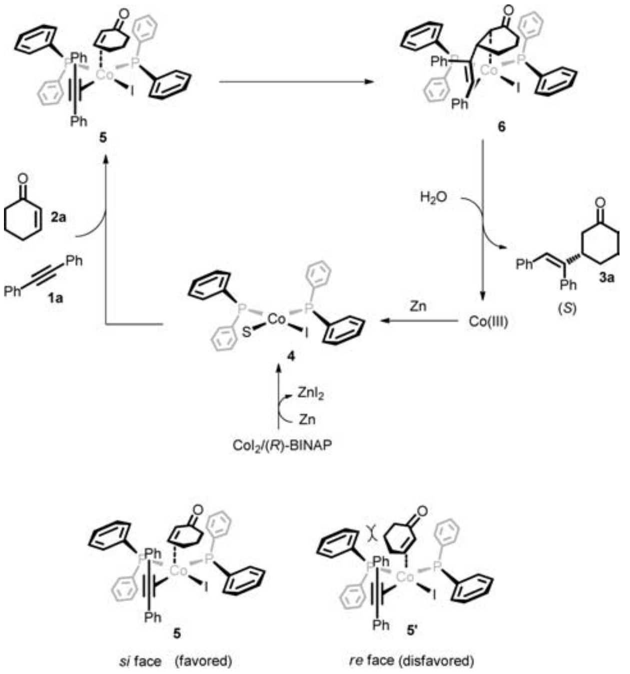


Figure 1. ORTEP representation of the oxime derivative of **3c**. Thermal ellipsoids are set at 50% probability.

Scheme 1. Proposed Mechanism for the Enantioselective Reductive Coupling of 1a and 2a



Under similar reaction conditions, unsymmetrical alkynes also underwent the reductive coupling reaction effectively, providing the corresponding products with high enantio-, regio- and stereoselectivities. Thus, 1-phenyl-1-propyne (**1d**) and 2-naphthyl-1-propyne (**1e**) afforded **3d** and **3e**, respectively in good yields with high *ee* values (entries 4 and 5). Similarly, electron-deficient alkyne **1f** nicely coupled with **2b** to give **3h** in 83% yield with 86% *ee* (entry 8). It is noteworthy that the present reductive coupling reaction is not suitable for terminal alkynes but instead leads to facile homocyclotrimerization of the alkynes under the optimized reaction conditions.

The present catalytic reaction was also successfully extended to various types of cyclic enones (Table 2). Thus, 2-cyclopentenone (**2b**) effectively coupled with **1c** and **1a** to give reductive coupling products **3f** and **3g**, respectively, in 72−81% yield with 85−90% *ee* (entries 6 and 7). Similarly, 4,4-dimethyl-2-cyclopentenone (**2c**) reacted with **1a** and **1d** to afford products **3i** and **3j**, respectively, in good yields with excellent *ee* values (92−95%) (entries 9 and 10). 2-Cycloheptenone (**2d**) also underwent asymmetric reductive coupling with alkynes **1a** and **1d** to provide **3k** and **3l** in good yields with 96 and 85% *ee*, respectively. In the present catalytic asymmetric reaction, it appears that increasing the ring size of the cyclic enone and the size of the substituent on the alkyne lead to an increase in the *ee* of the product. For example, the reactions of **1a** with **2a**−**d** afforded the reductive coupling products with enantioselectivites that increased with the size of the cyclic enone ring. Furthermore, the *ee* values for the coupling of cyclic 2-enones with diarylacetylenes **1a**−**c** were higher than that with 1-phenyl-1-propyne **1d** in most cases (except for **3j**).

A mechanism for this present catalytic reaction that accounts for the absolute configuration of the product **3a** is proposed in Scheme 1. The reaction is likely initiated by the reduction of Co(II)[7a] to Co(I) species **4** by Zn dust. Coordination of **1a** at the equatorial position and **2a** with its *si* face at the axial position of the Co(I) center to form **5** followed by oxidative cyclization then gives cobaltacyclopentene intermediate **6**.[7b] Protonation of **6** affords product **3a** and a Co(III) species that is reduced by Zn dust to regenerate Co(I).

In conclusion, we have successfully demonstrated an atom-economical, cobalt-catalyzed enantioselective reductive coupling of internal alkynes with cyclic enones. The catalytic reaction proceeds with high regio- and stereoselectivity and provides various *β*-substituted ketones in good yields with high *ee* values. The reaction employs an air-stable, less expensive cobalt catalyst, a mild reducing agent (Zn), and a simple hydrogen source (water).

ASSOCIATED CONTENT

Ⓢ **Supporting Information.** General experimental procedures and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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