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Cobalt-Catalyzed Reductive Coupling of Activated Alkenes with Alkynes

Hong-Tai Chang, Thiruvellore Thatai Jayanth, Chun-Chih Wang, and
Chien-Hong Cheng*

*Contribution from the Department of Chemistry, National Tsing Hua University,
Hsinchu 30013, Taiwan*

Received May 19, 2007; E-mail: chcheng@mx.nthu.edu.tw

Abstract: Cobalt complex/Zn systems effectively catalyze the reductive coupling of activated alkenes with alkynes in the presence of water to give substituted alkenes with very high regio- and stereoselectivity in excellent yields. While the intermolecular reaction of acrylates, acrylonitriles, and vinyl sulfones with alkynes takes place in the presence of $CoI_2(PPh_3)_2$/Zn, the reaction of enones and enals with alkynes requires the use of the CoI_2(dppe)/Zn/ZnI_2 system. The intramolecular reductive coupling of activated alkenes (enones, enals, acrylates, and acrylonitriles) with alkynes also works efficiently. Further a variety of cyclic lactones and lactams were prepared using this methodology. Possible mechanistic pathways are proposed based on a deuterium-labeling experiment carried out in the presence of D_2O.

Introduction

Catalytic reactions that effect carbon−carbon bond formation by uniting readily available π-components in a highly atom-economical way is very important to the development of organic synthesis.(1) Among these the coupling of alkynes and a double bonded component leading to highly substituted alkenes is particularly interesting.(2) The Alder-ene reaction of alkynes with alkenes catalyzed by ruthenium to form dienes has been extensively studied by Trost's group.(3) Another variant involves catalytic reductive couplings. Most widely studied in this type is the nickel-catalyzed reductive coupling of alkynes with carbonyl compounds or imines leading to allylic alcohols or amines.(4) Nickel-catalyzed reductive coupling of alkynes and alkenes involving an organometallic reagent as a third component is known, but simple reductive couplings are unknown.(5) Coupling of alkenes and alkynes via palladium-catalyzed hydropalladation of alkenes is also known.(6) Krische has reported related reductive couplings of alkynes with carbonyl compounds or imines under hydrogenation conditions using rhodium as a catalyst.(7) The efficacy of these types of reaction leading to highly substituted alkenes heavily depends on the selectivity that can be achieved.

Cobalt also has been employed as highly reactive catalysts for the carbon−carbon bond forming reaction by Oshima,[8a−c] Knochel,[8d,e] Gosmini,[8f,g] our group[8h−j] and others. In this context, we have earlier reported a cobalt-catalyzed intermolecular reductive coupling of alkynes and conjugated alkenes in a highly chemo-, regio-, and stereoselective fashion.(9) To the

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(5) For very recent examples, see: (a) Ho, C.-Y.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 782. (b) Ng, S.-S.; Ho, C.-Y.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 11513. (b) Song, M.; Montgomery, J. *Tetrahedron* **2005**, *61*, 11440. (c) Ng, S.-S.; Jamison, T. F. *Tetrahedron* **2005**, *61*, 11405. (d) Takimoto, M.; Kajima, Y.; Sato, Y.; Mori, M. *J. Org. Chem.* **2005**, *70*, 8605. (e) Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 7320. (f) Hratchian, H. P.; Chowdhury, S. K.; Gutierrez-Garcia, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636. (g) Kimura, M.; Ezoe, A.; Mori, M.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 201. (h) Shirakawa, E.; Yamamoto, Y.; Nakao, Y.; Oda, S.; Tsuchimoto, T.; Hiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 3448. For earlier references, see ref 2c. See also: (i) Yi, C. S.; Lee, D. W.; Chen, Y. *Organometallics* **1999**, *18*, 2043. (j) Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. Organometallics **1995**, *14*, 5015. (k) Ikeda, S.; Cui, D. M.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4712.

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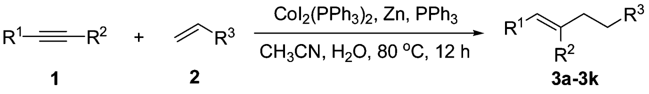
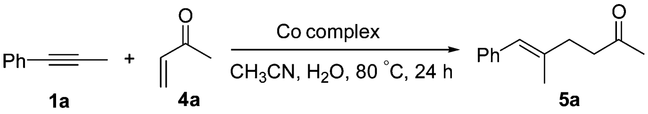
Scheme 1. Co-Catalyzed Reductive Coupling of Acrylates, Acrylonitriles, and Vinyl Sulfones with Alkynes



1a R^1 = Ph , R^2 = Me
1b R^1 = Ph , R^2 = Ph
1c R^1 = Et , R^2 = Et
1d R^1 = Ph , R^2 = $(CH_2)_3OH$
1e R^1 = CO_2Et , R^2 = Ph
1f R^1 = CO_2Me , R^2 = $(CH_2)_4CH_3$
1g R^1 = CO_2Et , R^2 = $Si(CH_3)_3$
1h R^1 = Ph , R^2 = $(CH_2)_2OH$

2a R^3 = CO_2Bu
2b R^3 = CN
2c R^3 = SO_2Ph
2d R^3 = CO_2Me

Table 1. Optimization Studies for the Co-Catalyzed Reductive Coupling of Enones with Alkynes[a]



entry	catalyst	additive	yield (%)[b]
1	Zn	-	0
2	$CoI_2(PPh_3)_2$, Zn, 3PPh$_3$	-	0
3	$CoI_2(PPh_3)_2$, Zn, 3 PPh_3	$ZnCl_2$	trace
4	CoI_2(dppe), Zn	-	22
5	CoI_2(dppe), Zn	$ZnCl_2$	75
6	CoI_2(dppe), Zn, dppe	$ZnCl_2$	71
7	$CoCl_2$(dppe), Zn	$ZnCl_2$	70
8	$CoCl_2$(dppm), Zn	$ZnCl_2$	70
9	$CoCl_2$(dppb), Zn	$ZnCl_2$	63
10	CoI_2(dppe), Zn	ZnI_2	94
11	CoI_2(dppe), Zn	$Zn(OAc)_2$	36
12	CoI_2(dppe), Zn	CuI	85
13	CoI_2(dppe), Zn	CuCl	64
14	CoI_2(dppe), Zn	LiCl	0
15	CoI_2(dppe), Zn	$MgCl_2$	0

[a] Reaction conditions: alkyne (1.00 mmol), alkene (1.20 mmol), cobalt complex (0.050 mmol; 5.0 mol %), Zn (2.75 mmol), additive (0.10 mmol), H_2O (2.0 mmol), CH_3CN (2.0 mL) at 80 °C for 24 h. [b]Isolated yields.

best of our knowledge this is the first and only catalytic intermolecular reductive ene−yne coupling known until now. In this article we disclose a significantly expanded scope of this cobalt-catalyzed reductive coupling. In the preliminary communication, the alkene used was restricted to acrylates, acrylonitriles, and vinyl sulfones. Herein, we report that, by a suitable modification of the reaction conditions, enones and enals were successfully employed in this reductive coupling. An intramolecular version of this reaction was also accomplished. Further, we also wish to describe some useful applications of this reductive coupling methodology via synthesis of six- and seven-membered lactones and lactams.

Results and Discussion

Earlier we found that internal alkynes and alkenes especially acrylates, acrylonitrile, and vinyl sulfones undergo reductive coupling in the presence of a cobalt catalyst to give highly substituted alkenes (Scheme 1). In order to widen the scope of this reaction, enones were employed as the alkene partner. But when methylphenylacetylene (**1a**) was treated with methyl vinyl ketone (**4a**) under the same reaction conditions (entry 2, Table 1) employed for the reductive coupling of acrylates with alkynes, no expected reductive coupling product was observed. During our search for suitable reaction conditions for the alkyne−enone coupling, we observed that the use of $ZnCl_2$ gave a trace amount of the reductive coupling product **5a** (entry 3). The use of CoI_2(dppe) and Zn gave the reductive coupling product obtained in 22% yield (entry 4). When CoI_2(dppe)/Zn/H_2O was employed along with $ZnCl_2$, the yield of reductive coupling product was increased to 75% yield (entry 5). Subsequently, a variety of Lewis acids were tried. The use of ZnI_2 gave the highest yield of **5a** with complete regio- and stereoselectivity (entry 10). As shown in entries 12 and 13, CuCl and CuI also worked well for this reaction.

A variety of internal alkynes reacted with enones to give the reductive coupling product in good yields in a regio- and stereoselective manner. The regio- and stereochemistry of the products was determined by NOE experiments. Table 2 illustrates the scope of this coupling reaction. Diphenylacetylene (**1b**) coupled with methyl vinyl ketone (**4a**) to give **5b** in 88% yield (entry 2). Naphthyl-1-propyne (**1i**) also reacted well with **4a** to afford the corresponding reductive coupling product **5c** in 74% yield (entry 3). Dieneyne **1j** gave the corresponding diene **5d** in 81% yield (entry 4). Dialkylalkynes **1c** also coupled smoothly (entry 5). A heteroaromatic alkyne, 2-pyridine-1-propyne (**1k**), also reacted successfully with **4a** to give the corresponding substituted alkene **5f** in 84% yield (entry 6). Similarly, various enones underwent the expected reductive coupling. For example, phenyl vinyl ketone (**4c**) coupled with **1a** providing **5i** in 74% yield (entry 9). Enal **4e** also reacted efficiently with alkyne **1a** under the standard reaction conditions to afford **5k**, albeit in a lower yield (entry 11). Cyclic enones, like cyclopentenone and cyclohexenone, were compatible for this coupling (entries 13−17). While all the above reductive coupling reactions occurred in a highly regio- and stereoselective fashion, the corresponding reductive coupling of propiolates **1f** and **1g** with enone **4a** took place with low regioselectivity leading to two regioisomers (entries 18 and 19).

Intramolecular reductive coupling of an alkyne and an activated alkene group was also possible under the standard reaction conditions. The reaction worked equally well with both *cis* and *trans* isomers of **6** to give the reductive coupling product in almost the same yields (Table 3, entries 1, 2, 4, 5, 7, and 8). Compounds ***E*-6a**, ***Z*-6a**, and **6b** (*E* form), terminal alkynes tethered with enones, underwent intramolecular enyne coupling to give **7a** and **7b** in very high yields (Table 3, entries 1 to 3). It is interesting to note that for the intermolecular version of enyne reductive coupling, terminal alkynes generally do not react with activated alkenes to give the expected products (see Table 2). Internal alkynes with an aryl or alkyl substituent were compatible for the present intramolecular reductive coupling. Both electron-withdrawing and electron-donating phenyl substituents worked equally well (entries 4−9). 1-Naphthyl and 2-thienyl substituted alkynes tethered to an enone group formed the five-membered ring product in good yields (entries 10−12). Tether length can also be increased to form a cyclohexane derivative (entry 13). Oxygen tethered enynes also underwent reductive coupling to afford substituted tetrahydrofurans in very good yields (entries 14 and 15). Similarly, acrylonitrile and acrylate tethered alkynes also worked efficiently (entries 16 and 17).

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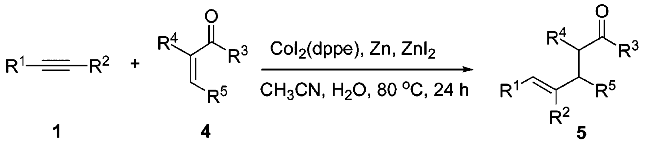
Table 2. Co-Catalyzed Intermolecular Reductive Coupling of Enones and Enals with Alkynes[a]



1i R^1 = 1-naphthyl, $R^2 = CH_3$
1j R^1 = PhCHCH-, $R^2 = CH_3$
1k R^1 = 2-pyridyl, $R^2 = CH_3$
1l $R^1 = R^2$ = *n*-propyl

4a $R^3 = CH_3$, R^4 = H, R^5 = H
4b $R^3 = CH_2CH_3$, R^4 = H, R^5 = H
4c R^3 = Ph, R^4 = H, R^5 = H
4d $R^3 = CH_3$, R^4 = H, $R^5 = CH_3$
4e R^3 = H, R^4 = H, R^5 = H
4f R^3 = H, $R^4 = CH_3$, R^5 = H
4g 2-cyclopentene-1-one
4h 2-cyclohexene-1-one

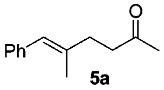
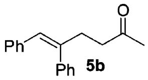
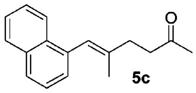
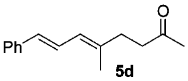
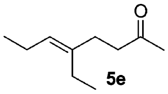
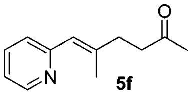
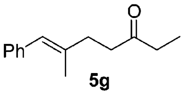
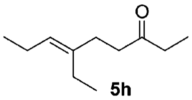
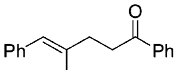
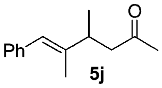
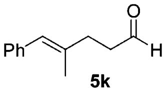
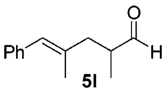
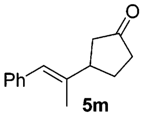
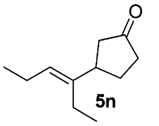
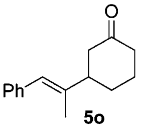
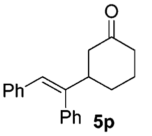
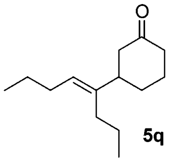
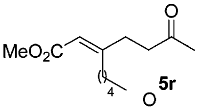
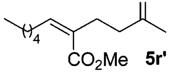
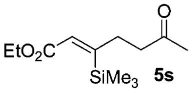
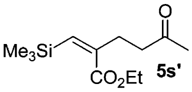
Entry	Alkyne **1**	Alkene **4**	Product **5**	Yield (%)[b]
1	**1a**	**4a**	 **5a**	94
2	**1b**	**4a**	 **5b**	88
3	**1i**	**4a**	 **5c**	74
4	**1j**	**4a**	 **5d**	81
5	**1c**	**4a**	 **5e**	71
6	**1k**	**4a**	 **5f**	84
7	**1a**	**4b**	 **5g**	86
8	**1c**	**4b**	 **5h**	68
9	**1a**	**4c**	 **5i**	74
10	**1a**	**4d**	 **5j**	71
11	**1a**	**4e**	 **5k**	52
12	**1a**	**4f**	 **5l**	36

Table 2. (Continued)

Entry	Alkyne **1**	Alkene **4**	Product **5**	Yield (%)[b]
13	**1a**	**4g**	 **5m**	65
14	**1c**	**4g**	 **5n**	58
15	**1a**	**4h**	 **5o**	74
16	**1b**	**4h**	 **5p**	72
17	**1l**	**4h**	 **5q**	70
18	**1f**	**4a**	 **5r**  **5r'**	71 (56:44)
19	**1g**	**4a**	 **5s**  **5s'**	67 (79:21)

[a] Reaction conditions: alkyne (1.00 mmol), alkene (1.20 mmol), CoI_2(dppe) (0.050 mmol; 5.0 mol %), Zn (2.75 mmol), ZnI_2 (0.10 mmol), H_2O (2.0 mmol), CH_3CN (2.0 mL) at 80 °C for 24 h. [b]Isolated yields.

The success of the reductive coupling reaction of alkynes with both acrylates and enones encouraged us to look for further utility of this reaction. The highly atom-economical nature and complete regio- and stereoselectivity of this reductive coupling as well as the use of acrylates compelled us to think that a strategic positioning of a hydroxyl group in the alkyne moiety will lead to lactones. In this context, we have also reported several metal-catalyzed coupling/lactonization strategies to synthesize a variety of interesting lactones.[10] Small and medium ring lactones are very important in organic chemistry, as they are contained in an ever-growing number of natural products.[11,12] When phenyl propargyl alcohol (**8a**) was treated with methyl acrylate (**2d**) under the reaction conditions shown in Scheme 1, the expected lactone formed albeit in a very low yield of 20%. After a series of attempts to optimize the reaction conditions, we found that CoI_2(dppe) and a proper ratio of CH_3CN and 1,4-dioxane as solvent gave the six-membered ring

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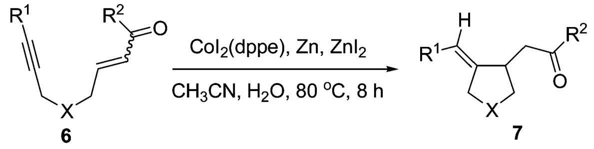
(10) (a) Rayabarapu, D. K.; Sambaiah, T.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1286. (b) Rayabarapu, D. K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 5630. (c) Rayabarapu, D. K.; Shukla, P.; Cheng, C.-H. *Org. Lett.* **2003**, *5*, 4903. (d) Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2005**, *39*, 4955.

(11) (a) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911. (b) El Ali, B.; Alper, H. *Synlett.* **2000**, 161. (c) Shiina, I. *Chem. Rev.* **2007**, *107*, 239.

(12) (a) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777. (b) Bringmann, G.; Hinrichs, J.; Henschel, P.; Peters, K.; Peters, E.-M. *Synlett* **2000**, 1822. (c) Hosmi, F.; Rousseau, G. *J. Org. Chem.* **1998**, *63*, 5255. (d) Grigg, R.; Khalil, H.; Levett, P.; Virica, J.; Sridharan, V. *Tetrahedron Lett.* **1994**, *35*, 3197. (e) Ali, B. E.; Okura, K.; Vasapolla, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264. (f) Williams, A. S.; Firmenich, S. A. *Synthesis* **1999**, *10*, 1707. (g) Wang, Y.; Tennyson, R. L.; Romo, D. *Heterocycles* **2004**, *64*, 605. (h) Yoneda, E.; Zhang, S. W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* **2001**, *42*, 5459.

Table 3. Co-Catalyzed Intramolecular Reductive Coupling of Activated Alkenes with Alkynes[a]



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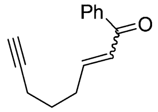
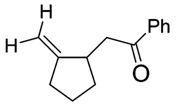
1		*E*-6a		7a	99
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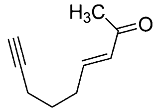
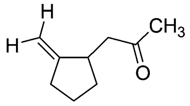
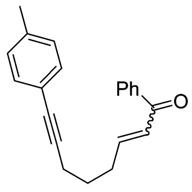
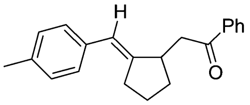
3		6b		7b	80
4		*E*-6c		7c	95
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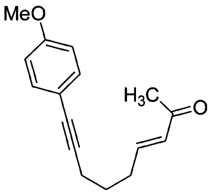
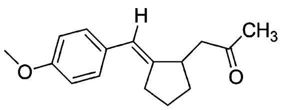
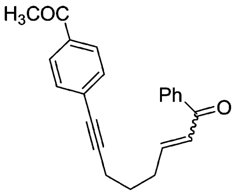
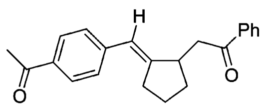
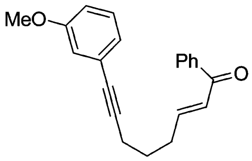
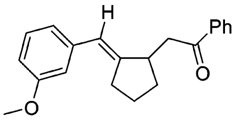
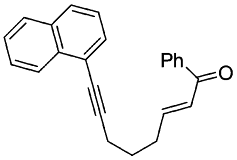
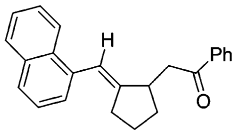
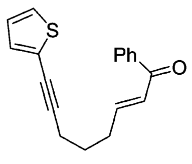
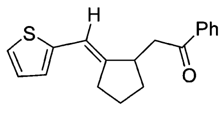
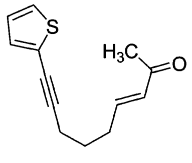
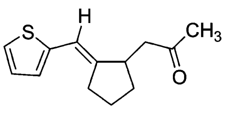
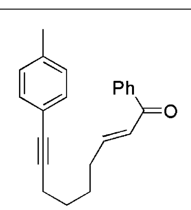
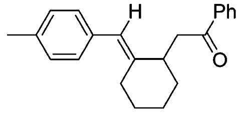
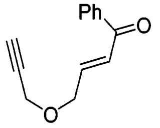
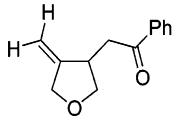
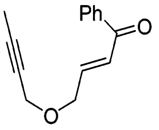
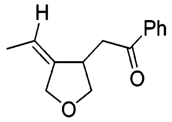
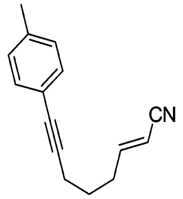
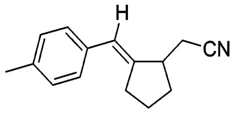
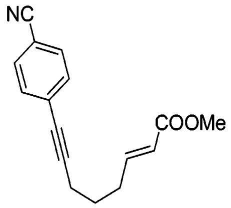
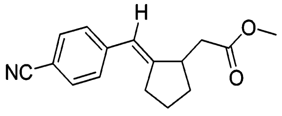
6		6d		7d	85
7		*E*-6e		7e	87
8		*Z*-6e			82
9		6f		7f	92
10		6g		7g	88
11		6h		7h	87
12		6i		7i	84

Table 3. (Continued)

entry	6		7		Yield (%)[b]
13		6j		7j	61
14		6k		7k	94
15		6l		7l	86
16		6m		7m	74
17		6n		7n	71

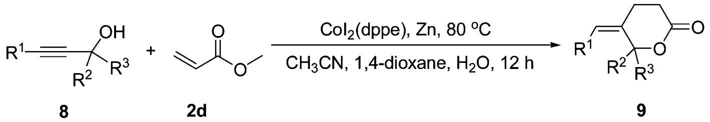
[a] Reaction conditions: enyne **6** (1.00 mmol), $CoI_2(dppe)$ (0.050 mmol; 5.0 mol %), Zn (2.75 mmol), ZnI_2 (0.10 mmol), H_2O (2.0 mmol), CH_3CN (2.0 mL) at 80 °C for 8 h. [b] Isolated yields.

lactone in high 80% yield (Table 4, entry 1). The generality of this reaction is demonstrated by the successful extension to a variety of propargyl alcohols (entries 2−4). More importantly, substitution at the propargylic position also gave the corresponding six-membered ring lactones (entries 5−8). The *Z* stereochemistry of the exo-double bond of the lactone was confirmed by NOE experiments. When phenyl propargyl amine was used, no lactam was observed. Introduction of a suitable protecting group (BOC) to the amine group gave the reductive coupling in high yields (Scheme 2). The lactamization was realized by heating the reductive coupling product in the presence of TFA for 1 h. Both electron-donating and electron-withdrawing group substituted phenyl propargyl amines **10** formed the six-membered lactams **11**. 9-Phenanthrenyl propargyl amine (**10b**) gave the expected product **11b** in 73% yield.

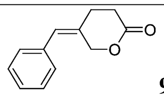
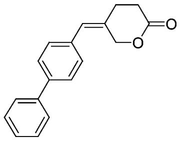
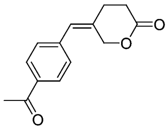
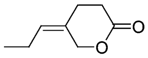
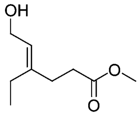
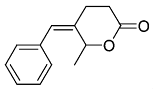
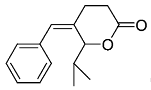
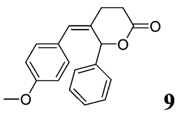
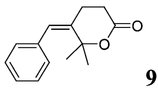
When **8i**, a phenyl propargyl alcohol possessing an ester group at the ortho position of the phenyl ring, was treated with acrylate **2a** the corresponding seven-membered ring lactone **12a** was obtained in 65% yield (Table 5, entry 1). The formation of another possible product, a six-membered cyclic lactone, was not observed. This was inferred from the presence of the *n*-butyl group of the acrylate on the product and no methyl group of the ester on the ortho position of the aromatic ring. The formation of seven-membered ring lactones was further confirmed by comparing the chemical shifts in the ^1H NMR. The protons of the methylene group on the lactone ring of all the seven-membered ring lactones (Table 5) including **12a** appeared between 4.36 and 4.47 ppm, whereas the protons of the methylene group of the six-membered ring lactones (Table 4) appeared between 5.05 and 5.13 ppm. The formation of seven-membered lactone could be effected with different alkenes like acrylonitrile **2b**, vinyl sulfone **2c**, and diethylacryl amide **2e** (entries 2−5). Alkynes with different substituents (**8j**−**l**) at the propargylic position formed the seven-membered ring lactones in modest yields (entries 6−9). The high stereo- and regioselectivity of the reductive coupling alkyne and alkene is very crucial for the success of the synthesis of the six- and seven-membered ring lactones. For example, the lack of regioselectivity for the reaction of **8d** and **2d** (entry 4, Table 4) leads to two products, and one of the products fails to lactonize.

Mechanistic Discussion. To understand the role of water and to help elucidate the mechanism of the present catalytic reaction, an isotope-labeling experiment using D_2O (99.9%) to replace normal water for the reductive coupling of ethyl vinyl ketone **4b** with alkyne **1a** to give product **5g**−**d** was carried out. The results show that the olefinic proton and one of the protons

Table 4. Synthesis of Six-Membered Cyclic Lactone via Co-Catalyzed Intermolecular Reductive Coupling/Lactonization of Acrylates with Propargyl Alcohols[a]



8a R^1 = Ph, R^2 = H, R^3 = H
8b R^1 = biphenyl, R^2 = H, R^3 = H
8c R^1 = 4-CH_3OC-C_6H_4, R^2 = H, R^3 = H
8d R^1 = Et, R^2 = H, R^3 = H
8e R^1 = Ph, R^2 = Me, R^3 = H
8f R^1 = Ph, R^2 = $CH(CH_3)_2$, R^3 = H
8g R^1 = 4-CH_3O-C_6H_4 R^2 = Ph, R^3 = H
8h R^1 = Ph, R^2 = Me, R^3 = Me

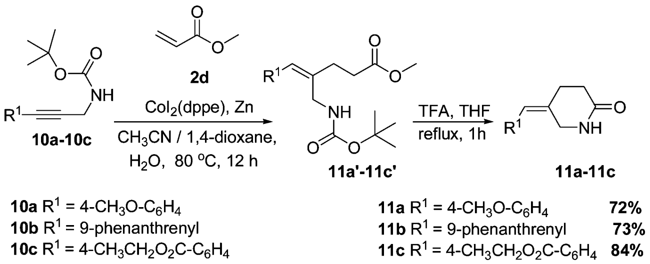
Entry	Propargyl alcohol	Product	Yield (%)[b]
1	**8a**	 **9a**	80
2	**8b**	 **9b**	61
3	**8c**	 **9c**	70
4	**8d**	 **9d**  **9d'**	30 61
5	**8e**	 **9e**	70
6	**8f**	 **9f**	88
7	**8g**	 **9g**	34
8	**8h**	 **9h**	40

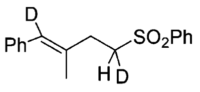
[a] Reaction conditions: propargyl alcohol (1.00 mmol), methyl acrylate (1.20 mmol), CoI_2(dppe) (0.05 mmol; 5.0 mol %), Zn (2.75 mmol), H_2O (2.0 mmol), CH_3CN (0.80 mL), 1,4-dioxane (2.20 mL) at 80 °C for 12 h. [b]Isolated yields.

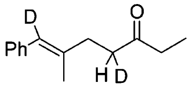
attached to the α-carbon atom of ketone in **5g−d** were deuterated in 84 and 80%, respectively. No deuterium-labeling for other protons in this product was observed. The isotope abundance was determined by the ^1H NMR integration method. In agreement with the results of ^1H NMR analysis, the ^{13}C NMR spectrum of **5g−d** reveals two characteristic deuterium coupled triplets at 125.3 and 40.6 ppm for the olefin and methylene carbons, respectively.

A similar D_2O study involving the reaction of phenyl vinyl sulfone (**2c**) with alkyne **1a** also gave analogous results.[8] The

Scheme 2. Synthesis of Six-Membered Cyclic Lactams via Co-Catalyzed Intermolecular Reductive Coupling/Lactamization of Acrylates with Propargyl Amines




3c-*d*


5g-*d*

mechanism of the present reductive coupling is interesting in view of the ability of the catalyst to assemble an alkyne and an alkene molecule for coupling and hydrogenation in one pot in a regio- and stereoselective fashion. A straightforward route that can explain well the observed regio- and stereochemistry is the formation of a cobaltacyclopentene intermediate from cyclometalation of an alkyne and alkene to the cobalt(I) center followed by protonation of the intermediate by water (Scheme 3, Cycle I). Such a metallocyclopentene species has been proposed as a key intermediate in the ene−yne coupling catalyzed by ruthenium and nickel complexes.[2] The results of the above deuterium isotope-labeling experiment strongly support this pathway. An alternative mechanism involves a cobalt(III) hydride generated from protonation of cobalt(I) by water followed by insertion of an alkene into the metal−hydride bond giving a five-membered ring species (Cycle 2). A similar five-membered ketone chelate complex of rhodium and palladium has been isolated[13] However, in the present case, this pathway can be ruled out considering that the five-membered ring intermediate generated by a cyclic enone such as 2-cyclopenten-1-one would contain a strained five-membered ring.

The role of ZnI_2 is believed to be twofold: (1) to remove the iodide from the Co(I)(dppe)I complex (generated from the one-electron reduction of pre-catalyst $Co(dppe)I_2$) thereby generating a more active cationic cobalt complex; (2) to activate the vinyl ketone by Lewis acid catalysis.

High selectivities were obtained for the formation of a seven-membered ring over a six-membered ring in entries 1 and 4, Table 5. These results are interesting in view of the fact that the formation of a six-membered ring is generally more favorable than a seven-membered ring. The seven-membered ring lactonization is more entropically favorable due to a transition state arising from a near planar structure of the styrenyl moiety **12a′**. However, we did not observe any **12a′** while monitoring the reaction at various time intervals. Thus the possibility of cobaltacyclopentene intermediate **12a-C** formed for the reaction of **8i** and **2a** in entry 1, Table 5 forming a seven-membered ring lactone **12a** (even before the catalytic cycle is complete) without going through **12a′** cannot be ruled out completely.

Some of the products obtained via the present cobalt-catalyzed reductive coupling invite an interesting comparison with 1,4-addition reactions of enones. 1,4-Addition of organometallic reagents to α,β-unsaturated ketones is one of the basic synthetic reactions often used for the carbon−carbon bond formation.[14,15] The reaction presented here, especially in Table 2, offers a more efficient route to 1,4 addition products because these reactions do not require the use of an organometallic reagent (Scheme 4).[16]

The ruthenium-catalyzed Alder-ene reaction involves the formation of a diene from the reaction of an alkyne and alkene. The high atom economy offered by this reaction has led to many useful applications of this reaction toward total synthesis of naturally occurring compounds. The present cobalt-catalyzed reductive coupling also involves the reaction of simple alkenes and alkynes to give highly substituted alkenes. The pre-catalyst CoI_2(dppe) is easy to prepare, handle, and store. Cobalt salts are relatively cheap and environmentally friendly. The very mild reducing agent zinc is used. The simplest hydrogen source water is employed. Thus, this methodology, the one that offers a simple and highly atom-economical approach to carbon−carbon bond formation, will find wide applications in organic synthesis.

Conclusion

In conclusion, we have developed a novel simple method for the assembling of an alkene and alkyne via a cobalt-catalyzed reductive-coupling mode. This reaction is highly chemo-, regio-, and stereoselective. The generality of the reaction was demonstrated by the employment of various activated alkenes like acrylates, acrylonitriles, vinyl sulfones, enones (cyclic and acyclic), and enals and of a wide range of alkynes. Both inter- and intramolecular versions work very well. The methodology was used to synthesize six- and seven-membered cyclic lactones. Further studies toward the asymmetric version and application of this methodology in total synthesis and the use of cobalt catalyst for carbon−carbon bond formation are underway in our laboratories.

Experimental Section

A few representative examples are listed here. Experimental procedures and spectroscopic data for all compounds can be found in the Supporting Information.

Typical Procedure for the Reductive Coupling of Enones with Alkynes: A round-bottom sidearm flask containing CoI_2(dppe) (0.0500 mmol), zinc powder (2.75 mmol), and zinc iodide (0.100 mmol) was evacuated and purged with nitrogen gas three times. Freshly distilled CH_3CN (2.0 mL), alkyne **1** (1.00 mmol), ketone **4** (1.20 mmol), and H_2O (2.00 mmol) were added via syringes. The reaction mixture was heated with stirring at 80 °C for 24 h and was then cooled, diluted with dichloromethane, and stirred in the air for 10 min. The mixture was filtered through a Celite and silica gel pad and washed with dichloromethane. The filtrate was concentrated, and the residue was purified on a silica gel column using hexane-ethyl acetate as eluent to afford the desired product **5**.

Intramolecular reductive coupling was performed following the above procedure with **6** instead of **1** and **4**.

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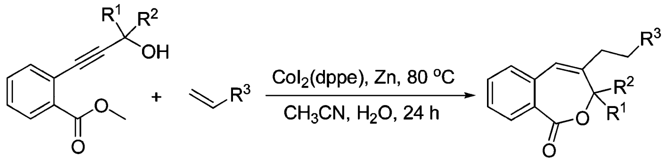
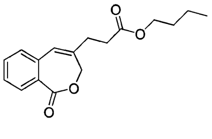
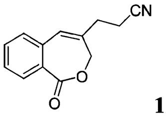
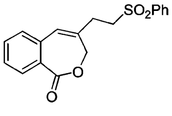
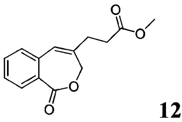
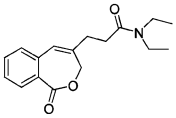
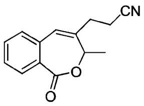
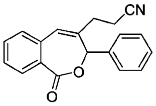
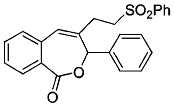
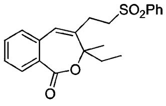
Table 5. Synthesis of Seven-Membered Cyclic Lactone via Co-Catalyzed Intermolecular Reductive Coupling/Lactonization[a]



8 **2** **12**

8i R^1 = H, R^2 = H
8j R^1 = Me, R^2 = H
8k R^1 = Ph, R^2 = H
8l R^1 = Me, R^2 = Et

2a R^3 = CO_2Bu
2b R^3 = CN
2c R^3 = SO_2Ph
2d R^3 = CO_2Me
2e R^3 = $CONEt_2$

Entry	Alkyne	Alkene	Product	Yield[b] (%)
1	**8i**	**2a**	 **12a**	65
2	**8i**	**2b**	 **12b**	85
3	**8i**	**2c**	 **12c**	60
4	**8i**	**2d**	 **12d**	69
5	**8i**	**2e**	 **12e**	55
6	**8j**	**2b**	 **12f**	61
7	**8k**	**2b**	 **12g**	58
8	**8k**	**2c**	 **12h**	42
9	**8l**	**2c**	 **12i**	43

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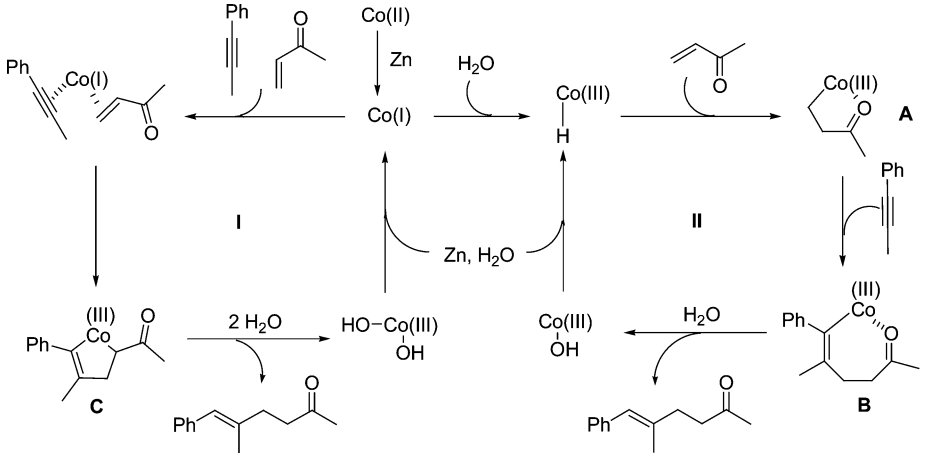
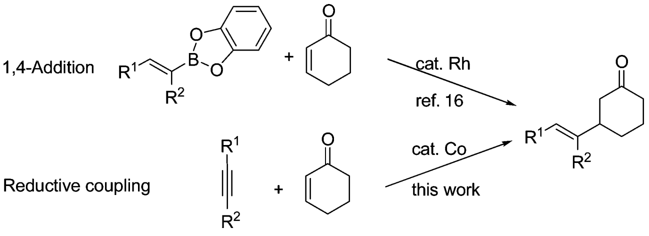
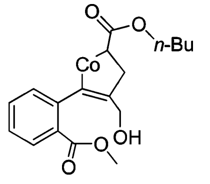
[a] Reaction conditions: alkynes (1.00 mmol), alkenes (1.20 mmol), CoI_2(dppe) (0.050 mmol; 5.0 mol %), Zn (2.75 mmol), H_2O (2.0 mmol), CH_3CN (3.0 mL) at 80 °C for 24 h. [b] Isolated yields.

Scheme 3. Plausible Mechanistic Pathways

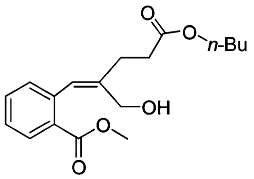


Scheme 4. Comparison of 1,4-Addition and Reductive Coupling





12a-C



12a'

(*E*)-5-Methyl-6-phenylhex-5-en-2-one (5a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (t, $J = 7.2$ Hz, 2H), 7.20 (d, $J = 7.2$ Hz, 2H), 7.17 (t, $J = 7.2$ Hz, 1H), 6.26 (s, 1H), 2.64 (t, $J = 8.0$ Hz, 2H), 2.43 (t, $J = 8.0$ Hz, 2H), 2.17 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.31, 138.10, 137.32, 128.75, 128.00, 126.02, 125.36, 42.22, 34.36, 29.94, 17.77. HRMS calcd for $C_{13}H_{16}O$ 188.1201; found 188.1207.

2-(2-Methylenecyclopentyl)-1-phenylethanone (7a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, $J = 7.2$ Hz, $J = 5.2$ Hz, 2H), 7.54 (tt, $J = 7.2$ Hz, $J = 1.2$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 2H), 4.91 (d, $J = 2.0$ Hz, 1H), 4.80 (dd, $J = 2.0$ Hz, $J = 2.0$ Hz, 1H), 3.22 (dd, $J = 15.2$ Hz, $J = 3.2$ Hz, 1H), 2.96−2.90 (m, 2H), 2.44−2.30 (m, 2H), 2.06−1.98 (m, 1H), 1.76−1.71 (m, 1H), 1.70−1.54 (m, 1H), 1.32−1.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.75, 155.85, 137.21, 132.90, 128.54, 128.06, 104.62, 43.61, 39.79, 33.35, 32.92, 24.08. HRMS calcd for $C_{14}H_{16}O$ 200.1201; found 200.1195.

Typical Procedure for the Synthesis of Six-Membered Ring Lactones: A round-bottom sidearm flask containing CoI_2(dppe) (0.0500 mmol) and zinc powder (2.75 mmol) was evacuated and purged with nitrogen gas three times. Freshly distilled CH_3CN (0.8 mL) and 1,4-dioxane (2.2 mL), propargyl alcohol **8** (1.00 mmol), methyl acrylate **2d** (1.20 mmol), and H_2O (2.00 mmol) were added to the flask via syringes. The reaction mixture was heated with stirring at 80 °C for 12 h and was then cooled, diluted with dichloromethane, and stirred in the air for 10 min. The mixture was filtered through a Celite and silica gel pad and washed with dichloromethane. The filtrate was concentrated, and the residue was purified on a silica gel column using hexane−ethyl acetate as eluent to afford the desired product **9**.

Similar procedures were employed to prepare **11a′**−**c′** from **10** and **2d**. Compounds **11a′**−**c′** were deprotected followed by lactamization to the corresponding **11a**−**c** by refluxing in THF in the presence of trifluoroacetic acid.

5-[(*Z*)-1-Phenylmethylidene]tetrahydro-2*H*-2-pyranone (9a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (t, $J = 7.2$ Hz, 2H), 7.27 (t, $J = 7.2$ Hz, 1H), 7.08 (d, $J = 7.2$ Hz, 2H), 6.55 (s, 1H), 5.06 (s, 2H), 2.78−2.75 (m, 2H), 2.70−2.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.68, 135.74, 131.04, 128.44 (2C), 127.53, 127.34, 68.02, 30.34, 27.83. HRMS calcd for $C_{12}H_{12}O_2$ 188.0837; found 188.0844.

5-[(*Z*)-1-(4-Methoxyphenyl)methylidene]-2-piperidinone (11a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, $J = 9.2$ Hz, 2H), 6.87 (d, $J = 9.2$ Hz, 2H), 6.84 (s, 1H), 6.25 (br, 1H), 4.22 (s, 2H), 3.79 (s, 3H), 2.62 (t, $J = 6.4$ Hz, 2H), 2.45 (t, $J = 6.4$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.10, 158.52, 130.24, 129.76, 128.85, 125.56, 113.75, 55.21, 43.62, 32.32, 30.51. HRMS calcd for $C_{13}H_{15}NO_2$ 217.1103; found 217.1110.

Butyl 3-(1-Oxo-1,3-dihydro-2-benzoxepin-4-yl)propanoate (12a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, $J = 8.0$ Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 1H), 7.36 (t, $J = 8.0$ Hz, 1H), 7.20 (d, $J = 8.0$ Hz, 1H), 6.65 (s, 1H), 4.43 (s, 2H), 4.08 (t, $J = 6.4$ Hz, 2H), 2.70 (t, $J = 6.4$ Hz, 2H), 2.59 (t, $J = 6.4$ Hz, 2H), 1.62−1.55 (m, 2H), 1.37−1.32 (m, 2H), 0.90 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.36, 170.13, 141.62, 135.66, 132.58, 132.17, 130.87, 130.21, 128.69, 127.86, 66.34, 64.63, 32.81, 31.44, 30.64, 19.10, 13.63. HRMS calcd for $C_{17}H_{20}O_4$ 288.1362; found 288.1358.

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

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