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Palladium(II)-Catalyzed Enyne Coupling Reaction Initiated by Acetoxypalladation of Alkynes and Quenched by Protonolysis of the Carbon−Palladium Bond

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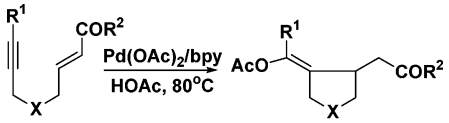

X = C, NTs, O.
R^1 = alkyl
R^2 = H, alkyl

Divalent palladium-catalyzed inter- and intramolecular enyne coupling reactions initiated by acetoxypalladation of alkynes were developed. The reaction involves the acetoxypalladation of the alkyne, followed by the insertion of the alkene and the protonolysis of the carbon−palladium bond. The protonolysis of the carbon−palladium bond in the presence of bidentate nitrogen containing ligands is the key step in completing the Pd(II) catalytic cycle. The nitrogen-containing ligands, like halides, served to favor the protonolysis of the carbon−palladium bond over the β-H elimination in the Pd(II)-mediated reactions. The intermolecular coupling reactions provide an efficient method for synthesizing γ,δ-unsaturated carbonyls. The intramolecular coupling reactions offer a method to construct a variety of synthetically important carbo- and heterocycles. The asymmetric version of such a cyclization was developed with moderate enantioselectivity when employing pymox (pyridyl monooxazoline) as the ligand.

Introduction

In recent years, enyne coupling has been achieved with a wide range of transition-metal complexes either in a catalytic or in a stoichiometric manner, which represents a versatile approach to a variety of products by a simple manipulation.[1] In palladium chemistry, formation of carbon−carbon bonds via vinylpalladium intermediates offers a useful tool for constructing some synthetically important polyfunctionalized molecules with high efficiency.[2] In general, vinylpalladium intermediates mainly come from two pathways: the addition of palladium hydride species (usually generated from Pd(0) species) to alkynes[3] and the oxidative addition of Pd(0) onto vinylhalides or triflates.[4] These two pathways all require Pd(0) species as the catalyst.

We are interested in the method of assembling the γ-lactone ring by intramolecular enyne coupling: α-alkylidene-γ-butyrolactones could be constructed conveniently from the easily available acyclic allylic 2-alkynoate precursors.[5] However, zerovalent palladium-catalyzed cyclization of unsaturated allylic esters has not been studied, probably due to the possible allylic carbon−

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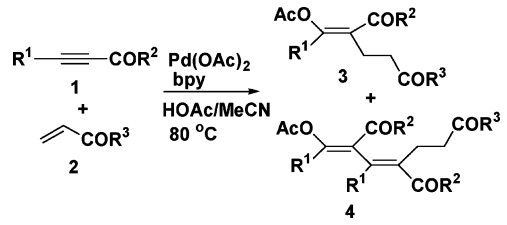
SCHEME 1

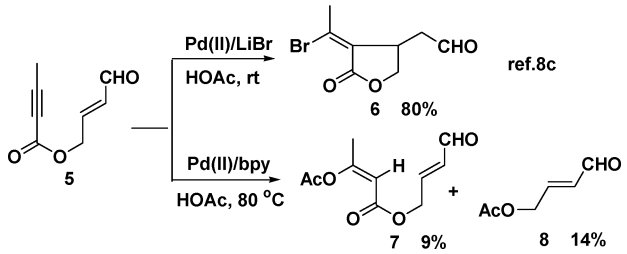


oxygen bond cleavage by the Pd(0) catalyst.[6] In the literature where a divalent palladium complex is the catalytically active species, zerovalent palladium is generally formed during the reaction and then reoxidized to complete the catalytic cycle.[7] In our synthetic application studies directed to a number of bioactive γ-lactone natural products, a Pd(II)-catalyzed cyclization of 4′-X-2′-butenyl 2-alkynoates (X = leaving groups) or 4′-oxo-2′-butenyl 2-alkynoates has been developed for the synthesis of γ-butyrolactones, using halide ions as the nucleophile to attack the Pd(II)-coordinated alkynes as the initial step and β-heteroatom elimination (when X = leaving group) or protonolysis (when 4′-oxo substrates were used) as the final step.[8] However, there exist problems in the method of developing the catalytic asymmetric version of these reactions. A major problem lies in the inevitable disturbance of the excess of requisite halide ions to the coordination of chiral ligands with palladium species. To solve this problem, we developed the first example of asymmetric synthesis of γ-butyrolactones under Pd(II) catalysis in the presence of chiral nitrogen ligands using acetoxypalladation as the first step and β-deacetoxypalladation as the final step.[9] The problem arouse whether or not the acetoxypalladation initiated reaction can take place with protonolysis as the quenching step. Herein we wish to report our recent results.[10]

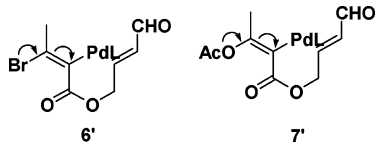
Results and Discussion

Intermolecular Enyne Coupling Reaction. A divalent palladium-catalyzed coupling reaction of electron-deficient alkynes and acrolein or MVK (methyl vinyl ketone) was developed (Scheme 1).[10,11] The reaction provides an efficient method to synthesize γ,δ-unsaturated carbonyls and involves a Pd(II)-catalyzed tandem reaction initiated by acetoxypalladation of alkynes and regeneration of Pd(II) species via protonolysis of the C−Pd bond in the presence of nitrogen-containing ligands, which are crucial to this reaction.[9b]

SCHEME 2



SCHEME 3



Intramolecular Enyne Coupling Reaction. With the three-component coupling of nonterminal alkynes, acrolein or MVK, and acetic acid to form γ,δ-unsaturated carbonyls in hand, we wish to extend this catalytic system to the intramolecular version. In our previous work, we established an efficient method for synthesizing α-alkylidene-γ-butyrolactone derivatives using halopalladation-intramolecular olefin insertion-protonolysis as the key step.[5,8c] In this reaction, the 4′-oxoallylic alkynoate (**5**) cyclized under the catalysis of Pd(II) to give the aldehydic γ-lactone derivative (**6**) with high yield (Scheme 2).[8c] Unfortunately, when 4′-oxoallylic alkynoate (**5**) (0.5 mmol) was treated with $Pd(OAc)_2$ (0.025 mmol) and bpy (0.030 mmol) in acetic acid, no cyclization products can be isolated after heating for 24 h at 80 °C (Scheme 2). Compound **7** was the simple hydroacetoxylation product and compound **8** may result from the ester exchange of HOAc and the starting material. The slower rate for the insertion of the disubstituted alkenes in the intramolecular reaction and the easy protonolysis of the vinylpalladium species formed from acetoxypalladation of alkynoates before the insertion of the olefinic double bond might be the reason for the failure of this reaction (Scheme 2).

On comparing the intermediate structures of the halopalladation and the acetoxypalladation of 4′-oxoallylic alkynoates, the electronic effect of the acetoxy group may allow the vinylic carbon−palladium bond to be easily protonized (Scheme 3).

The tethered atom is another factor that is needs to be considered because the electronic effect of the carbonyl group also influences the reactivity of the vinylpalladium intermediate to some extent. As an example, Pd(II)-catalyzed construction of α-alkylidene-γ-butyrolactams from *N*-allylic alkynamides has been developed in our group.[12] Compound **9** was treated with the present catalytic system; fortunately, cyclization product **10** was isolated even though with a low yield (Scheme 4). This result clearly shows that the difference in the electronic effect of the carbonyl group of the ester and the amide can also influence the reactivity of the vinylpalladium intermediate.

From the results obtained above, it occurs to us that the electronic nature of the alkyne part of the substrate

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(11) Fora similar process initiated by halopalladation, see: Wang, Z.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1996**, 535.

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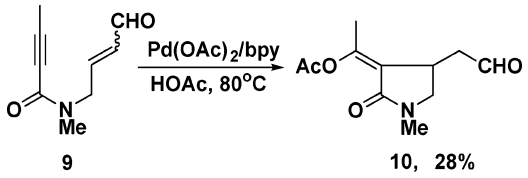
SCHEME 4



9 10, 28%

may have an important influence to the competition between the protonolysis step and the olefin insertion step. Fortunately, on switching from the electron-deficient alkynes to the electron-rich alkynes, most of the substrates can proceed smoothly to afford desirable cyclization products in the present catalytic system. The scope and generality of the present reaction was studied as shown in Table 1. The reaction of carbon, oxygen, nitrogen-tethered enyne substrates proceeded smoothly and five- or six-membered carbo- or heterocycles products were obtained in moderate to good yields.

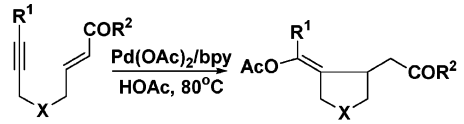
In some of our reported reactions, only substrates with (*Z*)-olefin are efficient in cyclization;[9] however, in the present system, most of the (*E*)-enyne substrates can also proceed smoothly to afford the cyclization products.[13] Terminal alkyne is still not feasible in the present system (entry 1).[9,10] Alkyl-substituted enynes (entries 3 and 4) usually need shorter reaction time and afford better results compared to aryl-substituted enynes (entry 5). Phenyl vinyl ketone is not reactive in intermolecular reactions; however, compound **15b** can easily undergo cyclization (entry 10). Using this reaction, the tetrahydropyrrole and hexahydrobenzofuran skeleton can be constructed conveniently in a single step with moderate yields (entries 11 and 12). Enynes usually afforded five-membered-ring products in the present catalytic system. However, the five (**12f**)- and six (**12g**)-membered ring product was found when using **11f** as substrate (entry 6). The presence of two symmetric oxygen atoms in the molecule (**11**) may be the cause of the different regioselectivity of the cyclization. Furthermore, employing an electron-withdrawing group in substrate **21** gave only six-membered-ring product **22** in 76% yield. Substrate **23** afforded six-membered-ring **24** with high regioselectivity (Scheme 5). The stereochemistry of the exocyclic double bond was deduced by NOESY spectra as the (*Z*) form on the cyclization product **12b**. The stereochemistry of the fused ring in compound **20** was proved also by NOESY spectra as cis in compound **20**.

To test the effect of changing the length of the tethered atoms, a 1,7-enyne **25** was tried. While no cyclization product was observed, the reaction can only give the hydroacetoxylation product **26** in 76% yield (Scheme 6).

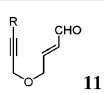
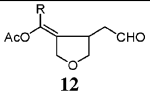
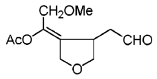
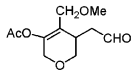
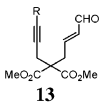
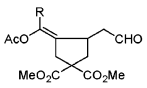
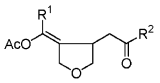
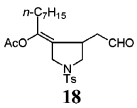
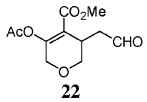
Proposed Mechanism for the Coupling Reaction. The mechanism for the intramolecular cyclization is believed to be analogous to that of the halopalladation initiated enyne coupling reactions (Scheme 7).[8c,11] This will involve insertion of the pendant olefin into the vinylpalladium intermediate formed by *trans*-acetoxypalladation of the carbon−carbon triple bond, followed by the protonolysis of the carbon−palladium bond to regenerate

(13) It was found that (*Z*)-enyne substrates were not stable in acidic medium forming a mixture of (*E*)- and (*Z*)-4′-oxoallylic alkynyl ethers. Thus, (*E*)-enyne substrates were used in this work except for compound **19** (Table 1, entry 12).

TABLE 1. Pd(II)-Catalyzed Intramolecular Enyne Coupling Reactions[a]

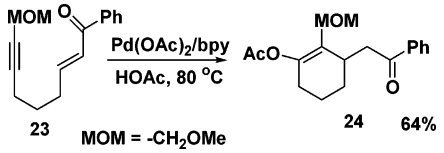


X = C, NTs, O.

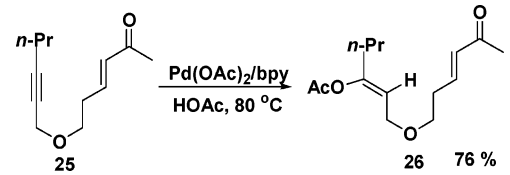
Entry	Enyne	T(°C)/h	Products	Yield(%)[b]
	 **11**		 **12**	
1	R=H **11a**	80/24	**12a**	0[c]
2	R=Me **11b**	80/12	**12b**	53
3	R=*n*-C_5H_{11} **11c**	80/12	**12c**	84
4	R=*n*-C_7H_{15} **11d**	80/12	**12d**	96
5	R=Ph **11e**	100/24	**12e**	65
6	R=CH_2OMe **11f**	80/24	 **12f**	**12f** 47
			 **12g**	**12g** 38
	 **13**		 **14**	
7[d]	R=Me **13a**	100/24	**14a**	70
8[d]	R=*n*-C_7H_{15} **13b**	100/27	**14b**	63
	 **15**		 **16**	
9[d]	R^1=R^2=Me **15a**	100/24	**16a**	60
10[d]	R^1=*n*-C_7H_{15}, R^2=Ph **15b**	100/6	**16b**	80
11	 **17**	80/24	 **18**	75
12[d]	**19**	80/12	**20**	66
13[d]	 **21**	80/24	 **22**	76

[a] Reaction conditions: A mixture of enyne substrate (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), and bpy (0.05 mmol) in HOAc (7.5 mL) and 1,4-dioxane (7.5 mL) was heated at the temperature and the time indicated. [b] Isolated yield. [c] Disordered reaction. [d] HOAc (4 mL) was used as the solvent.

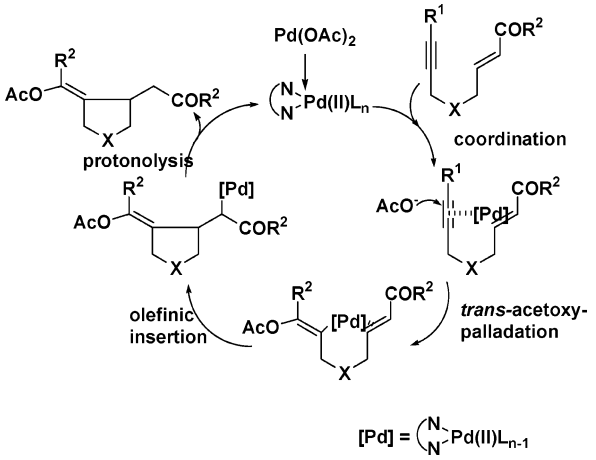
SCHEME 5



SCHEME 6



SCHEME 7

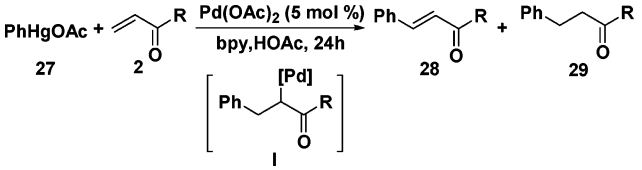


the catalytic Pd(II) species, giving cyclization products, respectively. Here, the nitrogen-containing ligand was crucial to the reaction. It not only played the same role as the halide ions to inhibit the β-hydride elimination but also stabilized the vinylpalladium intermediate and promoted the intramolecular olefinic insertion into the vinyl-palladium bond.[9]

The stereospecific (*Z*)-configuration of the exocyclic double bond in the cyclization products supports the mechanism of the *trans*-acetoxypalladation of alkynes. This point is different from the halopalladation of alkynes where *cis*-halopalladation is manifested especially in the case of low concentration of halides ions.[8b,14]

Role of Nitrogen-Containing Ligands. In our previous paper on Pd(II)-catalyzed reactions initiated by halopalladation of an alkyne, we found that halide ion plays an important role in inhibiting the β-hydride elimination and promoting the β-heteroatom elimination or protonolysis of the carbon palladium bond to make the regeneration of the Pd(II) species possible.[15] In our recent study of Pd(II)-catalyzed reactions initiated by acetoxypalladation and quenched by β-heteratom elimination, it was found that nitrogen-containing ligands are crucial for the success of the cyclization of enyne esters.[9] In this work, we found that the bpy ligand is also important here. To study the role of bpy in the above catalytic system, we investigated a catalytic process incorporating Pd(II)-mediated transmetalation. The reaction of phenylmercuric acetate with acrolein or MVK in the presence of 5 mol % of $Pd(OAc)_2$ in HOAc was conducted by different loading of bpy as shown in Table 2. With the increase of the amount of bpy, the total yield of the product increased obviously and the protonolysis product **29** was dominant compared to β-hydride elimination product **28**. Employment of 1,10-phenanthroline as the ligand gave a similar result to that of bpy. The results strongly supported the fact that these nitrogen-containing ligands play a crucial role in inhibiting the β-H elimination of intermediate (**I**) and promoting the proton-

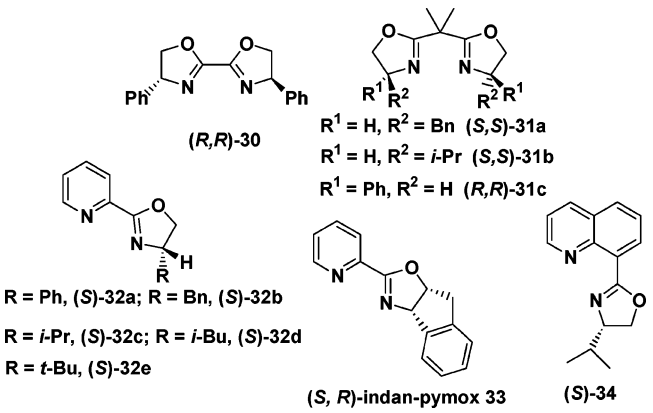
TABLE 2. Pd(II)-Catalyzed Reactions of Phenylmercuric Acetate with Acrolein or MVK[a]



entry	R	bpy, mol %	*t*, °C	yield,[b] %	**28**:**29**[c]
1	H	0	70	6	86:14
2	H	10	70	48	15:85
3	H	25	70	78	<3:97
4	Me	0	50	7	>97:3
5	Me	10	50	47	27:73
6	Me	25	50	47	15:85
7[d]	H	25	70	76	<3:97

[a] Reaction conditions: PhHgOAc (1 mmol), acrolein or MVK (5 mmol), $Pd(OAc)_2$ (0.05 mol), and HOAc (4 mL) were heated at the indicated temperature. [b] Isolated total yield of **28** and **29**. [c] The ratio of **28** and **29** was determined by ^{1}H NMR (300 MHz) spectra. [d] Using 1,10-phenanthroline as ligand.

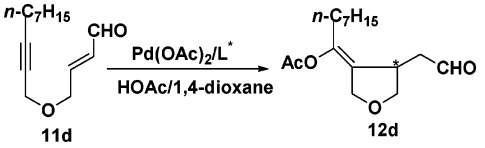
SCHEME 8



(14) (a) Maitlis, P. M. *The Organic Chemistry of Palladium*; Academic Press: New, York, 1971; Vol. 1, p 79. (b) Maitlis, P. M. *Acc. Chem. Res*. **1976**, *9*, 93−99. (c) Larock, R. C.; Riefling, B. *Tetrahedron Lett*. **1976**, *17*, 4661. (d) Kaneda, K.; Uchiyama, T.; Fujiwarka, Y.; Teranishi, S. *J. Org. Chem*. **1979**, *44*, 55. (e) Lambert, C.; Utimoto K.; Nazaki, H. *Tetrahedron Lett*. **1984**, *25*, 5323. (f) Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753. (g) Arcardi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem*. **1992**, *57*, 976. (h) Kosugim, M.; Sakavya, T.; Ogawa, S.; Migita, T. *Bull. Chem. Soc. Jpn*. **1993**, *66*, 3058. (i) Bäckvall, J.-E.; Nilsson, Y. I. M.; Andersson, P. G.; Gatti, R. G. P.; Wu, J. *Tetrahedron Lett*. **1994**, *35*, 5713. (j) Bäckvall, J.-E.; Nilsson, Y. I. M.; Gatti, R. G. P. *Organometallics* **1995**, *14*, 4242.

(15) In the Pd(II)-catalyzed coupling reactions, the halide ion can prohibit the β-H elimination of a carbon−palladium bond, giving preferentially the protonolysis or β-heteroatom elimination product, see: (a) Wang, Z.; Zhang, Z.; Lu, X. *Organometallics* **2000**, *19*, 775. (b) Zhang, Z.; Lu, X.; Xu, Z.; Zhang, Q.; Han, X. *Organometallics* **2001**, *20*, 3724.

TABLE 3. Asymmrtric Cyclization of 11d Employing Oxazoline Ligands[a]



entry	ligand (mol %)	*T*, °C	yield,[b] %	ee % of **12d**[c]
1	(*S*)-**32a** (20)	60	72	66
2	(*S*)-**32b** (20)	60	30	66
3	(*S*)-**32c** (10)	80	32	53
4	(*S*)-**32c** (20)	60	65	77
5	(*S*)-**32d** (20)	60	29	75
6	(*S*)-**32e** (20)	60	50	29
7	(*S*)-**33** (10)	80	32	40
8	(*S*)-**34** (20)	60	37	29

[a] The reaction was carried out under the following conditions: **11d** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), and chiral ligand in HOAc/1,4-dioxane (7.5 mL/7.5 mL), 24 h. [b] Isolated yield. [c] Determined by chiral GC with ChiralDexG-TA column.

olysis of the carbon−palladium bond making the catalytic cycles possible.

Asymmetric Version of the Cyclization. With these results in hand, further effort to develope an aymmmetric version of this reaction was made, using the homochiral nitrogen-containing ligands (Scheme 8).[16] Unfortunately, when we used the C_2-symmetric bisoxazoline ligands **30** and **31**, the present reaction turned to a disordered reaction. Using pymox (pyridyl monooxazoline) as ligand, the cyclization proceeded more efficiently and led to moderated yield and enantioselectivity (entries 1−5, Table 3). Employment of isopropyl-substituted pyridyl monooxazoline gave the highest enantioselectivity (77% ee) (Table 3, entry 4). Two other enyne substrates of **15b** also afforded a similar yield (64%) and ee value (77%).[17]

Conclusion

In summary, we developed a novel Pd(II)-catalyzed enyne coupling reaction initiated by acetoxypalladation of alkynes, in which the carbon−palladium bond was quenched by protonolysis in the presence of nitrogen-containing ligands. This is a reaction using Pd(II) catalyst without the use of additional additives or redox systems. While the intermolecular coupling reactions provide an efficient method to synthesize γ,δ-unsaturated carbonyls, the intramolecular version offers a method to construct a variety of synthetically important carbo- and heterocycles.

Experimental Section

Typical Procedure for the Intramolecular Enyne Coupling Reaction. To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and 2,2′-bipyridine (7.8 mg, 0.05 mmol) in a mixture of HOAc (7.5 mL) and 1,4-dioxane (7.5 mL) at 80 °C was added **11d** (111 mg, 0.5 mmol) with stirring. After the reaction was complete as monitored by TLC, the reaction mixture was neutralized with saturated $NaHCO_3$ and extracted with Et_2O. The combined ether solution was washed with saturated NaCl, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (EtOAc:petroleum ether = 1:4) to give the coupling product **12d** in 96% yield: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 4.29 (d, J = 13.2 Hz, 1H), 4.14 (d, J = 13.2 Hz, 1H), 3.87 (dd, J = 9.2 Hz, J = 5.4 Hz, 1H), 3.74 (d, J = 9.2 Hz, 1H), 3.25 (m, 1H), 2.79 (dd, J = 18.3 Hz, J = 10.0 Hz, 1H), 2.60 (d, J = 18.3 Hz, 1H), 2.23 (t, J = 7.2 Hz, 2H), 2.15 (s, 3H), 1.41−1.26 (m, 10H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 168.4, 141.2, 128.7, 73.9, 68.3, 47.5, 35.5, 31.7, 31.2, 29.2, 29.0, 26.4, 22.6, 20.6, 14.0; IR (neat) ν 2930, 2858, 1757, 1723, 1693, 1371, 1207, 1142, 929 cm^{-1}; MS (EI) *m/z* 241, 223 (M^+ − OAc), 181, 43 (100); HRMS calcd for $C_{14}H_{22}O_2$ [M^+ − HOAc] 222.1620, found 222.1612.

The intramolecular coupling reaction of other substrates was carried out with a similar procedure. For the detailed procedure and characterization data of the new compounds, see the Supporting Information.

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Supporting Information Available: Experimental procedures for all the substrates, copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **12b**−**g**, **14a**,**b**, **16a**, **18**, **20**, **22**, **24**, and **26**, and NOESY spectra for compounds **12b** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For recent contributions to enantioselective enyne cyclizations, see: (a) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704. (b) Chakrapani, H.; Liu, C.; Widenhoefer, R. A. *Org. Lett.* **200**3, *5*, 157. (c) Lei, A.; Waldkirch, J. P.; He, M.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526. (d) Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **2000**, *39*, 4104.

(17) The enantioselectivity of compound **10b** was determined by chiral HPLC, using chiralcel OJ column (λ = 214 nm).