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Synthesis of Multisubstituted 2-(Dihydrofuran-2(3H)-ylidene)acetates via Intramolecular Carboalkoxylation by Platinum–Olefin Catalyst System

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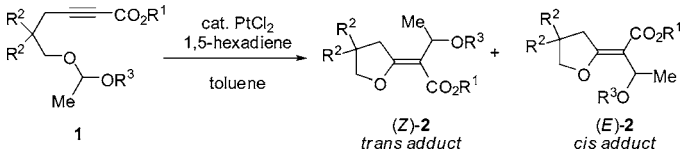
ABSTRACT



The cyclization of 6-(1-alkoxyethyl)hex-2-ynoates in the presence of a platinum–olefin catalyst system gave the corresponding multisubstituted 2-(dihydrofuran-2(3H)-ylidene)acetates in good to high yields. The *Z*/*E* selectivity is controlled by the electronic property of the ester group; the 2,2,2-trichloroethyl ester led to the *Z* isomer, while the phenyl ester gave the *E* isomer.

The cataytic cyclization reaction for alkynylamines, -alcohols, and -thiols, which proceeds through intramolecular addition of N−H, O−H, and S−H bonds to the triple bond, is one of the most powerful tools to synthesize heterocyclic compounds (eq 1).[1] Recently, Lewis acidic transition metal-catalyzed cyclization of *o*-alkynylphenyl ethers,[2] *o*-alkynylanilines,[2a,b,3] and *o*-alkynylphenyl sulfides[4] having a carbon migrating group (CR_3), such as allyl, acyl, *p*-methoxyphenyl (MPM), and α-alkoxylalkyl groups, on the heteroatom (Y), which proceed through a carbon−heteroatom bond addition have been developed as a synthetic method for 2,3-disubstituted benzofurans, indoles, and benzothiophenes (eq 2). However, these Lewis acidic transition metal-catalyzed carbon−heteroatom bond addition reactions have rarely employed substrates which have an alkyl chain between the alkyne moiety and the heteroatom as its starting material. To the best of our knowledge, a single known instance is the platinum-catalyzed cyclization of allylic ethers reported by Fürstner's group (eq 3).[5] Herein, we report that the cyclization of 6-(1-alkoxyethyl)hex-2-ynoates **1** in the pres-

(1) For a review, see: (a) Hosokawa, T.; Murahashi, S.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2000; Vol. 3.2.1, p 2169. (b) Hosokawa, T. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2000; Vol. 3.3.1, p 2211. (c) Gabriele, B.; Salerno, G. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2000; Vol. I4.4.2, p 2623. (d) Schmalz, H. G.; Geis, O. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2000; Vol. I.2.1.3, p 2377. (e) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (f) Brunet, J. J.; Neibecker, D. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds., Wiley-VCH Verlag GmbH: Weinheim; 2001; p 91. (g) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (h) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.

(2) Migration of allyl groups: (a) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001. (b) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. Propargyl groups: (c) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101. Acyl groups: (d) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546. α-Alkoxyalkyl group: (e) Nakamura, I.; Mizushima, Y.; Yamagishi, U.; Yamamoto, Y. *Tetrahedron* **2007**, *63*, 8670.

(3) Allyl groups: (a) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (b) Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* **1998**, 741. (c) Monterio, N.; Balme, G. *Synlett* **1998**, 746. α-Alkoxyalkyl groups: (d) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (e) Fürstner, A.; Heilmann, E.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760.

(4) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473.

(5) (a) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863.

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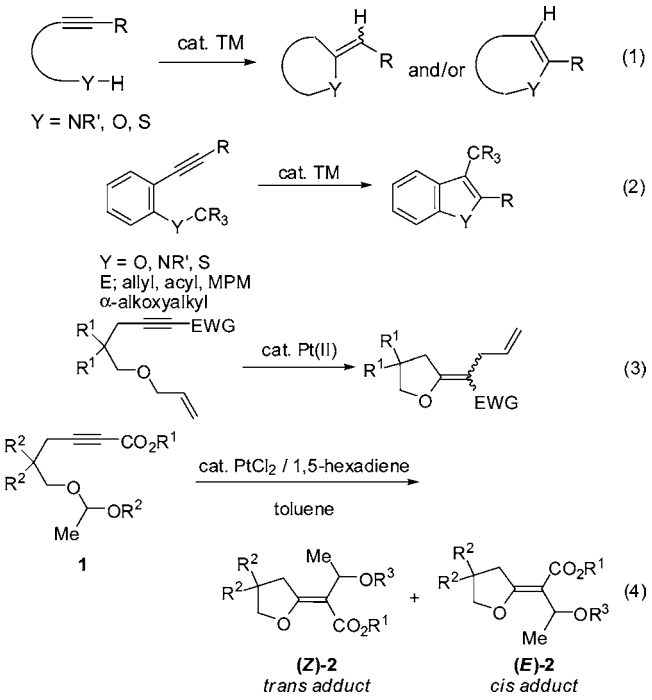
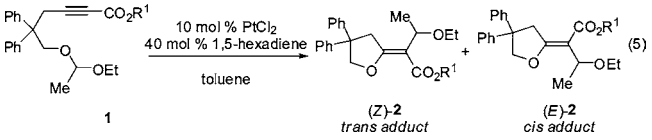
ence of a platinum−olefin catalyst system gave the corresponding multisubstituted 2-(dihydrofuran-2(3H)-ylidene)-acetates **2** in good to high yields (eq 4). The stereo configuration outcome can be controlled by switching the electronic property of the ester group.



The results of the platinum−olefin catalyzed cyclization of 5,5-diphenyl-6-(1-ethoxyethyl)hex-2-ynoates **1a**−**h** are summarized in Table 1 (eq 5). The reaction of the 2,2,2-trichloroethyl ester **1a** in the presence of 10 mol % of $PtCl_2$ and 40 mol % of 1,5-hexadiene in toluene at 35 °C gave (*Z*)-**2a**, deriving from *trans*-addition of the acetal C−O bond to the alkynyl moiety, in 84% yield with exclusive *Z* stereoselectivity (entry 1). The reaction in the absence of 1,5-hexadiene did not proceed at all.[6] Interestingly, the reaction of the substrates **1a**, **1b**, **1c**, and **1d** having electron-deficient ester groups afforded *Z* isomers as major products (entries 1−4), while those having a relatively electron-rich ester, such as **1f**, **1g**, and **1h**, proceeded more slowly and gave the *E* isomers, deriving from formal *cis*-addition of the acetal C−O bond (entries 6−8). Particularly, the reaction of the phenyl ester **1h** gave (*E*)-**2h** in a good yield with an exclusive *E* selectivity (entry 8). The stereochemistry of the product was determined by NOE experiments. Furthermore, the structure of (*Z*)-**2e** was unambiguously determined by X-ray crystallographic analysis.[7]

We explored the substrate scope of the platinum-olefin-catalyzed cyclization of the 2,2,2-trichloroethyl esters (Table 2, eq 6). Regardless of the bulkiness of the acetal moiety, substrates **1a**, **1i**, and **1j** bearing a gem-diphenyl group solely produced *Z* isomers (*Z*)-**2a**, (*Z*)-**2i**, and (*Z*)-**2j**, respectively, in high yields (entries 1−3). The reaction of **1l** having a gem-dimethyl group produced **2l** with a good stereoselectivity, while that of **1k** having a spirocyclohexyl group proceeded with poor stereoselectivity (entries 4 and 5). The substrate **1m**, which did not have a geminal substituent in the tether moiety, was converted to **2m** in a good yield with an acceptable stereoselectivity (entry 6).

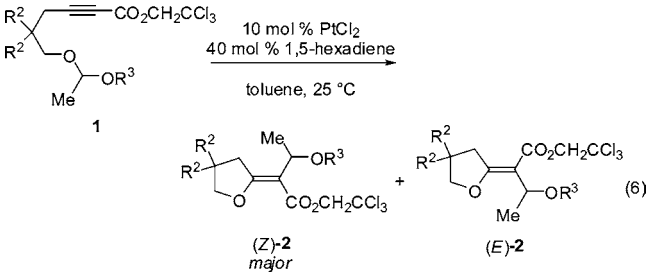
Table 1. Cyclization of 5,5-diphenyl-6-(1-ethoxyethyl)hex-2-ynoates **1a**−**h**[a]



entry	**1**	R^1	time/h	**2**	yield/%[b]	*Z*/*E*[c]
1	**1a**	Cl_3CCH_2	1.5	**2a**	84	100:0
2	**1b**	*p*-O_2N−C_6H_4	3.5	**2b**	83	96:4
3	**1c**	*p*-Cl−C_6H_4	4	**2c**	84	95:5
4	**1d**	*p*-Br−C_6H_4	4.5	**2d**	87	95:5
5[d]	**1e**	Me	4.5	**2e**	54	31:69
6[d]	**1f**	Et	13	**2f**	50	0:100
7[d]	**1g**	*p*-MeO−C_6H_4	24	**2g**	32	0:100
8[d]	**1h**	Ph	48	**2h**	69	0:100

[a] The reaction of **1** was carried out in the presence of 10 mol % of $PtCl_2$ and 40 mol % of 1,5-hexadiene in toluene at 25 °C. [b] ^{1}H NMR yield using 1,3-benzodioxole as an internal standard. [c] The ratio was determined by ^{1}H NMR. [d] At 35 °C.

Table 2. Cyclization of the 2,2,2-Trichloroethyl Ester **1a** and **1i**−**m**[a]



entry	**1**	R^2	R^3	time/h	**2**	yield/%[b]	*Z*/*E*[c]
1	**1a**	Ph	Et	1.5	**2a**	84[d]	100:0
2	**1i**	Ph	*i*-Pr	1	**2i**	88	100:0
3	**1j**	Ph	*i*-Bu	3	**2j**	78	100:0
4	**1k**	-$(CH_2)_5$-	Et	4	**2k**	88	53:47
5	**1l**	Me	Et	2.5	**2l**	56[d]	71:29
6	**1m**	H	Et	1	**2m**	75	78:22

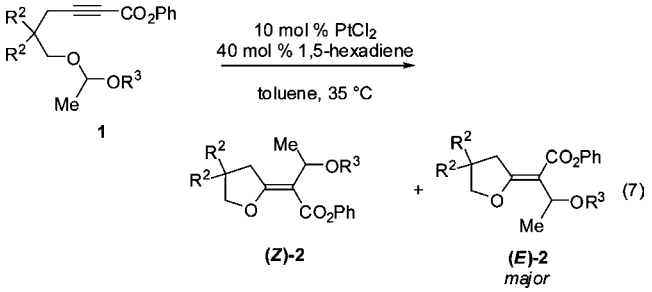
[a] The reaction of **1** was carried out in the presence of 10 mol % of $PtCl_2$ and 40 mol % of 1,5-hexadiene in toluene at 25 °C. [b] Isolated yield. [c] The ratio was determined by ^{1}H NMR. [d] ^{1}H NMR yield using 1,3-benzodioxole as an internal standard.

(6) 1,5-Hexadiene breaks the aggregate structure of polymeric $PtCl_2$, thereby possibly increasing the number of active sites available for the reaction. (a) Jensen, K. A. *Acta Chem. Scand.* **1953**, *7*, 866. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

(7) CCDC-667034 contains the supplementary crystallographic data for (*Z*)-**2e**. The data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

Next we attempted selective synthesis of the *E* isomers using substrates having a phenyl ester (Table 3, eq 7). The

Table 3. Cyclization of the Phenyl Ester **1h** and **1n**−**r**[a]

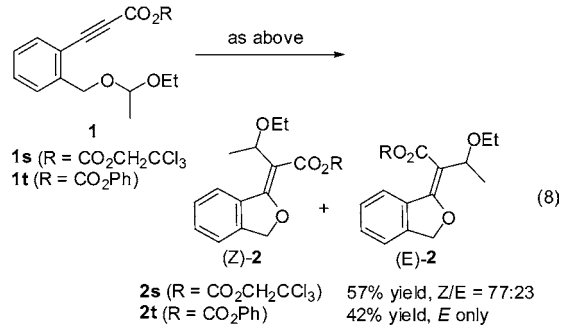


entry	1	R^2	R^3	time/h	2	yield/%[b]	Z/E[c]
1	**1h**	Ph	Et	48	**2h**	69	0:100
2	**1n**	Ph	*i*-Pr	48	**2n**	58	12:88
3	**1o**	Ph	*i*-Bu	38	**2o**	55	18:82
4	**1p**	-$(CH_2)_5$-	Et	43	**2p**	56	0:100
5	**1q**	Me	Et	19	**2q**	58[d]	3:97
6	**1r**	H	Et	1	**2r**	58	48:52

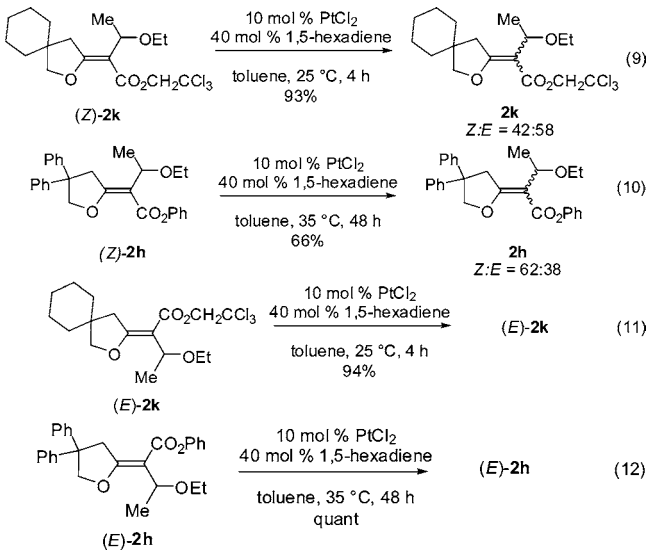
[a] The reaction of **1o**−**t** was carried out in the presence of 10 mol % of $PtCl_2$ and 40 mol % of 1,5-hexadiene in toluene at 35 °C. [b] Isolated yield. [c] The ratio was determined by ^1H NMR. [d] ^1H NMR yield using 1,3-benzodioxole as an internal standard.

reaction of substrates having a substituent at the tether moiety (R^2) gave the corresponding *E* isomers as major products (entries 1−5). In contrast, the reaction of **1r**, which did not have any substituents at R^2 afforded a 1:1 mixture of the *E*/*Z* isomers (entry 6).

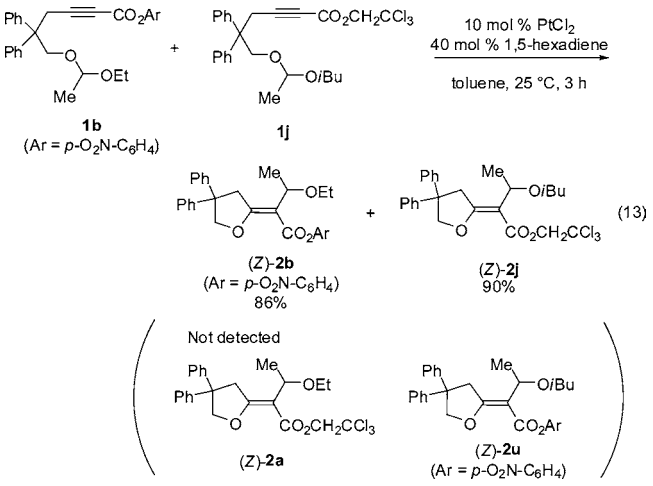
We extended the present reaction for the synthesis of substitued dihydroisobenzofurans (eq 8). The reaction of the trichloroethyl ester of 4-[*o*-{(1-ethoxyethoxy)methyl}phenyl]-but-2-ynoic acid **1s** gave **2s** in 57% yield with a moderate *Z* stereoselectivity, while the phenyl ester **1t** solely afforded the *E* isomer (*E*)-**2t**.



We also observed isomerization from the *Z* product to its corresponding *E* geometrical isomer in the presence of the platinum−olefin catalysts.[8] The isolated 2,2,2-trichloroethyl ester (*Z*)-**2k** was rapidly converted to a 42:58 mixture of the *Z*/*E* isomers in the presence of the platinum catalyst, indicating that (*E*)-**2k** was formed mainly by platinum-catalyzed isomerization from (*Z*)-**2k** in the reaction **1k** (eq 9). On the other hand, the isolated (*Z*)-**2h** was converted to a 62:38 mixture of the *Z*/*E* stereoisomers under the reaction conditions, indicating that the *Z*/*E* isomerization occurs on the way of cyclization proceess and the interconversion from *Z* isomer to *E* isomer is a minor reaction pathway in the reaction of **1h**, since the ratio of interconversion from (*Z*)-**2h** to (*E*)-**2h** was, however, much less than that in the cyclization reaction of **1h** (eq 10 vs Table 1, entry 8), In contrast, the isolated (*E*)-**2k** and (*E*)-**2h** remained unchanged under the reaction conditions, suggesting that the *E* isomers were thermodynamically more stable than the *Z* isomers (eqs 11 and 12).

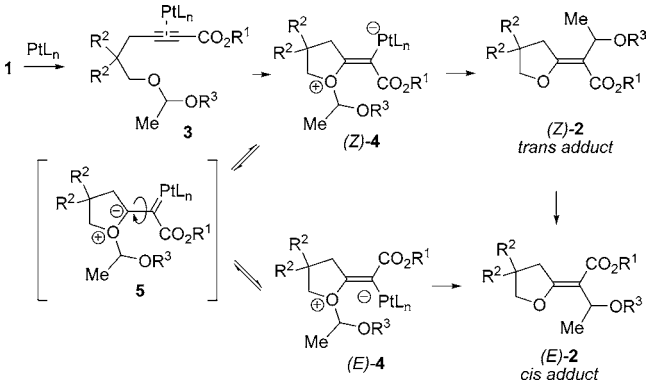


To find out if the migration of the α-alkoxyalkyl group occurs in an intramolecular or intermolecular fashion, we performed crossover experiment (eq 13). The reaction of a 1:1 mixture of **1b** and **1j** under the standard reaction conditions gave the corresponding products (*Z*)-**2b** and (*Z*)-**2j** in 86 and 90% yields, respectively; the crossover products, such as (*Z*)-**2a** and (*Z*)-**2u,** were not detected by GC−mass and NMR analysis. This result clearly indicates that the migration of the α-alkoxyalkyl group proceeds in an intramolecular manner.



On the basis of these experiments, we propose a mechanism of this reaction as shown in Scheme 1. A Lewis acidic

Scheme 1. Plausible Mechanism



platinum catalyst would coordinate to the triple bond of the substrate **1**, forming π-complex **3**. Nucleophilc attack of the oxygen atom of the acetal moiety to the electron-deficient alkynyl moiety would lead to the cyclized intermediate (*Z*)-**4**. [1,3]-Migration of α-alkoxyalkyl group followed by elimination of the platinum catalyst, so-called carbodemetalation, would give the *Z*-isomer. In the reaction of the phenyl esters (**1h**, **1n**−**r**, and **1t**), the isomerization from (*Z*)-**4** to (*E*)-**4** through the platinum carbene intermediate **5** would take place.[9] Similarly, the following carbodemetalation would give the *E* isomer. In the reaction of the 2,2,2-trichloroethyl ester, a strongly electron-withdrawing group facilitates elimination of the α-alkoxyalkyl group, leading to fast carbodemetalation from (*Z*)-**4** to (*Z*)-**2**. The *E* product would also then be formed via isomerization from the *Z* product.[10] The reaction pathway for the formation of the *E* isomer depends on the substrate's structure.

In conclusion, we are now in a position to synthesize multisubstituted 2-(dihydrofuran-2(3H)-ylidene)acetates stereoselectively by changing a substituent at the ester moiety. This present reaction, which proceeds with an addition of an acetal C−O bond, which we termed carboalkoxylation, is a useful methodology to synthesize (dihydrofuran-2(3H)-ylidene)acetates in an efficient and atom-economic manner.

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Supporting Information Available: Experimental procedures and characterization of the products **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The *Z* and *E* isomers did not isomerize in the absence of the platinum catalysts.

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