JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Regiocontrolled Palladium-Catalyzed Arylative Cyclizations of Alkynols

Daishi Fujino,[†] Hideki Yorimitsu,*[,†,‡] and Atsuhiro Osuka[†]

[†]Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan
[‡]ACT-C, JST, Sakyo-ku, Kyoto 606-8502, Japan

Supporting Information

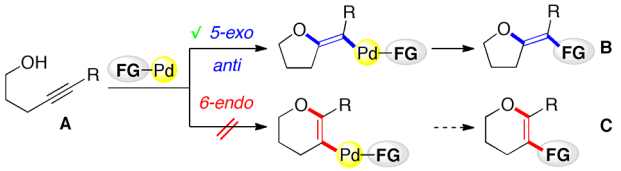
ABSTRACT: Tuning the reactivity of arylpalladium intermediates enables control of catalytic arylative 5-*exo* and 6-*endo* cyclizations of alkynols. The two modes of cyclizations represent a rare example of controllable, regioselective difunctionalization of alkynes. The cyclizations are useful in offering a divergent synthesis of oxygen-containing heterocycles, which is of synthetic use for further derivatization. Formal synthesis of an hNK-1 receptor antagonist also showcases the utility of our arylative cyclization.

The prevalence of oxygen heterocycles in bioactive compounds and natural products has led to the development of a number of cyclization reactions. A particularly attractive method to synthesize cyclic ethers is metal-catalyzed intramolecular addition of an O−H nucleophile across an unsaturated carbon−carbon bond.[1] These reactions are regarded as a part of hydrofunctionalization, in which numerous efforts have been devoted to the development of controllable, regioselective reactions by tuning a metal catalyst.[1,2] For instance, W-, Rh-, and Ru-catalyzed cyclizations of 4-alkyn-1-ols bearing a terminal alkyne provide 6-*endo* cyclic products via distinct metal-vinylidene intermediates[3] while other metals usually give kinetically favorable 5-*exo* products. However, both modes of cyclizations commonly resulted in protonation, which lacks the divergence of products.[4]

Palladium catalysts are often employed for difunctionalization of unsaturated bonds due to their remarkable ability to create new carbon−carbon or carbon−heteroatom bonds.[5] Particularly, difunctionalization that involves intramolecular cyclization should offer regio- and stereoselective approaches to complex cyclic skeletons in a single operation.[5−7] However, the regioselectivity of cyclization heavily depends on the substrate structure in most cases, which severely limits the diversity of the products available by this methodology.[6] For instance, palladium-catalyzed cyclization of alcohol **A** proceeds in an *anti*-5-*exo* mode selectively to afford tetrahydrofuran derivative **B** and avoids the formation of dihydropyran **C** in a kinetically disfavored 6-*endo* fashion (Scheme 1).[8]

Recently, our group became interested in developing new palladium-catalyzed arylative cyclization reactions of unsaturated compounds bearing a nucleophilic moiety.[9] Along this line, we disclose herein controllable, regioselective arylative cyclization reactions of alkynols, leading to the divergent formations of *exo* and *endo* cyclic products. Thus, kinetically

Scheme 1. Pd-Catalyzed *anti*-5-*exo*-Selective Cyclization



favored 5-*exo* cyclization changed to a 6-*endo* mode, not by substrate structures but largely by catalysts. Therefore, the present synthetic protocols can be regarded as catalyst-controlled oxyarylations of alkyne,[10] leading to highly functionalized tetrasubstituted alkenes in regiocontrolled manners.[11] Such controllable difunctionalizations of alkynes by a metal catalyst are still rare despite persistent interest.[12]

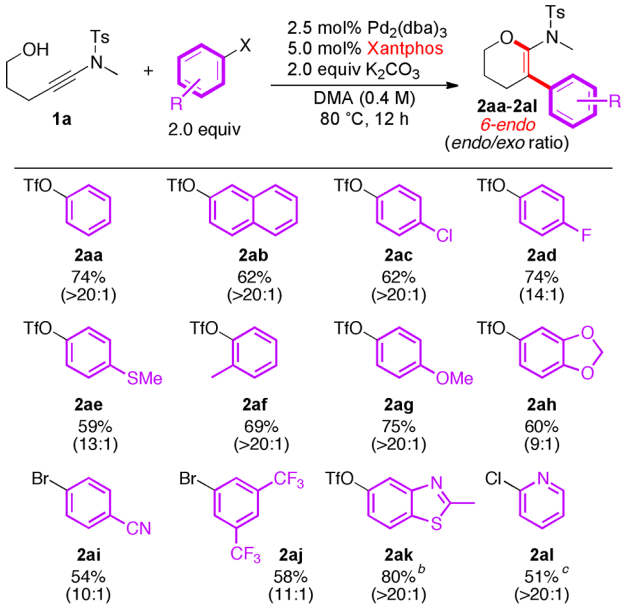
Our attempt began with alcohol **1a** bearing an ynamide moiety since ynamides display attractive reactivities and enable installation of an amino group in products.[13,14] Table S1 shows the effect of ligands on phenylative cyclizations of **1a** with phenyl triflate (see Supporting Information (SI)). Employment of PPh_3, DPPF, XPhos, and PCy_3 gave *exo* cyclic compound **3aa** as a major product with concomitant formation of *endo* cyclic compound **2aa** (Table S1, entries 1−4).[15] To our surprise, X-ray crystal structure analysis revealed that *exo* cyclic product **3aa** is a *syn* adduct, which represents the first palladium-catalyzed intramolecular *syn*-oxyarylation of alkynes.[6,16] Further ligand screening revealed oxygen-linked bidentate ligands such as DPEphos and Xantphos were exceptionally effective for conventionally unfavorable 6-*endo* cyclization (entries 5 and 6). It is in stark contrast to the fact that ynamides usually react with transition metal complexes, except for gold,[17] to place the metal center at the α-position owing to the directing effect of the amido group.[18]

The scope of aryl sources in this unusual *endo*-selective cyclization was investigated as shown in Table 1. Chloro, fluoro, and methylthio groups were compatible with the reaction (**2ac**, **2ad**, and **2ae**). The use of bulky *o*-tolyl triflate provided **2af** in good yield. Electron-rich aryl triflates also participated in the cyclization (**2ag** and **2ah**) although 1,3-benzodioxolyl triflate gave slightly lower selectivity. Electron-deficient aryl groups were introduced to 6-*endo* products **2ai** and **2aj** by using the corresponding bromides, since the use of the corresponding triflates resulted in the formation of complex mixtures.

Received: March 22, 2014
Published: April 15, 2014

dx.doi.org/10.1021/ja5029028 | J. Am. Chem. Soc. 2014, 136, 6255−6258

Table 1. Scope of Aryl Sources for *endo* Cyclization[a]

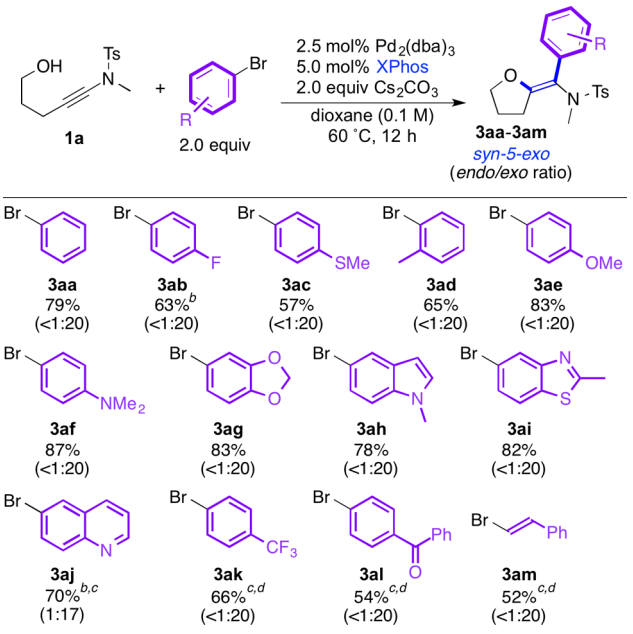


[a]*Endo/exo* ratios were determined by ^{1}H NMR. Isolated yield. [b]Reaction was carried out at 100 °C. [c]5.0 mol % of $Pd_2(dba)_3$, 10 mol % Xantphos, and 3.0 equiv of 2-chloropyridine were used.

Furthermore, heteroaryl groups could be installed into *endo* cyclic products (**2ak** and **2al**).

Next, we focused on developing a new *syn*-5-*exo* cyclization by adjusting the reactivity of palladium catalysts. After extensive screening, conditions employing XPhos as a ligand and aryl bromides as an aryl source realized expected *exo*-selective cyclization (Table 2). The scope of aryl bromides is wide, except for electron-deficient aryl bromides that lead to 6-*endo* cyclization. Further optimization of reaction conditions

Table 2. Scope of Aryl Bromides for *syn*-5-*exo* Cyclization[a]

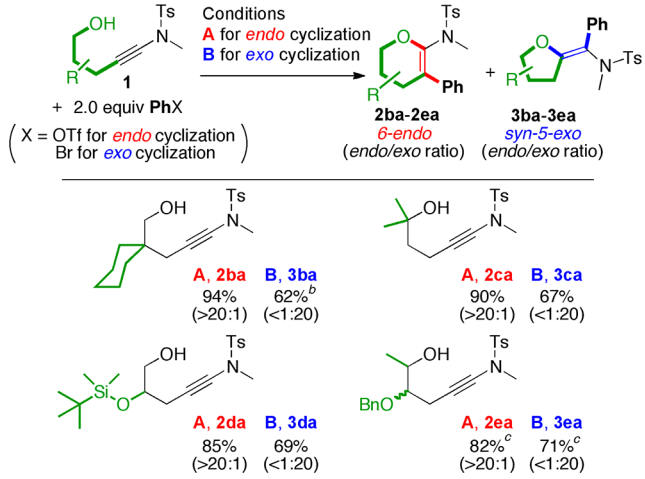


[a]*Endo/exo* ratios were determined by ^{1}H NMR. Isolated yield. [b]Reaction was carried out at 100 °C. [c]20 mol % of P(2-furyl)$_3$ was used. [d]2.0 equiv of NaOH were used.

eventually allowed us to use electron-deficient aryl bromides with the aid of $Pd_2(dba)_3$/P(2-furyl)$_3$/NaOH, avoiding concomitant formation of the *endo* cyclic products (**3ak** and **3al**). Additionally, alkenyl bromide could be used for *exo* cyclization (**3am**).

The regioselectivity of cyclization was independent of the substrate structures, which often determined the mode of cyclization (Table 3).[6] An alcohol bearing a bulky cyclohexyl

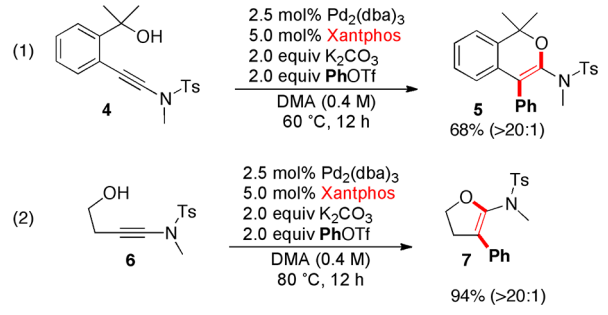
Table 3. Scope of Alkynols[a]



[a]Conditions A and B correspond to the conditions in Tables 1 and 2, respectively. *Endo/exo* ratios were determined by ^{1}H NMR. Isolated yield. [b]Reaction was carried out at 80 °C. [c]The products as well as the starting material are diastereomeric mixtures (*trans*/*cis* = 70:30).

group or a dimethyl group gave the corresponding 6-*endo* and *syn*-5-*exo* products with high regioselectivity depending on the conditions (**2ba**/**3ba** and **2ca**/**3ca**). *tert*-Butyldimethylsilyl ether was tolerated under the reaction conditions without conceivable decomposition (**2da**/**3da**). Notably, conditions A could be used for the synthesis of amino-substituted glycal[19] derivative **2ea** while conditions B afforded *exo* cyclic product **3ea**.

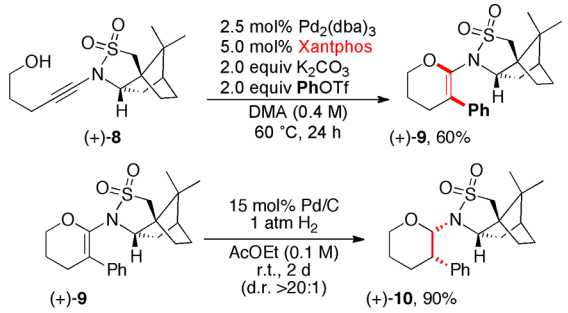
Our reaction conditions for *endo* cyclization could be extended to the synthesis of the other frameworks. Benzene-fused substrate **4** was converted to isochromene derivative **5** in good yield (eq 1). We also found 5-*endo* cyclization of **6** afforded amino-substituted dihydrofuran **7** in high yield (eq 2).



The 6-*endo* cyclization of (+)-**8** bearing a camphor sultam chiral auxiliary was successful to afford (+)-**9** (Scheme 2). Although hydrogenation of a tetrasubstituted double bond is difficult due to its steric hindrance, we were pleased to accomplish the highly diastereoselective hydrogenation of (+)-**9** with Pd/C under atmospheric hydrogen to yield

dx.doi.org/10.1021/ja5029028 | J. Am. Chem. Soc. 2014, 136, 6255−6258

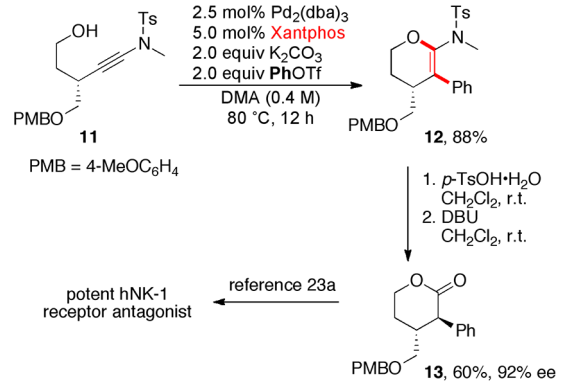
Scheme 2. Transformation of Optically Active *endo* Cyclic Products



(+)-**10**.[20,21] The present transformation offers a new route to optically active cyclic *N,O*-acetals, which are often found in a number of bioactive and naturally occurring products.[22]

The *endo*-selective arylative cyclization was also applied to the formal synthesis of a potent hNK-1 receptor antagonist (Scheme 3 and SI).[23] Readily available chiral alkynol **11** was

Scheme 3. Formal Synthesis of Potent hNK-1 Receptor Antagonist

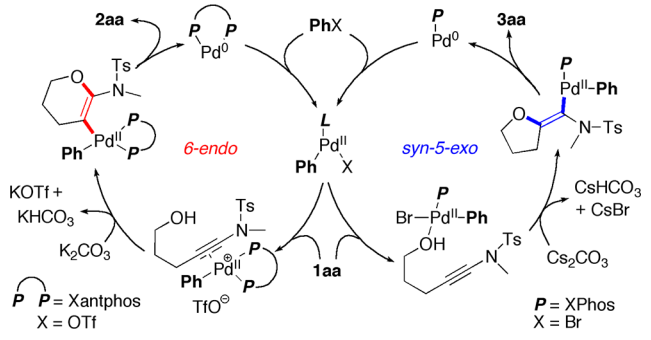


smoothly converted to *endo* cyclic product **12**, which was hydrolyzed into lactone **13**, a key synthetic intermediate of the antagonist.

We also developed some other useful transformations of the ketene *N,O*-acetal product (see SI). Thus, the *endo* cyclic products could be used for a variety of arylated oxacycles.

We performed careful NMR experiments (see SI for details) to account for the selectivity control and propose a plausible mechanism in Scheme 4. According to the implication of the NMR analysis, initially formed oxidative adduct [ArPdBr(XPhos)] would have a preferential affinity for a hydroxy group whereas the other intermediate [ArPd(Xantphos)]$^+$OTf$^-$[24] would not have such an apparent affinity but interacts with an ynamide moiety. Thus, Lewis acidic cationic [ArPd(Xantphos)]$^+$OTf$^-$ would be coordinated by the ynamide moiety, thereby efficiently activating the triple bond to develop a positive charge at the α-position ready for the *6-endo* cyclization. As for the *5-exo* cyclization, preferential coordination of the hydroxy group to [ArPdBr(XPhos)] followed by base-mediated alkoxide formation might lead to *syn*-insertion of the alkyne moiety to the oxygen−palladium bond.[25]

Scheme 4. Plausible Mechanism



In conclusion, we have disclosed the first catalyst-dependent *6-endo*/*syn*-*5-exo* regioselective arylative cyclization of alkynols. Coordination environments around the palladium centers of arylpalladium intermediates, rather than substrate structures, precisely dictate the regioselectivity. The present reactions afford a variety of five- and six-membered heterocycles from simple common substrates. The *6-endo* products are useful building blocks in organic synthesis, as specially exemplified in the preparation of a key intermediate for the synthesis of an hNK-1 receptor antagonist.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, spectroscopic data, ^{1}H/^{13}C NMR spectra, and X-ray crystallographic analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

yori@kuchem.kyoto-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid from MEXT (Nos.: 24106721 "Reaction Integration" and 25107002 "Science of Atomic Layers") and from JSPS (Nos.: 25220802 (Scientific Research (S)), 24685007 (Young Scientists (A)), 23655037 (Exploratory Research)). D.F. acknowledges a JSPS Fellowship for Young Scientists.

■ REFERENCES

(1) Selected recent reviews: (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398. (b) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683−2723. (c) Hintermann, K. C. *Top. Organomet. Chem.* **2010**, *31*, 123−155. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079−3159.

(2) Recent review of catalyst-controlled, regioselective synthesis: Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10954−10990.

(3) Reviews of *endo*-selective cyclizations via metal vinylidene intermediates: (a) Trost, B. M.; McClory, A. *Chem.—Asian J.* **2008**, *3*, 164−194. (b) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176−2203. (c) McDonald, F. E. *Chem.—Eur. J.* **1999**, *5*, 3103−3106.

(4) For a few examples of cyclizations that did not result in protonation, see: (a) Compernolle, F.; Mao, H.; Tahri, A.; Kozlecki, T.; Van der Eycken, E.; Medaer, B.; Hoornaert, G. J. *Tetrahedron Lett.* **2002**, *43*, 3011−3015. (b) Blandino, M.; McNelis, E. *Org. Lett.* **2002**, *4*, 3387−3390.

(5) Recent reviews of palladium-catalyzed difunctionalization of unsaturated bonds: (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2014**, *114*, 1783−1826. (b) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*,

9412−9423. (c) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083−4088. (d) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981−3019. (e) Sehnal, P. S.; Taylor, R. J.; Farlamb, J. S. *Chem. Rev.* **2010**, *110*, 824−889. (f) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910−1923. (g) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem.* **2004**, *2*, 2551−2554. (h) *Synthesis of Heterocycles via Metal-Catalyzed Reactions that Generate One or More Carbon-Heteroatom Bonds*; Wolfe, J. P., Ed.; Springer: 2013.

(6) Reviews of palladium-catalyzed cyclization reactions: (a) Balme, G.; Bouyssi, D.; Lomberget, T.; Monterio, N. *Synthesis* **2003**, 2115−2134. (b) Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.* **2011**, *44*, 111−122. (c) Wolfe, J. P. *Synlett* **2008**, 2913−2937. (d) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, 351−361. (e) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644−4680. (f) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101−4111. (g) Balme, G.; Bouyssi, D.; Monteiro, N. *Pure Appl. Chem.* **2006**, *78*, 231−239. (h) Ohno, H. *Asian J. Org. Chem.* **2013**, *2*, 18−28. (i) Deng, Y.; Persson, A. K.; Bäckvall, J.-E. *Chem.—Eur. J.* **2012**, *18*, 11498−11523. (j) Bouyssi, D.; Monterio, N.; Balme, G. *Beilstein J. Org. Chem.* **2011**, *7*, 1387−1406.

(7) (a) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404−406 and references cited therein. (b) Bard, A. J. *Integrated Chemical Systems*; Wiley: 1994. (c) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Ed.; Wiley: 2005.

(8) Luo, F.-T.; Schreusder, I.; Wang, R.-T. *J. Org. Chem.* **1992**, *57*, 2213−2215.

(9) (a) Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052−2053. (b) Hayashi, S.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7224−7226. (c) Fujino, D.; Hayashi, S.; Yorimitsu, H.; Oshima, K. *Chem. Commun.* **2009**, 5754−5756. (d) Fujino, D.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2011**, *133*, 9682−9685. (e) Fujino, D.; Yorimitsu, H.; Osuka, A. *Org. Lett.* **2012**, *14*, 2914−2917.

(10) Selected recent examples of oxyarylation of unsaturated bond catalyzed by other metals: (a) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474−1475. (b) Melhado, A. D.; Brenzovich, W. E.; Lackner, A. D.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8885−8887. (c) Miller, Y.; Miao, L.; Hosseini, A. S.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 12149−12156. (d) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332−5335. (e) Fumagalli, G.; Boyd, S.; Greaney, M. F. *Org. Lett.* **2013**, *15*, 4398−4401. (f) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 9548−9551. (g) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *Chem. Lett.* **2011**, *40*, 322−323.

(11) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698−4745.

(12) (a) Ohmura, T.; Oshima, K.; Taniguchi, H.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 12194−12196. (b) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923−8930. (c) Hilt, G.; Janikowski, J.; Hess, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 5204−5206. (d) Kezuka, S.; Tanaka, S.; Ohe, T.; Nakaya, Y.; Takeuchi, R. *J. Org. Chem.* **2009**, *131*, 2052−2053.

(13) Recent reviews of ynamides: (a) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840−2859. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064−5106.

(14) ω-Hydroxy ynamides were synthesized in four steps in overall yields ranging from 56 to 79%. See SI for details.

(15) The structures of *endo* and *exo* cyclic products were unambiguously determined by X-ray diffraction analysis of **2aa** and **3af**. See SI for details.

(16) Palladium-catalyzed intermolecular *syn*-oxyarylation to form benzofurans and isochromenes was reported: Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270−3271.

(17) Selected examples of the reactions of ynamides with a gold catalyst: (a) Davies, P. W.; Cremonesi, A.; Dumitrescu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8931−8935. (b) Dateer, R. B.; Shaibu, B. S.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2012**, *51*, 113−117. (c) Kramer, S.; Odabachian, Y.; Overgaard, J.; Rottländer, M.; Gagosz, F.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 5090−5094.

(18) Selected recent examples: (a) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820−1821. (b) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802−3803. (c) Saito, N.; Katayama, T.; Sato, Y. *Adv. Synth. Catal.* **2013**, *355*, 853−856. (d) Saito, N.; Saito, K.; Sato, H.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829−3832. (e) Minko, Y.; Pasco, M.; Lercher, L.; Botoshansky, M.; Marek, I. *Nature* **2012**, *490*, 522−526.

(19) McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* **1998**, *120*, 4246−4247.

(20) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3069.

(21) The absolute stereochemistry of (+)-**10** was determined by X-ray crystallographic analysis. For details, see SI.

(22) (a) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216−12217. (b) Zheng, J.; Urkalan, K. B.; Herzon, S. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 6068−6071 and references therein.

(23) (a) Nelson, T. D.; Rosen, J. D.; Smitrovich, J. H.; Payack, J.; Craig, B.; Matty, L.; Huffman, M. A.; McNamara, J. *Org. Lett.* **2005**, *7*, 55−58. (b) Sugawara, K.; Hashiyama, T. *Tetrahedron Lett.* **2007**, *48*, 3723−3726. (c) Raubo, P.; Giuliano, C.; Hill, A. W.; Huscroft, I. T.; London, C.; Reeve, A.; Seward, E. M.; Swain, C. G.; Kulagowski, J. J. *Synlett* **2006**, *4*, 600−604. (d) Huffman, M. A.; Smitrovich, J. H.; Rosen, J. D.; Boice, G. N.; Qu, C.; Nelson, T. D.; McNakamura, J. M. *J. Org. Chem.* **2005**, *70*, 4409−4413.

(24) The formation of the cationic complex is strongly suggested by X-ray crystallographic analysis. See SI for details. Also see: Zuideveld, M. A.; Swennenhuis, B. H. G.; Boele, M. D. K.; Guari, Y.; van Strijdonck, G. P. F.; Reek, J. N. H.; Kamer, P. C. J.; Goubitz, K.; Fraanje, J.; Lutz, M.; Spek, A. L.; van Leeuwen, P. W. N. M. *Dalton Trans.* **2002**, 2308−2317.

(25) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893−2901.