Organic LETTERS

Letter

pubs.acs.org/OrgLett

Dual Gold Catalysis: A Novel Synthesis of Bicyclic and Tricyclic Pyrroles from *N*-Propargyl Ynamides

Yusuke Tokimizu,[†] Marcel Wieteck,[‡] Matthias Rudolph,[‡] Shinya Oishi,[†] Nobutaka Fujii,[†] A. Stephen K. Hashmi,*[,‡,§] and Hiroaki Ohno*[,†]

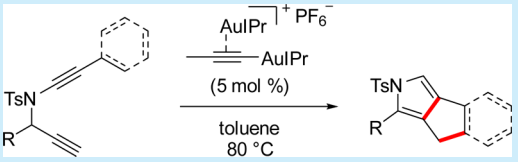
[†]Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

[‡]Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany

[§]Chemistry Department, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia

Supporting Information

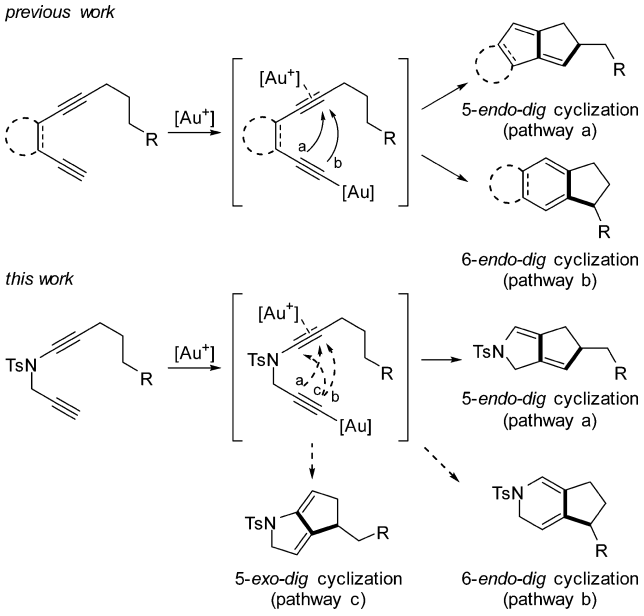
ABSTRACT: Various *N*-propargyl ynamides were converted to bicylic and tricyclic pyrroles by the use of a cationic dual-activation gold catalyst. This reaction starts with the nucleophilic addition of a gold acetylide onto an ynamide triple bond at the *β*-position of the nitrogen atom. Thus, gold vinylidene is formed, and then a second cyclization takes place. The formation of the gold vinylidene is indicated by the evidence that not only aryl ynamides but also alkyl ynamides undergo C−H activation in these reactions.



Ynamides have attracted growing attention as useful building blocks for the formation of nitrogen-containing compounds.[1] Recent progress of alkynylation chemistry has been facilitating the development of synthesis and valuable transformations of ynamides under mild conditions.[2] Since ynamides are more electrophilic than simple alkynes, nucleophilic additions occur in a regioselective manner at the *α*-position to the nitrogen atom in most cases. This regioselectivity arises from the lone pair of the nitrogen atom directly bound to the alkyne, which polarizes the ynamide triple bond.

Homogenous gold catalysts are well-known as a useful tool for the activation of alkynes[3] including ynamides,[4] which facilitates addition of various types of nucleophiles onto alkynes. Recently, the groups of Hashmi and Zhang independently reported the novel and fascinating gold-catalyzed cascade cyclization of diynes involving a C−H activation step (Scheme 1).[5] In these reactions, a cationic gold catalyst activates two alkynes; the terminal by *σ*-coordination and the internal by *π*-coordination, thus promoting the nucleophilic attack of gold acetylide onto the internal alkyne. The nucleophilic position of gold acetylide depends on the tether of two alkynes. While 5-*endo-dig* cyclization takes place with phenylene-,[5a,c,d] 3,4-thiophenylene-,[5k] or ethylene-tethered[5l] diynes (pathway a), 6-*endo-dig* cyclization takes place with vinylene-[5h] or 2,3-thiophenylene-tethered[5f] diynes (pathway b). Although the computational studies[5j,k] suggested that the electronic effect of the tether is important for the selectivity, additional experimental studies are needed to clarify the whole picture of diyne reactions. Our attention was next focused on the reactivity of *N*-propargyl ynamides. In this case, 5-*exo-dig* cyclization (pathway c) would be another possible reaction course, considering the general regioselectivity in the ynamide reactions, in addition to the 5-*endo-dig* and 6-*endo-dig* pathways (a and b). Herein we report the selective synthesis of bicyclic and tricyclic pyrroles based on gold(I)-catalyzed ynamide cyclization via pathway a.

Scheme 1. Reactivity of Gold Acetylide onto the Other Alkyne



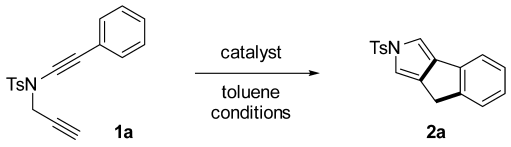
At the outset of this work, we examined the reaction of *N*-propargyl ynamide **1a** with 5 mol % of a gold catalyst. The use of DAC-NTf_2 (DAC = dual activation catalyst), which gave good results in the previous study,[5f] allowed the formation of tricyclic pyrrole **2a** in 62% yield (Table 1, entry 1). Though

Received: December 16, 2014

 © XXXX American Chemical Society

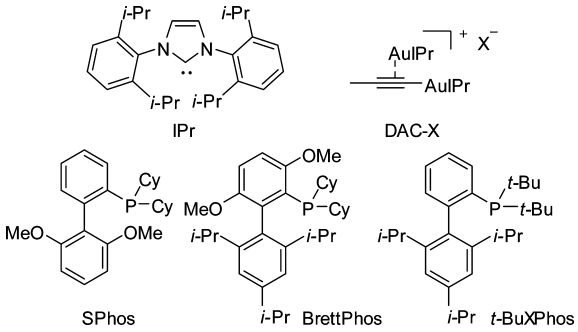
DOI: 10.1021/ol503623m
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Conditions



entry	catalyst (mol %)	conditions	yield[a] (%)
1	DAC-NTf$_2$ (5)	80 °C, 1 h	62
2	IPrAuNTf$_2$ (5)	80 °C, 8 h	<66[b]
3	PPh$_3$AuNTf$_2$ (5)	80 °C, 15 h	10
4	SPhosAuNTf$_2$ (5)	80 °C, 7 h	35
5	BrettPhosAuNTf$_2$ (5)	80 °C, 2 h	46
6	*t*-BuXphosAuNTf$_2$ (5)	80 °C, 4 h	42
7	**DAC-PF$_6$ (5)**	**80 °C, 1 h**	**86**
8	DAC-PF$_6$ (2.5)	80 °C, 1 h	74
9	none	110 °C, 1 h	dec

[a]Isolated yield. [b]Produced as an inseparable mixture.



IPrAuNTf$_2$ showed a similar reactivity, the desired pyrrole **2a** was obtained as an inseparable mixture (entry 2). Several phosphine ligands were also tested for the reaction (entries 3−6). While use of PPh$_3$ significantly decreased the reaction rate and yield (entry 3), other phosphine ligands such as SPhos, BrettPhos, and *t*-BuXPhos gave the pyrrole **2a** in slightly better yields (35−46%, entries 4−6). Fortunately, employment of DAC-PF$_6$ improved the yield to 86% (entry 7). When the loading of DAC-PF$_6$ was decreased to 2.5 mol %, 74% yield of **2a** was produced (entry 8). Without using any catalysts, only the decomposition of starting material **1a** was observed upon heating at 110 °C (entry 9).

Having established efficient conditions for the synthesis of pyrrole **2a** (Table 1, entry 7), we evaluated the substrate scope (Figure 1). Both electron-withdrawing and -donating functional groups were tolerated in the *para* position of the phenyl group, including the synthetically useful halogen substituents (**2b−f**; 72−77% yields). 3,5-Dimethyphenyl-substituted *N*-propargyl ynamide **1g** showed the most efficient conversion to give pyrrole **2g** in 87% yield. A thiophene-based substrate could also be used, providing the corresponding pyrrole **2h** containing a 5,5,5-fused ring system (68%). Replacement of the tosyl (Ts) by a 2-nosyl (*o*-Ns) group was also successful (**2i**; 81%). Branched propargyl ynamides (R^1 = alkyl) provided the corresponding pyrroles **2j−l** in moderate yields (64−65%).

A plausible[6] mechanism for the reaction is shown in Scheme 2. As is the case with the reported reactions,[5c,l] *N*-propargyl ynamide **1** is converted to dual σ/π-activated alkyne intermediate **I** by the action of DAC-PF$_6$. The cationic gold is transferred to the ynamide alkyne (intermediate **II**), which facilitates the nucleophilic addition of the gold acetylide, leading to formation of gold vinylidene **III**. The subsequent

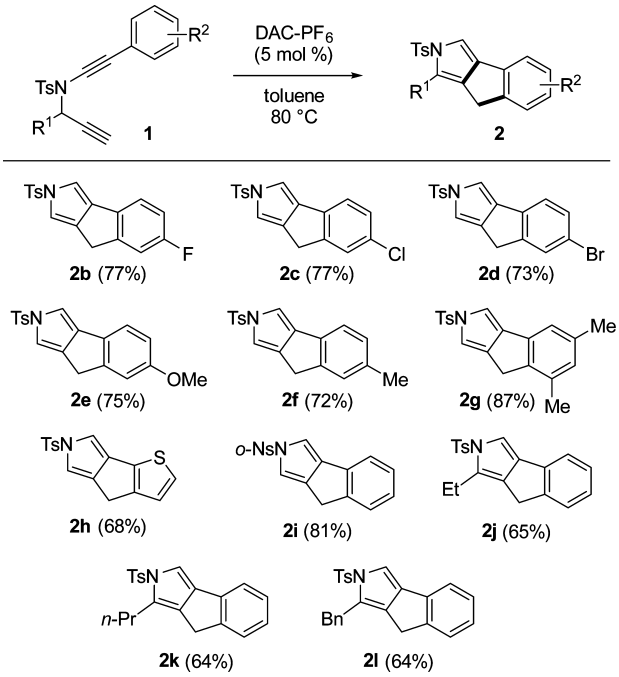
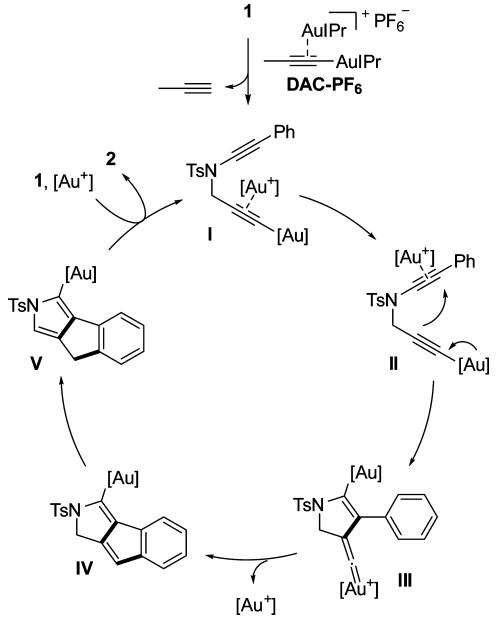


Figure 1. Gold-catalyzed cyclization of aryl-substituted *N*-propargyl ynamides. [a]Isolated yield.

Scheme 2. Plausible Reaction Mechanism

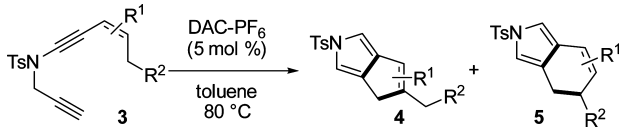


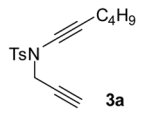
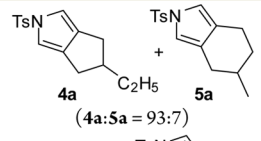
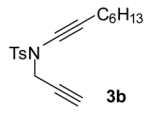
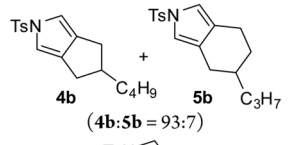
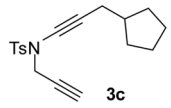
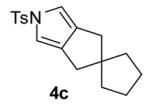
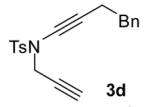
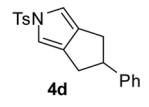
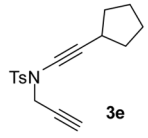
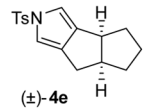
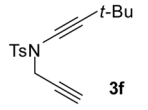
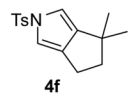
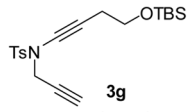
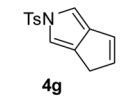
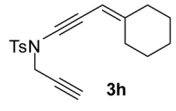
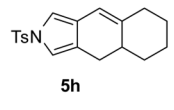
arylation of the gold vinylidene forms vinylgold complex **IV** via nucleophilic addition or C−H insertion pathway. After the aromatization of intermediate **IV** (which might also occur after the protodeauration of **IV**), the catalytic cycle can be terminated by a catalyst transfer from intermediate **V** to *N*-propargyl ynamide **1** to produce pyrrole **2**. It is worth mentioning that the electrophilic carbon of ynamide triple bond in this reaction is not the α- but the β-position to the nitrogen atom, contrary to the general preference in many gold-catalyzed reactions of ynamides.[7]

To confirm the formation of gold vinylidene **III** (Scheme 2), we then investigated C(sp^3)−H activation reactions using alkyl-substituted *N*-propargyl ynamides **3** (Table 2). In the case of

DOI: 10.1021/ol503623m
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Gold-Catalyzed Cyclization of Alkyl-Substituted *N*-Propargyl Ynamides



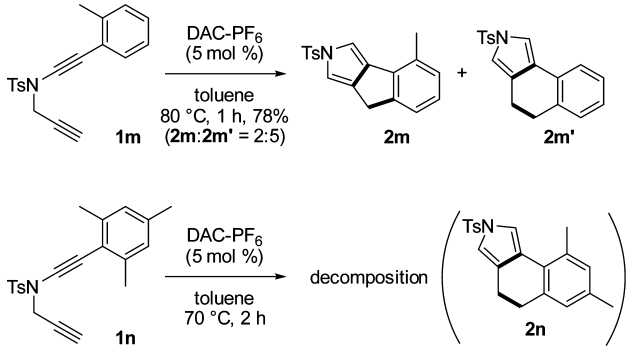
entry	substrate	product (ratio[a])	yield (%)[b]
1		 (**4a**:**5a** = 93:7)	52
2		 (**4b**:**5b** = 93:7)	51
3			50[c]
4			36
5			44
6			60
7			49
8			57

[a]The ratio of **4**:**5** was determined by NMR analysis. [b]Isolated yield. [c]NMR yield.

N-propargyl ynamides **3a** and **3b**, both 5-membered (**4**) and 6-membered ring compounds (**5**) were formed (52 and 51% combined yields, entries 1 and 2), the former of which was the major isomer (**4**/**5** = 93:7). It is notable that a tertiary C−H bond in a cycloalkyl substituent was more reactive than a secondary C−H bond; predominantly, the spirocyclic compound **4c** with a quaternary carbon atom was produced (entry 3).[8] Selective formation of cyclopenta[*c*]pyrrole derivative **4d** from substrate **3d** bearing a benzyl group showed higher reactivity of the benzylic C(sp^3)−H bond than that of the C(sp^2)−H bond of the phenyl group. With *N*-propargyl ynamides **3e**−**g** not having an appropriate C−H bond for the 6-membered ring formation, only the cyclopentane-fused pyrroles **4e**−**g** were obtained (44−60%, entries 5−7) as we expected. The pyrrole **4g** was produced from *N*-propargyl ynamide **3g** via the elimination of OTBS group (entry 7). In the case using **3h**, bearing a conjugated enynamide moiety, the pyrrole **5h** containing a 6-membered ring was obtained (57%, entry 8) via the reaction with a C(sp^3)−H bond at the allylic position.

At the end, we checked the reaction of aryl *N*-propargyl ynamides bearing a methyl group at the *ortho* position of the phenyl group (Scheme 3). In this case, both aryl C−H and benzyl C−H bonds are potentially reactive. The reaction of *N*-propargyl ynamide **1m** generated a mixture of **2m** and **2m**′ with a moderate regioselectivity (2:5; 78% combined yield). On the other hand, the reaction of *N*-propargyl ynamide **1n** with two *ortho* methyl groups led to decomposition without formation of detectable amount of **2n**, presumably due to the steric hindrance of the ynamide moiety.[9]

Scheme 3. Reaction of 2-Methylphenyl-Substituted *N*-Propargyl Ynamides



In conclusion, we have developed a novel cyclization reaction of *N*-propargyl ynamides for the synthesis of multisubstituted pyrroles. The first cyclization step selectively proceeded via 5-*endo-dig* cyclization on the *β*-carbon of the ynamide, contrary to the general preference for the *α*-carbon in many gold-catalyzed reactions of ynamides. Both aryl and alkyl C−H bonds can be used for the second cyclization step, and corresponding pyrroles are obtained in moderate to good yields.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hashmi@hashmi.de.
*E-mail: hohno@pharm.kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for the Encouragement of Young Scientists (A), and Platform for Drug Design, Discovery, and Development from the MEXT, Japan. Y.T. is grateful for the Strategic Young Researcher Overseas Visits Program for Accelerating Brain Circulation as well as Research Fellowships for Young Scientists from the Japan Society for the Promotion of Science (JSPS).

■ REFERENCES

(1) For reviews on ynamides, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.*

DOI: 10.1021/ol503623m
Org. Lett. XXXX, XXX, XXX−XXX

2010, *49*, 2840. (c) Wang, X.; Yeom, H.; Fang, L.; He, S.; Ma, Z.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560.

(2) For selected publications for the synthesis of ynamides, see: (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368. (b) Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 783. (c) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170. (d) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (e) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381.

(3) For selected reviews, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (e) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (f) Widenhoefer, R. A. *Chem.—Eur. J.* **2008**, *14*, 5382. (g) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (h) Bandini, M. *Chem. Soc. Rev.* **2011**, *40*, 1358. (i) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. (j) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994.

(4) For ynamide reactions with a gold catalyst reported by our groups, see: (a) Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, R.; Oeser, T. *Chem.—Eur. J.* **2008**, *14*, 6672. (b) Rettenmeier, E.; Schuster, A. M.; Rudolph, M.; Rominger, F.; Gade, C. A.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 5880. (c) Jaimes, M. C. B.; Weingand, V.; Rominger, F.; Hashmi, A. S. K. *Chem.—Eur. J.* **2013**, *19*, 12504. (d) Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2014**, *16*, 3138.

(5) (a) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31. (b) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644. (c) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Nösel, P.; Jongboed, L.; Rudolph, M.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 555. (d) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4456. (e) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10633. (f) Hansmann, M. M.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2593. (g) Vachhani, D. D.; Galli, M.; Jacobs, J.; Van Meervelt, L.; Van der Eycken, E. V. *Chem. Commun.* **2013**, *49*, 7171. (h) Wang, Y.; Yepremyan, A.; Ghorai, S.; Todd, R.; Aue, D. H.; Zhang, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 7795. (i) Graf, K.; Hindenberg, P. D.; Tokimizu, Y.; Naoe, S.; Rudolph, M.; Rominger, F.; Ohno, H.; Hashmi, A. S. K. *ChemCatChem.* **2014**, *6*, 199. (j) Vihelmsen, M. H.; Hashmi, A. S. K. *Chem.—Eur. J.* **2014**, *20*, 1901. (k) Hansmann, M. M.; Tsupova, S.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Chem.—Eur. J.* **2014**, *20*, 2215. (l) Wieteck, M.; Tokimizu, Y.; Rudolph, M.; Rominger, F.; Ohno, H.; Fujii, N.; Hashmi, A. S. K. *Chem.—Eur. J.* **2014**, *20*, 16331. (m) Bucher, J.; Stößer, T.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2014**, DOI: 10.1002/anie.201409859.

(6) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232.

(7) See ref 1a,b for the general electrophilicity of ynamides.

(8) In this case, **4c** was obtained as an inseparable mixture including some unidentified compounds. The NMR yield of **4c** was evaluated using 1,1,2,2-tetrachloroethane as an internal standard.

(9) The same trend was observed with the reaction of 3,4-thiophenylene-tethered diynes. See ref 5f for more information.

DOI: 10.1021/ol503623m
Org. Lett. XXXX, XXX, XXX−XXX