Organic LETTERS

Letter

pubs.acs.org/OrgLett

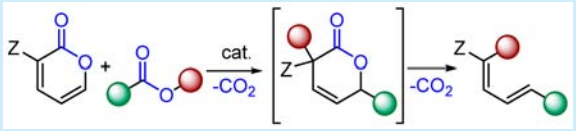
Palladium-Catalyzed Double-Decarboxylative Addition to Pyrones: Synthesis of Conjugated Dienoic Esters

Tapan Maji and Jon A. Tunge*

Department of Chemistry, The University of Kansas, 2010 Malott Hall, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, United States

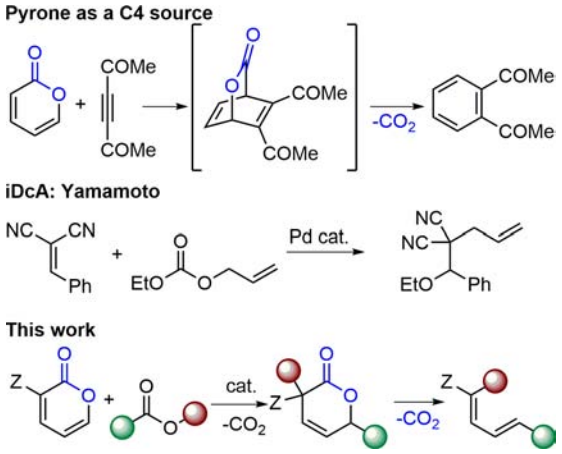
Supporting Information

ABSTRACT: An interceptive decarboxylative allylation protocol has been developed utilizing pyrone as a C4 synthon. This palladium-catalyzed transformation difunctionalizes the pyrone moiety by *in situ* generation and activation of both the electrophile and nucleophile via a double decarboxylation pathway. Ultimately, allyl carbonates react smoothly with 2-carboxypyrone under mild reaction conditions to generate synthetically useful acyclic dienoic esters, forming carbon dioxide as the sole byproduct.



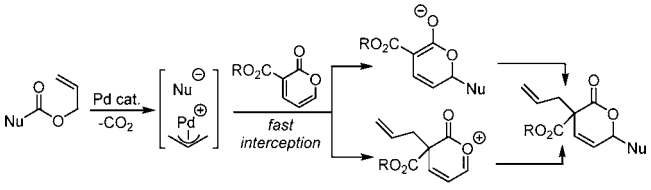
Pyrones are well-known as C4 synthons, particularly in Diels–Alder reactions, where cycloaddition is followed by decarboxylation.[1] However, the use of pyrones as a C4 equivalent outside the realm of cycloadditions is much more rare.[2] Nonetheless, 3,6-addition of any nucleophile/electrophile pair to pyrones could, in principle, give rise to useful acyclic dienes after decarboxylation (Scheme 1). Herein, we report that pyrones engage in a unique palladium-catalyzed double-decarboxylative addition of allyl carbonates to form conjugated acyclic dienes.

Scheme 1. Decarboxylative Diene Synthesis Concept



Previously, we and others have demonstrated that good Michael acceptors can be utilized in interceptive decarboxylative allylation (iDcA, Scheme 1) reactions.[3] These reactions are typically limited to the use of extremely electrophilic olefins, and benzylidene malonic esters rarely undergo addition. Thus, the combination of decarboxylative addition to pyrones with iDcA reactions required careful consideration. To begin, we chose to focus on reactions of 2-carboxypyrones due to their high electrophilicity.[4] Second, the nucleophile that is generated by decarboxylation of the allyl ester should not react (or react very slowly) with the π-allylpalladium electrophile to allow "interception" by the pyrone (Scheme 2). Since palladium-π-allyl complexes are soft electrophiles, we anticipated that hard anions which react slowly with palladium allyl complexes would be the best nucleophiles to investigate.[5] Thus, allylic carbonates, which generate alkoxides via decarboxylation, were seen as ideal reagents for initial investigation.[3c]

Scheme 2. Interceptive Decarboxylative Allylation of Pyrone

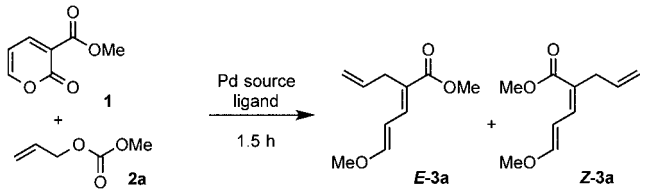


The reaction of methyl 2-pyrone-3-carboxylate **1** with allyl methyl carbonate (**2a**) was explored to screen the reaction conditions using Pd(0) as a catalyst (Table 1). When pyrone **1** was treated with allyl carbonate **2a** in the presence of $Pd(PPh_3)_4$ (5 mol %) in dichloromethane at 80 °C, allylated dienoic ester **3a** was generated as a 6.6:1 mixture of geometric isomers. Separation and isolation of both isomers followed by spectroscopic analysis[6] revealed that ***E*-3a** was generated as the major product in 51% yield (Table 1, entry 1). Altering the reaction time did not lead to further improvement in the isolated yield of the diene product (Table 1, entry 2); however, lowering the temperature to 50 °C provided an improved yield of product ***E*-3a** (60%, entry 3). Unfortunately, further lowering of the reaction temperature diminished the yield (Table 1, entry 4) and did not improve the ratio of geometric isomers.

Received: August 8, 2015
Published: September 16, 2015

DOI: 10.1021/acs.orglett.5b02308
Org. Lett. 2015, 17, 4766–4769

Table 1. Optimization of Reaction Conditions



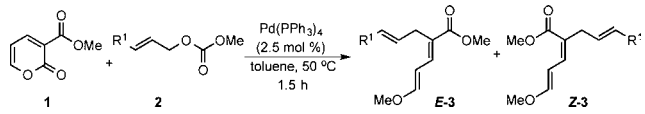
entry	Pd source	ligand	solvent	temp (°C)	yield (%)[a] *E*-3a
1	$Pd(PPh_3)_4$ 5 mol %	none	CH_2Cl_2	80	51
2	$Pd(PPh_3)_4$ 5 mol %	none	CH_2Cl_2	80	52[b]
3	$Pd(PPh_3)_4$ 5 mol %	none	CH_2Cl_2	50	60
4	$Pd(PPh_3)_4$ 5 mol %	none	CH_2Cl_2	40	49
5	$Pd(PPh_3)_4$ 5 mol %	none	1,4-dioxane	50	63
6	$Pd(PPh_3)_4$ 5 mol %	none	toluene	50	69
7	**$Pd(PPh_3)_4$ 2.5 mol %**	**none**	**toluene**	**50**	**68** (4)[c]
8	$Pd_2(dba)_3$ 3 mol %	xantphos 6 mol %	toluene	50	14
9	$Pd_2(dba)_3$ 3 mol %	*rac.* BINAP 6 mol %	toluene	50	6
10	CpPdallyl 3 mol %	dppf 6 mol %	toluene	50	19 (22)[c]

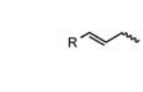
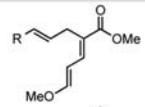
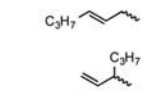
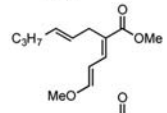
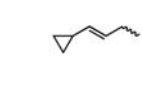
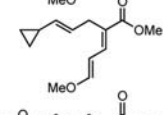
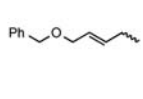
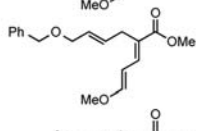
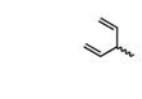
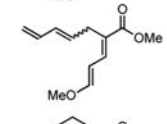
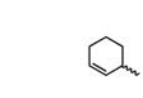
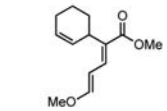
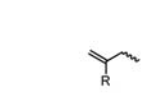
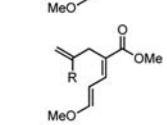
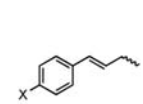
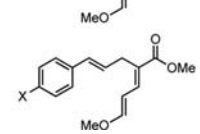
[a]Isolated yield of ***E*-3a** after purification by column chromatography on SiO_2. [b]Isolated yield of ***E*-3a** after 4 h. [c]Numbers in parentheses are the isolated yield of ***Z*-3a**.

For continued reaction optimization, different solvents were also evaluated. Doing so revealed that toluene was the best solvent for this transformation (cf. entries 5 and 6) and allowed lowering the catalyst loading to 2.5 mol % without sacrificing yield (entry 7). Lastly, other catalyst and ligand combinations were briefly examined (entries 8–10); however, none were as efficient as $Pd(PPh_3)_4$. Nonetheless, it is notable that the combination of CpPd(allyl) and diphenylphosphinoferrocene (dppf) generated the ***Z*-3a** as the major diastereomer (entry 10), indicating some catalyst control of the olefin stereochemistry.

Having found an effective protocol for the double decarboxylative allylation of pyrone **1**, the scope of the reaction was explored using different allyl carbonates under the optimized conditions (1 equiv of **1**, 1.2 equiv of **2**, 2.5 mol % of $Pd(PPh_3)_4$, toluene at 50 °C for 1.5 h). Under these conditions, regardless of the substitution pattern, allyl methyl carbonates **2** couple with pyrone **1** to provide the conjugated 1,3 dienoic ester derivatives ***E*-3a–l** in moderate to good isolated yields (Table 2). Analysis of the crude reaction mixtures showed uniform *E*-selectivity, but the *E*/*Z* ratio varied from moderate (3.8:1, entry 5) to good (9.1:1, entry 4). Fortunately, the geometric isomers were separable via column chromatography. For example, the commercially available carbonate **2a** provided 68% isolated yield of ***E*-3a** (Table 2, entry 1) along with a 4% isolated yield of isomeric ***Z*-3a**. Both aliphatic (**2a–h**) and aromatic (**2i–l**) allyl carbonates undergo the coupling, with cinnamyl carbonates (**2j–l**), giving higher yields of *E*-dienoate products. The intermediacy of palldium-π-allyl intermediates is supported by the fact that isomeric primary and secondary allyl carbonates react to provide the

Table 2. Palladium(0)-Catalyzed Allylation



entry	allylic carbonate	product	*E*-3:*Z*-3[a]	yield (%)[b] *E*-3
1			***E*-3a**, R = H	6.6:1	68[c]
2			***E*-3b**, R = Me	6.3:1	44
3			***E*-3c**	8.3:1	60
4				9.1:1	55
5			***E*-3d**	3.8:1	46
6			***E*-3e**	4.0:1	61
7			***E*-3f**	6.3:1	61[d]
8			***E*-3g**	ND	14
9			***E*-3h**, R = Me	7.7:1	44
10			***E*-3i**, R = Ph	7.7:1	52
11			***E*-3j**, X = H	6.3:1	74
12			***E*-3k**, X = OMe	4.2:1	68
13			***E*-3l**, X = NO_2	6.8:1	82

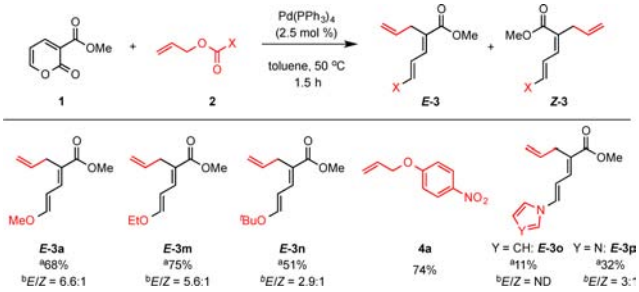
[a]*E*/*Z* ratio detremined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b]Isolated yield of ***E*-3** after purification. [c]Isolated yield of ***Z*-3a** was 4%. [d]Inseparable 1:1 mixture.

same linear allylation product (***E*-3c**) in comparable yield (entries 3 and 4, Table 2). Similarly, a pentadienyl carbonate gives the linear diene **3f** as an inseparable mixture of cis/trans isomers about the terminal diene (entry 7). Notably, 3-cyclopropyl allyl carbonate was also a suitable coupling partner for this method (entry 5), while a cyclic secondary allyl carbonate provided the allylated product ***E*-3g** in poor yield.

We next investigated the scope of nucleophiles that participate in the reaction by use of various allylic carbonates and carbamates (Scheme 3). While methoxide, ethoxide, and *tert*-butoxide were all effective nucleophiles for the transformation, the *E*/*Z* selectivity decreased with the bulkier *tert*-butoxide nucleophile (***E*-3a**, ***E*-3m**, and ***E*-3n**, Scheme 3). It is noteworthy that transesterification does not occur, and the methyl ester of the pyrone remains intact when ethoxide or *tert*-butoxide nucleophiles are utilized. Expectedly, attempts to couple a much softer phenoxide nucleophile[7] failed to provide the product of interceptive coupling. Instead, typical decarboxylative coupling took place to form the *O*-allylated product **4a** (Scheme 3).[3b,8] After demonstrating the feasibility of utilizing allylic carbonates, the more difficult task of allylation employing allylic carbamates was addressed.[9] An allylic carbamate derived

DOI: 10.1021/acs.orglett.5b02308
Org. Lett. 2015, 17, 4766–4769

Scheme 3. Scope of Nucleophiles

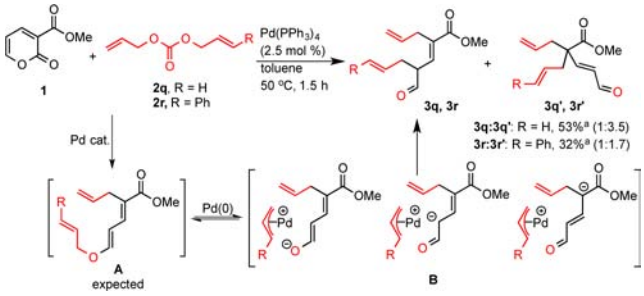


[a]Isolated yield of *E*-**3** after column chromatography. [b]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

from pyrrole indeed reacted with **1** under our standard reaction conditions to deliver the corresponding allylated product *E*-**3o**, albeit in low yield (Scheme 3). Although the yield of *E*-**3o** was not significant, the demonstrated reactivity of the allyl carbamate prompted us to test a related imidazole-derived allylic carbamate. This substrate formed the desired product in better yield; however, the yield was still low (*E*-**3p**).

We envisioned a further extension of the scope of this new protocol by utilizing diallyl carbonates, which should generate the *O*-allyl product **A** (Scheme 4). Interestingly, the reaction of

Scheme 4. Allylation with Diallylic Carbonate

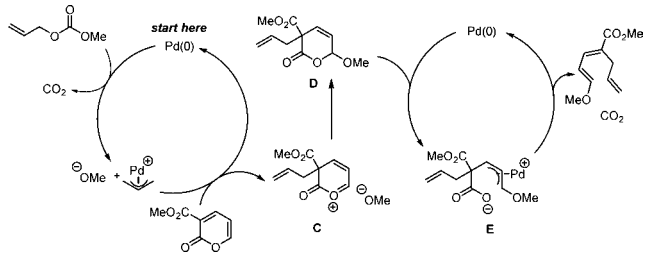


[a]Combined yield

1 and **2q** did not provide the expected product **A**, but instead formed a 1:3.5 mixture of *C*-allylated aldehydes **3q** and **3q′**. The observation of these products suggests that **A** underwent rearrangement. The observed products could have arisen via Claisen (**3q**) and Claisen/Cope (**3q′**) rearrangement sequences, or alternatively, both products could arise from a palladium-catalyzed rearrangement that proceeds through intermediate **B** (Scheme 4).[10] To distinguish between these mechanisms, a substituted diallyl carbonate **2r** was allowed to react under identical conditions. In this case products **3r**/**3r′** were formed. The linear allyl regiochemistry of **3r′** cannot arise from a concerted Claisen rearrangement of **A**; however, this regiochemistry is consistent with a palladium-catalyzed rearrangement mechanism where attack on the palldium-π-allyl complex preferentially occurs at the less substituted carbon (Scheme 4).[7a]

Although a detailed mechanistic picture of the double-decarboxylative addition to 2-carboxypyrone requires further studies, the above-mentioned experimental results and literature reports[3c,11] suggest a logical catalytic pathway for the formation of dienoates **3** (Scheme 5). It is likely that the allylic carbonate undergoes oxidative addition to Pd(0) to generate a π-allyl-Pd complex and, after decarboxylation, an

Scheme 5. Possible Mechanism



alkoxide nucleophile.[12] While it may be possible for the alkoxide to react with the pyrone (Scheme 2), we favor a mechanism involving prior allylation of the pyrone to generate intermediate **C** on the basis of observations made by Yamamoto (Scheme 5).[3c] Nucleophilic trapping of intermediate **C** would afford intermediate **D**. The observed diene then can be readily formed by oxidative addition of intermediate **D** to palladium to form **E**. Subsequent decarboxylative elimination would provide the diene and regenerate the palladium catalyst.[3b,13] Alternatively, one could envision a direct retro-cycloaddition of CO_2 from intermediate **D**; however, related decarboxylations require substantially higher temperatures than those employed in our reaction.[1c−f,14] Thus, we favor a metal-catalyzed decarboxylation process.

In conclusion, we have developed a double decarboxylative coupling of allylic carbonates and 2-carboxypyrone. This is a rare example of the use of a pyrone as an acyclic diene source. The protocol constitutes a practical, user-friendly, and operationally simple strategy for the synthesis of a variety of donor−acceptor conjugated dienes in a short reaction time. The process is highlighted by its double decarboxylation pathway which leads to the formation of dieneoate products with carbon dioxide as the only byproduct. Dienoic esters obtained by this method can serve as effective substrates for 1,6-conjugate addition reactions.[15]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02308.

Experimental procedures and characterization data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tunge@ku.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for this research was provided by the National Science Foundation (CHE-1465172) and the Kansas Bioscience Authority Rising Star Program.

■ REFERENCES

(1) (a) Zhao, P.; Beaudry, C. M. *Org. Lett.* **2013**, *15*, 402−405. (b) Woodard, B. T.; Posner, G. H. *Adv. Cycloaddit.* **1999**, *5*, 47−83. (c) Goldstein, M. J.; Thayer, G. L. *J. Am. Chem. Soc.* **1965**, *87*, 1925−1933. (d) Corey, E. J.; Watt, D. S. *J. Am. Chem. Soc.* **1973**, *95*, 2303−

DOI: 10.1021/acs.orglett.5b02308
Org. Lett. 2015, 17, 4766−4769

2311. (e) Zhao, P.; Beaudry, C. M. *Angew. Chem.* **2014**, *126*, 10668−10671. (f) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111−9171.
(2) (a) Chergui, D.; Hamdi, M.; Babouléne, M.; Spéziale, V.; Lattes, A. *J. Heterocycl. Chem.* **1986**, *23*, 1721−1724. (b) Padwa, A.; Hartman, R. *Tetrahedron Lett.* **1966**, *7*, 2277−2281. (c) Molodtsov, V.; Fleming, P. R.; Eyermann, C. J.; Ferguson, A. D.; Foulk, M. A.; McKinney, D. C.; Masse, C. E.; Buurman, E. T.; Murakami, K. S. *J. Med. Chem.* **2015**, *58*, 3156−3171. (d) Demuner, A. J.; Valente, V. M. M.; Barbosa, L. C. A.; Rathi, A. H.; Donohoe, T. J.; Thompson, A. L. *Molecules* **2009**, *14*, 4973−4986. (e) Posner, G. H.; Harrison, W.; Wettlaufer, D. G. *J. Org. Chem.* **1985**, *50*, 5041−5044. (f) Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lu, F.-J.; Schmidt, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 4285−4299.
(3) (a) Ariyarathna, Y.; Tunge, J. A. *Chem. Commun.* **2014**, *50*, 14049−14052. (b) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846−1913. (c) Patil, N. T.; Yamamoto, Y. *Synlett* **2007**, *2007*, 1994−2005. (d) Wang, C.; Tunge, J. A. *Org. Lett.* **2005**, *7*, 2137−2139. (e) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, *2005*, 1715−1726. (f) Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2010**, *2*, 192−196. (g) Nakamura, H.; Sekido, M.; Ito, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6838−6839.
(4) Trost, B. M.; Schneider, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 213−215.
(5) (a) Keinan, E.; Roth, Z. *J. Org. Chem.* **1983**, *48*, 1769−1772. (b) Sha, S.-C.; Zhang, J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 17602−17609.
(6) The geometry of dienoic ester was determined by a 1D 1H NOESY experiment of ***E*-3a**. See Supporting Information for more details.
(7) (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (b) Goux, C.; Massacret, M.; Lhoste, P.; Sinou, D. *Organometallics* **1995**, *14*, 4585−4593. (c) Kuwano, R.; Kusano, H. *Org. Lett.* **2008**, *10*, 1979−1982.
(8) (a) Larock, R. C.; Lee, N. H. *Tetrahedron Lett.* **1991**, *32*, 6315−6318. (b) Trivedi, R.; Tunge, J. A. *Org. Lett.* **2009**, *11*, 5650−5652. (c) Austeri, M.; Linder, D.; Lacour, J. *Chem. - Eur. J.* **2008**, *14*, 5737−5741.
(9) Mellegaard-Waetzig, S. R.; Rayabarapu, D. K.; Tunge, J. A. *Synlett* **2005**, 2759−2762.
(10) (a) Wei, X.; Lorenz, J. C.; Kapadia, S.; Saha, A.; Haddad, N.; Busacca, C. A.; Senanayake, C. H. *J. Org. Chem.* **2007**, *72*, 4250−4253. (b) Waetzig, S. R.; Rayabarapu, D. K.; Weaver, J. D.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4977−4980. (c) van der Baan, J. L.; Bickelhaupt, F. *Tetrahedron Lett.* **1986**, *27*, 6267−6270. (d) Nakamura, H.; Iwama, H.; Ito, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 10850−10851.
(11) (a) Holzapfel, C. W.; Engelbrecht, G. J.; Marais, L.; Toerien, F. *Tetrahedron* **1997**, *53*, 3957−3974. (b) Chia, M.; Haider, M. A.; Pollock, G.; Kraus, G. A.; Neurock, M.; Dumesic, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 5699−5708.
(12) Jiménez-Halla, J. O. C.; Kalek, M.; Stawinski, J.; Himo, F. *Chem. - Eur. J.* **2012**, *18*, 12424−12436.
(13) (a) Shintani, R.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12356−12357. (b) Shintani, R.; Park, S.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14866−14867. (c) Shintani, R.; Murakami, M.; Hayashi, T. *Pure Appl. Chem.* **2008**, *80*, 1135−1140. (d) Shintani, R.; Tsuji, T.; Park, S.; Hayashi, T. *Chem. Commun.* **2010**, *46*, 1697−1699. (e) Shintani, R.; Hayashi, S.-y.; Murakami, M.; Takeda, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3754−3756. (f) Shintani, R.; Park, S.; Shirozu, F.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 16174−16175. (g) Shintani, R.; Ito, T.; Hayashi, T. *Org. Lett.* **2012**, *14*, 2410−2413.
(14) (a) Sakurai, H.; Eriyama, Y.; Hosomi, A.; Nakadaira, Y.; Kabuto, C. *Chem. Lett.* **1984**, 595−598. (b) Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124−6134. (c) Weintraub, P. M. *J. Chem. Soc. D* **1970**, 760−761. (d) Gotthardt, H.; Huisgen, R. *Chem. Ber.* **1968**, *101*, 552−563.
(15) de la Herrán, G. d.-l.; Csákÿ, A. G. *Synlett* **2009**, *2009*, 585−588.

DOI: 10.1021/acs.orglett.5b02308
Org. Lett. 2015, 17, 4766−4769