JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Palladium-Catalyzed Carbonylative Couplings of Vinylogous Enolates: Application to Statin Structures

Ilya S. Makarov,[†] Takashi Kuwahara,[†,‡] Xavier Jusseau,[†] Ilhyong Ryu,[‡] Anders T. Lindhardt,[*,§] and Troels Skrydstrup[*,†]

[†]Carbon Dioxide Activation Center (CADIAC), The Interdisciplinary Nanoscience Center (iNANO) and Department of Chemistry, Aarhus University, Gustav Wieds Vej 14, 8000 Aarhus, Denmark

[‡]Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

[§]Carbon Dioxide Activation Center (CADIAC), The Interdisciplinary Nanoscience Center (iNANO), Biological and Chemical Engineering, Department of Engineering, Aarhus University, Finlandsgade 22, 8200 Aarhus N, Denmark

Supporting Information

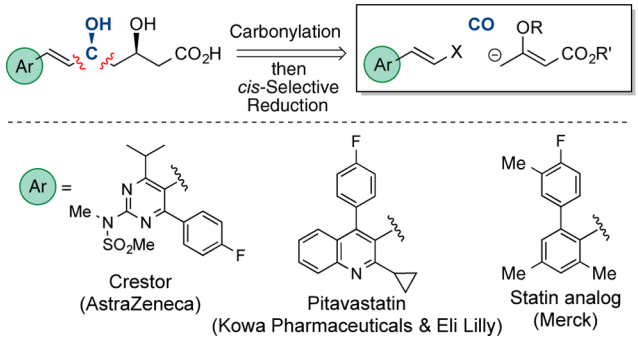
ABSTRACT: The first Pd-catalyzed carbonylative couplings of aryl and vinyl halides with vinylogous enolates are reported generating products derived from C−C bond formation exclusively at the γ-position. Good results were obtained with a dienolate derivative of acetoacetate (1,3-dioxin-4-one). These transformations occurred at room temperature and importantly with only stoichiometric carbon monoxide in a two-chamber reactor. The methodology was applied to the synthesis of two members of the statin family generating the *cis*-3,5-diol acid motif by a γ-selective carbonylation followed by a *cis*-stereoselective reduction of the 3,5-dicarbonyl acid intermediates.

The palladium-catalyzed arylation or vinylation of enolizable carbonyl and related compounds represent a viable and useful C−C bond forming reaction widely applied in synthetic organic chemistry.[1] Notably, the groups of Buchwald[2] and Hartwig,[3] among others,[4] have identified useful catalytic conditions for this synthetic transformation involving enolate or enolate-type intermediates. The majority of this work has been focused on the installment of an aryl or vinyl substituent in the α-position, but few reports have been made extending the methodology to the γ-position of α,β-unsaturated ketones[5] and esters,[6] thereby including vinylogous enolates in the repertoire of reactive intermediates.

Recently, we reported a useful carbonylative version of the α-arylation allowing access to 1,3-diketones,[7] β-ketoesters,[8] and amides,[9] as well as α-nitroketones,[10] 3-acyl-2-oxindoles,[11] and others.[12,13] An intriguing question therefore arose as to whether vinylogous enolates also could become useful substrates in this carbonylative arylation or vinylation, and if so, would carbonylation likewise be directed to the γ-position? Furthermore, if such a transformation could be adapted to the use of acetoacetate dienolates or dienol silyl ethers, this methodology could provide a carbonylative version toward the common *cis*-3,5-diol acid pharmacophore of a range of HMG-CoA reductase inhibitor drugs, better known as the family of statins (Scheme 1).[14]

In this communication, we report on the development of such a Pd-catalyzed carbonylative protocol, which provides a direct entry to 3,5-dicarbonyl acids from the coupling of a dienolate equivalent of acetoacetate to a variety of functionalized aryl or vinyl iodides. The reactions occur in good yields and with complete γ-selectivity and can be performed using only stoichiometric amounts of carbon monoxide (CO). Moreover, this methodology allows access to an alternative carbon isotope labeling strategy of the statin family.

Scheme 1. Strategy for Carbonylative Coupling of Vinylogous Enolates

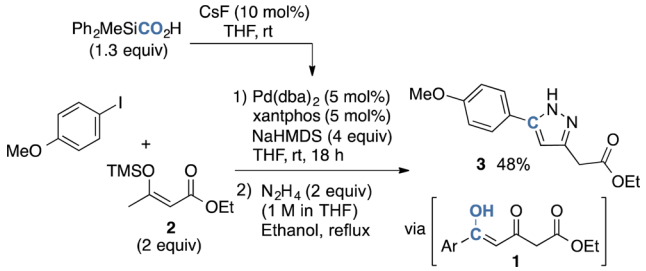


In initial studies, efforts were directed to identifying suitable reaction conditions for the carbonylative coupling of the dianion of ethyl acetoacetate with 4-iodoanisole. A two-chamber reactor system was employed with SilaCOgen as the carbon monoxide source.[15] After extensive screening, the desired diketoester **1** could be generated (Scheme 2), but at best as a 1:7 mixture with the side-product originating from the direct coupling without CO incorporation. Alternatively, the silyl enol derivative **2** proved more promising and with better selectivity. Treatment of **2** with NaHMDS (2 equiv) and then injection into a two-chamber system containing $Pd(dba)_2$, Xantphos, and 4-iodoanisole provided, according to ^1H NMR analysis, the desired tricarbonyl derivative, though as a monoenol tautomer. Although this compound proved difficult to isolate, its treatment with hydrazine led to the more manageable pyrazole **3**. Nevertheless, efforts to improve this two-step yield to over 50% proved unrewarding.[16]

Received: September 3, 2015
Published: October 22, 2015

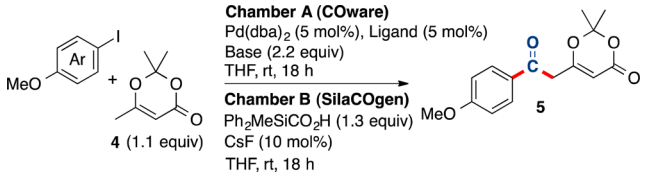
DOI: 10.1021/jacs.5b09342
J. Am. Chem. Soc. 2015, 137, 14043−14046

Scheme 2. Attempted Carbonylative Coupling of the TMS Enol Ether of Ethyl Acetoacetate with 4-Iodoanisole



We suspected that the high basicity and hence instability of the carbon nucleophile could be the cause of the low carbonylative coupling efficiency. Subsequently, efforts were focused toward 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4**), which immediately under the screening process proved to be superior to **2**.[17] As can be seen from Table 1, entry 1, NaHMDS could

Table 1. Screening of Conditions for the Carbonylative Coupling of 4 with 4-Iodoanisole



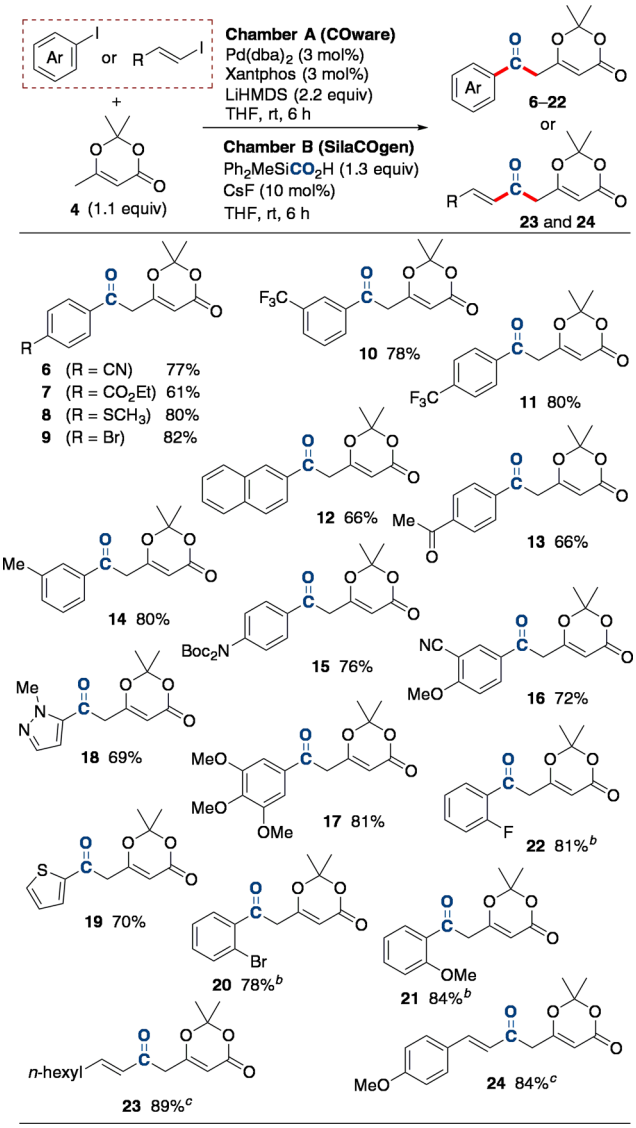
entry	ligand	base	conv. [%][a]	yield [%][a]
1	Xantphos	LiHMDS	100	95 (71)[b]
2	Xantphos	LiO*t*Bu	86	58
3	Xantphos	NaO*t*Bu	100	0
4	Xantphos	Cs_2CO_3	n.d.[c]	0
5	Xantphos	K_2CO_3	0	0
6	DPPP	LiHMDS	0	0
7	DPPF	LiHMDS	n.d.	52
8	DiPrPF	LiHMDS	n.d.	96
9[d]	Xantphos	LiHMDS	100	99 (71)[b]
10[d,e]	Xantphos	LiHMDS	100	>95
11[d,e,f]	Xantphos	LiHMDS	100	99 (82)[b]

[a]Determined by ^{1}H NMR using $MeNO_2$ as an internal standard. [b]Isolated yield. [c]Not determined. [d]3 mol % of $Pd(dba)_2$ and ligand. [e]Reaction time of 6 h. [f]CsF (1.3 equiv).

be replaced with LiHMDS,[18] and only a slight excess of the dioxin-4-one compared to 4-iodoanisole was required this time. With Xantphos as the ligand, an excellent conversion and the isolation of 71% of ketone **5** were obtained. Importantly, no products from the direct α-arylation were detected. Use of other bases provided inferior results (entries 2−5). Testing of other bidentate ligands was also less rewarding (entries 6−8), although application of DiPrPF provided a satisfactory NMR yield of **5** (entry 8). Other solvents such as dioxane, toluene, or acetonitrile led to inferior conversion rates (results not shown). Finally, reduction of the catalyst loading to 3 mol % did not effect the yield (entry 9), and by decreasing the reaction time to 6 h, a satisfactory 82% isolated yield of **5** could be secured (entry 11).

With good carbonylative and γ-selective coupling conditions identified, we next scoped out the reaction with a number of substituted aryl or vinyl iodides, the results of which are depicted in Scheme 3. The developed conditions proved

Scheme 3. Carbonylative Vinylogous Couplings of 4 with Aryl and Vinyl Iodides[a]



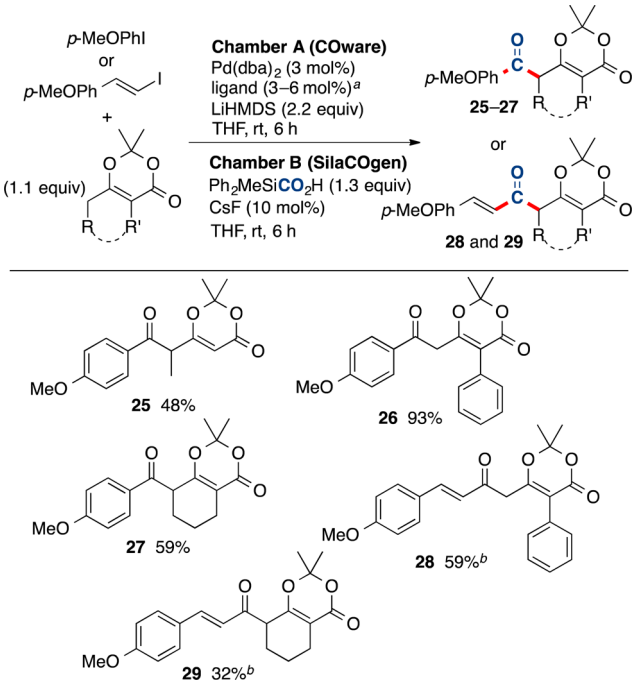
[a]All reactions were run in a two-chamber system on a 0.5 mmol scale (c = 0.167 M). [b]Reaction time of 18 h. [c]Triphenylphosphine (6 mol %) was used, and LiHMDS (1.0 M in hexane) was added at 0 °C.

equally effective for substrates bearing either electron-donating or -withdrawing substituents with yields in the 61−84% range. Satisfyingly, *ortho*-substituents on the aryl ring, including fluoride, bromide, and a methoxy group, were also well tolerated (compounds **20**, **21**, and **22**), although prolonged reaction times (18 h) were required for efficient conversion. For similar couplings to vinyl iodides, direct coupling of **4** to the activated alkene proved to be a serious side product. Subsequently, a ligand screening was undertaken, revealing PPh_3 to be an appropriate ligand in couplings to vinyl iodides as well as suppressing the direct coupling (see Supporting Information). In this way, compounds **23** and **24** could be furnished in isolated yields of 89% and 84%, respectively.[19]

Additionally, we applied this methodology to a range of substituted dioxinones as depicted in Scheme 4. When a substituent is placed on the γ-position of the dioxinone, the reactivity of the entering nucleophile decreases, since the yields drop significantly for both aryl iodides and vinyl iodides

DOI: 10.1021/jacs.5b09342
J. Am. Chem. Soc. 2015, 137, 14043−14046

Scheme 4. Carbonylative Coupling with Substituted Dioxinones

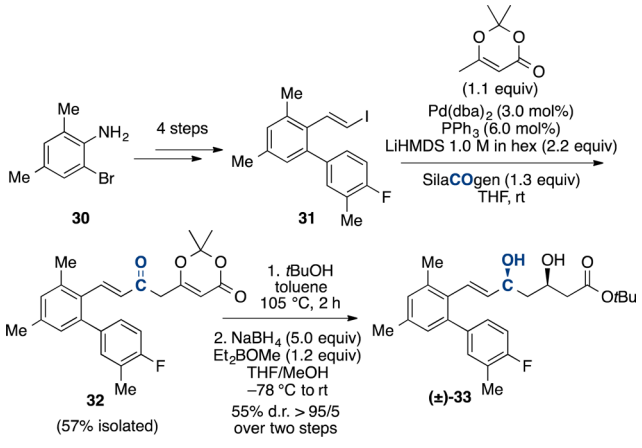


[a]3.0 mol % of Xanthphos was used for aryl iodides and 6.0 mol % of PPh_3 was used for vinyl iodides. [b]LiHMDS (1.0 M in hexane) was added at 0 °C.

(compounds **25**, **27**, and **29**). However, when the substituent was placed on the α-position of the dioxinone, an excellent yield of 93% was obtained with iodoanisole and a good yield of 59% was obtained for the (*E*)-1-(2-iodovinyl)-4-methoxybenzene, although with the necessity of adding the base at 0 °C for the latter (compounds **26** and **28**, respectively).

In light of the suitability of vinyl iodides as the electrophilic partner for the Pd-catalyzed carbonylative coupling with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4**), we next applied this strategy for the synthesis of HMG-CoA reductase inhibitors. Initial efforts were directed to the drug candidate developed by Merck in the early 1990s for the treatment of hypercholesterolaemia (Scheme 5). (*E*)-4′-Fluoro-2-(2-iodovinyl)-3,3′,5-trimethyl-

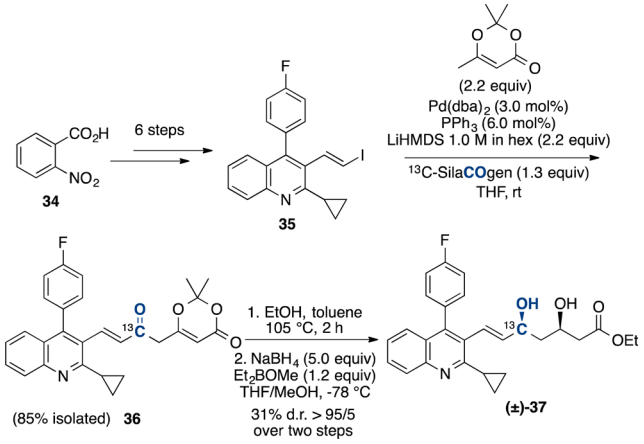
Scheme 5. Synthesis of the *t*Butyl Ester of the HMG-CoA Reductase Inhibitor 33



1,1′-biphenyl (**31**) was readily accessible from commercially available 2-bromo-4,6-dimethylaniline (**30**) in four steps.[20] The Pd-catalyzed carbonylative coupling was then conducted leading to the formation of the dioxinone **32** in a good isolated yield of 57%. From intermediate **32**, a two-step procedure could be applied to achieve the *tert*-butyl ester **33** of the HMG-CoA reductase inhibitor as a racemic mixture. The dioxinone was opened by thermal decomposition and trapped with *tert*-butanol. Diastereoselective reduction using sodium borohydride combined with diethylmethoxyborane as the chelating agent afforded the *syn*-1,3-diol **33** with complete diastereoselectivity in an overall yield of 55% yield for two steps.[21]

With the successful obtainment of compound **33**, we then considered the possibility of exploiting the developed method toward the specific carbon isotope labeling of the statin family, and in particular the commercially available drug, Pitavastatin. As illustrated in Scheme 6, (*E*)-2-cyclopropyl-4-(4-fluorophen-

Scheme 6. Synthesis of (±)-^{13}C-Pitavastatin Ethyl Ester



yl)-3-(2-iodovinyl)quinoline (**35**) was readily prepared in six steps from 2-nitrobenzoic acid (**34**).[22] Subsequently, its participation in the Pd-catalyzed carbonylative coupling using ^{13}C-SilaCOgen produced the ^{13}C-labeled dioxinone **36** in an excellent isolated yield of 85%.[23] Afterward, dioxinone opening was accomplished using ethanol in toluene followed by the *syn*-diastereoselective reduction of the two ketones, ultimately affording the ^{13}C-labeled ethyl ester of (±)-Pitavastatin **37** in a 31% isolated yield over two steps.[24]

In conclusion, we have for the first time expanded the usefulness of the Pd-catalyzed carbonylation couplings to a new class of nucleophiles, namely vinylogous enolates. In particular, the dienolate derivative of acetoacetate could be coupled to a range of aryl and vinyl iodides providing 3,5-dicarbonyl acids with complete γ-selectivity. Furthermore, the carbonylation reactions could be performed at room temperature and with stoichiometric carbon monoxide. Finally, we could adapt this methodology to the synthesis of statins including specific carbon isotope labeling. Further work is now ongoing to examine other vinylogous enolates as substrates for this interesting three-component coupling reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09342.

DOI: 10.1021/jacs.5b09342
J. Am. Chem. Soc. 2015, 137, 14043−14046

Copies of ^{1}H NMR and ^{13}C NMR spectra for all coupling products, as well as details on experimental procedures (PDF)

AUTHOR INFORMATION

Corresponding Authors

*lindhardt@eng.au.dk

*ts@chem.au.dk

Notes

The authors declare the following competing financial interest(s): Anders T. Lindhardt and Troels Skrydstrup are co-owners of SyTracks a/s, which commercializes the two-chamber technology.

ACKNOWLEDGMENTS

We are deeply appreciative of generous financial support of this work from the Danish National Research Foundation (Grant No. DNRF118), the Villum Foundation, the Danish Council for Independent Research: Technology and Production Sciences, the Lundbeck Foundation, and Aarhus University. This paper is dedicated to the 60th birthday of Professor Samir Z. Zard.

REFERENCES

(1) For reviews on Pd-catalyzed α-arylations, see: (a) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953. (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (c) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. (d) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (e) Prim, D.; Marque, S.; Gaucher, A.; Campagne, J.-M. *Org. React.* **2011**, *76*, 49.

(2) For selected examples, see: (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996. (c) Biscoe, M. R.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 1773.

(3) For selected examples, see: (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (b) Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182. (c) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (d) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127.

(4) For selected examples, see: (a) Satoh, T.; Inoh, J.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. (b) Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194. (c) Cossy, J.; de Filippis, A.; Pardo, D. G. *Org. Lett.* **2003**, *5*, 3037.

(5) (a) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203. (b) Martin, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236. (c) Varseev, G. N.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3881. (d) Hyde, A. M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 177.

(6) (a) Huang, D. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 5757. (b) Hyde, A. M.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 2663. (c) Yamamoto, Y.; Hatsuya, S.; Yamada, J.-I. *J. Chem. Soc., Chem. Commun.* **1988**, 86.

(7) (a) Gøgsig, T. M.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 798. (b) Korsager, S.; Nielsen, D. U.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *Chem. - Eur. J.* **2013**, *19*, 17687. (c) Nielsen, D. U.; Lescot, C.; Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Chem. - Eur. J.* **2013**, *19*, 17926.

(8) Korsager, S.; Nielsen, D. U.; Taaning, R. H.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 9763.

(9) Nielsen, D. U.; Korsager, S.; Lindhardt, A. T.; Skrydstrup, T. *Adv. Synth. Catal.* **2014**, *356*, 3519.

(10) Lian, Z.; Friis, S. D.; Skrydstrup, T. *Chem. Commun.* **2015**, *51*, 3600.

(11) Lian, Z.; Friis, S. D.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 9582.

(12) Jusseau, X.; Yin, H.; Lindhardt, A. T.; Skrydstrup, T. *Chem. - Eur. J.* **2014**, *20*, 15785.

(13) For some recent reviews on Pd-catalyzed carbonylations, see: (a) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1. (b) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986. (c) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. (d) Brennführer, A.; Neumann, H.; Beller, M. *ChemCatChem* **2009**, *1*, 28.

(14) (a) Fritz, G. *Int. J. Oncol.* **2005**, *27*, 1401. (b) Maron, D. J.; Fazio, S.; Linton, M. F. *Circulation* **2000**, *101*, 207. (c) Demierre, M.-F.; Higgins, P. D. R.; Gruber, S. B.; Hawk, E.; Lippman, S. M. *Nat. Rev. Cancer* **2005**, *5*, 930. (d) Istvan, E. S.; Deisenhofer, J. *Science* **2001**, *292*, 1160.

(15) Friis, S. D.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 18114.

(16) A reagent ratio of 4-iodoanisole/**2**/NaHMDS of 1:2:4 proved to be the best ratio for obtaining the reported yield of compound **3**.

(17) The γ-selective alkylation and chlorination of the dienolate of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one is known. For example see: (a) Smith, A. B., III; Scarborough, R. M., Jr. *Tetrahedron Lett.* **1978**, *19*, 4193. (b) Boeckman, R. K., Jr.; Perni, R. B.; Macdonald, J. E.; Thomas, A. J. *Org. Synth.* **1988**, *66*, 194.

(18) We have earlier shown that LiHMDS is not an effective base for the Pd-catalyzed carbonylative α-arylation of simple ketones, whereas NaHMDS is (see ref 7a). We are currently examining the role of the counterion in carbonylation reactions with other enolates in order to understand this effect.

(19) Despite extensive screening of palladium sources, ligands, solvents, and bases, no conversion was observed for the corresponding aryl bromides. On the other hand, compound **24** could be obtained from the vinyl bromide equivalent, although at best with an NMR yield of approximately 50%.

(20) (a) Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, E. J.; Deana, A. A.; Gilfillan, J. L.; Hirshfield, J.; Holtz, W. J.; Hoffman, W. F.; Huff, J. W.; Lee, T. J.; Novello, F. C.; Prugh, J. D.; Rooney, C. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 170. (b) Naskar, D.; Chowdhury, S.; Roy, S. *Tetrahedron Lett.* **1998**, *39*, 699. (c) Naskar, D.; Roy, S. *Tetrahedron* **2000**, *56*, 1369.

(21) Hiyama, T.; Reddy, G. B.; Minami, T.; Hanamoto, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 350.

(22) (a) Zhang, J.; Zhu, D.; Yu, C.; Wan, C.; Wang, Z. *Org. Lett.* **2010**, *12*, 2841. (b) Counceller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021. (c) Suzuki, M.; Iwasaki, H.; Fujikawa, Y.; Kitahara, M.; Sakashita, M.; Sakoda, R. *Bioorg. Med. Chem.* **2001**, *9*, 2727. (d) Sliskovic, D. R.; Picard, J. A.; Roark, W. H.; Roth, B. D.; Ferguson, E.; Krause, B. R.; Newton, R. S.; Sekerke, C.; Shaw, M. K. *J. Med. Chem.* **1991**, *34*, 367.

(23) The 2.2 equiv of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one and 2.2 equiv of LiHMDS were premixed at 0 °C prior to the addition to the reaction mixture. See Supporting Information for the detailed procedure. The addition of 2.2 equiv of LiHMDS to the reaction mixture at room temperature did not afford dioxinone **35**, probably because of the acidity of the cyclopropylic proton at the 2-position of the quinoline.

(24) The low yield is explained by the competitive 1,6-addition of the hydride compared to the 1,4-addition during the reduction step, leading to a 2/1 mixture of alkene and alkane, which are difficult to separate.

DOI: 10.1021/jacs.5b09342
J. Am. Chem. Soc. 2015, 137, 14043−14046