Organic LETTERS

Letter

pubs.acs.org/OrgLett

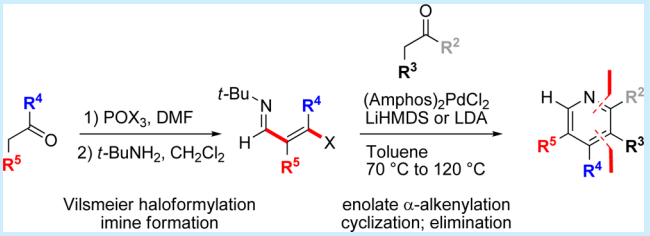
Modular Synthesis of Highly Substituted Pyridines via Enolate α-Alkenylation

Leo A. Hardegger, Jacqueline Habegger, and Timothy J. Donohoe*

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K.

Supporting Information

ABSTRACT: A novel methodology for the synthesis of highly substituted pyridines based on the palladium-catalyzed enolate α-alkenylation of ketones is presented; the formation of aromatic compounds is a new direction for this catalytic C−C bond forming reaction. In the key step, a protected β-haloalkenylaldehyde participates in α-alkenylation with a ketone to afford a 1,5-dicarbonyl surrogate, which then undergoes cyclization/double elimination to the corresponding pyridine product, all in one pot. The β-haloalkenylaldehyde starting materials can be obtained from the corresponding methylene ketone via Vilsmeier haloformylation. Using this concise route, a variety of highly substituted pyridines were synthesized in three steps from commercially available compounds.



The regioselective formation of multiply substituted pyridines remains an important synthetic challenge. In view of the scale of production of various pyridine compounds and the importance of pyridines in the pharmaceutical, agrochemical, and material sciences, a concise synthetic route to highly and selectively substituted pyridines is very desirable.[1] We have previously reported several modular routes to pyridines in which the *N*-heterocycle was formed either by ring-closing metathesis of a diene or by cyclization of a 1,5-dicarbonyl, prepared by cross-metathesis, with a nitrogen source.[2] As part of a research program designed to utilize new catalytic reactions in arene synthesis, we envisioned that the Pd-catalyzed enolate α-alkenylation reaction[3] of ketone **1** and protected β-haloalkenylaldehyde **2** could lead to masked 1,5-dicarbonyl compound **3** capable of forming pyridine **4** after treatment with a nitrogen source (Figure 1). This proposed synthesis takes advantage of

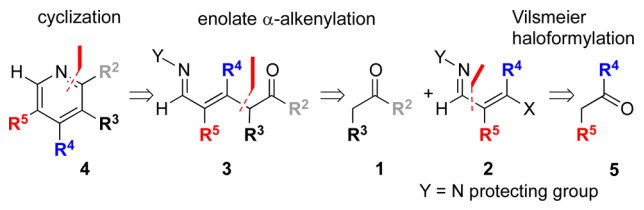


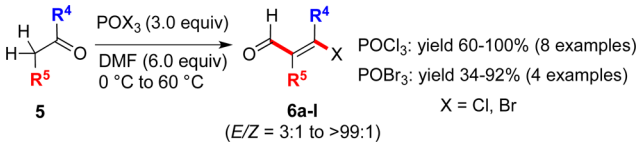
Figure 1. Enolate α-alkenylation approach to pyridines.

the Pd-catalyzed enolate α-alkenylation reaction which has remained under-utilized in chemical synthesis and is almost unknown in applications such as the *de novo* synthesis of aromatic compounds.[4] In addition to expanding the scope of the method, our approach provides complete regioselectivity and omits the problem of isomer formation that is often encountered in pyridine syntheses.

We decided to explore a haloformylation approach to make the α-alkenylation precursor **2**; therefore pyridines **4** all contain hydrogen in the C6 position. Efforts at developing reaction conditions giving access to pyridines with five substituents are underway, and their results will be reported in due course.

Alkenyl derivatives **6a−l** can be obtained in one step from methylene ketones **5** in a Vilsmeier haloformylation reaction (Scheme 1).[5,6] The yields of this transformation were generally

Scheme 1. Vilsmeier Haloformylation of Ketones



good, and highest when the reactions were carried out in the presence of 6 equiv of DMF without using any other solvent. Both alkenyl chlorides and alkenyl bromides could be accessed using $POCl_3$ or $POBr_3$, respectively. In our hands, $POCl_3$ was easier to handle and resulted in a more homogeneous reaction mixture leading to higher yields as compared to $POBr_3$. As detailed below, both alkenyl chlorides and bromides can be employed in the enolate α-alkenylation. While most β-haloalkenylaldehydes **6** were obtained as a mixture of stereoisomers, the stereochemistry of the intermediate is inconsequential to the success of subsequent reactions, *vide infra*.

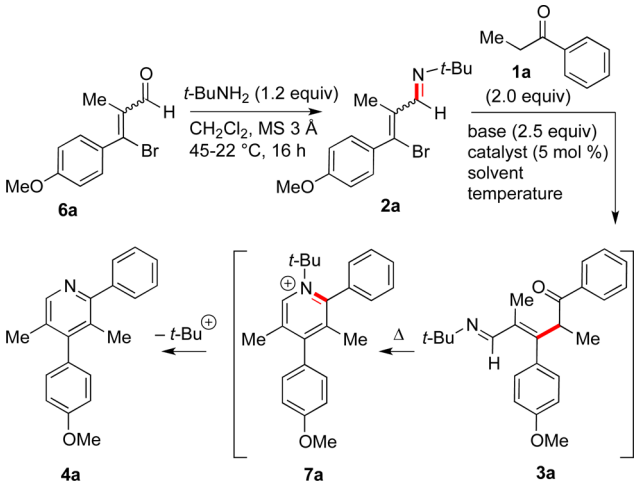
As suspected, the reaction of the parent aldehyde **6a** (R^4 = 4-MeO-Ph, R^5 = Me, X = Br) with propiophenone under alkenylation conditions gave a complex mixture of compounds

Received: May 5, 2015

DOI: 10.1021/acs.orglett.5b01312
Org. Lett. XXXX, XXX, XXX−XXX

probably arising from aldol-type chemistry. In order to find optimal reaction conditions, various protected derivatives of the aldehydes **6**, such as oximes and imines, were subjected to palladium catalysis under conditions described previously (base, (D*t*-BPF)$PdCl_2$, THF).[3c,7] This work showed that employing *tert*-butylimines **2** as the carbonyl surrogates was optimal for yields, and this group was adopted for further study. Note that imines **2** are readily available by the addition of *t*-$BuNH_2$ to aldehydes **6** and stirring the reaction mixture with molecular sieves in CH_2Cl_2; after evaporation, no purification was necessary. In the reaction of **2a** and propiophenone **1a**, chosen as a model, the acyclic coupled intermediate **3a** could not be isolated since it reacted *in situ* to yield pyridine **4a** directly in 43% (Table 1, entry 1) in 6.5 h.

Table 1. Optimization of the Alkenylation and Cyclization/Aromatization Protocol



entry	base	catalyst	solvent	temp (°C)	time (h)	yield[a] (%)
1	LiHMDS[b]	(D*t*-BPF)$PdCl_2$	THF	70	6.5	43
2	LiHMDS[b]	(D*t*-BPF)$PdCl_2$	Toluene	80-110	4.5	69
3	LiHMDS[b]	(D*t*-BPF)$PdCl_2$	Dioxane	110	54	12
4	LiO*t*Bu	(D*t*-BPF)$PdCl_2$	Toluene	70-120	48	27
5	NaO*t*Bu	(D*t*-BPF)$PdCl_2$	Toluene	70-120	9	39
6	NaHMDS	(D*t*-BPF)$PdCl_2$	Toluene	70-120	23	37
7	LDA[b]	(D*t*-BPF)$PdCl_2$	Toluene	70-120	6.5	69
8	LiHMDS[b]	(D*t*-BPF)$PdCl_2$	Toluene	70-120	5.5	71
9	LiHMDS[b]	none	Toluene	70-120	6.5	0
10	LiHMDS[b]	$Pd_2(dba)_3$, Qphos	Toluene	70-120	23	31
11	LiHMDS[b]	$Pd(OAc)_2$, Qphos	THF	20-70	48	0
12	LiHMDS[b]	PEPPSI	Toluene	70-120	26	51
13	LiHMDS[b]	$(Amphos)_2PdCl_2$	Toluene	70-120	4	76

[a]Yield of **4a** over two steps based on aldehyde **6a**. [b]Prepared *in situ*. Amphos = di-*tert*-butyl(4-dimethylaminophenyl)phosphine.

A screen of bases and their loadings, solvents, catalysts, and reaction temperatures resulted in optimized conditions for the enolate α-alkenylation cross-coupling/aromatization reaction cascade (Table 1). Changing the solvent from THF to toluene facilitated cleavage of the *t*-Bu from pyridinium intermediate **7a** and increased the yield of **4a** to 69% (Table 1, entry 2). Conversely, performing the reaction in 1,4-dioxane resulted in the formation of only 12% pyridine **4a** (Table 1, entry 3) even after a prolonged reaction time. From screening different reaction temperatures in toluene, it was found that greater yields of the pyridine product were obtained when the temperature of the mixture was increased gradually for each step of the cascade reaction (see Supporting Information (SI)). Monitoring the reaction progress by MS showed that the enolate α-alkenylation cross-coupling between alkenyl halide **2a** and propiophenone **1a** to the acyclic intermediate **3a** occurred at 70 °C, cyclization and elimination to pyridinium **7a** were optimal at 90 °C, and finally elimination of *t*-Bu at 120 °C gave pyridine **4a**. Simply running the whole reaction at 110 °C from the beginning led mostly to the dehalogenated alkenyl derivative.

Weaker bases such as LiO*t*-Bu (27%, Table 1, entry 4) or NaO*t*-Bu (39%, Table 1, entry 5) gave low yields. Commercial NaHMDS (37%, Table 1, entry 6) also performed poorly compared to *in situ* prepared LDA (69%, Table 1, entry 7), which gave pyridine **4a** in a similar yield to LiHMDS (71%, Table 1, entry 8). Later studies showed that, for aromatic ketones **1** (R^2 = aromatic), *in situ* prepared LiHMDS was the base of choice, whereas, for the less acidic aliphatic ketones **1** (R^2 = aliphatic), *in situ* prepared LDA gave the best results.

No conversion of alkenyl halide **2a** was observed in the absence of palladium (Table 1, entry 9). When (D*t*-BPF)$PdCl_2$ was exchanged for a Pd(0) species (Pd_2dba_3, Qphos), the yield dropped to 31% (Table 1, entry 10). Applying conditions which have recently been shown to catalyze enolate α-alkenylations even at 0 °C did not lead to pyridine formation (Table 1, entry 11), and only traces of α-alkenylation product **3a** were observed by MS.[3b] Moreover, the use of an *N*-heterocyclic carbene ligand (PEPPSI) afforded pyridine **4a** in moderate yield (51%, Table 1, entry 12). When moving to the preformed catalyst with bulky monodentate phosphine ligands $(Amphos)_2PdCl_2$, the yield of **4a** could be increased to 76% with fewer side products observed (Table 1, entry 13).

It is important to note that at least 2 equiv of base are required for this transformation, presumably because the coupling product is more acidic than the starting ketone. With only 1.2 equiv of base added, the reaction did not reach completion and, instead, a mixture of the desired product and intermediates was observed. However, the yields were comparable if 2.1, 2.5, or 3.0 equiv of LiHMDS were used. The only byproduct that we were able to observe in the sequence was the dehalogenated analogue of imine **2a**.

With the optimal conditions in hand, modification at the pyridine positions R^2/R^3 (C2 and C3) was then achieved using different ketone enolates **1** (Figure 2). The conditions for the enolate α-alkenylation reaction are compatible with electron-deficient (**4b**) and -rich (**4c**) aromatic substituents. Hetero-aromatic substituents give the desired pyridines (**4e**, **4f**) in reasonable yields. Using a methyl ketone (R^3 = H) gives the corresponding trisubstituted pyridine **4g** in 58% yield; increasing the steric bulk at position R^3 leads to lower product formation for pyridines **4h** and **4i**. Interestingly, elimination of the *t*-Bu group from pyridinium **7g** (R^2 = Ph, R^3 = H) occurs at 70 °C, a temperature much lower than that for the corresponding pyridines with $R^3 \neq$ H. This observation may be explained by considering the increased steric congestion present at the pyridine nitrogen when the aromatic ring at R^2 is in conjugation with the pyridine π-system. For the synthesis of the aliphatic substituted pyridines **4j** and **4k**, a slightly modified procedure using LDA gave the best results. Pyridine **4l**, in which the ketone is part of a six-membered ring, could be synthesized in 26% yield.

Substituents R^4 and R^5 (C4 and C5) are introduced via different alkenyl derivatives **6**, and this feature was examined next (Figure 3). Aromatic substituents at R^4 can be decorated with electron-donating (**4a**, **4d**, **4m**) and electron-withdrawing (**4n**)

DOI: 10.1021/acs.orglett.5b01312
Org. Lett. XXXX, XXX, XXX−XXX

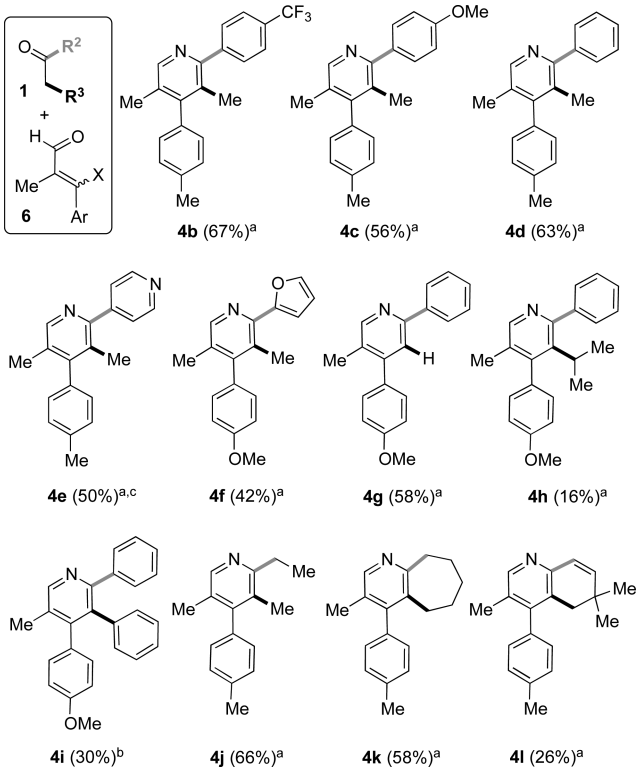


Figure 2. Variation in the ketone component. Yields over two steps: (i) **6**, *t*-BuNH$_2$, 3 Å MS, CH_2Cl_2; (ii) ketone (2 equiv), LiHMDS (2.5 equiv), (Amphos)$_2$PdCl$_2$ (5 mol %), toluene, 70−120 °C. LDA used for **4j**, **4k**. [a] X = Br. [b] X = Cl. [c] (D*t*-BPF)PdCl$_2$ (5 mol %) cat.

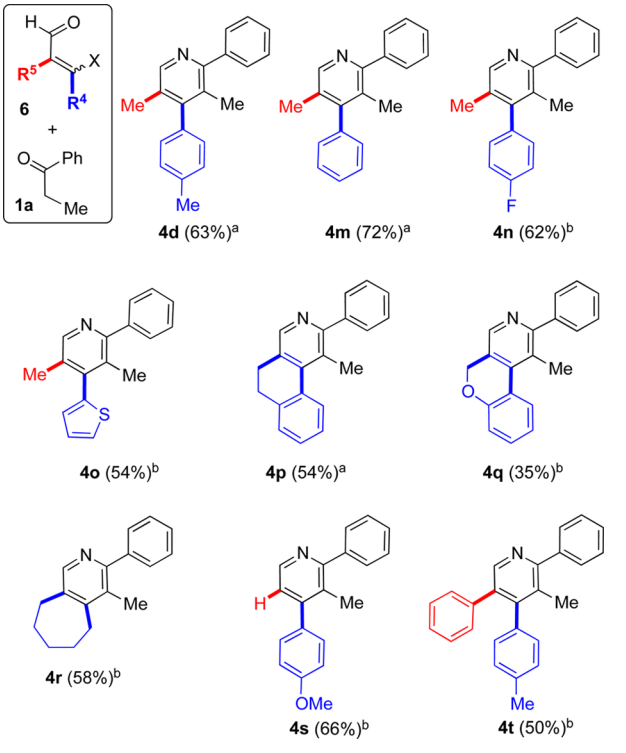


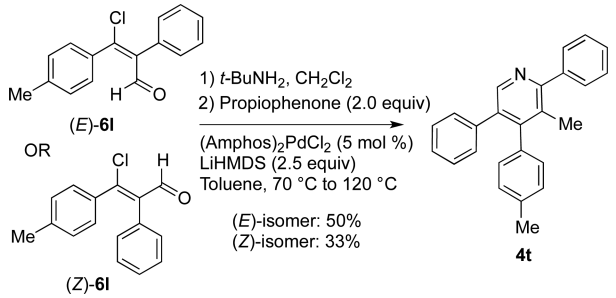
Figure 3. Variation in the halide component. Yields over two steps: (i) **6**, *t*-BuNH$_2$, 3 Å MS, CH_2Cl_2; (ii) ketone (2 equiv), LiHMDS (2.5 equiv), (Amphos)$_2$PdCl$_2$ (5 mol %), toluene, 70−120 °C. LDA used for **4r**. [a] X = Br. [b] X = Cl.

groups and may be heteroaromatic (**4o**). We were pleased to find that cyclic alkenyl derivatives can be employed under the reaction conditions and the aromatic, R^4−R^5-fused pyridines **4p** and **4q** could be obtained in moderate yields, as well as the seven-membered aliphatic pyridine **4r**. The reaction conditions are also compatible with R^5 = H, and trisubstituted pyridine **4s** was obtained in good overall yield. The crystal structures of substituted pyridines **4o** and **4s** were obtained, confirming the formation of pyridines through enolate α-alkenylation (see SI for details).[8] Steric repulsion appears to have a smaller influence on R^5 than on R^3, and pyridine **4t** with R^5 = Ph could be synthesized in 50% yield. Alkenyl derivatives in which the double bond was part of a five- or six-membered ring, or when the alkenyl halide was substituted with OMe or CF_3, gave the corresponding pyridines in <25% yield.

Generally, we found that both alkenyl bromides and alkenyl chlorides could be used in the key transformation, although as expected the alkenyl bromides tended to couple more rapidly than their chloride counterparts. This result is in agreement with a similar observation made for related enolate α-arylations and can be explained by the higher preference of Pd(0) to insert into C−Br bonds than C−Cl bonds.[9] Once the enolate is coupled to the alkenyl halide, the cyclization was completed within 3 h for both types of substrate. For example, the yield of product **4d** was similar when starting from the bromide (63%) and the chloride derivative (61%).

Finally, we studied the role of alkene geometry in the alkenyl halide coupling partner and found that the (*E*)- and (*Z*)-isomer of alkenyl chlorides **6l** could be separated by MPLC (these were unambiguously assigned by using the nuclear Overhauser effect, SI). The aldehydes were converted into the corresponding imines and subjected to the optimized reaction conditions (Scheme 2). While the enolate α-alkenylation for both the (*Z*)-

Scheme 2. Studies on Alkenyl Halide Geometry

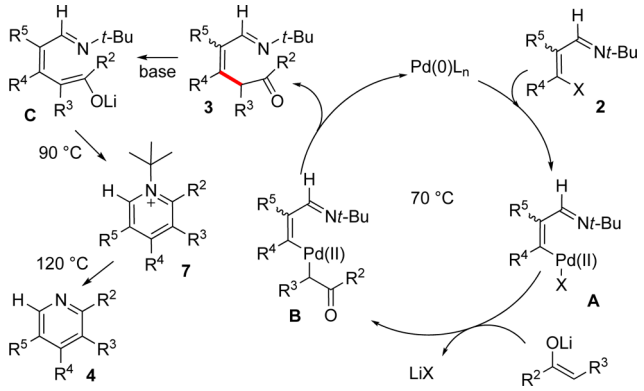


and the (*E*)-isomer was slow (16 h at 70 °C), the following cyclization of the (*Z*)-isomer was almost instantaneous as judged by MS analysis. The coupled intermediate immediately cyclizes and aromatizes, and an m/z = 392.2 was observed for the pyridinium intermediate. In the case of the (*E*)-isomer, on the other hand, double bond isomerization and subsequent cyclization appear to be slow and only occur at elevated temperatures and longer reaction times (24 h at 120 °C). Note that the isomer (*Z*)-**6l** was unstable as judged by ^{1}H NMR spectroscopy, which could explain the reduced yield for the transformation into pyridine **4t**.

A catalytic cycle for the enolate α-alkenylation reaction is proposed which is similar to the one published for the enolate α-arylation reaction.[10] The Pd(0) catalyst undergoes oxidative addition into the C−X bond of the alkenyl halide **2** to give complex **A** (Scheme 3). The Li-enolate, formed from ketones **1**,

DOI: 10.1021/acs.orglett.5b01312
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. A Preliminary Mechanistic Interpretation



undergoes transmetalation to give intermediate **B**. Reductive elimination from **B** regenerates catalytic Pd(0) and affords the acyclic intermediate **3**, which is most likely deprotonated by a second equivalent of base to give intermediate **C**. It is suggested that a 6-π electrocyclization is operative (clearly this requires the correct alkene geometry to proceed), followed by aromatization (loss of Li_2O[11]) and finally loss of the *t*-Bu cation from pyridinium **7** at 120 °C to deliver pyridine **4**.

In summary, a modular synthesis based on the Pd-catalyzed α-alkenylation reaction of ketones was developed to afford a variety of highly substituted pyridines in only three synthetic steps from commercially available compounds with complete regiocontrol over the four substituents R^2–R^5. The reaction conditions are compatible with electron-deficient, electron-rich, and heteroaromatic as well as aliphatic residues on both ketones **1** and alkenyl halides **2**. Alkenyl bromides and chlorides were found to couple to a variety of ketones, regardless of their double bond geometry. Not only does this disconnection greatly simplify the synthesis of multisubstituted pyridines, but this methodology also enhances the range of functionalized alkenyl halides that have been shown to be viable for enolate cross-coupling reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds; copies of ^{1}H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01312.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: timothy.donohoe@chem.ox.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPSRC for support (Established Career Fellowship, T.J.D.). This work was also supported by the Swiss National Science Foundation and Marie Curie actions fellowships (L.A.H.) and a Berrow Foundation Lord Florey scholarship (J.H.).

■ REFERENCES

(1) For reviews on applications of pyridine derivatives and pyridine syntheses, see: (a) Hill, M. D. *Chem.—Eur. J.* **2010**, *16*, 12052. (b) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. For recent examples of pyridine syntheses, see: (c) Li, Z.; Huang, X.; Chen, F.; Zhang, C.; Wang, X.; Jiao, N. *Org. Lett.* **2015**, *17*, 584. (d) Wu, K.; Huang, Z.; Liu, C.; Zhang, H.; Lei, A. *Chem. Commun.* **2015**, *51*, 2286. (e) Jiang, Y.; Park, C.-M.; Loh, T.-P. *Org. Lett.* **2014**, *16*, 3432. (f) Wei, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 3756. (g) Srimani, D.; Ben-David, Y.; Milstein, D. *Chem. Commun.* **2013**, *49*, 6632. (h) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2012**, *77*, 2501. (i) Regás, D.; Afonso, M. M.; Palenzuela, J. A. *Tetrahedron* **2012**, *68*, 9345.

(2) (a) Donohoe, T. J.; Basutto, J. A.; Bower, J. F.; Rathi, A. *Org. Lett.* **2011**, *13*, 1036. (b) Donohoe, T. J.; Bower, J. F.; Basutto, J. A.; Fishlock, L. P.; Procopiou, P. A.; Callens, C. K. A. *Tetrahedron* **2009**, *65*, 8969. For a review, see (c) Donohoe, T. J.; Bower, J. F.; Chan, L. K. M. *Org. Biomol. Chem.* **2012**, *10*, 1322.

(3) For a review on Pd- and Ni-catalyzed alkenylation of enolates, see: (a) Ankner, T.; Cosner, C. C.; Helquist, P. *Chem.—Eur. J.* **2013**, *19*, 1858. For selected examples on the development of the Pd-catalyzed α-alkenylation of enolates, see: (b) Grigalunas, M.; Ankner, T.; Norrby, P.-O.; Wiest, O.; Helquist, P. *Org. Lett.* **2014**, *16*, 3970. (c) Huang, J.; Bunel, E.; Faul, M. M. *Org. Lett.* **2007**, *9*, 4343. (d) Solé, D.; Urbaneja, X.; Bonjoch, J. *Adv. Synth. Catal.* **2004**, *346*, 1646. (e) Hamada, T.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 999. (f) Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897. (g) Piers, E.; Oballa, R. M. *Tetrahedron Lett.* **1995**, *36*, 5857. (h) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3434. For recent examples of the use of Pd-catalyzed α-alkenylation in synthesis, see: (i) Liu, F.; Li, C. *Org. Biomol. Chem.* **2014**, *12*, 637. (j) Cosner, C. C.; Iska, V. B. R.; Chatterjee, A.; Markiewicz, J. T.; Corden, S. J.; Löfstedt, J.; Ankner, T.; Richer, J.; Hulett, T.; Schauer, D. J.; Wiest, O.; Helquist, P. *Eur. J. Org. Chem.* **2013**, 162. (k) Yao, Y.; Liang, G. *Org. Lett.* **2012**, *14*, 5499. (l) Edwankar, C. R.; Edwankar, R. V.; Deschamps, J. R.; Cook, J. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11762.

(4) (a) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225. (b) Solé, D.; Diaba, F.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746. (c) For a review of enolate arylation in arene forming reactions, see: Potukuchi, H. K.; Spork, A. P.; Donohoe, T. J. *Org. Biomol. Chem.* **2015**, *13*, 4367.

(5) Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. *Org. Lett.* **2010**, *12*, 2884.

(6) For a review of the reaction of carbonyl compounds with the Vilsmeier reagent, see: Marson, C. *Tetrahedron* **1992**, *48*, 3659.

(7) Pilgrim, B. S.; Gatland, A. E.; McTernan, C. T.; Panayiotis, P. A.; Donohoe, T. J. *Org. Lett.* **2013**, *15*, 6190.

(8) Low temperature, single crystal X-ray diffraction data were collected using a Nonius K-CCD diffractometer or an Oxford Diffraction SuperNova Diffractometer. Data were reduced DENZO/SCALEPACK [Otwinowski, Z.; Minor, W. In *Methods in Enzymology*; Carter, C. W., Sweet, R. M., Eds.; Academic Press: 1997; Vol. *276*, p 307.] using CrysAlisPro as appropriate, and solved using SuperFlip [Palatinus, L.; Chapuis, G. *J. Appl. Crystallogr.* **2007**, *40*, 786.] and refined within the CRYSTALS suite [Parois, P.; Cooper, R. I.; Thompson, A. L. *Chem. Cent.*, in press. Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr.* **2010**, *43*, 1100. Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr.* **2011**, *44*, 1017.]. Full refinement details are given in the Supporting Information (CIF). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1061007–1061008) and can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

(9) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375.

(10) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

(11) (a) Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 7943. (b) Cohen, T.; Yu, L.-C. *J. Org. Chem.* **1984**, *49*, 605. (c) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4527.

DOI: 10.1021/acs.orglett.5b01312
Org. Lett. XXXX, XXX, XXX–XXX