OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

Divergent Enantioselective Synthesis of (Nor)illudalane Sesquiterpenes via Pd^0-Catalyzed Asymmetric $C(sp^3)$–H Activation

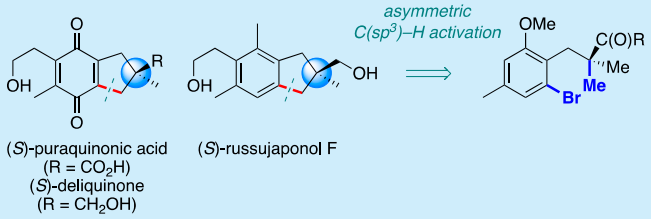
Romain Melot,[†,§] Marcus V. Craveiro,[†,§] Thomas Bürgi,[‡] and Olivier Baudoin*[,†]

[†]University of Basel, Department of Chemistry, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

[‡]Department of Physical Chemistry, University of Geneva, 30 Quai Ernest-Ansermet, 1211 Geneva 4, Switzerland

Supporting Information

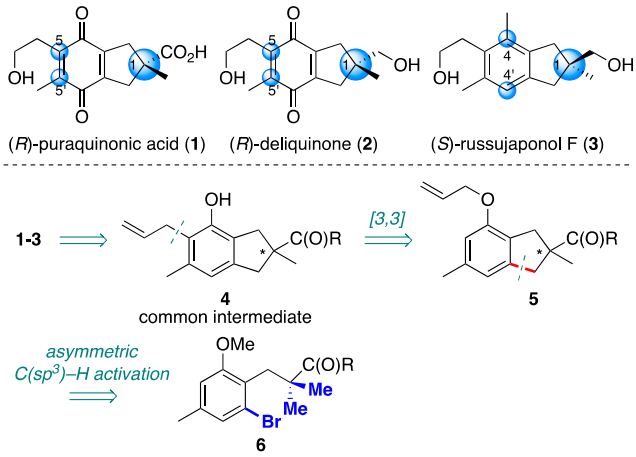
ABSTRACT: A divergent enantioselective synthesis of (nor)-illudalane sesquiterpenes was designed by using a Pd^0-catalyzed asymmetric $C(sp^3)$–H arylation as a key step to control the isolated, highly symmetric quaternary stereocenter of the target molecules. A matched combination of chiral substrate and catalyst proved optimal to reach good levels of stereoselectivity. This approach enabled the synthesis of three (nor)illudalanes, including (*S*)-deliquinone and (*S*)-russujaponol F, which are synthesized for the first time in enantioenriched form.



Higher fungi are sources of diverse bioactive illudalane and norilludalane sesquiterpenes such as the fused benzoquinones puraquinonic acid (**1**)[1] and deliquinone (**2**)[2] and the indane russujaponol F (**3**)[3] (Scheme 1, top). In particular, the former was shown to induce the differentiation of HL-60 cells.[1] In addition to a densely functionalized 6-membered ring, the most striking common structural feature of compounds **1**–**3** is certainly the presence of a single, highly symmetric quaternary stereocenter, which arises from the presence of different substituents three (**3**) or four (**1** and **2**) carbons away. Despite very low specific rotations, compounds **1**–**3** have been reported to occur as single enantiomers with the (*R*) (**1** and **2**) or (*S*) (**3**) absolute configuration.[1−3] The presence of this isolated quaternary stereocenter represents a major challenge for the enantioselective synthesis of these natural products.[4] Indeed, despite a deceptively simple structure, only two enantioselective syntheses of puraquinonic acid have been reported and none for deliquinone, russujaponol F, or other (nor)illudalanes of this type.[5,6] The first synthesis of (*S*)-puraquinonic acid by Clive and co-workers featured 31 steps and showcased the difficulty of controlling the isolated quaternary stereocenter by classic chiral auxiliary-based approaches.[5a,b] It also established the absolute configuration of natural puraquinonic acid as (*R*). The number of steps was greatly improved in a more recent synthesis of (*R*)-puraquinonic acid by Gleason and co-workers.[5c] The quaternary stereocenter was installed at an early stage of the synthesis by diastereoselective alkylations from an in-house chiral auxiliary.[7] Subsequently, the indane system was efficiently constructed by enyne metathesis and Diels–Alder cycloaddition. The chiral auxiliary was removed in the last steps of the synthesis prior to the oxidization of the benzene ring to the benzoquinone. This strategy resulted in a much shorter and efficient enantioselective synthesis −12 steps, 20% overall yield from the chiral auxiliary, or 15 steps, 14% from (*S*)-valinol.

Previous work from our group[8] led us to consider an alternative and, in principle, more divergent approach to (nor)illudalane sesquiterpenes **1**–**3** by means of Pd^0-catalyzed enantioselective $C(sp^3)$–H activation (Scheme 1, bottom).[9,10] Benzoquinone- and benzene-fused cyclopentanes **1**–**3** would arise from the same indane precursor **4**, which should be easily accessible from the less substituted intermediate **5** through aromatic Claisen rearrangement.[5a,b,6] Indane **5** would be obtained by Pd^0-catalyzed enantioselective $C(sp^3)$–H arylation from a structurally simple aryl bromide **6**. In this step, the

Scheme 1. (Nor)illudalane Targets Featuring a Highly Symmetric Quaternary Stereocenter and Retrosynthetic Analysis



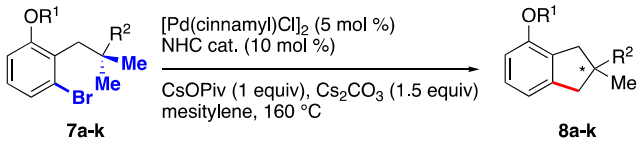
Received: December 21, 2018

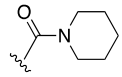
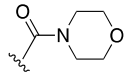
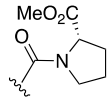
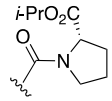
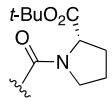
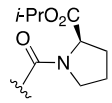
DOI: 10.1021/acs.orglett.8b04086
Org. Lett. XXXX, XXX, XXX–XXX

chiral catalyst would achieve the desymmetrization of the two methyl groups in **6** and generate the quaternary stereocenter at the adjacent position. We previously reported the enantioselective synthesis of indanes by Pd^0-catalyzed C(sp^3)−H arylation in the presence of a chiral phosphine.[11] In this case, two isopropyl groups were desymmetrized to generate a quaternary stereocenter two carbons away from the cleaved C−H bond. Besides, the desymmetrization of *gem*-dimethyl groups on a tetrasubstituted carbon was reported by our group in the context of indoline synthesis, through the use of a catalytic chiral phosphate.[12] The enantioselectivity was good but lower than the one achieved with compounds bearing trisubstituted carbons.[13] In addition, in both precedents the more substituted linker between Pd and the cleaved C−H bond favored the intramolecular C−H activation step by Thorpe−Ingold-type effects. Hence, we anticipated that the enantioselective C−H arylation of substrate **6** would be challenging both because of the lack of conformational bias and the presence of the adjacent quaternary carbon. On the other hand, this new route would allow introduction of the quaternary stereocenter at a later stage compared to previous syntheses and would be more enantiodivergent, i.e., more flexible to access the desired (*R*) or (*S*) enantiomer of (nor)illudalanes **1**−**3**. Herein, we report the implementation of this C(sp^3)−H activation-based strategy[14] for the enantioselective synthesis of compounds **1**−**3** with the (*S*) absolute configuration.

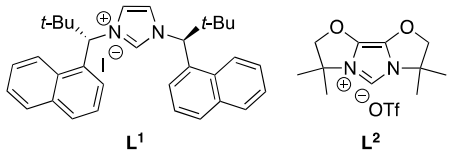
We first searched for the most selective substrate/catalyst combination and prepared model substrates **7a**−**k** lacking the 5′-methyl group of the target molecules (Table 1). The effect of R^1 and R^2 groups on the yield and enantioselectivity was studied with various ligands that were previously employed in enantioselective C(sp^3)−H activation reactions by our group and others (Table S1).[15] Bulky chiral NHCs [NHC = *N*-heterocyclic carbene] developed by Kündig and co-workers[13a,d] were the only tested ligands that provided good yields and significant enantioselectivities for methyl ester **7a** (entry 1). The tested chiral phosphorus ligands including binepines,[11] phosphoramidites,[16] and phosphonites[17] provided low yields and enantioselectivities. Increasing the bulk of the phenol substituent provided a minor improvement (entry 2), which was not judged sufficient in light of the expected cleavage issues at a later stage of the synthesis. Replacing the methyl ester with a nitrile (entry 3) or a *tert*-butyl ester (entry 4) led to decreased yields and enantioselectivities. We then prepared more bulky amide substrates (entries 5−7), which indeed provided better enantioselectivities. However, attempts at hydrolyzing the amide group on products **8e**−**g** were successful only for the least enantioenriched morpholinamide **8g**. Testing other chiral NHCs in the reaction of **7g** failed to improve the enantioselectivity (Table S2). As a consequence, we considered employing chiral proline-derived substrates, which would both be cleavable and provide a cheap source of additional chirality. The L-proline-derived amide **7h** indeed furnished a promising diastereoselectivity of 83:17 (entry 8). Optimizing the ester substituent (entries 10 and 12) led to a further improvement of the diastereoselectivity for isopropyl ester **7i** (entry 10). The D-proline-derived amide **7k** provided a lower dr than its enantiomer **7i** in combination with $\mathbf{L^1}$, indicative of matched−mismatched effects (entry 14). To further dissect the stereochemical induction by the substrate vs the ligand, we tested achiral NHCs, and the most efficient one turned out to be $IBioxMe_4$ ($\mathbf{L^2}$), developed by Glorius and co-workers.[18] This ligand provided lower levels of diastereoselectivity with **7i** (66:34, entry 11) and **7k** (36:64, entry 15) than the combination of **7i** and $\mathbf{L^1}$ (87:13, entry 10). A similar outcome was observed for substrates **7h** and **7j** (entries 8, 9 and 12, 13). Moreover, combining **7k** and $\mathbf{L^1}$ led to a 63:37 ratio in favor of the same major diastereoisomer as from **7i**. These results show that (1) the chiral ligand is able to override the induction by the chiral substrate (entries 14 and 15) and (2) L-prolinamide substrate **7i** and ligand $\mathbf{L^1}$ afford a matched combination. We failed to further increase the stereoselectivity by modifying the substrate, ligand, or reaction conditions. However, motivated by the excellent yield achieved in this step, we planned to perform a recrystallization at a later stage of the synthesis to improve the enantiopurity while preserving a good overall yield for the target molecules. To maximize the efficiency of the crystallization, we chose the double stereoinduction system (**7i**) providing an 87:13 dr against the best cleavable single induction system (**7g**) providing an 80:20 er.

Table 1. Optimization of Reaction Conditions[a]



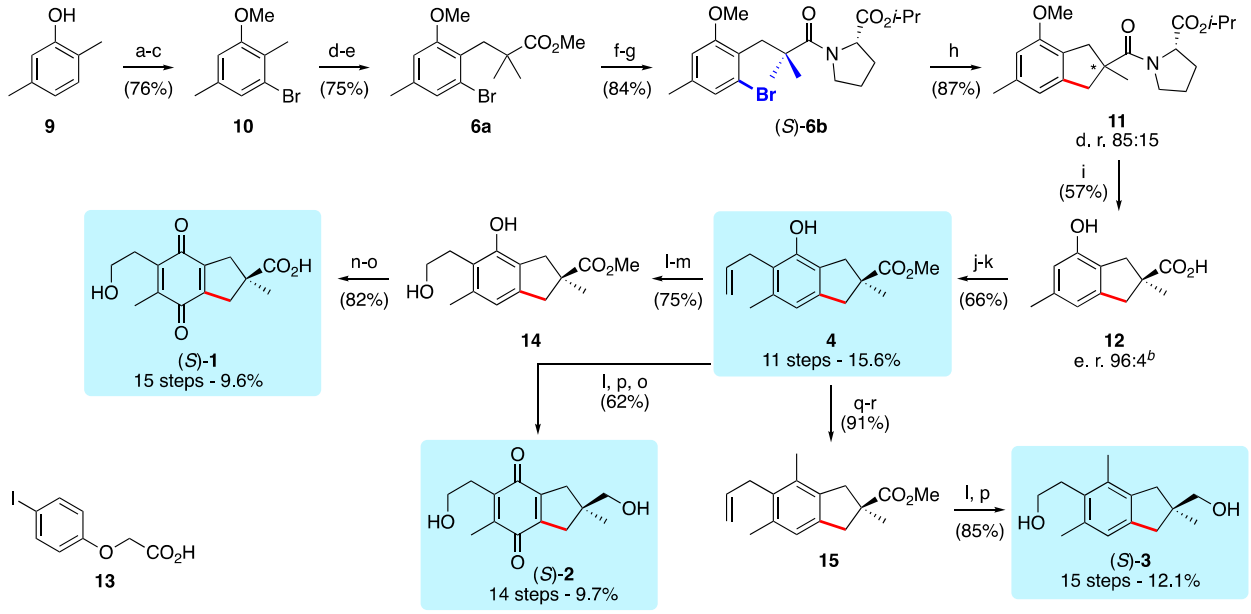
entry	R^1	R^2	NHC	conv. (%)[a,b]	er/dr[c]
1	Me (**7a**)	CO_2Me	$\mathbf{L^1}$	100 (92)	66:34
2	*i*-Pr (**7b**)	CO_2Me	$\mathbf{L^1}$	100 (93)	71:29
3	Me (**7c**)	CN	$\mathbf{L^1}$	10	–
4	Me (**7d**)	CO_2t-Bu	$\mathbf{L^1}$	30	58:42
5	Me (**7e**)	$CONMe_2$	$\mathbf{L^1}$	100 (95)	82:18
6	Me (**7f**)		$\mathbf{L^1}$	100 (95)	85:15
7	Me (**7g**)		$\mathbf{L^1}$	100 (95)	80:20
8	Me (**7h**)		$\mathbf{L^1}$	100 (82)	83:17
9			$\mathbf{L^2}$	100 (65)	64:36
10	Me (**7i**)		$\mathbf{L^1}$	100 (82)	87:13
11			$\mathbf{L^2}$	100 (80)	66:34
12	Me (**7j**)		$\mathbf{L^1}$	100 (84)	83:17
13			$\mathbf{L^2}$	100 (84)	62:38
14	Me (**7k**)		$\mathbf{L^1}$	100 (81)	63:37
15			$\mathbf{L^2}$	100 (82)	36:64

[a]Based on GC/MS analysis. [b]Yield of isolated product **8** in parentheses. [c]Determined by HPLC on a chiral stationary phase.



DOI: 10.1021/acs.orglett.8b04086
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Divergent Synthesis of (*S*)-Puraquinonic Acid, (*S*)-Deliquinone, and (*S*)-Russujaponol[a]



[a]Reagents and conditions: (a) Br_2, $AlBr_3$, CH_2Cl_2, 0 °C; (b) HI aq, reflux; (c) K_2CO_3, MeI, acetone, reflux; (d) *N*-bromosuccinimide, AIBN, CCl_4, reflux; (e) *i*-$PrCO_2Me$, LDA, THF, 0 °C, then aryl bromide, 0 → 20 °C; (f) LiOH aq, THF/MeOH, 80 °C; (g) $(COCl)_2$, DMF cat., CH_2Cl_2, 20 °C, then L-Pro-O*i*-Pr; (h) $[Pd(cinnamyl)Cl]_2$ (5 mol %), $\mathbf{L^1}$ (10 mol %), CsOPiv, Cs_2CO_3, mesitylene, 160 °C; (i) HBr aq, AcOH, reflux, then recrystallization from $CHCl_3/C_6H_{12}$ 3:1; (j) $KHCO_3$, MeI, DMF, 40 °C, then NaH, allyl bromide; (k) $PhNEt_2$, 200 °C; (l) OsO_4 (5 mol %), $NaIO_4$, AcOEt/H_2O, 20 °C; (m) $NaBH_4$, MeOH, 0 °C; (n) LiOH aq, dioxane, reflux; (o) **13** (10 mol %), Oxone, CF_3CH_2OH/H_2O, 20 °C; (p) $LiAlH_4$, THF, 0 → 20 °C; (q) Tf_2O, pyridine, CH_2Cl_2, 0 → 20 °C; (r) $[Pd_2dba_3{\cdot}CHCl_3]$ (2.5 mol %), XPhos (5 mol %), DABCO·$2AlMe_3$, THF, reflux. DABCO = 1,4-diazabicyclo[2.2.2]octane; XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [b]Measured by HPLC on a chiral stationary phase using the racemic compound as reference.

The common intermediate **4**, containing the required additional methyl group on the benzene ring, was then synthesized as described in Scheme 2. Perbromination and selective debromination[19] of commercially available phenol **9** (31 CHF/100 g), followed by phenoxide methylation, afforded aryl bromide **10** on a 50 g scale. Selective radical bromination[20] and enolate alkylation generated **6a**, which was converted to the L-proline-derived C−H activation precursor (*S*)-**6b** in two additional steps. Application of the optimized reaction conditions employing chiral NHC $\mathbf{L^1}$ furnished indane **11** in good yield (87%) and with a slightly diminished dr compared to **8i** lacking the 5′-methyl group (85:15 instead of 87:13). Next, the concomitant prolinamide hydrolysis and methyl ether cleavage were performed with hydrobromic acid in refluxing acetic acid. Slow crystallization from chloroform and cyclohexane provided a greatly improved er of 96:4 for the solid isolated from the mother liquor (57% yield). This ratio was measured after the next step (j) against a racemic sample, which was prepared through a similar synthetic sequence using achiral NHC $\mathbf{L^2}$ as the ligand.[15] The configuration of the major enantiomer of **12** was determined to be (*S*) by vibrational circular dichroism (VCD, Figures S1−S5) and NOESY NMR (Figure S6) analysis of derivatives. To our dismay, and despite numerous efforts, none of the compounds of the whole synthetic sequence or derivatives thereof provided crystals suitable for Xray diffraction analysis. From **12**, sequential selective alkylations of the carboxylic acid and the phenol and aromatic Claisen rearrangement[6b] led to the common intermediate **4** in 66% yield over three steps and good overall yield from phenol **9** (15.6% over 11 steps).

Compound **4** was first converted to (*S*)-puraquinonic acid **1**. Lemieux−Johnson oxidation[21] and reduction of the resulting aldehyde furnished primary alcohol **14**. Previous work by Kraus hinted that the ester hydrolysis should be performed prior to the phenol oxidation.[6b] Indeed, after standard hydrolysis with lithium hydroxide, the phenol oxidation was performed under mild conditions using the catalytic hypervalent iodine reagent reported by Yakura and Konishi[22] to give (*S*)-puraquinonic acid in 82% yield over two steps and 9.6% overall yield over 15 steps from **9**. (*S*)-Deliquinone **2** was obtained in a similar way by Johnson−Lemieux oxidation, reduction of the aldehyde and ester groups with $LiAlH_4$, and phenol oxidation, hence leading to the first enantioselective synthesis of this molecule with an overall yield of 9.7% over 14 steps. Finally, (*S*)-russujaponol F (**3**) was synthesized in four steps from **4** starting with triflation and Pd^0-catalyzed cross-coupling with the air-stable DABCO-trimethylaluminum complex introduced by Woodward and co-workers,[23] which furnished indane **15** in 85% yield. Lemieux−Johnson oxidation and ester reduction completed the synthesis of (*S*)-**3** in 15 steps, 11.6% overall yield from phenol **9**. Of note, the racemic natural products were also synthesized according to a similar pathway involving the C−H activation of **6a** in the presence of achiral NHC $\mathbf{L^2}$.[15] This sequence avoiding the formation of prolinamide **6b** led to racemic targets **1**−**3** in two steps fewer (12 overall for **2** and 13 for **1** and **3**).

The specific rotations of the synthetic products **1**−**3** were found to be +1.4, +0.9 ,and +2.1, respectively. The reported specific rotations of the natural products in the same solvents are −2.2 for (*R*)-**1**,[5a,b] −0.5 for (*R*)-**2**,[2] and +1.3 for (*S*)-**3**.[3] Hence, our values are consistent with (*S*) enantiomers for the three final products. This assignment was confirmed by the

DOI: 10.1021/acs.orglett.8b04086
Org. Lett. XXXX, XXX, XXX−XXX

above-mentioned VCD and NMR analyses.[15] Hence, we have synthesized natural russujaponol F (**3**) and the antipodes of natural puraquinonic acid (**1**) and deliquinone (**2**).

In conclusion, a divergent enantioselective synthesis of (nor)illudalane sesquiterpenes was designed by using a Pd^0-catalyzed asymmetric $C(sp^3)$−H arylation as the key step. This first application of such reaction in natural product synthesis demonstrates its great potential to construct isolated quaternary stereocenters in complex molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04086.

Supplementary tables and figures; procedural and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: olivier.baudoin@unibas.ch.

ORCID

Thomas Bürgi: 0000-0003-0906-082X

Olivier Baudoin: 0000-0002-0847-8493

Author Contributions

§R.M. and M.V.C. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the University of Basel and Fundação de Amparo à Pesquisa do Estado de São Paulo, Brazil (FAPESP - process 2016/22636-2). We thank A. Huber, University of Basel, for preparative work, Dr. D. Häussinger, University of Basel, for assistance with NMR experiments, S. Mittelheisser, Dr. H. Nadig, and Dr. M. Pfeffer, University of Basel, for MS analyses, and Prof. Dr. E. P. Kündig, University of Geneva, for a gift of chiral NHC ligand.

■ REFERENCES

(1) Becker, U.; Erkel, G.; Anke, T.; Sterner, O. *Nat. Prod. Lett.* **1997**, *9*, 229.

(2) Clericuzio, M.; Han, F.; Pan, F.; Pang, Z.; Sterner, O. *Acta Chem. Scand.* **1998**, *52*, 1333.

(3) Yoshikawa, K.; Kaneko, A.; Matsumoto, Y.; Hama, H.; Arihara, S. *J. Nat. Prod.* **2006**, *69*, 1267.

(4) Prusov, E. V. *Angew. Chem., Int. Ed.* **2017**, *56*, 14356.

(5) (a) Clive, D. L. J.; Yu, M. *Chem. Commun.* **2002**, 2380. (b) Clive, D. L. J.; Yu, M.; Sannigrahi, M. *J. Org. Chem.* **2004**, *69*, 4116. (c) Tiong, E. A.; Rivalti, D.; Williams, B. M.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 3442.

(6) In addition, racemic **1** was synthesized in 15 steps: (a) Hisaindee, S.; Clive, D. L. J. *Tetrahedron Lett.* **2001**, *42*, 2253. Racemic **2** was synthesized in 10 steps: (b) Kraus, G. A.; Choudhury, P. K. *J. Org. Chem.* **2002**, *67*, 5857.

(7) Arpin, A.; Manthorpe, J. M.; Gleason, J. L. *Org. Lett.* **2006**, *8*, 1359.

(8) Baudoin, O. *Acc. Chem. Res.* **2017**, *50*, 1114.

(9) Leading reviews on catalytic enantioselective C−H activation: (a) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. *Chem. Rev.* **2017**, *117*, 8908. (b) Saint-Denis, T. G.; Zhu, R.-Y.; Chen, G.; Wu, Q.-F.; Yu, J.-Q. *Science* **2018**, *359*, 759.

(10) For recent reviews on catalytic enantioselective methods to construct quaternary stereocenters, see: (a) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181. (b) Zeng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330.

(11) (a) Martin, N.; Pierre, C.; Davi, M.; Jazzar, R.; Baudoin, O. *Chem. - Eur. J.* **2012**, *18*, 4480. (b) Holstein, P. M.; Vogler, M.; Larini, P.; Pilet, G.; Clot, E.; Baudoin, O. *ACS Catal.* **2015**, *5*, 4300.

(12) (b) Yang, L.; Melot, R.; Neuburger, M.; Baudoin, O. *Chem. Sci.* **2017**, *8*, 1344.

(13) See also: (a) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438. (b) Anas, S.; Cordi, A.; Kagan, H. B. *Chem. Commun.* **2011**, *47*, 11483. (c) Saget, T.; Lemouzy, S. J.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 2238. (d) Larionov, E.; Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Chem. Sci.* **2013**, *4*, 1995.

(14) (a) Dailler, D.; Danoun, G.; Baudoin, O. *Top. Organomet. Chem.* **2015**, *56*, 133. (b) Brady, P. B.; Bhat, V. *Eur. J. Org. Chem.* **2017**, *2017*, 5179.

(15) See the Supporting Information for details.

(16) (a) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 12842. (b) Pedroni, J.; Cramer, N. *Angew. Chem., Int. Ed.* **2015**, *54*, 11826. For a review, see: (c) Pedroni, J.; Cramer, N. *Chem. Commun.* **2015**, *51*, 17647.

(17) Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 9064.

(18) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195.

(19) Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.* **1991**, *56*, 2289.

(20) Hirano, Y.; Tokudome, K.; Takikawa, H.; Suzuki, K. *Synlett* **2017**, *28*, 214.

(21) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(22) Yakura, T.; Konishi, T. *Synlett* **2007**, *2007*, 765.

(23) Cooper, T.; Novak, A.; Humphreys, L. D.; Walker, M. D.; Woodward, S. *Adv. Synth. Catal.* **2006**, *348*, 686.

DOI: 10.1021/acs.orglett.8b04086
Org. Lett. XXXX, XXX, XXX−XXX