ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

pubs.acs.org/OPRD

Communication

The Impact of Solvent Quality on the Heck Reaction: Detection of Hydroperoxide in 1-Methyl-2-pyrrolidinone (NMP)

Qiaogong Su* and Hayao Matsuhashi

Cite This: https://dx.doi.org/10.1021/acs.oprd.0c00432

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Unexpected failures of a Heck reaction in the lab led to the detection of 5-hydroperoxy-1-methyl-2-pyrrolidinone (NMP-5-OOH) in the cosolvent 1-methyl-2-pyrrolidinone (NMP). This hydroperoxide, formed by autoxidation in the presence of air, oxidized the ligand tri(*o*-tolyl)phosphine (P(*o*-tol)$_3$) to tri(*o*-tolyl)phosphine oxide (O=P(*o*-tol)$_3$) and ultimately slowed down the Heck reaction. Because of this finding, control strategies were implemented for NMP quality and air exclusion during manufacturing campaigns, which ensured delivery of metric tons of compound **2** en route to Ronacaleret Hydrochloride used in clinical studies. Similar detrimental impact of NMP-5-OOH to the ligand-free Heck reaction was also demonstrated.

KEYWORDS: *Heck reaction, 1-methyl-2-pyrrolidinone, NMP, 5-hydroperoxy-1-methyl-2-pyrrolidinone, NMP-5-OOH*

The Heck (also known as the Mizoroki−Heck) reaction, the palladium-catalyzed arylation or alkenylation of olefins, has become one of the most important carbon−carbon bond-forming methods in synthetic organic chemistry. Since its discovery in the early 1970s,[1] it has found increasing applications in syntheses of natural products and active pharmaceutical ingredients (APIs) because of its tolerance toward a wide range of functional groups and high stereoselectivity.[2] Phosphine ligands are usually required to stabilize the active palladium species for less reactive bromides and chlorides. 1-Methyl-2-pyrrolidinone (NMP) has been a commonly used solvent for palladium-catalyzed cross-coupling reactions including Heck reaction, presumably because of its good solubility for organic compounds and high boiling point.

The Heck reaction of bromide **1** with ethyl acrylate to produce ethyl cinnamate **2** was a crucial step in the final synthetic route of Ronacaleret Hydrochloride, a potent and selective calcium sensing receptor antagonist in development as an oral anabolic agent for the treatment of osteoporosis and fracture healing (Scheme 1).[3]

The optimized reaction conditions employed 0.5 mol % of Pd(OAc)$_2$ and 1.5 mol % of P(*o*-tol)$_3$ using toluene as solvent (3 vol) with NMP (0.75 vol) as the cosolvent to increase the solubility of the starting material. The reaction was typically complete in 2−3 h at 95 °C with less than 0.5% area of **1** left by HPLC if sufficient N_2 purge of the reaction mixture was performed prior to the addition of ethyl acrylate and heating of the reaction. However, at one point during process development, we were plagued by reaction failures in the lab; the reactions were slower than normal and sometimes stalled even with stringent N_2 purges and low O_2 levels which had been previously demonstrated to be tolerable. With the aim to produce metric tons of **2** via this Heck reaction in the manufacturing plant, a detailed investigation to probe the source of the problem was carried out.

First, it was found that the HPLC of these slow reactions showed a higher amount of O=P(*o*-tol)$_3$ than normally observed. A thorough examination of the reaction inputs soon identified that the old bottle of NMP used in the reaction was the root cause. Over time, NMP had reacted with O_2 in the air to form 5-hydroperoxy-1-methylpyrrolidinone (NMP-5-OOH, Scheme 2) which could be detected by ^{1}H NMR and LCMS. This hydroperoxide oxidized the P(*o*-tol)$_3$ ligand to O=P(*o*-tol)$_3$ and ultimately slowed down the Heck reaction.

It is known that oxidation of *N*-alkyl- and *N,N*-dialkylamides takes place at the carbon adjacent to the nitrogen; because the amide has a very weak basic nitrogen donor site, formation of the corresponding *N*-oxide is less likely.[4a] Lactams such as NMP can be oxidized at the ring methylene group α to the amide nitrogen.[5] Drago's group first reported the generation of NMP-5-OOH by direct reaction of NMP and O_2 at 75 °C and 50 psig.[4] They also demonstrated the ability of NMP-5-OOH to oxidize PPh_3 to O=PPh_3 and conducted ^{13}C and ^{31}P NMR studies which indicated that the oxygen-atom transfer occurs via nucleophilic attack of the substrate on the peroxide to generate 5-hydroxy-1-methyl-2-pyrrolidinone (NMP-5-OH). In the presence of O_2, NMP-5-OH is rapidly converted to *N*-methylsuccinimide (NMS, Scheme 2).[4b]

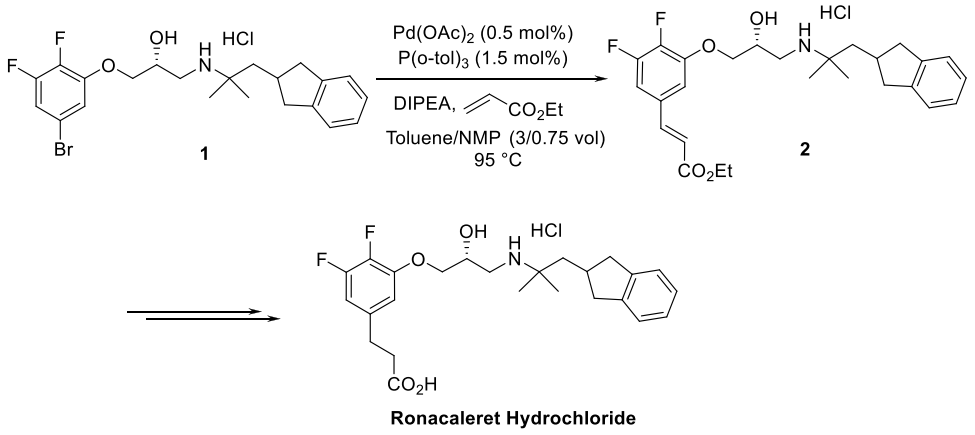
If a new bottle of NMP with undetectable hydroperoxide was not kept under N_2 after opening, the amount of NMP-5-OOH reached 0.1 mol % after 1 month (Table 1, entries 1 and 2). The hydroperoxide amount was calculated based on the ^{1}H NMR analysis by comparing the integral of the peroxide proton (δ 12.10) or the proton α to both nitrogen and oxygen (δ 4.80) with that of the *N*-Me protons in NMP (Figure 1). When an old bottle of NMP had been used for 5 months in the

Special Issue: Celebrating Women in Process Chemistry

Received: September 28, 2020

https://dx.doi.org/10.1021/acs.oprd.0c00432
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 1. Heck Reaction Using NMP as the Cosolvent in the Synthesis of Ronacaleret Hydrochloride



Scheme 2. Formation of NMP-5-OOH and the Subsequent Oxidation of Substrate

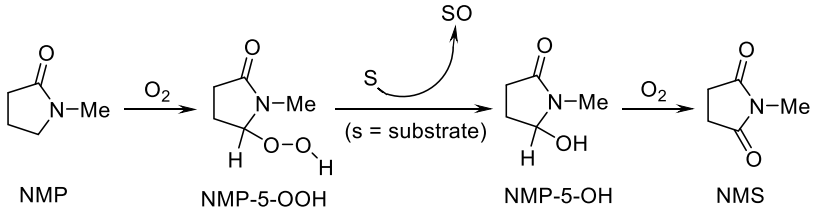


Table 1. Treatment of P(*o*-tol)$_3$ with NMP Containing Different Levels of NMP-5-OOH

Entry	Time since NMP bottle opened	NMP-5-OOH content in NMP (mol %)	O=P(*o*-tol)$_3$/P(*o*-tol)$_3$ (% area/% area by HPLC[a])
1	new	not detected	4:96
2	1 month	0.1	8:92
3	5 months	0.46	100:0
4	(no NMP used)	–	4:96

[a]After 2.5 h at 95 °C.

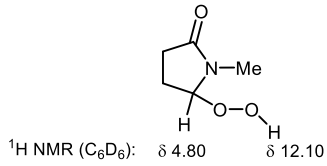


Figure 1. ^{1}H NMR detection of NMP-5-OOH in NMP.

lab without N_2 purging after each use, 0.46 mol % of NMP-5-OOH was detected (Table 1, entry 3). Based on the calculations,[6] when 0.75 volume of this old NMP was applied in the above Heck reaction, 1.8 mol % of NMP-5-OOH would be present, and this amount exceeded the 1.5 mol % of P(*o*-tol)$_3$ ligand employed in the reaction, indicating that all P(*o*-tol)$_3$ ligand used in the Heck reaction could potentially be oxidized to O=P(*o*-tol)$_3$.

The fourth column in Table 1 entries 1−3 shows the experimental results of treating P(*o*-tol)$_3$ in toluene with the new and old bottles of NMP under the Heck reaction conditions illustrated in Scheme 1, but without charging **1**, Pd(OAc)$_2$, Hünig's base (DIPEA), or ethyl acrylate. As expected, P(*o*-tol)$_3$ was completely oxidized to O=P(*o*-tol)$_3$ in the reaction with the NMP containing 0.46 mol % of NMP-5-OOH (entry 3), in agreement with the above-mentioned calculations.[6] Interestingly, the reaction with the new bottle of NMP still gave 4% area of O=P(*o*-tol)$_3$ (entry 1), and the same result was generated when no NMP was used (entry 4); this oxidation was probably caused by the small amount of O_2 presented in the reaction.[7]

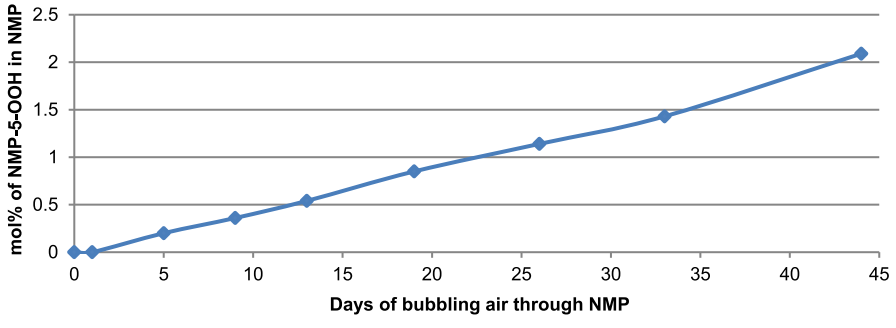
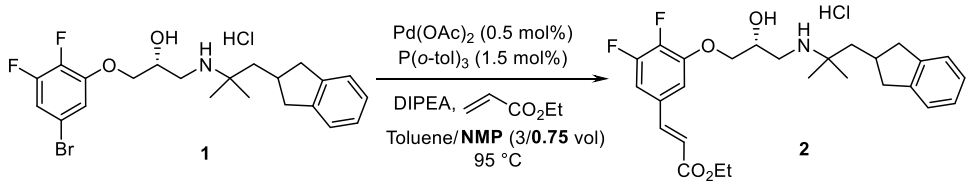


Figure 2. NMP-5-OOH generated by bubbling air through NMP at room temperature.

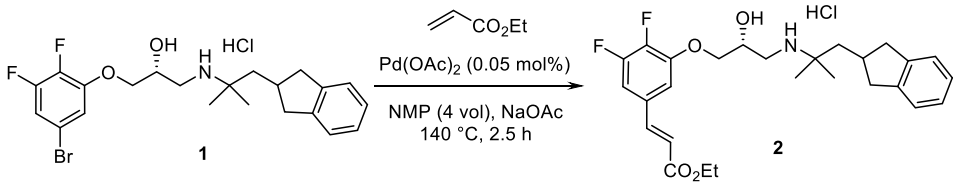
https://dx.doi.org/10.1021/acs.oprd.0c00432
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 3. Impact of NMP-5-OOH on the Heck Reaction with P(*o*-tol)$_3$ Ligand



NMP	reaction time (hours)	unreacted **1** (% area)
New bottle (no NMP-5-OOH)	2	<0.2
Old bottle (0.46 mol% NMP-5-OOH)	2	15
Old bottle (0.46 mol% NMP-5-OOH)	5	5
Old bottle (0.46 mol% NMP-5-OOH)	21	1

Scheme 4. Impact of NMP-5-OOH on the Ligand-Free Heck Reaction



NMP	unreacted **1** (% area)	solution yield of **2** (% yield)
New NMP (no NMP-5-OOH)	0.4	93
Old NMP (0.46 mol% NMP-5-OOH)	9.0	52

Drago et al. had reported formation of 2 M of NMP-5-OOH in NMP under 50 psig O_2 at 75 °C after 72 h, which was equal to 19 mol % of NMP-5-OOH in NMP.[4a] To see how fast the hydroperoxide can be produced at room temperature, we bubbled air through NMP (150 mL) for a period of time and monitored the level of the hydroperoxide by ^{1}H NMR. The experiment indicated an induction period of at least 24 h since no hydroperoxide was detected after 1 day, and then it gradually increased to 2.1 mol % at the end of the 44-day study period (Figure 2).

The effect of NMP-5-OOH on the above Heck reaction can be profound. For example, on a 20 g scale, when a new bottle of NMP was used, the Heck reaction was complete in 2 h at 95 °C with less than 0.2% area of residual starting material **1** based on HPLC monitoring. However, when the NMP containing 0.46 mol % of the hydroperoxide was used, 15% area of **1** still remained after 2 h, and the reaction could not reach the same level of completion (<0.2% area of **1**) even after an extended reaction time. There were 5% and 1% area of unreacted **1** after 5 and 21 h, respectively. So only 4% area of further conversion was observed over the last 16 h (Scheme 3).

To circumvent the slow Heck reaction caused by NMP-5-OOH, it was found in the lab that one can either increase the phosphine loading to 3.5 mol % or charge 0.5 equiv of additive Bu_4NBr at the beginning of the reaction. Both conditions gave complete reactions in 2 h using NMP containing 0.46 mol % of NMP-5-OOH.[8] The latter experiment was based on the work by Jeffery who found that quaternary ammonium salts could stabilize the palladium catalyst during Heck reactions without phosphine ligand.[9] While we did not apply increased amount of phosphine ligand or addition of quaternary ammonium salts to reduce the risk of slow reaction due to accidental contamination of NMP-5-OOH, these measures could be considered as a potential risk mitigation to improve reaction robustness.

In the end, to ensure a successful process in the manufacturing plant, ^{1}H NMR analysis of the NMP was implemented prior to the plant campaign to make sure no NMP-5-OOH was present. A drum isolator was used during solvent charging to ensure the operation was under N_2, and a thorough N_2 purge of the initial reaction content was performed.

NMP-5-OOH not only negatively impacts the Heck reaction by oxidizing the phosphine ligand, but it could also oxidize the active Pd(0) species leading to reaction failure.[10] To test this, we compared the ligand-free Heck reaction using the new and the old bottle of NMP on a 1 g scale (Scheme 4). The results were convincing; in the presence of 0.46 mol % of NMP-5-OOH, the reaction was much slower with 9% area vs 0.4% area of **1** left after 2.5 h at 140 °C, and the HPLC solution yield of product **2** dropped dramatically (52% vs 93%).[11]

In conclusion, a small amount of NMP-5-OOH formed in NMP was identified as the root cause for slow or failed Heck reactions in the lab. Because of this finding, we took careful note of the quality of NMP and implemented stringent measures to protect it from air. These efforts led to reproducible lab results, better controlled plant runs, and successful delivery of compound **2** for supplying Ronacaleret Hydrochloride clinical studies. While NMP is a common solvent for Heck reactions with or without ligand, our study has shown that NMP-5-OOH in NMP can lead to reaction failure by oxidizing the phosphine ligand and also potentially oxidizing the active Pd(0) species in the Heck reaction. It would not be surprising to see similar detrimental impact of NMP-5-OOH on other Pd(0) catalyzed reactions; hence, it would be worth paying close attention to the quality of NMP regarding the formation of NMP-5-OOH. This risk can be mitigated by simply using a new bottle of NMP, storing it under nitrogen, analyzing for the hydroperoxide prior to use, and discarding opened bottles within 1 year.[12]

https://dx.doi.org/10.1021/acs.oprd.0c00432
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

EXPERIMENTAL SECTION

General Information. All solvents and reagents were obtained from commercial sources and used as they were received. The melting point was measured in a Mettler Toledo MP 90 Melting Point System at a 3 °C/min ramp, and the result was not corrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer, and chemical shifts (δ) are reported in parts per million (ppm), with multiplicities abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets. Residual solvent signals were used as references. HRMS (m/z) was measured using a LTQ Discovery Orbitrap (Thermo) mass spectrometer equipped with a heated electrospray ionization (HESI) ion source.

*(R,E)-Ethyl 3-(3-(3-((1-(2,3-Dihydro-1H-inden-2-yl)-2-methylpropan-2-yl)amino)-2-hydroxypropoxy)-4,5-difluorophenyl)acrylate Hydrochloride (**2**). Method A (Schemes 1 and 3). Heck Reaction with Ligand P(o-tol)$_3$.* A mixture of (*R*)-1-(5-bromo-2,3-difluorophenoxy)-3-((1-(2,3-dihydro-1*H*-inden-2-yl)-2-methylpropan-2-yl)amino)propan-2-ol hydrochloride (**1**) (150.0 kg, 305.6 mol), toluene (450 L), NMP (113 L), and *N*,*N*-diisopropylethylamine (DIPEA) (99.0 kg, 764.0 mol) was stirred at 20 °C and degassed by bubbling nitrogen through for at least 1 h. Tri(*o*-tolyl)phosphine (1.395 kg, 4.58 mol) and $Pd(OAc)_2$ (0.343 kg, 1.53 mol) were added. The headspace of the reactor was degassed by evacuating and refilling with nitrogen for three cycles. Ethyl acrylate (**carcinogenic!** 42.8 kg, 427.8 mol) was added followed by setting the reactor's nitrogen flow to 1−2 SCFM for at least 5 min. The reaction was slowly heated to 94−99 °C and stirred for 2 h. After the reaction was deemed complete by HPLC monitoring, the mixture was cooled to 50−60 °C, and H_2O (375 L) was added. After being stirred for 15 min, the mixture was filtered through Celite and washed with 50 °C toluene (225 L). The layers were separated, and 15% w/w aqueous HCl (450 L) was added slowly to the organic layer at 45−55 °C. The layers were separated after stirring for 15 min, and H_2O (22.5 L) was added slowly to the organic layer at 45−55 °C. The reaction mixture was cooled slowly to 20−40 °C and aged for 30 min after crystallization began. The resulting slurry was cooled slowly to 5−10 °C, and filtered and washed with cold TBME (450 L). To the wet cake was then added EtOH (375 L). The mixture was heated to 25−60 °C to dissolve the solid and then charged with H_2O (300 L) while maintaining the solution temperature at 40−45 °C. The reaction mixture was cooled to 30−35 °C, seeded with **2** (15.0 g), and aged for 30 min after the solid began to form. The slurry was cooled to 3−7 °C, filtered, and washed with TBME (450 L). The product was dried under vacuum at 40−45 °C to afford **2** (138.5 kg, 271.8 mol, 89% yield) as a white solid: mp. 156.4 °C. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.93 (m, 1H), 8.58 (m, 1H), 7.60 (d, J = 16.1 Hz, 1H), 7.50−7.52 (m, 2H), 7.18 (m, 2H), 7.10 (m, 2H), 6.78 (d, J = 16.1 Hz, 1H), 5.97 (d, J = 4.5 Hz, 1H), 4.20−4.29 (m, 5H), 3.20 (m, 1H), 3.09 (dd, J = 14.3, 7.0 Hz, 2H), 2.98 (m, 1H), 2.60 (m, 1H), 2.56 (m, 1H), 1.97 (d, J = 5.5 Hz, 2H), 1.40 (s, 6H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 166.4 (s, 1C), 150.6 (dd, J = 244.5, 11.1 Hz, 1C), 148.4 (dd, J = 8.0, 4.0 Hz, 1C), 143.2 (s, 2C), 143.2 (s, 1C), 141.5 (dd, J = 250.5, 14.1 Hz, 1C), 131.1 (dd, J = 9.1, 5.0 Hz, 1C), 126.6 (s, 2C), 124.4 (s, 2C), 120.3 (s, 1C), 111.0 (s, 1C), 109.9 (d, J = 18.1 Hz, 1C), 71.8 (s, 1C), 65.8 (s, 1C), 60.6 (s, 1C), 60.1 (s, 1C), 44.2 (s, 1C), 43.1 (s, 1C), 40.9 (s, 2C), 35.9 (s, 1C), 23.8 (s, 2C), 14.6 (s, 1C). HRMS (ESI) m/z calcd for C27H34F2NO4 (free base MH^+), 474.2450; found, 474.2449.

Method B. Ligand-Free Heck Reaction (Scheme 4). A mixture of (*R*)-1-(5-bromo-2,3-difluorophenoxy)-3-((1-(2,3-dihydro-1*H*-inden-2-yl)-2-methylpropan-2-yl)amino)propan-2-ol hydrochloride (**1**) (1.0 g, 2.04 mmol), NMP (4.0 mL), and sodium acetate (0.2 g, 2.44 mmol) was stirred at 20 °C and degassed by slowly bubbling nitrogen for 5 min. Ethyl acrylate (**carcinogenic!** 0.27 mL, 2.44 mmol) was added, followed by $Pd(OAc)_2$ (0.23 mg, 0.0010 mmol, charged by taking 0.5 mL of a premade solution of $Pd(OAc)_2$ in NMP with 0.46 mg/mL concentration). The reaction was slowly heated to 140 °C and stirred for 2.5 h, and a sample was taken for HPLC to monitor the reaction progress. The reaction was then cooled to room temperature, filtered through filter paper, and washed with 3 mL of EtOAc. The resulting solution was analyzed for the solution yield.

*Study of the Oxidation of P(o-tol)$_3$ with NMP-5-OOH Presented in NMP (Table 1); the Amounts of Solvents and P(o-tol)$_3$ Charged Were Calculated Based on a Heck Reaction for 2 g of **1** (Scheme 1).* To four vials each containing a stir bar were charged toluene (6 mL), NMP with different levels of NMP-5-OOH (1.5 mL, except in the fourth vial no NMP was added), and P(*o*-tol)$_3$ (18.6 mg). Each reaction was bubbled with N_2 for 5 min at room temperature, and then capped and heated to 98 °C. Samples were taken for HPLC testing after 2.5 h.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00432.

Copies of ^{1}H and ^{13}C NMR spectra for **1**; ^{1}H NMR monitoring of NMP-5-OOH generated by bubbling air through NMP; LCMS detection of NMP-5-OOH (PDF)

AUTHOR INFORMATION

Corresponding Author

Qiaogong Su − *Chemical Development, GlaxoSmithKline, Collegeville, Pennsylvania 19426, United States;* orcid.org/0000-0002-3127-4309; Email: qiaogong.su@gsk.com

Author

Hayao Matsuhashi − *Chemical Development, GlaxoSmithKline, Collegeville, Pennsylvania 19426, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.0c00432

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank Mark Bokhart for HRMS determination, Alan Freyer for NMR analysis, and Michael Liangmin Wu (deceased) for LCMS determination.

https://dx.doi.org/10.1021/acs.oprd.0c00432
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

REFERENCES

(1) (a) Mizoroki, T.; Mori, K.; Ozaki, A. Arylation of Olefin with Aryl Iodide Catalyzed by Palladium. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P. Palladium-catalyzed Vinylic Hydrogen Substitution Reactions with Aryl, Benzyl, and Styryl Halides. *J. Org. Chem.* **1972**, *37*, 2320. (c) Heck, R. F. Palladium-Catalyzed Vinylation of Organic Halides. *Organic Reactions* **1982**, *27*, 345.

(2) (a) Seechurn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-catalyzed Cross-coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062. (b) Roy, D.; Uozumi, Y. Recent Advances in Palladium-Catalyzed Cross-Coupling Reactions at ppm to ppb Molar Catalyst Loadings. *Adv. Synth. Catal.* **2018**, *360*, 602. (c) Beletskaya, I. P.; Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **2000**, *100*, 3009. (d) Bollikonda, S.; Mohanarangam, S.; Jinna, R. R.; Kandirelli, V. K. K.; Makthala, L.; Sen, S.; Chaplin, D. A.; Lloyd, R. C.; Mahoney, T.; Dahanukar, V. H.; Oruganti, S.; Fox, M. E. An Enantioselective Formal Synthesis of Montelukast Sodium. *J. Org. Chem.* **2015**, *80*, 3891. (e) Daves, G. D., Jr.; Hallberg, A. 1,2-Additions to heteroatom-substituted olefins by organopalladium reagents. *Chem. Rev.* **1989**, *89* (7), 1433.

(3) (a) Trivedi, R.; Mithal, A.; Chattopadhyay, N. Pharmacological Manipulation of Calcium-Sensing Receptor: Prospect as Anabolic Therapy for Postmenopausal Osteoporosis. *Drugs Future* **2009**, *34*, 803. (b) Marquis, R. W., Jr.; Ramanjulu, J. M.; Casillas, L. N. Preparation of Acyloxy-amino-functionalized-aromatic Carboxy Compounds as Calcilytic Compounds Useful Against Bone and Mineral Diseases. *PCT Int. Appl.*, WO 2005077886, August 25, 2005. (c) Marquis, R. W.; Casillas, L. N.; Ramanjulu, J. M.; Callahan, J. F. Preparation of Phenylalkanoic Acids as Calcilytic Compounds. *PCT Int. Appl.*, WO 2004047751, June 10, 2014.

(4) (a) Drago, R. S.; Riley, R. Oxidation of *N*-Alkylamides to Novel Hydroperoxides by Dioxygen. *J. Am. Chem. Soc.* **1990**, *112*, 215. (b) Patton, D. E.; Drago, R. S. Regenerable *N*-Alkylamide Hydroperoxide for Catalytic Substrate Oxidation. *J. Chem. Soc., Perkin Trans. 1* **1993**, *14*, 1611.

(5) (a) Needles, H. L.; Whitfield, R. E. Free-Radical Chemistry of Peptide Bonds. II. Conversion of Lactams to Imides. *J. Org. Chem.* **1966**, *31*, 341. (b) Doumaux, A. R.; McKeon, J. E.; Trecker, D. J. The Metal Ion Catalyzed Peroxide Oxidation of Organic Substrates. A Selective Synthesis of Imides. *J. Am. Chem. Soc.* **1969**, *91*, 3992.

(6) For example, the Heck reaction with 1 g (2.037 mmol) of starting material **1** (molecular weight 490.8) would employ 0.75 mL (0.771 g, 7.78 mmol) of NMP (density 1.028 g/mL, molecular weight 99.133 g/mol). So for the old bottle of NMP containing 0.46 mol% of NMP-5-OOH, the hydroperoxide amount presented in the 0.75 mL NMP was 0.0358 mmol which is 1.8 mol% compared to **1** (2.037 mmol), exceeding the 1.5 mol% of $P(o\text{-tol})_3$ ligand used in the Heck reaction.

(7) Buckler, S. A. Autoxidation of Trialkylphosphines. *J. Am. Chem. Soc.* **1962**, *84*, 3093.

(8) We did not test any mild reductant which could react with NMP-5-OOH before addition of the phosphine and starting the Heck reaction.

(9) Jeffery, T.; David, M. [Pd/Base/QX] Catalyst Systems for Directing Heck-type Reactions. *Tetrahedron Lett.* **1998**, *39*, 5751.

(10) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. Ligand-Promoted Palladium-Catalyzed Aerobic Oxidation Reactions. *Chem. Rev.* **2018**, *118*, 2636.

(11) The reaction was very messy in the presence of 0.46 mol% of NMP-5-OOH, with an increased amount of the double Heck impurity, formed by a Heck reaction involving **1** and the product **2**, as the major impurity. The ligand-free Heck reaction to prepare **2** was not as clean as the Heck reaction with $P(o\text{-tol})_3$; therefore, it was not used in the manufacturing process.

(12) As a peroxide-forming solvent, NMP should be checked for the presence of any peroxide before distillation or evaporation. In our laboratories, any potential peroxide-forming solvent must be labeled with the date of opening and disposed after 6 months. For more information on general handling and use guidelines for peroxidizable solvents, please see: (a) Kelly, R. J. Review of Safety Guidelines for Peroxidizable Organic Compounds. *Chem. Health Saf.* **1996**, *3* (5), 28−36. (b) Clark, D. E. Peroxides and Peroxide-Forming Compounds. *Chem. Health Saf.* **2001**, *8* (5), 12−22.

https://dx.doi.org/10.1021/acs.oprd.0c00432
Org. Process Res. Dev. XXXX, XXX, XXX−XXX