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Pd-Catalyzed Selective Chlorination of Acrylamides at Room Temperature

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02750 Read Online

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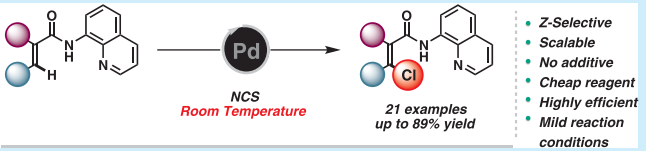
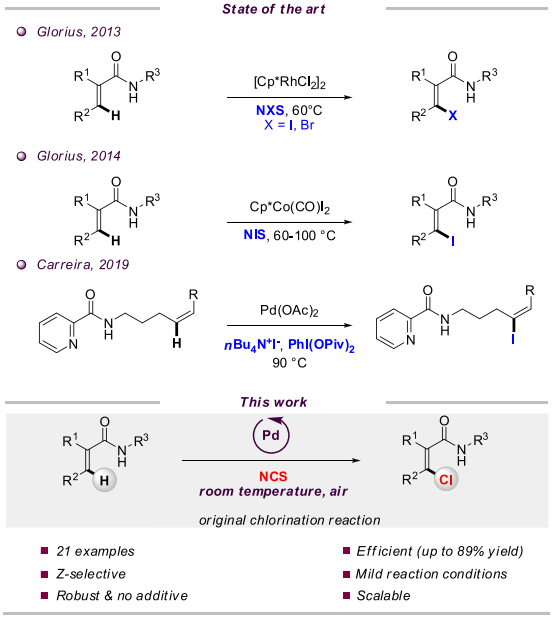
ABSTRACT: In this Letter, the transition-metal-catalyzed chlorination of alkenes is reported. In the presence of the commercially available and inexpensive *N*-chlorosuccinimide and without additive, the Pd-catalyzed chlorination of acrylamides by C−H bond activation was developed at room temperature under air. Under these mild reaction conditions, the versatility of the methodology was demonstrated as an array of acrylamides was functionalized to selectively provide the corresponding difficult-to-synthesize chlorinated olefins as a single Z stereoisomer. Mechanistic studies were conducted to get insights into the reaction mechanism, and post-functionalization reactions further demonstrated the synthetic utility of the approach toward the access to high value-added chlorinated compounds.



Chlorinated molecules are widely present in compounds of interest such as pharmaceuticals, agrochemicals, and natural products.[1] In particular, halogenation of aromatic derivatives is at the forefront of innovation because they have widespread applications in organic chemistry. Therefore, the development of novel methods to access them has attracted strong interest from the scientific community.[2] Among them, special attention has been paid to the transition-metal-catalyzed halogenation of aromatic derivatives by C−H bond activation with I, Br, and Cl atoms.[3] Indeed, transition-metal-catalyzed C−H bond functionalizations have completely reshaped the field of organic chemistry.[4] This straightforward tool for molecular synthesis has further opened the chemical space, enabling applications to various fields.[5] In particular, the transition-metal-catalyzed directed functionalization of the more challenging vinylic derivatives by C−H bond activation has been well studied over the years, offering straightforward and selective access to the difficult-to-synthesize *Z* isomer.[6] In sharp contrast, the halogenation of vinylic derivatives by C−H bond activation[6] still remains restricted to a handful of examples and requires further investigation as it offers selective access to the challenging and ubiquitous *Z*-olefinic moiety. The quest for efficient and selective tools toward *Z*-olefins is of high importance because this scaffold might be found in several bioactive compounds, such as Selinexor.

In the realm of the transition-metal-catalyzed halogenation of olefins by C−H activation, bromination and iodination reactions have been mainly studied using various transition-metal catalysts and have led to major contributions. In 2013, Glorius reported the Rh(III)-catalyzed bromination and iodination of acrylamides,[7] and one year later, they depicted the iodination of acrylamides[8] via a Cp*Co(III) catalysis. In 2019, Carreira described the Pd-catalyzed iodination of unactivated olefins using picolamide as a directing group (Scheme 1).[9] However, the direct and regioselective synthesis of *Z*-chlorinated acrylic acid derivatives is still elusive despite the

Scheme 1. State of the Art and Present Work



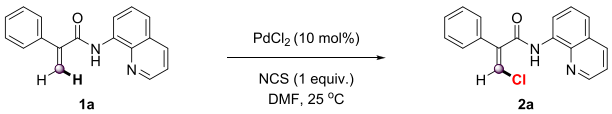
Received: August 17, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02750
Org. Lett. XXXX, XXX, XXX−XXX

clear interest in the corresponding vinyl chloride compounds.[1] Therefore, the elaboration of a new synthetic approach toward these chlorinated molecules represents a significant challenge in modern organic chemistry and is still an unmet goal. To date, the existing methods to synthesize *Z*-*β*-chloroacrylic acid derivatives generally rely on a Vilsmeier−Haack reaction,[10] a Wittig reaction,[11] a chloropalladation/Heck reaction sequence,[12] chlorination of propagyl alcohols,[13] as well as hydrochlorination,[14] chloroacylation,[15] and chlorocarbonylation[16] reactions of alkynes, among others. A lack of *E*/*Z* selectivity and the need to have the proper alkynes are the main synthetic limitations of these methods that need to be overcome. In addition, to meet the continuous demand for more sustainable transformations, the development of C−H activation reactions under mild conditions (no additives, room temperature) is still highly desirable. Keeping these considerations in mind and pursuing our current interest in the functionalization of vinylic derivatives by C−H bond activation,[17] we report herein the unprecedented Pd(II)-catalyzed chlorination of various *α*- and *α*,*β*-substituted acrylamide derivatives at room temperature.

At the outset of the study, the Pd-catalyzed chlorination of the *α*-phenylacrylamide **1a** was studied (Table 1). In the presence of

Table 1. Reaction of 1a with NCS: Optimization Studies



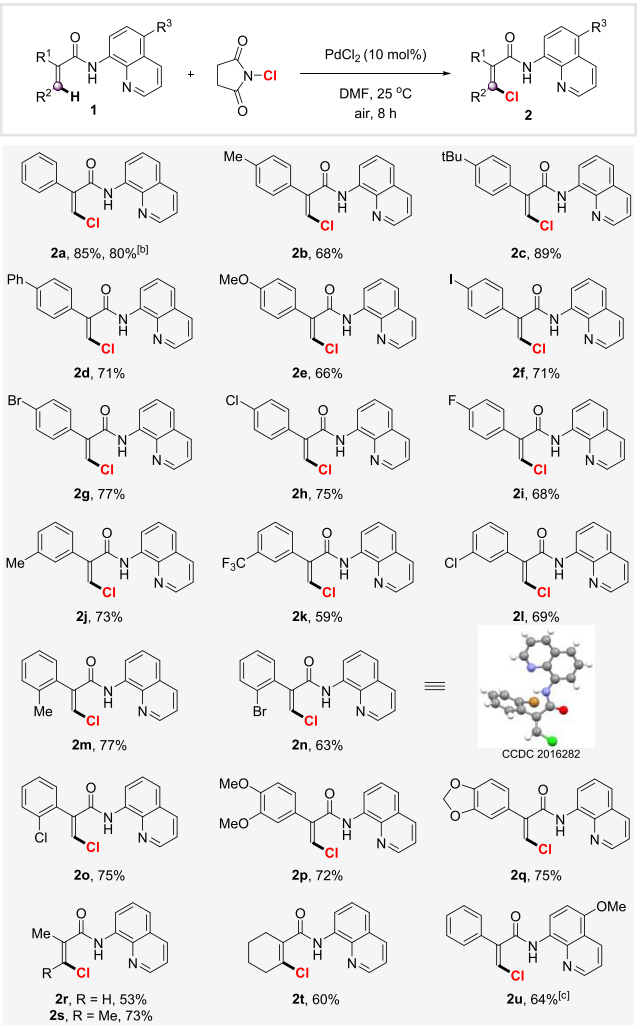
entry	variation from standard conditions	yield (%)[a]
1	none	85
2	CuI instead of $PdCl_2$	0
3	$CuCl_2$ instead of $PdCl_2$	0
4	5 mol % of $PdCl_2$ instead of 10 mol %	25[b]
5	no catalyst	0
6	16 h instead of 8 h	82
7	Ar atmosphere instead of air	83
8	no distilled DMF instead of distilled one	75
9	DMF/H_2O (9:1) instead of DMF	48

[a]Isolated yields. All reactions were performed on a 0.2 mmol scale. [b]Product was obtained along with the product resulting from the chlorination at the C5 position of the 8-aminoquinoline part in 31% yield.

a stoichiometric amount of NCS and using $PdCl_2$ as a catalyst, **1a** was smoothly converted into the corresponding chlorinated product **2a** in 85% yield under an air atmosphere in 8 h (Table 1, entry 1). The reaction turned out to be completely diastereoselective, as a single *Z*-isomer was obtained, as ascertained by 2D NMR experiments.[18] The replacement of $PdCl_2$ by other copper-based catalysts (Table 1, entries 2 and 3) led to no expected product **2a**, and only the product resulting from the chlorination at the C5 position of the 8-aminoquinoline part was observed. The catalyst loading was also important to selectively get the functionalization of the olefin. Indeed, when 5 mol % of the catalyst was used, the reaction furnished **2a** in only 25% yield, along with the chlorinated product on the aminoquinoline part (Table 1, entry 4). A control experiment was conducted, and in the absence of a catalyst, **2a** was not obtained, and the same side reaction was prominent (Table 1, entry 5). Increasing the reaction time (Table 1, entry 6) or running the reaction under an inert atmosphere (Table 1, entry 7) did not have any significant impact on the outcome of the reaction. Finally, using nondistilled DMF or a mixture of DMF/H_2O (9:1), the reaction afforded **2a**, albeit in somewhat lower yields (Table 1, entries 8 and 9), hence showcasing the robustness of the transformation. Note that attempts to extend the reaction to the bromination of **1a** were unsuccessful.[19]

With the best reaction conditions in hand, access to trisubstituted acrylamides was achieved via the Pd-catalyzed chlorination of an array of *α*-aryl-substituted acrylamides (Scheme 2, **2a**−**q**). When **1a** was used as the substrate, the

Scheme 2. Scope of the Chlorination Reaction[a]



[a]Reaction conditions: acrylamide 1 (0.2 mmol), NCS (1 equiv), $PdCl_2$ (10 mol %), DMF (2 mL), 25 °C, 8 h, air. Isolated yields are given. [b]Reaction performed on a 4 mmol scale (1.1 g of **1a**), 20 h. [c]20 h.

reaction was efficiently 20 times scaled up, offering access to ∼1 g of **2a** (0.99 g, 80%) without erosion of the yield (85% on 0.2 mmol scale). The reaction turned out to be highly regio- and diastereoselective to the expected product, and only the monochlorination of the olefin part was observed. Several acrylamides bearing an arene at the *α*-position substituted by an electron-donating (**1b**−**e**) group or halogens (**1f**−**i**) at the para position were chlorinated. The reaction was also tolerant of the trifluoromethyl group (**2k**). Meta- and ortho-substituted *α*-aryl acrylamides (**2j**−**o**) were chlorinated, and the substitution pattern on the arenes did not have any impact on the efficiency

https://dx.doi.org/10.1021/acs.orglett.0c02750
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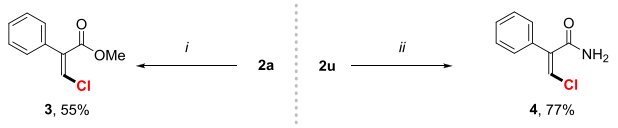
of the transformation (similar yields for compounds **2b**, **2j**, **2m**). Note that the structure of **2n** was further confirmed by X-ray analysis (CCDC 2016282). Acrylamides with disubstituted arenes (**1p** and **1q**) were also suitable substrates in this transformation. The methodology was successfully extended to the chlorination of the methacrylamide **1r**, leading to the corresponding product **2r** in 53% yield.

Pleasingly, the approach was successfully applied to the functionalization of the α,β-disubstituted acrylamides, with the stereoselective access to the tetrasubstituted acyclic olefin still being a synthetic challenge. α,β-Disubstituted acrylamides such as the dimethyl acrylamide (**1s**) and the cyclohex-1-enecarboxamide (**1t**) were smoothly converted into the fully decorated olefins **2s** and **2t**. Even the amide derived from the 5-methoxy-8-aminoquinoline **1u** was smoothly functionalized in a longer time.

To further illustrate the modularity of the chlorinated amides, they were easily converted into other classes of compounds. The directing group was cleaved under various reaction conditions (Scheme 3). When **2a** and **2u** were engaged under acidic or oxidative conditions, the corresponding ester **3** and the primary amide **4** were obtained in 55 and 77% yields, respectively.

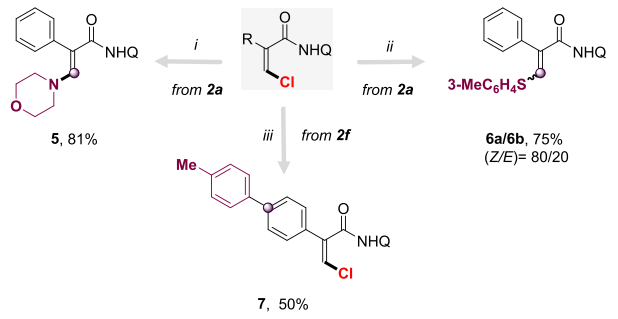
Scheme 3. Deprotection of the Directing Group[a]



[a]Reactions were carried out on a 0.1 mmol scale. Isolated yields are given. (i) TsOH (3 equiv), MeOH (0.2 M), 100 °C, 7 days, Ar. (ii) CAN (3 equiv), $MeCN/H_2O$ (5:1, 0.3 M), 25 °C, 16 h, Ar.

Taking advantage of the versatility brought by the introduction of a chlorine atom on the olefinic derivative as a "synthetic transformable handle" for post-functionalization, we investigated further structural modifications by the transformation of the carbon−chlorine bond into other carbon-functional groups (Scheme 4). The reaction of **2a** with morpholine led to the corresponding product **5** as the single *E*-isomer, ascertained by NMR.[18] The subsequent thiolation of **2a** provided an inseparable *Z*/*E* mixture of the thiolated

Scheme 4. Synthetic Applications[a]

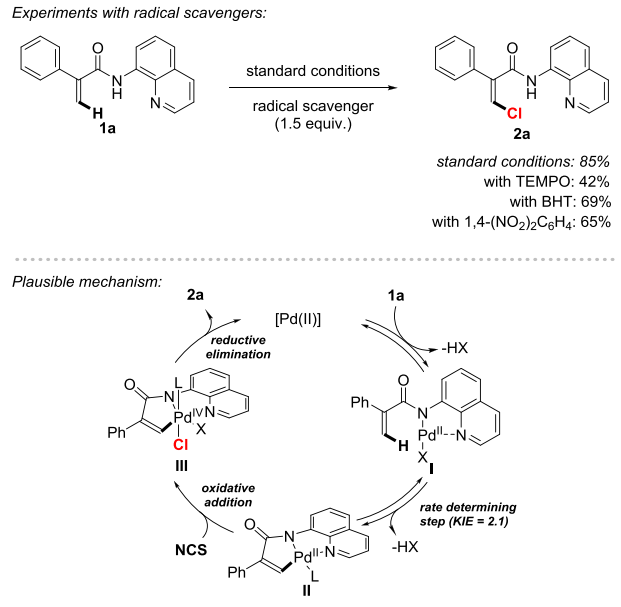


[a]Reactions were carried out on a 0.1 mmol scale. Isolated yields are given. (i) Morpholine (1.5 equiv), DMF (0.2 M), 90 °C, 16 h, Ar. (ii) 3-Methylbenzenethiol (1.5 equiv), Et_3N (1.5 equiv), DMF (0.2 M), 50 °C, 24 h, Ar. (iii) $Pd(PPh_3)_4$ (5 mol %), *p*-tolylboronic acid (2 equiv), K_2CO_3 (1.5 equiv), toluene (0.2 M), 100 °C, 16 h, Ar. Q = 8-quinolyl.

compound (**6a**/**6b**) in 75% yield, with the *Z*-isomer being the major one.[20] Moreover, taking advantage of the presence of an iodine atom on the aromatic ring of **2f**, a Suzuki reaction was performed, leading to the corresponding compound **7**, with the chlorinated olefin part remaining intact at the end of the reaction.

To gain more insight into the mechanism of the reaction, several experiments were conducted.[18] First, when scrambling experiments were performed, an H/D exchange was observed, suggesting that the C−H bond activation step is reversible. Then, **1i** and the isotopically labeled olefin [D]-**1i** were engaged in parallel reactions, and a kinetic isotopic effect (KIE) of 2.1 was measured. These results indicated that the rate-determining step is most likely the palladacycle formation. Experiments conducted with **1a** in the presence of TEMPO, BHT, and 1,4-dinitrobenezene as radical scavengers showed no significant effect on the outcome of the reaction; the reaction was just slowed down (remaining unreacted **1a** at the end of the reaction), explaining the slightly lower yields.[18] Therefore, a radical process might be ruled out. On the basis of these considerations, the following plausible mechanism was suggested: At first, coordination of the Pd(II) catalyst with the bidentate directing group of **1a** followed by the reversible formation of the palladacycle **II**. This latter underwent an oxidative addition followed by a reductive elimination to furnish the expected product **2a** and to regenerate the catalyst (Scheme 5). Note that a redox neutral Pd(II)-based mechanism might not be excluded.[21]

Scheme 5. Suggested Mechanism



In summary, we developed a new methodology allowing the direct chlorination of acrylamide derivatives under Pd catalysis by C−H bond activation. This approach offered access to tri- and tetra-substituted olefins in a complete stereoselective manner toward the *Z*-isomer (21 examples, up to 89% yield). This original transformation occurred at room temperature and was suitable for a broad variety of acrylamides. Indeed, α-substituted and α,β-disubstituted acrylamide derivatives were efficiently functionalized. The salient features of this chlorination transformation are the lack of additives (oxidant, ligand, acid or base, etc.), the air and moisture tolerance, the total

https://dx.doi.org/10.1021/acs.orglett.0c02750
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control of the regio- and diastereoselectivity, the very mild reaction conditions (room temperature), and the easy scale-up. Moreover, access to value-added scaffolds, which hinged on the use of the chlorine atom as a linchpin, further demonstrated the key importance of chlorinated compounds and the need to develop methodologies to reach them. By tackling an unmet synthetic goal, this new approach considerably extends the portfolio of chlorinated molecules and paves the way toward original synthetic routes to unsaturated chlorinated compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02750.

Experimental procedures, compound characterization data, and ^{1}H and ^{13}C spectra of the products (PDF)

Accession Codes

CCDC 2016282 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by Normandie Université (NU), the Région Normandie, the Centre National de la Recherche Scientifique (CNRS), Université de Rouen Normandie (URN), INSA Rouen Normandie, Labex SynOrg (ANR-11-LABX-0029), the French National Research Agency (ANR-17-CE07-0038-01), and Innovation Chimie Carnot (I2C). T.B. thanks the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement no. 758710). M.-Y.C. thanks the French National Research Agency for a doctoral fellowship (ANR-17-CE07-0038-01). We are thankful to Prof. Hassan Oulyadi for his help with NMR analysis.

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