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Pd-Catalyzed Selective Chlorination of Acrylamides at Room Temperature.

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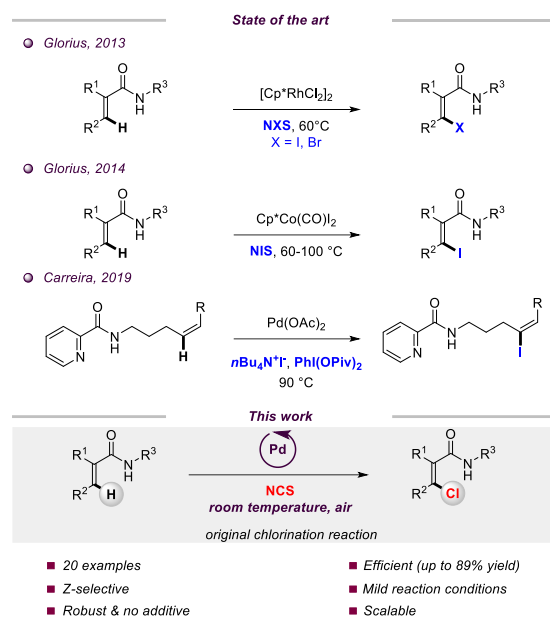
ABSTRACT: In this manuscript, the transition metal catalyzed chlorination of alkenes was reported. In the presence of the commercially available and inexpensive *N*-chlorosuccinimide and without additive, the Pd-catalyzed chlorination of acrylamides by C-H bond activation was developed at room temperature 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 towards 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 Especially, halogenation of aromatic derivatives is at the forefront of innovation since they have widespread applications in organic chemistry. Therefore, the development of novel methods to access them has attracted a strong interest from the scientific community.² Among them, a special attention was 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 further opened the chemical space, enabling applications to various fields.⁵ Especially, the transition metal catalyzed directed functionalization of the more challenging vinylic derivatives by C-H bond activation was well studied over the years, offering a straightforward and

selective access to the difficult-to-synthesize *Z* isomer.⁶ In sharp contrast, the halogenation of vinylic derivatives by C-H bond activation⁶ still remains restricted to a handful of examples and requires to be further investigated as it offers a selective access to the challenging and ubiquitous *Z* olefinic moiety. The quest to efficient and selective tools towards the difficult-to-synthesize *Z*-olefins is of high importance, since this scaffold might be found in several bioactive compounds such as Selinexor®.

In the realm of transition metal catalyzed halogenation of olefins by C-H activation, bromination and iodination reactions were mainly studied using various transition metal catalysts and led to major contributions. In 2013, Glorius reported the Rh(III)-catalyzed bromination and iodination of acrylamides⁷ and one year later they depicted the iodination of acrylamides⁸ *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 clear interest of the corresponding vinyl chloride compounds.¹ Therefore, the elaboration of a new synthetic approach towards these chlorinated molecules represents a significant challenge in modern organic chemistry and is still an unmet goal. Up to date, the existing methods to synthesize *Z*- β -chloroacrylic acid derivatives generally relied on a Vilsmeier-Haack reaction,¹⁰ a Wittig reaction,¹¹ a chloropalladation/Heck reaction sequence,¹² chlorination of propargyl alcohols,¹³ as well as hydrochlorination,¹⁴ chloroacylation¹⁵ and chlorocarbonylation¹⁶ reactions of alkynes, among others. A lack of *E/Z* selectivity or the need to have the proper alkynes are the main synthetic limitations of these methods that are needed 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 towards the functionalization of vinylic derivatives by C-H bond activation,¹⁷ we report herein the unprecedented Pd(II)-catalyzed

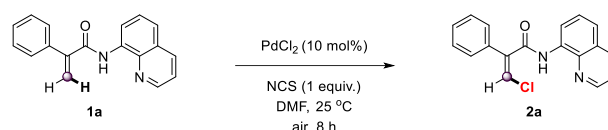
chlorination of various α - and α,β -substituted acrylamide derivatives at room temperature.



Scheme 1. State of the art and present work.

At the outset of the study, the Pd-catalyzed chlorination of the α -phenylacrylamide **1a** was studied (Table 1). In the presence of a stoichiometric amount of NCS and using PdCl₂ 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 PdCl₂ 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 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 inert atmosphere (Table 1, entry 7) did not have any significant impact on the outcome of the

reaction. Finally, using non-distilled DMF or a mixture of DMF/H₂O (9:1), the reaction afforded **2a** albeit in somehow lower yields (Table 1, entries 8 and 9), showcasing hence the robustness of the transformation. Note that attempts to extend the reaction to the bromination of **1a** was unsuccessful.¹⁹



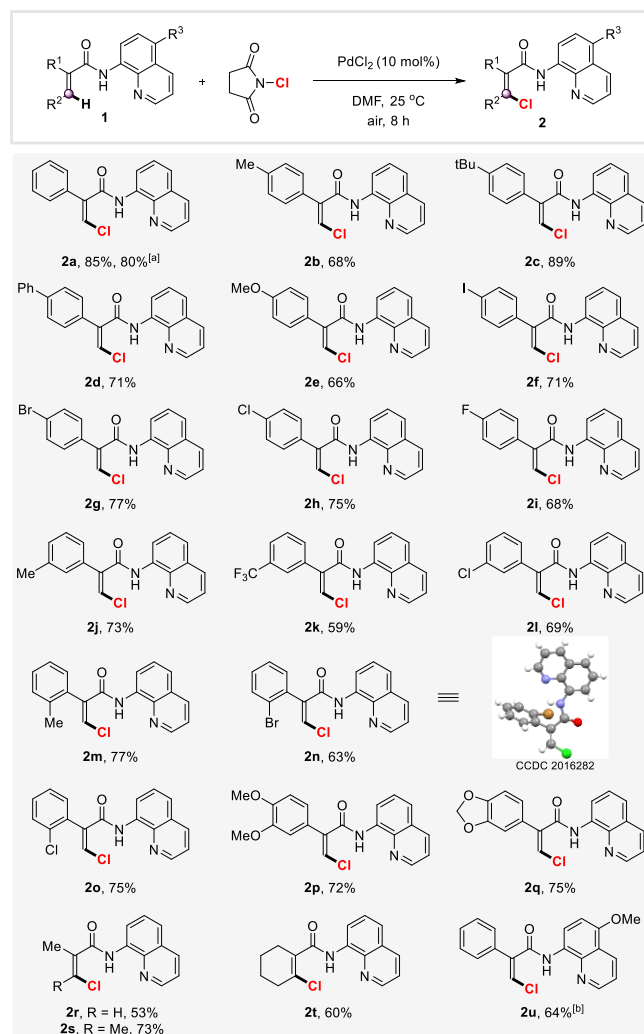
entry	variation from standard conditions	yields (%) ^a
1	None	85
2	CuI instead of PdCl ₂	0
3	CuCl ₂ instead of PdCl ₂	0
4	5 mol% of PdCl ₂ instead of 10 mol%	25 ^b
5	No catalyst	0
6	16 h instead of 8 h	82
7	Ar atmosphere instead of air	83
8	No distilled DMF instead of distilled one	75
9	DMF/H ₂ O (9:1) instead of DMF	48

Table 1. Reaction of **1a** with NCS: optimization studies.

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

With the best reaction conditions in hand, an access to tri-substituted acrylamides was achieved *via* the Pd-catalyzed chlorination of an array of α -aryl-substituted acrylamides (Scheme 2, **2a-2q**). When **1a** was used as the substrate, the reaction was efficiently 20-fold time scaled up, offering an access to about 1g 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 diastereo-selective to the expected

product and only the mono-chlorination 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 to the trifluoromethyl group (**2k**). *Meta* and *ortho* substituted β -aryl acrylamides (**2j-2o**) were chlorinated and the substitution pattern on the arenes did not have any impact on the efficiency 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).²⁰ 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.

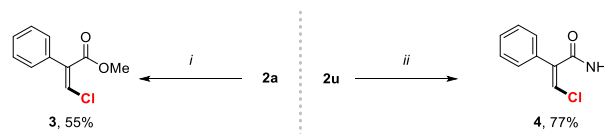


Scheme 2. Scope of the chlorination reaction.

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

Pleasingly, the approach was successfully applied to the functionalization of the α,β -substituted acrylamides, the stereoselective access to tetrasubstituted acyclic olefin being still a synthetic challenge. β,β -Substituted 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.

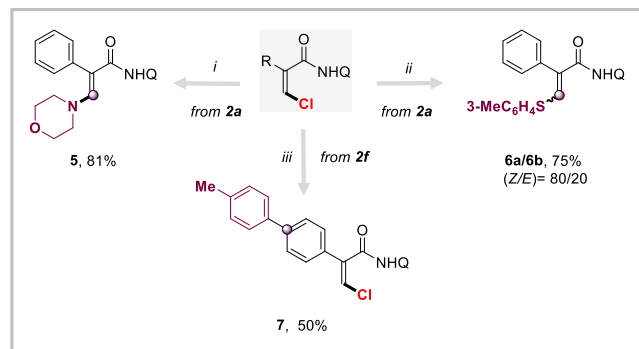


Scheme 3. Deprotection of the directing group.

i: TsOH (3 equiv.), MeOH (0.2 M), 100 °C, 7 days, Ar. *ii*: CAN (3 equiv.), MeCN/H₂O (5:1, 0.3 M), 25 °C, 16 h, Ar.

Taking benefit from 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). Reaction of **2a** with morpholine led to the corresponding product **5** as the single *E*-isomer, ascertained by NMR.¹⁸ Subsequent thiolation of **2a** provided an inseparable *Z/E* mixture of the thiolated compound (**6a/6b**) in 75% yield, the *Z*-isomer being the major one.²¹ Moreover, taking benefit from the presence of an iodine atom on the aromatic ring of **2f**, a Suzuki reaction was performed leading to the corresponding compound **7**, the

chlorinated olefin part remaining intact at the end of the reaction.

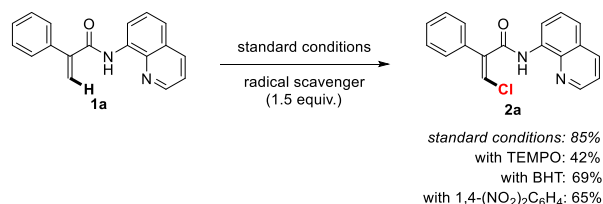


Scheme 4. Synthetic Applications.

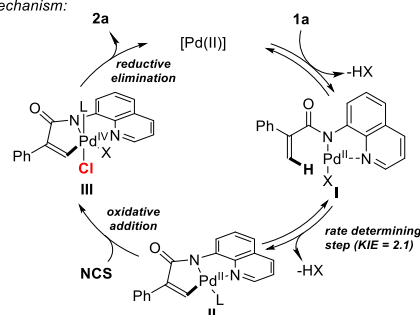
Reactions were carried out on 0.1 mmol scale. Isolated yields were given. *i.* Morpholine (1.5 equiv.), DMF (0.2 M), 90 °C, 16 h, Ar. *ii.* 3-Methylbenzenethiol (1.5 equiv.), Et₃N (1.5 equiv.), DMF (0.2 M), 50 °C, 24 h, Ar. *iii.* Pd(PPh₃)₄ (5 mol%), *p*-tolylboronic acid (2 equiv.), K₂CO₃ (1.5 equiv.), toluene (0.2 M), 100 °C, 16 h, Ar. Q = 8-quinolyl.

To gain more insight into the mechanism of the reaction, several experiments were conducted.¹⁸ First, when scrambling experiments were performed, a 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-dinitrobenzene 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. Based on these considerations, the following plausible mechanism was suggested: at first, coordination of the Pd(II) catalyst with the bidentate directing group of **1a** followed that 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.²²

Experiments with radical scavengers:



Plausible mechanism:



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 an access to tri- and tetra-substituted olefins in a complete stereoselective manner towards the *Z*-isomer (20 examples, up to 89% yield). This original transformation occurred at room temperature and was suitable with 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...), the air and moisture tolerance, a total control of the regio- and diastereoselectivity, the very mild reaction conditions (room temperature) and an easy scale-up. Moreover, access to value-added scaffolds, which hinged on the use of the chlorine atom as a linchpin, demonstrated further 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 extended the portfolio of chlorinated molecules and paved the way towards original synthetic routes to unsaturated chlorinated compounds.

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(18) See the Supporting Information for details.

(19) When phthalimide bromide was used instead of NCS, the product resulting from the selective bromination of **1a** at the C5 position of the 8-aminoquinoline moiety was isolated in 66% yield.

(20) CCDC 2016282 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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