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Direct Access to 9-Chloro-1*H*-benzo[*b*]furo[3,4-*e*]azepin-1-ones via Palladium(II)-Catalyzed Intramolecular *syn*-Oxypalladation/Olefin Insertion/sp^2-C−H Bond Activation Cascade

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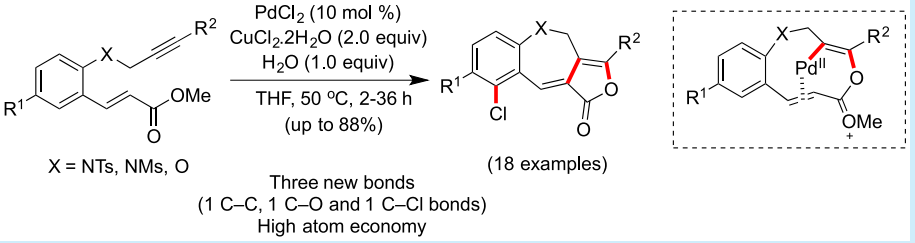
Supporting Information

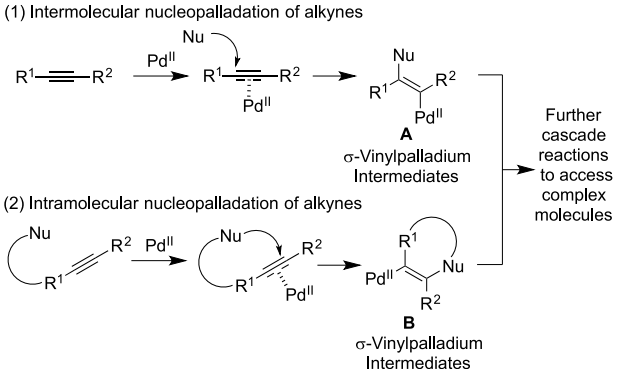


ABSTRACT: An efficient Pd(II)-catalyzed cascade approach was established for the synthesis of 9-chloro-1*H*-benzo[*b*]furo-[3,4-*e*]azepin-1-ones starting from *N*-propargyl arylamines having a pendant *α*,*β*-unsaturated ester scaffold. The mechanism of this sequential process involved intramolecular *syn*-oxypalladation followed by olefin insertion and *ortho* sp^2-C−Cl bond formation reactions. This high atom- and step-economical cascade sequence generated two heterocycle rings and three new bonds in a single synthetic operation.

Medium-sized benzannulated aza-heterocycles comprise the core structure of numerous biologically active compounds that exhibit a broad range of pharmacological activities.[1,2] Among these compounds, seven-membered nitrogen heterocycles including benzazepines represent an important class of natural products and show antidepressant, anxiolytic, and neuroleptic activities.[3,4] For instance, LY-411575 has been identified as an effective *γ*-secretase inhibitor for the treatment of Alzheimer's and Parkinson's diseases,[5] and fenoldopam, a chiral benzo[*d*]azepine, acts as dopamine D1 receptor agonist and is used as antihypertensive agent.[6] Further, mozavaptan, an analogue of 1*H*-benzo[*b*]azepine, is a vasopressin V-2 receptor antagonist, and lotensin is a commercially available drug used for the treatment of high blood pressure and congestive heart failure.[7] Compounds containing a benzazepine nucleus as the key subunit serve as selective 5-HT$_{2C}$ receptor agonists for the treatment of obesity.[8] Although a considerable number of approaches have been developed for the synthesis of these valuable compounds, straightforward methods to access densely functionalized benzazepine analogues are rather limited.[9]

Inter- and intramolecular nucleopalladation of alkynes and successive cascade reactions via *σ*-vinylpalladium intermediates

Scheme 1. Inter- and Intramolecular Nucleopalladation of Alkynes



remain excellent strategies to access various structurally diverse molecules in a single synthetic operation (Scheme 1).[10] The in situ generated *σ*-vinylpalladium intermediates could be captured by carbon monoxide, allylic alcohols, halides, esters,

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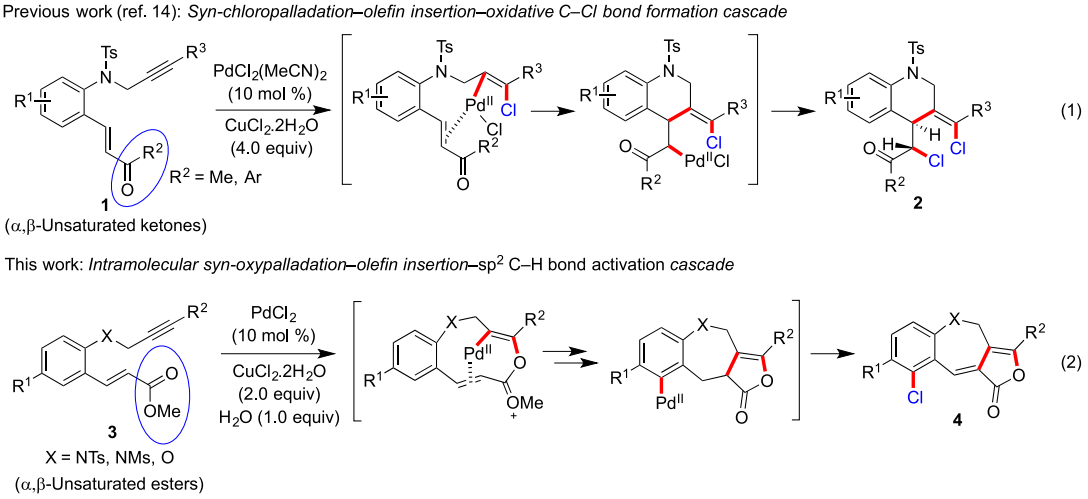
Scheme 2. Nucleopalladation-Initiated Cascade Reactions of *N*-Propargyl Arylamines with Pendant *α,β*-Unsaturated Carbonyl Compounds

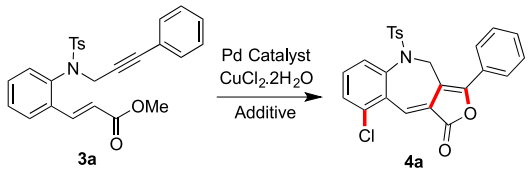


allenes, *α,β*-unsaturated carbonyl compounds, norbornene, styrene, unactivated alkenes, nitriles, and isonitriles to obtain complex compounds.[11] Among the various nucleopalladation reactions, oxypalladation-initiated cascade reactions are particularly important as these reactions lead to a variety of biologically significant compounds including oxygen heterocycles.[12,13]

Recently, we established a *syn*-chloropalladation/olefin insertion/oxidative chlorination cascade for the synthesis of dichlorinated tetrahydroquinolines **2** starting from *N*-propargyl arylamines **1** tethered with *α,β*-unsaturated ketones in the presence of a palladium catalyst and $CuCl_2{\cdot}2H_2O$ as the chloride source (Scheme 2, eq 1).[14] When we swapped the *α,β*-unsaturated ketone moiety of **1** with *α,β*-unsaturated ester (compound **3**), the reactivity was entirely altered and the unpredicted 1*H*-benzo[*b*]furo[3,4-*e*]azepin-1-ones **4** bearing an Ar−Cl substituent was obtained as the major product (Scheme 2, eq 2). This interesting cascade transformation intrigued us to further explore the reactivity of compounds **3** to obtain the biologically significant tricyclic 1*H*-benzo[*b*]furo-[3,4-*e*]azepin-1-ones **4** and to investigate the mechanism of the annulation/sp^2-C−Cl bond formation cascade.

Initially, we tested the reaction conditions established for the *syn*-chloropalladation-initiated cascade[14] using *N*-propargyl arylamine **3a** bearing an *α,β*-unsaturated ester functionality as the model substrate, and only traces of product **4a** were observed in the presence of 10 mol % of $Pd(OAc)_2$ and 2 equiv of $CuCl_2{\cdot}2H_2O$ in THF and DME at ambient temperature (Table 1, entries 1 and 2). Remarkably, an increase of the reaction temperature to 50 °C in THF triggered the cascade transformation to allow access to the desired product **4a** in 58% yield, and the results in DME were inferior (entries 3 and 4). Our investigation moved forward when switching the catalyst to $PdCl_2$, and a maximum yield of 66% of **4a** was observed after 7 h in THF at 50 °C (entries 5−8). Subsequently, with an aim to further improve the yield, we tested the reaction in various common organic solvents including MeCN (entry 9), toluene, DCM, DCE, ethanol, methanol, DMSO, and DMF. Nonetheless, these solvents were completely ineffective to furnish the desired product irrespective of the polarity effects (not shown in the table). It is interesting to note that, in addition to THF (entries 3 and

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (10 mol %)	solvent	additive (equiv)	time (h)	yield of **4a** (%)[b]
1	$Pd(OAc)_2$	THF		48	traces[c]
2	$Pd(OAc)_2$	DME		48	traces[c]
3	$Pd(OAc)_2$	THF		7	58
4	$Pd(OAc)_2$	DME		48	14
5	$PdCl_2$	THF		48	13[c]
6	$PdCl_2$	DME		48	10[c]
7	$PdCl_2$	THF		7	66
8	$PdCl_2$	DME		48	23
9	$PdCl_2$	MeCN		48	*d*
10	$PdCl_2$	dioxane		7	38
11	$PdCl_2$	2-MeTHF		8	68
12[e]	$PdCl_2$	2-MeTHF		4	69
13[f]	$PdCl_2$	2-MeTHF		16	63
14	$PdCl_2$	2-MeTHF	H_2O (4)	5	72
15	$PdCl_2$	2-MeTHF	H_2O (1)	5	77
16	$PdCl_2$	THF	H_2O (4)	5	71
17[g]	$PdCl_2$	THF	H_2O (1)	5	84
18	$Pd(OAc)_2$	THF	H_2O (1)	5	76
19	$PdCl_2(PPh_3)_2$	THF	H_2O (1)	48	*d*
20	$PdCl_2(MeCN)_2$	THF	H_2O (1)	5	83
21	$Pd(OTf)_2$	THF	H_2O (1)	20	31
22[h]	$PdCl_2$	THF	H_2O (1)	28	42
23		THF	H_2O (1)	48	*d*
24[e]		THF	H_2O (1)	48	*d*
25[i]	$PdCl_2$	THF	H_2O (1)	48	traces
26[j]	$PdCl_2$	THF	H_2O (1)	48	*d*

[a]Unless otherwise noted, all reactions were carried out with **3a** (0.5 mmol), $CuCl_2{\cdot}2H_2O$ (2.0 equiv), palladium catalyst (10 mol %) in 6 mL of solvent at 50 °C. [b]Isolated yield. [c]Reactions were carried out at room temperature. [d]No reaction. [e]4.0 equiv of $CuCl_2{\cdot}2H_2O$ was used. [f]1.0 equiv of $CuCl_2{\cdot}2H_2O$ was used. [g]Optimized reaction condition. [h]5 mol % of catalyst was used. [i]Reaction was carried out without $CuCl_2{\cdot}2H_2O$. [j]2.0 equiv of $CuBr_2$ was used.

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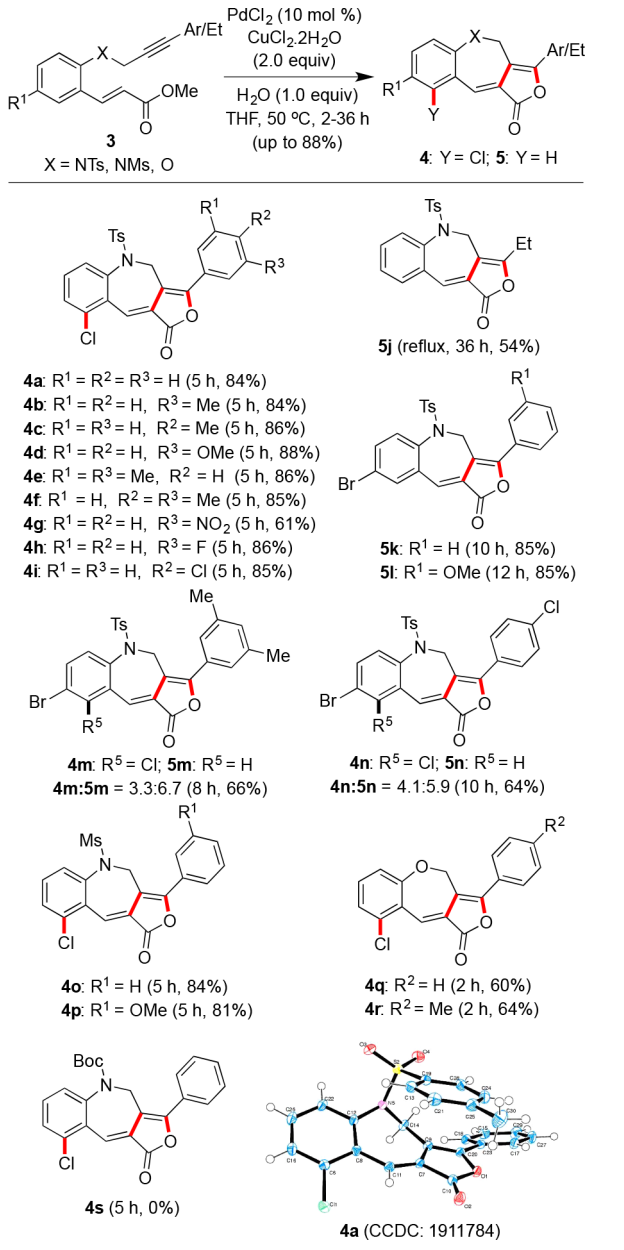
7) and DME (entry 8), other ethereal solvents including dioxane and 2-MeTHF were efficient and made the cascade process attainable (entries 10 and 11). Although DME and dioxane could not deliver the product in appreciable yields, the highest yield of 68% was achieved in 2-MeTHF (entry 11). Increasing the amount of $CuCl_2{\cdot}2H_2O$ to 4 equiv did not improve the yield significantly; however, the reaction time was reduced to 4 h (entry 12). Further, the reaction delivered the desired product in a comparable yield of 63% in the presence of 1 equiv of $CuCl_2{\cdot}2H_2O$ in 16 h (entry 13).

Owing to the crucial role of water in the proposed cascade process, the reaction was further investigated in the presence of water as the additive. As anticipated, addition of 1 equiv of water increased the yield to 77%, and the reaction was completed within 4 h in 2-MeTHF (entries 14 and 15). Substantial improvement was observed in THF under similar conditions with a maximum yield of 84% (entries 16 and 17). Next, 10 mol % of palladium catalyst, 2 equiv of $CuCl_2{\cdot}2H_2O$, 1 equiv of H_2O, and THF solvent were employed to further screen palladium catalysts including $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2(MeCN)_2$, and $Pd(OTf)_2$ (entries 18−21). In the list of tested catalysts, $PdCl_2(MeCN)_2$ furnished the product in a manner comparable to that of $PdCl_2$, and other catalysts displayed inferior results. As shown in entry 22, 5 mol % of $PdCl_2$ was inefficient and delivered only 42% of the product after 28 h. To prove the role of both palladium catalyst and $CuCl_2{\cdot}2H_2O$ in the cascade process, the reaction was tested only with 2−4 equiv of $CuCl_2{\cdot}2H_2O$ (entries 23 and 24) and with 10 mol % of $PdCl_2$ without $CuCl_2{\cdot}2H_2O$ (entry 25). In the former case, no product formation was observed and traces of the product were noted in the absence of copper salt. Finally, $CuBr_2$ was tested instead of $CuCl_2{\cdot}2H_2O$ to access the corresponding brominated benzazepine; however, the reaction failed to deliver the desired product (entry 26). After an extensive optimization study, the condition given in entry 17 was elected to investigate the scope and limitations of the cascade process (10 mol % of $PdCl_2$, 2 equiv of $CuCl_2{\cdot}2H_2O$, 1 equiv of H_2O, THF, 50 °C).

With the optimal reaction conditions established, the scope and limitations of the cascade process were investigated (Scheme 3). A variety of *N*(*O*)-propargyl arylamines **3a−s** bearing an *α*,*β*-unsaturated ester moiety were treated with 10 mol % of $PdCl_2$, 2 equiv of $CuCl_2{\cdot}2H_2O$, and 1 equiv of water in THF at 50 °C to access the corresponding 9-chloro-1*H*-benzo[*b*]furo[3,4-*e*]azepin-1-ones **4**. At the outset, a series of electron-donating and -withdrawing substituents were introduced at R^1, R^2, and R^3 positions (Me: **4b**, **4c**, **4e**, and **4f**; OMe: **4d**; F: **4h**; Cl: **4i**), and in all cases, the desired products were obtained in high yields of 84−88%. The *N*-propargyl arylamine **3g** with a strong electron-withdrawing *m*-nitro substituent delivered the corresponding product **4g** in moderate yield (61%).

The alkyne bearing a terminal ethyl group delivered the nonchlorinated 1*H*-benzo[*b*]furo[3,4-*e*]azepin-1-one **5j** in 54% yield under reflux conditions in 36 h, and attempts to insert the 9-chloro substituent by adding excess $CuCl_2{\cdot}2H_2O$ were unsuccessful. Further, a set of *N*-propargyl arylamines **3k−n** bearing a bromo substituent on the *N*-aryl ring was synthesized to derive densely substituted benzazepines. Unexpectedly, alkynes **3k** and **3l** afforded the nonchlorinated products **5k** and **5l** in 85% yields under the optimized conditions. In the cases of alkynes **3m** and **3n**, inseparable mixtures of chlorinated benzazepines **4** together with nonchlorinated products **5** in

Scheme 3. Scope and Limitations of the *syn*-Oxypalladation-Initiated Cascade



64−66% overall yields were isolated. The reaction also tolerated an additional N-protecting mesyl functionality. Two examples of *N*-mesyl 9-chloro-1*H*-benzo[*b*]furo[3,4-*e*]azepin-1-ones **4o** and **4p** were synthesized in 81−84% yields under similar conditions. Next, benzo[*b*]furo[3,4-*e*]oxepin-1-ones **4q** and **4r** were derived in 60−64% yields starting from the corresponding *O*-propargyl arylamines. Finally, the *tert*-butyloxycarbonyl (Boc)-protected *N*-propargyl arylamine **3s** was also tested; however, the reaction failed to furnish the desired product **4s** due to the poor stability of compound **3s** under the experimental conditions. The structures of the synthesized compounds were established by NMR and confirmed by single-crystal X-ray analysis of the representative compound **4a**.

Our mechanistic rationale for the cascade process involves the activation of alkyne **3** by a palladium(II) catalyst followed by intramolecular *syn*-oxypalladation to generate *σ*-vinyl-

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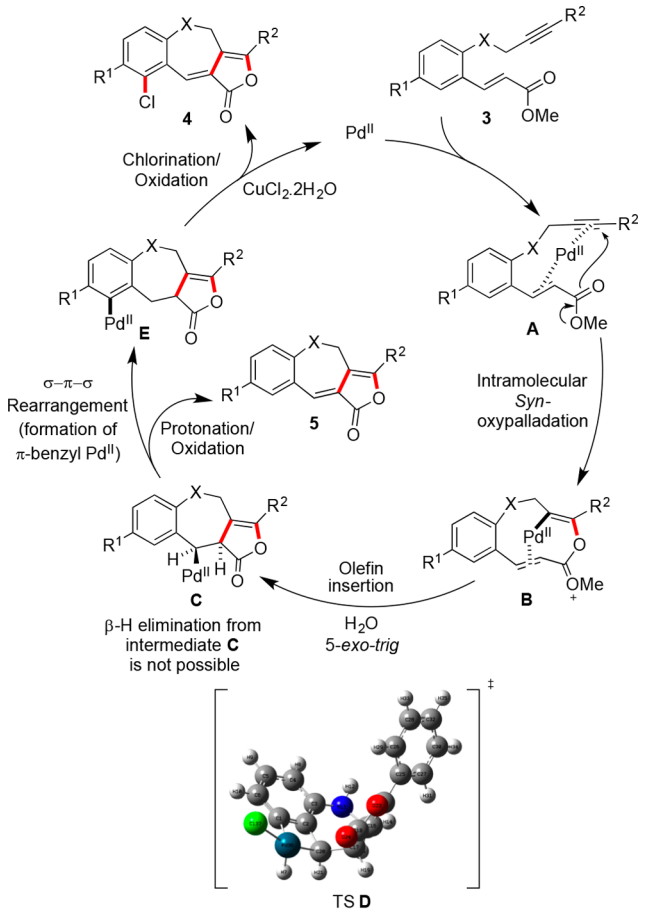
palladium intermediate **B** via species **A** (Scheme 4).[12a,c] Subsequent olefin insertion comprising a 5-*exo*-*trig* cyclization

Scheme 4. Plausible Mechanism for the *syn*-Oxypalladation-Initiated Cascade



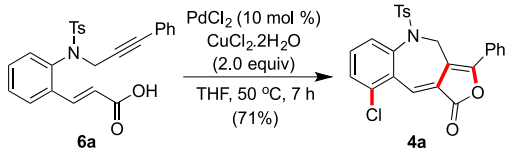
generates intermediate **C** bearing the furanone ring system, where *β*-hydride elimination would be difficult to occur due to geometrical constrains. The *ortho*-chlorination process involving sp^2-C−H bond activation could be visualized through *σ*−*π*−*σ* rearrangement of intermediate **C** to deliver species **E** via *π*-benzylpalladium(II) species involving the dearomatization reaction as summarized by Trost.[15,16] Final rearomatization followed by the $CuCl_2{\cdot}2H_2O$-mediated *ortho*-chlorination/oxidation sequence would afford the desired product **4** via the intermediacy of **E** by regenerating the Pd(II) species.

Further, we carried out DFT calculations using the M062x functional to understand the formation of intermediate **E** from species **C**. Our study reveals the formation of intermediate **E** by migration of the hydrogen atom from sp^2-C to sp^3-C via transition state **D**. Such a migration process is triggered by sp^2-C−H bond activation by an adjacent Pd(II) species. The activation energy of this transformation is estimated to be about 53.7 kcal mol^{-1} in our calculations. Additional computational calculations to understand the reaction pathway in detail are in progress.

Formation of nonchlorinated 1*H*-benzo[*b*]furo[3,4-*e*]-azepin-1-ones **5** observed in sterically hindered substrates (R^1 = Br) could be explained by protonation followed by $CuCl_2{\cdot}2H_2O$-mediated oxidation of intermediate **C**, where *σ*−*π*−*σ* rearrangement would be difficult due to the presence of the bulky bromine atom.

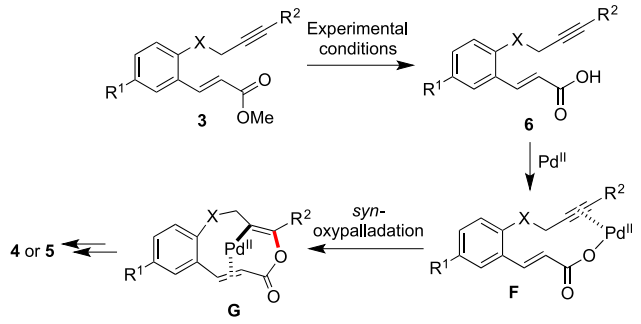
To further attain additional information concerning the mechanism of the cascade process, the reaction was performed using *α*,*β*-unsaturated acid **6a** under optimized conditions, and the expected product **4a** was obtained in 71% yield (Scheme 5). On the basis of this experiment, an alternative mechanism

Scheme 5. Annulation of *α*,*β*-Unsaturated Acid 6a



involving a carboxylic acid intermediate is depicted in Scheme 6. Initial hydrolysis of ester **3** to carboxylic acid **6** could be

Scheme 6. Proposed Mechanism via a Carboxylic Acid Intermediate



achieved under the experimental conditions, which would generate the key *σ*-vinylpalladium intermediate **G** via *syn*-oxypalladation of palladium species **F** generated in situ from the carboxylic acid **6** and the palladium catalyst.

In summary, we have established a Pd(II)-catalyzed nucleopalladation-initiated cascade process for the direct synthesis 9-chloro-1*H*-benzo[*b*]furo[3,4-*e*]azepin-1-ones in good yields. The reaction involved a sequential intramolecular *syn*-oxypalladation/olefin insertion/sp^2-C−H bond activation of *N*-propargyl arylamines bearing an *α*,*β*-unsaturated ester moiety. Insertion of an *ortho*-chloro substituent was visualized via *σ*−*π*−*σ* rearrangement involving a dearomatization process followed by a rearomatization/chlorination sequence. This simple high atom-economical cascade approach allowed the construction of two heterocycle rings including seven- and five-membered rings and three new bonds (1 C−C, 1 C−O, and 1 C−Cl bonds) under mild conditions in a single operation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01482.

Experimental details, characterization data of compounds, NMR, and X-ray crystallographic data (PDF)

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Accession Codes

CCDC 1911784 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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Notes

The authors declare no competing financial interest.

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