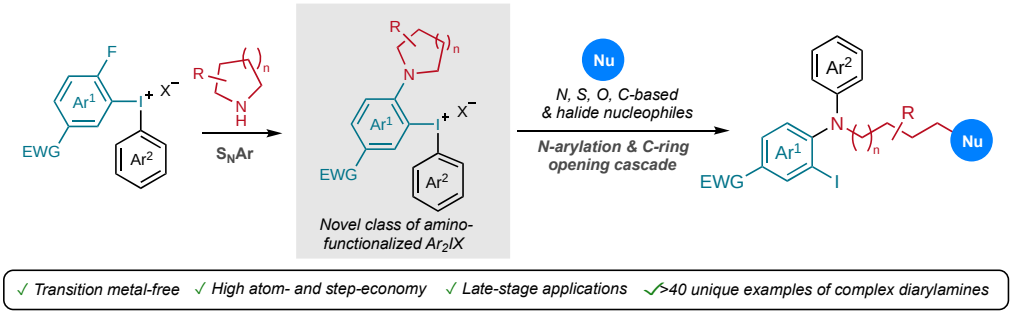
Synthesis of Highly Functionalized Diarylamines through an *N*-, *C*-Cascade Reaction via Ammonium Salts

Erika Linde and Berit Olofsson*

Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University, SE-106 91 Stockholm (Sweden)
Berit.Olofsson@su.se



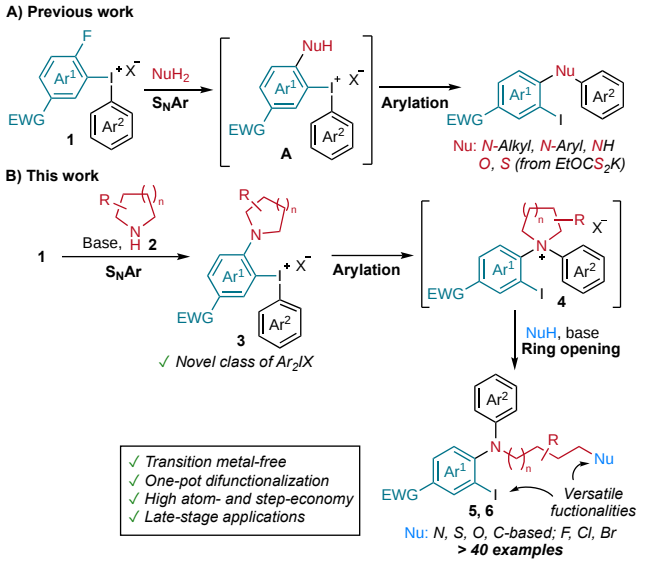
ABSTRACT: The diarylation and skeletal diversification of unstrained cyclic amines was exploited to expand and modify the favorable properties of this important substrate class with pivotal roles in drug discovery. Cyclic amines were employed in the synthesis of a novel class of amino-substituted diaryliodonium salts, which were converted to highly functionalized diarylamines through an atom-efficient one-pot *N*-arylation/ ring opening reaction with external nucleophiles. The reaction proceeds through the *in situ* formation of a diarylammonium intermediate that undergoes a nucleophilic ring opening by cleavage of the strong *C*-*N* bond. A wide variety of diarylamines was obtained through introduction of two different aryl groups of varied electronics, and the retained iodo-substituent enables downfield diversifications of the products. More than 20 nucleophiles, including amines, phenols, carboxylic acids, thiols and halides, were alkylated with high functional group tolerance, and the strategy could be utilized in late-stage functionalization of natural products and pharmaceuticals.

INTRODUCTION

Arylated amines are valuable motifs in organic synthesis due to their prevalence in natural products, pharmaceuticals and functional materials.[1] *N*-aryl amines are commonly prepared through transition-metal catalyzed cross-couplings[2] or by the increasingly popular C-H aminations.[3] These methods are undeniably efficient and well established, however, their overall sustainability is compromised by the requirement of scarce metals and often expensive / time-consuming multi-step synthesis to attain more complex products with different *N*-aryl groups. Cyclic aliphatic amines constitute essential cornerstones in drug discovery, and methods for functionalization to modify their biological properties is of high value. Skeletal diversification trough ring opening by selective breakage of the strong *C*-*N* σ-bond[4] is a powerful strategy to change the overall shape of the molecule and achieve increased structural complexity.[5] Such modifications have in the past been attained through reductive[6] or oxidative[7] pathways using transition metals or by von Braun type degradation via ammonium intermediates.[8] However, there are limited examples of *C*-*N* bond cleavage that occur with simultaneous introduction of versatile functionalities at both the *N*- and *C*-terminal to afford complex value-added products, especially for unstrained cyclic amines.[8a, 9]

Diaryliodonium salts (Ar_2IX) are acknowledged as excellent electrophilic arylating agents with desirable properties such as high reactivity, stability and synthetic accessibility.[10] They have found extensive application in arylations of both carbon and heteroatom nucleophiles,[10] and are recognized as attractive multi-purpose reagents also in material chemistry.[11] Their main drawback is the generation of stoichiometric ArI waste in the majority of their arylation pathways.[12] To overcome this atom-economy limitation, our group recently developed a sustainable strategy for incorporation of both aryl groups and the iodine of diaryliodonium salts **1** onto *N*-, *O*- and *S*-nucleophiles through a metal-free cascade reaction (Scheme 1A).[13] Mechanistic studies suggested this atom-efficient diarylation to proceed through a novel pathway, with initial nucleophilic aromatic substitution (S_NAr) followed by intramolecular arylation, as supported by isolation of S_NAr intermediates **A** with *O*- and *S*-nucleophiles.[13]

We envisioned that utilization of secondary amines in our diarylation strategy could lead to potent cascade reactions to yield a wide scope of functionalized diarylamines. Novel *ortho*-



Scheme 1. Strategy for diarylation/ring-opening reaction of unstrained cyclic amines. EWG = electron-withdrawing group.

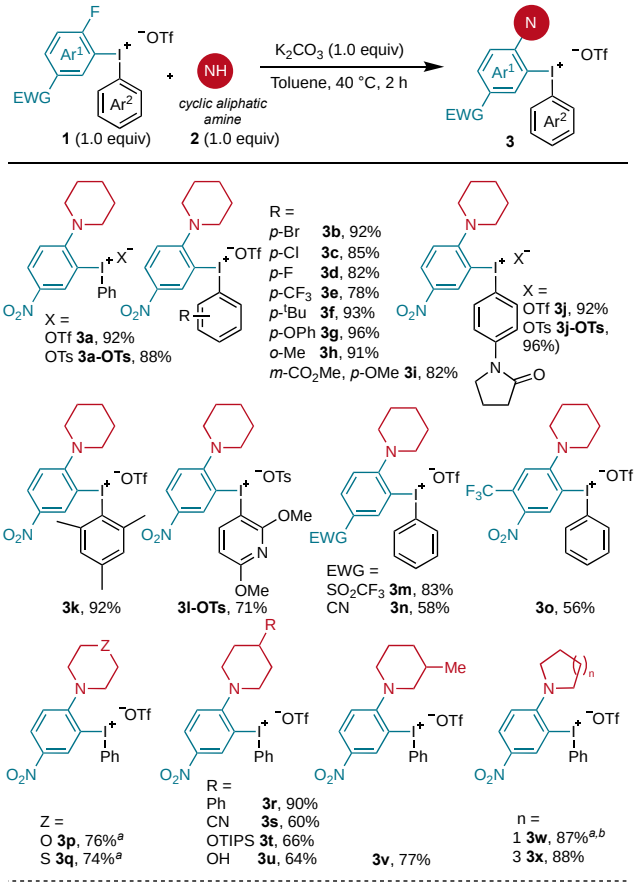
amino-functionalized diaryliodonium salts **3** could be synthesized through SNAr on **1**, followed by a one-pot sequential arylation and ring-opening pathway via ammonium intermediates **4** (Scheme 1B). Upon *C-N* cleavage of **4** by external nucleophiles,[14] highly functionalized diarylamines **5**, **6** would be obtained with excellent atom- and step economy. Moreover, diaryliodonium salts **3** with unprotected aliphatic amine substituents, could have interesting applications in organic synthesis and materials chemistry. They are, to the best of our knowledge, unknown in literature, which is likely due to the incompatibility of such functionalities with the oxidizing and acidic conditions required for the synthesis of diaryliodonium salts.

RESULTS AND DISCUSSION

Piperidine derivatives are particularly interesting compounds due to their versatile medicinal properties, *e.g.* as anticancer, antipsychotic and anti-Alzheimer agents.[15] The introduction of such nucleophiles to iodonium salts **1** could hence be of special interest, and piperidine (**2a**) was chosen as the model substrate in reactions with **1a**. To our delight, the desired product **3a** was obtained in excellent yield under the conditions used in the previous isolation of SNAr intermediate **A** with water (EtOAc, 40 °C, 2 h),[13a] A small optimization study revealed that toluene was the superior solvent for most substrates (see SI, Table S1). The substrate scope of salts **3** was first evaluated by varying aryl group Ar^2, and both electron rich and electron deficient substituents in *ortho*-, *para*- and *meta*-position were tolerated, giving the corresponding products **3b-j** in high to excellent yields (Scheme 2). Carbonyl containing aryl groups could be incorporated, as demonstrated by products **3i-j**, and sterically congested Ar^2 were well tolerated (**3k-3l**).

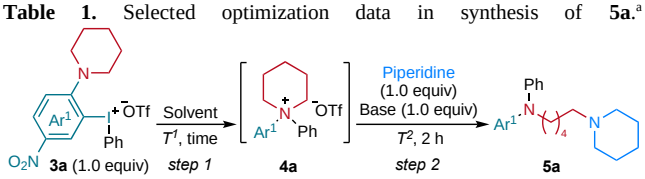
Variations on aryl group Ar^1 are more restricted, to retain the required SNAr reactivity of this moiety. Thus, we were pleased to see that the electron-withdrawing group (EWG) could be varied from nitro to other activating groups *e.g.* SO_2CF_3 and CN (**3m**, **3n**), and allow for introduction of additional substituents such as CF_3 (**3o**). Other cyclic amines, such as morpholine and thiomorpholine, were also productive in the reaction with salt **1a** (**3p**, **3q**). Additional functionality could be introduced by decorating amines **2** with a variety of functional groups (**3r-3v**), including a free hydroxyl group (**3u)**. Also 5- and 7-membered cyclic amines **2** could be utilized, giving products **3w** and **3x** in 87% and 88% yield, respectively. Limitations of the scope were encountered with acyclic aliphatic amines, which underwent a competing reductive pathway (see SI, section 3.1). Since the synthesis of salts **3** was performed without excess reagents, the pure products were generally isolated after a simple filtration to remove the base residues.

Next, the envisioned arylation/ ring-opening sequence was investigated using salt **3a** and piperidine as the external nucleophile for the ring-opening of **4a**, with the aim to install this valuable moiety at the end of the carbon chain of **5a** (Table 1). The synthesis of organic ammonium salts is generally difficult, and only a few examples are known in literature.[16] Our key intermediate, ammonium salt **4**, could be particularly challenging due to the high steric congestion from the two aryl moieties as well as the large *ortho*-iodo substituent. To our delight, the reaction proved to be possible using a mild base and no excess reagents, by heating salt **3a** in MeCN at 100 °C for 4 h followed by reaction with K_2CO_3 and piperidine at rt for 2 h, to provide **5a** as the only product in 47% yield (entry 1). Extension of the reaction time of step 1 to 16 h, to allow full formation of **4a** prior to the piperidine addition, provided **5a** in 93% yield (entry 2). Lowering the temperature had a negative impact on the yield (entry 3), as did using the other explored solvents and bases (entries 4-



Scheme 2. Scope of diaryliodonium salts **3**. [a] EtOAc as solvent. [b] Performed at -78 °C to rt for 6 h.

Table 1. Selected optimization data in synthesis of **5a**.[a]



Entry	Base	Solvent	Time (h)	T^1 (°C)	T^2 (°C)	Yield (%)[b]
1	K_2CO_3	MeCN	4	100	rt	47
2	K_2CO_3	MeCN	16	100	rt	93
3	K_2CO_3	MeCN	24	90	rt	54
4	K_2CO_3	EtOAc	16	100	100	21
5	K_2CO_3	THF	16	100	100	31
6	K_2CO_3	PhMe	16	100	100	28
7	Cs_2CO_3	MeCN	24	100	rt	70
8	NaH	MeCN	24	100	rt	70
9	^{t}BuOK	MeCN	24	100	rt	44
10[c]	Na_2CO_3	PhMe	4	110	-	31

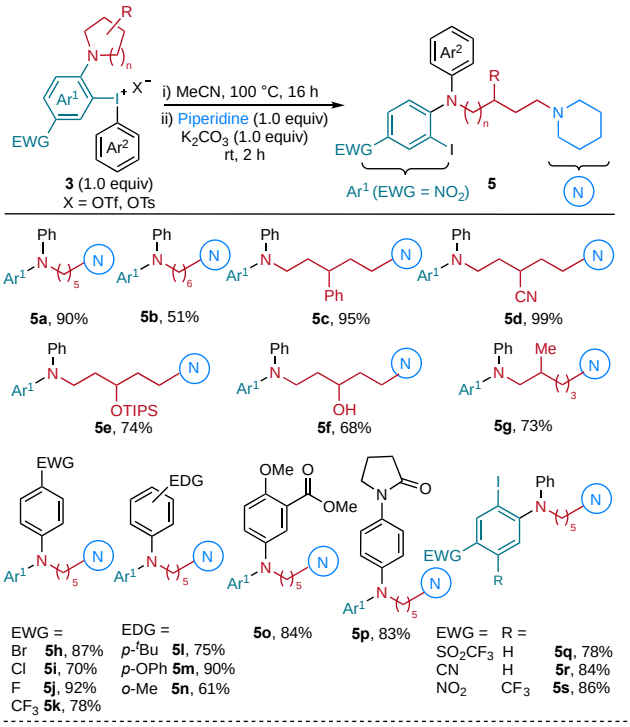
[a] Ar^1 = 2-iodo-4-nitrophenyl. [b] NMR yields with 1,3,5-trimethoxybenzene as internal standard. [c] Reaction performed without isolation of **3a**.

9). While the full synthesis sequence from salt **1a** to product **5a** could be performed in one pot without isolation of **3a**, the yields of **5a** were considerably decreased (entry 10, see SI section 2.2.1 for further details).

The substrate scope was first evaluated by variation of iodonium salt **3**, using piperidine as the external nucleophile (Scheme 3). Purification of **5a** did not require column chromatography; an aqueous wash to remove inorganic impurities was sufficient to isolate **5a** in 90% yield. The reaction was also possible using the 7-membered substrate **3x** to provide **5b** in a moderate yield, whereas the 5-membered substrate **3w** decomposed upon heating. To the contrary, substrates **3r-v**, containing decorated amine cores, reacted efficiently and delivered the corresponding products **5c-g** in high to excellent yields. Even hydroxy-substituted substrate **3u**, comprising of a competing nucleophilic site, reacted with complete selectivity in the desired pathway to afford amino alcohol **5f.**

The generality of the *N*-arylation was then evaluated with substrates **3b-o**, carrying a variety of aryl groups. Satisfyingly, transfer of Ar^2 with varied electronic properties proceeded smoothly, delivering a range of electron deficient and electron rich products **5h-n** in 61-92% yields. Even functional groups susceptible to nucleophilic additions, such as esters and amides, remained unaltered in the products **5o** and **5p**. The sterically congested *ortho*-Me product **5n** could also be synthesized, whereas mesityl substrate **3k** proved unreactive under the current conditions. The pyridinyl salt **3l-OTs** was also unproductive, as the reaction with piperidine led to complex reaction mixtures. Substrates **3** with alterations on Ar^1 efficiently underwent the desired transformation, yielding products **5q-s** in 78-86% yield.

Next, our focus was directed towards prospective nucleophiles for the ring opening of **4** (Scheme 3). To make this step efficient for less potent nucleophiles than piperidine, two methods were developed. For aliphatic and aromatic amines, the reactions were performed for 2-6 h at 50-60 °C (method A), to give

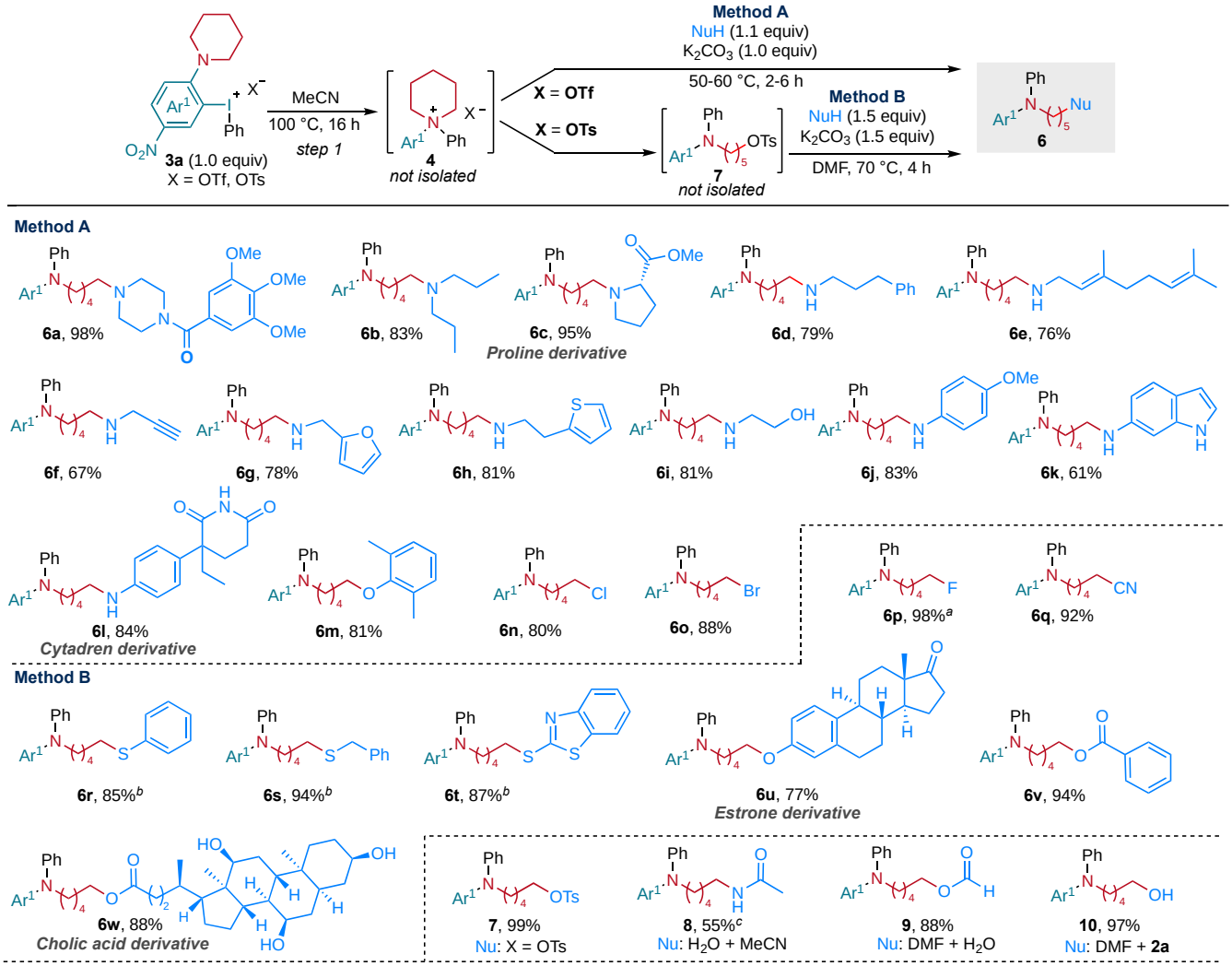


Scheme 3. Scope of products **5** from variation of substrates **3**.

products **6a-o** in good to excellent yields. Cyclic and acyclic secondary amines were proficient nucleophiles (**6a-c**), including the proline methyl ester, forming **6c** in 95% yield. A common issue with *N*-alkylation strategies is the challenge to avoid over-alkylation.[17] Thus, we were pleased to achieve selective monoalkylation of primary amine nucleophiles, with no detectable trace of dialkylated products. The methodology was compatible with a range of functionalities *e.g.* olefins, alkenyls, furanyl and thionyl groups (**6d-h**). Even the ambident nucleophile 2-aminoethanol reacted with complete selectivity for the *C*-*N* bond formation, giving **6i** in 81% yield. Anilines could also be employed in the ring-opening, despite being weaker nucleophiles, and could be used for incorporation of an indolyl functionality and for derivatization of the commercial pharmaceutical cytadren, affording **6j-l** in 61-84% yield. While an *ortho*-blocked phenol was efficient in the ring opening of **4a** to provide **6m**, unhindered phenols underwent a competing S_NAr pathway with the ammonium moiety as the leaving group (see SI section 3.4). Halogenations were easily achieved with CsCl and KBr, providing products **6n** and **6o** in 80% and 88% yield, respectively.

Some nucleophiles proved incompatible with the conditions of method A, either due to competing pathways (ArOH, CsF, KCN) or by causing decomposition of **4a** (*S*-nucleophiles). Method B was designed to overcome this limitation through the use of substrates **3-OTs** (Scheme 4). Upon formation of ammonium salts **4-OTs**, direct ring-opening by the tosylate takes place, giving products **7** in quantitative yield with 100% atom economy (see SI section 3.3). Compounds **7** then undergo an *in situ* S_N2 reaction with the external nucleophile to yield the target products **6**. A short optimization revealed that the second S_N2 reaction was more efficient in DMF at 70 °C for 4 h (see SI Table S3).

Fluorine incorporation into organic molecules has spurred a large research interest due to the favorable medicinal properties and the importance of ^{18}F radiolabeled pharmaceuticals.[9b, 18]

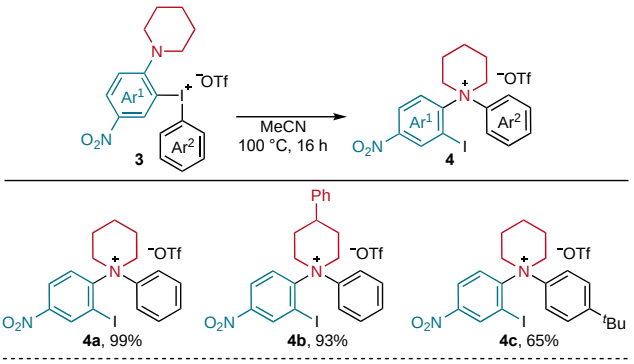


Scheme 4. Scope of products **5** from variation of NuH. [a] 80 °C, 16 h. [b] Reaction performed under dark conditions. [c] Ring-opening step at 100 °C, 2 h.

Using method B, efficient fluorination was achieved in quantitative yield, allowing straightforward isolation of the pure product **6p** by filtration. Furthermore, a range of *C*-, *S*- and *O*-nucleophiles with varying nucleophilicity could be employed, such as cyanide, aromatic/aliphatic thiols, thioamides, phenols and carboxylic acids, to afford products **6q-w** in good to excellent yields. Notably, the competing S_NAr pathway observed for phenols with method A was circumvented, and even complex substrates such as the steroid estrone could be derivatized into **6u** in 77% yield. Moreover, the unprotected natural product cholic acid, with three competing nucleophilic hydroxy groups, underwent selective alkylation of the carboxylate moiety, to give product **6w** in 88% yield.

Some nucleophiles reacted in unexpected ways with **4a**. For instance, the addition of water resulted in amide product **8** in 55% yield (see SI section 3.3), rather than the intended ring opening by hydroxide. The formation of **8** can be rationalized through a Ritter-type reaction in the presence of the MeCN solvent.[19] Surprisingly, also DMF could be used as a productive nucleophile for the ring opening of **4a**. When **3a** was heated in DMF instead of MeCN, followed by addition of piperidine at room temperature, the formate product **9** was obtained in 88% yield. Furthermore, when the reaction was performed without addition of an external nucleophile, the primary alcohol product **10** was obtained in quantitative yield after aqueous workup. We anticipate that products **9** and **10** stem from an iminium intermediate formed through the ring opening of **4a** by DMF in similarity with the Vilsmeier-Haack intermediate[20] (see SI section 3.3).

Ammonium salt **4** are potentially interesting compounds since organic ammonium salts find various industrial applications[16] owing to their antimicrobial,[21] antistatic[22] and surfactant[22a, 23] properties. To demonstrate the efficient preparation of **4**, a small set of these products were synthesized by heating of **3**, and isolated in good to excellent yields by simple evaporation of the solvent (Scheme 5).



Scheme 5. Isolation of ammonium salts **4**.

CONCLUSIONS

We herein present a method for preparation of previously synthetically inaccessible amino-functionalized diaryliodonium salts through an S_NAr reaction with fluorinated diaryliodonium salts. After incorporation of a range of cyclic amines, these salts were efficiently utilized in a sequential arylation/ring opening pathway, allowing for skeletal diversification of this valued substrate class. The reaction takes place via an intramolecular arylation, forming an ammonium salt, which upon ring opening by external nucleophiles affords *C*- and *N*-functionalized diaryl amines. The reaction displays excellent functional group tolerance and transfer of aryl groups with varied electronic properties was demonstrated. The ring-opening allows for incorporation of common *N*-, *O*-, *S*-, *C*-, and halogen nucleophiles and derivatization of various natural products, giving a versatile set of amine products in a metal-free manner with high atom- and step-economy. The majority of the products contain a range of reactive sites/unprotected polar functionalities that increase their versatility and likeliness to attain medicinal applicability.[5b]

ASSOCIATED CONTENT

Supporting Information

Additional optimization, mechanistic suggestions, full experimental details, and analytical data (PDF).

AUTHOR INFORMATION

Corresponding Author

Berit Olofsson
Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University, SE-106 91 Stockholm (Sweden)
E-mail: Berit.Olofsson@su.se

Author Contributions

E. L. and B. O. designed the study; E. L. performed all experimental and analytical work; E. L. and B. O. wrote the manuscript; E. L. wrote the SI.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial support for this study was provided through the Swedish Research Council (2019-04232).

REFERENCES

(1) (a) Ruiz-Castillo, P.; Buchwald, S. L., Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016,** *116*, 12564-12649. (b) Wang, J.; Liu, K.; Ma, L.; Zhan, X., Triarylamine: Versatile Platform for Organic, Dye-Sensitized, and Perovskite Solar Cells. *Chem. Rev.* **2016,** *116*, 14675-14725. (c) Van Emelen, L.; Henrion, M.; Lemmens, R.; De Vos, D., C–N coupling reactions with arenes through C–H activation: the state-of-the-art versus the principles of green chemistry. *Catal. Sci. Tech.* **2022,** *12*, 360-389.

(2) (a) Bariwal, J.; Van der Eycken, E., C–N bond forming cross-coupling reactions: an overview. *Chem. Soc. Rev.* **2013,** *42*, 9283-9303. (b) Forero-Cortés, P. A.; Haydl, A. M., The 25th Anniversary of the Buchwald–Hartwig Amination: Development, Applications, and Outlook. *Org. Process Res. Dev.* **2019,** *23*, 1478-1483. (c) West, M. J.; Fyfe, J. W. B.; Vantourout, J. C.; Watson, A. J. B., Mechanistic Development and Recent Applications of the Chan–Lam Amination. *Chem. Rev.* **2019,** *119*, 12491-12523.

(3) Park, Y.; Kim, Y.; Chang, S., Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017,** *117*, 9247-9301.

(4) (a) Ouyang, K.; Hao, W.; Zhang, W.-X.; Xi, Z., Transition-Metal-Catalyzed Cleavage of C–N Single Bonds. *Chem. Rev.* **2015,** *115*, 12045-12090. (b) Wang, Q.; Su, Y.; Li, L.; Huang, H., Transition-metal catalysed C–N bond activation. *Chem. Soc. Rev.* **2016,** *45*, 1257-1272.

(5) (a) Karageorgis, G.; Foley, D. J.; Laraia, L.; Waldmann, H., Principle and design of pseudo-natural products. *Nat. Chem.* **2020,** *12*, 227-235. (b) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A., Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem.* **2018,** *10*, 383-394. (c) He, Y.; Zheng, Z.; Yang, J.; Zhang, X.; Fan, X., Recent advances in the functionalization of saturated cyclic amines. *Org. Chem. Front.* **2021,** *8*, 4582-4606.

(6) (a) Louwrier, S.; Tuynman, A.; Hiemstra, H., Synthesis of bicyclic guanidines from pyrrolidin-2-one. *Tetrahedron* **1996,** *52*, 2629-2646. (b) Van Betsbrugge, J.; Van Den Nest, W.; Verheyden, P.; Tourwé, D., New amino acids derived from L-pyroglutamic acid: Synthesis of Trans-4-benzyl-cis-5-phenyl-L-proline, L-α-(2-benzyl-3-phenylpropyl)-glycine and L-α-(3-phenylpropyl)-glycine. *Tetrahedron* **1998,** *54*, 1753-1762. (c) Honda, T.; Ishikawa, F., Reductive deamination of α-amino carbonyl compounds by means of samarium iodide. *Chem. Commun.* **1999**, 1065-1066. (d) Azzena, U.; Demartis, S.; Pilo, L.; Piras, E., Reductive Cleavage of Benzannelated Cyclic Ethers and Amines: Synthetic Applications. *Tetrahedron* **2000,** *56*, 8375-8382.

(7) (a) Castaño, A. M.; Cuerva, J. M.; Echavarren, A. M., A concise synthesis of (±)-monomorine i by way of a palladium-catalyzed reductive coupling. *Tetrahedron Lett.* **1994,** *35*, 7435-7438. (b) Cocquet, G.; Ferroud, C.; Guy, A., A Mild and Efficient Procedure for Ring-Opening Reactions of Piperidine and Pyrrolidine Derivatives by Single Electron Transfer Photooxidation. *Tetrahedron* **2000,** *56*, 2975-2984. (c) Ito, R.; Umezawa, N.; Higuchi, T., Unique Oxidation Reaction of Amides with Pyridine-N-oxide Catalyzed by Ruthenium Porphyrin: Direct Oxidative Conversion of N-Acyl-l-proline to N-Acyl-l-glutamate. *J. Am. Chem. Soc.* **2005,** *127*, 834-835. (d) Liu, P.; Liu, Y.; Wong, E. L.-M.; Xiang, S.; Che, C.-M., Iron oligopyridine complexes as efficient catalysts for practical oxidation of arenes, alkanes, tertiary amines and N-acyl cyclic amines with Oxone. *Chem. Sci.* **2011,** *2*, 2187-2195. (e) Osberger, T. J.; Rogness, D. C.; Kohrt, J. T.; Stepan, A. F.; White, M. C., Oxidative diversification of amino acids and peptides by small-molecule iron catalysis. *Nature* **2016,** *537*, 214-219.

(8) (a) Kim, Y.; Heo, J.; Kim, D.; Chang, S.; Seo, S., Ring-opening functionalizations of unstrained cyclic amines enabled by difluorocarbene transfer. *Nat. Commun.* **2020,** *11*, 4761. (b) Hageman, H. A., The von Braun Cyanogen Bromide Reaction. *Org. React. 7*, 198-262. (c) v. Braun, J., Die Einwirkung von Bromcyan auf tertiäre Amine. *Ber. Dtsch. Chem. Ges.* **1900,** *33*, 1438-1452. (d) Magnier, E.; Langlois, Y.; Mérienne, C., Stereoselective synthesis of the tricyclic

core of manzamine a: The bradsher cycloaddition route. *Tetrahedron Lett.* **1995,** *36*, 9475-9478. (e) Paciaroni, N. G.; Ratnayake, R.; Matthews, J. H.; Norwood IV, V. M.; Arnold, A. C.; Dang, L. H.; Luesch, H.; Huigens III, R. W., A Tryptoline Ring-Distortion Strategy Leads to Complex and Diverse Biologically Active Molecules from the Indole Alkaloid Yohimbine. *Chem. Eur. J.* **2017,** *23*, 4327-4335. (f) Seong, S.; Lim, H.; Han, S., Biosynthetically Inspired Transformation of Iboga to Monomeric Post-iboga Alkaloids. *Chem* **2019,** *5*, 353-363. (g) Yu, C.; Shoaib, M. A.; Iqbal, N.; Kim, J. S.; Ha, H.-J.; Cho, E. J., Selective Ring-Opening of N-Alkyl Pyrrolidines with Chloroformates to 4-Chlorobutyl Carbamates. *J. Org. Chem.* **2017,** *82*, 6615-6620.

(9) (a) Hong, S.; Kweon, B.; Lee, W.; Chang, S.; Hong, S., Deconstructive Pyridylation of Unstrained Cyclic Amines through a One-Pot Umpolung Approach. *Org. Lett.* **2023**. (b) Roque, J. B.; Kuroda, Y.; Göttemann, L. T.; Sarpong, R., Deconstructive fluorination of cyclic amines by carbon-carbon cleavage. *Science.* **2018,** *361*, 171-174.

(10) (a) Yoshimura, A.; Zhdankin, V. V., Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chem. Rev.* **2016,** *116*, 3328-3435. (b) Olofsson, B.; Marek, I.; Rappoport, Z., In *Patai's Chemistry of Functional Groups: The Chemistry of Hypervalent Halogen Compounds Part 1*, John Wiley & Sons: 2019; pp 1-300. (c) Merritt, E. A.; Olofsson, B., Diaryliodonium Salts: A Journey from Obscurity to Fame. *Angew. Chem. Int. Ed.* **2009,** *48*, 9052-9070. (d) Wirth, T., *Hypervalent Iodine Chemistry*. Springer International Publishing: Cham, 2016.

(11) Petko, F.; Galek, M.; Hola, E.; Topa-Skwarczyńska, M.; Tomal, W.; Jankowska, M.; Pilch, M.; Popielarz, R.; Graff, B.; Morlet-Savary, F.; Lalevee, J.; Ortyl, J., Symmetric Iodonium Salts Based on Benzylidene as One-Component Photoinitiators for Applications in 3D Printing. *Chem. Mater.* **2022,** *34*, 10077-10092.

(12) (a) Boelke, A.; Finkbeiner, P.; Nachtsheim, B. J., Atom-economical group-transfer reactions with hypervalent iodine compounds. *Beilstein J. Org. Chem.* **2018,** *14*, 1263-1280. (b) Wang, M.; Chen, S.; Jiang, X., Atom-Economical Applications of Diaryliodonium Salts. *Chem. Asian J.* **2018,** *13*, 2195-2207.

(13) (a) Linde, E.; Bulfield, D.; Kervefors, G.; Purkait, N.; Olofsson, B., Diarylation of N- and O-nucleophiles through a metal-free cascade reaction. *Chem* **2022,** *8*, 850-865. (b) Mondal, S.; Di Tommaso, E. M.; Olofsson, B., Transition-Metal-Free Difunctionalization of Sulfur Nucleophiles. *Angew. Chem. Int. Ed.* **2023,** *62*, e202216296.

(14) Diaryliodonium salts have been used in monoarylation of the tertiary amine DABCO to give strained ammonium salts, which after isolation could be ring opened by external nucleophiles, see Bugaenko, D. I.; Yurovskaya, M. A.; Karchava, A. V., N-Arylation of DABCO with Diaryliodonium Salts: General Synthesis of N-Aryl-DABCO Salts as Precursors for 1,4-Disubstituted Piperazines. *Org. Lett.* **2018,** *20*, 6389-6393.

(15) Abdelshaheed, M. M.; Fawzy, I. M.; El-Subbagh, H. I.; Youssef, K. M., Piperidine nucleus in the field of drug discovery. *Future Journal of Pharmaceutical Sciences* **2021,** *7*, 188.

(16) Arava, S.; Diesendruck, C. E., Strategies for the Synthesis of N-Arylammonium Salts. *Synthesis* **2017,** *49*, 3535-3545.

(17) Guillena, G.; Ramón, D. J.; Yus, M., Hydrogen Autotransfer in the N-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles. *Chem. Rev.* **2010,** *110*, 1611-1641.

(18) (a) Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M., Fluorine in Medicinal Chemistry. *ChemBioChem* **2004,** *5*, 637-643. (b) Phelps, M. E., Positron emission tomography provides molecular imaging of biological processes. *Proc. Natl. Acad. Sci. USA* **2000,** *97*, 9226-9233.

(19) Krimen, L. I.; Cota, D. J., The Ritter Reaction. In *Org. React.*, pp 213-325.

(20) Su, W.; Weng, Y.; Jiang, L.; Yang, Y.; Zhao, L.; Chen, Z.; Li, Z.; Li, J., Recent Progress in the Use of Vilsmeier-Type Reagents. *Org. Prep. Proced. Int.* **2010,** *42*, 503-555.

(21) (a) Jennings, M. C.; Minbiole, K. P. C.; Wuest, W. M., Quaternary Ammonium Compounds: An Antimicrobial Mainstay and Platform for Innovation to Address Bacterial Resistance. *ACS Infectious Diseases* **2015,** *1*, 288-303. (b) Muñoz-Bonilla, A.; Fernández-García, M., Polymeric materials with antimicrobial activity. *Prog. Polym. Sci.* **2012,** *37*, 281-339.

(22) (a) Hong, J. W.; Kim, H. K.; Yu, J. A.; Kim, Y. B., Characterization of UV-curable reactive diluent containing quaternary ammonium salts for antistatic coating. *J. Appl. Polym. Sci.* **2002,** *84*, 132-137. (b) Kuang, M.; Zhou, S.; Lei, J.; Li, Q., Low environmental sensitive antistatic material based on poly(vinyl chloride)/quaternary ammonium salt by blending with poly(ethylene oxide). *J. Appl. Polym. Sci.* **2008,** *109*, 3887-3891.

(23) Branzoi, V.; Branzoi, F.; Baibarac, M., The inhibition of the corrosion of Armco iron in HCl solutions in the presence of surfactants of the type of N-alkyl quaternary ammonium salts. *Mater. Chem. Phys.* **2000,** *65*, 288-297.