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Transition Metal-Free Synthesis of *meta*-Bromo- and *meta*-Trifluoromethylanilines from Cyclopentanones by a Cascade Reaction

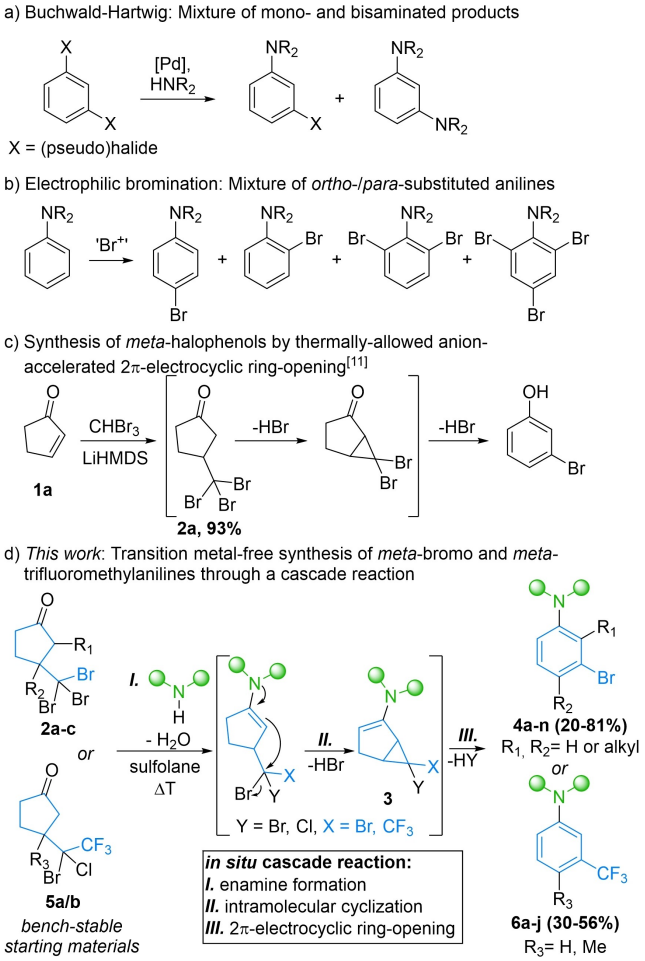
Markus Staudt,*[a] Adnan Cetin,[a, b] and Lennart Bunch*[a]

Abstract: Anilines are key constituents in biologically active compounds and often obtained from transition metal-catalyzed coupling of an aryl halide with an amine. In this work, we report a transition metal-free method for the synthesis of *meta*-bromo- and *meta*-trifluoromethylanilines starting from 3-tribromomethylcyclopentanone or 3-(2-bromo-2-chloro-1,1,1-trifluoroethyl)cyclopentanone, respectively. The scope of the transformation is shown by application of primary, secondary and aromatic amines. The reaction proceeds in acceptable to high yields (20–81%), and allows for the synthesis of anilines with substitution patterns otherwise difficult to access.

Anilines are important building blocks for the synthesis of biologically active compounds.[1] Their synthesis often relies on carbon-nitrogen bond formation by transition metal based protocols such as Buchwald-Hartwig aminations (Scheme 1a).[2] However, selectivity issues may arise if the starting (pseudo)-haloarene carries multiple (pseudo)halogens, resulting in multiple and difficult-to-separate regioisomers as side products (Scheme 1a). Furthermore, physicochemical properties of the employed amines, for example nucleophilicity and steric demand have a profound impact on reaction outcome, which makes reaction optimization an often arduous process.[3] Alternatively, classical electrophilic bromination of anilines (Scheme 1b) yield mixtures of *ortho*-/para-substituted mono- and dibromoanilines, underlining the intrinsic difficulties in accessing *meta*-bromoanilines in a regio- and chemoselective manner.

To overcome problems of regioselectivity, de novo synthesis of the aromatic core through 2π-electrocyclic ring-openings[4] of bicyclo[3.1.0]hex-3-en-2-ones can be employed.[5] Alternatively, the use of more easily accessible 6-halobicyclo[3.1.0]hexan-2-ones has attracted recent attention. This approach has enabled regioselective synthesis of substituted naphthalenes,[6] various heterocycles,[7] as well as phenols and anilines.[8] However, a critical and limiting factor of these methodologies lies in extending the scope to more sterically encumbered and potentially unstable 6,6-disubstituted-bicyclo[3.1.0]hexan-2-ones as starting materials.

While the synthesis and electrocylic ring-opening of *gem*-dihalocyclopropanes is well established,[9] application thereof in the synthesis of halo-substituted aromatic compounds is still limited.[7,10] Our recent report on the synthesis of substituted



Scheme 1. Synthesis of anilines.

[a] *Dr. M. Staudt, Dr. A. Cetin, Prof. L. Bunch*
Department of Drug Design and Pharmacology
Faculty of Health and Medical Sciences
University of Copenhagen
2100 Copenhagen Ø (Denmark)
E-mail: markus.staudt@sund.ku.dk
lebu@sund.ku.dk

[b] *Dr. A. Cetin*
Department of Sciences
Faculty of Education
University of Muş Alparslan
49250, Muş (Turkey)

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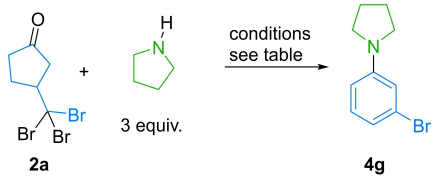
meta-bromo- and iodophenols circumvented instability issues by in situ formation of the 6,6-dihalo-bicyclo[3.1.0]hexan-2-ones, followed by a rapid anion-accelerated 2π-electrocyclic ring-opening (Scheme 1c).[11] As a part of that study, we also found that the intermediate 3-tribromomethylcyclopentanone **2a** could be isolated in high yields when using an excess amount of base (3 equiv. of LiHMDS), as a bench-stable crystalline material. We envisioned that enamine formation directly on **2a** could lead to an intramolecular cyclization, followed by electrocyclic ring-opening of the thus obtained 6,6-dibromobicyclo[3.1.0]hex-2-en-2-amine **3** to give the corresponding aniline with full regio- and chemoselectivity (Scheme 1d).

At first, we investigated standard acid catalyzed enamine formation in tetrahydrofuran (THF) at room temperature, with removal of in situ formed water by molecular sieves. This in fact resulted in the desired *meta*-bromoaniline **4g** in 14% isolated yield. Apparently, the electrocyclic ring-opening took place even at room temperature, albeit at a very slow rate (20 h reaction time). Heating to 60 °C under the same conditions gave 55% yield of aniline **4g**, with no increase in yield on stirring beyond 20 h. Switching solvent to sulfolane and further increasing the temperature to 100 °C gave an increase in yield to 73% after four hours (optimal reaction time). Interestingly, neither acid catalysis nor the need to remove the in situ formed water was needed, allowing for a very convenient reaction setup. Since using four equivalents of amine might be undesirable in some cases, we investigated use of a sacrificial base. Using previously optimized conditions with one equivalent of pyrrolidine and three equivalents of triethylamine (Table 1, entry 5) gave the desired compound in comparable yields (69%). Prolonged stirring for eight hours gave no further increase in yield. Furthermore, we found that the cascade reaction could also be performed at only 60 °C in water with 5 weight percent of the surfactant DL-α-tocopherol methoxypolyethylene glycol succinate added.[12] Despite being an attractive green solvent, we decided to carry out the study of scope and limitations in sulfolane due to the higher yield.

Application of the identified reaction conditions in sulfolane allowed for the synthesis of a wide variety of primary and secondary amines in yields of 22 to 81% (Figure 1), including the sterically demanding amines *tert*-butylamine and 1-adamantylamine, both being notoriously difficult amines to employ in conventional Buchwald-Hartwig-amination reactions. Furthermore aromatic and heteroaromatic amines were shown to convert well to their corresponding anilines, albeit in lower yields (20–65%).

Isolation of the 1,4-adducts of bromoform to monosubstituted cyclopentenones **1b** and **1c** proved to be challenging, requiring diligent control of temperature and reaction time. Hereafter, 1,4-adducts **2b** and **2c** were isolated in 88% and 27% yield, respectively. We believe, the low yield of **2c** was due to the reaction being run with only 1 equiv. of LiHMDS. The exact cause of the required excess of base to obtain high yields was not investigated further. Subsequent reaction with benzylamine afforded expected aniline products **4o** and **4p** in acceptable to high yields (30% and 82%, respectively). These transformations exemplarily prove the strength and applicabil-

Table 1. Initial screening of solvent, additives and reaction conditions.[a]



Entry	Solvent	T [°C]	t [h]	Additive	Isolated yield [%]
1	THF	rt	20	*p*TsOH, 3 Å MS	14
2	THF	60	20	*p*TsOH, 3 Å MS	55
3	Sulfolane	100	1	–	58
4	Sulfolane	100	4	–	73
5	Sulfolane	100	4	NEt_3[c]	69
6	Sulfolane	100	8	NEt_3[c]	67
7	Water[b]	60	4	–	60

[a] Reactions were performed on a 0.5 mmol scale, using 4.0 equiv. of pyrrolidine. [b] containing 5 w% DL-α-tocopherol methoxypolyethylene glycol succinate. [c] 3 equiv. of triethylamine and 1.0 equiv. of pyrrolidine. MS: molecular sieves.

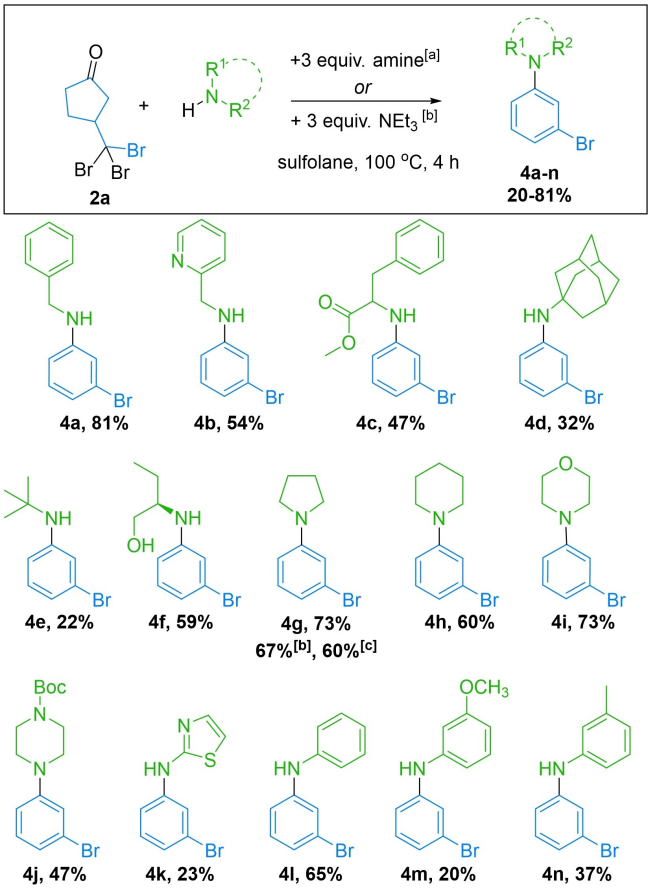


Figure 1. Scope of the *meta*-bromoaniline synthesis. [a] Reactions were performed on a 0.5 mmol scale, using 4.0 equiv. of amine. Yields given are of the isolated product. [b] 1.0 equiv. of amine and 3.0 equiv. of NEt_3 used. [c] 5 w% DL-α-tocopherol methoxypolyethylene glycol succinate in H_2O used as solvent at 60 °C, 8 h.

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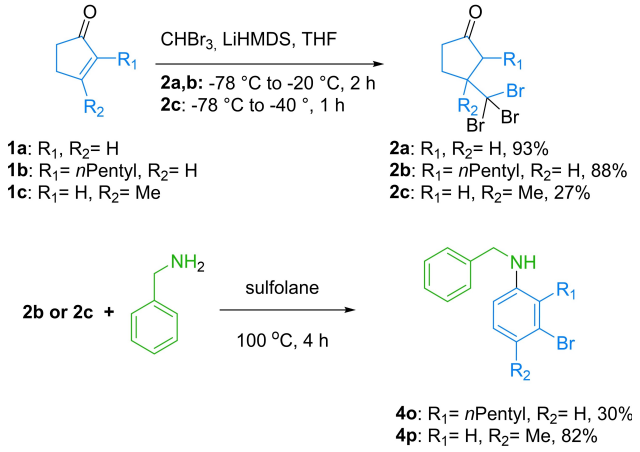
ity of this methodology to the synthesis of substituted anilines (Scheme 2).

While a *meta*-bromo substituent on an aniline core is indeed an attractive synthon for further functionalization, we wanted to explore the generality of the methodology to the synthesis of other substituents in the meta-position. In this respect, commercially available halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) seemed as an attractive reagent as it would give rise to *meta*-trifluoromethylanilines. To our delight, application of halothane to cyclopentenones **1a** and **1c** gave their corresponding 1,4-adducts **5a** and **5b** in 63% and 20% yield, respectively. On the reaction with primary, secondary and aromatic amines, their corresponding unsubstituted as well as 4-methyl-substituted *meta*-trifluoromethylanilines were isolated in 30–56% yield (Figure 2).



Scheme 2. Synthesis of alkyl-substituted 3-(tribromomethyl)cyclopentan-1-ones **2a c** (for **2a,b**: 3.1 equiv. of LiHMDS, for **2c**: 1 equiv. of LiHMDS used) and *meta*-bromoanilines **4o** and **4p**.

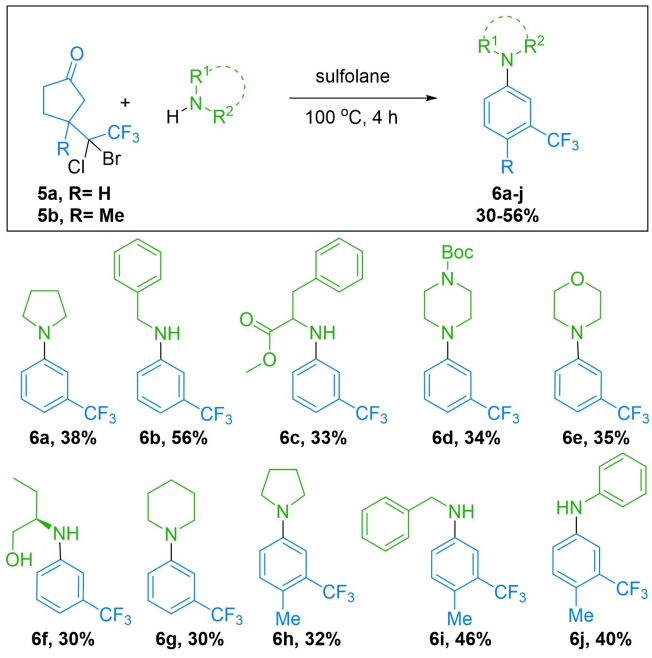
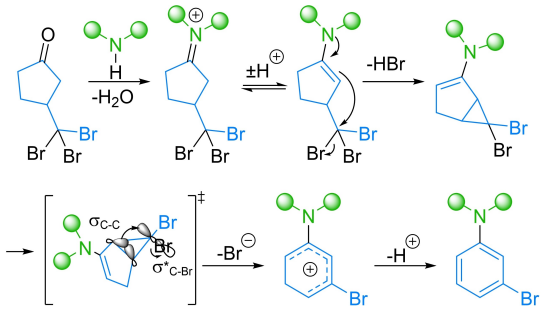


Figure 2. Scope of the *meta*-trifluoromethylaniline synthesis. Reactions were performed on a 0.5 mmol scale, using 4.0 equiv. of amine. Yields given are of the isolated product.



Scheme 3. Proposed mechanism.

In conclusion, we have developed a transition metal free methodology for the synthesis of *meta*-bromo- and *meta*-trifluoromethylanilines starting from the bench-stable, non-aromatic precursors 3-substituted cyclopentanones and an amine. We propose the cascade reaction commences by imine formation followed by tautomerization to the enamine which then undergoes cyclization to the corresponding cyclopropane. Hereafter, the thermally allowed, 2π-disrotatory electrocyclic ring-opening can proceed to form the aromatic aniline core in good to high yields (Scheme 3). The scope of the reaction was shown by application of a range of primary, secondary and aromatic amines, and even sterically demanding ones were successful. Examples of alkyl substituted cyclopentanones as starting materials were also reported, which underlines the versatility of this methodology to grant expedite access to anilines which are otherwise arduous to synthesize. Finally, the transition metal free nature makes this method especially attractive for industrial scale drug synthesis.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: anilines · drug synthesis · electrocyclic ring-opening · new methodology · transition metal-free

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