Synthetic Methods

International Edition: DOI: 10.1002/anie.201508161
German Edition: DOI: 10.1002/ange.201508161

Destruction and Construction: Application of Dearomatization Strategy in Aromatic Carbon–Nitrogen Bond Functionalization

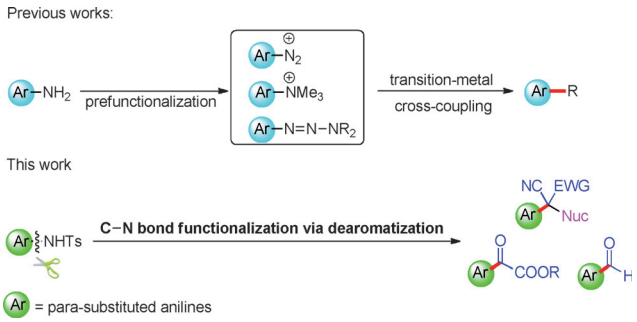
Shuo-En Wang, Linfei Wang, Qiuqin He, and Renhua Fan**

Dedicated to Professor Xue-Long Hou on the occasion of his 60th birthday

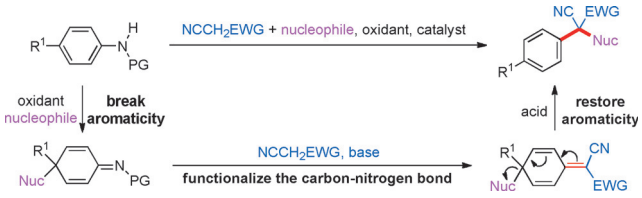
Abstract: *The formation of carbon–carbon bonds through the functionalization of aromatic carbon–nitrogen bonds is a highly attractive synthetic strategy in the synthesis of aromatic molecules. In this paper, we report a novel aromatic carbon–nitrogen bond functionalization reaction by using a simple dearomatization strategy. Through this process para-substituted anilines serve as a potential aryl source in the construction of a range of functionalized aromatic molecules, such as quaternary carbon centers, α-keto esters, and aldehydes.*

The formation of carbon–carbon bonds by the functionalization of aromatic carbon–nitrogen bonds is an attractive synthetic strategy because of the wide availability of anilines,[1] and organic chemists have devoted significant efforts to exploring effective methods to implement this strategy. An example is the copper(I)-mediated arylation of olefins by arenediazonium salts, the so-called Meerwein reaction.[2] However, the narrow scope of this reaction has restricted its application. A breakthrough in this area has been the Matsuda–Heck reaction of arenediazonium salts.[3] Work on this reaction has led to an extensive investigation into the palladium-catalyzed cross-coupling reactions of arenediazonium salts.[4] In recent reports, other aniline derivatives such as areneammonium salts,[5] triazenes[6] or imidazoles[7] have also proved to be suitable reaction partners in transition metal-catalyzed cross-coupling reactions. The ruthenium-catalyzed direct functionalization of the aromatic carbon–nitrogen bonds of *o*-acylanilines has been developed.[8] Such elegant transition metal-catalyzed synthetic tactics have enabled the rapid synthesis of a range of aryl, alkenyl or alkyl-substituted aromatic molecules. In this communication, we report a novel aromatic carbon–nitrogen bond functionalization reaction by using a dearomatization strategy. This protocol provides a simple and direct way to convert *para*-substituted anilines to quaternary carbon centers, α-keto esters or aldehydes (Scheme 1).

The dearomatization[9] of anilines provides an economical and efficient way to prepare nitrogen-containing complex molecules by selective *ortho*[10] or *meta* substitutions.[11] We originally conceived that the dearomatization of anilines might also offer a unique strategic opportunity to functionalize the aromatic carbon–nitrogen bonds through simple conversions. The underlying principle is depicted in Scheme 2. The transformation of the electron-rich aromatic system of anilines to the electron-deficient cyclohexadienimine system through oxidative dearomatization might be followed by a Knoevenagel-type condensation with active nitriles. Subsequent allylic rearrangement might restore the aromaticity and complete the construction of cyano-substituted α-aryl quaternary carbon centers, which are attractive synthetic targets owing to the remarkable biological activities.[12,13]



Scheme 1. Functionalization of the carbon–nitrogen bonds in anilines.



Scheme 2. Construction of cyano-substituted α-aryl quaternary carbon centers.

Challenges to the implementation of this strategy were the competition between the Knoevenagel-type condensation and the 1,4-additions related to the electrophilicity of the C-4 carbon atom of the cyclohexadienimine system. Secondary amines such as L-proline catalyzed condensation of α,β-unsaturated system and might be suitable for our proposed process. To avoid potential oxidation of the N-atom of L-proline, an oxidant should be added to facilitate oxidative dearomatization before adding L-proline. In testing this strategy, we were delighted to find that the reaction of *p*-toluidine **1** with ethyl 2-cyanoacetate in the presence of 1.1 equivalents of iodosylbenzene (PhIO)[14] and 20 mol% of L-proline in methanol afforded the desired quaternary product **2** in 23% yield [Eq. (1)]. However, when pyrrolidine was used

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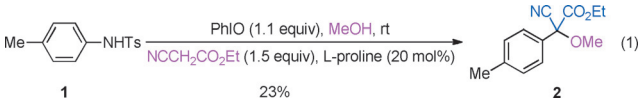
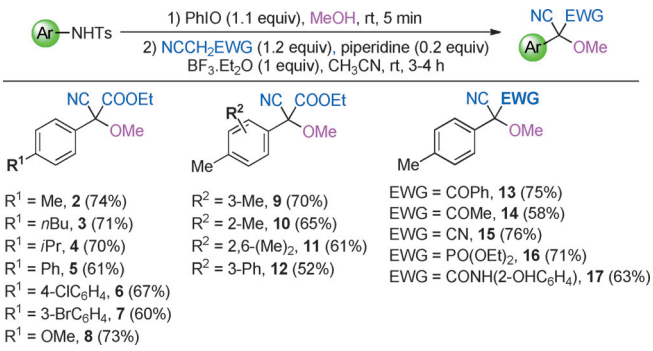
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201508161.

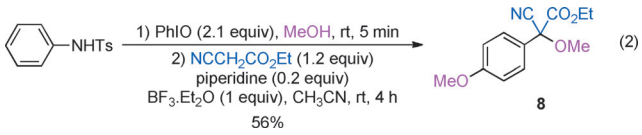


instead of L-proline, the reactions only provided the Knoevenagel condensation product in 47% yield. This result indicated that the presence of an acid might be essential for the formation of the quaternary product. Therefore, various combinations of secondary amines and acids were examined (see Table S1 in the Supporting Information). When 0.2 equivalents of piperidine were used together with 1 equivalent of $BF_3{\cdot}Et_2O$, compound **2** was obtained in 31% yield. However, while the addition of acids promotes the allylic rearrangement, it also promotes the 1,4-additions of cyclohexadienimine by MeOH or cyanoacetate. Further optimization revealed that a one-pot stepwise procedure could be employed to avoid the deleterious side reactions. Toluidine was treated with iodosylbenzene in methanol (0.1M) at room temperature for 5 minutes. After removal of the methanol in vacuum, acetonitrile, 2-cyanoacetate, and piperidine were added. The resulting mixture was stirred at room temperature for 3 h, and then $BF_3{\cdot}Et_2O$ was added. This reaction afforded compound **2** in 74% yield.

As shown in Scheme 3, reactions of a range of anilines with 2-cyanoacetate proceeded smoothly. The *para*-substituent in the anilines could be a linear or branched alkyl group, an aryl group, or a methoxy group. The oxidative dearomatization of 4-iodoaniline was complex. With multi-substituted anilines, the desired products were formed in reasonable yields but the steric hindrance caused by a 2-substituent in substrates tended to diminish the reaction yield. For example, compared with the reaction of 3,4-dimethylbenzenamine, the reaction of 2,4-dimethylbenzenamine or 2,4,6-trimethylbenzenamine afforded products in lower yields. The unsubstituted benzenamine could also be used as substrate. The reaction, in which 2.1 equivalents of PhIO were used to facilitate the oxidative dearomatization, provided the same product as the reaction of 4-methoxy benzenamine [Eq. (2)]. With respect to other nitriles, 3-oxo-3-phenylpropanenitrile, 3-oxobutanenitrile, diethyl cyanomethylphosphonate, malononitrile, and 2-cyano-*N*-(2-hydroxyphenyl)acetamide were suitable reaction partners in this process and gave a set of quaternary products, isolable in moderate to good yields.

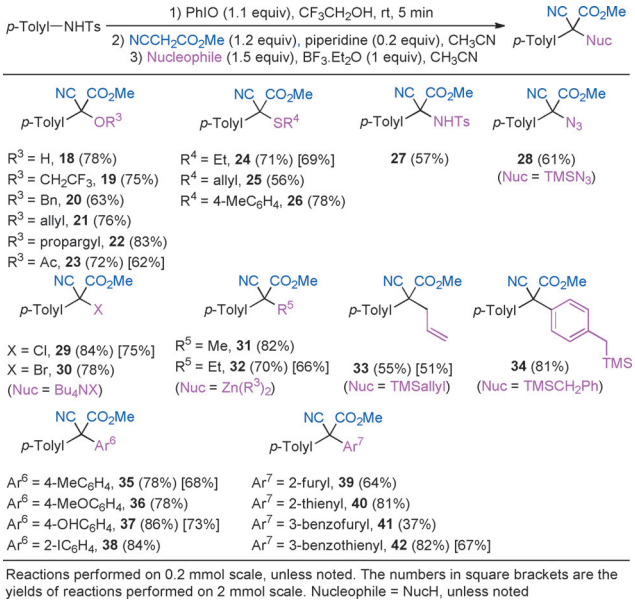


Scheme 3. Investigation of the scope of anilines and nitriles.



In an experiment designed to elucidate the reaction pathway, 1 equivalent of CD_3OD was added to the model reaction, leading to incorporation of the OCD_3 group into compound **2**. This result indicated that an added nucleophile might be incorporated into the structure of quaternary carbon centers. To evade competition between the added nucleophile and methanol, the oxidative dearomatization was conducted in the less nucleophilic 2,2,2-trifluoroethanol. First, a reaction using water as the added nucleophile was examined. The one-pot reaction conducted under the previously established conditions not only gave rise to the desired tertiaryalcohol **18** in 27% yield, but also produced the CF_3CH_2O-substituted compound **19** in 11% yield and the TsNH-substituted compound **27** in 13% yield (Ts = tosyl = toluene-sulfonyl). To inhibit the formation of the latter two by-products, a simple workup process was used to remove the residual CF_3CH_2OH and the generated $TsNH_2$ before adding water and $BF_3{\cdot}Et_2O$. In this way, the tertiary alcohol **18** was obtained in 78% yield.

A wide range of nucleophilic reagents could serve as the added nucleophile in this transformation (Scheme 4). For oxygen nucleophiles (alcohols and acids), and sulfur nucleophiles (thiols and thiophenols), the reactions proceeded smoothly affording the corresponding quaternary products in moderate to good yields. For nitrogen nucleophiles, the reaction of 4-methylbenzenesulfonamide gave rise to compound **27** in 57% yield, but the reaction of butylamine or

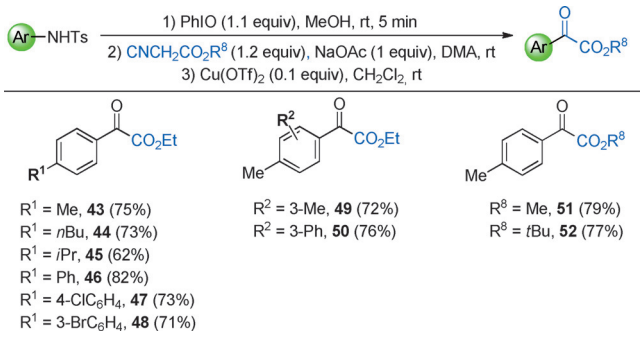


Reactions performed on 0.2 mmol scale, unless noted. The numbers in square brackets are the yields of reactions performed on 2 mmol scale. Nucleophile = NucH, unless noted

Scheme 4. Investigation of the scope of nucleophiles.

benzenamine was more complex. An azido group could be incorporated into the quaternary carbon center by use of azidotrimethylsilane. For tetrabutylammonium halides, the reaction of tetrabutylammonium chloride or tetrabutylammonium bromide provided the chloro or the bromo-substituted quaternary product in 84% and 78% yield, respectively. This strategy could also be used to construct all-carbon quaternary centers which, given the steric congestion between the carbon substituents, is challenging. For example, a methyl or ethyl group can be incorporated into the quaternary centers with organozinc reagents, and an allyl group can be introduced with allyltrimethylsilane as the added nucleophile. Interestingly, the reaction of benzyltrimethylsilane under the same conditions failed to produce the benzyl-substituted product, but instead afforded a phenyl-substituted compound **34** in 81% yield. Indeed, a range of diaryl quaternary centers were formed in good yields when electron-rich aromatic or heteroaromatic compounds were employed. When pyrrole or indole was employed as nucleophile, the reaction was complex. When some reactions were performed on 2 mmol scale, the corresponding products were obtained in acceptable yields.

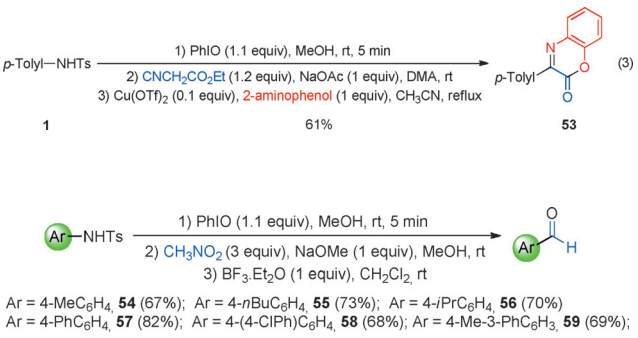
To further investigate the scope of this transformation, other active methylene compounds were examined. The reactions of malonates, β-keto esters or 1,3-diones gave rise to 3-substituted anilines, the products of the corresponding 1,4-addition to cyclohexadienimine. When 2-isocyanoacetates was used instead of 2-cyanoacetate, the reaction under the previously established conditions gave rise to α-keto ester **43** in 32% yield. It is proposed that this compound was generated from the decomposition of the unstable α-isocyano quaternary product. Further optimization improved the yield to 75% (Scheme 5). When 2-aminophenol was introduced into this reaction at the third step, the reaction afforded benzoxazinone **53** in 61% yield [Eq. (3)].



Scheme 5. Conversion of *para*-substituted anilines to α-keto esters.

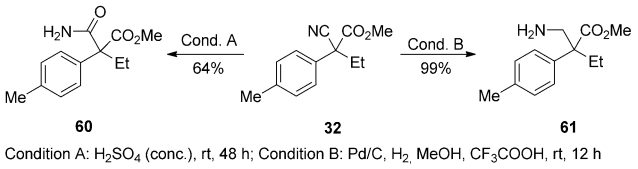
Moreover, nitromethane was also a suitable reaction partner in this transformation. With the aid of 1 equivalent of $BF_3{\cdot}Et_2O$, the one-pot stepwise reaction with nitromethane converted *para*-substituted anilines to the corresponding aromatic aldehydes in moderate to good yields (Scheme 6).

Through the manipulation of the cyano group, the cyano-substituted quaternary centers obtained in this reaction can



Scheme 6. Conversion of *para*-substituted anilines to aromatic aldehydes.

be readily converted into other quaternary compounds. For example, the hydrolysis of compound **32** under acid conditions produced the amide **60**, and reduction afforded β-amino ester **61** (Scheme 7).



Scheme 7. Transformation of cyano-substituted quaternary carbon center.

In conclusion, we have developed an aromatic carbon–nitrogen bond functionalization reaction by using a simple dearomatization strategy. Through this process *para*-substituted anilines serve as a potential aryl source in the construction of a range of functionalized aromatic molecules, such as quaternary carbon centers, α-keto esters, and aldehydes. The limitation at this stage is that this strategy may apply only *para*-substituted aniline system. The extension of this strategy to other aniline system and the applications of this strategy to the synthesis of natural products are in progress.

Experimental Section

Representative procedure: PhIO (0.22 mmol) was added to a solution of *N*-Ts *p*-toluidine (**1**) (0.2 mmol) in MeOH (2.0 mL) at 25 °C. After 5 min, the reaction mixture was concentrated in vacuo. The resulting mixture was mixed with 2-cyanoacetate (0.24 mmol) and piperidine (0.04 mmol) in MeCN (2 mL). The reaction was stirred at room temperature for 3 h, then $BF_3{\cdot}Et_2O$ (0.2 mmol) was added. After the substrate was completely consumed (monitored by TLC analysis), the reaction was quenched with saturated $NaHCO_3$ (25 mL), and extracted with EtOAc (25 mL × 3). The organic layer was dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/EtOAc) to furnish the desired compound **2**.

Acknowledgements

We are grateful to the National Science Foundation of China (grant numbers 21332009 and 21302021), the Shanghai Science and Technology Committee (grant number 13431900103), and the Shanghai Municipal Natural Science Foundation (grant number 13ZR1402200) for support of this research.

Keywords: cyanides · dearomatization · functionalization of carbon–nitrogen bonds · quaternary carbon centers · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 13655–13658
Angew. Chem. **2015**, *127*, 13859–13862

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Received: August 31, 2015
Published online: October 12, 2015

