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This work may now be cited as: *Chin. J. Chem.* **2021**, *39,* 10.1002/cjoc.202100430.

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ISSN 1001-604X • CN 31-1547/O6
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Report

Cite this paper: *Chin. J. Chem.* **2021**, *39*, XXX—XXX. **DOI: 10.1002/cjoc.202100XXX**

Selective carbon-carbon bond amination with redox-active aminating reagents: A direct approach to anilines

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This paper is dedicated to the memory of Professor Ei-ichi Negishi.

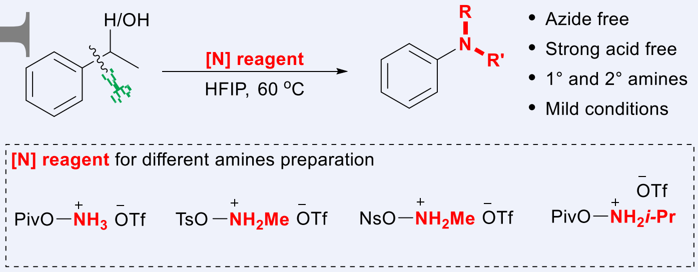
Keywords

anilines | carbon-carbon bond cleavage | amination reagents | nitrogenation|alkylarenes

Main observation and conclusion

Amines are among the most fundamental motifs in chemical synthesis, and the introduction of amine building blocks via selective C-C bond cleavage allows the construction of nitrogen compounds from simple hydrocarbons through direct skeleton modification. Herein, we report a novel method for the preparation of anilines from alkylarenes via Schmidt-type rearrangement using redox-active amination reagents, which are easily prepared from hydroxylamine. Primary amines and secondary amines were prepared from corresponding alkylarenes or benzyl alcohols under mild conditions. Good compatibility and valuable applications of the transformation were also displayed.

Comprehensive Graphic Content



- Azide free
- Strong acid free
- 1° and 2° amines
- Mild conditions

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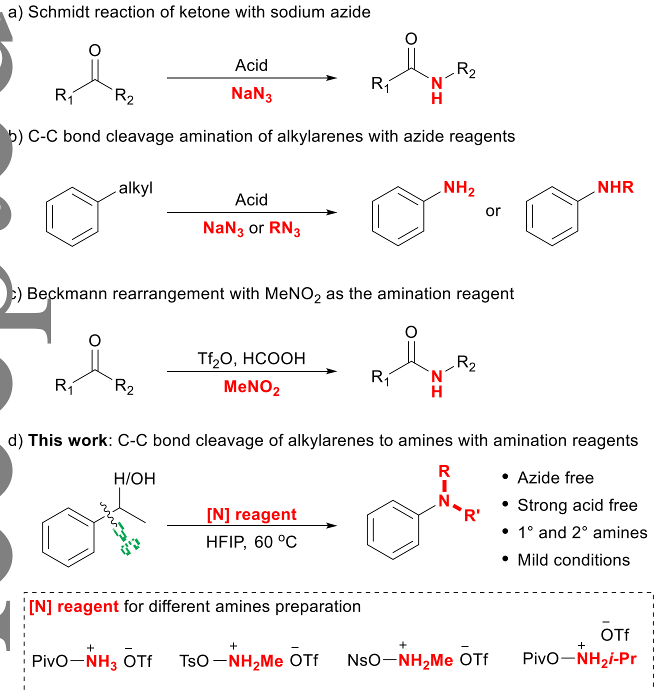
Background and Originality Content

The introduction of nitrogen-containing fragments into compounds is a vital transformation for the synthesis of bioactive molecules and natural products.[1] In particular, efficient methods for the preparation of amines have been broadly studied in the past decades via C-H bond functionalization,[2] coupling strategies[3] or addition reactions.[4] Despite the significance of the developed methods, site-selective amination of simple hydrocarbons or complex molecules via late-stage modification are still highly desired.[5]

Carbon skeletons exist ubiquitously in bulk chemicals, biomass and chemical synthetics.[6] Direct skeleton modification of alkylarenes via C-C bond amination would facilitate access to value-added amines, especially anilines.[7] Schmidt rearrangement provides a milestone for the intermolecular C-C bond nitrogenation reaction of carbonyl substrates (**Scheme 1**(a)).[8] In recent years, the C-C bond amination of alkylarenes with sodium azide or alkyl azide have been developed for the preparation of arylamines (**Scheme 1**(b)).[9] However, the use of sodium azide in strong acid conditions limited their application in practical production.[10] Considering the pursuit of secure efficient methods for the preparation of nitrogen compounds, we recently disclosed the Schmidt-type reaction of carbonyl compounds and alkynes using $MeNO_2$ as the N-source to replace the azide reagents in the traditional Schmidt reaction (**Scheme 1**(c)).[11]

Scheme 1 C-C bond cleavage amination with amination reagents.



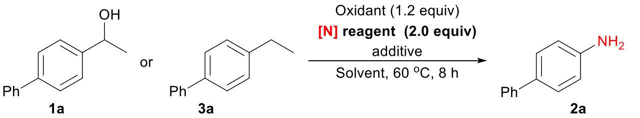
Recently, hydroxylamine derivatives have attracted a lot of attentions, and have been used as efficient redox-active aminating reagents in C-H or C-B amination reaction.[12,13] In contrast, the direct C-C bond amination with these significant non-azido reagents was still rarely achieved. With our continuous effort in the C-C bond nitrogenation reactions,[9,11,14] we envisioned that these amination reagents might be effective for the direct amination of alkylarenes through selective C-C bond cleavage. Herein, we report a novel C-C bond amination reaction of alkylarenes for the efficient synthesis of primary and secondary anilines (**Scheme 1**(d)). Different amination reagents were prepared and applied in this C-C bond amination transformation. With HFIP as the solvent, strong acids were not required.

Results and Discussion

We initially tried to use $PivONH_2·HOTf$ as the amination reagent (**Table 1**), which has been widely used in efficient amination reactions.[15] Interestingly, the experiment with 1-([1,1'-biphenyl]-4-yl)ethan-1-ol (**1a**) and $PivONH_2·HOTf$ (2 equiv) in HFIP at 60 °C for 8 hours provided the desired [1,1'-biphenyl]-4-amine (**2a**) with 63% yield (entry 1, Table 1). Considering the key role of the amination reagent in the transformation, different hydroxylamine reagents have been tested in the reaction (entry 2-6), but only $AcONH_2·HOTf$ worked and afforded the product with 32% yield. The addition of H_2O (5 equiv) could increase the yield to 85% (entry 7), which might accelerate the hydrolysis of the imine intermediate for the final generation of anilines, while more water would be adverse (entry 8) possibly for its competing effect with amination reagent. Other solvents like TFE and TFA were not beneficial (entries 9-10).

It is noteworthy that the simple alkyl benzene substrates can also be converted into the corresponding aniline products with $PivONH_2·HOTf$ as the amination reagent (entries 11-16, Table 1). In these cases, oxidant was essential for the reaction. With the 4-ethyl-1,1'-biphenyl (**3a**) as the substrate, the screening of different oxidants proved that DDQ was far more efficient than other oxidants for the C-C bond cleavage amination of alkylarenes and gave the product with 69% yield (entry 11-16).

Table 1 Screening of the reaction conditions[a]

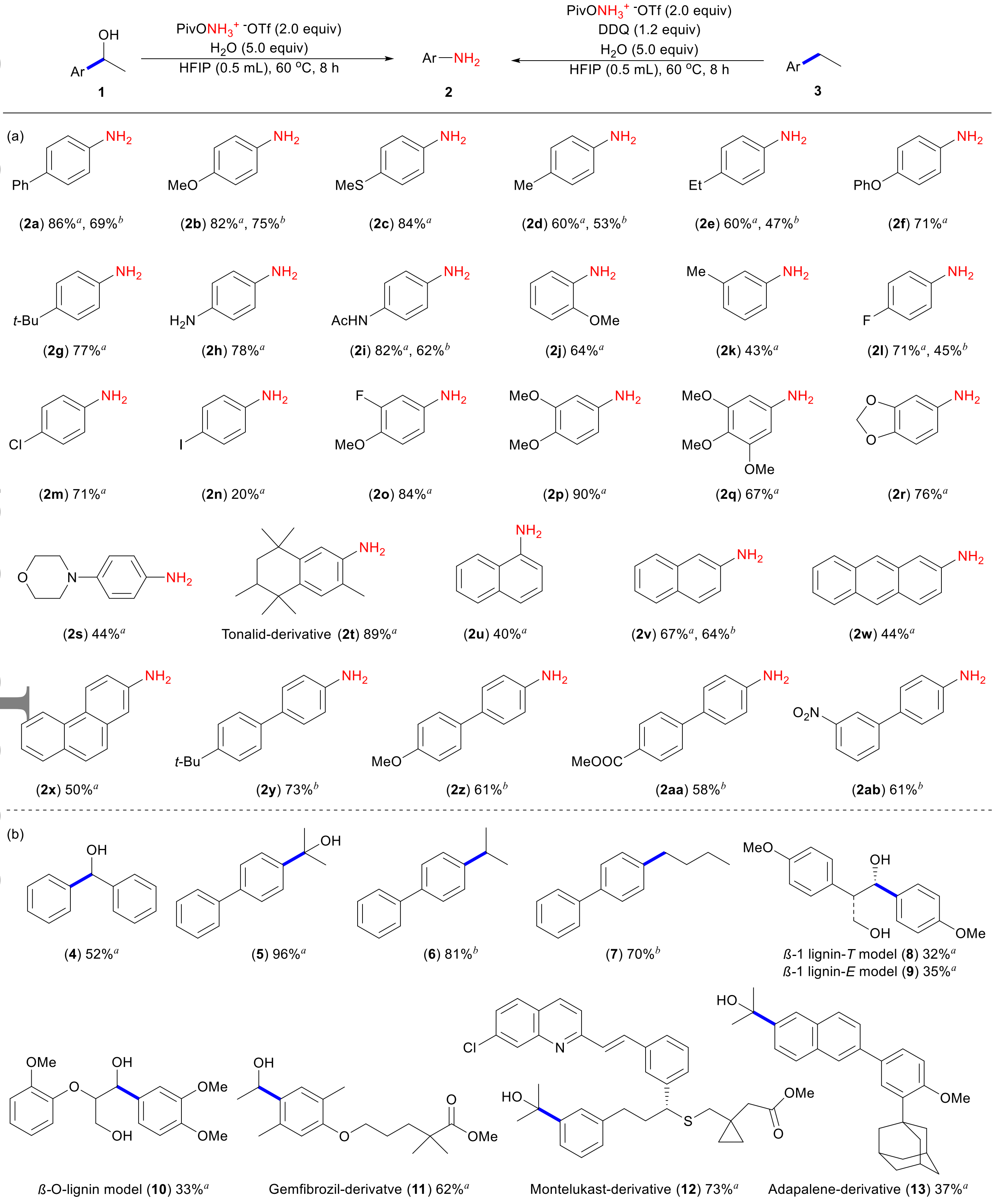


Entry	Sub	Oxidant	[N] reagent (2.0 equiv)	additive	Solvent	Yield **2a**[b] [%]
1	**1a**	-	$PivONH_2·HOTf$	-	HFIP	63
2	**1a**	-	$AcONH_2·HOTf$	-	HFIP	32
3	**1a**	-	PivONHBoc	-	HFIP	0
4	**1a**	-	$HOSO_2ONH_2$	-	HFIP	0
5	**1a**	-	$NH_2OH·HCl$	-	HFIP	0
6	**1a**	-	$MeONH_2·HCl$	-	HFIP	0
7	**1a**	**-**	**$PivONH_2·HOTf$**	**H_2O (5 equiv)**	**HFIP**	**85**
8	**1a**	-	$PivONH_2·HOTf$	H_2O (10 equiv)	HFIP	72
9	**1a**	-	$PivONH_2·HOTf$	H_2O (5 equiv)	TFA	48
10	**1a**	-	$PivONH_2·HOTf$	H_2O (5 equiv)	TFE	55
11	**3a**	**DDQ**	**$PivONH_2·HOTf$**	**H_2O (5 equiv)**	**HFIP**	**69**
12	**3a**	TBHP	$PivONH_2·HOTf$	H_2O (5 equiv)	HFIP	0
13	**3a**	Oxone	$PivONH_2·HOTf$	H_2O (5 equiv)	HFIP	5
14	**3a**	$K_2S_2O_8$	$PivONH_2·HOTf$	H_2O (5 equiv)	HFIP	0
15	**3a**	PIDA	$PivONH_2·HOTf$	H_2O (5 equiv)	HFIP	5
16	**3a**	CAN	$PivONH_2·HOTf$	H_2O (5 equiv)	HFIP	0

[a] Reaction conditions: Substrate (0.3 mmol), Oxidant, [N] reagent (0.6 mmol, 2.0 equiv) and additive were stirred in solvent (0.5 mL) at 60 °C for 8 h under air. [b] Yields were determined from isolated **2a**.

Under the optimized conditions, the scope of benzyl alcohols and alkylarenes have been explored (**Table 2**). With ethylarenes and secondary alcohols as substrate, different functional groups substitutions were tested. Substrates bearing electron-donating groups including ether groups, amino alkyl and amide (**2b**-**k**) underwent the cleavage well and provided corresponding anilines with 43% to 84% yields. Besides, the cleavage amination of benzyl alcohols substituted with electron-withdrawing halogen groups (**2l**-**n**) and ethylarenes with arenes substituents (**2y**-**ab**) could also lead to the desired anilines. Interestingly, 1,4-diethylbenzene (**3e**) could also undergo the selective C-C bond cleavage and provided 4-ethylaniline (**2e**) as the only product. Benzyl alcohols with *ortho*- substituted OMe (**2j**) and *meta*-substituted Me (**2k**) and multi-substituents (**2o**-**r**) conducted the transformation well with

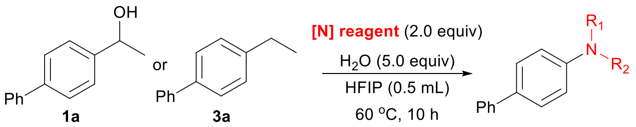
Table 2 Substrate scope for the synthesis of anilines



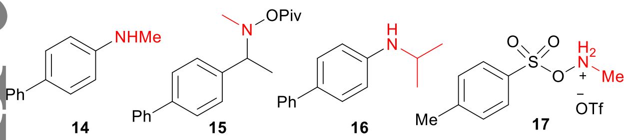
[a] Reaction conditions: Benzyl alcohol substrate (0.3 mmol), PivONH$_2$·HOTf (0.6 mmol, 2.0 equiv) and H$_2$O (1.5 mmol, 5.0 equiv) were stirred in

HFIP (0.5 mL) at 60 °C for 8 h under air. [b] Alkylarene substrate (0.3 mmol), DDQ (0.36 mmol, 1.2 equiv), PivONH$_2$·HOTf (0.6 mmol, 2.0 equiv) and H$_2$O (1.5 mmol, 5.0 equiv) were stirred in HFIP (0.5 mL) at 60 °C for 8 h under air. Yields were determined from isolated product.

Table 3 C-C bond cleavage amination with alkyl amination reagents[a]

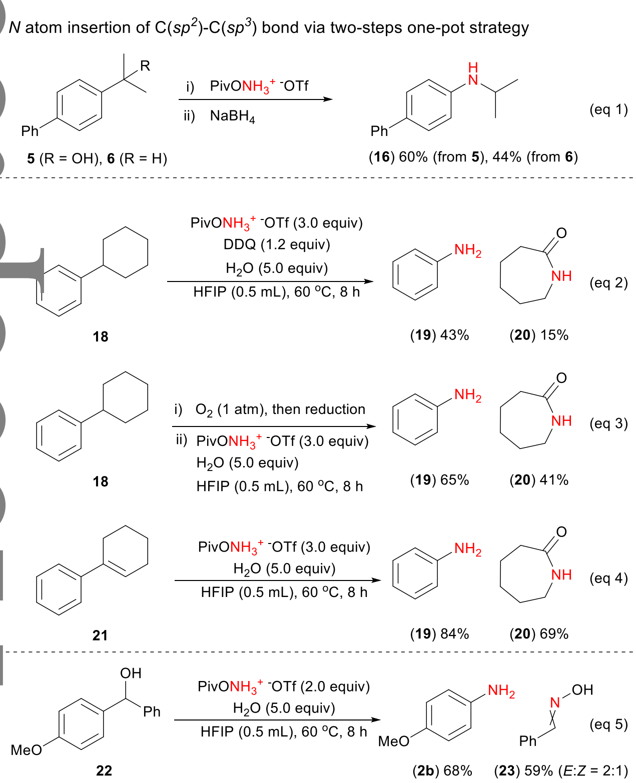


Entry	Substrate	**[N] reagent** (2.0 equiv)	Yield of products
1	**1a**	$PivO\overset{+}{N}H_2Me\ \overset{-}{O}Tf$	(**14**) 22%, (**15**) 50%
2	**1a**	$NsO\overset{+}{N}H_2Me\ \overset{-}{O}Tf$	(**14**) 62%
3	**3a**	$TsO\overset{+}{N}H_2Me\ \overset{-}{O}Tf$ (**17**)	(**14**) 60%[b]
4	**1a**	$TsO\overset{+}{N}H_2Me\ \overset{-}{O}Tf$ (**17**)	(**14**) 70%
5	**1a**	$PivO\overset{+}{N}H_2i\text{-}Pr\ \overset{-}{O}Tf$	(**16**) 32%



[a] Reaction conditions: Substrate (0.3 mmol), [N] reagent (0.6 mmol, 2.0 equiv) and H$_2$O (1.5 mmol, 5.0 equiv) were stirred in HFIP (0.5 mL) at 60 °C for 10 h under air. [b] DDQ (0.36 mmol, 1.2 equiv) was added. Yields were determined from isolated products.

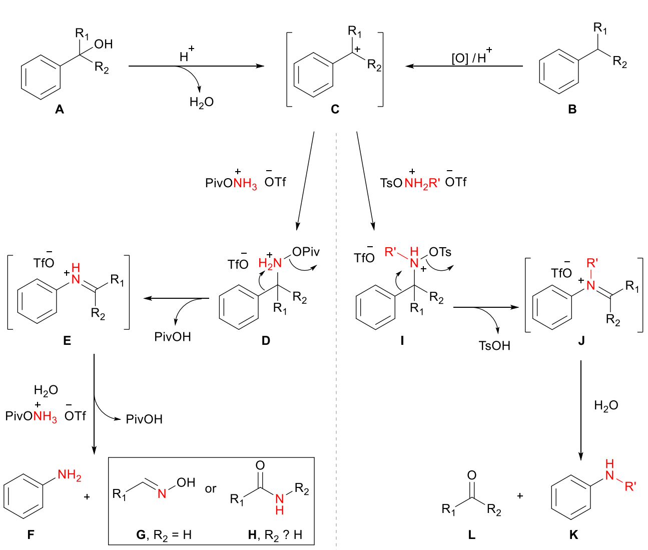
Scheme 2 More transformations and mechanism studies.



the yields of 43% to 90%. In addition, polycyclic anilines (**2u**-**x**) were also available with this method, which are poorly prepared with the reported method with sodium azide as the nitrogen source. Based on these results, transformation of more different alkyl substituted arenes have been investigated. Diphenylmethanol (**4**) could be transformed into aniline with 52% yield. The C-C bond cleavage amination of tertiary alcohol (**5**) and 4-isopropyl-1,1'- biphenyl (**6**) afford the product [1,1'-biphenyl]-4-amine (**2a**) with the yields of 96% and 81% respectively, which indicates that tertiary carbon possesses a better reactivity than secondary carbon. While longer carbon chain has no influence to the reactivity (**7**). Thinking of the great importance of anilines in bioactive molecules, the modification of the derivatives of Tonalid (**1t**), Gemfibrozil (**11**), Montelukast (**12**) and Adapalene (**13**) were conducted, and provided corresponding anilines with 37% to 89% yields, ester group, olefins, quinoline and other groups were well tolerated, which shown the potential application of this method in the late-stage functionalization of complex compounds. Benzyl alcohols are widespread in natural biomass such as lignin. Thinking of the pursuit of the degradation of these bio-renewable matters into value-added chemical materials, [16] different lignin model molecules were applied in the transformation, corresponding anilines 3,4-4-methoxyaniline (**2b**) and dimethoxyaniline (**2p**) were obtained with 32% to 35% yields, the mild and safe reaction conditions and easily accessible reagents make this method potential for industrial application.

With the developed method, we further investigated more amination reagents for the preparation of secondary amines (**Table 3**). Reaction with the PivONHMe·HOTf as the amination reagent was proven feasible for the transformation, but only with 22% yield of the product **14** and 50% yield of the byproduct **15** without rearrangement (entry 1). Further optimization found that NsONHMe·HOTf and TsONHMe·HOTf (**17**) were more efficient for the C-C bond cleavage amination of **1a** and **3a** (entry 2-4). Amination reagents with PivOH as the leaving group afforded the products with moderate yields (entry 5). While the preparation of tertiary morpholine amination reagent with TsOH as leaving group failed using the standard procedure.

Scheme 3 Mechanism of C-C bond cleavage amination reaction



To investigate the mechanism of the reaction, more transformations of different alkylarenes have been accomplished (**Scheme 2**). The insertion of nitrogen atom into the inert C(sp^2)-C(sp^3) bond of alkylarenes could achieve the direct skeleton modification of the molecules, this process has been fulfilled with **5** or **6** as the substrate by two-steps one-pot with $NaBH_4$ as the reductant (eq 1). Cyclohexylbenzene (**18**) could be transformed into aniline (**19**) and caprolactam (**20**) with DDQ as the oxidant by this protocol (eq 2). A more efficient method was fulfilled by using O_2 as the oxidant, which is a cheaper and greener oxidant for practical production (eq 3). In addition, the C(sp^2)-C(sp^2) bond cleavage amination of 1-phenylcyclohexene (**21**) without oxidants also afforded aniline and caprolactam in 84% and 69% yields respectively (eq 4), which indicated that this method also works well for the C-C bond cleavage of aryl olefins. The reaction of (4-methoxyphenyl)(phenyl)methanol (**22**) provided **2b** and benzaldehyde oxime (**23**) with 68% and 59% yields respectively, which might hint that 2 equivalences of PivONH$_2$·HOTf get involved in the C-C bond cleavage amination process (eq 5).

A mechanistic rationale for this C-C bond amination reaction is shown in **Scheme 3**. The carbon cation **C** generated from benzyl alcohols **A**, alkylarene **B** or aryl olefins was attacked by hydroxylamine reagents. Then further rearrangements of the obtained intermediates (**D**, **I**) promoted by HFIP afford the imine intermediates (**E**, **J**), with PivOH or TsOH as the leaving part. The final hydrolysis or attraction by amination reagent provides the desired amines.

Conclusions

In summary, a novel selective C-C bond cleavage amination of alkylarenes to prepare anilines and secondary amines was demonstrated. The mild conditions, safe redox-active aminating reagents make this method very practical in chemical synthesis. The application in the modification of complex bioactive molecules, lignin model compounds and cyclohexylbenzene to value added products displayed good application prospects. The nitrogen atom insertion of inert C-C bonds of alkylarenes possesses potential value for new reactions of simple hydrocarbons.

Experimental

General procedure for C-C amination of secondary alcohols: To a 20 mL vial equipped with a stir bar was added secondary alcohols (0.3 mmol), amination reagents (0.6 mmol), HFIP (0.5 mL) followed by the addition of H_2O (1.5 mmol), then the mixture was stirred under air at 60 °C for 8 h. After cooling down to room temperature, the reaction mixture was quenched by 2 M NaOH (5 mL), extracted by EA (5 × 2 mL), the combined organic phase was washed with brine and dried over Na_2SO_4. Then the mixture was concentrated and purified by flash chromatography on a short silica gel (eluent: PE/EA = 10/1) to afford the desired anilines.

General procedure for C-C amination of alkylarenes: To a 20 mL vial equipped with a stir bar was added alkylarenes (0.3 mmol), amination reagents (0.6 mmol), DDQ (0.36 mmol), HFIP (0.5 mL) followed by the addition of H_2O (1.5 mmol), then the mixture was stirred under air at 60 °C for 8 h. After cooling down to room temperature, the reaction mixture was quenched by 2 M NaOH (5 mL), extracted by EA (5 × 2 mL), the combined organic phase was washed with brine and dried over Na_2SO_4. Then the mixture was concentrated and purified by flash chromatography on a short silica gel (eluent: PE/EA = 10/1) to afford the desired anilines.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

Acknowledgement (optional)

Financial support from the National Natural Science Foundation of China (21772002, 21901010, and 21901012), the Drug Innovation Major Project (2018ZX09711-001), and the Open Research Fund of State Key Laboratory of Catalytic Materials and Reaction Engineering (RIPP, SINOPEC) is greatly appreciated.

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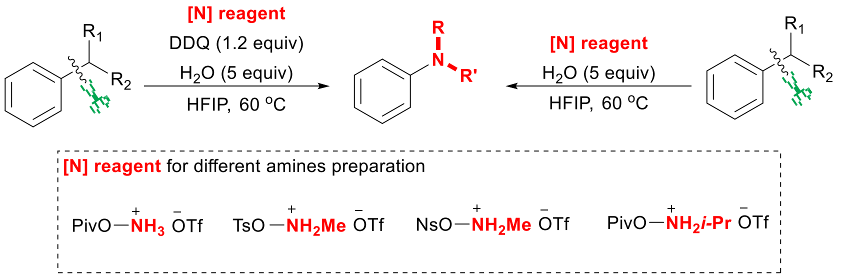
(The following will be filled in by the editorial staff)
Manuscript received: XXXX, 2021
Manuscript revised: XXXX, 2021
Manuscript accepted: XXXX, 2021
Accepted manuscript online: XXXX, 2021
Version of record online: XXXX, 2021

Entry for the Table of Contents

Selective carbon-carbon bond amination with redox-active ami-nating reagents: A direct approach to anilines

Xu Qiu,[a,b] Yachong Wang,[a,b] Lingyu Su,[a] Rui Jin,[a,c] Song Song,[a] Qixue Qin,[a] Junhua Li,[a] Baoning Zong,[c] and Ning Jiao*[,a,d]

Chin. J. Chem. **2021**, *39*, XXX—XXX. **DOI: 10.1002/cjoc.202100XXX**



We have developed the selective C-C bond cleavage amination of alkylarenes to prepare anilines and secondary arylamines, the mild conditions, safe redox-active aminating reagents and the use of O_2 as the environmentally benign oxidant make this method more practical. Applications in the modification of complex bioactive molecules and C-C bond cleavage transformation of lignin model compounds and cyclohexylbenzene to value added products were conducted.