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From alkylarenes to anilines via site-directed carbon–carbon amination

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Anilines are fundamental motifs in various chemical contexts, and are widely used in the industrial production of fine chemicals, polymers, agrochemicals and pharmaceuticals. A recent development for the synthesis of anilines uses the primary amination of C–H bonds in electron-rich arenes. However, there are limitations to this strategy: the amination of electron-deficient arenes remains a challenging task and the amination of electron-rich arenes has a limited control over regioselectivity—the formation of *meta*-aminated products is especially difficult. Here we report a site-directed C–C bond primary amination of simple and readily available alkylarenes or benzyl alcohols for the direct and efficient preparation of anilines. This chemistry involves a novel C–C bond transformation and offers a versatile protocol for the synthesis of substituted anilines. The use of O_2 as an environmentally benign oxidant is demonstrated, and studies on model compounds suggest that this method may also be used for the depolymerization of lignin.

Anilines are among the most common and important chemicals, and are widely applied in the synthesis of natural products, pharmaceuticals, agrochemicals, dyes and polymers[1]. One of the most step- and atom-economic approaches to the synthesis of anilines is to decorate the aromatic hydrocarbons directly with the NH_2 group[2,3]. However, the direct incorporation of the NH_2 moiety to alkylarenes through C–H and/or C–C bond cleavage has three formidable challenges: (1) the high bond dissociation energy, (2) the potential competitive chelation of aniline products to the catalyst and (3) the instability of aniline products under strong oxidative conditions. Apart from the traditional nitration/hydrogenation process under harsh conditions[4] and the Buchwald–Hartwig type of cross-coupling with aryl halides[5–9] or arylmetals[10–12], efficient approaches to anilines through C–H primary amination have been elegantly developed using electrochemical catalysis[13], photoredox catalysis[14,15] or novel electrophilic amination reagents[16] (Fig. 1a). Despite the breakthroughs in C–H primary amination, there remain some unresolved issues. The reported aminations of arenes are hindered by the limited control of regioselectivity between the *para*- and *ortho*-products, the difficulty to carry out the selective *meta*-amination of electron-rich arenes and the challenging amination of electron-deficient arenes (Fig. 1b).

Alternatively, a more straightforward route to incorporate the NH_2 group into substituted arenes would be via a site-directed C–C bond cleavage[17–25] to form substituted anilines. We envision that this strategy will open new opportunities to functionalize inert bonds and provide a chance to prepare primary anilines via the position of the C–C bond cleavage. Alkylarenes are readily available from coal and crude oil, and offer a fertile test ground for the invention of new chemical transformations in both the academic and industrial fields. The cumene–phenol process (Hock process), which produces more than nine million tonnes of phenol per year, represents one of the most successful transformations of alkylarenes (Fig. 1c)[26]. However, to the best of our knowledge, the highly attractive transformation from cumene to aniline is still unknown because of the non-polar inert chemicals and the high bond dissociation energy. In the case of ethylbenzene and cumene, the bond dissociation energy of the C(sp^2)–C(sp^3) bond (98–100 kcal mol^{-1}) is higher than that of C(sp^3)–C(sp^3) bonds (76–77 kcal mol^{-1})[27,28]. Additionally, the C(sp^2)–C(sp^3) bonds are surrounded and hindered by more C–H and C–C bonds. Therefore, such C–C σ bonds are thermodynamically stable and kinetically inert (Fig. 1c), which, in turn, has led to direct C–C bond functionalization[29–37] being underdeveloped. Here we report a previously elusive C–C amination protocol for aniline synthesis from simple and readily available alkylarenes or substituted benzyl alcohols to achieve a site-directed aniline preparation. This chemistry proposes a novel C–C bond transformation. The most common linkage motifs in lignin could also be cleaved into the corresponding anilines, which demonstrates a potential extraction of higher value from the waste lignin product in the pulp and paper industry[38,39]. Notably, this transformation can also be accomplished with O_2 as the environmentally benign oxidant.

Results and discussion

In line with the nitrogenation of the simple hydrocarbons[40–42], we hypothesized that a suitable nitrogen source could enable this direct C–C amination from the readily available alkylarenes. We initially investigated the reactions of 4-isopropyl-1,1′-biphenyl (**1a**) with different nitrogenation reagents. Unfortunately, some nitrogen sources, such as *tert*-butyl nitrite, $NaNO_2$, $AgNO_2$, $NH_2OH{\cdot}HCl$ and *N*-sulfonyl azide in common solvents failed to provide the desired primary anilines (Supplementary Table 3). Interestingly, the reaction in the presence of NaN_3, which is readily available and features a lower toxicity and volatility than other azide reagents[43], afforded the aniline product **2a** in a 70% yield under air with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant (Table 1, reaction A). The oxidant and pK_a value of the acid are vitally important for this transformation. Other oxidants, such as *tert*-butyl hydroperoxide, *N*-fluorodibenzenesulfonimide, Selectfluor and Oxone showed a low efficiency.

Inspired by these results, we envisioned that the redox-neutral C–C amination is more attractive. Thus, the simple secondary alcohols,

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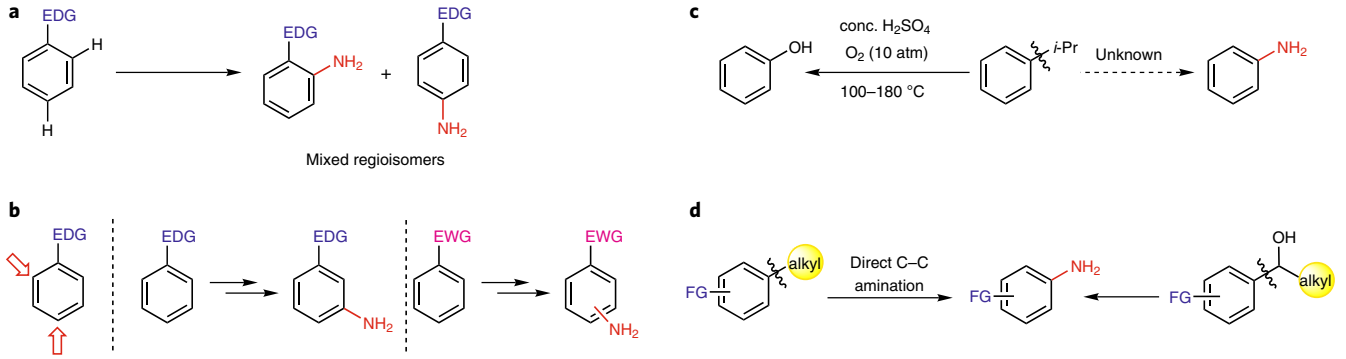


Fig. 1 | Efficient synthesis of anilines. a, The development of aryl C–H primary amination through traditional nitration/hydrogenation processes, transition metal catalysis with novel amination reagents, electrochemical catalysis or photoredox catalysis with the formation of the mixed regioisomers products. **b**, Long-standing unsolved problems in the direct primary amination of arene C–H bonds: difficulties in the separation of regioisomers, limited substrate scope, multisteps required for selective *para*- or *ortho*-amination, selective *meta*-amination of electron-rich arenes remains difficult and challenging amination of electron-deficient arenes. **c**, The Hock process represents one of the most successful transformations of the alkylarenes. However, other transformations of alkylarenes, such as the previously elusive C–C amination of cumene to aniline are still unknown. **d**, This work can address the above problems via site-directed C–C amination of the alkylarenes or the corresponding benzyl alcohols. EDG, electron-donating group; FG, functional group. conc., concentrated.

which are also easily accessible, were investigated in the absence of oxidant. Excitingly, the simple secondary alcohols **3** could also be efficiently transformed into the anilines in *n*-hexane with acid as an additive instead of solvent. This demonstrates another pathway without the use of oxidant (Table 1, reaction B) that provides a milder protocol and widens the scope of this transformation.

Having developed the optimum conditions, the scope of this C–C amination reaction was then investigated with both alkylarenes and benzyl alcohols as substrates (Table 1). Various *para*-substituted anilines were efficiently synthesized with the corresponding isopropylbenzenes and secondary alcohol derivatives regardless of the electronic properties of the substrates. For example, halogenated isopropylbenzene and benzyl alcohols endured to deliver the site-specific anilines (**2b**, **2g** and **2h**), respectively, to leave the halogens available for downstream synthetic manipulation. It is noteworthy that the electron-withdrawing anilines, which are inaccessible through C–H amination, could also be efficiently synthesized using this newly developed method (**2m**, **2n** and **2p**)[13–16]. Moreover, the carboxylic group, which is generally known to undergo the undesired Schmidt reaction under acidic conditions, remained unchanged in this C–C bond functionalization, albeit in low yield due to isolation problems (**2p**), which highlights the high chemoselectivity of this transformation. The potentially sensitive unprotected hydroxyl group (**2o**) and the free amine group (**2u**) were also compatible with this C–C amination process.

As expected, *ortho*-substituted anilines were prepared through the benzyl alcohols. Notably, compared with the traditional nitration and hydrogenation of the corresponding bromobenzene, 2-bromoaniline (**2q**) was synthesized through this site-directed C–C activation efficiently and selectively without the cumbersome isolation operation of the mixed regioisomers[44]. Excitingly, *meta*-substituted anilines with different functional groups, which originally could not be directly synthesized through the traditional electrophilic C–H amination process[13–16], can now be prepared efficiently by this C–C amination protocol (**2u**–**2za**, Table 1). We then investigated alkyl scope of the C(Ar)–C(alkyl) bond cleavage in the alkylarenes C–C amination process (**4a**–**4e**). As shown in Table 2, alkylarenes that bear a series of alkyl groups (Et, *i*-Pr, *n*-Bu, Bn and Cy) could be selectively cleaved.

From a green and sustainable chemistry aspect, O_2 has been considered an ideal oxidant. We therefore decided to test the use of O_2, instead of DDQ, as the oxidant in the direct C–C amination of alkylarenes. Notably, the readily available industrial feedstocks ethylbenzene (**4a**), cumene (**4b**) and 4-isopropyl-1,1'-biphenyl (**1a**) all performed well, and produced the corresponding anilines products in moderate yields by using an aerobic oxidation/hydrogenation process with 1 atm O_2 as the oxidant (Table 3).

The newly developed procedure was found to be different from traditional organic reactions, which require pure starting materials. Under the reaction conditions, the mixture of alkyl benzenes (**4a**, **4b** and **4d**) was transformed into **5a** with a 60% yield (Fig. 2a), which highlights the potential application of this chemistry to transform a crude mixture of aromatic hydrocarbons from the oil and coal industry into a single aniline product. Furthermore, we carried out gram-scale reactions under O_2 conditions which gave a higher yield in comparison to the small-scale reaction (Fig. 2a and Table 3). These results demonstrate the potential practicability of this protocol as well as indicate the possibility for the industrial application of this transformation, as with the Hock process.

To evaluate the feasibility of this C–C amination for late-stage functionalization, two clinical local anaesthetics, benzocaine (**7a**) and procaine (**7b**), were synthesized from the corresponding secondary alcohols. As shown in Fig. 2b, a variety of secondary or tertiary alcohols (**6c**–**6f**) derived from representative pharmaceuticals, which included the antilipaemic gemfibrozil, antipsychotic iloperidone, acne-curative adapalene and antihyperglycaemic repaglinide, were proven to be tolerated in this protocol and produced the corresponding aniline derivatives (**7c**–**7f**) in good yields. These transformations accommodated various functional groups, including sensitive esters, amides and N-heterocycles, which suggests the mildness and practicality of this protocol.

Biorenewable lignin is regarded as a waste aromatic chemical source from the pulp and paper industry[38,39]. Thus, the extraction of higher value-added products from lignin is appealing to satisfy an economically sustainable development. Interestingly, the present chemistry could be applied in the cleavage of the β-1 and β-O-4 lignin model compounds, which are prevalent chemical linkages in lignin from spruce trees. As described in Fig. 2c, 8-β-1 lignin-T and 8-β-1 lignin-E model compounds could be converted into the corresponding 4-methoxyaniline (**2c**, 53% and 49% yields, respectively), and the β-O-4 lignin model compound **9** could be converted into 3,4-dimethoxyaniline (**10**) in a 40% yield, which provides a potentially applicable protocol to depolymerize the biorenewable lignin to high value-added chemicals.

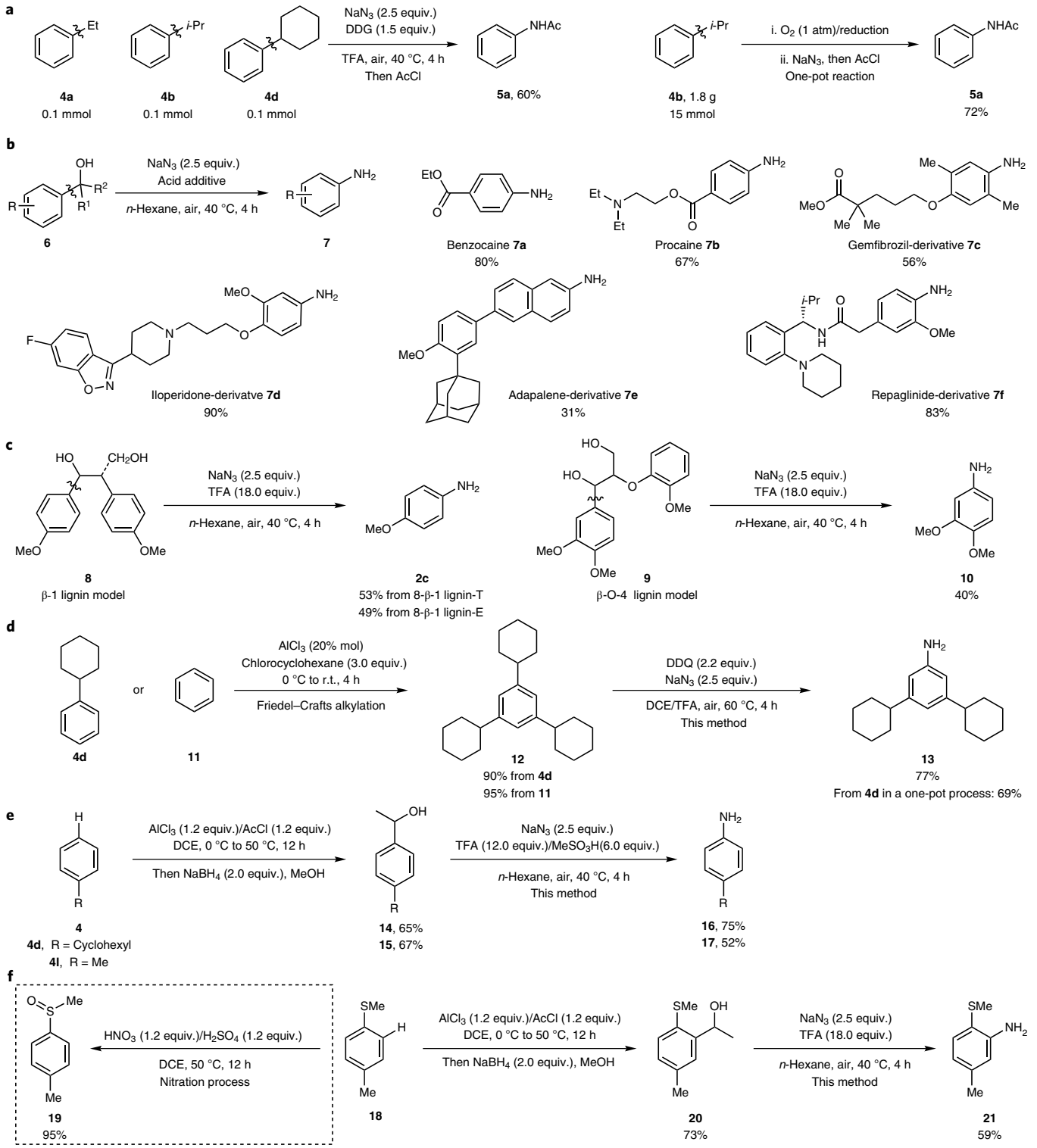


Fig. 2 | Synthetic applications of the site-directed C–C amination. a, A mixture of alkylarenes can be transformed into the desired products by this protocol. Compared with a small-scale reaction (Table 3), a gram-scale reaction with substrate **4b** under O_2 conditions produced a higher yield, which demonstrates the potential industrial application of this transformation. **b**, Late-stage C–C amination reactions for the synthesis and modification of the representative pharmaceuticals. **c**, Cleavage of the β-1 and β-O-4 lignin models to anilines provides a potentially applicable protocol for the synthesis of high value-added chemicals from the biorenewable lignin. **d**, Friedel–Crafts alkylation for the selective and efficient synthesis of 1,3,5-tricyclohexylbenzene **12**[45], followed by our presented selective C–C primary amination process to give 3,5-dicyclohexylaniline **13** (77% yield). The reaction of **4d** could also be carried out in one pot with a 69% yield. **e**, Synthesis of secondary benzyl alcohols **14** and **15** from cyclohexylbenzene **4d** and toluene **4l**, followed by our presented selective C–C primary amination process to give the 4-alkyl substituted anilines **16** and **17**. **f**, Under traditional nitration conditions, the thioether substituent **18** would typically be oxidized to give the corresponding sulfoxide **19**. Here we show that the Friedel–Crafts acylation followed by reduction and the present C–C amination process produces **21**. DCE, dichloroethane. r.t., room temperature.

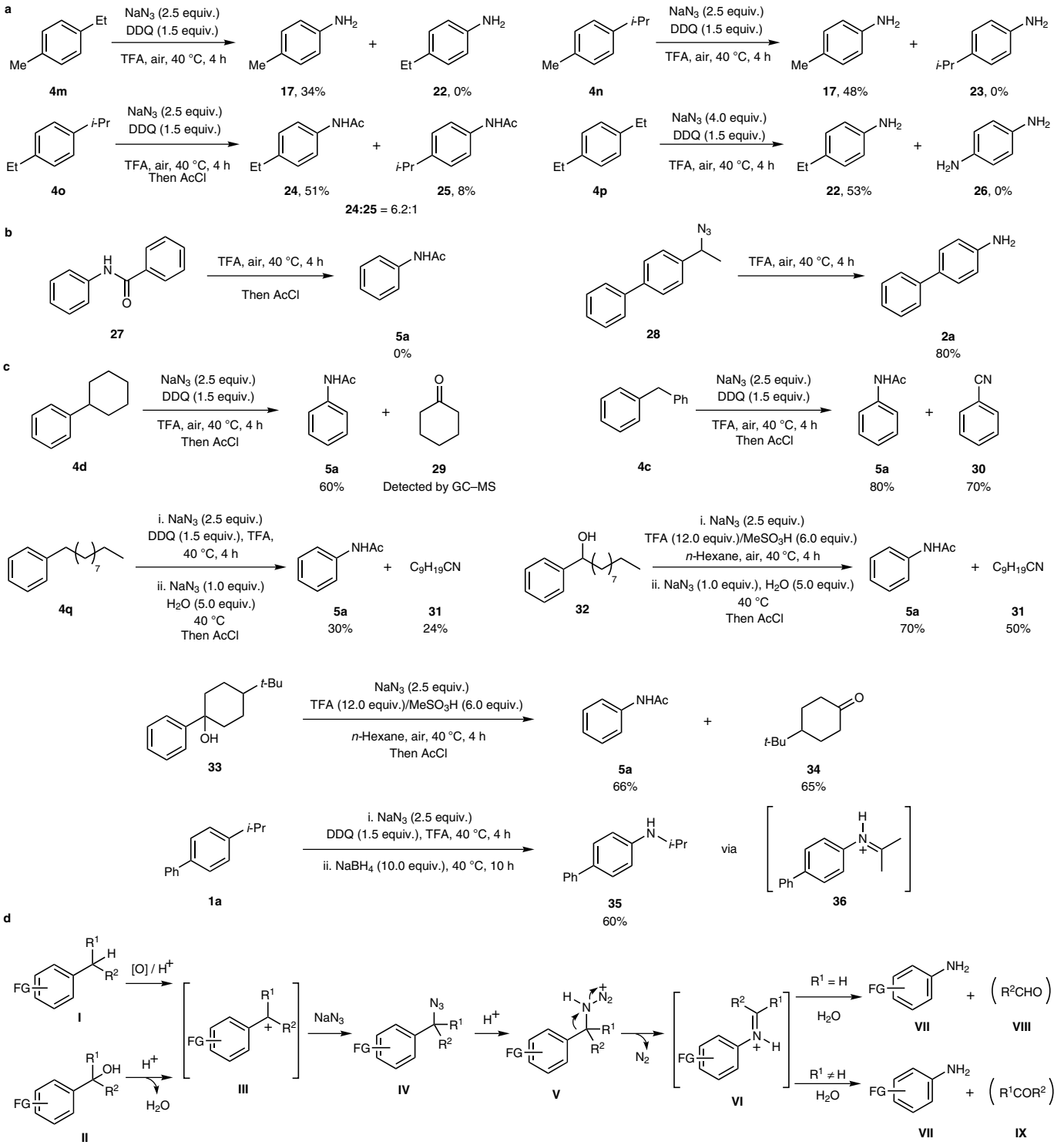
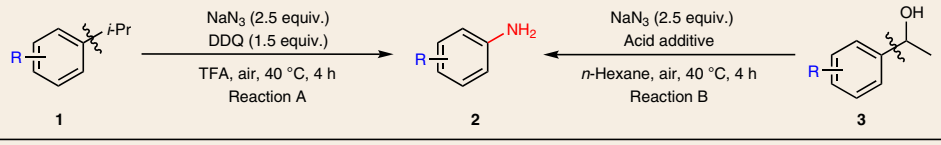


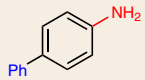
Fig. 3 | Mechanistic experiments. a, The reactivity of the alkyl group is primary carbon < secondary carbon < tertiary carbon, and that when there are two alkyl groups only one alkyl group is cleaved. **b**, Control experiments with **27** and **28**. **c**, Experiments that show the capture of the alkyl groups. The reaction of **1a** to give **35** suggests that the imine **36** is the intermediate. **d**, Proposed mechanism for this dealkylating C–C amination.

To make a clear comparison between the Friedel–Crafts alkylation followed by dealkylation pathway and the direct electrophilic nitration-and-reduction sequence, we conducted further experiments to clarify some preferable results (Fig. 2d). As reported[45], the simple benzene **11** and cyclohexylbenzene **4d** were used in the electrophilic Friedel–Crafts alkylation reaction for the selective and efficient synthesis of 1,3,5-tricyclohexylbenzene **12**, which could then be highly efficiently converted into 3,5-dicyclohexylaniline **13** by our present selective C–C primary amination process (Fig. 2d.). These transformations could even be carried out in a one-pot reaction with a high efficiency (Fig. 2d). In contrast, the nitration of **4d** can only afford the mixture of *ortho*- and *para*-cyclohexyl nitrobenzene (Supplementary Section F). The direct nitration/reduction of 1,3-disubstituted arenes did not produce the 3,5-disubstituted

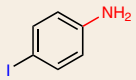
Table 1 | Substrate scope for the aniline synthesis from isopropylbenzene derivatives and secondary alcohols



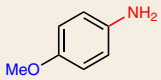
Para-substituted anilines



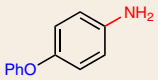
2a
Reaction A, 70%
Reaction B, 90%



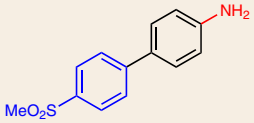
2b
Reaction A, 61%
Reaction B, 90%



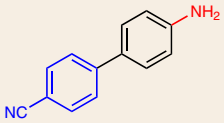
2c
Reaction A, 60%
Reaction B, 69%[a]



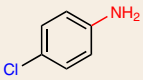
2d
Reaction A, 64%



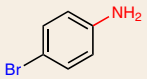
2e
Reaction A, 70%



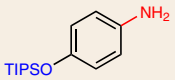
2f
Reaction A, 60%



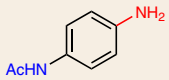
2g
Reaction B, 81%



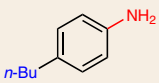
2h
Reaction B, 78%



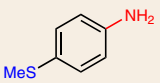
2i
Reaction A, 45%



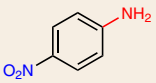
2j
Reaction B, 76%[a]



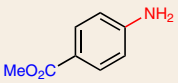
2k
Reaction B, 70%[a]



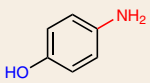
2l
Reaction B, 95%[a]



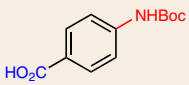
2m
Reaction B, 78%[b]



2n
Reaction B, 84%



2o
Reaction A, 30%

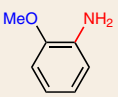


2p
Reaction B, 30%[c]

Ortho-substituted anilines

2q
Reaction B, 78%[a]

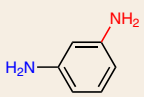
2r
Reaction B, 89%[a]



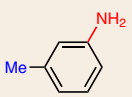
2s
Reaction B, 60%[a]

2t
Reaction B, 89%[a]

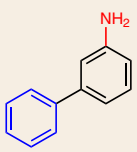
Meta-substituted anilines



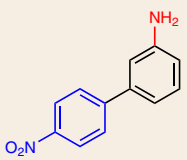
2u
Reaction B, 87%[a]



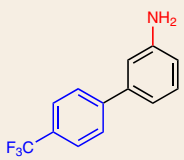
2v
Reaction B, 53%[a]



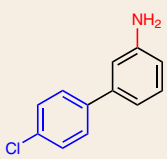
2w
Reaction A, 72%



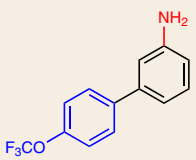
2x
Reaction A, 26%



2y
Reaction A, 40%



2z
Reaction A, 53%



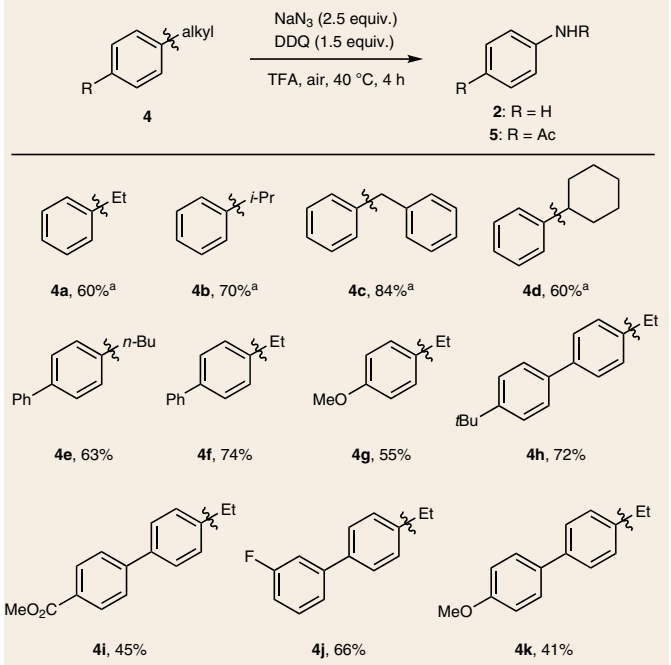
2za
Reaction A, 55%

Reaction A: reactions were performed with **1** (0.30 mmol), NaN_3 (0.75 mmol) and DDQ (0.45 mmol) in TFA (1.0 ml) at 40 °C under air for 4 h. Isolated yield. Reaction B: unless otherwise indicated, reactions were performed with **3** (0.30 mmol), NaN_3 (0.75 mmol) and TFA (3.6 mmol), $MeSO_3H$ (1.8 mmol) (as the acid) in *n*-hexane (1.0 ml) at 40 °C under air for 4 h. [a]TFA (5.4 mmol) was used as the acid. [b]$MeSO_3H$ (7.2 mmol) was used as the acid. [c]The crude product was *tert*-butoxycarbonyl protected by Boc_2O after the reaction.

aniline **13** because of the strong orientation effect of the two alkyl groups, but instead produced a mixture of 2,6-disubstituted and 2,4-disubstituted anilines[46]. In addition, this protocol provides an efficient and concise synthetic method for the synthesis of 3,5-disubstituted anilines from simple arenes. For example, 3,5-dicyclohexylaniline **13**[47] is often produced through multiple steps from the prefunctionalized nitrobenzene derivatives, compared to our one-pot method, which starts from the simple benzene **11** and cyclohexylbenzene **4d**.

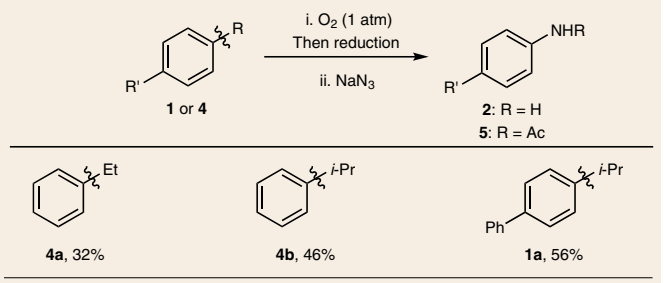
To compare our method with the traditional nitration/reduction process, we conducted other experiments to demonstrate the regioselectivity and compatibility of the Friedel–Crafts acylation, reduction and C–C amination process (Fig. 2e). For example, the simple cyclohexylbenzene **4d**[48] and toluene **4l**[49] were selectively acylated at the *para*-position of the alkyl group to form the 4-alkyl-substituted acetophenones, which were then reduced with $NaBH_4$ to the corresponding secondary benzyl alcohols (**14** and **15**, respectively). Following our presented protocol, the alcohols could then be converted into the 4-alkyl-substituted anilines **16** and **17**, respectively (Fig. 2e). In contrast, the direct nitration and reduction sequence of toluene **4l** and cyclohexylbenzene **4d**[50] provided a mixture of the aniline and nitration products (Supplementary Section F). Moreover, the nitration conditions are normally harsh with a strong oxidation ability, which means that some functional groups could not be compatible (Fig. 2f). An example of this is the thioether substituent, which could not be tolerated in the traditional nitration

Table 2 | Substrate scope of other alkyl group substituted alkylarenes



Reaction conditions: reactions were performed with **4** (0.30 mmol), NaN_3 (0.75 mmol) and DDQ (0.45 mmol) in TFA (1.0 ml) at 40 °C under air for 4 h. Isolated yield. [a]The crude product was acetylated by acetyl chloride after reaction.

Table 3 | Substrate scope with O_2 as the oxidant in one-pot reaction



Supplementary Section D gives experimental details and reaction conditions.

process as it is usually oxidized to give the corresponding sulfoxide **19** in a 95% yield under the nitration conditions. However, under our developed route, substrate **18**, which contains the thioether substituent underwent the Friedel–Crafts acylation well, which enabled the reduction and the present C–C amination processes to proceed smoothly to give **21** in a 59% yield (Fig. 2f).

Further experiments showed that the reactivity is in the order primary carbon < secondary carbon < tertiary carbon, and that the process cleaves only one alkyl group in the presence of two alkyl groups (Fig. 3a). In addition, control experiments with an amide (**27**) and a benzyl azide (**28**) as the substrates indicated that the benzyl azide might be involved in this C–C amination process (Fig. 3b). To identify the by-products of the aliphatic partner in this C–C amination process, cyclohexylbenzene (**4d**) was investigated as the substrate, and the corresponding cyclohexanone (**29**) was detected by gas chromatography–mass spectrometry. Also, diphenylmethane (**4c**) provided the desired aniline product with the formation of the benzonitrile by-product **30** in 70% yield, which might be produced by the reaction of the corresponding aldehydes with NaN_3. We further investigated the reaction of alkylarenes substrates, such as **4q**, and the benzyl alcohols substrates **32** and **33**. The results demonstrate that the corresponding aldehydes and ketones are the by-products of the reaction (for example, ketone **34** in the reaction of **33**). In the case of substrates that contain a secondary alkyl chain (**4q** and **32**), the generated aliphatic aldehydes were hard to separate and purify. Therefore, more NaN_3 was added after the reaction, which enabled the further Schmidt reaction of the generated aldehydes and afforded the corresponding alkyl nitriles **31**. All these results suggest that the corresponding aldehydes and ketones are the by-product of this transformation (Fig. 3c).

Moreover, to capture the intermediates of this process, we conducted an in situ reduction reaction, using $NaBH_4$ as the hydrogenation reagent, which produced arylamine **35** in 60% yield and indicates that the protonated imine **36** was the intermediate of this reaction (Fig. 3c). Based on these results, a mechanism for this C–C primary amination was proposed (Fig. 3d). First, the alkylarenes is oxidized to carbon cation, followed by an immediate attack from NaN_3 to generate the benzyl azide intermediate. Finally, the protonated azido intermediate under acidic conditions undergoes rearrangement and a subsequent hydrolysis process to produce the desired anilines.

Conclusions

This chemistry demonstrates a novel direct C–C bond transformation. The dealkylating C–C amination described here enables the efficient and site-directed preparation of anilines from the widely available alkylarenes. The common chemical linkage in the lignin could also be cleaved to give the corresponding value-added anilines. The present transformation can be accomplished with O_2 as the environmentally benign oxidant through a one-pot procedure. Furthermore, the readily available secondary alcohols can also be efficiently and selectively transformed into the corresponding anilines without any oxidant. This protocol features easily accessible hydrocarbon substrates, operationally simple conditions and a high site selectivity. It provides an alternative advance in the development of amination chemistry and demonstrates a great potential in the academic and industrial preparation of substituted anilines.

Methods

The general procedure for the C–C amination of alkylarenes is as follows. A 20 ml vial equipped with a magnetic stirring bar was charged with alkylarenes (0.3 mmol, 1 equiv.), NaN_3 (0.75 mmol, 2.5 equiv.), DDQ (0.45 mmol, 1.5 equiv.) and trifluoroacetic acid (TFA) (1.0 ml, 0.3 M). The vial was sealed and stirred under air at 40 °C for 4 h. On completion, the reaction mixture was quenched by 2 M NaOH (5 ml), extracted by ethyl acetate (5 × 2 ml) and 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 column.

The general procedure for the C–C amination of secondary alcohols is as follows. A 20 ml vial equipped with a magnetic stirring bar was charged with secondary alcohols (0.3 mmol, 1 equiv.), NaN_3 (0.75 mmol, 2.5 equiv.), *n*-hexane (1.0 ml, 0.3 M) and TFA (5.4 mmol, 18 equiv.) or a mixture of TFA (3.6 mmol, 12 equiv.) and $MeSO_3H$ (1.8 mmol, 6 equiv.). The vial was sealed and stirred under air at 40 °C for 4 h. On completion, the reaction mixture was quenched by 2 M NaOH (5 m), extracted by ethyl acetate (5 × 2 m) and 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 column.

Data availability

Full experimental procedures and spectral data for all the new compounds as well as computational details are included in the Supplementary Information and are available from the corresponding authors on request.

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Author contributions

J.L. and N.J. conceived and designed the experiments; J.L., X.Q. and C.Z. carried out most of experiments; J.L., X.Q., X.L., J.W., J.P. and N.J. analysed data; J.L., X.Q., X.H., J.W., J.P., Y.L., Y.Z., Q.Q., S.S. and N.J. participated in discussion and co-wrote the paper; N.J. directed the project.

Competing interests

The authors declare no competing interests.

Additional information

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