

Cite this: *Chem. Sci.*, 2022, 13, 2105

All publication charges for this article have been paid for by the Royal Society of Chemistry

Practical synthesis of 3-aryl anthranils *via* an electrophilic aromatic substitution strategy†

Yang Gao,^a Simin Yang,^a Minwei She,^a Jianhong Nie,^a Yanping Huo,^a Qian Chen,^a Xianwei Li^a and Xiao-Qiang Hu^b

We report a practical route for the synthesis of valuable 3-aryl anthranils from readily available anthranils and simple arenes by using the classical electrophilic aromatic substitution (EAS) strategy. This transformation goes through an electrophilic substitution and rearomatisation sequence by employing TiF_4 as an effective activator. A wide range of arenes were compatible in this transformation, delivering various structurally diversified 3-aryl anthranils in good yields and high regioselectivity. In addition, a variety of readily available feedstocks such as olefins, alkenyl triflates, silyl enoethers, carbonyl compounds, thiophenols and thiols could also participate in the reaction to achieve the C3 alkenylation, alkylation and thioetherification of anthranils. Of note, the synthesized 3-aryl anthranils proved to be a highly robust platform to access a series of biologically active compounds, drug derivatives and organic optoelectronic materials.

Received 25th November 2021
Accepted 27th January 2022

DOI: 10.1039/d1sc06565c

rsc.li/chemical-science

Introduction

Bi(hetero)aryls are important architectures that are widely found in a myriad of biologically active compounds, drugs, ligands, and organic functional materials.¹ Among them, 3-aryl anthranils are privileged motifs with a broad spectrum of pharmacological activities (Fig. 1a).² Remarkably, the facile reductive cleavage of the isoxazole rings to 2-aminodiaryl ketones renders them key synthetic precursors towards several marketed nonsteroidal anti-inflammatory drugs (NSAIDs) such as amfenac, bromfenac and nepafenac (Fig. 1b).³ Chlordiazepoxide, derived from 3-phenyl anthranil, is used for the treatment of anxiety, insomnia, and withdrawal symptoms (Fig. 1c).⁴ The clinically useful proquazone and fluproquazone as analgesics and NSAIDs can also be easily acquired from 3-aryl anthranils.⁵ In addition, anthranils are highly versatile synthons, which exhibit rich and tunable chemical reactivity in transition metal-catalysed process for the synthesis of valuable *N*-heterocycles (Fig. S1†).⁶

The 3-aryl anthranil frameworks were traditionally obtained through the *de novo* synthesis of the isoxazole ring,⁷ which suffered from limited substrate scope, toxic reagents, harsh conditions, and/or inconvenient substrates. Beyond these

methods, the direct C–H arylation of simple anthranils has been established as a powerful strategy to access 3-aryl anthranils (Fig. 1d). In 2015, a palladium-catalysed C–H arylation of anthranils with aryl iodides was first achieved.⁸ In addition, the Hashmi group disclosed a photoredox C–H arylation of anthranils with aryl diazonium tetrafluoroborates as aryl sources.⁹ Despite these advances, the direct oxidative C–H/C–H cross-coupling (also known as cross-dehydrogenative-coupling)¹⁰ of anthranils and simple arenes should be the most straightforward and desirable route to assemble 3-aryl anthranil frameworks by avoiding the use of prefunctionalised aryl sources.

Electrophilic aromatic substitution (EAS) is a textbook organic reaction, which enables efficient acylation, alkylation, halogenation, nitration and sulfonation of simple arenes. With our continuous interest in anthranil chemistry,¹¹ we recently envisioned the feasibility of synthesis of 3-aryl anthranils from anthranils and simple arenes by using the classical electrophilic aromatic substitution strategy. Given the resonance structure of anthranils (Fig. 1e),^{7a} we presumed that the electrophilicity of anthranils at the C3 position might be further enhanced by an activator such as trifluoromethanesulfonic anhydride (TiF_4)¹² *via* the formation of a cation species **A**. This intermediate would undergo electrophilic substitution with electron-rich arenes, and the expected 3-aryl anthranils could be obtained through a subsequent rearomatisation. Though this proposal seems logical, several issues might be encountered: (1) competitive reactions caused by the reactive intermediate **A**; (2) regioselectivity of arenes with multiple nucleophilic centers; (3) the compatibility of arenes with mild nucleophilicity and other normal nucleophiles such as olefins, carbonyl compounds,

^aSchool of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou, 510006, China. E-mail: gaoyang@gdut.edu.cn

^bKey Laboratory of Catalysis and Energy Materials Chemistry of Ministry of Education & Hubei Key Laboratory of Catalysis and Materials Science, School of Chemistry and Materials Science, South-Central University for Nationalities, Wuhan 430074, China

† Electronic supplementary information (ESI) available. CCDC 2094464. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc06565c



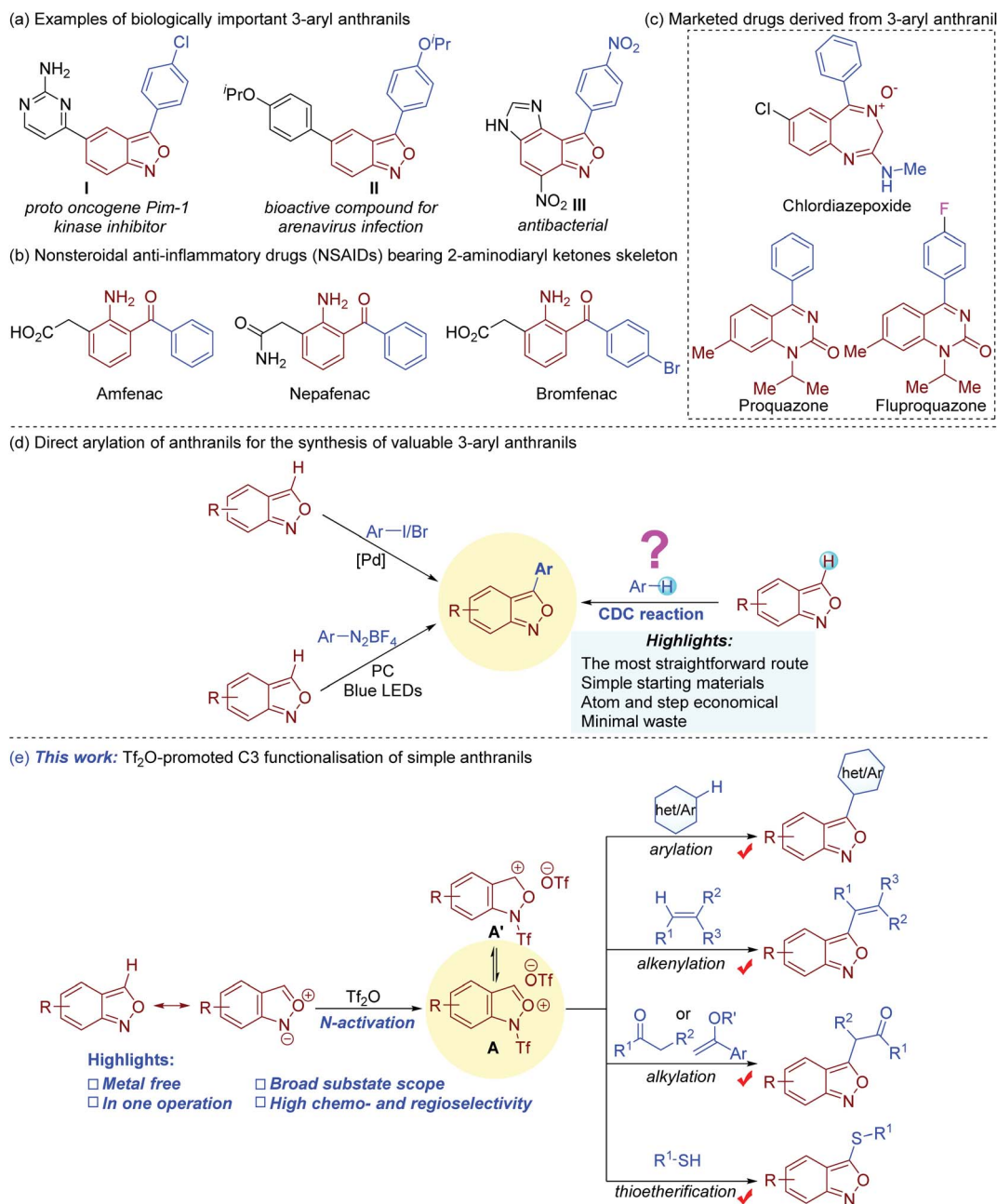


Fig. 1 The importance of 3-aryl anthranils (a–c) and strategies to C3 functionalisation of anthranils (d and e).

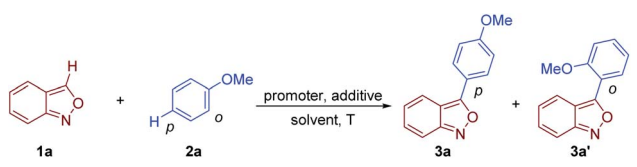
alcohols, thiols, and sulphonamides *etc.* In addition, to avoid an additional rearomatisation step,^{12a,b} one-pot operation also needs to be considered. Consequently, an appropriate activator and reaction system become essential to realize this novel transformation. Herein, we report our recent progress on a Tf₂O-promoted formal oxidative cross-coupling of anthranils for the synthesis of C3 functionalised anthranils.

Results and discussion

The investigation commenced with anthranil **1a** and anisole **2a** as the model substrates. To our delight, the expected product **3a** was obtained in 68% yield when Tf₂O (1.0 equiv.) was used as

a promoter in 1,2-dichloroethane (DCE) at room temperature (Table 1, entry 1). In sharp contrast, no desired product was detected when other anhydrides such as acetic anhydride (Ac₂O), trifluoroacetic anhydride (TFAA) and methanesulfonic anhydride (Ms₂O) were used (entries 2–4). In addition, trifluoromethanesulfonic acid (TfOH) and other Lewis acids such as In(OTf)₃ and B(C₆F₅)₃ proved to be ineffective for this transformation (entries 5–7). The yield of **3a** increased to 81% when Tf₂O was added at –20 °C and then slowly warmed the resulting mixture to room temperature (entry 8). The addition of 20 mol% pyridine or 20 mol% 2,6-di-*tert*-butylpyridine as an activator has an inferior effect on the yield (entries 9 and 10).^{12c} 3 Å molecular sieves and MgSO₄ were used to remove moisture, however,



Table 1 Optimisation of the reaction conditions^a


Entry	Promoter	Additive	T/ ^o C	<i>p</i> : <i>o</i> ^b	Yield of 3a (%) ^c
1	Tf ₂ O	—	rt	13 : 1	68
2	Ac ₂ O	—	rt	—	0
3	TFAA	—	rt	—	0
4	Ms ₂ O	—	rt	—	0
5	TfOH	—	rt	—	0
6	In(OTf) ₃	—	rt	—	0
7	B(C ₆ F ₅) ₃	—	rt	—	0
8	Tf ₂ O	—	−20	14 : 1	81
9	Tf ₂ O	Pyridine	−20	13 : 1	72
10	Tf ₂ O	2,6-Di- <i>tert</i> -butylpyridine	−20	12 : 1	68
11	Tf ₂ O	3 Å MS	−20	13 : 1	73
12	Tf ₂ O	Mg ₂ SO ₄	−20	13 : 1	72
13 ^d	Tf ₂ O	—	−20	14 : 1	86 (81)

^a Reaction conditions: to a solution of **1a** (0.2 mmol) in DCE (1.0 mL), the promoter (0.2 mmol) was added at a specified temperature. Subsequently, **2a** (0.2 mmol) was added. The resulting mixture was slowly warmed to room temperature, and continued to stir under an air atmosphere for 5 h.

^b Ratio was determined by GC-MS analysis. ^c Yields were determined by ¹H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. The yield in parentheses is the isolated yield. ^d Tf₂O (0.22 mmol) and **2a** (0.24 mmol) were used.

decreased yields were observed (entries 11 and 12). Finally, the desired product **3a** was obtained in 86% yield when 1.1 equivalents of Tf₂O and 1.2 equivalents of anisole were used (entry 13). Notably, all the fruitful conditions gave **3a** in high *para*-selectivity probably because of the bulky secondary carbocation.

As shown in Fig. 2, a wide range of arenes and heteroarenes undergo oxidative cross-coupling with anthranil **1a** to afford the desired 3-aryl anthranils in generally good yields with high regioselectivity. Remarkably, toluene (**3b**), naphthalene (**3c**) and 1,2,3,4-tetrahydronaphthalene (**3d**) that are mild nucleophiles reacted smoothly with anthranil **1a** under the current conditions. Phenol (**3e**) and naphthalen-2-ol (**3f**) bearing a free −OH group were compatible in this reaction. Oxydibenzene (**3g**) and diphenylsulfane (**3h**) gave rise to the corresponding products in high *para*-selectivity. Triphenylamine (**3i**), a widely used electron donor in organic optoelectronic materials,¹³ was successfully converted to the desired product in 74% yield. Double functionalisation of oxydibenzene and triphenylamine (**3g'** and **3i'**) was also achieved by improving the amount of **1a** to 2.5 equivalents. A variety of functional groups such as fluoro (**3j**), chloro (**3k**), bromo (**3l**), iodo (**3m**), phenyl (**3n**), ester (**3q**), benzoyl (**3r**) and allyloxy (**3y**) were well tolerated in this transformation. Electron withdrawing groups (EWGs) including cyano (**3s**), carbonyl (**3t** and **3u**), acid (**3v**) and amide (**3w**) were also compatible in this transformation when they are not conjugated to the phenyl group. Notably, a 73% yield of **3x** bearing 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Bipn) was obtained with a slight *ipso* deboration by-product. Poly-substituted arenes also took part in the reaction (**3z-3ad**), and even the sterically hindered 1,2,3,4,5-pentamethylbenzene (**3ae**) delivered the expected product in 55% yield. Polycyclic aromatic

hydrocarbons (PAHs) such as naphthalene (**3af**), 9H-fluorene (**3ag** and **3ah**), pyrene (**3ai**) and anthracene (**3aj**) were successfully converted into the expected products in moderate to good yields (56–88%). Similar to the electrophilic bromination of PAHs, the reaction occurs selectively at the most nucleophilic carbon atom of the benzene ring with the lowest aromaticity (please see the ESI† for details).¹⁴ 1,1,2-Tetraphenylethene (TPE) **3ak**, an AIEgen molecule having wide application in materials science,¹⁵ was an active substrate in this reaction. Significantly, a large set of heterocycles such as indole (**3al-3ao**), furan (**3ap**), thiophene (**3aq**), benzothiophene (**3ar** and **3as**), carbazole (**3at**), dibenzofuran (**3au**), 9H-xanthene (**3av**), dibenzothiophene (**3aw**), and 10-methylphenothiazine (**3ax**) proved to be suitable, furnishing the expected products in good yields with high regioselectivity. This protocol was applied in the late-stage modification of several readily available pharmaceutical derivatives. As outlined in Fig. 2 (bottom), the anthranil motif was successfully introduced into the derivatives of gemfibrozil (**3ay**), naproxen (**3az**), aspirin (**3ba**) and tocopherol (**3bb**) with high efficiency.

Next, the scope of anthranils was investigated in this novel oxidative cross-coupling reaction. As shown in Fig. 3, various substituents including F (**3bc** and **3bd**), Cl (**3be**, **3bf** and **3bg**), Br (**3bh** and **3bi**), OBz (**3bj** and **3bk**), allyloxy (**3bl** and **3bm**), TsO (**3bn**), Ph (**3bo** and **3bp**), and CF₃ (**3bs**) were well tolerated, giving rise to the desired poly-substituted 3-aryl anthranils in good yields (46–85%). When 5-(trifluoromethyl)benzo[*c*]isoxazole **1k** was applied as a substrate, the rearomatisation process in the formation of **3bs** is much slower than other tested anthranils probably because of the stabilisation of the strong electron-withdrawing group. Notably, C4 substituted anthranils



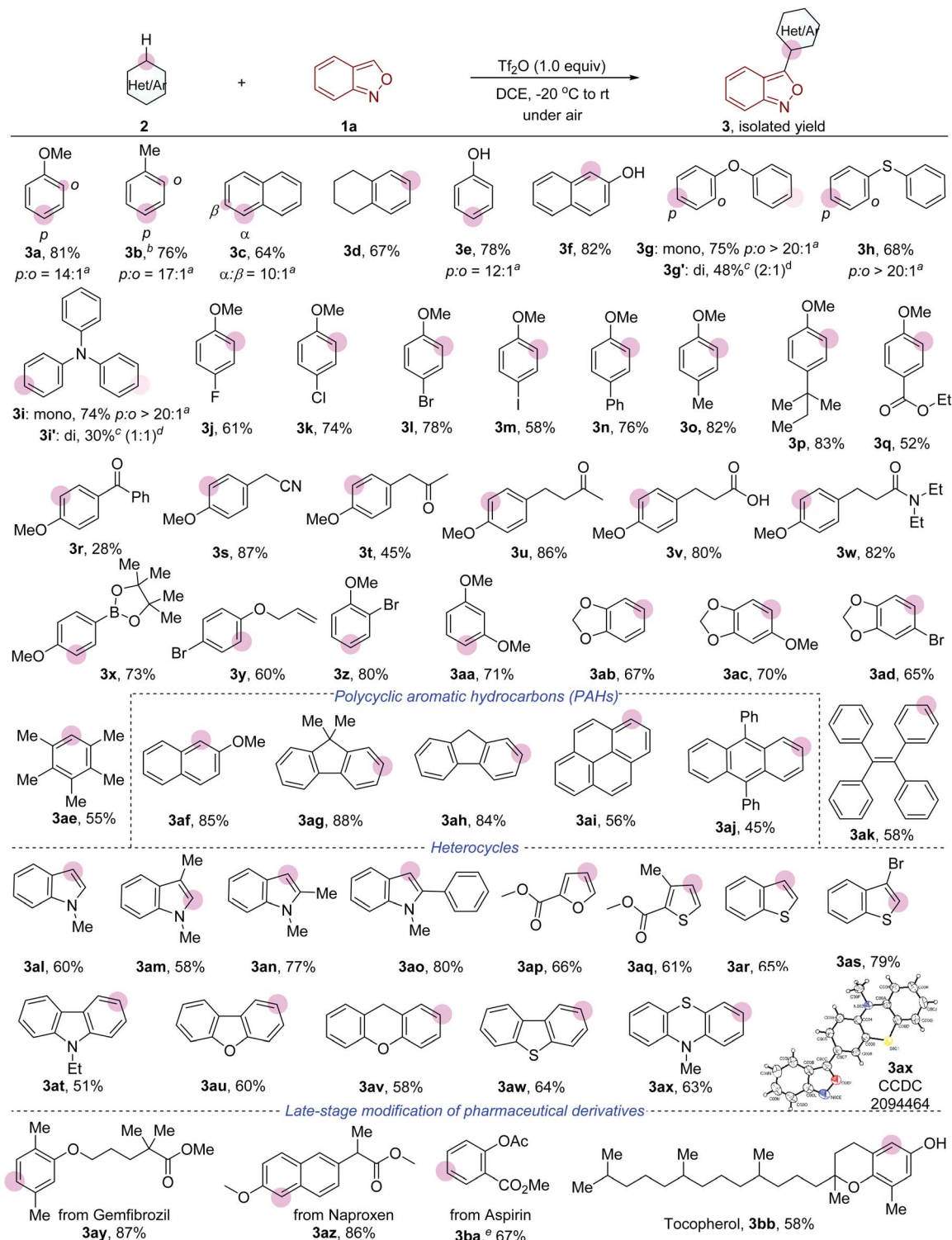


Fig. 2 Scope of arenes. Standard reaction conditions: to a solution of **1a** (0.3 mmol) in DCE (1.0 mL), Tf_2O (0.33 mmol) was added dropwise at $-20\text{ }^\circ\text{C}$. Subsequently, **2** (0.36 mmol) was added. The resulting mixture was slowly warmed to room temperature, and continued to stir under an air atmosphere for 5 h. Isolated yields are given. ^a Ratio was determined by GC-MS analysis of the crude product. ^b 3.0 equivalents of toluene were used. ^c 2.5 equivalents of **1a** and Tf_2O were used. ^d The ratio indicates the yields of difunctionalisation and monofunctionalisation. ^e Deacetylated product was obtained.

such as 4-fluorobenzo[*c*]isoxazole (**3bt**) and 4-chlorobenzo[*c*]isoxazole (**3bu**) also showed high reaction efficiency in this transformation.

Apart from arenes, other readily available nucleophiles such as alkenes, ketones, alkenyl triflates, silyl enoethers, thiophenols and thiols are also compatible in this oxidative cross-



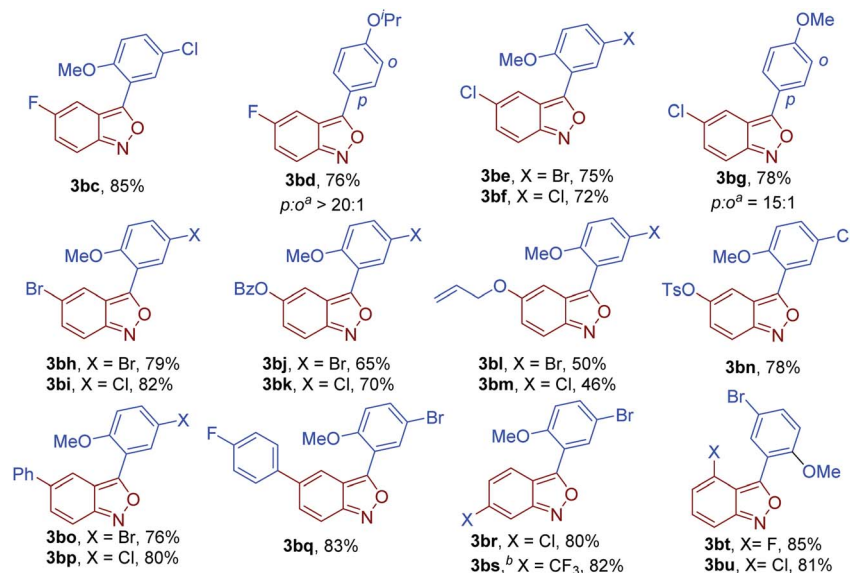


Fig. 3 Scope of anthranils. ^a Ratio was determined by GC-MS analysis of the crude product. ^b After the addition of 1-bromo-4-methoxybenzene for 2 h, the reaction temperature was increased to 60 °C for another 3 h.

coupling reaction. For instance, C3 alkenylation of anthranils was achieved with simple alkenes, furnishing the corresponding 3-alkenyl anthranils in satisfactory yields (Fig. 4a).¹⁶ When cyclohexene was used as a substrate, products with positional isomerism of the double bond were obtained (5f). The isomers might be formed *via* the migration of carbocation intermediates. In addition, 1-phenylvinyl trifluoromethanesulfonate and trimethyl((1-phenylvinyl)oxy)silane also served as effective nucleophiles in the reaction with anthranils to give the

corresponding carbonyl compounds (Fig. 4b). Remarkably, similar products were obtained by employing simple carbonyl compounds **8** in the reaction system. Both 1,3-dicarbonyl compounds (**7c**, **7d** and **7e**) and simple ketones (**7f–7i**) could react with anthranil **1a** to afford the corresponding 3-alkylated anthranils in 42–82% yields. Moreover, heteroatom nucleophiles such as alcohols, thiols, thiophenols and sulfonamides were tested in this transformation (Fig. 4c). Decane-1-thiol and 2-chlorobenzenethiol gave the desired C3 thioetherified

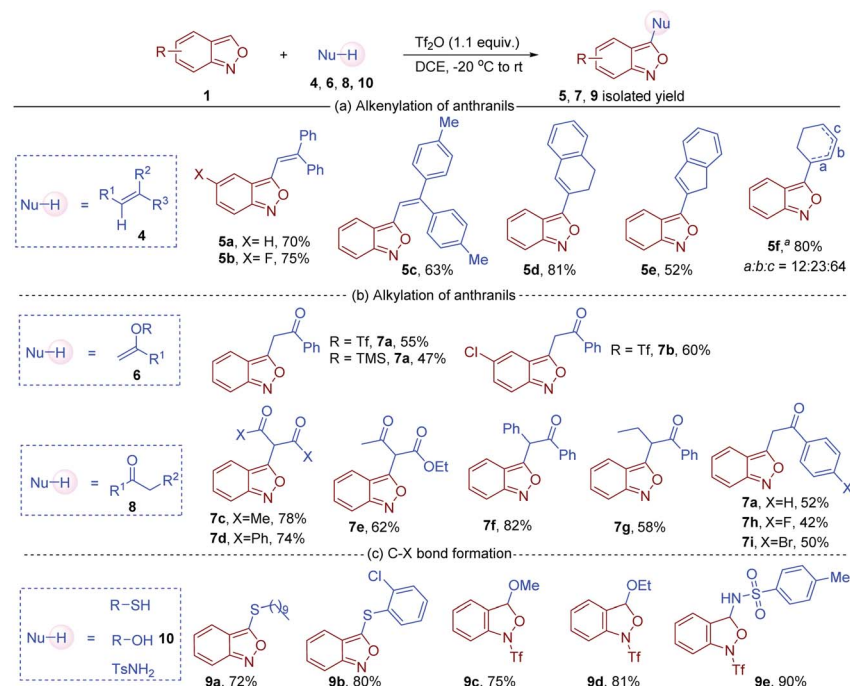


Fig. 4 Nucleophile screening in C3 functionalisation of anthranils. ^a From cyclohexene. The marked a/b/c indicates the position of the double bond.



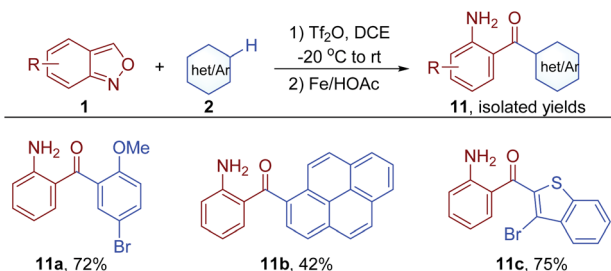


Fig. 5 Synthesis of 2-aminodiaryl ketones.

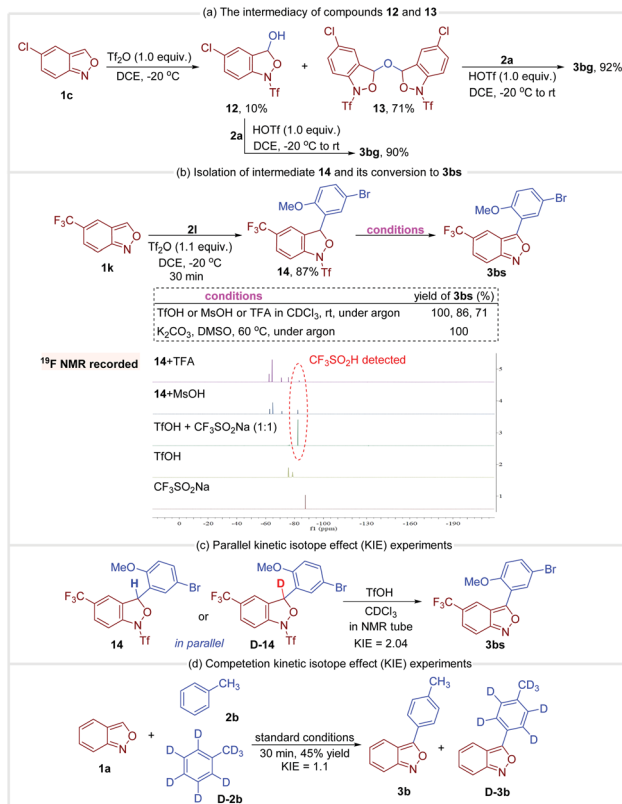


Fig. 6 Mechanistic studies.

anthranils **9a** and **9b** in 74% and 80% yields, respectively. However, MeOH, EtOH and TsNH₂ could only afford the nucleophilic addition products **9c**, **9d** and **9e**, and the aromatisation step is sluggish under the current reaction conditions.

2-Aminodiaryl ketones are core skeletons of nonsteroidal anti-inflammatory drugs (NSAIDs) and key intermediates for drug synthesis.³ They were readily obtained through this oxidative cross-coupling and a subsequent reductive ring opening from anthranils and simple arenes in one pot (Fig. 5).

A series of control experiments were conducted to gain more insight into the mechanism. First, anthranil **1c** was rapidly converted to **12** and **13** once treated with Tf₂O (Fig. 6a). The formation of **12** and **13** was presumably from the reaction of a trace amount of H₂O with the proposed oxonium species **A**. As illustrated in Fig. 6a, these two species reacted smoothly with anisole to give the desired 3-aryl anthranil **3bg** in the presence of TfOH, which revealed the intermediacy of compounds **12** and **13** in this transformation. The reaction of 5-(trifluoromethyl) benzo[*c*]isoxazole **1k** and 1-bromo-4-methoxybenzene **2l** was quenched in 30 min to obtain another fully characterized intermediate **14** in 87% yield (Fig. 6b). The aromatisation of **14** may go through two possible pathways, namely, direct elimination of CF₃SO₂H or amide hydrolysis/oxidative aromatisation cascade.^{12a} Control experiments in Fig. 6b indicate that the aromatisation could occur under both acidic and basic conditions without any additional oxidants. Moreover, CF₃SO₂H was detected by ¹⁹F NMR when MsOH or TFA was used as an additive in the aromatisation of **14** (please see the ESI† for details). Therefore, the aromatisation of **14** is likely to be an elimination process of CF₃SO₂H. Subsequently, the observed *K_H*/*K_D* is 2.04 in parallel kinetic experiments of **14** and **D-14** (Fig. 6c). In comparison, there is no significant kinetic isotope effect (*KIE* = 1.1) in competitive experiments of toluene and toluene-*d*8 (Fig. 6d). These results support that elimination of CF₃SO₂H is likely the rate-determining step in this oxidative cross-coupling reaction.

According to the above results and the previous studies,^{12a} a plausible mechanism is proposed in Fig. 7. The reaction begins with the activation of anthranil **1c** by Tf₂O, leading to reactive oxonium species **1A** and its tautomers **1A'** and **1A''**.

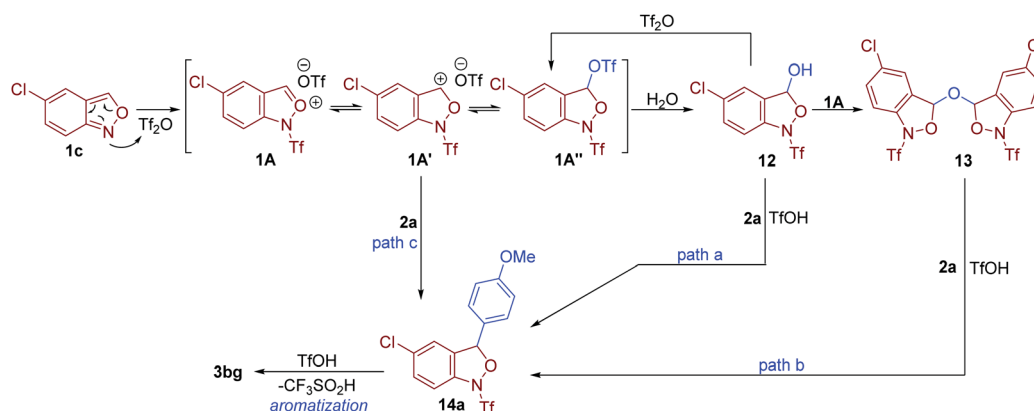


Fig. 7 Plausible mechanism.



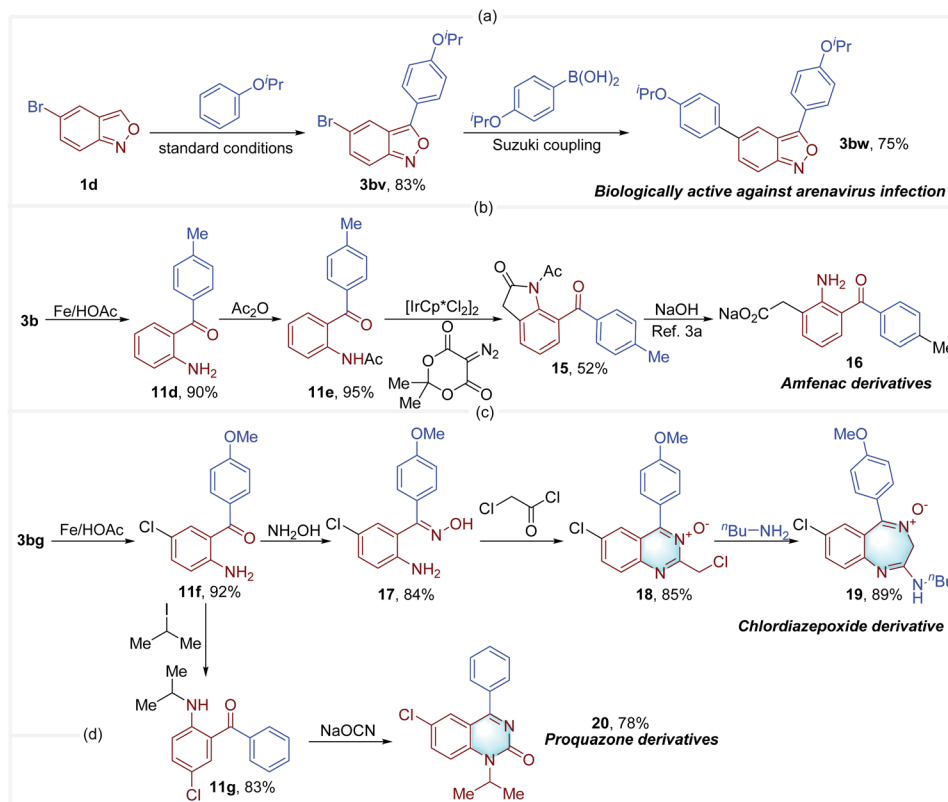


Fig. 8 The construction of biologically active compounds and drug derivatives from 3-aryl anthranils.

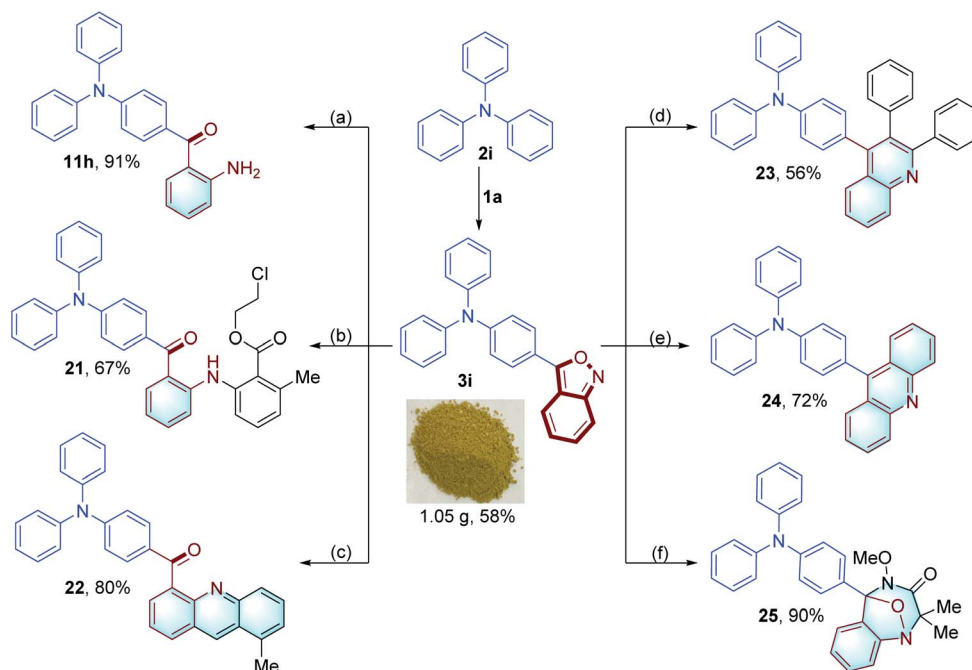


Fig. 9 Derivatization of the anthranil framework. (a) **3i** (0.1 mmol), Fe powder (0.2 mmol) in HOAc/H₂O (2 : 1) at 90 °C. (b) **3i** (0.1 mmol), 2-methylbenzoic acid (0.15 mmol), [RhCp*Cl₂]₂ (4 mol%), AgSbF₆ (10 mol%), K₂CO₃ (0.15 mmol) in DCE (2.0 mL) at 100 °C. (c) **3i** (0.1 mmol), 2-methylbenzaldehyde (0.15 mmol), [RhCp*Cl₂]₂ (4 mol%), AgSbF₆ (10 mol%), HOAc (0.1 mmol) in DCE (2.0 mL) at 100 °C. (d) **3i** (0.1 mmol), diphenylacetylene (0.1 mmol), Ni(BF₄)₂·6H₂O (5 mol%), 6,6'-dimethyl-2,2'-bipyridin (5.5 mol%), Me(OEt)₂SiH (0.2 mmol) in DMA (1.0 mL). (e) **3i** (0.1 mmol), PhZnOPiv (0.12 mmol), CoCl₂ (10 mol%) in THF (1.0 mL) at room temperature. After 5 h, the solvent was removed and TFA (1 mL) as added. The resulting mixture was stirred at 80 °C for 2 h. (f) **3i** (0.1 mmol), 2-bromo-*N*-methoxy-2-methylpropanamide (0.2 mmol) and K₂CO₃ (0.2 mmol) in HFIP (1 mL) at room temperature.



Then, H₂O attacks **1A** to deliver intermediate **12**, which further adds to another oxonium species giving rise to intermediate **13**. In the presence of in situ-generated TfOH, electron-rich arene **2a** undergoes electrophilic substitution with intermediate **12** and **13** to give **14a** (path a and b). In addition, intermediate **14a** may also generate from the direct reaction of arenes **2a** and cation species **1A** (path c). Finally, the elimination of CF₃SO₂H from **14a** affords the expected 3-aryl anthranil product.^{12a,17}

A series of biologically active compounds and drug derivatives were successfully synthesized to demonstrate the practical utility of our method. 3-Aryl anthranil **3bw** that is effective against arenavirus infection was obtained in good yield through the established oxidative cross-coupling and a subsequent Suzuki coupling (Fig. 8a).^{2d} The key intermediate **15** for the synthesis of Amfenac derivative **16** was concisely prepared from **3b**,^{3a} in which Ir-catalyzed C–H alkylation with diazotized Meldrum's acid is a key step (Fig. 8b).¹⁸ In addition, chlordinazepoxide analogue **19** and proquazone derivative **20** were facily obtained through the routes illustrated in Fig. 8c and d.^{4,5} These examples further demonstrate the importance of 3-aryl anthranils and the synthetic potential of this oxidative cross-coupling reaction.

In addition, the anthranil backbone can be facily converted to other useful motifs. As illustrated in Fig. 9, anthranil **3i** was reduced by Fe powder to give 2-amino benzophenone **11h** in 91% yield. **3i** was applied as a robust aminating reagent in Rh-catalyzed sp² C–H amination of 2-methylbenzoic acid and 2-methylbenzaldehyde, affording compounds **21** and **22**.^{6e,11e} Quinoline **23** was produced in 56% yield through a Ni-catalyzed hydroamination/cyclisation cascade of **3i** and 1,2-diphenylethyne.^{11a} Acridine derivative **24** was obtained through a Co-catalyzed electrophilic amination and tandem cyclisation,^{6b} which was widely used as a fluorescent probe and a luminescence material in organic light emitting diode (OLED) emitters.¹³ In addition, **3i** took part in a [4+3] cycloaddition with the azaoxyallyl cation, providing a biologically important benzodiazepine derivative **25** in 90% yield.^{6m}

The photophysical properties of **3i**, **22**, **23** and **24** bearing a donor–acceptor (D–A) structure were further investigated and summarized in Table 2. The fluorescence quantum yield ($\Phi_{F,soln}$) values of **3i**, **22**, **23** and **24** in THF solutions (1×10^{-5} mol L⁻¹) were measured to be 43.0%, 0.8%, 81.7%, 88.4%. All of these four compounds exhibited a marked solid luminescence phenomenon under the excitation of 365 nm

Table 2 Photophysical properties of **3i**, **22**, **23** and **24** in THF solutions (10^{-5} M)

Comp.	λ_{max} abs. (nm)	λ_{max} em. (nm)	Φ (%) ^a	τ (ns)
3i	400	486	43	1.85
22	358	475	0.8	7.47
23	298	464	81.7	3.93
24	260	528	88.4	7.74

^a Fluorescence quantum yields with anthracene in ethanol ($\Phi = 27\%$) as standard.

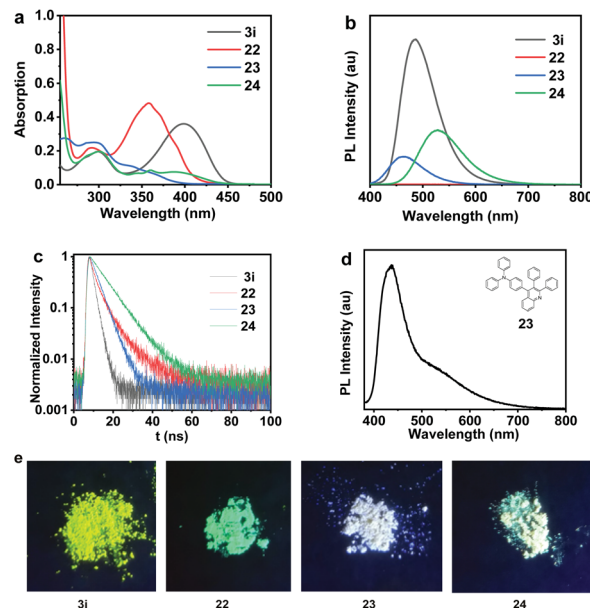


Fig. 10 (a) The absorption spectra of **3i**, **22**, **23** and **24** in THF solutions (10^{-5} M). (b) The emission spectra of **3i**, **22**, **23** and **24** in THF solutions (10^{-5} M). (c) Time-correlated single photon counting in solution (10^{-5} M in THF). (d) The emission spectra of **23** (solid). (e) **3i**, **22**, **23** and **24** under the irradiation of 365 nm light.

ultraviolet light as shown in Fig. 10. Remarkably, compound **23** displays white-light emission in the solid state, and the photoluminescence of **23** is at 450 and 550 nm (Fig. 10d). This kind of white-light emitting material with a simple molecular structure is in great demand in organic optoelectronic materials.¹⁹

Conclusions

In summary, a Tf₂O-mediated formal oxidative cross-coupling of readily available anthranils and simple arenes has been developed. This metal-free protocol is implemented in one operation under mild conditions, providing an efficient and environmentally benign route to acquire the privileged 3-functionalised anthranils. In addition, a wide array of olefins, alkenyl triflates, silyl enoethers, carbonyl compounds, thiophenols and thiols could serve as effective nucleophiles in this transformation. Mechanistic insights revealed that H₂O induced intermediates are involved in this reaction and elimination of CF₃SO₂H is likely to be the rate-determining step. The synthetic utility of this protocol was demonstrated by the broad substrate scope (98 examples, up to 88% yield), the late-stage modification of pharmaceutical derivatives, and the diverse derivatization of the anthranil framework as well as the concise synthesis of biologically active compounds and drug derivatives. Moreover, through preliminary studies on photophysical properties, a novel white-light emitting material was synthesized from 3-aryl anthranils. Given the increasing importance of 3-aryl anthranils as synthetic precursors and building blocks, this protocol substantially streamlines their synthetic routes and would have broad applications in the construction of pharmaceuticals and optoelectronic materials.



Data availability

Detailed experimental procedures and NMR spectra for all compounds are available in the ESI.†

Author contributions

Y. G. supervised the project. S. Y., M. S. and J. N. performed all the experiments. Y. G. and X.-Q. H. prepared the draft and Y. H., X.L. and Q. C. revised the manuscript. All the authors analysed the data, discussed the results and contributed to the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21901045, 21901258, U2001222), and the Technology Plan of Guangdong Province (2019A050510042).

Notes and references

- (a) A. M. Boldi, *Curr. Opin. Chem. Biol.*, 2004, **8**, 281–286; (b) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563–639; (c) D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 6338–6361; (d) K.-H. Kim and J.-J. Kim, *Adv. Mater.*, 2018, **30**, 1705600.
- (a) A. Chaker, E. Najahi, O. Chatriant, A. Valentin, N. Téné, M. Treilhou, F. Chabchoub and F. Nepveu, *Arabian J. Chem.*, 2017, **10**, S2464–S2470; (b) M. Rezazadeh, M. Pordel, A. Davoodnia and S. Saberi, *Chem. Heterocycl. Compd.*, 2015, **51**, 918–922; (c) A. C. Pierce, M. Jacobs and C. Stuver-Moody, *J. Med. Chem.*, 2008, **51**, 1972–1975; (d) M. Plewe, E. Brown, V. Gantla, G. Henkel, K. McCormack, N. V. Sokolova and Y.-J. Shin, *PCT Int. Appl.*, 2018, 2018013430.
- (a) D. A. Walsh, H. W. Moran, D. A. Shamblee, I. M. Uwaydah, W. J. Welstead, L. F. Sancio and W. N. Dannenburg, *J. Med. Chem.*, 1984, **27**, 1379–1388; (b) J. Koch-Weser, L. S. Simon and J. A. Mills, *N. Engl. J. Med.*, 1980, **302**, 1237–1243.
- (a) D. D. Morgan, J. D. Robinson and C. L. Mendenhall, *Eur. J. Clin. Pharmacol.*, 1981, **19**, 279–285; (b) D. W. Choi, D. H. Farb and G. D. Fischbach, *Nature*, 1977, **269**, 342–344.
- S. P. Clissold and R. Beresford, *Drugs*, 1987, **33**, 478–502.
- For a review: (a) Y. Gao, J. Nie, Y. Huo and X.-Q. Hu, *Org. Chem. Front.*, 2020, **7**, 1177–1196; for C-N coupling; (b) J. Li, E. Tan, N. Keller, Y.-H. Chen, P. M. Zehetmaier, A. C. Jakowetz, T. Bein and P. Knochel, *J. Am. Chem. Soc.*, 2019, **141**, 98–103; for Rh/Co-catalyzed C-H amination; (c) S. Yu, G. Tang, Y. Li, X. Zhou, Y. Lan and X. Li, *Angew. Chem., Int. Ed.*, 2016, **55**, 8696–8700; (d) R.-H. Liu, Q.-C. Shan, X.-H. Hu and T.-P. Loh, *Chem. Commun.*, 2019, **55**, 5519–5522; (e) S. Kim, S. H. Han, N. K. Mishra, R. Chun, Y. H. Jung, H. S. Kim, J. S. Park and I. S. Kim, *Org. Lett.*, 2018, **20**, 4010–4014; for gold-catalyzed nitrene-transfer reactions; (f) Z. Zeng, H. Jin, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2018, **57**, 16549–16553; (g) Z. Zeng, H. Jin, K. Sekine, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2018, **57**, 6935–6939; (h) R. L. Sahani and R. Liu, *Angew. Chem., Int. Ed.*, 2017, **56**, 12736–12740; (i) H. Jin, B. Tian, X. Song, J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2016, **55**, 12688–12692; (j) H. Jin, L. Huang, J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2016, **55**, 794–797 for [4+n] cycloaddition reactions; (k) C. Gao, X. Wang, J. Liu and X. Li, *ACS Catal.*, 2021, **11**, 2684–2690; (l) Q. Cheng, J. Xie, Y. Weng and S. You, *Angew. Chem., Int. Ed.*, 2019, **58**, 5739–5743; (m) J. Feng, M. Zhou, X. Lin, A. Lu, X. Zhang and M. Zhao, *Org. Lett.*, 2019, **21**, 6245–6248.
- (a) R. K. Smalley, *Sci. Synth.*, 2002, **11**, 337–382; (b) J. Chauhan and S. Fletcher, *Tetrahedron Lett.*, 2012, **53**, 4951–4954; (c) R. B. Davis and L. C. Pizzini, *J. Org. Chem.*, 1960, **25**, 1884–1888; (d) B. J. Stokes, C. V. Vogel, L. K. Urnezis, M. Pan and T. G. Driver, *Org. Lett.*, 2010, **12**, 2884–2887; (e) M. Zhang, Y. Meng, Y. Wu and C. Song, *J. Org. Chem.*, 2021, **86**, 7326–7332.
- (a) M. Shigenobu, K. Takenaka and H. Sasai, *Angew. Chem., Int. Ed.*, 2015, **54**, 9572–9576; (b) M. Aidene, F. Belkessam, J.-F. Soulé and H. Doucet, *ChemCatChem*, 2016, **8**, 1583–1590.
- T. Adak, C. Hu, M. Rudolph, J. Li and A. S. K. Hashmi, *Org. Lett.*, 2020, **22**, 5640–5644.
- (a) Y. Yang, J. Lan and J. You, *Chem. Rev.*, 2017, **117**, 8787–8863; (b) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi and A. Lei, *Chem. Rev.*, 2015, **115**, 12138–12204; (c) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447; (d) C.-J. Li and Z. Li, *Pure Appl. Chem.*, 2006, **78**, 935–945; (e) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335–344; (f) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215–1292.
- (a) Y. Gao, S. Yang, Y. Huo, Q. Chen, X. Li and X.-Q. Hu, *ACS Catal.*, 2021, **11**, 7772–7779; (b) Y. Gao, J. Nie, Y. Li, X. Li, Q. Chen, Y. Huo and X.-Q. Hu, *Org. Lett.*, 2020, **22**, 2600–2605; (c) Y. Gao, Y. Cui, Y. Huo, J. Chen, M. She, X. Li, Q. Chen and X.-Q. Hu, *J. Org. Chem.*, 2021, **86**, 12107–12118; (d) Y. Gao, S. Yang, Y. Li, Y. Huo, Z. Huang, Z. Chen and X.-Q. Hu, *J. Org. Chem.*, 2020, **85**, 10222–10231; (e) Y. Gao, J. Nie, Y. Li, G. Liao, Y. Huo and X. Hu, *ChemCatChem*, 2020, **12**, 2721–2725.
- (a) P.-Y. Jiang, K.-F. Fan, S. Li, S.-H. Xiang and B. Tan, *Nat. Commun.*, 2021, **12**, 2384; (b) E. J. Corey and Y. Tian, *Org. Lett.*, 2005, **7**, 5535–5537; (c) T. Yanagi, S. Otsuka, Y. Kasuga, K. Fujimoto, K. Murakami, K. Nogi, H. Yorimitsu and A. Osuka, *J. Am. Chem. Soc.*, 2016, **138**, 14582–14585; (d) S. Shaaban, V. Tona, B. Peng and N. Maulide, *Angew. Chem., Int. Ed.*, 2017, **56**, 10938–10941; (e) K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang and P.-Q. Huang, *Angew. Chem., Int. Ed.*, 2010, **49**, 3037–3040; (f) F. Berger,



- M. B. Plutschack, J. Riegger, W. Yu, S. Speicher, M. Ho, N. Frank and T. Ritter, *Nature*, 2019, **567**, 223–228; (g) I. L. Baraznenok, V. G. Nenajdenko and E. S. Balenkova, *Tetrahedron*, 2000, **56**, 3077–3119.
- 13 (a) L. Xu, L. Ni, L. Sun, F. Zeng and S. Wu, *Analyst*, 2019, **144**, 6570–6577; (b) C. Zhou, T. Zhang, S. Zhang, H. Liu, Y. Gao, Q. Su, Q. Wu, W. Li, J. Chen and B. Yang, *Dyes Pigm.*, 2017, **146**, 558–566; (c) W. Li, Y. Pan, L. Yao, H. Liu, S. Zhang, C. Wang, F. Shen, P. Lu, B. Yang and Y. Ma, *Adv. Opt. Mater.*, 2014, **2**, 892–901.
- 14 (a) M. Murai, T. Ogita and K. Takai, *Chem. Commun.*, 2019, **55**, 2332–2335; (b) X. Xiong, F. Tan and Y.-Y. Yeung, *Org. Lett.*, 2017, **19**, 4243–4246; (c) P. von R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao and N. J. R. van Eikema Hommes, *J. Am. Chem. Soc.*, 1996, **118**, 6317–6318.
- 15 (a) Y. Hong, J. W. Y. Lam and B. Z. Tang, *Chem. Soc. Rev.*, 2011, **40**, 5361–5388; (b) H. Tong, Y. Hong, Y. Dong, M. Häußler, J. W. Y. Lam, Z. Li, Z. Guo, Z. Guo and B. Z. Tang, *Chem. Commun.*, 2006, 3705–3707.
- 16 C. Gao, J. Xu, S. Zhu, K. Jian, Q. Xuan and Q. Song, *Chem. Commun.*, 2021, **57**, 2037–2040.
- 17 For the role of Tf_2O as an oxidizing agent, see: (a) V. G. Nenajdenko, P. V. Verteletzkiy, A. B. Koldobskij, I. V. Alabugin and E. S. Balenkova, *J. Org. Chem.*, 1997, **62**, 2483–2486; (b) X. Creary, *J. Org. Chem.*, 1980, **45**, 2727–2729.
- 18 P. Patel and G. Borah, *Chem. Commun.*, 2017, **53**, 443–446.
- 19 B. Xu, H. Wu, J. Chen, Z. Yang, Z. Yang, Y.-C. Wu, Y. Zhang, C. Jin, P.-Y. Lu, Z. Chi, S. Liu, J. Xu and M. Aldred, *Chem. Sci.*, 2017, **8**, 1909–1914.

