Oxidant evolution in metal free redox amination reactions

vom Fachbereich Chemie der Technischen Universität Kaiserslautern zur Verleihung des akademischen Grades 'Doktor der Naturwissenschaften' eingereichte Dissertation

D 386

vorgelegt von

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Kaiserslautern, 2018

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Datum der wissenschaftlichen Aussprache: 03.05.2018

Die vorliegende Arbeit entstand in der Zeit zwischen August 2014 und December 2017 in den Laboratorien des Fachbereichs Chemie an der Technischen Universität Kaiserslautern.

Eidesstattliche Erklärung

Hiermit versichere ich, dass ich die vorliegende Arbeit eigenständig verfasst, keine anderen als die angegebenen Quellen und Hilfsmittel verwendet und Literaturzitate kenntlich gemacht habe. Ich erkläre außerdem, dass diese Arbeit weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Kaiserslautern, den _____ _____

Rongwei Jin

To Xinyi Zhang & my parents

Acknowledgements

Hab keine Angst, dass das Leben einmal zu Ende geht. Hab eher Angst, dass es nie richtig anfängt.

As John Henry Newman said, when I finally reach the end of my PhD career, in the other way, a part of my life is finished. It's a long journey, however I never be alone. Be grateful to life, all the fantastic experience, people with individuality I've met will be deeply impressed in my heart.

First of all, I would like to thank Prof. Dr. Frederic W. Patureau, my supervisor of research and thesis, who offered me the chance to study in Germany three years ago. With his help and guidance, I could complete all the research projects in time. And I would like to express my sincere gratitude to Prof. Dr. Pierre H. Dixneuf, without his recommendation I cannot get the chance to start my research career in Europe.

Next I would like to thank Prof. Dr. Georg Manolikakes and Prof. Dr. Werner Thiel, for being in the examination committee of my dissertation.

Then I would like to thank the financial support for my Ph.D career, they are DFG-funded Transregional Collaborative Research Center SFB/TRR 88 'Cooperative effects in homo- and heterometallic complexes (3-MET)' and DFG-funded project PA 2395/2-1.

Technical and analytic staff who work in the chemisty department are also gratefully acknowledged for serving me the NMR, HRMS, Elemental Analysis and IR techniques.

As an international student, I'd like to thank the ISGS organization when I study in TU Kaiserslautern.

I also want to express my sincere gratitude to the secretaries in Physical chemistry and Organic Chemistry for their kind assistance and patience.

I am so grateful to all the colleagues and students during these years in TU Kaiserslautern, especially for Dr. Marie-laure Louillat, Dr. Alaleh Malekafzali, Alexander W. Jones, Christophe Heitz, Christina Bub and Congjun Yu. I would also like to thank Bünyamin Oezkaya, Christian Rank, Karina Malinovska and Alexander Konkel.

Additionally, I would like to thank Dr. Chengshuo Shen, Dr. Charles B. Bheeter and Dr. Kedong Yuan for reviewing my dissertation.

Last but not least, I woul like to extend my deep gratefulness to my family, especially to my fiancee Xinyi Zhang, whose encouragement and support have made my accomplishments possible.

Parts of this work have been published as following:

Publications

- M.-L. Louillat-Habermeyer, **R. Jin**, F. W. Patureau, *Angew. Chem. Int. Ed.* **2015**, *54*, 4102-4104: O_2-Mediated Dehydrogenative Amination of Phenols.
- **R. Jin**, F. W. Patureau, *ChemCatChem* **2015**, *7*, 223-225: Metal-free Dehydrogenative Isoquinolone Synthesis. (Highlights)
- **R. Jin**, F. W. Patureau, *Org. Lett.* **2016**, *18*, 4491-4493: Mild, Periodate-mediated, Dehydrogenative C-N bond Formation with Phenothiazines and Phenols.
- M. Goswami, A. Konkel, M. Rahimi, M.-L, Louillat-Habermeyer, H. Kelm, **R. Jin**, B. Bruin, F. W. Patureau, *Chem. Eur. J.* **2018**, *accepted*: Mechanism of the Dehydrogenative Phenothiazination of Phenols. (doi: 10.1002/chem.201800730)
- **R. Jin**, C. Bub, F. W. Patureau, *Org. Lett.* **2018**, *accepted*: Phenothiazinimides: Atom-efficient electrophilic amination reagents. (doi: 10.1021/acs.orglett.8b00914)

Abbreviations

Ac	Acetyl
acac	Acetylacetonate
Ar	Aryl
aq.	Aqueous solution
bpy	2,2'-Bipyridine
Bu	Butyl
*t*Bu	*tert*-Butyl
Boc	*tert*-Butyloxycarbonyl
cat.	Catalyst
CDC	Cross dehydrogenative coupling
COSY	COrrelation SpectroscopY
Cp*	Pentamethylcyclopentadiene
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DFT	Density functional theory
DG	Directing group
DMSO	Dimethylsulfoxide
DTBP	Di-*tert*-butyl peroxide
EDG	Electron-Donating Group
EI	Electronic impact
ESI	Electrospray Ionization
Et	Ethyl
eq.	Equivalent
EWG	Electron-Withdrawing Group
FG	Functional group
ΔG_a	Gibbs free energy
GC	Gas chromatography
h	hour
HAS	Homolytic aromatic substitution

HFIP	Hexafluoro-2-propanol
HMBC	Heteronuclear Multiple Bond Correlation
HRMS	High-Resolution Mass Spectrometry
I	Iodine
IR	Infra-red
KIE	Kinetic Isotope Effect
LED	Light-emitting diode
LG	Leaving group
M	Metal
Me	Methyl
Mes.	Mesitylene
min	minute
MW	Microwave
MS	Mass spectrometry
n-Bu	*n*-Butyl
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
Ns	4-Nitrobenzenesulfonyl
NOESY	Nuclear Overhauser Effect SpectroscopY
Oxi.	Oxidant
OTFA	Trifluoroacetoxy
Ph	Phenyl
Phth	Phthalimide
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PTZ	Phenothiazine
Rf	Retardation factor
RT	Room temperature
S_EAr	Aromatic electrophilic substitution
SET	Single electron transfer
t-Bu	*tert*-Butyl
TEMPO	2,2,6,6-Tetramethylpiperidinyloxyl
Tf	Trifluoromethanesulfonyl

TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
T.M.	Target Molecular
p-Tol	*para*-Tolyl
Ts	4-Toluenesulfonyl
XRD	X-Ray Diffraction

The multiplicity of the signals is given by the following abbreviations:
s for singlet, d for doublet, dd for doublet of doublets, t for triplet, dt for doublet of triplets, q for quartet, and m for multiplet.

Structure Numbering

The chemical structures of each chapter are numbered separately for clarity and readability. Both in the results section and in experimental section, the number is composed of a second level chapter number followed by hyphen and a structure number of the molecule.

Table of Contents

1. Abstract

The *N*-containing heterocycles have received strong attention from the organic synthesis field because of their importance for pharmaceutical and material sciences.[1] Nitrogen element plays an important role between inorganic salts and biomolecules, to search convenient methods combine C-N bond together become a hot topic in recent decades.

Since the early beginning of 20th century, transition-metal-catalyzed coupling reactions had been well-known and world widely spread in organic researchs, achieved abundant significant progress.[2] In the other side, the less toxic and more challenging transition metal free coupling method remained further potential value.

One of the most attractive and promising synthetic methods is the oxidative cross-dehydrogenative-coupling reaction, in which an excellent oxidant exhibits typically unique and remarkable features. The aim for my research is figuring out the ‘ key ’ to the transition-metal-free oxidative amination reaction.

References

[1] Moody CJ (ed), *Advances in nitrogen heterocycles.* JAI, Stamford, **1998**.

[2] M. Taillefer, D. Ma, *Amination and Formation of sp^2 C-N Bonds,* Springer, Verlag Berlin Heidelberg, **2013**.

Modern Amination Reactions and Oxidant Evolution: an Introduction

1.1 Introduction

The Carbon-Carbon/Heteroatom bonds formation reactions via transition-metal catalysis pathways were on behalf of modern organic chemistry development since the very beginning of the past century. Among the heteroatoms, nitrogen is ubiquitous in the nature environment. Those nitrogen-containing functional molecules motivated scientists to conduct novel and mild amination reactions. As a core reaction of organic synthesis, Carbon-Nitrogen bond formation reaction had been discovered and developed since the early 19 century.

Dating back to 1828, the first time when German chemist, Friedrich Wöhler accidentally synthesized urea from ammonium cyanate, ruining the skyscraper of vitalist hypothesis (Vitalism, a belief that living organisms are fundamentally different from non-living entities because they contain some non-physical element or are governed by different principles than are inanimate things, had a long history in medical philosophiles).[1] This breakthrough guided other chemists to touch the further research of organic synthesis, especially for the C-N bond formation reactions.

The first nitration to be reported was that of benzene itself by Mitscherlich in 1834. When he treated benzene with fuming nitric acid together, the unexpected nitrobenzene was formed.[2] After several decades, the transition-metal catalysts took over the stage when Ullmann accidentally discovered the copper-catalyzed amination of aryl halides in 1903.[3] However, it began booming in 1990s when Buchwald and Hartwig characterized this palladium-catalyzed amination reaction which was considered the state-of-the-art for C(sp^2)-N bond formation and in the following decade, numerous important approaches had been well-studied and developed.[4] Depending on the previous researches, a wide range of aminating reagents had been utilized in various kinds of C-N bond formation reactions (Figure 1).[5]

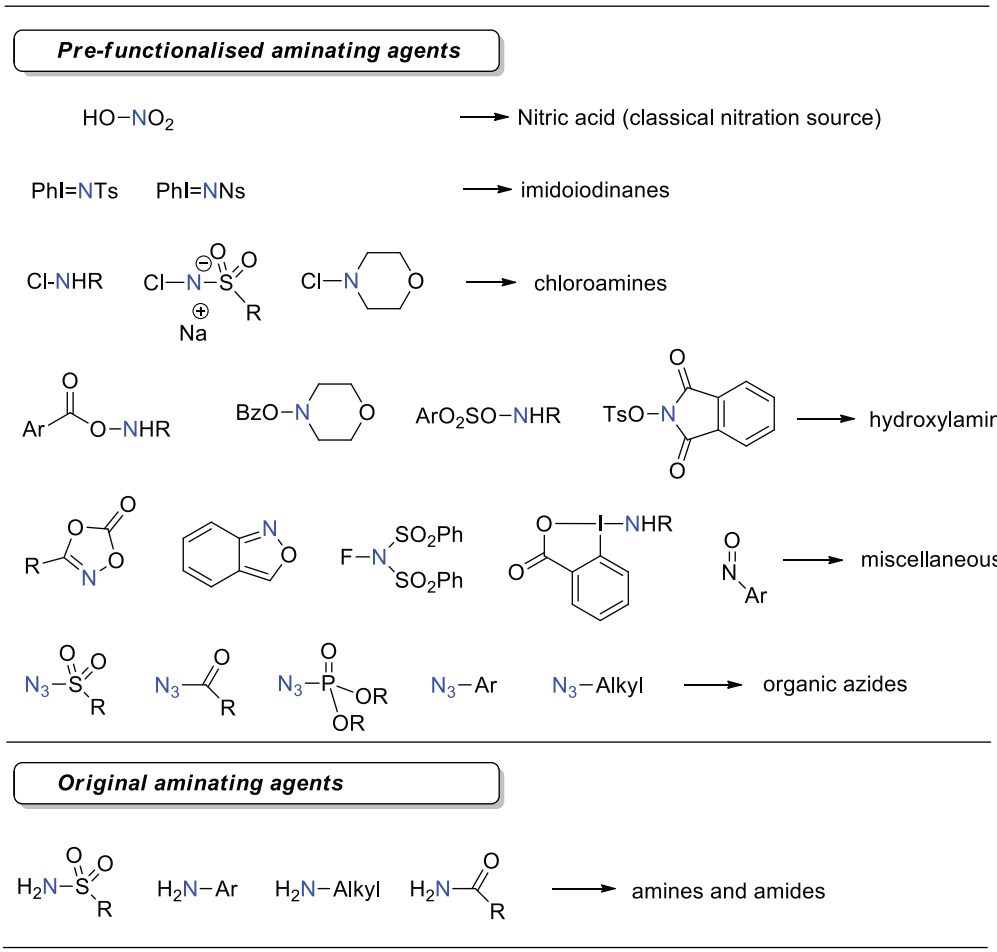


Figure 1. Commercial pre-functionalized and unprotected aminating reagents

It was well-developed for the combination of nucleophile and electrophile reagents to build new C-N bond, especially in the presence of numerous transition-metal catalysts.[6] However, it is still challenging for conducting C-N bond via C-nucleophile and N-nucleophile, especially using nonprefunctionalized amines or amides for direct cross-dehydrogenative-amination of C-H bond activation, since they were regarded as the most desirable aminating reagents.

Recent years, novel methods were widely applied in C-N bond formation reactions based on the classical transition-metal catalysis system[7], as well as non-traditional methods such as photocatalysis chemistry, organocatalysis chemistry, and electrosynthesis.[26,28,46,56] Alternatively, the external oxidant was required in C-nuleophile and N-nucleophile combination reaction, and transition metals or other organocatalysts could be abandoned.

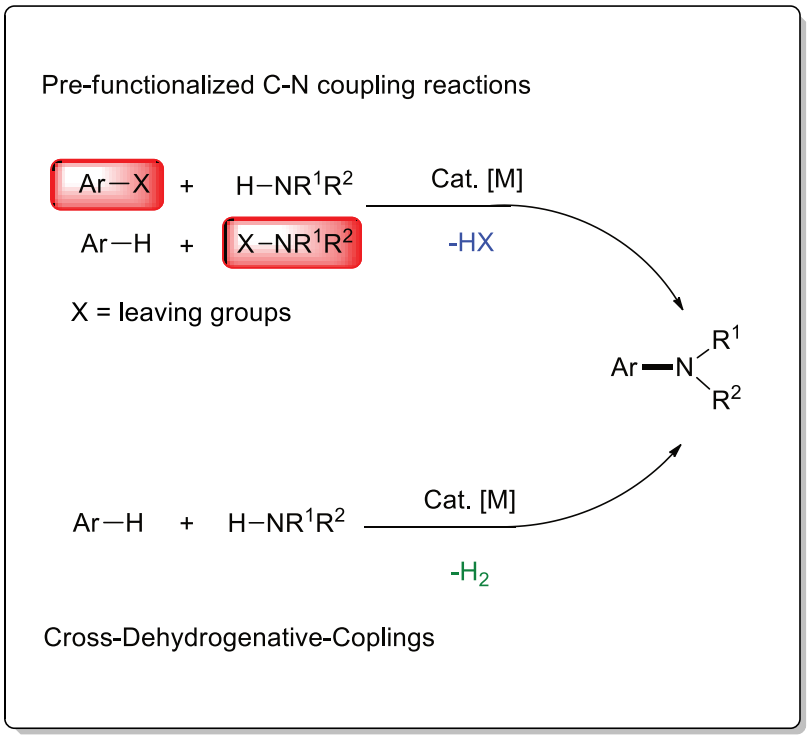
Following with this point, we researched on a series of oxidants for transition metal free oxidative amination reactions, including the controlling experiments to explain the plausible pathways. To further understand the background knowledge of modern amination reactions,

herein we address the evolution of the popular and novel methods reported for C-N bond formation from past century to recent years. Subsequently, we present our current preliminary results of non-transition metal aminations of phenothiazine derivatives with phenols or indoles.

1.2 Evolution of modern amination reactions

1.2.1 Transition metal-catalyzed C-N bond formation reactions

In our nature, most of the pharmaceutical biomolecules contain C-Hetero bonds, giving various functions in life process. For instance, enzymes, the biocatalysts for reactions in lives, contain large numbers of C-N bonds, serving important roles in biocatalysis processes. To mimic the nature and synthesize C-N bond contained compounds, transition-metal-catalyzed coupling reactions was developed by chemists and they played an important role nowadays. In most instances, two general approaches for C-N bond formation via transition metal catalyzed coupling reactions could be depicted(Scheme 1).

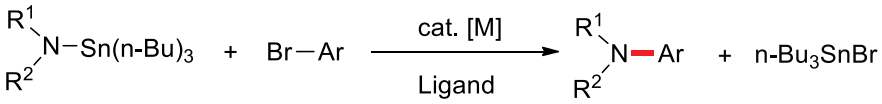


Scheme 1. Transtion Metal-Catalyzed C-N Bond Formation Reactions

1.2.1.1 Pre-functionalized aminating agents C-X/N-X for amination reactions

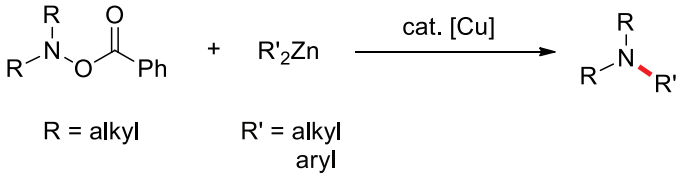
One of the most efficient and direct C-N bond formation synthetic method, for instance Buchwald-Hartwig amination, was utilizing pre-activated reagents containing halogens or other leaving groups on aryl- or amino- to form C-X/N-X, which can easily undergo cross couplings in an optimized condition, which extended the Ullmann-Goldberg type amination.[8] The advantages of these reactions were readily declare, efficient, high selectivity, board scope and strongly tolerance of function groups.

An early emerging strategy in prefunctionalizing both C-X and N-X was generated by Migita and co-workers in 1983.[9] The reaction between tributyltin amides and aryl bromides was catalyzed by palladium complex and phosphine ligand (Scheme 2). The limitation of this reaction was utilizing the dialkylamides and electron-netural aryl halides. The aryl halides containing either electron-deficient groups such as nitro, acyl or electron-rich groups such as methoxy perform unsatisfied results. On the other side, only unhindered dialkytin amides underwent well and gave good yields.



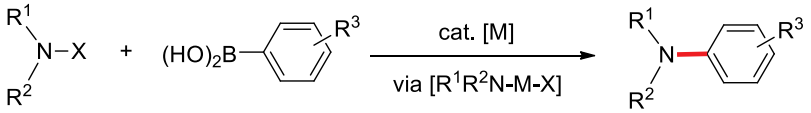
Scheme 2. C-X and N-X condensation reaction by Migita and co-workers

Since the *N*-nucleophile reagents were limited for C-N amination cooperating with C-H reagents, researchers considered to transform them straightforward into *N*-electrophiles. In 2004, Johnson *et al.* presented their work about copper-catalyzed electrophilic amination reaction (Scheme 3).[10,a] The represent widely used electrophilic aminating reagent *O*-benzoyl-hydroxylamines was emerged in the amination reaction. In this reaction, aryl reagent was prefunctionalized into diorganozinc style, then reacted with *O*-benzoyl-hydroxylamines and gave good to excellent yields of products. During the following years, they extended their strategy and improved the scope, giving renewed ideas for traditional amination reactions.[10,b,c]



Scheme 3. Electrophilic reagents engaged amination reaction presented by Johnson *et al.*

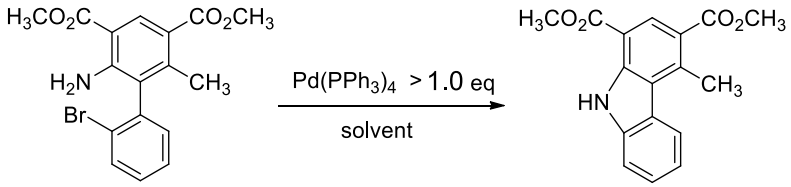
During the following several decades, the organometallic reagents mediated electrophilic amination reactions were attracted less attention. However, in 2008 Lei *et al.* published their results of Cu-catalyzed amination with arylboronic acids and N-chloroamides reagents, an outstanding C-X/N-X type C-N bond formation reaction (Scheme 4).[11] Such kind amination reaction shows wide tolerance to most of functional groups and mild condition. Moreover, the organometallic intermediate [R^1R^2NCuX] mentioned in the proposed catalytic cycle presented an innovation respected from Grignard reagent as well.



R^1, R^3 : Halo substituents

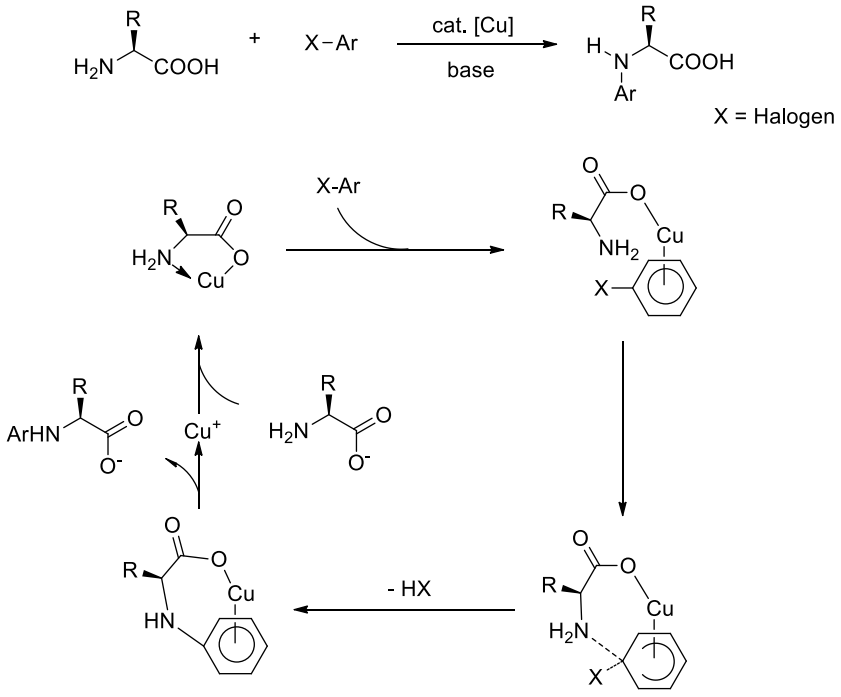
Scheme 4. Organometallic-mediated C-X/N-X amination reaction presented by Lei and co-workers

On the other side, the early amination research via C-X/N-H reagents was formulated in 1985, by Yasuda *et al.*, who reported the palladium(0)-mediated intramolecular amination ring-closing of β-Carboline synthesis reaction (Scheme 5).[12] This reaction was conducted in a harsh condition with stoichiometric amounts of [$Pd(PPh_3)_4$]. Perhaps it was due to the absence of base.



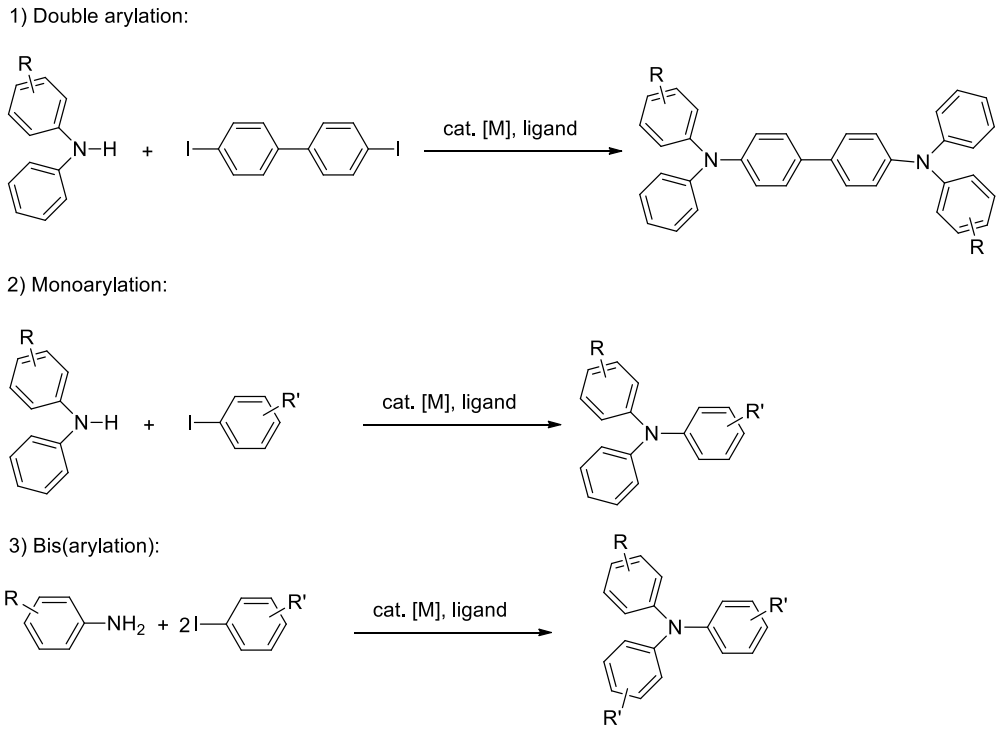
Scheme 5. C-X and N-H intramolecular ring-closing amination reaction presented by Yasuda *et al.*

After more than one decade, Ma group reported copper-catalyzed amination reaction of amino acid with aryl halides.[13] As one of the top biofunctional, best building blocks, and commercially available in optically pure form molecules, amino acid had been directed more and more attention in organic synthesis. Under the mild conditions, large scope of chiral N-aryl-α-amino acids was developed, which were common core structures for numerous biomolecules in pharmaceutical industries. Herein, we presented the reaction procedure and proposed catalytic cycle in Scheme 6.



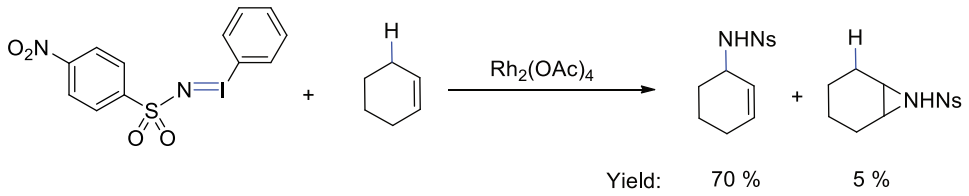
Scheme 6. C-X and N-H amino acid cross-coupling amination reaction from Ma *et al.*

In 1999, Hu developed the Copper-mediated amine Ullmann condensation reactions. The simple Copper(I) catalyst coordinated by ideal ligand 1, 10-phenanthroline produced significant rate acceleration.[14] Such optimized reaction condition shortened time and lowered the required temperature compared with traditional Ullmann reaction. This method was applied in multiple distinct types of Ullmann condensations: sequential double arylations, monoarylation, and bis(arylations) (Scheme 7).



Scheme 7. C-X and N-H Ullmann condensation amination reaction form Hu *et al.*

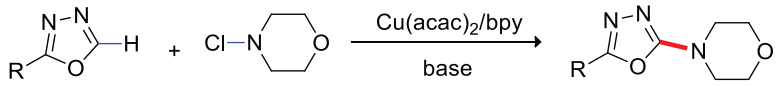
To avoid the multiple reaction steps, C-H activation and C-N bond formation in one step was more challenging and interesting, which encouraged researchers to make a breakthrough of previous C-X/N-H type amination reactions. In 1996, Müller *et al.* reported the dirhodium(II)-catalyzed amination of cyclohexene with NsN=IPh, intead of producing major product, aziridine, the linear arylsulfonamide product revealed better chemoselectivity (Scheme 8).[15,d] Interestingly, depending on different members of rings, the ratios between aziriding and allylic amines changed correspondingly. Further investigation was managed by the same group guiding with the first thorough study.[15,e]



Scheme 8. Electrophilic reagents NsN=IPh engaged amination reaction from Müller *et al.*

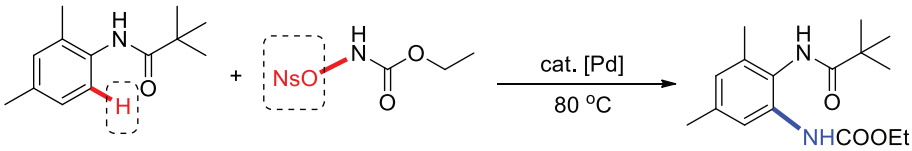
The NsN=IPh reagent was firstly synthesized by Okawara in 1975 and then was popularly applied in amination or aziridination reactions.[16] Afterwards, other common pre-functionalized N-X reagents such as *N*-carboxylates, *N*-tosylates, *N*-Cl, and azide substituents were also well developed and widely applied in C-N condensation reaction. For example, in

2010 Miura reported the copper-catalyzed direct amination of azoles with *N*-Cl source (Scheme 9).[17] The reaction underwent a mild condition in the presence of $Cu(acac)_2$/bpy and LiO-*t*-Bu base. The scope for the C-H heteroaromatic source was limited due to the highly demand of the low p*K*a of the C-H bond.



Scheme 9. C-H and N-X copper-catalyzed amination reaction of Miura *et al.*

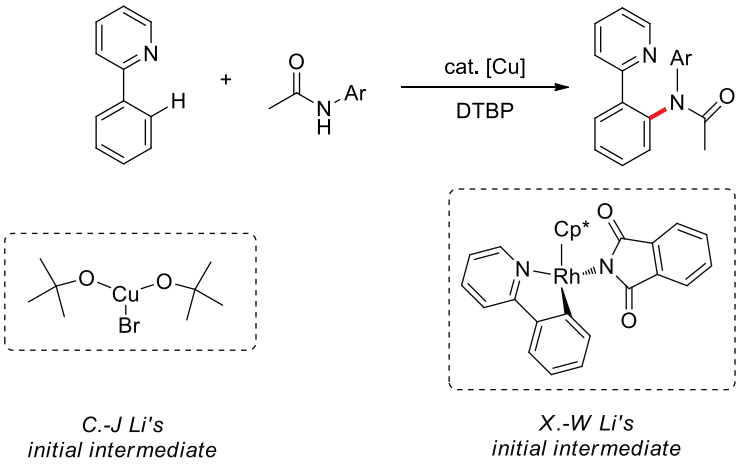
The same year, Yu developed the condensation reaction between anilides and *N*-nosyloxy-carbamates with a Pd catalyst to form aminoaniline derivatives (Scheme 10).[18] Guiding by a directing group, the C-H bond on the *ortho* position of anilides was activated. A mild condition was required in this reaction, despite of the specific pre-functionalized N-X group.



Scheme 10. Yu *et al.* anilides(C-H)/*N*-nosyloxycarbamate(N-X) condensation amination

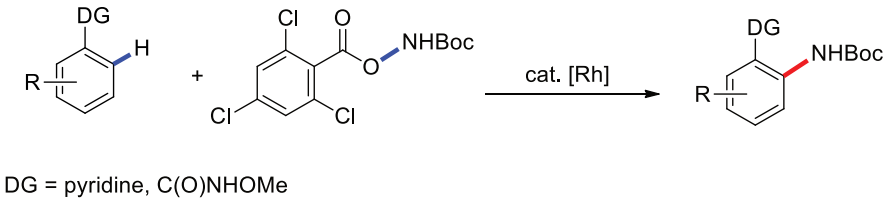
The third well known condensation reaction of aryl pyridines with acetanilies was published in 2010 by (Chao-Jun) Li and co-workers (Scheme 11).[19] In the redox system, DTBP as the oxidant initiate the catalytic cycle by oxidative addition to the Cu(I) precatalyst. Alternatively, the electrophilic aminating reagents such as *N*-arenesulfonated imides employed by (Xingwei) Li's group[20] indicated that the in situ pre-oxidation of the amide reagent cannot be excluded either. Those two pathways both remained possibility.

Besides to those electrophilic N-X reagents mentioned above, azides were attracted more attention in recent years. Representative examples were put forward by Chang, Glorius, Ackermann, and Jiao.[21,22,23,24] The advantages of this class of compounds are as follows, high reactivity, libration of N_2 as the only by-product, ubiquity and versatility of common blocks. However, limited from the high reactivity, azides were hazardous in this reaction.



Scheme 11. C.-J Li and X.-W Li's different electrophilic reagents and pathways

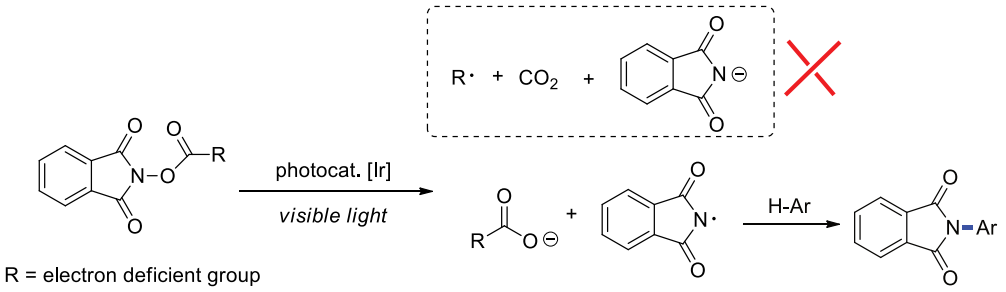
In 2013, Glorius group reported the Rh(III)-catalyzed amidation via C-H activation with *N*-Boc protected amines.[25] With the strong electron-deficient aroyloxycarbamates furnished on the *N*-Boc amines, an efficient electrophilic amidation reagent was produced (Scheme 12). Those substrates ensured wide functional groups tolerance under mild conditions, despite of the low atom economy from the large leaving group. Tendency to transfer the *N*-nucleophile to the *N*-electrophile kept moving, meanwhile, other novel methods occurred.



Scheme 12. Glorius *et al.* C-H/N-X Rh(III)-catalyzed *N*-Boc protected amidation reaction

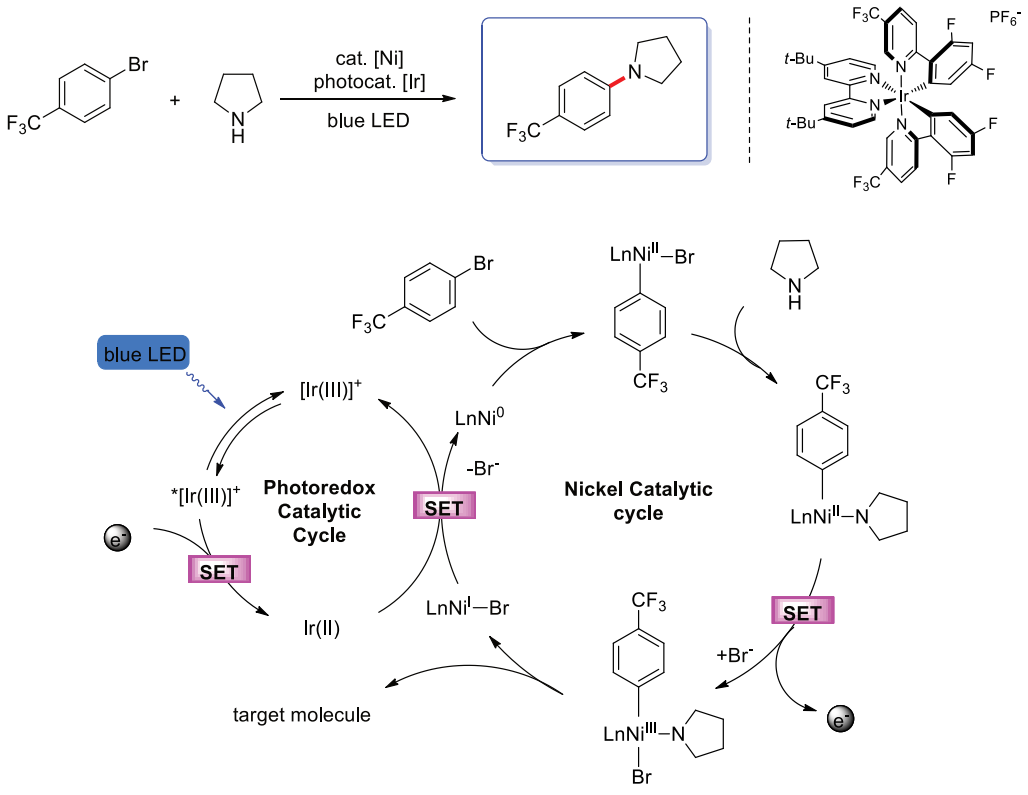
The following year, Sanford group presented the visible light promoted C-H amination of aromatics with N-acyloxyphthalimide in presence of photocatalyst.[26] Inspired by the earlier work from Skell, who investigated the UV photolysis of *N*-bromophthalimide to form radical N • reagent, which can participate in conducting C-N bond formation of the benzene solvent.[27] Instead of making an alkyl radical reagent, phthalimide anion, and releasing CO_2, electron deficient group furnished alkyl substituents favored fragmentation to release RCO_2^- and PhthN • radical, which then participated in C-N bond formation via Csp^2-H activation of aryl derivatives (Scheme 13). Those photocatalytic methods for C-H amination created new pathways of biologically active molecules synthesis. Mild conditions avoid of the excess of expensive oxidants as well as elevated temperature. However, limitations were clearly

obtained on this specific *N*-electrophilic reagent, and a promotion of atom efficiency was still required.



Scheme 13. Sanford *et al.* C-H/N-X Photocatalyzed radical amination reaction

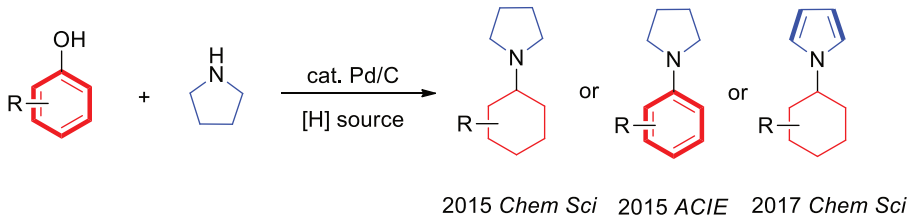
In 2016, with the development of transition metal catalysts and well control of the photocatalysis methods, MacMillan achieved an alternative approach to furnish C-N bond formation by using ligand-free nickel(II) salts, in which facile reductive elimination from the nickel metal center was induced via a photoredox-catalyzed electron-transfer process.[28] This method could be developed under the premise of the destabilization of a metal amido complex via photo catalysis (Scheme 14).



Scheme 14. MacMillan *et al.* C-X/N-H Photocatalyzed ligand-free amination reaction

The benefits of those novel photocatalyst-introduced methodologies were significant, milder conditions either base free or ligand free, cheaper transition metal catalyst or lower catalytic loading. Critically, either electrophilic reagent or prefunctionalized step is necessary, some of them are also hazardous. All these reasons drove researchers to develop more advanced and greener pathways to achieve the C-N bond formation.

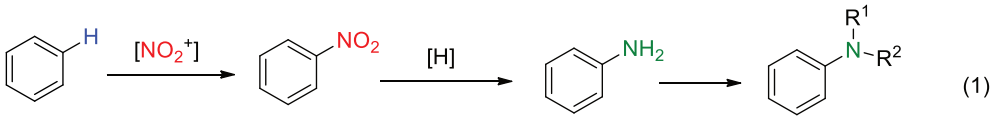
From 2015 to 2017, (C. -J) Li group reported a series of controlling reductive amination of phenols with anilines and amines (Scheme 15).[29] Phenol, one of the most abundant and important nature products, was made outstanding progress in catalytic conversion of lignin model compounds to valuable chemical by numerous researchers. Recent years, however, rare examples were presented related to the amination of phenols. Notably, this novel reductive amination represented a promising catalytic technique to promote a C-O bond cleavage.



Scheme 15. Controlling reductive amination of phenols: 1) Reduction of aromaticity, 2) Maintaining of aromaticity, 3) Transfer of aromaticity

1.2.1.2 Cross-dehydrogenative-couplings (CDCs) C-H/N-H for amination reactions

Before the well development of organometallic chemistry and one pot reaction in organic synthesis, there was a classical direct installation of amine moiety into phenyls which was conducted by electrophilic aromatic nitration pathway. This type of reactions required a harsh condition and multi steps: nitration of arenes in strongly acidic environment, strict reductive hydrogenation, and functionalization on N-H bond (eq 1).



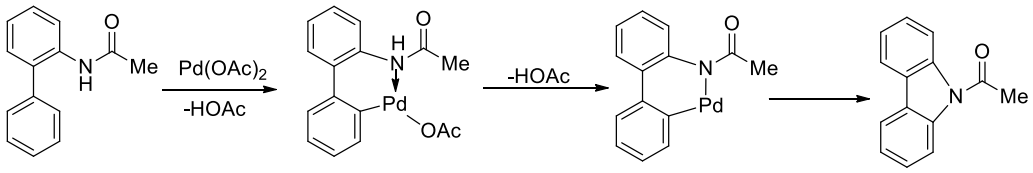
(1)

Obviously, the substrate scope was limited within the harsh conditions, which also presented less practical. Alternatively, the ideal reaction can be described as a cross-dehydrogenative

coupling between arenes and anilines in one step. The challenge of this reaction was that thermodynamically uphill as strong C-H (~113 kcal/mol) and N-H (~108 kcal/mol) bonds dissociation in exchange of weaker C-N (~103 kcal/mol) and H-H (~104 kcal/mol) bonds formation. Moreover, the high aryl C-H bond activation barrier also makes this amination kinetically sluggish. Either employing the energetic substrates or pre-functionalized aminating agents to dive the overall thermodynamics favorable, as mentioned above. Another way to achieve this challenge reaction was directly forming C-N bond via cross dehydrogenative couplings (CDCs) with a highly efficient catalytic systems to reduce the activation barrier.

The long sought cross dehydrogenative couplings (CDCs) for C-H amination reactions was considered as a quite popular method because it only required the original nucleophilic reagents and produced environmentally friendly by product either H_2 or H_2O. In most cases the H_2 was possibly not detected when the external oxidant exists in the reactions. In order to understand the emergence of the concept from a historical perspective, herein we listed several representative examples from last decade.

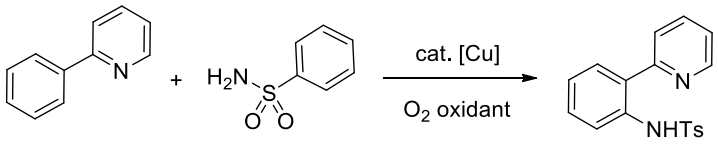
In 2005, Buchwald group reported the palladium catalyzed intramolecular CDC amination reactions to form carbazoles.[30] Guiding with the directing group on N-coupling partner, the Pd involved intermediate reduced the high energy barrier of the final C(sp^2)-N reductive elimination step (Scheme 16). As one of the early cases which proved in detail the concept of CDC aminations, it inspired other researchers to consider deeply of the novel CDC aminations and achieved more challenging goals.



Scheme 16. Palladium-catalyzed intramolecule CDC amination reaction

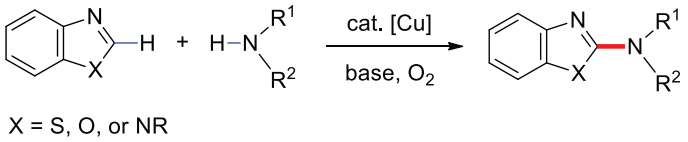
The following year, Wing-Yiu Yu and Chi-Ming Che groups discovered the amidation of amides with imine derivatives in the presence of palladium catalyst and excess peroxide oxidant.[31] The same year, Jinquan Yu and co-workers submitted the work of copper catalyzed intermolecular CDC amination reaction using oxygen as the oxidant (Scheme 17).[32] Notably, although there was only one amination example in this communication, it demonstrated a significant breakthrough for CDC amination reactions. The external oxidant was required in principle which meant an abundant, cheap, less toxic and efficient oxidant would be recommended indeed. Molecular oxygen as the ideal oxidant was successfully

introduced in this reaction indicating that the long potential of such kind CDC aminations could be achieved in milder conditions and more interesting examples.



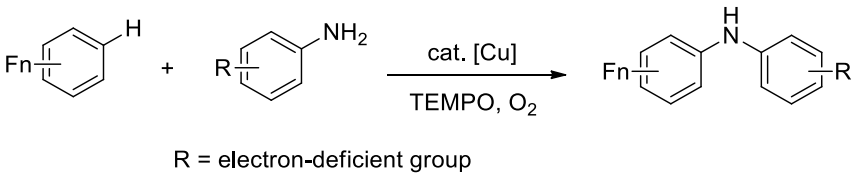
Scheme 17. Copper-catalyzed intermolecule CDC amination reaction with O_2

With the development of the cheap transition metal catalysts and its potential value to the C-N bond formation, copper catalysts took an important place in the C-H bond activation amination fields. In 2009, another highlighted examples using nonactivated amine as aminating reagent of azoles at C2-position under copper catalyzed aerobic conditions were reported by Schreiber and Mori (Scheme 18).[33] Due to the very acidic proton on C2 position of azoles, the reaction was suspiciously initiated by C-H bond cleavage and underwent in a basic condition. Since Mori extended the scope to cover (benzo)thiophenes and most secondary amines were tolerated, the acidic proton on a heterocyclic rings still remained.



Scheme 18. Copper-catalyzed oxidative amination reaction of azoles with amines under aerobic and basic conditions

Individually, Duan reported the nickel catalyzed amination of benzoxazoles and Panda showed the same reaction with heterogeneous manganese catalyst.[34] Due to the similarity of those reactions to the copper catalyzed examples, herein we only showed them in briefness.

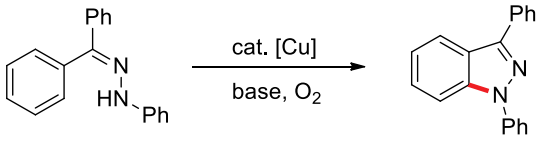


Scheme 19. Copper-catalyzed oxidative amination reaction of polyfluoroarenes with primary amines

To overcome the existing limitations, Su screened the arene derivatives and successfully developed the copper-catalyzed amination of acidic aryl C-H bonds of polyfluoroarenes with primary amines (Scheme 19) in 2010.[35] The proposed mechanism explicitly indicated that

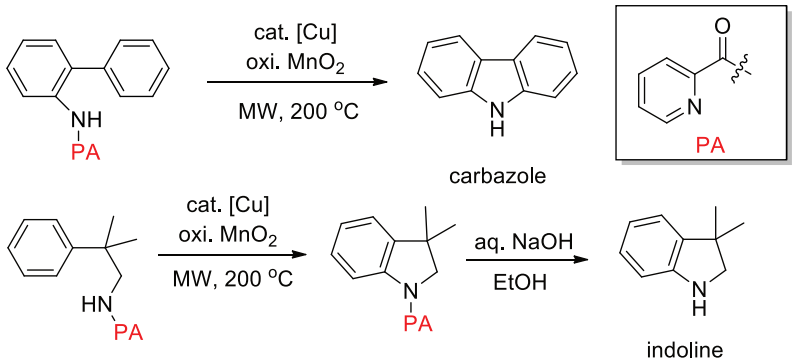
the role of the TEMPO co-oxidant, in combination with O_2, was the key to (re-)oxidize Cu(II) intermediate to Cu(III), thus facilitating the final C-N reductive elimination. This work created the possibility to achieve amination of arenes with all sorts of amines via CDCs pathways.

In 2013, Jiang group reported the intramolecular ring closing Cu-catalyzed oxidative amination of imine derivatives to form indazoles (Scheme 20).[36] Assisting with the directing group, the less acidic C_{sp2}-H still could be activated by Cu catalyst and then underwent the following step of reductive elimination. Notably, a series of controlling experiments were performed, indicating the involvement of a radical pathway, and the reaction survived from numerous radical scavengers.



Scheme 20. Copper-catalyzed intramolecular amination of indazoles synthesis

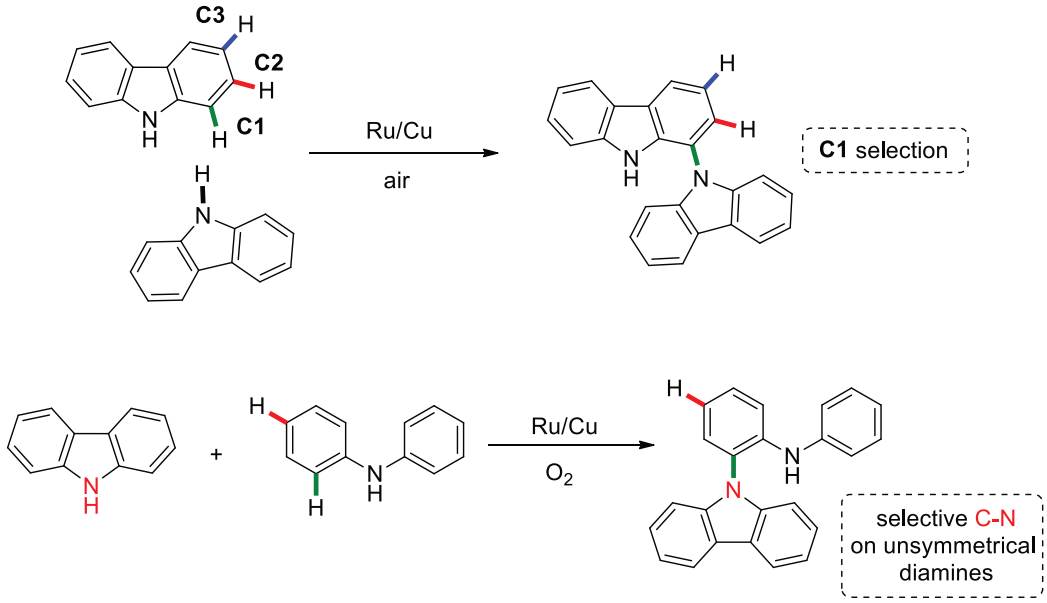
Not long afterwards, Miura group reported a picolinamide (PA)-directed intra molecular C-H amination of carbazoles synthesis.[37] This reaction underwent a novel microwave irradiation method and employed a stoichiometric manganese oxidant. This seminal reaction completed C-H functionalization and removal of directing group in one step, which was advantageous to give N-H carbazoles in high yield. Later in 2015, indoline derivatives were perfectly synthesized by this significant approach (Scheme 21).



Scheme 21. Microwave irradiation amination of carbazole and indoline synthesis

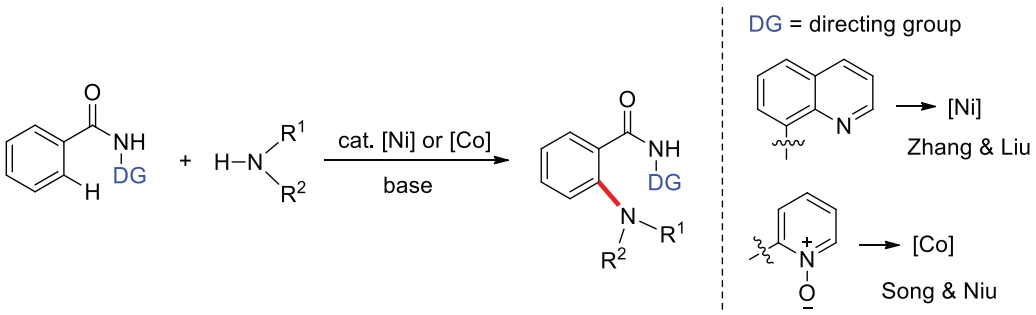
From 2013 to 2015, Patureau group reported the Ru/Cu catalyzed oxidative homo- and cross-couplings of carbazoles, via a CDC pathway (Scheme 22).[38] This high regio-selectivity C1

aminated product was formed in the absence of directing groups, which created a novel method to achieve the metal selectively catalyzed C-H bond activation amination of unprecedented unsymmetrical diamines.



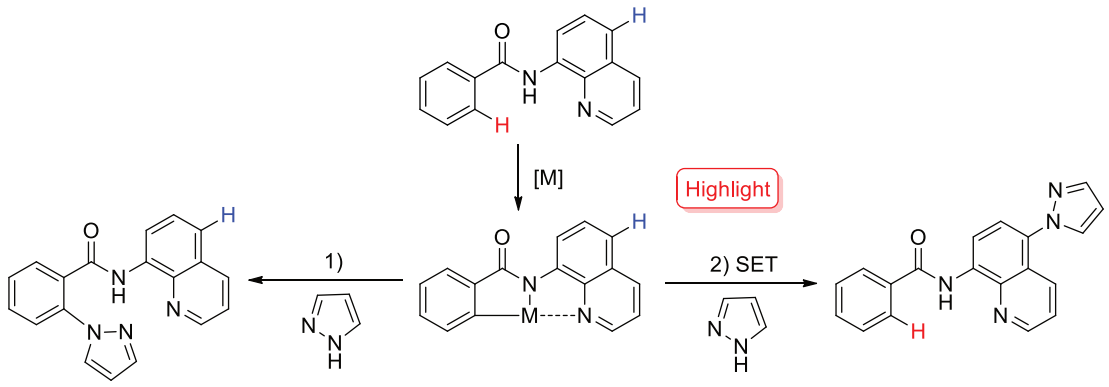
Scheme 22. Ru/Cu catalyzed regio-selective aminations of carbazoles and diamines

Later, Zhang and Liu reported the nickel-catalyzed direct C-H amination of arenes and after one year Song and Niu developed a similar system which involved a cobalt catalyst instead of nickel.[39] The key to success of those reactions were the judicious choice of directing groups: 8-aminoquinoline benzamide worked well with nickel catalyst while 2-benzamido-pyridine *N*-oxides led to a promising yield of amination with cobalt catalyst (Scheme 23). DFT calculations suggested that single electron transfer is involved in the catalytic pathway. As the first-row catalysis, copper, nickel and cobalt had been attracted lots attention in C-H bond activation amination reactions, those novel procedures will find a versatile utility in synthetic chemistry in the coming future.



Scheme 23. Nickel and cobalt catalyzed direct C-H amination reactions

Very recently, Lei group published the selective amination of 8-aminoquinoline at the C5 position with azoles (Scheme 24).[40] The classical and traditional coordination, C-H activation, subsequent transmetallation and reductive elimination pathways were well studied. This seminal method which underwent an entirely different pathway compared to the previous cases, created a coordination interaction-promoted selective special C-H activation strategy.



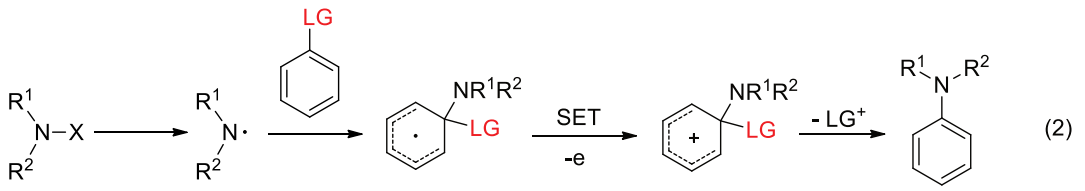
Scheme 24. Coordination interaction-promoted selective C-H amination reaction

1.2.2 Transition metal-free C-N bond formation reactions

In respect of the clarification of the concept on transition metal-free cross-coupling, it mainly could be identified in three types: 1) radical and cationic pathways, the hyperiodine-mediated oxidative reactions were the classical cases; 2) electrophilic and nucleophilic aromatic substitutions, as the traditional representative example the Friedel-Crafts reaction; 3) aryne and organocatalysis pathways.[41] All of those methods were widely applied in C-C coupling reactions and tremandous interesting results had been published.[42] However, until the beginning of this century, a few traditional transition metal-free methodologies had been successfully applied in Csp^2-N amination and amidation reactions. In this dissertation, the amination reactions with 1) radical and cationic pathways and 2) electrophilic and nucleophilic aromatic substitutions would be mainly discussed.

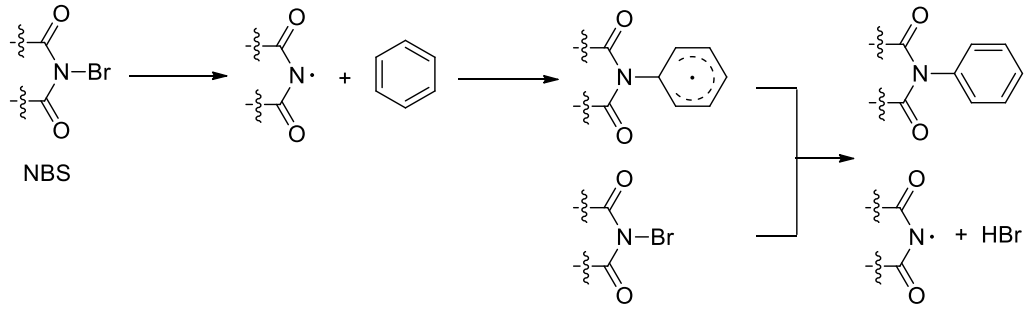
1.2.2.1 Radical and cationic pathways amination

The typical radical mediated reaction was homolytic aromatic substitution (HAS), which was defined as the replacement of a leaving group on arene by an attacking radical reagent (eq 2).



Generally, HAS reactions had a long history and had been regarded as one of the most important and straightforward synthetic methods to conduct C-C(X) couplings. There were numerous excellent candidates for performing radicals, such as aroyl peroxides, aryl halides, and aryl diazonium. Halides radical sources especially NBS and NIS became the better choices for such HAS amination reactions because of their activities and accessibility of the starting materials.

One of the early examples of amidation of NBS with arenes was traced back to 1970s, when Skell and co-workers reported the C-H imidation reactions via radical pathways (Scheme 25).[43] This brief report included important information and became the basis of the future researches such as visible-light promoted radical amination of arenes.

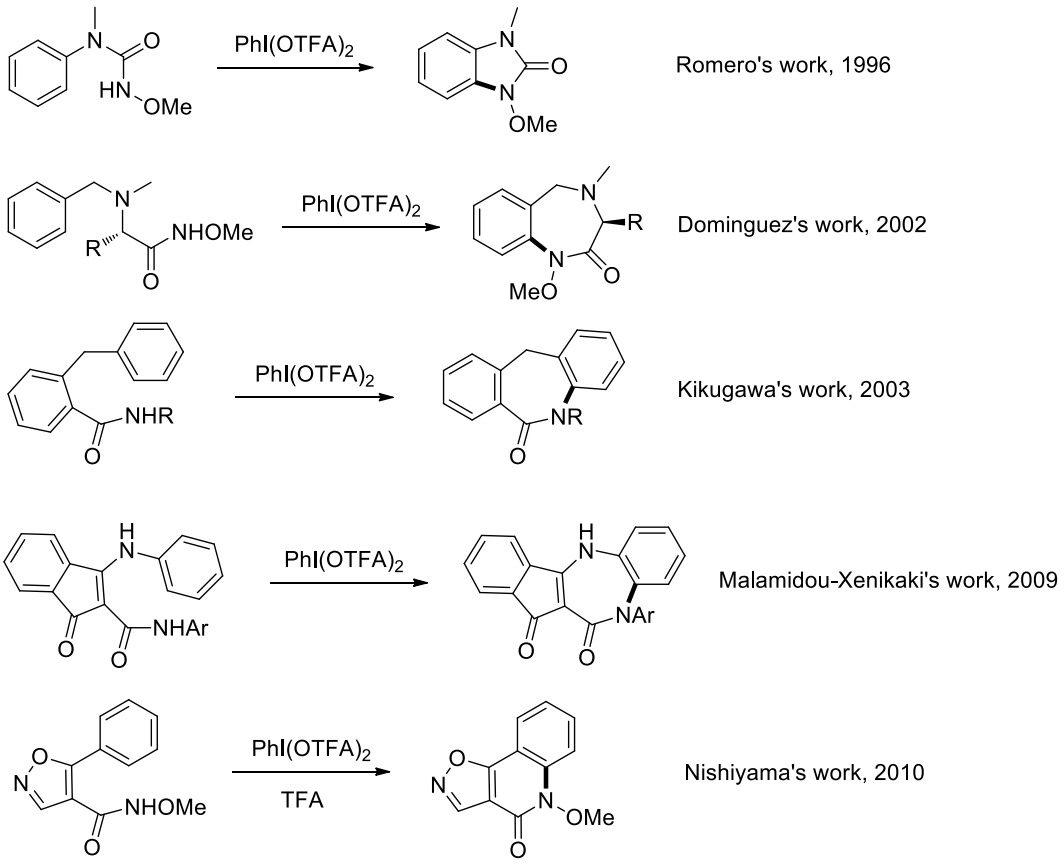


Scheme 25. Skell's radical imidation of arenes with NBS

On the other side, the early homolytic aromatic amination by the amino radical cation was developed by Ventura in 1984.[44] The behavior of the simple amino radical cation had been less investigated, and it carried out this model amination reaction. Despite that a harsh condition (stoichiometric amounts of ferrous salts) was required and *ortho*-, *meta*-, and *para*-aminated isomers produced, the concept of homolytic aromatic amination (HAA) had been further developed.

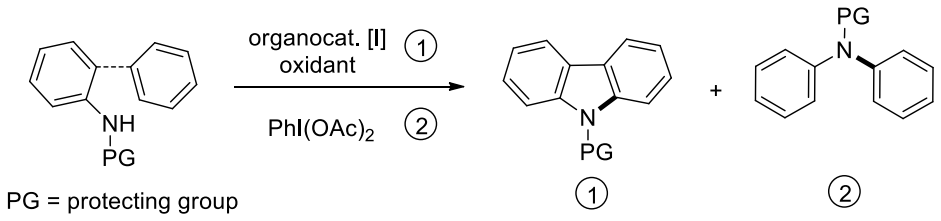
From 1996 to 2010, hypervalent iodine as an efficient oxidant promoted amidation of arenes had been well developed by several group. Romero[45,a], Dominguez[45,b,c,d], Malamidou-Xenikaki[45,e], Kikugawa[45,f], and Nishiyama[45,g] made contribution to a series of different 5,

6, 7-membered lactams synthesis through similar intramolecular trap of *N*-acylnitrenium ions (Scheme 26).



Scheme 26. Hypervalent iodine-mediated intramolecular cycloamidation evolution

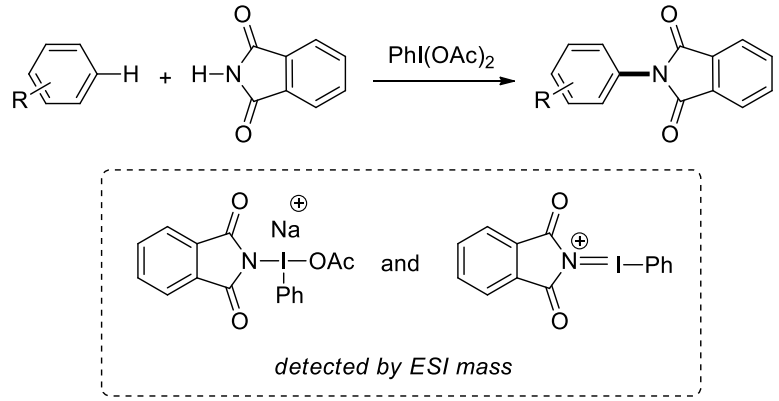
In 2011, Antonchick group published the work of hypervalent iodine-mediated cross amination of inactivated arenes.[46] In the same paper, a highly efficient, atomeconomical and green organocatalytic method for the synthesis of carbazoles was developed (Scheme 27). Both were operated in an ambient temperature, no additional energy was required. The mild conditions strongly demonstrated that hypervalent iodine reagents are important oxidants in modern organic synthesis but also alternatively efficient organocatalysts which could be applied in series of traditional transition-metal catalyzed cross coupling reactions. Due to their



Scheme 27. Iodine as the organocatalyst/oxidant performed intra/inter-molecular aminations

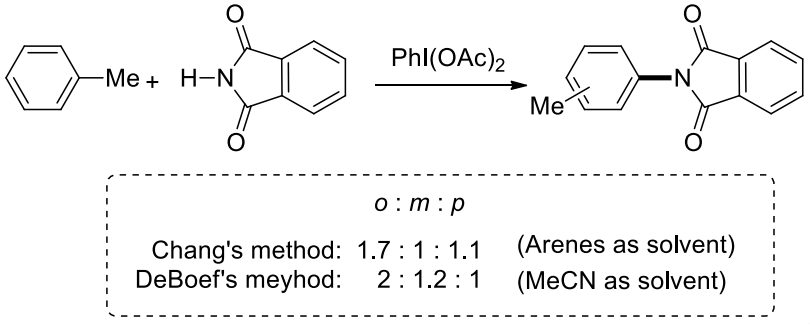
low toxicity, high stability, easy handleness, and abundant storage in nature, they served as a synthetic oxidant highly welcome both in academic research and chemical industry.

In the same year, Chang group found the copper-catalyzed intramolecular oxidative amination reaction for the synthesis of carbazoles.[47,a] Control experiments indicated that the transition-metal free conditions in the presence of hypervalent iodine reagents as oxidants alone underwent the annulation to afford carbazole derivatives, albeit the yields were from low to moderate. Respecting with this result, they reported another transition-metal free intermolecular oxidative amination reactions in the same year.[47,b] The control experiments and proposed mechanism indicated that the reaction underwent an ionic pathway (Scheme 28).



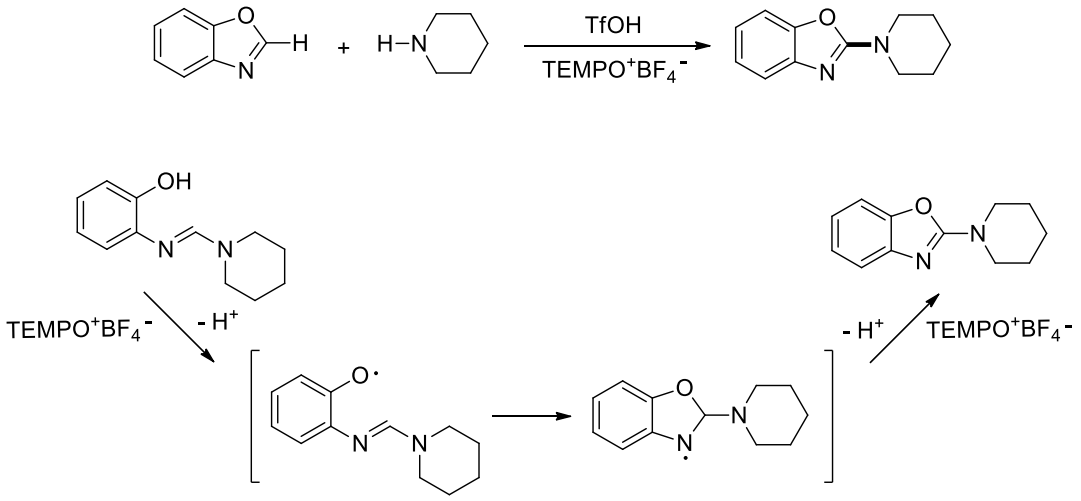
Scheme 28. Ionic pathway hypervalent iodine mediated amination reaction

Simultaneously, DeBoef reported a very close transition-metal free intermolecular amination reaction.[48] MeCN was selected as the optimal solvent which replaced the largely excessive amount of arenes and microwave irradiation was employed to increase the efficiency. However, both methods produced the substituted arenes in a low regioselectivity (Scheme 29).



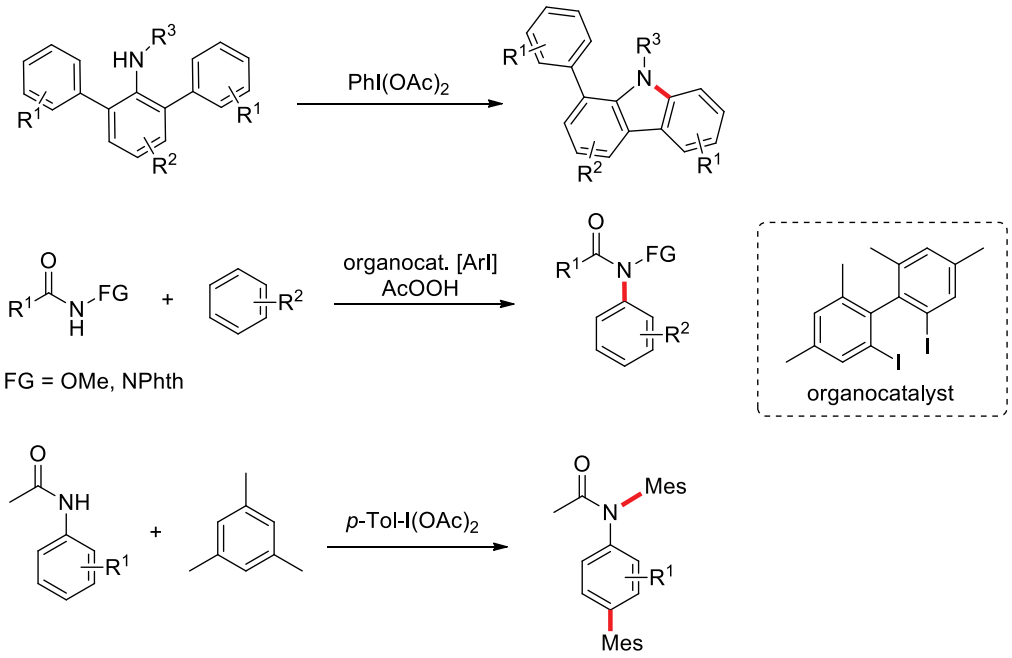
Scheme 29. Comparison of Chang and DeBoef's hypervalent iodine mediated amination reactions

Another unique amination method of TEMPO-mediated oxidative C-N bond formation reactions was developed by Studer and co-workers recently.[49] With a catalytic amount of TfOH, 2-aminobenzoxazoles was oxidized in the presence of $TEMPO^{+}BF4^{-}$, followed with two Single-electron transfer (SET) steps and one deprotonation, it conducted to the aminated product (Scheme 30). Several biomolecules were successfully synthesized adopting this method.



Scheme 30. TEMPO-mediated oxidative amination and mechanistic studies

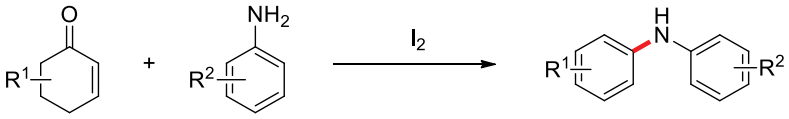
After one year, further research by Antonchick group expanded the oxidative amination



Scheme 31. Extending the synthesis system of Antonchick's hypervalent iodine mediated amination

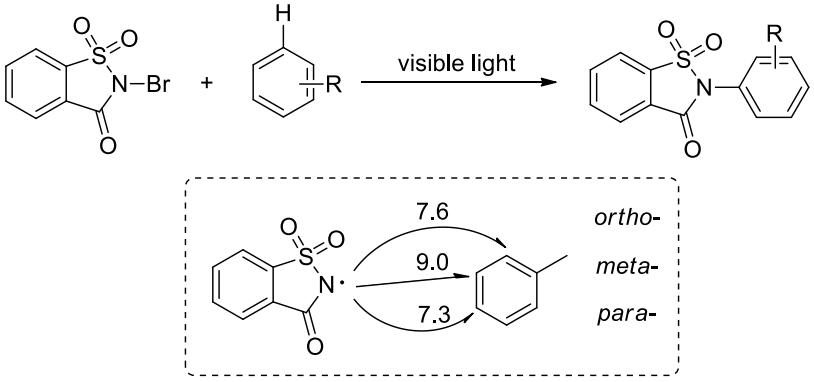
system to synthesis of 1-arylcarbazoles, *N*-methoxy-*N*-arylamides, and diarylation of anilides (selective formation of C-C and C-N bonds, see Scheme 31).[50]

The same year, Maycock and co-workers reported an iodine directly oxidized amination of 2-cyclohexenones (Scheme 32).[51] This creative method underwent a simplified condition and conducted a highly regioselective aliphatic-aromatic transformation. The success of iodine indicated that hypervalent iodine was not the only choice as an effective oxidant of oxidative amination reactions.



Scheme 32. Iodine mediated amination of 2-cyclohexnones to form *N*-arylanilines

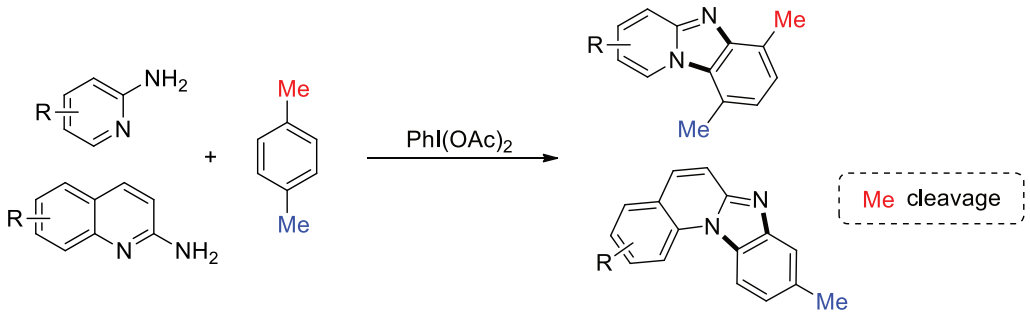
In 2014, inspired by Skell's previous work, Luo group reported a distinctive transition metal-free C-H imidation of arenes promoted by visible-light photolysis of *N*-bromosaccharin (Scheme 33).[52] The DFT calculations revealed that the addition of saccharin nitrogen radical is quite facile. The regioselectivity of this amidation of toluene was also investigated by DFT calculation, and only *para*- and *ortho*- amidation product was formed, in a ratio close to 1:1. This result was probably due to that the calculation showed a lower activation free energy for the radical addition onto the *para*- and *ortho*-positions.



Scheme 33. Visible light promoted amidation and origin of regioselectivity (ΔG_a [kcal.mol^{-1}])

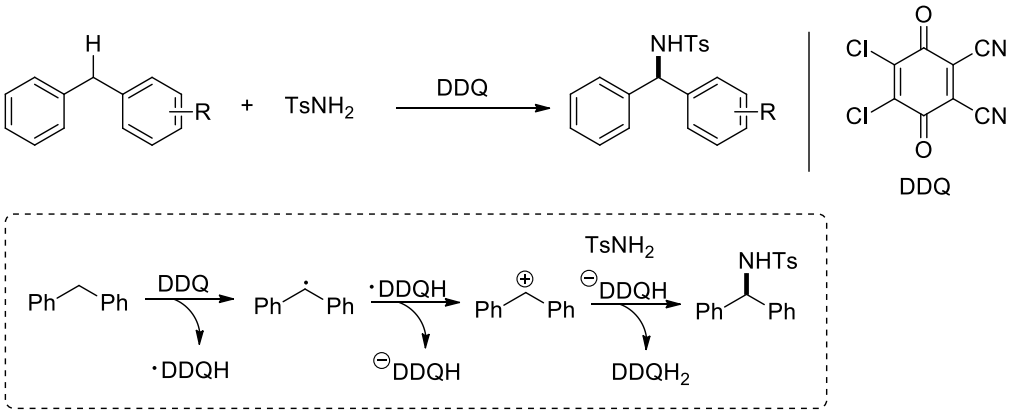
The same year, Antonchick and co-workers presented the work of annulation of arenes with 2-aminopyridine derivatives via combination of oxidative amination and ring closing two steps.[53] It was notable that the 2-aminopyridine underwent the CDCs pathway and gave the

dimethyl-remaining products while the 2-aminoquinoline provided mono-demethylated product under the same hypervalent iodine mediated conditions (Scheme 34).



Scheme 34. Hypervalent iodine mediated annulation of 2-aminopyridine and 2-amino-quinoline with arenes

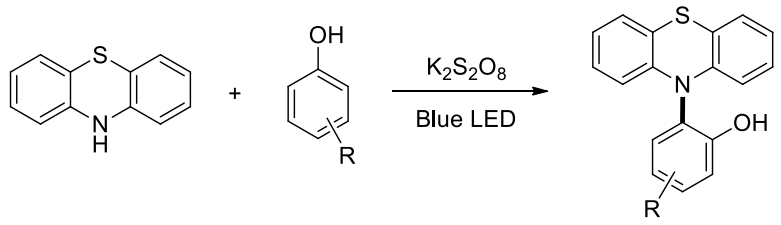
In 2015, Lei's group reported the oxidative amination of benzylic C-H bonds with amides.[54] In regard of literature, oxidative amination of Csp^3-H bond activation with hypervalent halogen sources was mostly limited. Therefore, the alternative oxidant, 2, 3-dichloro-5, 6-dicyano-*p*-benzoquinone (DDQ) was investigated in the intermolecular benzylic C-H amination reaction (Scheme 35). Based on the result of radical scavengers introduced reaction, the proposed mechanism predicted in a radical pathway and an imine substitute was formed with electron-deficient aniline.



Scheme 35. DDQ mediated oxidative amination of benzylic compound and proposed mechanism

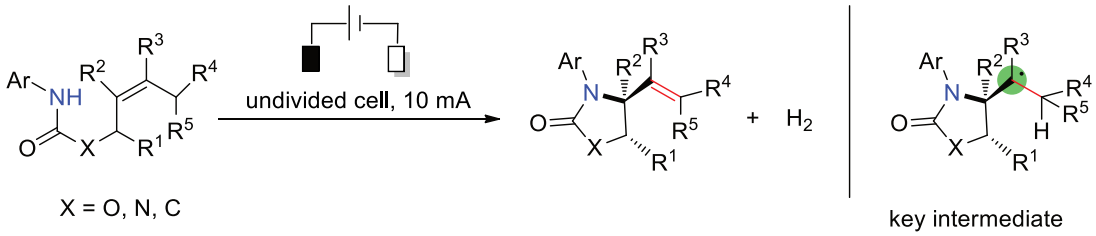
The following year, Xia and co-workers presented the work of visible-light mediated CDC-amination of phenols with phenothiazine derivatives (Scheme 36).[55] In this system, persulfate was used as the external oxidant and conducted the reaction via a radical pathway.

Significantly, the reaction benefited from its non-preactivated reagents, mild conditions, high regioselectivity, and needless use of photocatalysts. The limitation was the scope of phenols.



Scheme 36. Visible-light and persulfate mediated oxidative CDC-amination of phenols with phenothiazines

In the early of 2017, a novel electrochemical intramolecular oxidative amination of substituted olefins was developed by Xu and co-workers (Scheme 37).[56] This electrosynthetic method was broadly scoped and easily able to scale up. Based on the Nitrogen-centered radical (NCR) intermediates, the reaction underwent smoothly in electrochemically generated pathway. Advantageously, this procedure conducted to a metal- and reagent-free fashion to produce functionalized cyclic carbamates, ureas and lactams.

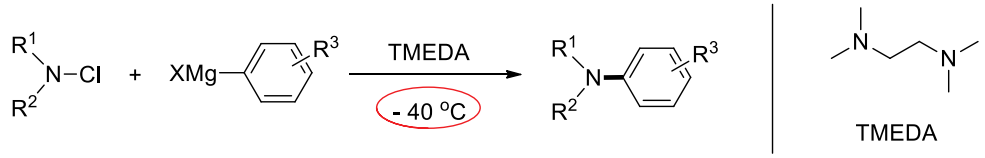


Scheme 37. Electrochemical intramolecular oxidative amination of substituted olefins

1.2.2.2 Electrophilic and nucleophilic aromatic substitution amination

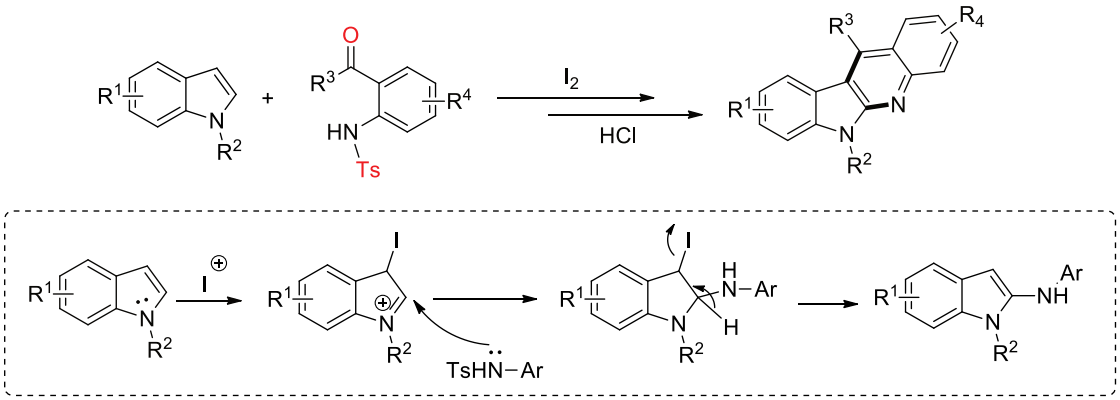
One of the classical electrophilic aromatic substitution reactions was Friedel-Crafts reaction, which had been widely studied since more than one century ago with numerous highlighted results already. On the other side, Grignard reaction, one of representative nucleophilic substitution, which was discovered by the French chemist François A. V. Grignard, was treated as an important tool for the cross-coupling reaction. To our best knowledge, the development of electrophilic or nucleophilic aromatic substitution amination with transition metal-free conditions was slow and limited, although typical electrophilic reagents such as *N*-chloroamines were efficiently used in transition metal catalysis systems and extended the scope of amination since several decades ago.

In 2010, Nakamura and co-workers presented the work of transition metal-free electrophilic amination of aryl Grignard reagents with *N*-chloroamine derivatives (See Scheme 38) in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA).[57] The advantages of this method were easily clarified as high chemoselectivity and high yield. While, there were still several drawbacks of this method, it was probably due to the pre-activated hazardous Grignard reagent and strict reaction condition (- 40 °C).



Scheme 38. Electrophilic amination of aryl Grignard reagents with *N*-chloroamines

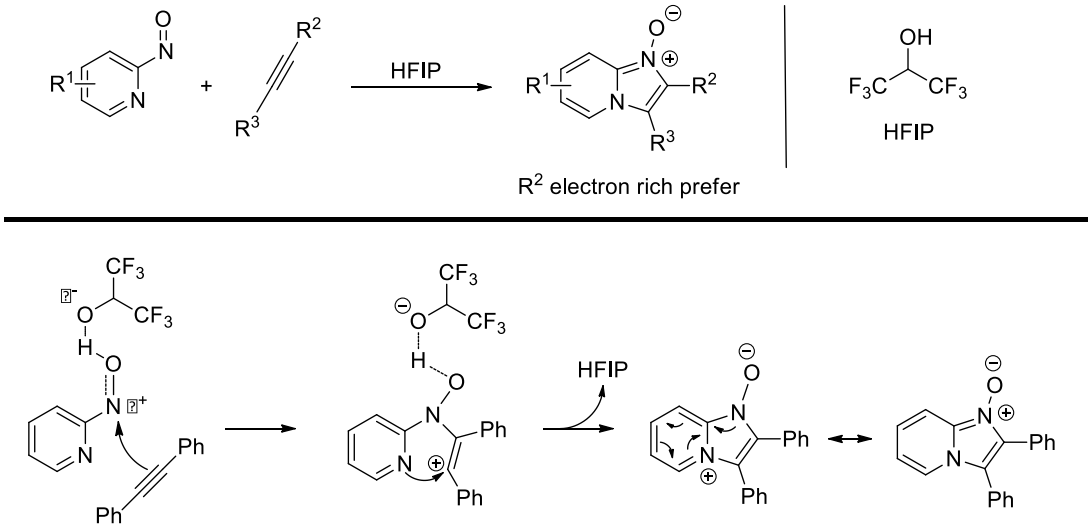
In 2011, Liang's group reported a synthesis method of indoloquinolines via electrophile-triggered cross-amination and Friedel-Crafts alkylation (Scheme 39).[58] Iodine was chosen as the efficient oxidant for the aminated step. The proposed mechanism predicted that iodonium attacked the 3-position of indole to form an electrophilic intermediate, which undergoes 2-amination with anilines. This one-pot transition metal-free synthesis of indoloquinolines potentially could be applied in the pharmaceutical industry.



Scheme 39. Amination step and proposed mechanism of indoloquinolines synthesis

In 2015, Antonchick and co-workers reported the annulation of nitrosopyridine with alkynes in a simplified reaction condition (Scheme 40).[59] The control experiment with radical scanvager proceeded smoothly, and electron rich alkynes reacted faster in comparison to electron deficient, which probably indicated that a nucleophilic attack by alkyne on the nitroso group. This mechanism also explained the regioselectivity of unsymmetrical alkynes

where the vinyl cation was generated at the benzylic position of the electron-rich side due to more efficient stabilization.

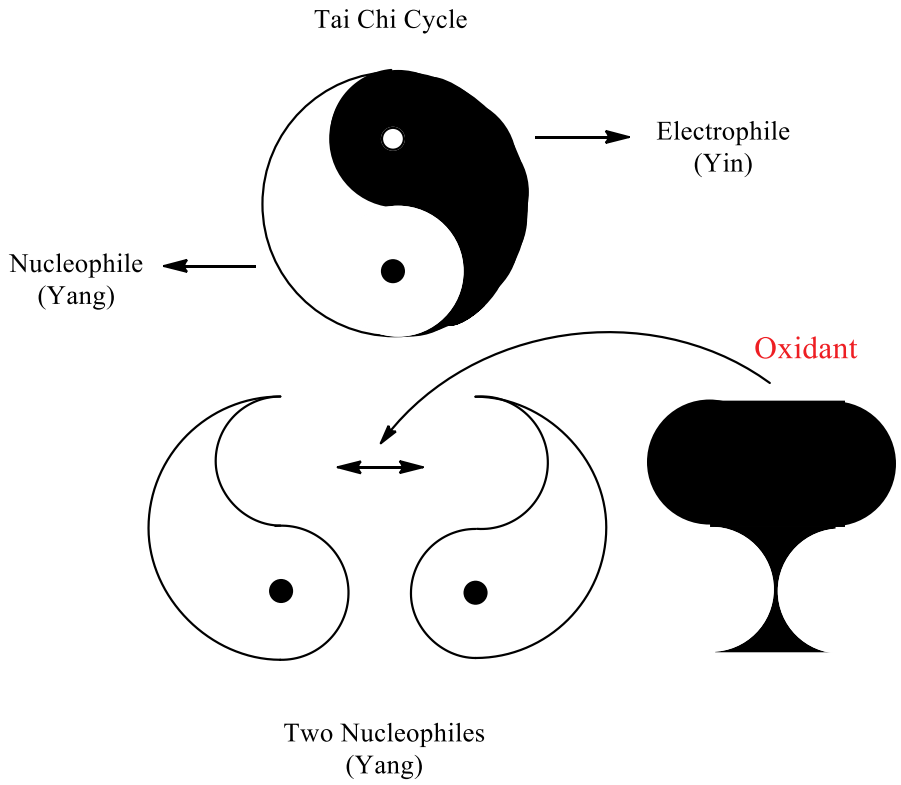


Scheme 40. Nucleophilic attack amination and proposed mechanism

1.3 Oxidant, the key to the redox-neutral CDC-amination reactions

The cross-coupling reactions follow with the theory of Tai Chi, nucleophile plays the role of Yang and electrophile plays the role of Yin. The balance of Yin and Yang facilitates their combination. The problem comes out when we want to generate two nucleophiles or electrophiles together, with some assistance from outside may solve the problem, and the key to make a combination of nucleophiles, is the oxidant (Scheme 41). Theoretically, all nucleophiles can be conducted; considering of atom economy, environmental friendliness and other reasons, one of the most promising and attractive methods is cross-dehydrogenative coupling (CDC) reaction.

Generally, the oxidative CDC reactions were well studied by employing different transition-metal catalysts and oxidants. The supplied "internal oxidant" in a transition-metal catalyzed reaction promised a milder and more selective reaction conditions.[60] However, some protocols were occasionally developed in the absence of transition-metal catalysts or



Scheme 41. Tai Chi theory of nucleophile and electrophile cross coupling and oxidant benefited couplings between two nucleophiles

transition-metal containing oxidants such as $Cu(OAc)_2$ when another efficient nonmetal oxidant was engaged. So far, a variety of oxidizing agents had been discovered and used in the redox-netural systems. Some of them were considered to play the same role of transition-metal catalysts or oxidants to initiate, and complete the whole reactions. Alternatively, some of them exhibited unique characters and remarkable features in the reactions via a completely different pathway. Parts of them which frequently used in oxidative C-N couplings were illustrated in Figure 2.

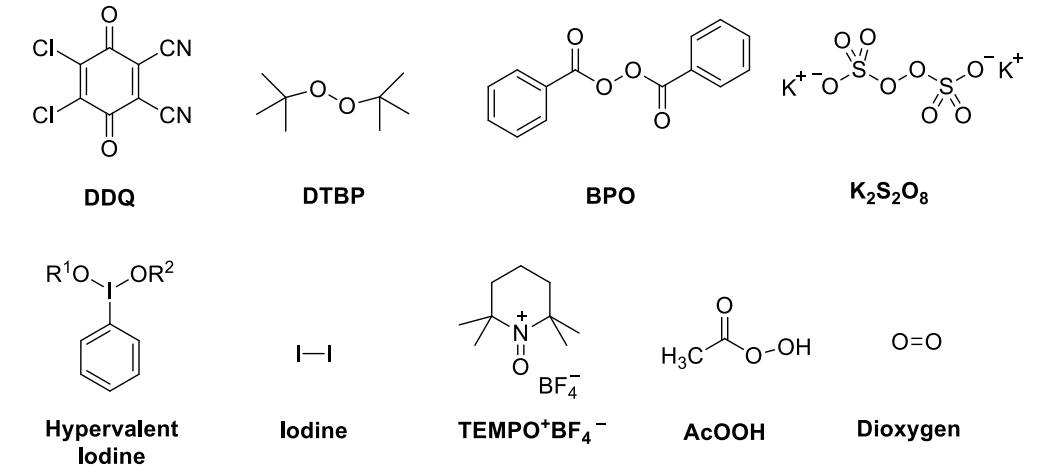


Figure 2. Frequently used oxidizing agents in oxidative aminations

Oxidants such as benzoquinone and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) conducted the reactions via a SET process and a proton abstraction process. One of the outstanding examples was the CDC amination of benzylic C-H bond with amides, developed by Lei in 2015. Besides, for the peroxide derivatives, Chao-Jun Li showed the well combination of copper and DTBP in the condensation of aryl pyridines with acetanilies in 2010.

However in the field of transition metal-free aminations, the hypervalent iodine possessed the most valuable position of oxidant since the earliest example of the PIFA-promoted oxidative coupling of phenol ethers with trimethylsilyl azides (TMSA) which was developed by Kita and co-workers in 1994.[61,62] During the following decades, numerous different *N*-atomnucleophiles have been studied and provided plentiful efficient and facile methods for the construction of C-N bond-containing heterocylcles by several of research groups.

On the other side, dioxygen, one of the most abundant and cheapest oxidants, was widely employed in the metal systems to re-oxidize the transition metal catalysts but few achievements in the transition metal-free CDC aminations. The drawbacks such as reaction in an industrial scaled-up context, which would obviate altogether the requirement of an oxidant, limited the use of molecular oxygen.

1.4 Designed research targets of the PhD period

With the above historical evolution of amination reactions and oxidants, more and more effective, simplified, and atom economic organic synthesis methods will come soon. And those stories also drove me to think about investigating the novel cross-dehydrogenative-coupling amination methods development as the topics of my PhD research.

Thus, we selected the phenothiazine derivatives as the *N*-nucleophile reagents and the phenols as the C-nucleophile reagents. To achieve the transition metal-free CDC aminations of phenols with phenothiazines, we scanned the chemical toolbox and tested a series of both common and uncommon oxidants.

In the chapter II, we start the condition in the presence of cumene and O_2. The proposed mechanism initiated by a Hock process, which would form in *situ* peroxo-species as initiator of the reaction. And the initial infra-red analysis predicted there is a strong O-H···N interaction.

In the chapter III, a series of iodines with different valance have been tested to achieve the C-N bond formation of phenols with phenothiazines. This time, a simplified and more efficient method had been developed, which also provides a wider scope of phenols. Several controlling experiments had been conducted for the plausible pathway research. Large-scale synthesis of target molecular was also successfully performed.

In the last chapter, we focus the research on the cross-coupling reaction of pre-oxidized(iminated) phenothiazine with ubiquitous phenols and indoles. In this task, we first regio-selectively synthesized the novel iminated phenothiazine derivatives with the traditional biocide and mild disinfectant, Chloramine T. Then the phenothiazinimine performed an ultra-simple condensation technique with phenol or indole coupling partners in a simplified condition. Parallel reactions were also performed to investigate the plausible pathway.

1.5 References

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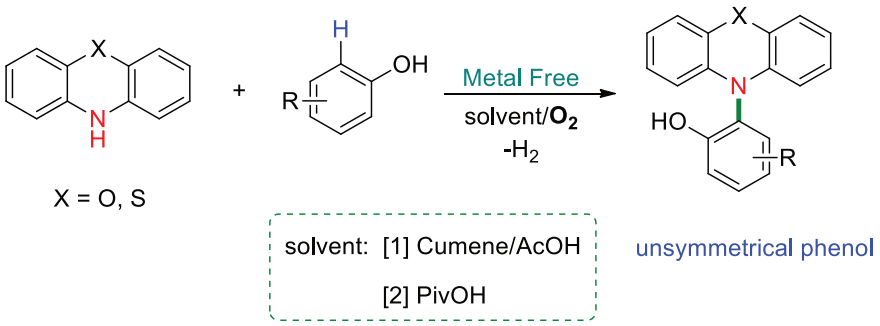
Oxidative Cross-Dehydrogenative-Coupling Amination of Phenols with Phenothiazines: O_2 as the effective oxidant



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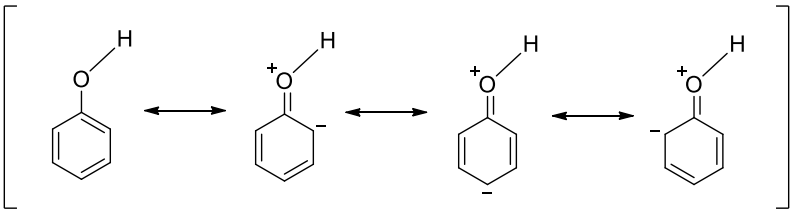
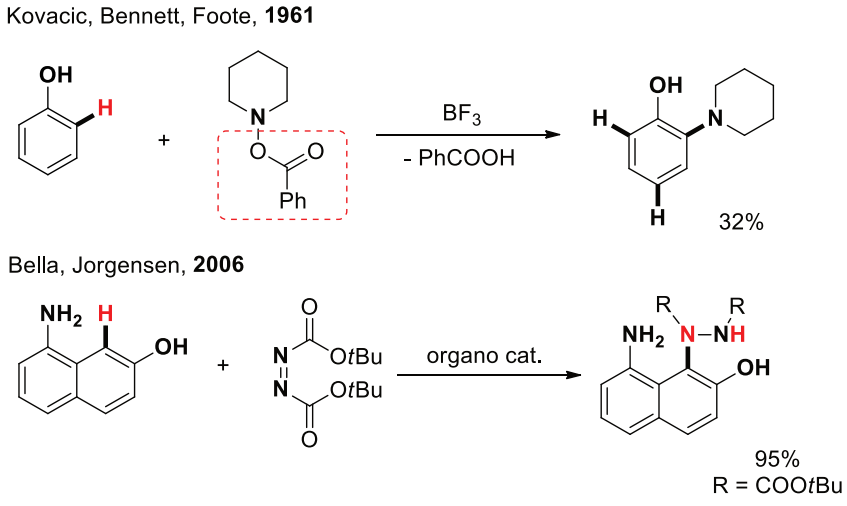
2.1 Introduction

Aryl amines are ubiquitous and important building blocks for various fine chemicals, pharmaceuticals, and industrial products.[1] Numerous novel and effective approaches for the synthesis of aryl amines had been developed during the decades.[2] The most popular and representative reactions were Buchwald-Hartwig coupling and Ullmann-type aminations, in which halides were used as electrophiles and coupled with amines. The generation of unwanted halide waste was the main drawback of these strategies.



(1)

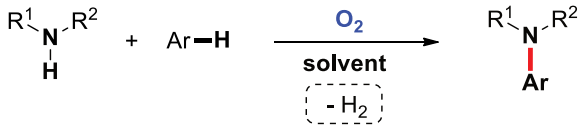
Alternatively, phenols, which mostly existed in their polymeric forms in lignin and coal, became a prevalent choice for the synthesis of aryl amines. Therefore, the direct coupling of phenol to get selective amination product had been a synthetic aspiration. Accordingly, the reactivity of phenol, *ortho*- and *para*-positions are known to be readily accessible by electrophilic aromatic substitution (S_EAr).[3] The electron-donating nature of hydroxyl group on the benzene ring result in more nucleophilic C2, C6(*ortho*-) and C4(*para*-) positions than others by resonance (eq 1). To our knowledge, no dehydrogenative aromatic amination reaction has been ever published, whether by electrophilic attack (Scheme 1) or homolytic substitution (HAS), in which the oxidized aminating substrate would be generated in situ, thus



Scheme 1. Metal-free amination reactions of phenols: Electrophilic attack

avoiding pre-activation steps for both coupling partners, and moreover without metal or halide additives.[4]

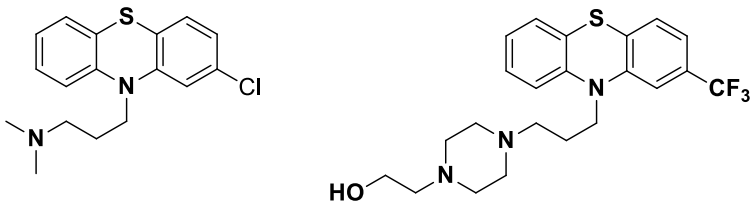
The challenge of this reaction is that the combination of two nucleophiles, unprotected phenol and secondary amine. Transition-metal catalyzed method was developed in recent years, as well as metal free oxidative conditions such as DDQ, hypervalent iodine mediated systems.[5,6] However, rare aerobic oxidative amination reactions were achieved. As a clean, highly atom-economical, and ubiquitous oxidant, oxygen was hardly employed in the direct oxidative C-N bond formations. Herein, we described a novel aerobic oxidative amination of electro-enriched arenes and secondary amines in a dehydrogenative fashion without any pre-functionalized steps or transition metals (Scheme 2).



Scheme 2. Dehydrogenative aromatic amination reactions: aerobic oxidation strategy

2.2 Results and discussion

Regarding to the previous work in the laboratory, we tested series of secondary aryl amines such as diphenylamines, and phenothiazine derivatives.[7] On the other side, we also selected several arenes like phenols, and indoles as the C(sp^2)-H providers. Phenothiazines are notably considered among the most important class of antipsychotic drugs, 2-chloro-pheno-thiazine and 2-trifluoromethyl-phenothiazine (Figure 1), for example, are the direct precursors of Chlorpromazine and Fluphenazine, respectively, which are very important antipsychotic drugs and are on the latest list of essential medicines from the World Health Organization (WHO).[8] We first obtained a new product when we mixed phenothiazine with phenol in the ruthenium catalyst system. After confirming the structure of the product, we optimized the



Chlorpromazine
anti-psychotic, WHO
Essential Medicine

Fluphenazine
anti-psychotic, WHO
Essential Medicine

Figure 1. World Health Organisation, (2013) WHO Model Lists of Essential Medicines

reaction conditions. To our delight, this reaction underwent well even in the absence of metal catalysts and additives. Thus, a highly efficient direct coupling method of phenols with phenothiazines in catalyst free, halide free conditions was developed.[9]

2.2.1 Optimization

Based on the previous work, we first used 4-*tert*-butylphenol (1.0 mmol), phenothiazine (1.5 mmol) to test the reaction conditions. In the presence of $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $Cu(OAc)_2$ (2.2 eq), and C_2Cl_4 (2.5 mL)/cumene (0.5 mL)/AcOH (0.5 mL) were engaged as solvent or co-solvent, the reaction was conducted in a screw cap vessel under aerobic atmosphere (O_2, 1 bar). Then the reaction mixture was stirred in a 150 ^oC oil bath for 24 hours. The crude mixture was then diluted by dichloromethane and injected in the GC-MS machine. The data showed in Figure 2, which indicated that phenothiazine was converted and gave

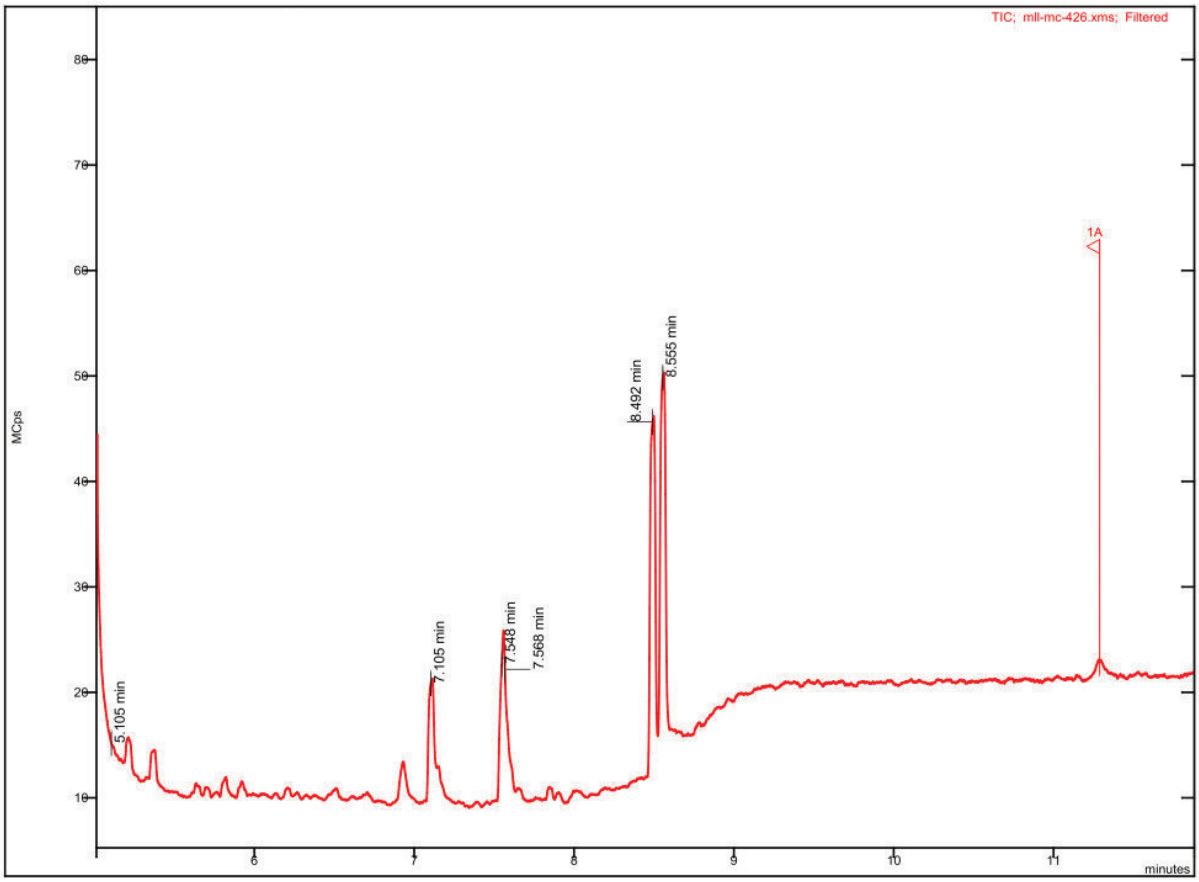
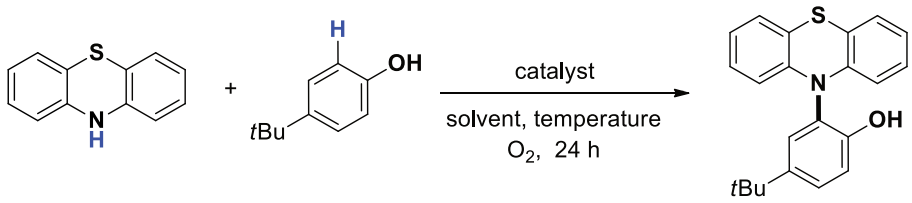


Figure 2. GC profile for the reaction of 4-*tert*-butylphenol with phenothiazine; New peak of predicted product m/z = 346.9 at 8.492 min

several products like 1) acetylated substrate (m/z = 241.1 at 7.105 min); 2) target heterocoupling substrate (m/z = 346.9 at 8.492 min); 3) acetylated heterocoupling substrate (m/z = 388.9 at 8.555 min).

Table 1: Optimization of reaction conditions for amination of 4-*tert*-butylphenol with phenothiazine [a]



1a 2a 3aa

Entry	Catalyst	Solvent	*T*/°C	Yield[b]/%
1	[Ru]/[Cu]	C_2Cl_4/cumene/AcOH	90	22
2	[Ru]/[Cu]	C_2Cl_4/cumene/AcOH	110	19
3	[Ru]/[Cu][c]	C_2Cl_4/cumene/AcOH	130	77
4	[Ru]	C_2Cl_4/cumene/AcOH	130	63
5	[Ru]/[Cu][d]	C_2Cl_4/cumene/AcOH	150	70
6	-	C_2Cl_4/cumene/AcOH	130	38
7	-	cumene/AcOH[e]	130	59
8	-	cumene/AcOH[e]	150	63
9	-	$(CH_3)_2CHCOOH$/AcOH[f]	150	49
10	-	PivOH[g]	150	37
11	-	PivOH[g]	130	68

[a] Reaction conditions: 1.0 mmol **1a**, 3.0 mmol **2a**, 5 mol% $[Ru(norbornadiene)Cl_2]_n$, 0.2 eq $Cu(OAc)_2$, 2.0 mL C_2Cl_4, 0.5 mL cumene, 0.5 mL AcOH, 1 bar O_2, 24 h. [b] Isolated yield. [c] 1.0 eq $Cu(OAc)_2$. [d] 5 mol% $[Ru(p\text{-cymene})Cl_2]_2$, 2.2 eq $Cu(OAc)_2$. [e] 2.5 mL cumene. [f] 2.5 mL isobutyric acid. [g] 3.5 mL Pivalic acid.

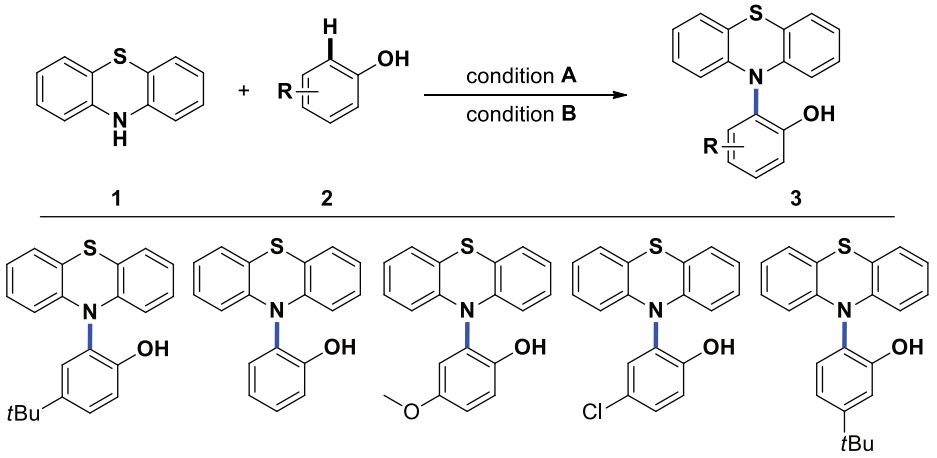
To further identify the structure of the correct mass peak for the target substrate, Marie-laure purified it by column chromatography of SiO_2 in 30% isolated yield. With the NMR and XRD analysis data, we confirmed the *ortho*-N-aminated phenol structure. (See Marie-Laure's PhD

Thesis, Chapter IV). Then we run series of parallel reactions to get the ideal conditions and isolated all the probative entries (Table 1).

Notably, the transition metal catalyst contained condition (Entry 3) gave the best yield in 77%. Alternatively, it was found that the product was obtained in 63% yield when only cumene/ AcOH were used as solvent in the absence of metals. After one more year, we found another alternative solvent pivalic acid, which also effectively conducted the reaction and produced **3a** in 68% yield. The optimized condition which we chose and put in the publication as follows: 1.0 mmol **1a**, 3.0 mmol **2a**, 2.5 mL cumene, and 0.5 mL AcOH were mixed in a screw caps vessel, then flushed with O_2 gas 1-2 min and transferred in a oil bath (130-150 ^oC) for 24 h. The temperature was decided by the reactivity and stability of the substrates, candidates such as phenoxazine and non-functionalized phenothiazine, low temperature (130 ^oC) provided better results. On the contrast, 2-trifluoromethyl-phenothiazine and other functionalized ones, a more satisfied yield was obtained in the high temperature (150 ^oC).

2.2.2 Scope and beyond scope limits

Table 2: Comparison of metal/metal-free conditions



A: 1.0 mmol **1**, 3.0 mmol **2**, 5 mol%$[Ru(norbornadiene)Cl_2]_n$, 1.0 mmol $Cu(OAc)_2$, 2.0 mL C_2Cl_4, 0.5 mL cumene, 0.5 mL AcOH, 1 bar O_2, 130^oC, 24 h.
B: 1.0 mmol **1**, 3.0 mmol **2**, 2.5 mL cumene, 0.5 mL AcOH, 1 bar O_2, 150 ^oC, 24 h.
[a] Reaction performed at 130^oC.

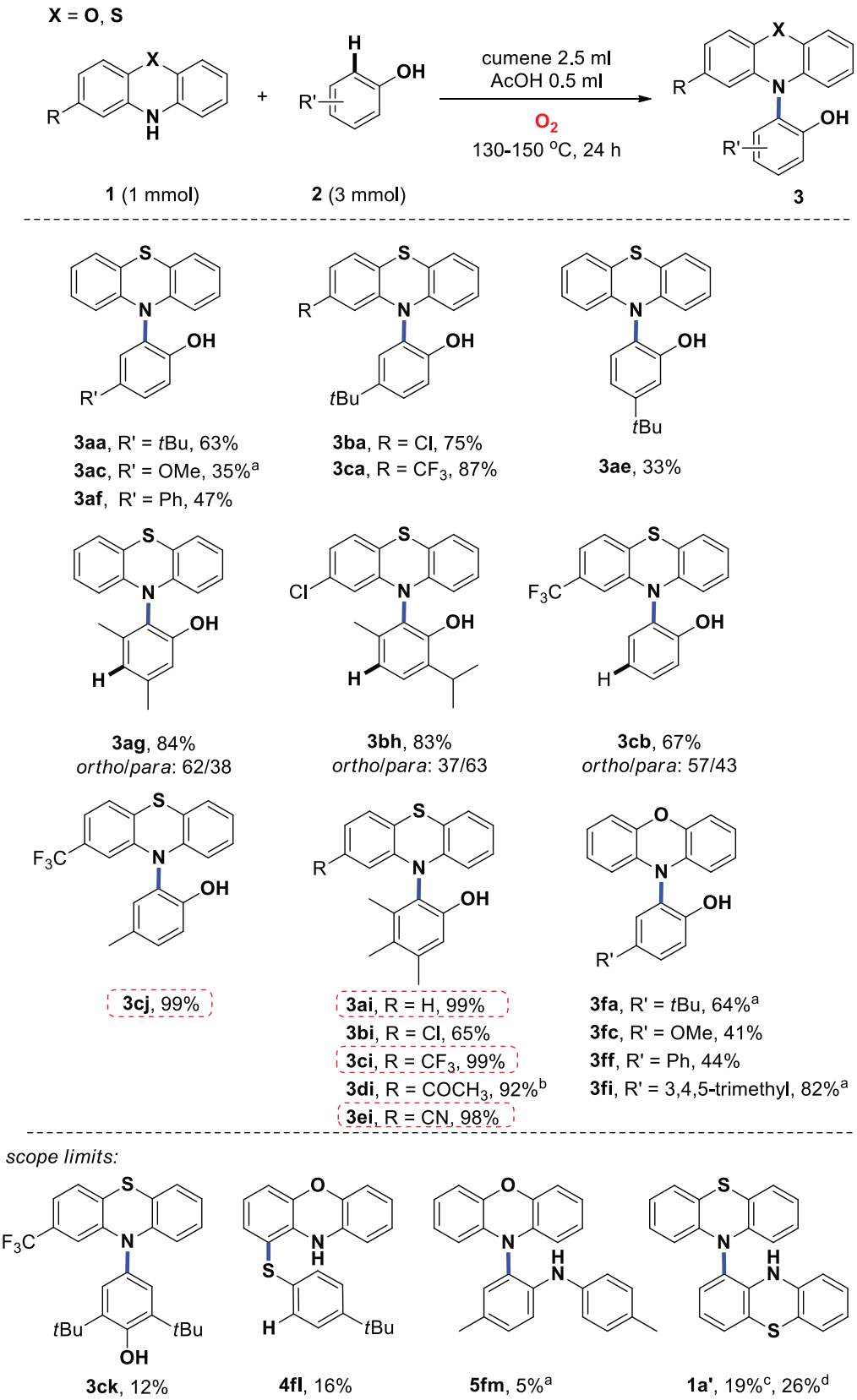
With the optimized reaction conditions in hand, we concentrated on investigating the scope of phenols. Out of our surprise, we found that some phenols provided in widely divergent results between metal catalyzed and metal-free reaction conditions (Table 2).

Notably, the neutral phenols had provided higher yields in the presence of metal catalysts than in the metal free conditions. Phenols with Electron-rich functional groups like methoxy performed similar results in those two different conditions. In contrast, electron-deficient phenols such as 4-chlorophenol (**2d**) reacted well under metal catalytic system to provide **3ad** with a yield of 51% but only traces were obtained in the absence of metals. Those results indicated there were at least two pathways to achieve the amination reactions of phenols with phenothiazines.

Following with the more attractive and environment friendly metal free conditions, we focused on the scope of neutral and electron-rich phenols. Variety of phenothiazine derivatives were tested in the amination reaction with selected phenols (Scheme 3).

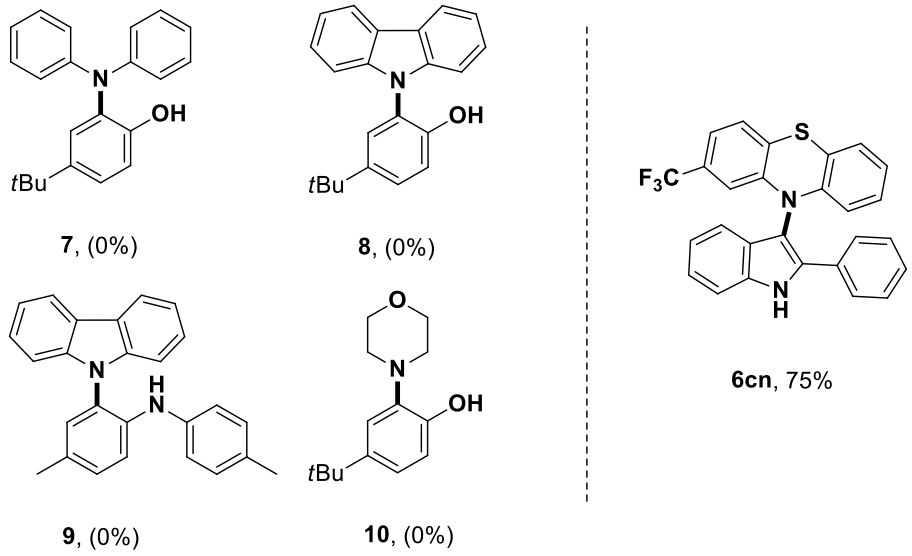
To our delight, a range of substituted phenothiazines showed efficient reactivity (**1a**-**1e**). Electron-deficient phenothiazines combined well with the electron-rich phenols, such as products **3cj**, **3ci**, **3di**, and **3ei**, which were isolated with average yields above 90%. On the other hand, phenoxazine, which was more reactive but less stable than phenothiazine, conducted well with electron-rich phenols and gave moderate yields (**3fa**, **3fc**, **3ff**). However, the electron-deficient phenols were less reactive under the metal-free conditions and provided products in low yields close to 50%. The non-functionalized phenol performed with 2-(trifluoromethyl)phenothiazine and provided **3cb** in 67% isolated yield (ratio of *ortho*/*para*: 6/4). Thymol (**2h**), the well known strong antimicrobiological molecule was engaged in the reaction conditions, producing **3bh** in 83% yield (ratio of *ortho*/*para*: 4/6). The difference of *o*/*p* ratio between the aminated phenol and thymol probably was due to the steric hindrance of isopropyl group.

Unfortunately, the overly rich and reactive phenol derivatives such as 2,6-di-*tert*-butylphenol (**2k**) and 4-*tert*-butylthiophenol (**2l**) mainly underwent either a C-C homocoupling step or a C-S bond formation step instead of the amination pathway. Interestingly, low amount of aminated product of *p*,*p*'-ditolylamine with phenoxazine was detected and the homocoupling substrate of phenothiazine via a C-N bond formation was also achieved in 26% yield.



Scheme 3. Scope of the cumene condition reaction and the limited substrates. [a] Reaction performed at 130 °C. [b] Reaction performed at 170 °C. [c] 2 mmol scale, 130 °C. [d] 2 mmol, 170 °C.

Further research was focused on the scope of *N*-coupling partner, we tested the popular and effective aminating reagents in our previous work, carbazoles and diphenylamines. Despite the fact that those reagents are efficient in the metal systems, trace amination products were observed in the cumene metal free conditions. We also engaged reagents like morpholine and others (Scheme 4), unfortunately the aminated products were not obtained. Those results indicated that the strained cyclic geometry of phenothiazines and phenoxazine, sometimes referred to as a butterfly-shaped structure, which may facilitate the oxidation step of *N*-coupling reagents. Another point was that the low bond dissociation energies (BDE) of secondary aromatic amines like phenothiazines and phenoxazines might have advantage in the oxidation rate comparing to others.[10] On the other side, an unexpected C3-aminated product (**6cn**) of unprotected indole with phenothiazine was obtained in 75% yield. This result extended the scope from electron rich phenols to more nucleophilic reagents.



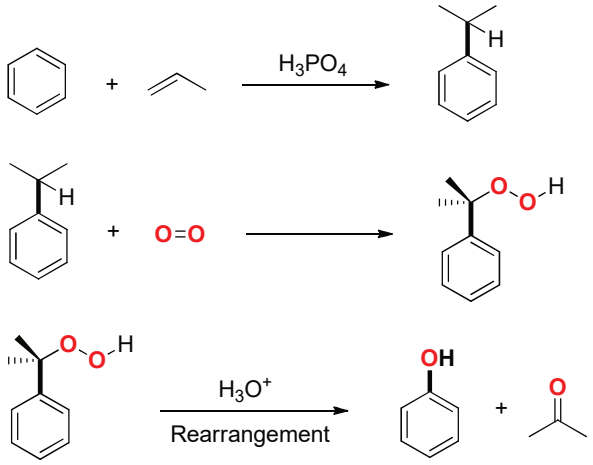
Scheme 4. Beyond scope of *N*-coupling reagents and unexpected indole example

2.2.3 Mechanistic studies and discussion

2.2.3.1 Proposed pathways

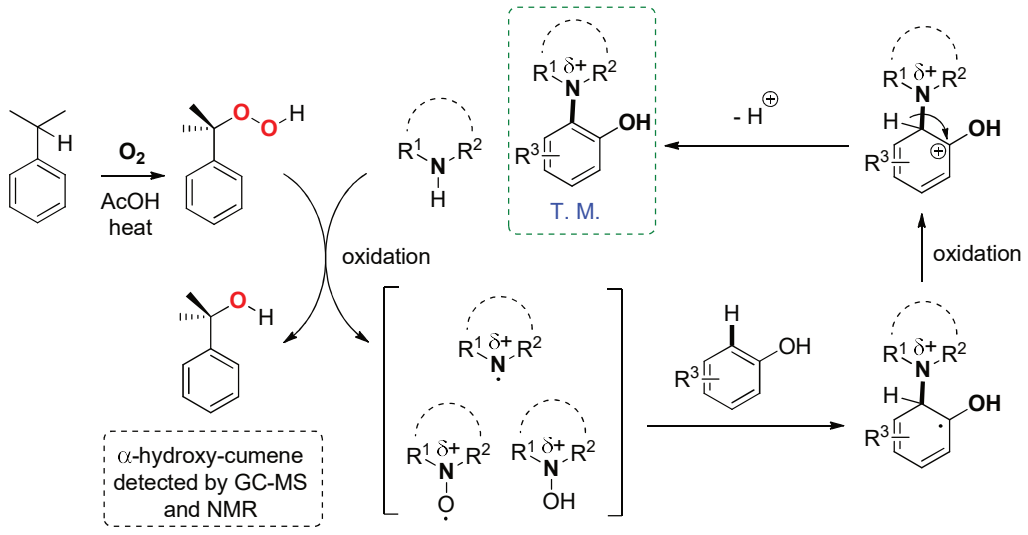
As the optimization table showed above, the series of transition metal free condition reactions indicated the key role of the solvents. We tested varieties of halo-contained solvents such as C_2Cl_4 and chlorobenzene, but the yields of products only ranged from low to moderate. In contrast, the radical potential solvents such as cumene, isobutyric acid, and pivalic acid conducted such kind of metal free amination reaction much better. These results strongly predicted that the oxidation of the radical solvent initiated the reaction, the cumene process

which widely employed in the industry for phenol and acetone synthesis was an excellent model (Scheme 5).[11]



Scheme 5. Industrial Hock Process for phenol and acetone synthesis

In parallel, the pathway begins with the oxidation of cumene by O_2, a step plausibly facilitated by the cosolvent, acetic acid. The controlling experiment which running the reaction under a strict N_2 atmosphere shuts down the reactivity confirms the essential role of O_2. Then, the stable α-peroxo-species might be transferred to the nitrogen, α-hydoxycumene was formed and detected by both GC-MS and NMR analysis. Attacked by phenol, a good nucleophile for S_EAr reaction, it provides the dehydrogenative amination product (Scheme 6).

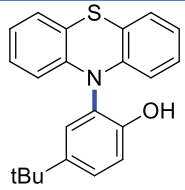
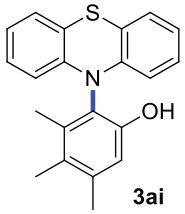
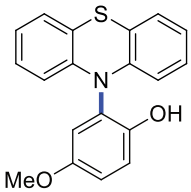
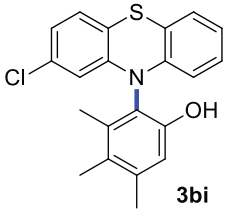
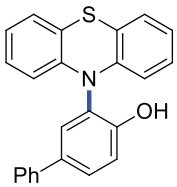
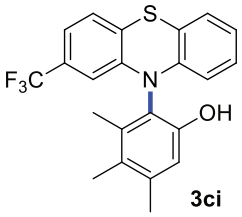
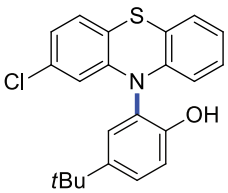
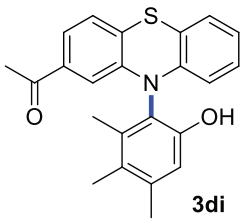
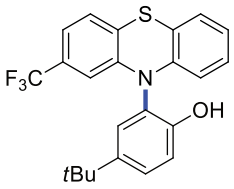
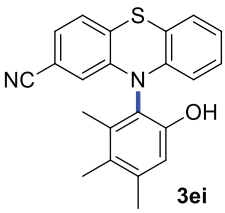
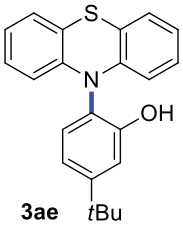
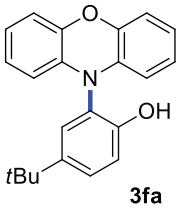


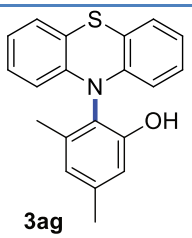
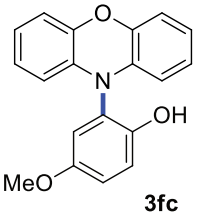
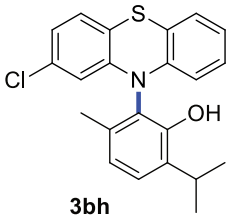
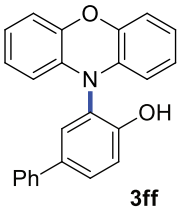
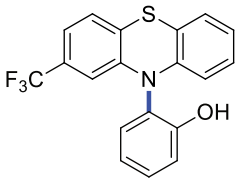
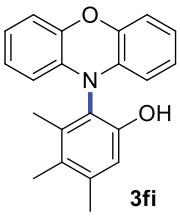
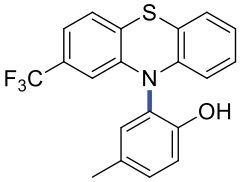
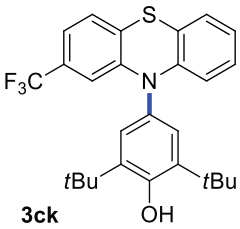
Scheme 6. Plausible pathway for the dehydrogenative amination reaction

2.2.3.2 Studies of the strength of Hydrogen bond

In order to evaluate the strength of the suspected intramolecular hydrogen bond in the products, we investigated the substrates with IR analysis spectroscopy (Table 3).

Table 3. Vibration frequency evolution of hydroxy group with electronic effects

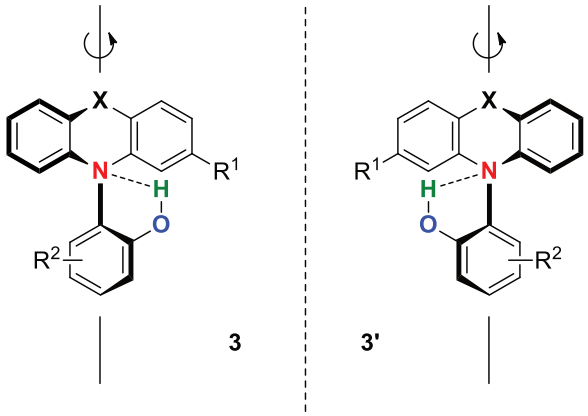
Substrate	ν (cm^{-1})	Substrate	ν (cm^{-1})
 **3aa**	3401	 **3ai**	3448
 **3ac**	3379	 **3bi**	3474
 **3af**	3383	 **3ci**	3499
 **3ba**	3361	 **3di**	3313
 **3ca**	3412	 **3ei**	3362
 **3ae**	3539	 **3fa**	3445

Substrate	ν (cm^{-1})	Substrate	ν (cm^{-1})
 **3ag**	*ortho*: 3479 *para*: 3572	 **3fc**	3449
 **3bh**	*ortho*: 3481 *para*: 3526	 **3ff**	3409
 **3cb**	3413	 **3fi**	3459
 **3cj**	3449	 **3ck**	3624

The reference shows that the IR value of hydroxy bond in phenols stretching vibration is significantly 3600-3650 cm^{-1}. However, the O-H bond vibration frequency of the *ortho*-functionalized aminated products was detected from 3300 to 3550 cm^{-1}. And the difference between *ortho*- and *para*-functionalized substrates was distinct, for example the *para*-product **3ck** was detected a high 3624 cm^{-1} value while the *ortho*-product **3ca** showed a low 3412 cm^{-1} value for the O-H stretching bond corresponding. Similarly, there was a difference of around 100 cm-1 between *ortho*- and *para*-products of **3ag**, except for the chlorine contained substrate which was probably due to the halo interaction.

With the data in hand, we proposed the plausible stereostructure which included the intramolecular hydrogen bond O-H···N (Scheme 7). The lowest values of substrates we obtained were **3di** (3313 cm^{-1}), **3ba** (3361 cm^{-1}), and **3af** (3383 cm^{-1}), which were the best combinations of EWG on phenothiazines (phenols) and EDG on the phenols (phenothiazines).

Further studies will be focused on the hypothesis confirmation. The unsymmetrical substrate **3di** is a potential suitable candidate for this study.



Scheme 7. Predicted H-Bonded Structure

2.3 Conclusion and pespective

In summary, we described a mild metal free method for the dehydrogenative amination of phenol and phenothiazine substrates. A key enabling advance in this work was the design of cumene with oxygen as precursors to nitrogen-based radical intermediates. The advantages of this dehydrogenative amination reaction were clean, abandoned pre-oxidation step, less hazardous side product, avoiding metal catalyst and chelating directing group. This reaction overcame the limit that wild oxidant like dioxygen could barely conduct a CDC reaction without metal catalyst and other additives.

According the current result, ongoing studies were focused on discovering the novel and effective oxidant and enlarging the scope of N-aminating reagents. To improve the yields of electron-deficient phenol and less stable but more reactive amine substitutes, a milder reaction condition was required. With the new class of products in hand, we tried to use them as special potential ligands in asymmetric catalysis. Moreover, we began gaining detailed insights into the reaction mechanism as well.

2.4 References

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2.5 Experimental section

2.5.1 General Information

All reactions were carried out in dried reaction vessels with **sealed** Teflon screw caps under **oxygen**, unless otherwise specified. NMR spectra were obtained on Bruker AMX 400 or on Bruker Avance 600 systems using $CDCl_3$, $(CD_3)_2SO$, or C_6D_6 as solvents, with proton and carbon resonances at 400/600 MHz and 101/151 MHz, respectively. Coupling constants (*J*) are quoted in Hz. Flash chromatography was performed on silica gel (40-63 mesh) by standard technique. GC-MS spectra were recorded on a Bruker 436-GC/SCION SQ Premium EI, 230 V, The major signals are quoted in m/z with the relative intensity in parentheses. The method used starts with the injection temperature T0. After holding this temperature for 3 min, the column is heated to temperature T1 (ramp) and this temperature is held for an additional time t. Method: 50_40: T0 = 50 °C, T1 = 320 °C, ramp = 40 °C/min; t = 5 min. Substrates were purchased either from Sigma Aldrich, Acros, TCI, or ABCR. Product **1a'** was already characterized by us in a previous report.[1]

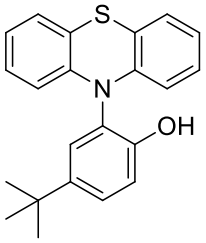
Figure 3. Reaction vessels and oil bath

2.5.2 Methods

Standard conditions: Unless otherwise specified, the phenothiazine or phenoxazine (1 mmol scale), and the phenol (3 mmol), cumene (2.5 mL) and AcOH (0.5 mL) are united under air in a 170 mL reactor equipped with Teflon screw cap. The reactor is then flushed with oxygen

atmosphere (1-2 min.), then sealed (tightly) and exposed to 130 (phenoxazine) or 150°C (phenothiazine) for 24 h. (magnetic stirring set to approx. 700 turns/min). The reactor is then cooled to room temperature. The crude is directly engaged (unless otherwise specified) on SiO_2 gel column chromatography for purification. The expected cross-coupling products are generally (but not always) the most apolar species of their respective reaction mixture, with Rf typically comprised between 0.3 and 0.7 in the given solvent systems.

2.5.3 Substrate Characterization



Chemical Formula: $C_{22}H_{21}NOS$
Exact Mass: 347,1344
Molecular Weight: 347,4732
m/z: 347.1344 (100.0%), 348.1377 (23.8%), 349.1302 (4.5%), 349.1411 (2.7%), 350.1335 (1.1%)
Elemental Analysis: C, 76.04; H, 6.09; N, 4.03; O, 4.60; S, 9.23

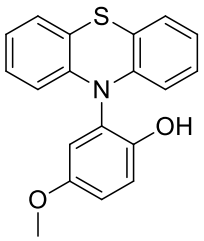
3aa. From phenothiazine and 4-*tert*-butylphenol. The reactor is cooled to room temperature and the crude mixture is filtrated with dichloromethane over a plug of silica gel. The concentrate is purified by SiO_2 gel column chromatography hexane/ethyl acetate (17:3). Isolated yield: 63% (white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.74 (s, OH), 7.39 (dd, 1H, ^3J = 8.4 Hz, J = 2.4 Hz), 7.15 (d, 1H, J = 2.4 Hz), 7.06 (d, 1H, ^3J = 8.8 Hz), 6.99 (dd, 2H, ^3J = 7.6 Hz, J = 1.6 Hz), 6.91 (~td, 2H, ^3J = 7.8 Hz, J = 1.5 Hz), 6.80 (~td, 2H, ^3J = 7.5 Hz, J = 1.1 Hz), 6.05 (dd, 2H, ^3J = 8.0 Hz, J = 1.2 Hz), 1.25 (s, 9H, *t*Bu).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 153.02 (s, C_{quat}), 143.68 (s, C_{quat}), 143.00 (s, C_{quat}), 127.40 (s, CH), 127.24 (s, CH), 126.85 (s, CH), 126.17 (s, CH), 125.66 (s, C_{quat}), 122.09 (s, CH), 118.35 (s, C_{quat}), 116.65 (s, CH), 115.33 (s, CH), 33.82 (s, C_{quat}), 31.29 (s, *t*Bu).

IR (neat, cm^{-1}): ν: 3401 (broad), 3189 (broad), 3060, 2960, 2866, 1587, 1572, 1503, 1461, 1443, 1364, 1345, 1308, 1285, 1238, 1216, 1172, 1158, 1044, 967, 925, 820, 729.

EI-HRMS: mass spectrometry: m/z calc. 347.1344 $[C_{22}H_{21}NOS]^{\bullet+}$, measured 347.1375.



Chemical Formula: $C_{19}H_{15}NO_2S$
Exact Mass: 321,0823
Molecular Weight: 321,3929
m/z: 321.0823 (100.0%), 322.0857 (20.5%), 323.0781 (4.5%), 323.0891 (2.0%)
Elemental Analysis: C, 71.00; H, 4.70; N, 4.36; O, 9.96; S, 9.98

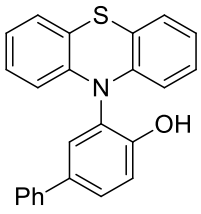
3ac. From phenothiazine and 4-methoxyphenol. Reaction temperature: 130°C. The reactor is cooled to room temperature and the crude mixture is filtrated with dichloromethane over a plug of silica gel. The concentrate is purified by SiO_2 gel column chromatography hexane/DCM (1:1) and a second time with hexane/ethyl acetate (4:1). Isolated yield: 35% (white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.47 (s, OH), 7.07 (d, 1H, ^3J = 9.2 Hz), 7.00-6.97 (m, 3H), 6.93-6.88 (m, 2H), 6.81-6.78 (m, 3H), 6.09 (dd, 2H, ^3J = 8.0 Hz, J = 1.0 Hz), 3.70 (s, 3H, OCH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 153.46 (s, C_{quat}), 149.23 (s, C_{quat}), 142.62 (s, C_{quat}), 127.23 (s, CH), 126.38 (s, C_{quat}), 126.13 (s, CH), 122.16 (s, CH), 118.19 (s, C_{quat}), 117.74 (s, CH), 116.17 (s, CH), 115.32 (s, CH), 115.30 (s, CH), 55.48 (s, OCH_3).

IR (neat, cm^{-1}): ν: 3379 (broad), 3199 (broad), 2954, 2929, 2833, 1621, 1590, 1569, 1497, 1461, 1438, 1345, 1308, 1281, 1235, 1217, 1154, 1104, 1076, 1036, 975, 966, 929, 920, 849, 810, 781, 743, 736, 720.

EI-HRMS: mass spectrometry: m/z calc. 321.0823 $[C_{19}H_{15}NO_2S]^{\bullet+}$, measured 321.0848.



Chemical Formula: $C_{24}H_{17}NOS$
Exact Mass: 367,1031
Molecular Weight: 367,4629
m/z: 367.1031 (100.0%), 368.1064 (26.0%), 369.0989 (4.5%), 369.1098 (3.2%), 370.1022 (1.2%)
Elemental Analysis: C, 78.45; H, 4.66; N, 3.81; O, 4.35; S, 8.73

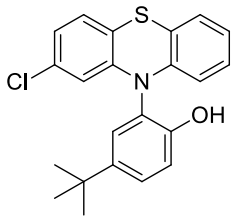
3af. From phenothiazine and 4-phenylphenol. The reactor is cooled to room temperature and the crude mixture is filtrated with dichloromethane over a plug of silica gel. The concentrate is purified by SiO_2 gel column chromatography hexane/ethyl acetate (17:3). Isolated yield: 47% (white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.16 (s, OH), 7.74 (dd, 1H, ^{3}J = 8.4 Hz, J = 2.0 Hz), 7.65 (d, 2H, ^{3}J = 7.2 Hz), 7.55 (d, 1H, J = 2.4 Hz), 7.40 (t, 2H, ^{3}J = 7.6 Hz), 7.28 (t, 1H, ^{3}J = 7.2 Hz), 7.24 (d, 1H, ^{3}J = 8.4 Hz), 7.00 (dd, 2H, ^{3}J = 7.2 Hz, J = 0.8 Hz), 6.92 (~t, 2H, ^{3}J = 7.7 Hz), 6.81 (~t, 2H, ^{3}J = 7.4 Hz), 6.14 (d, 2H, ^{3}J = 8.0 Hz).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 155.15 (s, C_{quat}), 142.74 (s, C_{quat}), 138.85 (s, C_{quat}), 133.09 (s, C_{quat}), 129.19 (s, CH), 128.86 (s, CH), 128.29 (s, CH), 127.28 (s, CH), 126.83 (s, CH), 126.20 (s, CH), 125.98 (s, CH), 122.20 (s, CH), 118.32 (s, C_{quat}), 117.83 (s, CH), 115.34 (s, CH). One C_{quat} is overlapped.

IR (neat, cm^{-1}): ν: 3383 (broad), 3220 (broad), 3062, 3032, 1589, 1574, 1509, 1484, 1459, 1442, 1313, 1296, 1283, 1271, 1232, 1205, 1162, 1111, 1077, 1042, 926, 910, 826, 748, 695.

EI-HRMS: mass spectrometry: m/z calc. 367.1031 $[C_{24}H_{17}NOS]^{\bullet+}$, measured 367.1056.



Chemical Formula: $C_{22}H_{20}ClNOS$
Exact Mass: 381,0954
Molecular Weight: 381,9183
m/z: 381.0954 (100.0%), 383.0925 (32.0%), 382.0988 (23.8%), 384.0958 (7.6%), 383.0912 (4.5%), 383.1021 (2.7%), 385.0883 (1.4%), 384.0946 (1.1%)
Elemental Analysis: C, 69.19; H, 5.28; Cl, 9.28; N, 3.67; O, 4.19; S, 8.40

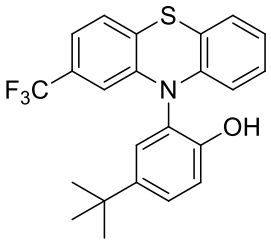
3ba. From 2-chlorophenothiazine and 4-*tert*-butylphenol. The reactor is cooled to room temperature and the crude mixture is filtrated with dichloromethane over a plug of silica gel. The concentrate is purified by SiO_2 gel column chromatography hexane/DCM (2:3). Isolated yield: 75% (white foam).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.89 (s, OH), 7.44 (dd, 1H, ^{3}J = 8.4 Hz, J = 2.4 Hz), 7.19 (d, 1H, J = 2.4 Hz), 7.09 (d, 1H, ^{3}J = 8.4 Hz), 7.05-7.01 (m, 2H), 6.96-6.91 (m, 1H), 6.88-6.82 (m, 2H), 6.05 (dd, 1H, ^{3}J = 8.0 Hz, J = 0.4 Hz), 5.98 (d, 1H, J = 2.0 Hz), 1.26 (s, 9H, *t*Bu).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.78 (s, C_{quat}), 144.38 (s, C_{quat}), 144.01 (s, C_{quat}), 142.31 (s, C_{quat}), 131.67 (s, C_{quat}), 127.59 (s, CH), 127.52 (s, CH), 127.35 (s, CH), 127.26 (s, CH), 126.38 (s, CH), 125.14 (s, C_{quat}), 122.81(s, CH), 121.68 (s, CH), 118.14 (s, C_{quat}), 117.67 (s, C_{quat}), 116.86 (s, CH), 115.72 (s, CH), 114.73 (s, CH), 33.94 (s, C_{quat}), 31.31 (s, *t*Bu).

IR (neat, cm^{-1}): ν: 3361, 3172, 2963, 1591, 1567, 1504, 1459, 1439, 1392, 1363, 1312, 1300, 1285, 1238, 1220, 1159, 1126, 1106, 1039, 968, 944, 851, 831, 819, 803, 783, 748.

EI-HRMS: mass spectrometry: m/z calc. 381.0954 $[C_{22}H_{20}ClNOS]^{\bullet+}$, measured 381.1005.



Chemical Formula: $C_{23}H_{20}F_3NOS$
Exact Mass: 415,1218
Molecular Weight: 415,4712
m/z: 415.1218 (100.0%), 416.1251 (24.9%), 417.1176 (4.5%), 417.1285 (3.0%), 418.1209 (1.1%)
Elemental Analysis: C, 66.49; H, 4.85; F, 13.72; N, 3.37; O, 3.85; S, 7.72

3ca. From 2-trifluorophenothiazine and 4-*tert*-butylphenol. The reactor is cooled to room temperature and the crude mixture is filtrated with dichloromethane over a plug of silica gel. The concentrate is purified by SiO_2 gel column chromatography hexane/ethyl acetate (18:2 to 17:3). Isolated yield: 87% (yellow sticky foam).

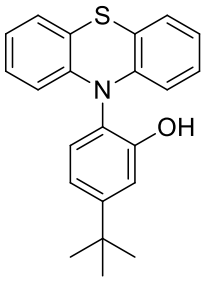
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.91 (s, OH), 7.43 (dd, 1H, ^3J = 8.4 Hz, J = 2.4 Hz), 7.22-7.20 (m, 2H), 7.11-7.09 (m, 2H), 7.02 (dd, 1H, ^3J = 7.6 Hz, J = 1.2 Hz), 6.95 (~td, 1H, ^3J = 7.8 Hz, J = 1.5 Hz), 6.80 (~td, 1H, ^3J = 7.3 Hz, J = 0.8 Hz), 6.20 (s, 1H), 6.05 (d, 1H, ^3J = 8.0 Hz), 1.25 (s, 9H, *t*Bu).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.69 (s, C_{quat}), 143.97 (s, C_{quat}), 143.52 (s, C_{quat}), 142.12 (s, C_{quat}), 127.77 (s, CH), 127.75 (q, ^2J = 31.9 Hz, C_{quat}), 127.37 (s, CH), 127.29 (s, CH), 126.96 (s, CH), 126.36 (s, CH), 124.84 (s, C_{quat}), 124.16 (s, C_{quat}), 123.87 (q, ^1J = 273.5 Hz, C_{quat}), 122.90 (s, CH), 118.50 (q, ^3J = 3.6 Hz, CH), 117.37 (s, C_{quat}), 116.85 (s, CH), 115.68 (s, CH), 110.70 (q, ^3J = 4.6 Hz, CH), 33.86 (s, C_{quat}), 31.20 (s, *t*Bu).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.80 (s, CF_3).

IR (neat, cm^{-1}): ν: 3412 (broad), 2962, 2907, 2870, 1602, 1570, 1507, 1467, 1442, 1411, 1365, 1326, 1286, 1272, 1236, 1212, 1197, 1164, 1102, 1086, 1041, 970, 948, 875, 818, 745, 733.

EI-HRMS: mass spectrometry: m/z calc. 415.1218 $[C_{23}H_{20}F_3NOS]^{\bullet+}$, measured 415.1219.



Chemical Formula: $C_{22}H_{21}NOS$
Exact Mass: 347,1344
Molecular Weight: 347,4732
m/z: 347.1344 (100.0%), 348.1377 (23.8%), 349.1302 (4.5%), 349.1411 (2.7%), 350.1335 (1.1%)
Elemental Analysis: C, 76.04; H, 6.09; N, 4.03; O, 4.60; S, 9.23

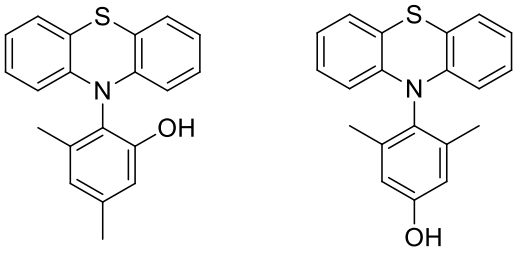
3ae. From phenothiazine and 3-*tert*-butylphenol. The reactor is cooled to room temperature and the crude mixture is filtrated with dichloromethane over a plug of silica gel. The concentrate is purified by SiO_2 gel column chromatography hexane/ethyl acetate (17:3). Isolated yield: 33% (yellow sticky foam).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.94 (s, OH), 7.14 (d, J = 2.1 Hz, 1H), 7.11 (d, ^3J = 8.1 Hz, 1H), 7.03 (dd, 1H, ^3J = 8.2 Hz, J = 2.2 Hz), 6.97 (dd, 2H, ^3J = 7.6 Hz, J = 1.6 Hz), 6.88 (~td, ^3J = 7.8 Hz, J = 1.5 Hz, 2H), 6.78 (~td, ^3J = 7.4 Hz, J = 1.1 Hz, 2H), 6.03 (dd, 2H, ^3J = 8.2 Hz, J = 1.0 Hz), 1.31 (s, 9H, *t*Bu).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 154.76 (s, C_{quat}), 153.10 (s, C_{quat}), 142.89 (s, C_{quat}), 130.55 (s, CH), 127.18 (s, CH), 126.18 (s, CH), 123.64 (s, C_{quat}), 122.16 (s, CH), 118.22 (s, C_{quat}), 118.01 (s, CH), 115.24 (s, CH), 113.97 (s, CH), 34.42 (s, C_{quat}), 31.06 (s, CH_3, *t*Bu).

IR (neat, cm^{-1}): ν: 3539, 3494, 3062, 2958, 2864, 1574, 1506, 1481, 1459, 1443, 1437, 1394, 1363, 1297, 1269, 1256, 1234, 1198, 1172, 1124, 1093, 1072, 1041, 945, 914, 901, 884, 831, 815, 729, 659.

EI-HRMS: mass spectrometry: m/z calc. 347.1344 $[C_{22}H_{21}NOS]^{\bullet+}$, measured 347.1359.



Chemical Formula: $C_{20}H_{17}NOS$
Exact Mass: 319,1031
Molecular Weight: 319,4201
m/z: 319.1031 (100.0%), 320.1064 (21.6%), 321.0989 (4.5%), 321.1098 (2.2%)
Elemental Analysis: C, 75.20; H, 5.36; N, 4.39; O, 5.01; S, 10.04

3ag. From phenothiazine and 3,5-dimethylphenol. The reactor is cooled to room temperature and the crude mixture is filtrated with dichloromethane over a plug of silica gel. The concentrate is purified by SiO_2 gel column chromatography hexane/ethyl acetate (17:3). Isolated yield: 84%.

Ortho-functionalized product: 52% isolated yield (white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.67 (s, OH), 6.94 (dd, 2H, ^{3}J = 7.4 Hz, J = 1.0 Hz), 6.86 (~td, 2H, ^{3}J = 7.8 Hz, J = 1.2 Hz), 6.77-6.72 (m, 4H), 6.00 (d, 2H, ^{3}J = 8.0 Hz), 2.28 (s, CH_3), 2.07 (s, CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 155.72 (s, C_{quat}), 142.19 (s, C_{quat}), 139.36 (s, C_{quat}), 138.00 (s, C_{quat}), 127.75 (s, CH), 126.53 (s, CH), 123.24 (s, C_{quat}), 123.09 (s, CH), 122.49 (s, CH), 118.59 (s, C_{quat}), 115.44 (s, CH), 115.17 (s, CH), 21.42 (s, CH_3), 17.41 (s, CH_3).

IR (neat, cm^{-1}): ν: 3479 (broad), 2920 (broad), 1619, 1571, 1499, 1460, 1441, 1334, 1311, 1247, 1206, 1156, 1042, 968, 928, 840, 738.

EI-HRMS: mass spectrometry: m/z calc. 319.1031 $[C_{20}H_{17}NOS]^{\bullet+}$, measured 319.1035.

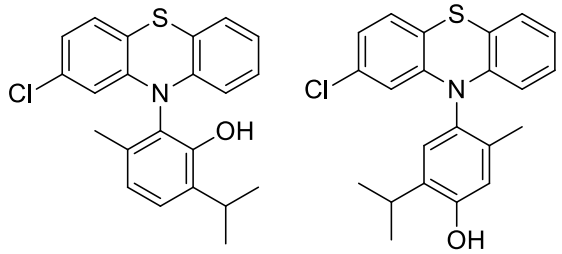
Para-functionalized product: 32% isolated yield (white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.62 (s, OH), 6.92 (d, 2H, ^{3}J = 6.8 Hz), 6.85 (~t, 2H, ^{3}J = 7.4 Hz), 6.75 (~t, 2H, ^{3}J = 7.2 Hz), 6.72 (s, 2H), 5.85 (d, 2H, ^{3}J = 8.0 Hz), 2.02 (s, 2*CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 156.98 (s, C_{quat}), 141.12 (s, C_{quat}), 138.42 (s, C_{quat}), 127.98 (s, C_{quat}), 127.55 (s, CH), 126.25 (s, CH), 122.18 (s, CH), 117.28 (s, C_{quat}), 115.97 (s, CH), 113.75 (s, CH), 17.53 (s, CH_3).

IR (neat, cm^{-1}): ν: 3572, 1595, 1459, 1436, 1312, 1243, 1182, 1144, 1031, 853, 747.

EI-HRMS: mass spectrometry: m/z calc. 319.1031 $[C_{20}H_{17}NOS]^{\bullet+}$, measured 319.1036.



Chemical Formula: $C_{22}H_{20}ClNOS$
Exact Mass: 381,0954
Molecular Weight: 381,9183
m/z: 381.0954 (100.0%), 383.0925 (32.0%), 382.0988 (23.8%), 384.0958 (7.6%), 383.0912 (4.5%), 383.1021 (2.7%), 385.0883 (1.4%), 384.0946 (1.1%)
Elemental Analysis: C, 69.19; H, 5.28; Cl, 9.28; N, 3.67; O, 4.19; S, 8.40

3bh. From 2-chlorophenothiazine and thymol. The reactor is cooled to room temperature and the crude mixture is filtrated with dichloromethane over a plug of silica gel. The concentrate is purified by SiO_2 gel column chromatography hexane/ethyl acetate (17:3) then a second time with hexane/DCM (3:1). Isolated yield: 83%.

Ortho-functionalized product: 31% (white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.12 (s, OH), 7.24 (d, 1H, ^{3}J = 7.6 Hz), 6.96 (d, 1H, ^{3}J = 8.2 Hz), 7.56 (dd, 1H, ^{3}J = 7.6 Hz, J = 1.5 Hz), 6.93-6.86 (m, 2H), 6.82-6.78 (m, 2H), 5.92 (dd, 1H, ^{3}J = 8.0 Hz, J = 1.2 Hz), 5.82 (d, 1H, J = 2.0 Hz), 3.31 (septuplet, 1H, ^{3}J = 6.8 Hz), 2.10 (s, 3H, CH_3), 1.23 (d, 1*CH_3, ^{3}J = 6.8 Hz), 1.21 (d, 1*CH_3, ^{3}J = 6.8 Hz).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.43 (s, C_{quat}), 142.79 (s, C_{quat}), 140.54 (s, C_{quat}), 134.23 (s, C_{quat}), 133.99 (s, C_{quat}), 131.48 (s, C_{quat}), 127.55 (s, CH), 127.21 (s, CH), 126.18 (s, CH), 126.12 (s, CH), 125.18 (s, C_{quat}), 122.73 (s, CH), 122.08 (s, CH), 121.54 (s, CH), 118.14 (s, C_{quat}), 117.61 (s, C_{quat}), 115.02 (s, CH), 114.03 (s, CH), 26.24 (s, CH), 22.74 (s, CH_3), 22.46 (s, CH_3), 16.85 (s, CH_3).

IR (neat, cm^{-1}): ν: 3481 (broad), 3058, 2963, 2925, 2869, 1611, 1590, 1566, 1499, 1483, 1455, 1438, 1424, 1393, 1345, 1285, 1266, 1239, 1192, 1168, 1145, 1127, 1104, 1081, 1067, 1043, 978, 952, 942, 851, 817, 801, 778, 745, 713, 670.

ESI H.R. mass spectrometry: m/z calc. 381.0954 $[C_{22}H_{20}ClNOS]^{\bullet+}$, measured 381.0970.

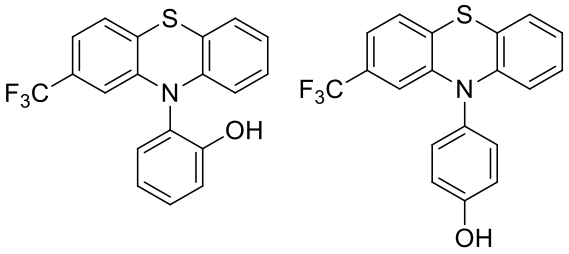
Para-functionalized product: 52% (yellow sticky solid)

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.75 (s, OH), 7.02-6.98 (m, 3H), 6.93-6.89 (m, 2H), 6.85-6.80 (m, 2H), 5.99 (dd, 1H, J = 8.4 Hz, J = 1.2 Hz), 5.88 (d, 1H, J = 2.4 Hz), 3.21 (septuplet, 1H, ^{3}J = 6.8 Hz), 1.98 (s, CH_3), 1.16 (d, 6H, ^{3}J = 7.2 Hz).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 154.58 (s, C_{quat}), 144.23 (s, C_{quat}), 141.98 (s, C_{quat}), 135.00 (s, C_{quat}), 134.81 (s, C_{quat}), 131.70 (s, C_{quat}), 128.54 (s, C_{quat}), 127.75 (s, CH), 127.64 (s, CH), 127.56 (s, CH), 126.43 (s, CH), 122.81 (s, CH), 121.64 (s, CH), 117.99 (s, CH), 117.61 (s, C_{quat}), 117.06 (s, C_{quat}), 115.08 (s, CH), 114.01 (s, CH), 26.28 (s, CH), 23.39 (s, CH_3), 16.78 (s, CH_3).

IR (neat, cm^{-1}): ν: 3526 (broad), 3425 (broad), 3059, 2960, 2924, 2868, 1616, 1591, 1565, 1508, 1460, 1439, 1411, 1392, 1341, 1293, 1236, 1160, 1126, 1100, 1041, 953, 909, 851, 797, 742.

ESI H.R. mass spectrometry: m/z calc. 381.0954 $[C_{22}H_{20}ClNOS]^{\bullet+}$, measured 381.0950.



Chemical Formula: $C_{19}H_{12}F_3NOS$
Exact Mass: 359,0592
Molecular Weight: 359,3649
m/z: 359.0592 (100.0%), 360.0625 (20.5%), 361.0550 (4.5%), 361.0659 (2.0%)
Elemental Analysis: C, 63.50; H, 3.37; F, 15.86; N, 3.90; O, 4.45; S, 8.92

3cb. From 2-trifluorophenothiazine and phenol. The crude is purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1) in order to collect the ortho isomer, then with hexane/ethyl acetate (8:2) in order to collect the para isomer. Both are white to very slightly yellow sticky solids. Overall isolated yield: 67%.

Ortho-functionalized product: 38%.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.18 (s, OH), 7.43 (ddd, $^3J \sim {}^3J \sim 7.8$ Hz, $J = 1.5$ Hz, 1H), 7.29 (dd, $^3J = 7.8$ Hz, $J = 1.8$ Hz, 1H), 7.20 (m, 2H), 7. 11 (dd, $^3J = 8.0$ Hz, $J = 1.0$ Hz, 1H), 7.06 (dd, $^3J = 7.6$ Hz, $J = 1.3$ Hz, 1H), 7.02 (dd, $^3J = 7.5$ Hz, $J = 1.5$ Hz, 1H), 6.93 (ddd, $^3J \sim {}^3J \sim 7.8$ Hz, $J = 1.5$ Hz, 1H), 6.84 (ddd, $^3J \sim {}^3J \sim 7.5$ Hz, $J = 1.0$ Hz, 1H), 6.21 (d, $J = 1.2$ Hz, 1H), 6.06 (dd, $^3J = 8.0$ Hz, $J = 0.8$ Hz, 1H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 155.35 (s, C_{quat}), 143.32 (s, C_{quat}), 141.96 (s, C_{quat}), 131.04 (s, CH), 130.81 (s, CH), 127.80 (q, $^2J = 31.7$ Hz, C_{quat}), 127.70 (s, CH), 126.95 (s, CH), 126.36 (s, CH), 125.58 (s, C_{quat}), 124.16 (broad s, C_{quat}), 123.87 (q, $^1J = 273.2$ Hz, C_{quat}), 122.94 (s, CH), 121.29 (s, CH), 118.56 (q, $^3J = 3.7$ Hz, CH), 117.37 (s, CH), 115.67 (s, CH), 110.64 (q, $^3J = 4.4$ Hz, CH). One C_{quat} line is overlapped.

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.78 (s, CF_3).

IR (neat, cm^{-1}): ν: 3413, 3068, 1592, 1501, 1488, 1473, 1439, 1409, 1328, 1290, 1255, 1229, 1202, 1160, 1142, 1112, 1100, 1089, 1044, 1028, 960, 938, 925, 871, 860, 818, 804, 749, 731, 722, 711, 704.

EI mass spectrometry: m/z calc. 359 $[C_{19}H_{12}F_3NOS]^{\bullet+}$, measured 359.

Para-functionalized product: 28%.

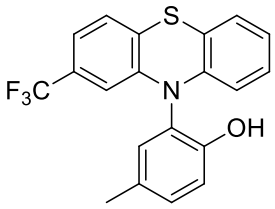
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.01 (s, OH), 7.24 (AA' half of AA'BB' 4 spin system, lines: 7.2639, 7.2558, 7.2508, 7.2389, 7.2338, 7.2257, 2H), 7.20 (d, ^{3}J = 8.0 Hz, 1H), 7.11 (dd, ^{3}J = 8.0 Hz, J = 1.3 Hz, 1H), 7.06 (BB' half of AA'BB' 4 spin system, lines: 7.0758, 7.0676, 7.0620, 7.0507, 7.0457, 7.0369, 2H), 7.02 (dd, ^{3}J = 7.5 Hz, J = 1.5 Hz, 1H), 6.92 (~ddd, $^{3}J \sim {}^{3}J \sim$ 7.8 Hz, J = 1.8 Hz, 1H), 6.84 (~ddd, $^{3}J \sim {}^{3}J \sim$ 7.4 Hz, J = 1.2 Hz, 1H), 6.25 (d, J = 1.5 Hz, 1H), 6.15 (dd, ^{3}J = 8.3 Hz, J = 1.0 Hz, 1H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 157.66 (s, C_{quat}), 144.66 (s, C_{quat}), 143.14 (s, C_{quat}), 131.58 (s, CH), 130.01 (s, C_{quat}), 127.67 (q, ^{2}J = 31.7 Hz, C_{quat}), 127.64 (s, CH), 127.12 (s, CH), 126.52 (s, CH), 124.22 (q, J = 1.5 Hz, C_{quat}), 123.77 (q, ^{1}J = 272.5 Hz, C_{quat}), 123.03 (s, CH), 118.65 (q, ^{3}J = 3.7 Hz, CH), 117.77 (s, CH), 117.41 (s, C_{quat}), 115.85 (s, CH), 110.66 (q, ^{3}J = 4.4 Hz, CH).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.80 (s, CF_3).

IR (neat, cm^{-1}): ν: 3391 (very broad), 3066, 1600, 1568, 1509, 1467, 1440, 1410, 1326, 1249, 1162, 1116, 1088, 1043, 1014, 962, 936, 921, 871, 841, 814, 791, 744, 719, 699, 675.

EI mass spectrometry: m/z calc. 359 $[C_{19}H_{12}F_3NOS]^{\bullet+}$, measured 359.



Chemical Formula: $C_{20}H_{14}F_3NOS$
Exact Mass: 373,0748
Molecular Weight: 373,3915
m/z: 373.0748 (100.0%), 374.0782 (21.6%), 375.0706 (4.5%), 375.0815 (2.2%)
Elemental Analysis: C, 64.33; H, 3.78; F, 15.26; N, 3.75; O, 4.28; S, 8.59

3cj. From 2-trifluoromethylphenothiazine and *p*-cresol. The crude mixture is purified by SiO_2 gel column chromatography hexane/Ethyl Acetate (9:1). Isolated yield: 99% (white to light yellow, foamy to crispy solid).

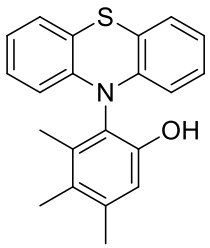
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.92 (s, OH), 7.22 (dd, ^{3}J = 8.3 Hz, J = 2.0 Hz, 1H), 7.21 (d, ^{3}J = 7.8 Hz, 1H), 7.12-7.07 (m, 3H), 7.02 (dd, ^{3}J = 7.6 Hz, J = 1.5 Hz, 1H), 6.93 (~td, ^{3}J = 7.8 Hz, J = 1.6 Hz, 1H), 6.84 (~td, ^{3}J = 7.4 Hz, J = 1.1 Hz, 1H), 6.25 (d, J = 1.4 Hz, 1H), 6.08 (dd, ^{3}J = 8.3 Hz, J = 1.0 Hz, 1H), 2.25 (s, CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 153.00 (s, C_{quat}), 143.34 (s, C_{quat}), 142.06 (s, C_{quat}), 131.21 (s, CH), 130.84 (s, CH), 130.31 (s, C_{quat}), 127.79 (q, ^{2}J = 31.9 Hz, CF_3-C_{quat}), 127.70 (s, CH), 126.93 (s, CH), 126.32 (s, CH), 125.21 (s, C_{quat}), 124.23 (s, C_{quat}), 123.89 (q, ^{1}J = 272.6 Hz, C_{quat}, CF_3), 122.90 (s, CH), 118.52 (q, ^{3}J = 3.6 Hz, CH), 117.47 (s, C_{quat}), 117.02 (s, CH), 115.82 (s, CH), 110.78 (q, ^{3}J = 4.6 Hz, CH), 19.79 (s, CH_3).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.70 (s, CF_3).

IR (neat, cm^{-1}): ν: 3449, 2927, 1593, 1572, 1505, 1469, 1440, 1408, 1386, 1326, 1306, 1282, 1260, 1230, 1214, 1161, 1113, 1086, 1043, 970, 953, 942, 923, 867, 813, 797, 770, 742, 717, 657.

EI-HRMS: mass spectrometry: *m/z* calc. 373.0748 $[C_{20}H_{14}F_3NOS]^{\bullet+}$, measured 373.0751.



Chemical Formula: $C_{21}H_{19}NOS$
Exact Mass: 333,1187
Molecular Weight: 333,4467
m/z: 333.1187 (100.0%), 334.1221 (22.7%), 335.1145 (4.5%), 335.1254 (2.5%), 336.1179 (1.0%)
Elemental Analysis: C, 75.64; H, 5.74; N, 4.20; O, 4.80; S, 9.62

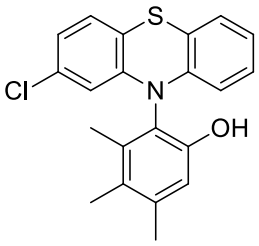
3ai. From phenothiazine and 3,4,5-trimethylphenol. The reactor is cooled to room temperature and the crude mixture is filtrated with dichloromethane over a plug of silica gel. The concentrate is purified by SiO_2 gel column chromatography hexane/ethyl acetate (18:2 to 15:5). Isolated yield: 99% (white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.40 (s, OH), 6.94 (dd, 2H, ^{3}J = 7.2.Hz, J = 1.6 Hz), 6.86 (dd, 1H, ^{3}J = 8.3 Hz, J = 1.8 Hz), 6.84 (dd, 1H, ^{3}J = 7.3 Hz, J = 1.8 Hz), 6.78 (s, 1H), 6.75 (td, 2H, ^{3}J = 7.3 Hz, J = 1.2 Hz), 5.97 (dd, 2H, ^{3}J = 8.0 Hz, J = 1.2 Hz), 2.25 (s, 3H, CH_3), 2.09 (s, 6H, CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.62 (s, C_{quat}), 142.00 (s, C_{quat}), 137.27 (s, C_{quat}), 135.82 (s, C_{quat}), 127.26 (s, CH), 126.64 (s, C_{quat}), 126.03 (s, CH), 123.04 (s, C_{quat}), 121.98 (s, CH), 118.11 (s, C_{quat}), 115.45 (s, CH), 114.97 (s, CH), 20.51 (s, CH_3), 15.24 (s, CH_3), 14.16 (s, CH_3).

IR (neat, cm^{-1}): ν: 3448 (bs), 3290 (bs), 3054 (bs), 2920, 2856, 1595, 1579, 1463, 1442, 1434, 1374, 1336, 1300, 1236, 1210, 1172, 1126, 1106, 1073, 1041, 917, 860, 780, 748.

IE-GCMS: *m/z* calc. $[C_{21}H_{19}NOS]^{\bullet+}$: 333.1 (100%), 334.4 (22.7), 335.1 (4.5), measured: 331.1 (100%), 334.1 (24.1), 335.1 (7.3).



Chemical Formula: $C_{21}H_{18}ClNOS$
Exact Mass: 367,0798
Molecular Weight: 367,8917
m/z: 367.0798 (100.0%), 369.0768 (32.0%), 368.0831 (22.7%), 370.0802 (7.3%), 369.0756 (4.5%), 369.0865 (2.5%), 371.0726 (1.4%), 370.0789 (1.0%)
Elemental Analysis: C, 68.56; H, 4.93; Cl, 9.64; N, 3.81; O, 4.35; S, 8.72

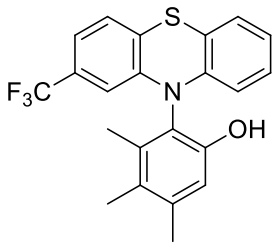
3bi. From 2-chloro-phenothiazine and 3,4,5-trimethylphenol. The crude mixture is purified by SiO_2 gel column chromatography hexane/Ethyl Acetate (9:1). Isolated yield: 65% (white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.56 (s, OH), 6.99 (d, ^{3}J = 8.3 Hz, 1H), 6.98 (dd, ^{3}J = 7.6 Hz, J = 1.5 Hz, 1H), 6.89 (~td, ^{3}J = 7.8 Hz, J = 1.6 Hz, 1H), 6.84-6.78 (aromatic area, 3H), 5.99 (dd, ^{3}J = 8.2 Hz, J = 0.8 Hz, 1H), 5.92 (d, J = 2.2 Hz, 1H), 2.27 (s, CH_3), 2.11 (s, CH_3), 2.10 (s, CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.42 (s, C_{quat}), 143.50 (s, C_{quat}), 141.29 (s, C_{quat}), 137.82 (s, C_{quat}), 135.55 (s, C_{quat}), 131.65 (s, C_{quat}), 127.53 (s, CH), 127.34 (s, CH), 126.95 (s, C_{quat}), 126.21 (s, CH), 122.70 (s, CH), 122.48 (s, C_{quat}), 121.51 (s, CH), 117.98 (s, C_{quat}), 117.47 (s, C_{quat}), 115.51 (s, CH), 115.39 (s, CH), 114.29 (s, CH), 20.55 (s, CH_3), 15.25 (s, CH_3), 14.05 (s, CH_3).

IR (neat, cm^{-1}): ν: 3474 (broad), 3312 (broad), 3058, 2921, 2855, 1583, 1566, 1464, 1437, 1393, 1337, 1301, 1287, 1234, 1211, 1172, 1126, 1107, 1071, 1041, 1000, 951, 901, 850, 795, 769, 744, 706, 670.

EI-HRMS: mass spectrometry: *m/z* calc. 367.0798 $[C_{21}H_{18}ClNOS]^{\bullet+}$, measured 367.0812.



Chemical Formula: $C_{22}H_{18}F_3NOS$
Exact Mass: 401,1061
Molecular Weight: 401,4446
m/z: 401.1061 (100.0%), 402.1095 (23.8%), 403.1019 (4.5%), 403.1128 (2.7%), 404.1053 (1.1%)
Elemental Analysis: C, 65.82; H, 4.52; F, 14.20; N, 3.49; O, 3.99; S, 7.99

3ci. From 2-trifluoromethylphenothiazine and 3,4,5-trimethylphenol. The crude mixture is purified by SiO_2 gel column chromatography hexane/Ethyl Acetate (9:1). Isolated yield: 99% (white to light yellow, foamy to crispy solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.62 (s, OH), 7.19 (d, ^{3}J = 7.8 Hz, 1H), 7.09 (d, ^{3}J = 7.8 Hz, 1H), 7.00 (d, ^{3}J = 7.3 Hz, 1H), 6.90 (~t, ^{3}J = 7.6 Hz, 1H), 6.82 (m, 2H), 6.16 (s, 1H), 5.98 (d, ^{3}J = 8.0 Hz, 1H), 2.27 (s, CH_3), 2.12 (s, CH_3), 2.10 (s, CH_3).

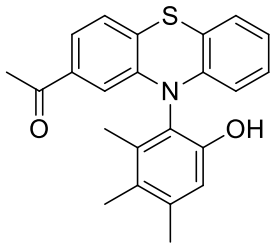
^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.52 (s, C_{quat}), 142.78 (s, C_{quat}), 141.32 (s, C_{quat}), 137.94 (s, C_{quat}), 135.49 (s, C_{quat}), 127.83 (q, ^{2}J = 31.0 Hz, CF_3-C_{quat}), 127.80 (s, CH), 126.95 (s, C_{quat}), 126.91 (s, CH), 126.30 (s, CH), 124.20 (~q, ^{4}J = 1.5 Hz, C_{quat}), 123. 90 (q, ^{1}J

= 272.6 Hz, C_{quat}, CF_3), 122.90 (s, CH), 122.28 (s, C_{quat}), 118.48 (q, ^3J = 3.6 Hz, CH), 117.50 (s, C_{quat}), 115.48 (s, CH), 115.44 (s, CH), 110.41 (q, ^3J = 3.6 Hz, CH), 20.54 (s, CH_3), 15.23 (s, CH_3), 14.01 (s, CH_3).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.62 (s, CF_3).

IR (neat, cm^{-1}): ν: 3499 (small broad), 3419 (small broad), 2921, 1604, 1588, 1570, 1496, 1469, 1441, 1411, 1325, 1303, 1246, 1210, 1164, 1143, 1119, 1085, 1040, 1001, 955, 904, 872, 814, 775, 744, 674.

EI-HRMS: mass spectrometry: *m/z* calc. 401.1061 $[C_{22}H_{18}F_3NOS]^{\bullet+}$, measured 401.1068.



Chemical Formula: $C_{23}H_{21}NO_2S$
Exact Mass: 375,1293
Molecular Weight: 375,4833
m/z: 375.1293 (100.0%), 376.1327 (24.9%), 377.1251 (4.5%), 377.1360 (3.0%), 378.1285 (1.1%)
Elemental Analysis: C, 73.57; H, 5.64; N, 3.73; O, 8.52; S, 8.54

3di. From 2-acetylphenothiazine and 3,4,5-trimethylphenol. The reactor is cooled to room temperature and the crude mixture is filtrated with dichloromethane over a plug of silica gel. The concentrate is purified by SiO_2 gel column chromatography hexane/ethyl acetate (18:2 to 15:5). Isolated yield: 92% (yellow foam).

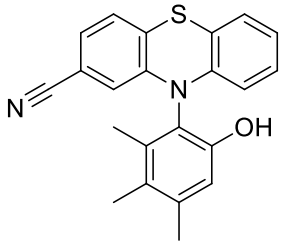
^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.48 (s, OH), 7.40 (dd, 1H, *J* = 8.0 Hz, *J* = 1.6 Hz), 7.10 (d, 1H, *J* = 8.0 Hz), 6.97 (dd, 1H, *J* = 7.6 Hz, *J* = 1.6 Hz), 6.89-6.85 (m, 1H), 6.79-6.76 (m, 2H), 6.50 (d, 1H, *J* = 1.6 Hz), 5.94 (dd, 1H, *J* = 8.0 Hz, *J* = 1.0 Hz), 2.36 (s, 3H), 2.28 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H).

^{13}C {^1H} NMR (101 MHz, DMSO-d_6) δ (ppm): 196.77 (s, C_{quat}), 152.61 (s, C_{quat}), 142.14 (s, C_{quat}), 141.46 (s, C_{quat}), 137.58 (s, C_{quat}), 135.84 (s, C_{quat}), 135.56 (s, C_{quat}), 127.74 (s, CH), 126.76 (s, C_{quat}), 126.16 (s, CH), 126.00 (s, CH), 125.57 (s, C_{quat}), 123.26 (s, CH), 122.65 (s,

C_{quat}), 122.38 (s, CH), 117.23 (s, C_{quat}), 115.51 (s, CH), 115.27 (s, CH), 112.66 (s, CH), 26.37 (s, CH_3), 20.56 (s, CH_3), 15.27 (s, CH_3), 14.08 (s, CH_3).

IR (neat, cm^{-1}): ν: 3313 (broad), 3061, 2919, 1654 (carbonyl), 1587, 1557, 1465, 1440, 1404, 1356, 1332, 1300, 1237, 1162, 1129, 1110, 1072, 1041, 995, 934, 880, 852, 805, 773, 748.

EI-HRMS: mass spectrometry: m/z calc. 375.1293 $[C_{23}H_{21}NO_2S]^{\bullet+}$, measured 375.1318.



Chemical Formula: $C_{22}H_{18}N_2OS$
Exact Mass: 358,1140
Molecular Weight: 358,4561
m/z: 358.1140 (100.0%), 359.1173 (23.8%), 360.1098 (4.5%), 360.1207 (2.7%), 361.1131 (1.1%)
Elemental Analysis: C, 73.71; H, 5.06; N, 7.82; O, 4.46; S, 8.95

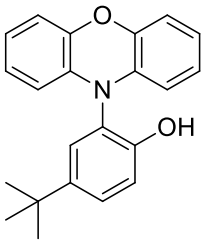
3ei. From 2-cyano-phenothiazine and 3,4,5-trimethylphenol. The crude mixture is purified by SiO_2 gel column chromatography hexane/Ethyl Acetate (8:2). Isolated yield: 98% (bright yellow solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.61 (s, OH), 7.19 (dd, ^3J = 7.9 Hz, J = 1.4 Hz, 1H), 7.16 (d, ^3J = 7.9 Hz, 1H), 6.98 (dd, ^3J = 7.4 Hz, J = 1.4 Hz, 1H), 6.92 (~td, ^3J = 7.8 Hz, J = 1.5 Hz, 1H), 6.82 (m, 2H), 6.06 (d, J = 1.1 Hz, 1H), 5.96 (d, ^3J = 7.5 Hz, 1H), 2.28 (s, CH_3), 2.11 (s, 6H, 2*CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.26 (s, C_{quat}), 142.65 (s, C_{quat}), 140.86 (s, C_{quat}), 138.05 (s, C_{quat}), 135.54 (s, C_{quat}), 127.97 (s, CH), 127.10 (s, CH), 126.31 (s, CH), 126.06 (s, C_{quat}), 125.59 (s, CH), 122.99 (s, CH), 122.00 (s, C_{quat}), 118.72 (s, C_{quat}), 117.02 (s, C_{quat}), 116.21 (s, CH), 115.69 (s, CH), 115.42 (s, CH), 109.47 (s, C_{quat}), 20.57 (s, CH_3), 15.26 (s, CH_3), 14.02 (s, CH_3). One C_{quat} line is overlapped.

IR (neat, cm^{-1}): ν: 3362 (large broad), 2916, 2857, 2231 (medium sharp, nitrile), 1589, 1555, 1492, 1460, 1439, 1419, 1399, 1333, 1300, 1265, 1240, 1127, 1108, 1071, 1062, 1042, 998, 985, 936, 862, 847, 810, 801, 774, 745, 713.

EI-HRMS: mass spectrometry: *m/z* calc. 358.1140 $[C_{22}H_{18}N_2OS]^{\bullet+}$, measured 358.1149.



Chemical Formula: $C_{22}H_{21}NO_2$
Exact Mass: 331,1572
Molecular Weight: 331,4076
m/z: 331.1572 (100.0%), 332.1606 (23.8%), 333.1639 (2.7%)
Elemental Analysis: C, 79.73; H, 6.39; N, 4.23; O, 9.66

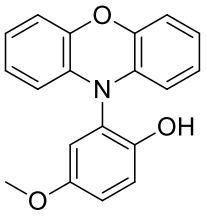
3fa. From phenoxazine and 4-*t*Butyl-phenol. The crude mixture is purified by SiO_2 gel column chromatography hexane/Ethyl Acetate (9:1). Isolated yield: 64% (white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.63 (s, OH), 7.37 (dd, ^3J = 8.5 Hz, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.04 (d, ^3J = 8.5 Hz, 1H), 6.70-6.59 (aromatic area, 6H), 5.81 (second order system, lines: 5.8345, 5.8226, 5.8163, 5.8069, 5.8038, 5.7994, 5.7881, 2H), 1.26 (s, 9H, *t*Bu).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.51 (s, C_{quat}), 143.43 (s, C_{quat}), 143.33 (s, C_{quat}), 133.56 (s, C_{quat}), 127.85 (s, CH), 126.72 (s, CH), 123.58 (s, CH), 122.87 (s, C_{quat}), 120.83 (s, CH), 117.19 (s, CH), 114.91 (s, CH), 112.63 (s, CH), 33.82 (s, C_{quat}), 31.27 (s, 3*CH_3).

IR (neat, cm^{-1}): ν: 3445, 2957, 1591, 1506, 1486, 1460, 1323, 1293, 1274, 1247, 1214, 1185, 1161, 1129, 1046, 835, 823, 746, 733, 713, 695.

EI-HRMS: mass spectrometry: *m/z* calc. 331.1572 $[C_{22}H_{21}NO_2]^{\bullet+}$, measured 331.1585.



Chemical Formula: $C_{19}H_{15}NO_3$
Exact Mass: 305.1052
Molecular Weight: 305.3273
m/z: 305.1052 (100.0%), 306.1085 (20.5%), 307.1119 (2.0%)
Elemental Analysis: C, 74.74; H, 4.95; N, 4.59; O, 15.72

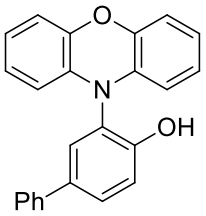
3fc. From phenoxazine and 4-methoxyphenol. The crude mixture is purified by SiO_2 gel column chromatography hexane/Ethyl Acetate (17:3). Isolated yield: 41% (yellow solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.37 (s, OH), 7.05 (d, ^3J = 8.8 Hz, 1H), 6.96 (dd, ^3J = 8.8 Hz, J = 2.8 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.66 (aromatic area, 6H), 5.87 (m, 2H), 3.70 (s, 3H, OCH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 153.25 (s, C_{quat}), 148.82 (s, C_{quat}), 143.26 (s, C_{quat}), 133.30 (s, C_{quat}), 123.68 (s, C_{quat}), 123.58 (s, CH), 120.94 (s, CH), 118.27 (s, CH), 116.14 (s, CH), 115.69 (s, CH), 114.92 (s, CH), 112.80 (s, CH), 55.50 (s, OCH_3).

IR (neat, cm^{-1}): ν: 3449, 3059 (board small signal), 2934 (bss), 2843 (ss), 1591, 1483, 1464, 1448, 1329, 1293, 1277, 1249, 1228, 1200, 1172, 1145, 1122, 1087, 1033, 973, 924, 864, 840, 821, 795.

EI-HRMS: mass spectrometry: *m/z* calc. 305.1052 $[C_{19}H_{15}NO_3]^{\bullet+}$, measured 305.1057.



Chemical Formula: $C_{24}H_{17}NO_2$
Exact Mass: 351.1259
Molecular Weight: 351.3973
m/z: 351.1259 (100.0%), 352.1293 (26.0%), 353.1326 (3.2%)
Elemental Analysis: C, 82.03; H, 4.88; N, 3.99; O, 9.11

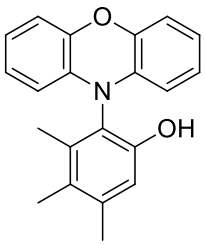
3ff. From phenoxazine and *p*-phenylphenol. The crude mixture is purified by SiO_2 gel column chromatography hexane/Ethyl Acetate (9:1). Isolated yield: 44% (white to light yellow, foamy to crispy solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.05 (s, OH), 7.71 (dd, ^3J = 8.4 Hz, J = 2.4 Hz, 1H), 7.65 (d, ^3J = 7.6 Hz, 2H), 7.58 (d, J = 2.4 Hz, 1H), 7.41 (t, ^3J = 7.6 Hz, 2H), 7.29 (t, ^3J = 7.6 Hz, 1H), 7.20 (d, ^3J = 8.4 Hz, 1H), 6.67 (aromatic area, 6H), 5.91 (m, 2H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 154.77 (s, C_{quat}), 143.31 (s, C_{quat}), 138.88 (s, C_{quat}), 133.39 (s, C_{quat}), 132.88 (s, C_{quat}), 129.58 (s, CH), 128.83 (s, CH), 128.22 (s, CH), 126.81 (s, CH), 125.96 (s, CH), 124.12 (s, C_{quat}), 123.64 (s, CH), 121.00 (s, CH), 118.31 (s, CH), 114.98 (s, CH), 112.80 (s, CH).

IR (neat, cm^{-1}): ν: 3409, 3033 (small signal), 1745 (broad small signal), 1590, 1475, 1464, 1410, 1330, 1292, 1270, 1240, 1200, 1177, 1153, 1127, 1094, 1077, 1044, 915, 887, 861, 844, 758, 747, 731, 694.

EI-HRMS: mass spectrometry: *m/z* calc. 351.1259 $[C_{24}H_{17}NO_2]^{\bullet+}$, measured 351.1248.



Chemical Formula: $C_{21}H_{19}NO_2$
Exact Mass: 317,1416
Molecular Weight: 317,3811
m/z: 317.1416 (100.0%), 318.1449 (22.7%), 319.1483 (2.5%)
Elemental Analysis: C, 79.47; H, 6.03; N, 4.41; O, 10.08

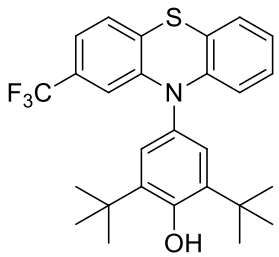
3fi. From phenoxazine and 3,4,5-trimethylphenol. The crude mixture is purified firstly by three sets of double crystallization from toluene. The remaining organic layers are purified by SiO_2 gel column chromatography hexane/Ethyl Acetate (9:1). Isolated yield: 82% (colorless to light yellow crystals).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.32 (s, OH), 6.75 (s, 1H), 6.66-6.56 (aromatic area, 6H), 5.70 (second order system, lines: 5.7185, 5.7160, 5.7059, 5.6984, 5.6953, 5.6896, 5.6827, 5.6740, 5.6702, 2H), 2.25 (s, CH_3), 2.10 (s, CH_3), 2.03 (s, CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.08 (s, C_{quat}), 143.25 (s, C_{quat}), 137.54 (s, C_{quat}), 136.83 (s, C_{quat}), 132.80 (s, C_{quat}), 126.42 (s, C_{quat}), 123.68 (s, CH), 120.79 (s, CH), 119.85 (s, C_{quat}), 115.84 (s, CH), 114.91 (s, CH), 112.12 (s, CH), 20.45 (s, CH_3), 15.09 (s, CH_3), 14.13 (s, CH_3).

IR (neat, cm^{-1}): ν: 3459, 3441, 3415, 2917, 1631, 1589, 1484, 1464, 1419, 1386, 1373, 1334, 1292, 1269, 1194, 1186, 1148, 1123, 1089, 1040, 997, 921, 904, 871, 862, 850, 805, 761, 739, 711, 682.

EI-HRMS: mass spectrometry: *m/z* calc. 317.1416 $[C_{21}H_{19}NO_2]^{\bullet+}$, measured 317.1437.



Chemical Formula: $C_{27}H_{28}F_3NOS$
Exact Mass: 471,1844
Molecular Weight: 471,5775
m/z: 471.1844 (100.0%), 472.1877 (29.2%), 473.1802 (4.5%), 473.1911 (4.1%), 474.1835 (1.3%)
Elemental Analysis: C, 68.77; H, 5.98; F, 12.09; N, 2.97; O, 3.39; S, 6.80

3ck. From 2-trifluoromethylphenothiazine and 2,4-tert-butylphenol. The reactor is cooled to room temperature and the crude mixture is filtrated with dichloromethane over a plug of silica gel. The concentrate is purified by SiO_2 gel column chromatography hexane/ethyl acetate (17:3). Isolated yield: 12% (white solid).

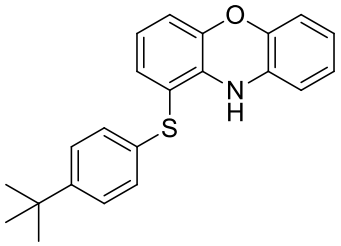
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.49 (broad s, OH), 7.23 (d, 1H, ^{3}J = 8.0 Hz), 7.12 (dd, 1H, ^{3}J = 8.0 Hz, J = 0.8 Hz), 7.08 (s, 2H), 7.06 (dd, 1H, ^{3}J = 7.6 Hz, J = 1.5 Hz), 6.97 (~td, ^{3}J = 7.3 Hz, J = 1.5 Hz, 1H), 6.87 (~td, ^{3}J = 7.3 Hz, J = 1.0 Hz, 1H), 6.27 (d, 1H, J = 1.6 Hz), 6.15 (dd, 1H, ^{3}J = 8.4 Hz, J = 0.8 Hz), 1.40 (s, 18H, *t*Bu).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 154.00 (s, C_{quat}), 144.81 (s, C_{quat}), 143.36 (s, C_{quat}), 142.43 (s, C_{quat}), 130.89 (s, C_{quat}), 127.87 (s, CH), 127.64 (q, ^{2}J = 31.9 Hz, C_{quat}-CF_3), 127.24 (s, CH), 126.63 (s, CH), 126.06 (s, CH), 124.27 (s, C_{quat}), 123.79 (q, ^{1}J = 273.5 Hz, C_{quat}, CF_3), 123.05 (s, CH), 118.68 (q, ^{3}J = 3.6 Hz, CH), 117.59 (s, C_{quat}), 115.85 (s, CH), 110.67 (q, ^{3}J = 3.6 Hz, CH), 34.80 (s, C_{quat}), 30.22 (s, *t*Bu).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -62.86 (s, CF_3).

IR: 3624, 3066, 2966 (broad), 2923 (broad), 2872 (broad), 1588, 1567, 1467, 1428, 1409, 1361, 1322, 1227, 1159, 1141, 1090, 1043, 995, 956, 875, 813, 773, 785, 717, 656.

EI-HRMS: mass spectrometry: m/z calc. 471.1844 $[C_{27}H_{28}F_3NOS]^{\bullet+}$, measured 471.1861.



Chemical Formula: $C_{22}H_{21}NOS$
Exact Mass: 347,1344
Molecular Weight: 347,4732
m/z: 347.1344 (100.0%), 348.1377 (23.8%), 349.1302 (4.5%), 349.1411 (2.7%), 350.1335 (1.1%)
Elemental Analysis: C, 76.04; H, 6.09; N, 4.03; O, 4.60; S, 9.23

4fl. From phenoxazine and 4-*t*Butyl-thiophenol. The crude mixture is purified by SiO_2 gel column chromatography hexane/Ethyl Acetate (98:2). Isolated yield: 16% (white solid).

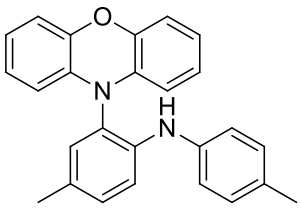
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.91 (s, NH, satellites: ~0.4% integration, d, $^{1}J_{1H\text{-}15N}$ = 94.2 Hz), 7.35 (half of AA'BB' pattern, lines: 7.3706, 7.3643, 7.3593, 7.3480, 7.3430, 7.3367, 2H), 7.12 (other half of AA'BB' pattern, lines: 7.1454, 7.1391, 7.1341, 7.1228, 7.1178, 7.1115, 2H), 6.89 (dd, ^{3}J = 7.8 Hz, J = 1.5 Hz, 1H), 6.86 (~dd, ^{3}J = 7.5 Hz, J = 1.2 Hz, 1H), 6.74-6.69 (aromatic area, 2H), 6.64-6.59 (aromatic area, 3H), 1.24 (s, 3*CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 148.73 (s, C_{quat}), 143.41 (s, C_{quat}), 142.63 (s, C_{quat}), 134.69 (s, C_{quat}), 132.61 (s, C_{quat}), 131.22 (s, C_{quat}), 131.10 (s, CH), 127.31 (s, CH),

126.21 (s, CH), 123.86 (s, CH), 121.25 (s, CH), 120.59 (s, CH), 116.26 (s, CH), 114.77 (s, CH), 114.76 (s, CH), 114.53 (s, C_{quat}), 34.13 (s, C_{quat}), 30.96 (s, 3*CH_3).

IR (neat, cm^{-1}): ν: 3383, 3058, 2961, 2923, 2865, 1586, 1571, 1490, 1459, 1398, 1362, 1285, 1274, 1245, 1214, 1197, 1179, 1152, 1117, 1106, 1078, 1062, 1030, 1011, 951, 922, 854, 835, 820, 774, 748, 721.

EI-HRMS: mass spectrometry: *m/z* calc. 347.1344 $[C_{22}H_{21}NOS]^{\bullet+}$, measured 347.1348.



Chemical Formula: $C_{26}H_{22}N_2O$
Exact Mass: 378,1732
Molecular Weight: 378,4657
m/z: 378.1732 (100.0%), 379.1766 (28.1%), 380.1799 (3.8%)
Elemental Analysis: C, 82.51; H, 5.86; N, 7.40; O, 4.23

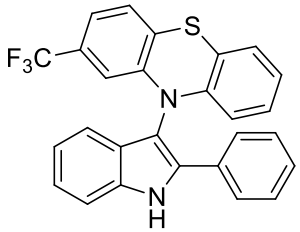
5fm. From phenoxazine and 4-*t*Butyl-thiophenol. The crude mixture is purified by SiO_2 gel column chromatography hexane/toluene (8:2). Isolated yield: 5% (white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.61 (s, NH, satellites: ~0.4% integration, d, $^1J_{1H\text{-}15N}$ = 90.4 Hz), 7.23 (d, ^3J = 8.4 Hz, 1H), 7.13 (dd, ^3J = 8.5 Hz, J = 1.8 Hz, 1H), 7.05-6.98 (aromatic area, 5H), 6.68-6.65 (aromatic area, 2H), 6.62 (second order pattern, lines: 6.6424, 6.6392, 6.6311, 6.6242, 6.6210, 6.6179, 6.6148, 6.6079, 6.5991, 6.5966, 4H), 5.91 (second order pattern, lines: 5.9292, 5.9198, 5.9117, 5.9092, 5.9029, 5.8960, 5.8872, 5.8841, 2H), 2.24 (s, CH_3), 2.21 (s, CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 143.69 (s, C_{quat}), 141.07 (s, C_{quat}), 140.17 (s, C_{quat}), 133.15 (s, C_{quat}), 130.74 (s, CH), 129.96 (s, CH), 129.89 (s, C_{quat}), 129.66 (s, C_{quat}), 129.34 (s, CH), 125.11 (s, C_{quat}), 123.44 (s, CH), 120.99 (s, CH), 119.83 (s, CH), 116.28 (s, CH), 114.87 (s, CH), 112.95 (s, CH), 20.29 (s, CH_3), 19.90 (s, CH_3).

IR (neat, cm^{-1}): ν: 3377, 2917, 2846, 1607, 1590, 1512, 1485, 1460, 1444, 1330, 1315, 1292, 1272, 1236, 1210, 1151, 1131, 1106, 1044, 823, 811, 798, 769, 736, 696, 659.

EI-HRMS: mass spectrometry: *m/z* calc. 378.1732 $[C_{26}H_{22}N_2O]^{\bullet+}$, measured 378.1742.



Chemical Formula: $C_{27}H_{17}F_3N_2S$
Exact Mass: 458,1065
Molecular Weight: 458,4975
m/z: 458.1065 (100.0%), 459.1098 (29.2%), 460.1022 (4.5%), 460.1132 (4.1%), 461.1056 (1.3%)
Elemental Analysis: C, 70.73; H, 3.74; F, 12.43; N, 6.11; S, 6.99

6cn. From 2-trifluoromethylphenothiazine and 2-phenylindole. The crude mixture is purified by SiO_2 gel column chromatography. Isolated yield: 75% (white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.04 (s, NH), 7.90 (d, ^3J = 7.2 Hz, 2H), 7.60 (d, ^3J = 8.0 Hz, 1H), 7.46 (t, ^3J = 7.6 Hz, 2H), 7.37-7.26 (aromatic area, 4H), 7.18-7.08 (aromatic area, 3H), 6.90 (2nd order m, 2H), 6.45 (d, J = 1.8 Hz, 1H), 6.28 (2nd order m, 1H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 143.98 (s, C_{quat}), 142.59 (s, C_{quat}), 135.06 (s, C_{quat}), 133.19 (s, C_{quat}), 130.21 (s, C_{quat}), 129.02 (s, CH), 128.41 (s, CH), 128.03 (s, CH), 127.91 (q, ^2J = 31.7 Hz, CF_3-C_{quat}), 127.48 (s, CH), 126.81 (s, CH), 126.14 (s, CH), 125.41 (s, C_{quat}), 125.11 (s, C_{quat}), 123.67 (q, ^1J = 273.2 Hz, CF_3, C_{quat}), 123.54 (s, CH), 123.05 (s, CH), 120.55 (s, CH), 119.22 (q, ^3J = 4.4 Hz, CH), 118.61 (s, C_{quat}), 117.61 (s, CH), 116.07 (s, CH), 112.62 (s, CH), 111.57 (s, C_{quat}), 111.03 (q, ^3J = 3.7 Hz, CH).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.75 (s, CF_3).

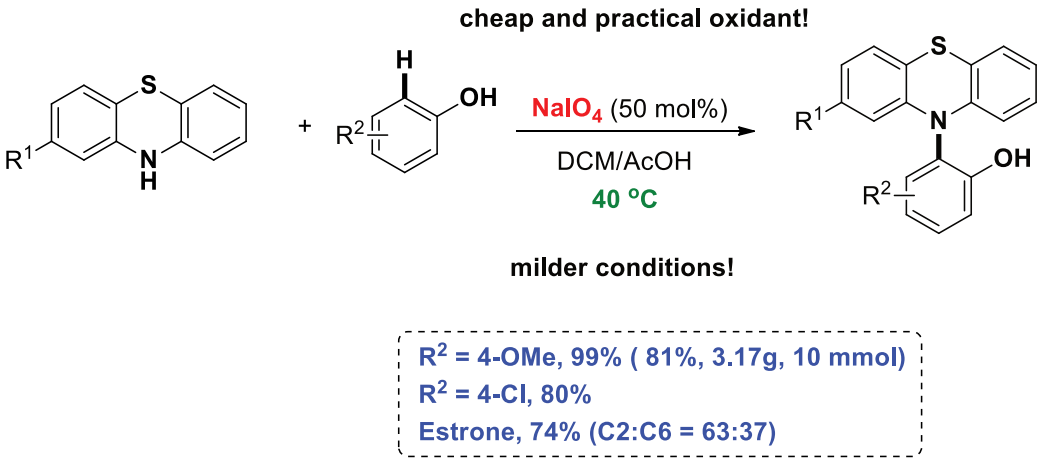
IR (neat, cm^{-1}): ν: 3461, 3061, 1601, 1587, 1567, 1487, 1464, 1450, 1441, 1411, 1373, 1323, 1284, 1249, 1170, 1141, 1110, 1093, 1080, 1038, 1010, 950, 893, 876, 819, 771, 752, 742, 717, 687, 653.

EI-HRMS: mass spectrometry: *m/z* calc. 458.1065 $[C_{27}H_{17}F_3N_2S]^{\bullet+}$, measured 458.1072.

2.5.4 References

[1] M.-L. Louillat, A. Biafora, F. Legros, F. W. Patureau, *Angew. Chem. Int. Ed.* **2014**, *53*, 3505-3509.

Oxidative Cross-Dehydrogenative-Coupling Amination of Phenols with Phenothiazines: Periodate as the Unexpected Oxidant



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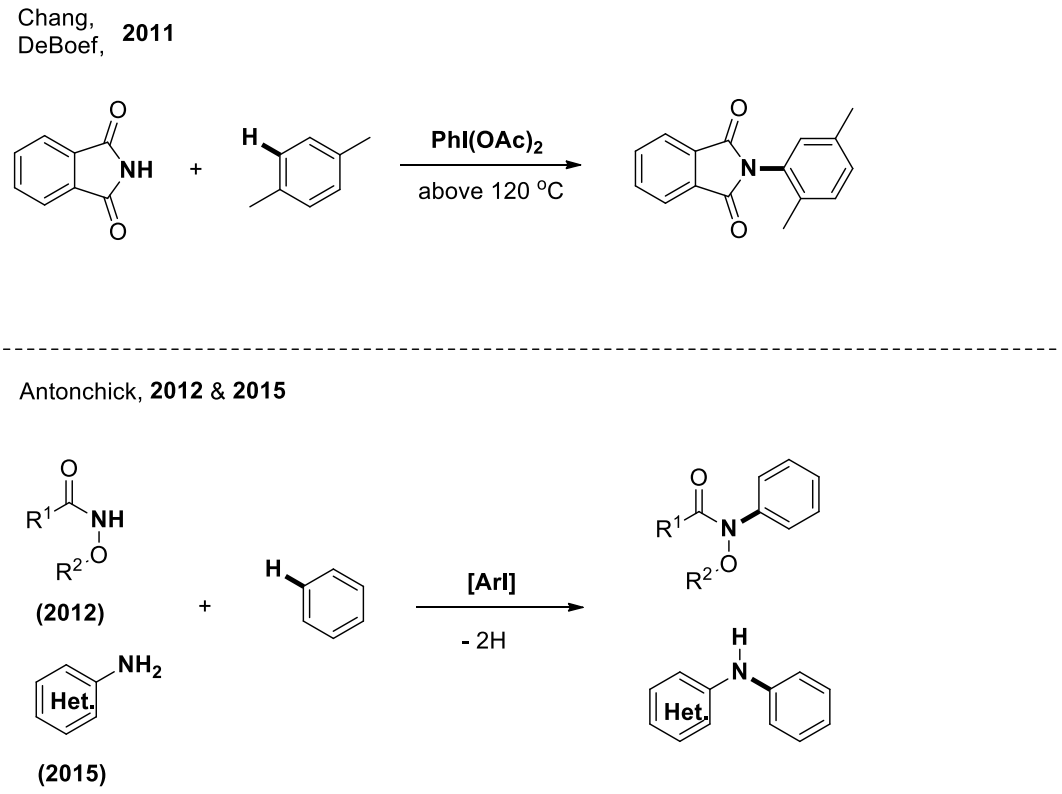
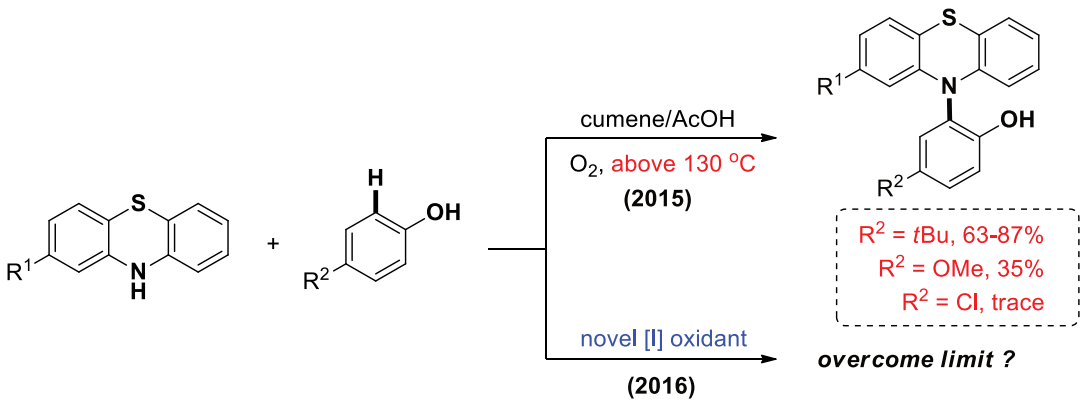
3.1 Introduction

The aryl amines and phenols are important structural motif for series of function molecules in pharmaceutical agents and ligands in transition-metal catalysis.[1] However, the synthesis of the aminated phenols is always difficult in the absence of metal catalyst. Since some metal free conditions were successfully achieved through aromatic amination reactions, which were assisted by either halo or triflate as leaving groups.[2] Few examples were mentioned for the CDC amination reactions in transition-metal free conditions and most of the strategies required either a hazardous leaving group or an electrophile for amination.[3] Cross-dehydrogenative couplings were considered as a promising strategy for the organic synthetic methods because of the removable prefunctionalization steps and less toxic side products.[4,5] Molecular oxygen is the ideal oxidant for the redox amination reactions with the following advantages: abundance, low cost and environmental friendly by-products. However, aerobic oxidation methods frequently face significant limitations with respect to selectivity and scope, such as the cumene mediated metal-free amination method of phenols which we recently reported.[6]



Scheme 1. A selection of hypervalent iodine mediated C(sp^2)-N bond formation reactions

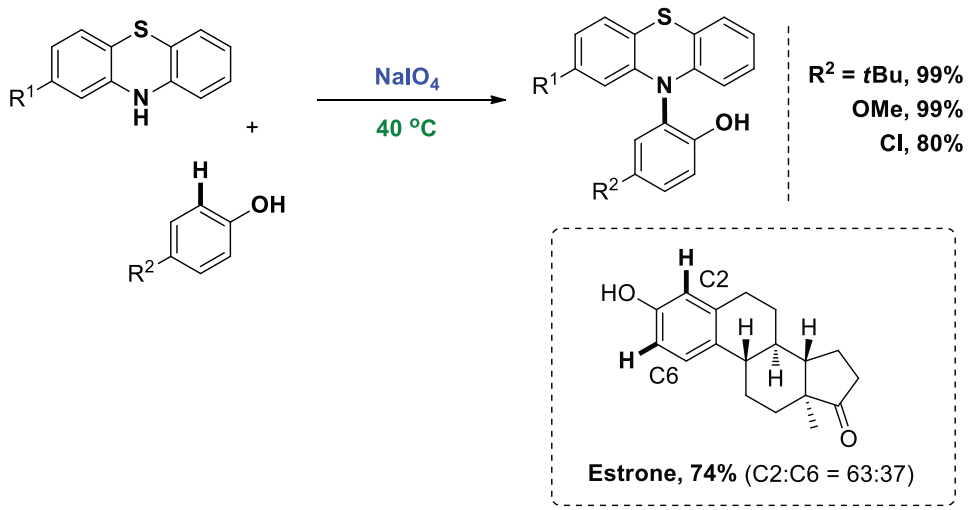
Alternatively, hypervalent iodine reagents play a key role in the fields of dehydrogenative amination methodologies.[7] The relatively benign character of iodine, such as the availability, the versatile redox activity, and its pronounced electrophilicity when in its higher oxidation state make it an effective approach for C-N bond formation protocols. Recent years, some outstanding cases of hypervalent iodine mediated dehydrogenative amination reactions were given by Antonchick,[7a,b,c] Chang,[8a] and DeBoeuf,[8b] who have brought this paradigm beyond classical Ullmann and Buchwald-Hartwig reactions (Scheme 1).[9] With respect to the limits of scope and the functional group tolerance in previous work, we decided to investigate novel amination methods of phenols with a kind of efficient hypervalent iodine oxidant (Scheme 2).



Scheme 2. Limits of previous cumene methods and perspective of hypervalent iodine

3.2 Results and discussion

The original target was concentrated on the development of novel conditions which might have chance to conduct the limited or beyond scope of previous work. With respect to the transition metal free reaction conditions, we started to search some alternative oxidants and solvents in order to achieve the goal. After careful consideration, the hypervalent iodine derivatives were selected as the (co-)oxidants and tested in the amination of phenols with phenothiazines and other *N*-containing reagents. With numerous optimizing experiments, we discovered the competitive reaction conditions and enlarged the scope of phenols which including some biofunctional molecules (Scheme 3).



Scheme 3. Periodate-mediated amination of phenols with phenothiazines

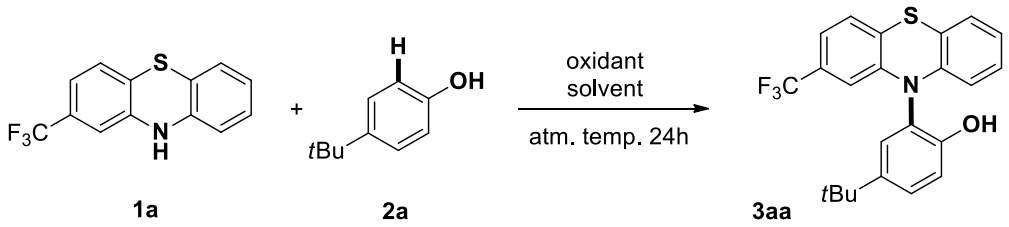
3.2.1 Optimization

The initial reaction we started was operated in the conditions of iodobenzene engaged and molecular oxygen. With the unsatisfied result we got, varieties of iodine substrates had been tested and finally the expected amination product **3aa** was obtained in 91% yield in the presence of periodate (entry 4, Table 1).[10] To get the best condition, we investigated a further study of the optimized conditions. Therefore, the detail of the finally determined reaction situations was as follows: phenothiazine (1.0 mmol), phenol (3.0 mmol), periodate (0.5 mmol), dichloromethane (2.5 mL), acetic acid (0.5 mL) were concentrated and stirred in a sealed screw caps vessel under air at 40 ^{o}C for 24 h. In Table 1, we studied effects of oxidants, solvents, and temperature of this reaction.

We selected a series of either combination of iodine reagents with dioxygen or independent hypervalent iodine derivatives as the oxidants to run the amination reaction of phenols. Significantly, with the increase of the valance of iodine, the yields of product also raised up. And periodates became the best choice (entry 4). Much to our surprise, the cation made a difference to the reactivity of periodate, with the sodium salt being notably superior to the potassium analogue and lithium periodate almost quenching the reaction (entry 15).

Cumene was regard as an efficient solvent in the radical reaction and successfully performed in the previous project. However, it was notably that in the presence of periodate cumene was no longer an essential solvent at low temperature. Unfortunately, the widely used solvents such as THF and chlorobenzene (entry 7,8) almost extinguished the reaction. To our delight, dichloromethane won the position of solvent and even conducted the reaction in a good yield

Table 1: Optimization



entry[a]	oxidant (mol%)	solvent	cosolvent	atm (1 bar)	temp (°C)	yield[b] (%)
1	Ph-I (50)	cumene	AcOH	O_2	50	-
2[c]	TBAI (50)	cumene	AcOH	O_2	50	-
3	I_2 (50)	cumene	AcOH	O_2	50	trace
4	KIO_4 (50)	cumene	AcOH	O_2	50	91
5	KIO_4 (50)	cumene	AcOH	O_2	rt	56
6[c]	KIO_4 (50)	DCM	AcOH	O_2	rt	78
7[c]	KIO_4 (50)	THF	AcOH	O_2	rt	trace
8[c]	KIO_4 (50)	PhCl	AcOH	O_2	rt	trace
9	KIO_4 (50)	DCM	-	O_2	rt	-
10	KIO_4 (5)	DCM	AcOH	O_2	rt	5
11	KIO_4 (50)	DCM	AcOH	air	rt	65
12	KIO_4 (50)	DCM	AcOH	air	40	95
13	KIO_4 (50)	DCM	AcOH	N_2	40	90
14	$NaIO_4$ (50)	DCM	AcOH	air	40	99
15	$LiIO_4$ (50)	DCM	AcOH	air	40	10
16	CuI (50)	cumene	AcOH	O_2	50	trace
17	I_2O_5 (50)	DCM	AcOH	air	40	95

[a]Reaction conditions: **1a** (1.0 mmol) and **2a** (3.0 mmol) in solvent (2.5 mL) and cosolvent (0.5 mL) for 24 h under O_2, N_2 or air. [b]Yield of isolated product. [c]TBAI = tetrabutylammonium iodide, DCM = dichloromethane, THF = tetrahydrofuran.

at room temperature (entry 6). In addition, the absence of acetic acid would also abandon the reaction (entry 9).

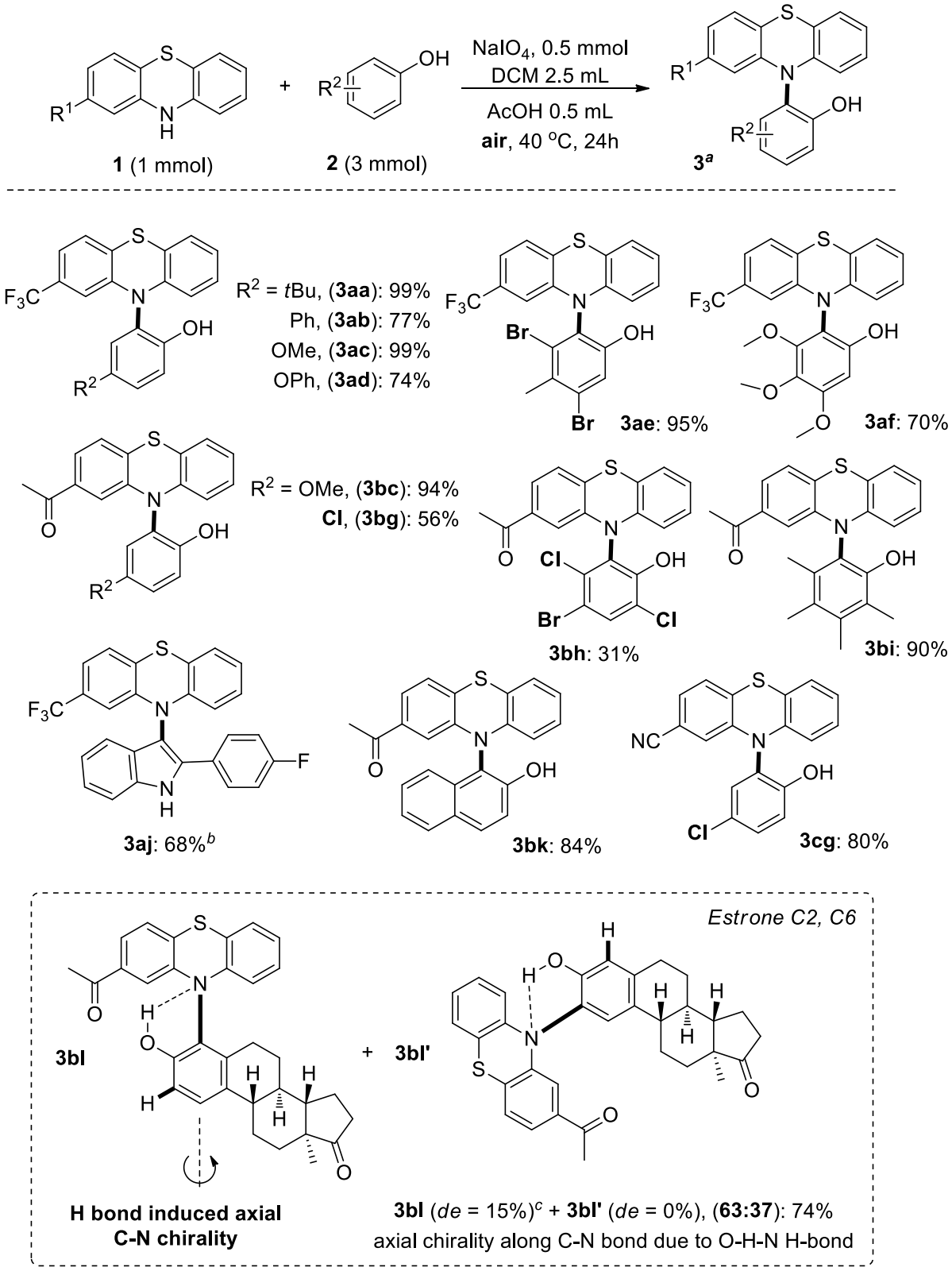
The moderate to high temperature increased the reactivity of most radical reactions. In the cumene/O_2 procedure, it was a key point for the conversion of product. In contrast, periodate conducted the reaction well even at room temperature, perhaps it was due to the strong oxidative ability. To keep a balance of reactivity and decomposition of reagents, we selected the reaction temperature at 40 ^{o}C.

It's worthy to mention that iodine pentoxide performed very well in this amination reaction, too (entry 17). And the final optimized conditions were determined as follows (entry 14): **1a** (1.0 mmol), **2a** (3.0 mmol), $NaIO_4$ (0.5 mmol), dichloromethane (2.5 mL), and AcOH (0.5 mL) were assembled in a screw-cap vessel and stirred at 40 ^{o}C for 24 h. Then the mixture was purified on a column chromatography of SiO_2.

3.2.2 Scope and beyond scope limits

With the optimized conditions in hand, we engaged both the limited case of halogenated phenols and very electron-rich phenols with a reputed tendency to overoxidize and decompose (Scheme 4). To our delight, the tolerance for both sides is astonishing. Monohalogenated phenols such as chloro- and bromophenols are particularly well tolerated (**3ae**, **3bg**, and **3cg**). Moreover, multihalogenated phenols were also bore and conducted in a moderate yield of 31% (**3bh**). The phenols with very rich function groups were well tolerated, too. Most of them showed good to excellent yields, such as 4-methoxylphenol (**3ac**, 99%), tetramethylphenol (**3bi**, 90%), or 2-naphthol (**3bk**, 84%).

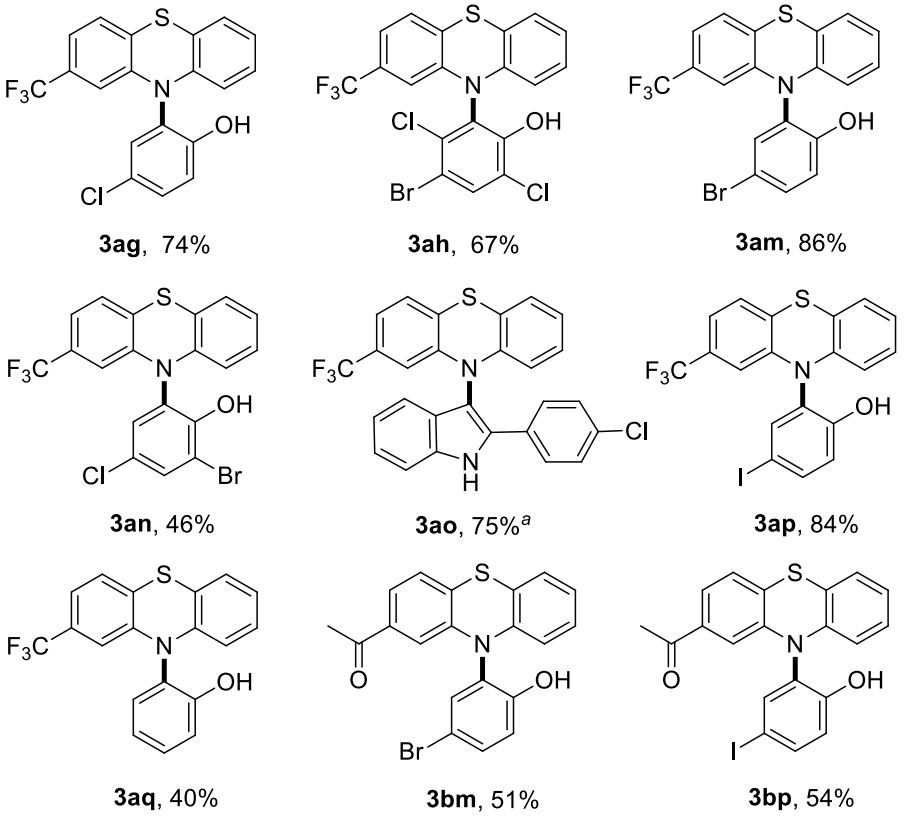
Estrone[11], the female hormone bioactive molecule, was also an interesting phenol derivative, albeit with moderate regio- and diastereoselectivity (**3bl** and **3bl'**). An exciting result occurred when we mixed 2-acetyl phenothiazine with estrone in the reaction conditions. The ^{1}H NMR data of products indicated that the more sterically congested regioisomer **3bl** displayed a probale OH−N H-bond stabilized axial chirality with a slight diastereomeric excess of 15%(± 4%), a low but encouraging diastereoselectivity for the development of future enatioselective versions of this reaction.



Scheme 4. Scope of periodate mediated amination of phenols (indole) [a]Conditions: **1** (1.0 mmol), **2** (3.0 mmol) in DCM (2.5 mL) and cosolvent AcOH (0.5 mL) under air at 40 °C for 24 h. [b]At 50 °C. [c]**3bl**: *de* = 15% ±4% depending on line broadening, phase correction and concentration with ^{1}H NMR intergration.

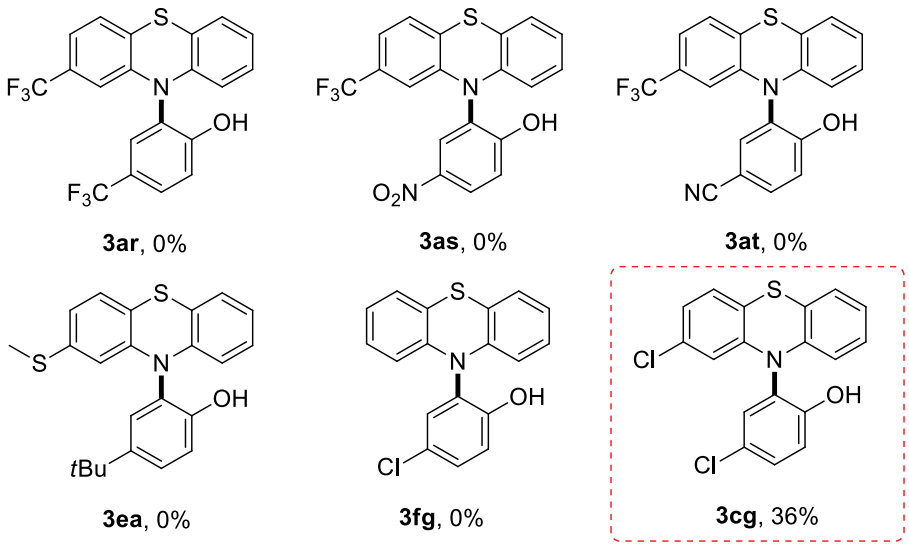
In parallel, indole performed well and gave **3aj** in moderate yield of 68% which was also tolerated in the cumene method.

Except for the successfully purified scopes in Scheme 4, we still discovered several examples with moderate to good GC yields. Unfortunately, the TLC indicated that the spot of product was close either to phenol or to side product so that the target substrate could not be easily purified by column chromatography of SiO_2. Major of the challenging scope contained one or more halogen elements which make them hard in separation (Scheme 5).



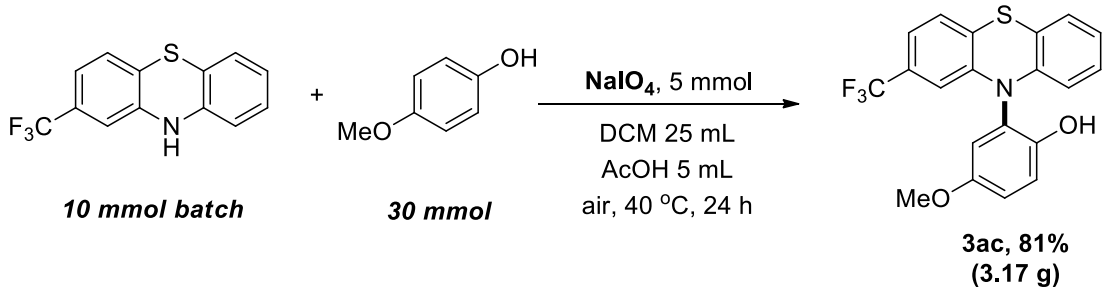
Scheme 5. Scope for challenging purification and their ^{1}H NMR corrected yields ^{a}At 50 ^{o}C.

In contrast, very electron-deficient phenols, such as 4-trifluoromethyl phenol, 4-nitrophenol , and 4-cyanophenol are still completely unreactive with this novel method. The TLC and GC-MS data predicted that a strong decomposition of phenothiazine occurred. Similarly, electron-rich phenothiazines were also can't afford expected results. Fortunately, electron-netural 2-chlorophenothiazine conducted **3cg** in an acceptable yield of 36% (Scheme 6). So far, other *N*-reagents like diphenyl amine, carbazole, and *N*-phenylbenzenesulfonamide still remained challenging.



Scheme 6. Beyond scope and unexpected substrate: **3cg**

Interestingly, we successfully demonstrate the robustness of this novel method with a multigram scale reaction, affording 3.17 g of **3ac** in one single batch (Scheme 7). This arguably constituted a notable advantage over the previous cumene method, particularly in terms of safety and practicality.



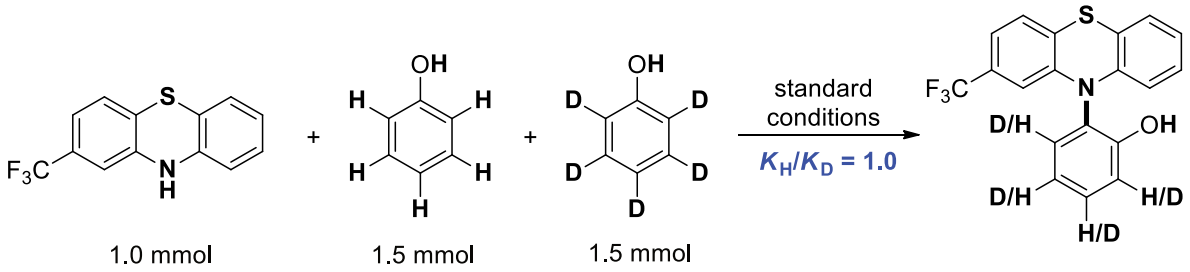
Scheme 7. Gram-Scale synthesis

3.2.3 Mechanistic studies and discussion

3.2.3.1 Controlling reactions and results

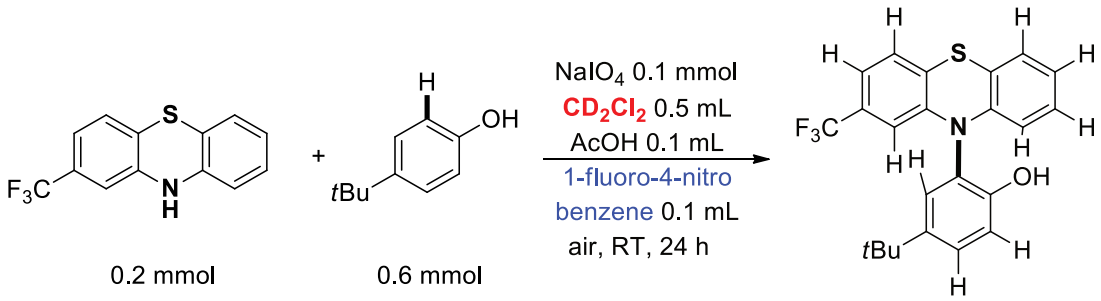
To gain an insight into the mechanism of this amination reaction, we conducted several parallel and kinetic experiments. Initially, we investigated phenol and phenol-d_5 under the standard conditions for the research of reaction rate (Scheme 8). The competition case between normal and deuterium-labeled phenols gave similar amount of amination products which were detected by crude NMR (KIE = 1.0). Interestingly, no significant H/D scrambling was observed, whether in the remaining reagents or in the substrates. Those results indicated

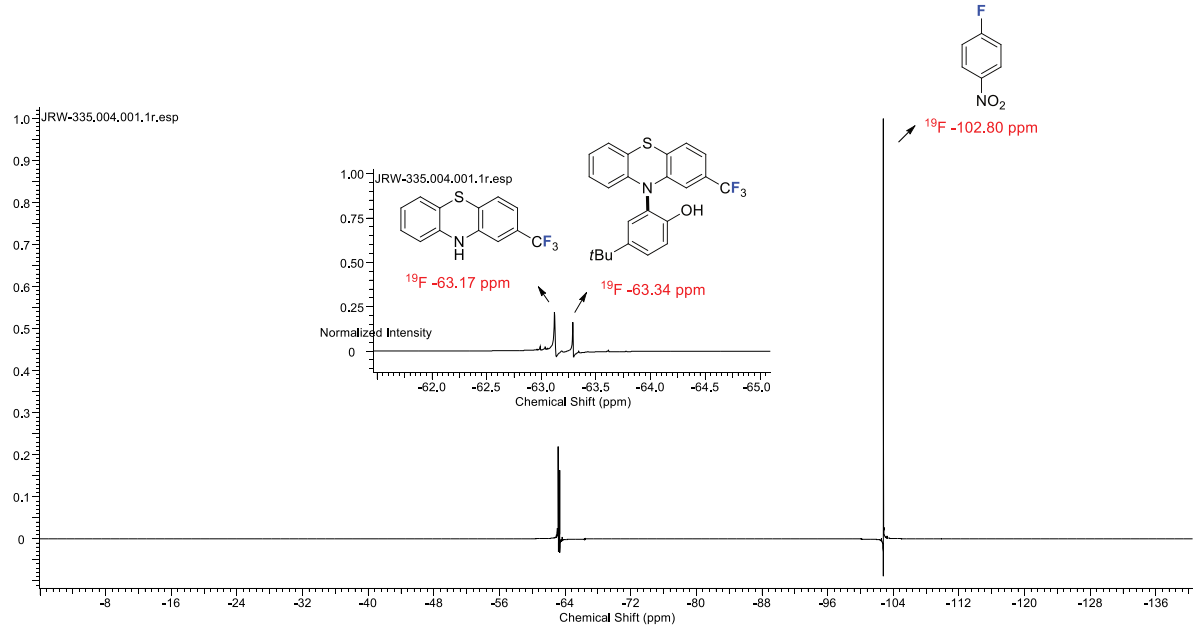
that the oxidation of phenol was not the rate-determining step of the reaction. However, phenothiazines were documented to own significantly low bond dissociation energy, and with the predicted pathways of cumene method, that the phenothiazine moiety was oxidized by periodate first then the reaction chain started.



Scheme 8. Deuterium scrambling experiment

Alternatively, we carried out the other reaction with deuterium-labeled dichloromethane (CD_2Cl_2) to investigate the effect of solvent. In this case we set 1-fluoro-4-nitrobenzene

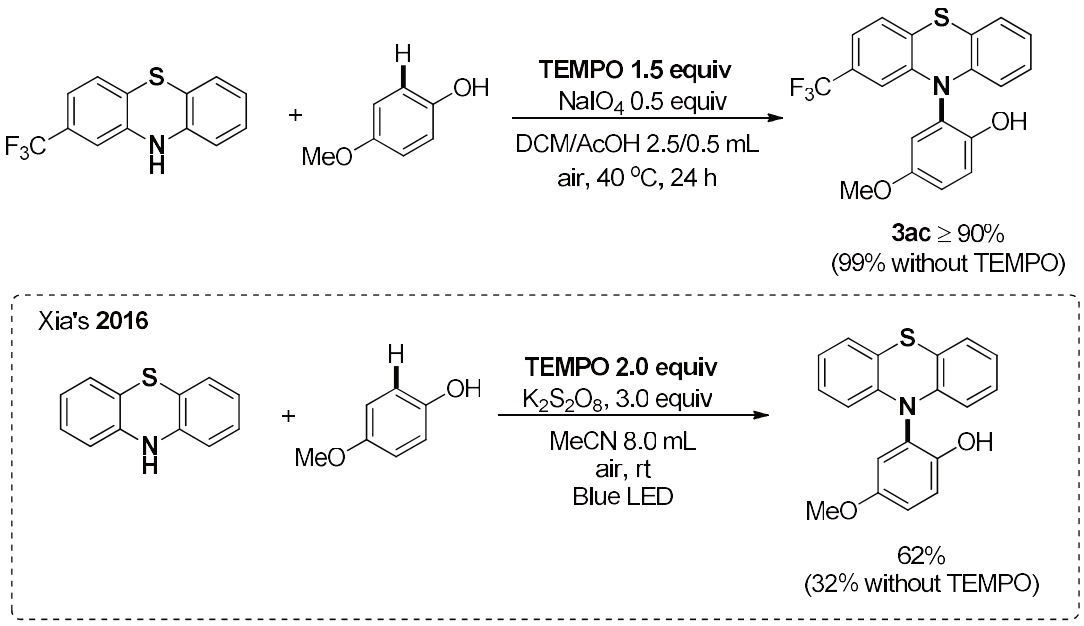




Scheme 9. Solvent-deuterium labeling experiment and ^{19}F NMR

(0.1 mL) as the standard solvent of ^{19}F NMR (Scheme 9). The result showed that the hydrogen atom in dichloromethane had neglected effect on the reaction pathways.

Furthermore, a radical trapping reaction was also performed. To our surprise, the classical radical scavenger TEMPO (2,2,6,6-Tetramethylpiperidine 1-oxyl, 1.5 equiv) was tolerated and provided **3ac** in a yield of more than 90%, which was consistent with the result of Xia in a related amination system (Scheme 10).[12]



Scheme 10. Radical trapping experiments with TEMPO

3.2.3.2 Discussion

The unexpected result forecasted this periodate-mediated amination reaction probably underwent a nucleophile attack pathway rather than a radical one. And because of the sodium periodate exists in two different forms: sodium *meta*-periodate ($NaIO_4$) and sodium *ortho*-periodate ($Na_2H_3IO_6$), especially in the presence of AcOH, the exactly effective one for the reaction remained to be proved. Clearly, the electrophilic iodine center might play an important coordinative role at the oxygen and/or nitrogen atoms of reagents. Unfortunately, the missing direct evidence for those interactions forbade a detailed mechanism at this stage.

3.3 Conclusion and pespective

In conclusion, a mild metal free dehydrogenative amination method of phenol which operated at only 40 ^{o}C and air-insensitive condition was developed. And we were able to extend the scope to some more ubiquitous and challenging phenols, whether polyhalogenated or electron-rich, than the previously reported cumene method. Despite of some substrates were difficultly purified by standard chromatography, the yields of converted reagents ranged from good to excellent. Moreover, we established a series of hypervalent iodine reactant, particularly $NaIO_4$, were competent oxidants for the direct elaboration of molecular complexity in the frame of CDC reactions. Furthermore, the large scale synthesis in such mild conditions indicated the potential value of this reaction in industrial process.

The limitations of this periodate-mediated metal-free amination reaction were as follows: weak tolerance of E-poor phenols and E-rich phenothiazines, unique aminating reagents (only phenothiazine and derivatives worked, either diphenylamines or carbazoles still remained challenge). What's more, further mechanistic studies of this reaction are required to gain better understanding the role of the specialized oxidant, periodate. And we expect that periodates will promote the field of novel cross-dehydrogenative amination reactions in future. Respectively, we will keep searching other efficient and unique oxidants for those kinds of mild amination reactions.

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3.5 Experimental section

3.5.1 General Information

All reactions were carried out in **dried reaction vessels** with **sealed Teflon** screw caps under air, unless otherwise specified. NMR spectra were obtained on Bruker AMX 400 or on Bruker Avance 600 systems using $CDCl_3$ or $(CD_3)_2SO$ as solvents, with proton and carbon resonances at 400/600 MHz and 101/151 MHz, respectively. Coupling constants (J) are quoted in Hz. Flash chromatography was performed on silica gel (40-63 mesh) by standard technique. Routine GC-MS spectra were recorded on a Bruker 436-GC/SCION SQ Premium EI, 230 V. HR-MS data were determined on a WATERS GCT-PremierTM mass spectrometer. The major signals are quoted in m/z with the relative intensity in parentheses. Some substrates were purchased either from Sigma Aldrich, Acros, TCI, or ABCR, and engaged directly. Other substrates were prepared according to standard procedures. The synthesis of tetramethylphenol (**2l**) was conducted according to the procedure described in this patent: R. Shapiro, US patent 0100802, 2003 May 29. Product **3 aa** was already characterized in a previous publication.[1]

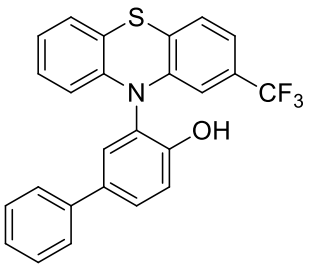
3.5.2 Experimental procedure

A 170 ml screw-cap vial is filled with phenothiazine (1.0 mmol), phenol (3.0 mmol), sodium periodate (0.5 mmol), dichloromethane (2.5 ml), acetic acid (0.5 ml) and a magnetic stirring bar. All the steps were operated in open air, and the reactor is then sealed, transferred into a 40 °C oil bath for 24h. (magnetic stirring set to approx. 450 turns/min). The crude mixture is thereafter directly purified with silica gel column chromatography (*n*-hexane/ethyl acetate 17:3 to 7:3), unless stated otherwise. The Rf are typically comprised between 0.25 and 0.68.

[1] M. -L, Louillat-Habermeyer, R. Jin, F. W. Patureau, *Angew. Chem. Int. Ed*. **2015**, *54*, 4102-4104.

3.5.3 Analytic data of new substrates

3ab : 3-(2-(trifluoromethyl)-10H-phenothiazin-10-yl)-[1,1'-biphenyl]-4-ol



Chemical Formula: $C_{25}H_{16}F_3NOS$
Exact Mass: 435,0905
Molecular Weight: 435,4608
m/z: 435.0905 (100.0%), 436.0938 (27.0%), 437.0863 (4.5%), 437.0972 (3.5%), 438.0896 (1.2%)
Elemental Analysis: C, 68.95; H, 3.70; F, 13.09; N, 3.22; O, 3.67; S, 7.36

3ab (JRW-258): Synthesized by 2-(trifluoromethyl)-10H-phenothiazine (1.0 mmol, 267 mg) and 4-phenyl -phenol (3.0 mmol, 510 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 17/3. Isolated yield: 77% (ivory powder).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.35 (s, 1H), 7.80 (dd, ^{3}J = 8.5 Hz, J = 2.3 Hz, 1H), 7.69 (~d, ^{3}J = 7.4 Hz, 2H), 7.64 (d, J = 2.4 Hz, 1H), 7.42 (~t, J = 7.7, 2H), 7.32-7.24 (m, 3H), 7.14 (dd, ^{3}J = 7.9 Hz, J = 1.0 Hz, 1H), 7.05 (dd ^{3}J = 7.5 Hz, J = 1.5 Hz, 1H), 6.96 (td, ^{3}J = 7.5 Hz, J = 1.5 Hz, 1H), 6.87 (td, ^{3}J = 7.6, J = 1.2 Hz, 1H), 6.28 (d, J = 1.2 Hz, 1H), 6.13 (dd, ^{3}J = 8.2 Hz, J = 1.0 Hz, 1H).

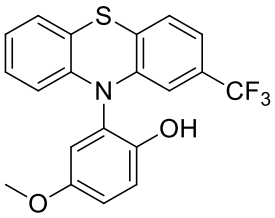
^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 154.95 (s, C_{quat}), 143.32 (s, C_{quat}), 142.04 (s, C_{quat}), 138.65 (s, C_{quat}), 133.33 (s, C_{quat}), 128.85 (s, CH), 128.84 (s, CH), 128.81 (s, CH), 127.90 (q, ^{2}J = 31.6 Hz, C_{quat}), 127.77 (s, CH), 126.99 (s, CH), 126.89 (s, CH), 126.38 (s, CH), 126.07 (s, C_{quat}), 125.96 (s, CH), 124.30 (s, C_{quat}), 123.88 (q, ^{1}J = 273.2 Hz, C_{quat}), 122.99 (s, CH), 118.63 (q, ^{3}J = 3.4 Hz, CH), 117.91 (s, CH), 117.53 (s, C_{quat}), 115.79 (s, CH), 110.76 (q, ^{3}J = 3.4 Hz, CH).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.66 (s, CF_3).

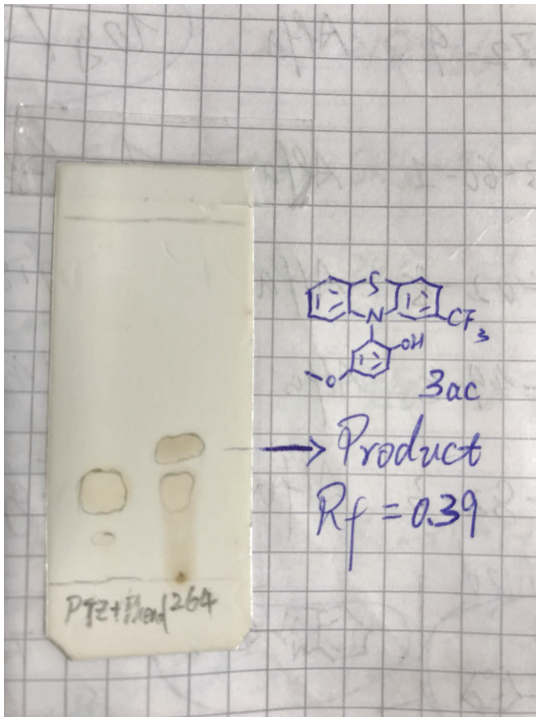
IR (neat, cm^{-1}): U: 3408, 3395, 3060, 3034, 2926, 1705, 1601, 1570, 1514, 1486, 1468, 1442, 1410, 1326, 1286, 1271, 1236, 1191, 1162, 1115, 1086, 1042, 961, 944, 871, 816, 744, 696, 660.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{25}H_{16}F_3NOS]^{\bullet+}$: 435.0905, found: 435.0916.

3ac : 4-methoxy-2-(2-(trifluoromethyl)-10H-phenothiazin-10-yl)phenol



Chemical Formula: $C_{20}H_{14}F_3NO_2S$
Exact Mass: 389,0697
Molecular Weight: 389,3909
m/z: 389.0697 (100.0%), 390.0731 (21.6%), 391.0655 (4.5%), 391.0764 (2.2%)
Elemental Analysis: C, 61.69; H, 3.62; F, 14.64; N, 3.60; O, 8.22; S, 8.23



3ac (JRW-264): Synthesized by 2-(trifluoromethyl)-10H-phenothiazine (1.0 mmol, 267 mg) and 4-methoxy -phenol (3.0 mmol, 372 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The Rf was calculated in 0.39 which relied on the TLC board

above. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 17/3. Isolated yield: 99% (beige powder).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.66 (s, 1H), 7.22 (d, ^{3}J = 7.9 Hz, 1H), 7.10 (d, ^{3}J = 8.9 Hz, 2H), 7.05-7.02 (m, 2H), 6.95 (td, ^{3}J = 8.2 Hz, J = 1.6 Hz, 1H), 6.87-6.84 (m, 2H), 6.25 (d, J = 1.4 Hz, 1H), 6.10 (dd, ^{3}J = 8.3 Hz, J = 1.1 Hz, 1H), 3.71 (s, 3H).

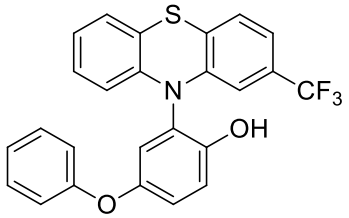
^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 153.60 (s, C_{quat}), 149.00 (s, C_{quat}), 143.17 (s, C_{quat}), 141.87 (s, C_{quat}), 127.83 (q, ^{2}J = 32.4 Hz, C_{quat}), 127.75 (s, CH), 126.93 (s, CH), 126.33 (s, CH), 125.56 (s, C_{quat}), 124.14 (s, C_{quat}), 123.88 (q, ^{1}J = 272.4 Hz, C_{quat}), 122.96 (s, CH), 118.59 (q, ^{3}J = 3.7 Hz, CH), 117.89 (s, CH), 117.35 (s, C_{quat}), 116.74 (s, CH), 115.75 (s, CH), 115.00 (s, CH), 110.74 (q, ^{3}J = 3.7 Hz, CH), 55.51 (s, CH_3).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.68 (s, CF_3).

IR (neat, cm^{-1}): U: 3402, 3068, 3006, 2952, 2837, 1737, 1601, 1570, 1500, 1468, 1440, 1410, 1324, 1277, 1215, 1152, 1113, 1085, 1033, 971, 952, 870, 847, 814, 744, 716, 678, 661.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{20}H_{14}F_3NO_2S]^{\bullet+}$: 389.0697, found: 389.0689.

3ad : 4-phenoxy-2-(2-(trifluoromethyl)-10H-phenothiazin-10-yl)phenol



Chemical Formula: $C_{25}H_{16}F_3NO_2S$
Exact Mass: 451,0854
Molecular Weight: 451,4602
m/z: 451.0854 (100.0%), 452.0887 (27.0%), 453.0812 (4.5%), 453.0921 (3.5%), 454.0845 (1.2%)
Elemental Analysis: C, 66.51; H, 3.57; F, 12.62; N, 3.10; O, 7.09; S, 7.10

3ad (JRW-275): Synthesized by 2-(trifluoromethyl)-10H-phenothiazine (1.0 mmol, 267 mg) and 4-phenoxy -phenol (3.0 mmol, 558 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography

on silica gel with the solution of hexane / ethyl acetate 17/3. Isolated yield: 74% (off-white powder).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.11 (s, 1H), 7.36-7.32 (t, ^{3}J = 7.6 Hz, 2H), 7.23-7.19 (m, 3H), 7.13 (d, ^{3}J = 7.9 Hz, 1H), 7.08 (t, ^{3}J = 7.4 Hz, 1H), 7.03-7.01 (m, 2H), 7.00-6.94 (m 3H), 6.87 (t, ^{3}J = 7.4 Hz, 1H), 6.24 (s, 1H), 6.15 (d, ^{3}J = 8.2 Hz, 1H).

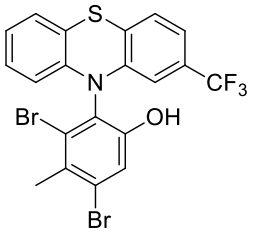
^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 157.86 (s, C_{quat}), 151.79 (s, C_{quat}), 149.47 (s, C_{quat}), 143.03 (s, C_{quat}), 141.59 (s, C_{quat}), 129.86 (s, CH), 129.30 (s, C_{quat}), 127.81 (q, ^{2}J = 32.4 Hz, C_{quat}), 127.79 (s, CH), 126.98 (s, CH), 126.37 (s, CH), 126.05 (s, C_{quat}), 124.20 (s, C_{quat}), 123.87 (q, ^{1}J = 273.2 Hz, C_{quat}), 123.05 (s, CH), 122.78 (s, CH), 122.34 (s, CH), 122.23 (s, CH), 118.67 (q, ^{3}J = 3.7 Hz, CH), 118.50 (s, CH), 117.27 (s, CH), 115.60 (s, CH), 110.53 (q, ^{3}J = 3.7 Hz, CH).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.78 (s, CF_3).

IR (neat, cm^{-1}): ʋ: 3422, 3060, 3040, 2972, 2956, 2926, 1738, 1590, 1485, 1468, 1442, 1410, 1325, 1280, 1255, 1212, 1162, 1117, 1085, 1042, 984, 953, 867, 816, 784, 743, 718, 690, 662.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{25}H_{16}F_3NO_2S]^{\bullet+}$: 451.0854, found: 451.0865.

3ae: 3,5-dibromo-4-methyl-2-(2-(trifluoromethyl)-10H-phenothiazin-10-yl) phenol



Chemical Formula: $C_{20}H_{12}Br_2F_3NOS$
Exact Mass: 528,8958
Molecular Weight: 531,1836
m/z: 530.8938 (100.0%), 528.8958 (51.4%), 532.8918 (48.6%), 531.8972 (21.6%), 529.8992 (11.1%), 533.8951 (10.5%), 532.8896 (4.5%), 530.8916 (2.3%), 532.9005 (2.2%), 534.8875 (2.2%), 530.9026 (1.1%), 534.8985 (1.1%)
Elemental Analysis: C, 45.22; H, 2.28; Br, 30.09; F, 10.73; N, 2.64; O, 3.01; S, 6.04

3ae (JRW-318): Synthesized by 2-(trifluoromethyl)-10H-phenothiazine (1.0 mmol, 267 mg) and 3,5-dibromo- 4-methylphenol (3.0 mmol, 798 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 95% (smoky gray powder).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.88 (s, 1H), 7.44 (s, 1H), 7.22 (d, ^{3}J = 7.9 Hz, 1H), 7.15 (dd, ^{3}J = 8.0 Hz, J = 1.1 Hz, 1H), 7.02 (dd, ^{3}J = 7.5 Hz, J = 1.6 Hz, 1H), 6.93 (td, ^{3}J = 7.5 Hz, J = 1.6 Hz, 1H), 6.87 (td, ^{3}J = 7.5 Hz, J = 1.2 Hz, 1H), 6.10 (d, J = 1.4 Hz, 1H), 5.98 (dd, ^{3}J = 8.2 Hz, J = 1.1 Hz, 1H), 2.51 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 155.21 (s, C_{quat}), 141.08 (s, C_{quat}), 139.65 (s, C_{quat}), 129.14 (s, C_{quat}), 128.01 (s, C_{quat}), 127.94 (s, CH), 127.81 (q, ^{2}J = 31.9 Hz, C_{quat}), 127.13 (s, CH), 126.44 (s, CH), 125.15 (s, C_{quat}), 124.85 (s, C_{quat}), 124.48 (s, C_{quat}), 123.76 (q, ^{1}J = 272.6 Hz, C_{quat}), 123.41 (s, CH), 119.87 (s, CH), 119.11 (q, ^{3}J = 3.7 Hz, CH), 117.58 (C_{quat}), 115.06 (s, CH), 109.80 (q, ^{3}J = 3.6 Hz, CH), 23.45 (s, CH_3).

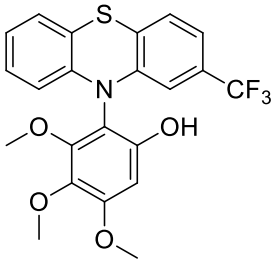
^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.66 (s, CF_3).

IR (neat, cm^{-1}): Ũ: 3457, 3221, 3082, 3017, 2952, 2926, 2881, 1738, 1588, 1563, 1470, 1455, 1412, 1380, 1325, 1275, 1229, 1202, 1169, 1119, 1089, 1043, 986, 909, 862, 817, 780, 747, 706.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{20}H_{12}Br_2F_3NOS]^{\bullet+}$: 530.8938, found: 530.8934.

3af:

3,4,5-trimethoxy-2-(2-(trifluoromethyl)-10H-phenothiazin-10-yl)phenol



Chemical Formula: $C_{22}H_{18}F_3NO_4S$
Exact Mass: 449,0909
Molecular Weight: 449,4428
m/z: 449.0909 (100.0%), 450.0942 (23.8%), 451.0867 (4.5%), 451.0976 (2.7%), 452.0900 (1.1%)
Elemental Analysis: C, 58.79; H, 4.04; F, 12.68; N, 3.12; O, 14.24; S, 7.13

3af (JRW-320): Synthesized by 2-(trifluoromethyl)-10H-phenothiazine (1.0 mmol, 267 mg) and 3,4,5-trimethoxyphenol (3.0 mmol, 552 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 17/3. Isolated yield: 70% (off-white powder).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.94 (s, 1H), 7.18 (d, ^{3}J = 7.9 Hz, 1H), 7.10 (d, ^{3}J = 7.8 Hz, 1H), 6.99 (dd, ^{3}J = 7.9 Hz, J = 1.2 Hz, 1H), 6.94 (td, ^{3}J = 7.8 Hz, J = 1.2 Hz, 1H), 6.83 (t, ^{3}J = 7.3 Hz, 1H), 6.55 (s, 1H), 6.24 (s, 1H), 6.10 (d, ^{3}J = 8.2 Hz, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 3.68 (s, 3H).

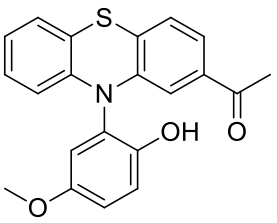
^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 154.14 (s, C_{quat}), 151.89 (s, C_{quat}), 151.01 (s, C_{quat}), 143.28 (s, C_{quat}), 141.80 (s, C_{quat}), 135.13 (s, C_{quat}), 127.74 (s, CH), 127.71 (q, ^{2}J = 31.9 Hz, C_{quat}), 126.83 (s, CH), 126.23 (s, CH), 124.28 (s, C_{quat}), 123.91 (q, ^{1}J = 272.6 Hz, C_{quat}), 122.89 (s, CH), 118.47 (q, ^{3}J = 4.5 Hz, CH), 117.43 (s, C_{quat}), 115.49 (s, CH), 111.47 (s, C_{quat}), 110.46 (q, ^{3}J = 4.5 Hz, CH), 95.89 (s, CH), 60.75 (s, CH_3), 60.72 (s, CH_3), 55.58 (s, CH_3).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.70 (s, CF_3).

IR (neat, cm^{-1}): U: 3402, 3060, 2994, 2971, 2939, 2856, 1738, 1605, 1490, 1468, 1443, 1411, 1378, 1326, 1258, 1226, 1196, 1165, 1116, 1089, 1040, 992, 956, 921, 871, 815, 790, 744.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{22}H_{18}F_3NO_4S]^{\bullet+}$: 449.0909, found: 449.0923.

3bc : 1-(10-(2-hydroxy-5-methoxyphenyl)-10H-phenothiazin-2-yl)ethanone



Chemical Formula: $C_{21}H_{17}NO_3S$
Exact Mass: 363,0929
Molecular Weight: 363,4296
m/z: 363.0929 (100.0%), 364.0963 (22.7%), 365.0887 (4.5%), 365.0996 (2.5%), 366.0921 (1.0%)
Elemental Analysis: C, 69.40; H, 4.71; N, 3.85; O, 13.21; S, 8.82

3bc (JRW-302): Synthesized by 2-(acetyl)-10H-phenothiazine (1.0 mmol, 241 mg) and 4-methoxyphenol (3.0 mmol, 372 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 94% (maroon powder).

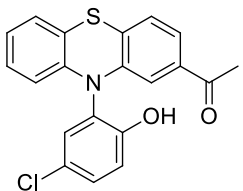
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.54 (s, 1H), 7.43 (dd, ^3J = 7.9 Hz, J = 1.6 Hz, 1H), 7.13 (d, ^3J = 7.9 Hz, 1H), 7.10 (d, ^3J = 8.9 Hz, 1H), 7.04-6.99 (m, 2H), 6.93 (td, ^3J = 7.4 Hz, J = 1.5 Hz, 1H), 6.84-6.80 (m, 2H), 6.59 (d, J = 1.6 Hz, 1H), 6.06 (dd, ^3J = 8.3 Hz, J = 1.0 Hz, 1H), 3.71 (s, 3H), 2.37 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 196.70 (C_{quat}), 153.50 (C_{quat}), 149.10 (C_{quat}), 142.60 (C_{quat}), 142.00 (C_{quat}), 135.77 (C_{quat}), 127.68, 126.20, 126.06, 125.91 (C_{quat}), 125.41 (C_{quat}), 123.21, 122.50, 117.86, 117.11 (C_{quat}), 116.39, 115.55, 115.14, 113.07, 55.49, 26.34.

IR (neat, cm^{-1}): U: 3368, 3118, 3104, 3001, 2971, 2950, 2865, 2835, 2734, 1738, 1661, 1587, 1557, 1502, 1464, 1438, 1404, 1300, 1276, 1217, 1151, 1107, 935, 812, 743, 712.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{21}H_{17}NO_3S]^{\bullet+}$: 363.0929, found: 363.0903.

3bg : 1-(10-(5-chloro-2-hydroxyphenyl)-10H-phenothiazin-2-yl)ethanone



Chemical Formula: $C_{20}H_{14}ClNO_2S$
Exact Mass: 367,0434
Molecular Weight: 367,8487
m/z: 367.0434 (100.0%), 369.0404 (32.0%), 368.0467 (21.6%), 370.0438 (6.9%), 369.0392 (4.5%), 369.0501 (2.2%), 371.0362 (1.4%)
Elemental Analysis: C, 65.30; H, 3.84; Cl, 9.64; N, 3.81; O, 8.70; S, 8.72

3bg (JRW-288): Synthesized by 2-(acetyl)-10H-phenothiazine (1.0 mmol, 241 mg) and 4-chlorophenol (3.0 mmol, 386 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 56% (light yellow powder).

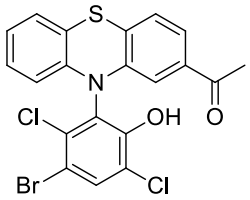
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.40 (s, 1H), 7.49 (dd, ^3J = 8.8 Hz, J = 2.8 Hz, 1H), 7.46 (dd, ^3J = 7.9 Hz, J = 1.6 Hz, 1H), 7.40 (d, J = 2.5 Hz, 1H), 7.20 (d, ^3J = 8.8 Hz, 1H), 7.15 (d, ^3J = 7.9 Hz, 1H), 7.02 (dd, ^3J = 7.5 Hz, J = 1.5 Hz, 1H), 6.94 (td, ^3J = 7.5 Hz, J = 1.5 Hz, 1H), 6.84 (td ^3J = 7.4 Hz, J = 1.2 Hz, 1H), 6.54 (d, J = 1.5 Hz, 1H), 6.04 (dd, ^3J = 8.3 Hz, J = 1.0 Hz, 1H), 2.38 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 196.64 (C_{quat}), 154.74 (C_{quat}), 142.23 (C_{quat}), 141.63 (C_{quat}), 135.75 (C_{quat}), 130.94, 130.50, 127.76, 127.11 (C_{quat}), 126.33, 126.20, 125.61 (C_{quat}), 123.55 (C_{quat}), 123.46, 122.74, 118.81, 117.28 (C_{quat}), 115.43, 112.80, 26.33.

IR (neat, cm^{-1}): U: 3271, 3059, 2971, 2953, 2925, 2865, 2724, 2685, 2655, 1739, 1660, 1586, 1556, 1486, 1466, 1439, 1403, 1361, 1301, 1231, 1200, 1157, 1116, 1100, 1056, 1042, 995, 935, 913, 883, 864, 816, 791, 744, 715, 690, 671.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{20}H_{14}ClNO_2S]^{\bullet+}$: 367.0434, found: 367.0439.

3bh: 1-(10-(3-bromo-2,5-dichloro-6-hydroxyphenyl)-10H-phenothiazin-2-yl) ethanone



Chemical Formula: $C_{20}H_{12}BrCl_2NO_2S$
Exact Mass: 478,9149
Molecular Weight: 481,1898
m/z: 478.9149 (100.0%), 480.9129 (97.3%), 480.9120 (63.9%), 482.9099 (62.2%), 479.9183 (21.6%), 481.9162 (21.1%), 481.9153 (13.8%), 483.9133 (13.5%), 482.9090 (10.2%), 484.9070 (10.0%), 480.9107 (4.5%), 482.9087 (4.4%), 482.9078 (2.9%), 484.9057 (2.8%), 480.9216 (2.2%), 483.9124 (2.2%), 482.9196 (2.2%), 485.9103 (2.2%), 482.9187 (1.4%), 484.9166 (1.4%)
Elemental Analysis: C, 49.92; H, 2.51; Br, 16.61; Cl, 14.74; N, 2.91; O, 6.65; S, 6.66

3bh (JRW-294): Synthesized by 2-(acetyl)-10H-phenothiazine (1.0 mmol, 241 mg) and 4-bromo-2,5-dichloro phenol (3.0 mmol, 726 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 31% (yellow powder).

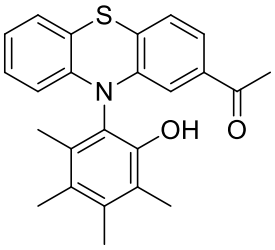
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.20 (s, 1H), 8.15 (s, 1H), 7.46 (dd, ^3J = 8.0 Hz, J = 1.4 Hz, 1H), 7.13 (d, ^3J = 7.9 Hz, 1H), 7.00 (dd, ^3J = 7.5 Hz, J = 1.3 Hz, 1H), 6.93 (broad t, ^3J = 7.5 Hz, 1H), 6.84 (t, ^3J = 7.5 Hz, 1H), 6.32 (d, J = 1.4 Hz, 1H), 5.94 (d, J = 8.2 Hz, 1H), 2.39 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 196.47 (C_{quat}), 153.25 (C_{quat}), 139.88 (C_{quat}), 139.13 (C_{quat}), 135.74 (C_{quat}), 134.03, 133.64 (C_{quat}), 128.01, 126.54 (C_{quat}), 126.36, 126.25, 125.90 (C_{quat}), 124.06, 123.21, 121.92 (C_{quat}), 117.37 (C_{quat}), 114.69, 111.65 (C_{quat}), 111.60, 26.31.

IR (neat, cm^{-1}): U: 3297, 3127, 3094, 3017, 2971, 2955, 2926, 2856, 1739, 1660, 1591, 1556, 1470, 1454, 1403, 1304, 1284, 1269, 1234, 1204, 1145, 1102, 1046, 978, 934, 864, 808, 745, 719.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{20}H_{12}BrCl_2NO_2S]^{\bullet+}$: 478.9149, found: 478.9158.

3bi : 1-(10-(2-hydroxy-3,4,5,6-tetramethylphenyl)-10H-phenothiazin-2-yl) ethanone



Chemical Formula: $C_{24}H_{23}NO_2S$
Exact Mass: 389,1449
Molecular Weight: 389,5099
m/z: 389.1449 (100.0%), 390.1483 (26.0%), 391.1407 (4.5%), 391.1517 (3.2%), 392.1441 (1.2%)
Elemental Analysis: C, 74.00; H, 5.95; N, 3.60; O, 8.22; S, 8.23

3bi (JRW-306): Synthesized by 2-(acetyl)-10H-phenothiazine (1.0 mmol, 241 mg) and 3,4,5,6-tetramethyl- phenol (3.0 mmol, 450 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 17/3. Isolated yield: 90% (lemon powder).

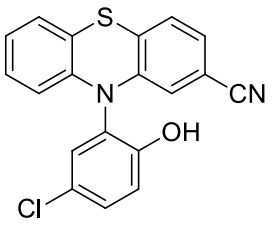
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.66 (s, 1H), 7.37 (dd, ^3J = 7.9 Hz, J = 1.4 Hz, 1H), 7.05 (d, ^3J = 7.9 Hz, 1H), 6.92 (dd, ^3J = 7.5 Hz, J = 1.2 Hz, 1H), 6.84 (td, ^3J = 7.9 Hz, J = 1.2 Hz, 1H), 6.75 (t, ^3J = 7.3 Hz, 1H), 6.40 (d, J = 1.4 Hz, 1H), 5.85 (d, ^3J = 8.0 Hz, 1H), 2.35 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H), 2.15 (s, 3H), 2.08 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 196.69 (C_{quat}), 150.55 (C_{quat}), 141.90 (C_{quat}), 141.08 (C_{quat}), 136.35 (C_{quat}), 135.75 (C_{quat}), 131.69 (C_{quat}), 127.69, 126.99 (C_{quat}), 125.95, 125.78, 125.59 (C_{quat}), 123.20, 123.08 (C_{quat}), 122.25, 121.71 (C_{quat}), 117.15 (C_{quat}), 115.15, 112.41, 26.32, 16.53, 16.04, 14.34, 12.96.

IR (neat, cm^{-1}): U: 3495, 3369, 3325, 3057, 2971, 2924, 2865, 1739, 1670, 1589, 1559, 1489, 1464, 1441, 1402, 1354, 1284, 1235, 1204, 1130, 1095, 1078, 1041, 1012, 929, 815, 765, 740, 671.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{24}H_{23}NO_2S]^{\bullet+}$: 389.1449, found: 389.1438.

3cg : 10-(5-chloro-2-hydroxyphenyl)-10H-phenothiazine-2-carbonitrile



Chemical Formula: $C_{19}H_{11}ClN_2OS$
Exact Mass: 350.0281
Molecular Weight: 350.8214
m/z: 350.0281 (100.0%), 352.0251 (32.0%), 351.0314 (20.5%), 353.0285 (6.6%), 352.0239 (4.5%), 352.0348 (2.0%), 354.0209 (1.4%)
Elemental Analysis: C, 65.05; H, 3.16; Cl, 10.11; N, 7.99; O, 4.56; S, 9.14

3cg (JRW-291): Synthesized by 2-(cyano)-10H-phenothiazine (1.0 mmol, 224 mg) and 4-chlorophenol (3.0 mmol, 386 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 80% (scarlet powder).

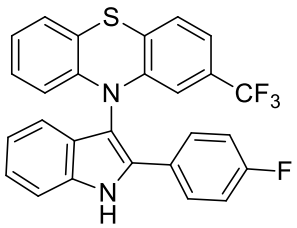
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.47 (s, 1H), 7.49 (dd, ^{3}J = 8.8 Hz, J = 2.6 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.26 (dd, ^{3}J = 7.9 Hz, J = 1.6 Hz, 1H), 7.21 (d, ^{3}J = 7.9 Hz, 1H), 7.20 (d, ^{3}J = 8.8 Hz, 1H), 7.03 (dd, ^{3}J = 7.5 Hz, J = 1.3 Hz, 1H), 6.96 (td, ^{3}J = 7.4 Hz, J = 1.5 Hz, 1H), 6.87 (td, ^{3}J = 7.5 Hz, J = 1.2 Hz, 1H), 6.18 (d, J = 1.3 Hz, 1H), 6.04 (dd, ^{3}J = 8.2 Hz, J = 1 Hz, 1H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 154.49 (C_{quat}), 142.80 (C_{quat}), 141.27 (C_{quat}), 130.87, 128.03, 127.29, 126.52 (C_{quat}), 126.48, 126.22 (C_{quat}), 126.08, 123.80, 123.33 (C_{quat}), 119.09, 118.63 (C_{quat}), 117.24 (C_{quat}), 116.69, 115.69, 109.58 (C_{quat}). One CH line is overlapped.

IR (neat, cm^{-1}): U: 3298, 3068, 2927, 2952, 2228, 1738, 1588, 1552, 1489, 1464, 1440, 1397, 1301, 1231, 1211, 1177, 1117, 1090, 1043, 987, 949, 867, 817, 744, 713, 676.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{19}H_{11}ClN_2OS]^{\bullet+}$: 350.0281, found: 350.0273.

3aj : 10-(2-(4-fluorophenyl)-1H-indol-3-yl)-2-(trifluoromethyl)-10H-pheno- thiazine



Chemical Formula: $C_{27}H_{16}F_4N_2S$
Exact Mass: 476,0970
Molecular Weight: 476,4880
m/z: 476.0970 (100.0%), 477.1004 (29.2%), 478.0928 (4.5%), 478.1037 (4.1%), 479.0962 (1.3%)
Elemental Analysis: C, 68.06; H, 3.38; F, 15.95; N, 5.88; S, 6.73

3aj (JRW-278): Synthesized by 2-(trifluoromethyl)-10H-phenothiazine (1.0 mmol, 267 mg) and 2-(4-fluorophenyl)-1H-indole (3.0 mmol, 633 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 17/3. Isolated yield: 68% (oyster white powder).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.06 (s, 1H), 7.93-7.90 (m, 2H), 7.60 (d, ^{3}J = 8.2 Hz, 1H), 7.36-7.27 (m, 5H), 7.18-7.08 (m, 3H), 6.90 (m, 2H), 6.46 (d, J = 1.4 Hz, 1H), 6.28 (m, 1H).

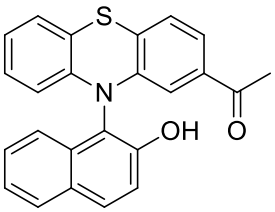
^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 161.88 (d, ^{1}J = 248.2 Hz, C_{quat}), 143.94 (s, C_{quat}), 142.56 (C_{quat}), 135.02 (s, C_{quat}), 132.40 (s, C_{quat}), 128.34 (d, ^{3}J = 8.8 Hz, CH), 128.06 (s, CH), 127.94 (q, ^{2}J = 31.9 Hz, C_{quat}), 127.52 (s, CH), 126.85 (s, CH), 126.79 (d, ^{4}J = 3.7 Hz, C_{quat}), 125.48 (s, C_{quat}), 125.02 (s, C_{quat}), 123.66 (q, ^{1}J = 273.2 Hz, C_{quat}), 123.59 (s, CH), 123.07 (s, CH), 120.60 (s, CH), 119.31 (q, ^{3}J = 4.4 Hz, CH), 118.67 (s, C_{quat}), 117.64 (s, CH), 116.22 (d, ^{2}J = 21.4 Hz, CH), 116.06 (s, CH), 112.61 (s, CH), 111.41 (s, C_{quat}), 111.02 (q, ^{3}J = 3.7 Hz, CH).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.79 (s, CF_3), -112.42.

IR (neat, cm^{-1}): U: 3409, 3059, 2971, 2954, 2926, 1738, 1602, 1567, 1507, 1490, 1467, 1411, 1324, 1234, 1159, 1117, 1092, 1079, 1040, 953, 871, 834, 816, 741, 717, 655.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{27}H_{16}F_4N_2S]^{\bullet+}$: 476.0970, found: 476.0988.

3bk: 1-(10-(2-hydroxynaphthalen-1-yl)-10H-phenothiazin-2-yl)ethanone



Chemical Formula: $C_{24}H_{17}NO_2S$
Exact Mass: 383,0980
Molecular Weight: 383,4623
m/z: 383.0980 (100.0%), 384.1014 (26.0%), 385.0938 (4.5%), 385.1047 (3.2%), 386.0972 (1.2%)
Elemental Analysis: C, 75.17; H, 4.47; N, 3.65; O, 8.34; S, 8.36

3bk (JRW-328): Synthesized by 2-(acetyl)-10H-phenothiazine (1.0 mmol, 241 mg) and 2-naphthol (3.0 mmol, 432 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 84% (flash yellow powder).

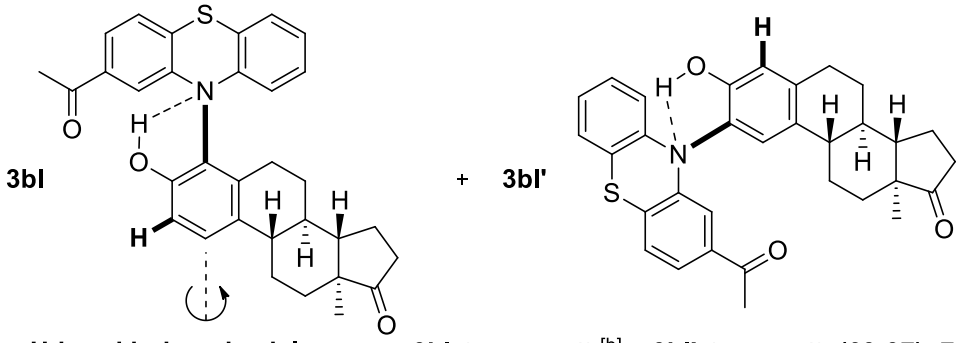
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.50 (s, 1H), 8.07 (d, ^{3}J = 8.9 Hz, 1H), 7.99 (d, ^{3}J = 7.9 Hz, 1H), 7.98 (d, ^{3}J = 8.0 Hz, 1H), 7.51 (d, ^{3}J = 9.0 Hz, 1H), 7.50 (td, ^{3}J = 7.7 Hz, J = 1.1 Hz, 1H), 7.46 (dd, ^{3}J = 7.9 Hz, J = 1.8 Hz, 1H), 7.40 (td, ^{3}J = 7.4 Hz, J = 1.0 Hz, 1H), 7.21 (d, ^{3}J = 7.9 Hz, 1H), 7.08 (m, 1H), 6.85 (m, 2H), 6.55 (d, J = 1.6 Hz, 1H), 6.02 (m, 1H), 2.33 (s, CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 196.59 (C_{quat}), 153.85 (C_{quat}), 142.15 (C_{quat}), 141.50 (C_{quat}), 135.87 (C_{quat}), 131.32 (C_{quat}), 130.61, 129.16 (C_{quat}), 128.56, 127.82, 127.77, 126.36, 126.21, 126.18 (C_{quat}), 123.61, 123.51, 122.71, 120.65, 118.95, 117.83 (C_{quat}), 117.35 (C_{quat}), 115.51, 112.90, 26.26.

IR (neat, cm^{-1}): U: 3300, 3060, 2972, 1738, 1660, 1590, 1556, 1510, 1465, 1439, 1404, 1374, 1355, 1299, 1280, 1260, 1236, 1218, 1161, 1129, 1102, 1041, 969, 936, 883, 812, 741.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{24}H_{17}NO_2S]^{\bullet+}$: 383.0980, found: 383.0972.

3bl + 3bl' :



H-bond induced axial C-N chirality

3bl *(de = 15%)* [b] + **3bl'** *(de = 0%),* **(63:37): 74%**
axial chirality along C-N bond due to O-H-N H-bond

Chemical Formula: $C_{32}H_{31}NO_3S$
Exact Mass: 509,2025
Molecular Weight: 509,6584
m/z: 509.2025 (100.0%), 510.2058 (34.6%), 511.2092 (5.8%), 511.1983 (4.5%), 512.2016 (1.6%)
Elemental Analysis: C, 75.41; H, 6.13; N, 2.75; O, 9.42; S, 6.29

3bl + 3bl' (JRW-299): Synthesized by 2-(acetyl)-10H-phenothiazine (1.0 mmol, 241 mg) and estrone (3.0 mmol, 810 mg) in dichloromethane (2.5 ml) and AcOH (0.5 ml) under 40 °C in the open air. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 17/3. Isolated yield: 74% (4 isomers, orange powder).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.74 (s, OH of maj dia of 3bl), 9.73 (s, OH of one dia of 3bl'), 9.72 (s, OH of other dia of 3bl'), 9.03 (s, OH of min dia of 3bl), 7.46-6.78 (aromatic area), 6.65 (broad s), 6.59 (d, J = 1.6 Hz), 6.55 (d, J = 1.5 Hz), 6.52 (dd, ^3J = 8.4 Hz, J = 2.4 Hz), 6.46 (d, J = 2.4 Hz), 6.05 (d, ^3J = 8.0 Hz), 5.99 (dd, ^3J = 8.3 Hz, J = 1.0 Hz), 2.95-1.15 (aliphatic area), 0.83 (s, CH_3 of major isomer 3bl), 0.81 (s, CH_3 of minor isomer 3bl').

Integration of previous ^{1}H NMR spectrum: All 4 OH (9.78 to 8.97) normalized at 1, the normal aromatic area (7.55-6.71) integrates for 7H, the "shifted aromatic area" corresponding to the phenothiazine *ortho* Hydrogen atoms (with respect to N) integrating for 2H, the aliphatic area (minus residual signal for DMSO-d6) integrating for ~18H, and the two signals at 0.83 and 0.81 integrating together for 3H (acetyl).

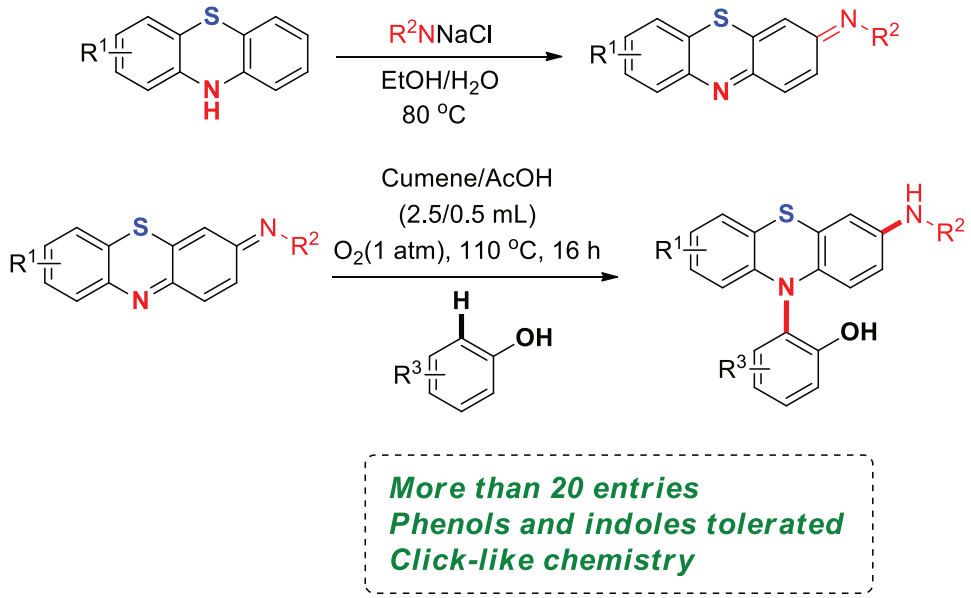
^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 219.69, 219.59, 196.89, 196.79, 196.70, 154.98, 153.50, 153.47, 153.00, 143.10, 142.61, 141.72, 141.65, 141.16, 140.94, 138.59, 137.31, 137.08, 135.88, 135.76, 135.69, 135.62, 132.55, 132.38, 129.87, 128.87, 128.18, 127.89, 127.80, 127.66, 127.36, 126.80, 126.20, 126.08, 126.05, 125.85, 125.28, 123.99,

123.78, 123.36, 123.30, 122.57, 122.39, 117.65, 117.52, 116.87, 115.81, 115.18, 114.92, 113.95, 113.16, 112.76, 112.63, 112.53, 49.55, 49.51, 49.44, 47.30, 47.25, 47.18, 43.42, 43.32, 37.92, 37.53, 37.18, 35.34, 35.26, 31.32, 31.26, 29.02, 28.84, 26.43, 26.37, 26.34, 26.11, 25.92, 25.52, 24.21, 21.10, 21.02, 13.53, 13.49.

IR (neat, cm^{-1}): U: 3415, 3239, 3019, 2971, 2926, 2865, 1737, 1678, 1589, 1501, 1466, 1440, 1404, 1374, 1301, 1230, 1218, 1162, 1129, 1100, 1055, 1041, 931, 873, 816, 786, 746, 665.

Elementary analysis: Theoretical: C: 75.41% H: 6.13% N: 2.75% O: 9.42% S: 6.29%
Found: C: 75.26% H: 6.47% N: 2.12% S: 5.10%

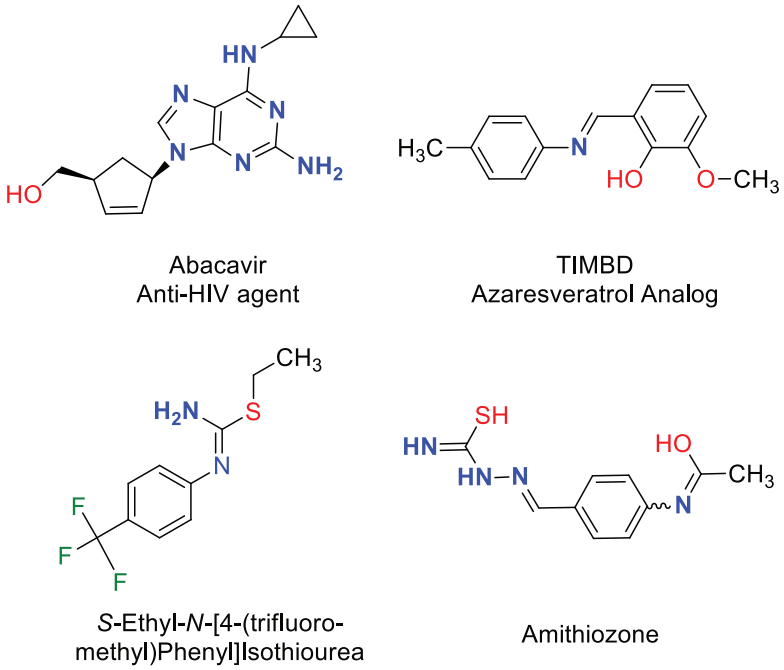
A New Class of Electrophilic Amination Reagents



*Part of this work has been published: "Reprinted with permission from Rongwei Jin, Christina L. Bub and Frederic W. Patureau, *Org. Lett.* **2018**, Article ASAP. (DOI: 10.1021/acs.orglett.8b00914) Copyright © 2018 American Chemical Society"

4.1 Introduction

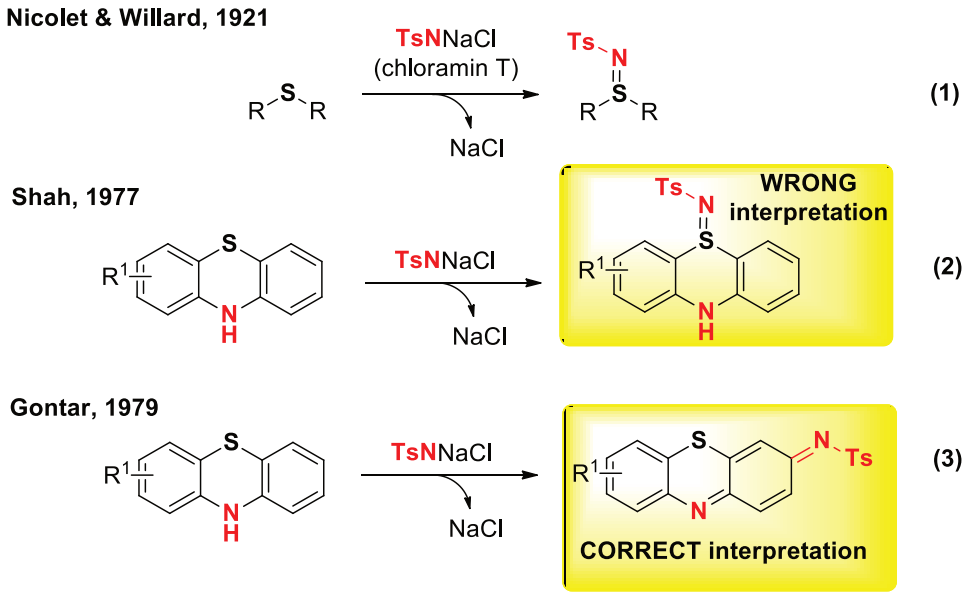
Imine was an important intermediate and substrate for organic synthesis, which was typically provided from the condensation of primary amine with aldehyde or less commonly ketone. In 1962, Layer demonstrated the similarity between the chemistry of imines and aldehydes , ketones.[1] Meanwhile, he pointed out that imines were somewhat unique. Moreover, imine derivatives were widely applied in pharmacy and industry, such as Abavavir, TIMBD, S-Ethyl-N-[4-(trifluoromethyl)Phenyl]Isothiourea and Amithiozone (Scheme 1).[2]



Scheme 1. Selected examples of bioactive imine derivatives

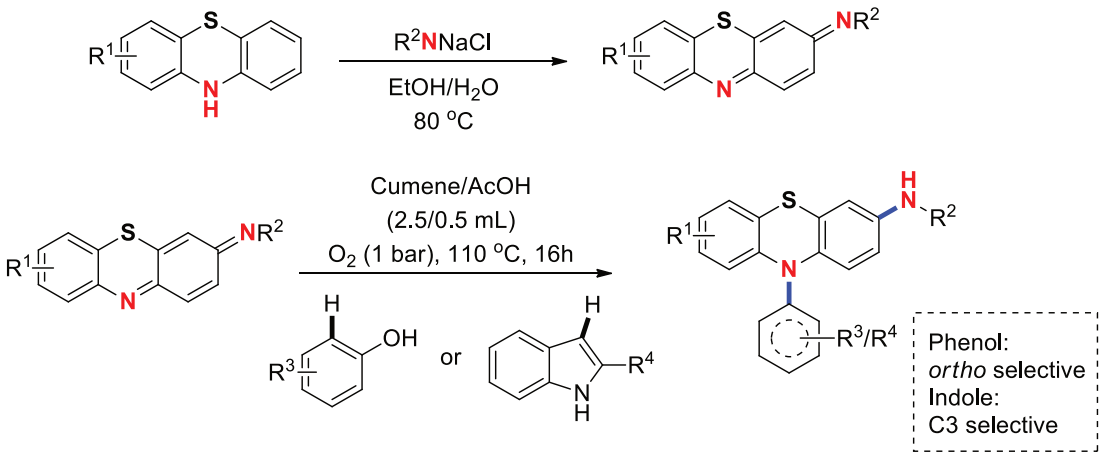
However, phenothiazinimines were rarely showed in the common *N*-containing biomolecular applications. As a barely known class of imines, they were prepared and detected to be particularly reactive as electrophilic aimiantion reagents for ubiquitous phenols and analogous substrates. In 1921, Nicolet and Willard successfully operated the condensation reaction of chloramine T with thioethers, which opened a novel avenue for the sulfonimines delivery.[3] With the simplified condition, such general method is still utilized to prepare sulfonimines in a single step nowadays.[4] Furthermore, Shah took this method and synthesized what he thought to be sulfonimine-phenothiazines.[5] Shah's claim lies solely on an IR band at 920 cm^{-1}, which he marked as the sulfonimine S=N double bond. In 1979 however, Gontar retried the reaction and predicted another structure of the same substrate. He claimed that the missing NH bond in the IR spectrum defeated the wrong one which Shah predicted before.[6] Gontar

proposed instead a carbon-based phenothiazinimine interpretation (Scheme 2). As far as we know, most of those compounds were theoretically insoluble, and the broadness of the NMR lines forbade a decisive interpretation as to the one or the orther structure, or possibly a mixture thereof.



Scheme 2. Sulfonimines and Phenothiazinimines

While developing the synthetic methodology of phenothiazines, our efforts and those of other famous groups began to focus on amination reactions of phenothiazinimines with nucleophiles as phenols or indoles. In this chapter, the reactivity of those amination reagents was clearly described for the first time, and thereby allowed to lift this structural ambiguity in favor of Gontar's interpretation. This amination reaction was still designed under mild and metal-free conditions (Scheme 3).



Scheme 3. Selective *N*-amination of phenothiazinimines with phenols and indoles

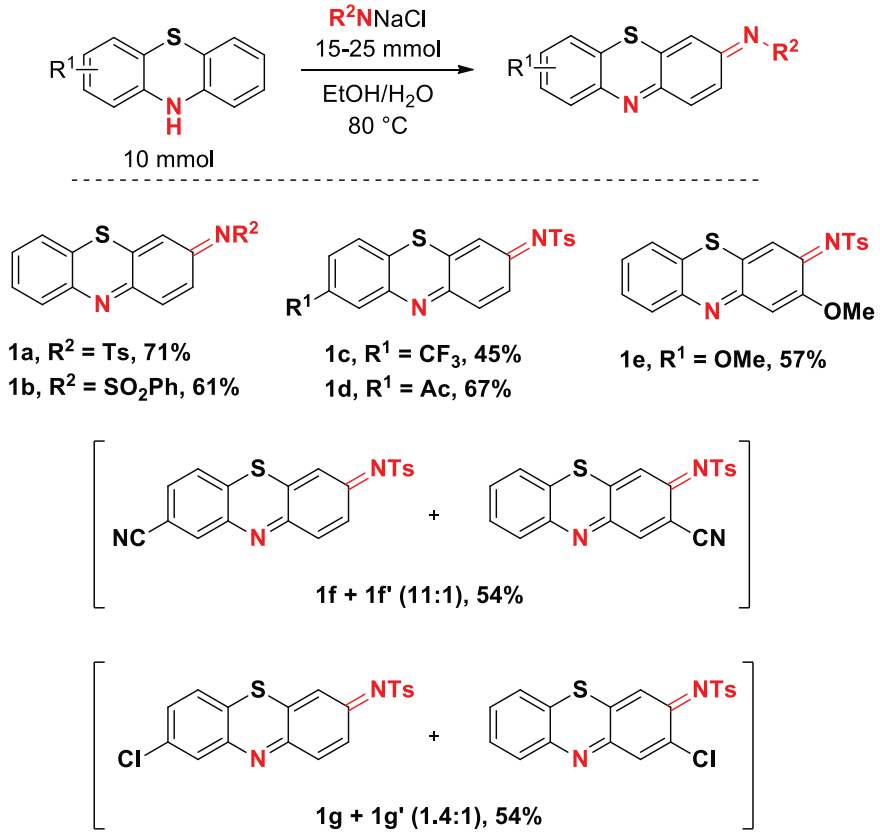
Those designed reaction had simple conditions, readily available starting materials, reagents and achieved high atom economy which fit the concept of click chemistry.[7] "Linkages of the type C-X-C are much easier to make than direct C-C linkages. So why not focus on them?", herein we will describe an efficient amination method to further elaborate the advantages of click chemistry.

4.2 Results and discussion

In the frame of our study on the development of ultra-simple direct C-H amination methods, we started to investigate the unexplored reactivity of the phenothiazinimines, in particular as electrophilic amination reagents.[8] The whole procedure was separated in two steps: 1) Synthesis of phenothiazinimines with Shah's protocol; 2) Amination of phenols with the synthesized *N*-reagents. For the latter C-N bond formation reaction, we optimized the metal-free cumene/O_2 conditions with respect to the modern amination methods and our previous manner with phenothiazines (See chapter II).[9]

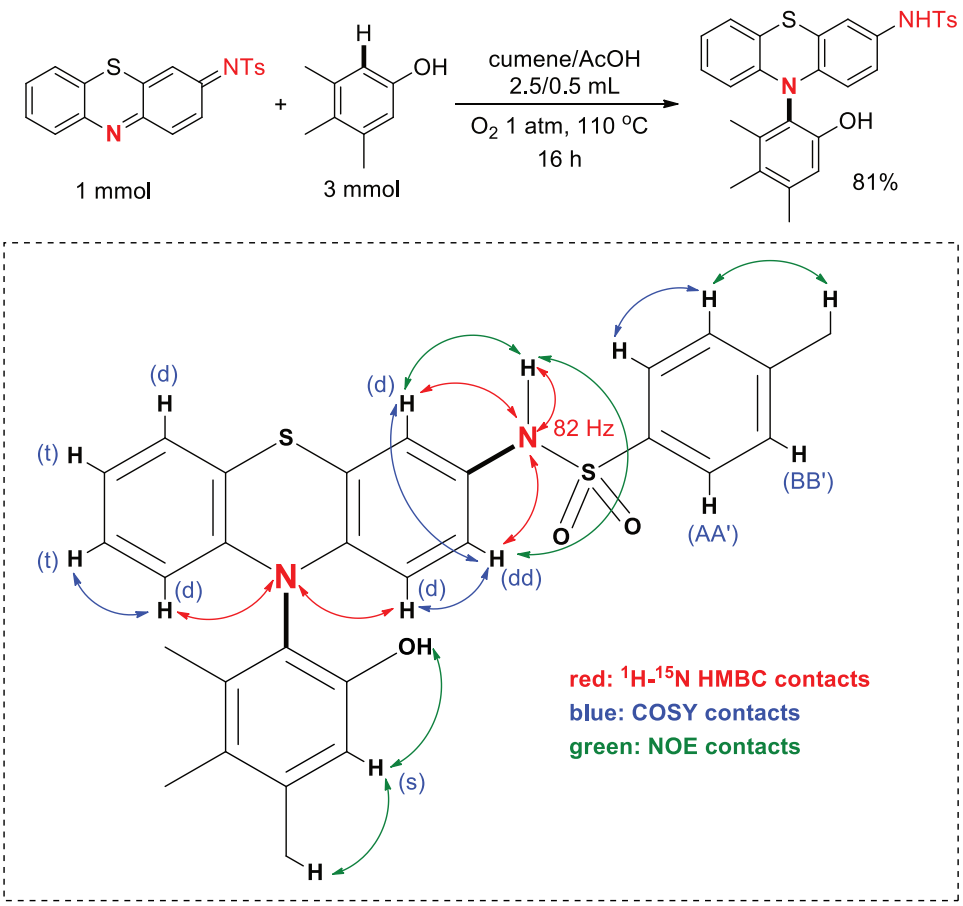
4.2.1 Optimization

Initially, we started to synthesize the phenothiazimines with a series of phenothiazines (PTZs) and chloramine derivatives. As expected, in the case of unsymmetrical PTZs, the imine was formed preferentially on the more electron-rich side. To our delight, the region-selectivity was typically good and the tolerance of function groups were also satisfied in most cases (Scheme 4).



Scheme 4. Scope of phenothiazinimines, chloramine reagents: 1.5-2.5 equiv., all the substrates are isolated by precipitation as deep purple and poorly soluble substances

After the imine reagents were prepared, we devoted them into an ultra-simple condensation technique with phenol coupling partners. The initial reaction conditions we choose were the metal-free cumene/O_2 procedure for phenothiazines and phenols.[10] However, a good conversion was obtained but the designed substrate was formed in a low yield. Hence, we decreased the temperature from 150 ^{o}C to 110 ^{o}C to prevent decomposition of those electrophilic imines and keep the reactivity of the reaction. Besides, we shortened the time from 24 h to 16 h as the same purpose. The finally determined conditions were described as follows: phenothiazinimine (1 mmol) and phenol (3.0 mmol) were typically placed in a screw-cap vessel, the cumene (2.5 mL) and acetic acid (0.5 mL) were then added, the reactor flushed with fresh O_2 about 1 min and transferred it into the oil bath, kept stirring at 110 ^{o}C for 16 h. During the first hours of the reaction, the dark purple to black suspension particularly and progressively turned to a lucid light blue or pink solution. Encouragingly, in the presence of phenothiazinimine and 3,4,5-trimethylphenol reagents, a new product was formed, which was fortunately more soluble and which we solved by a combination of COSY,

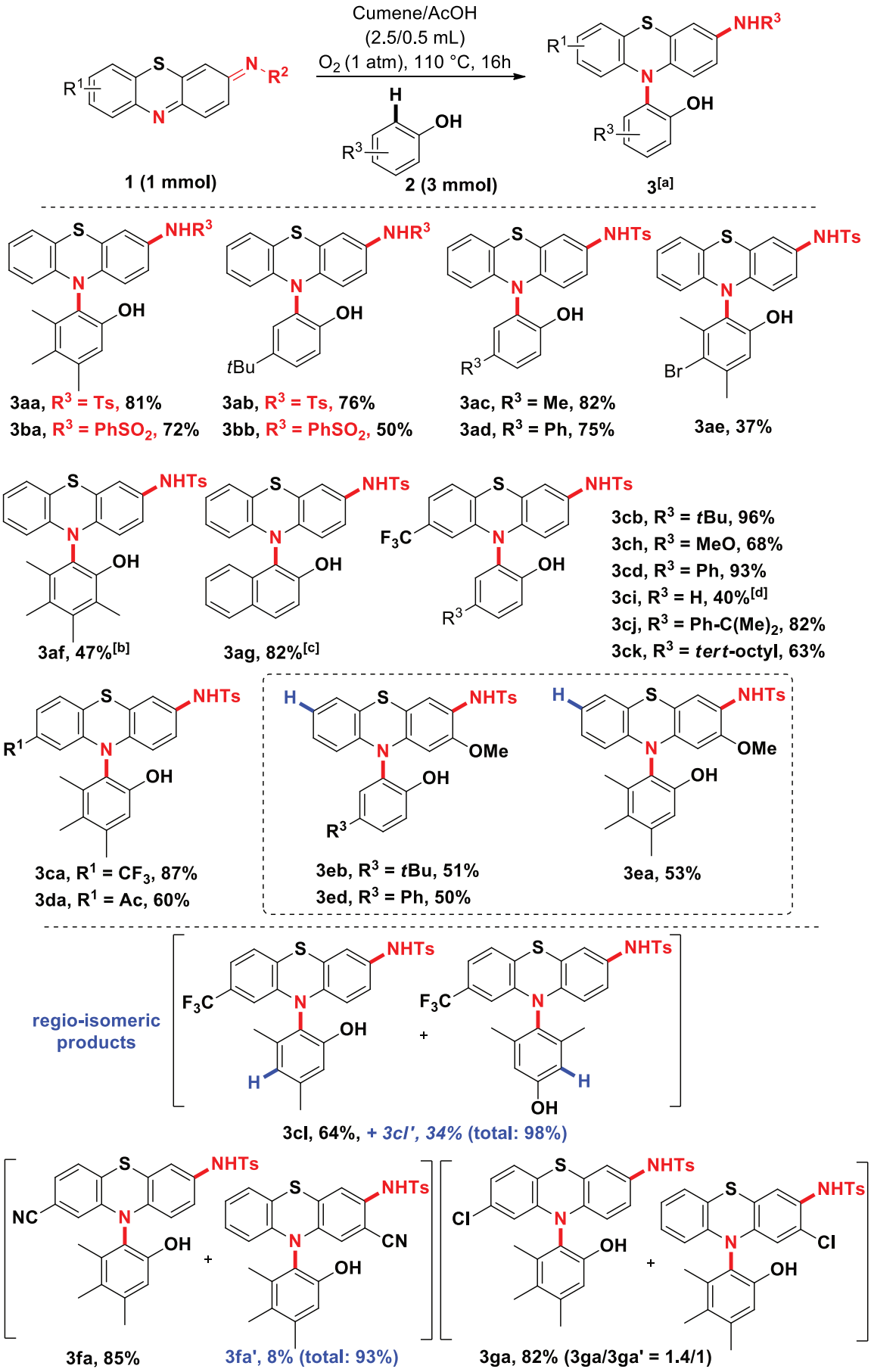


Scheme 5. Optimized conditions and COSY, NOESY, and ^{1}H-^{15}N HMBC NMR structural resolution

NOESY, and natural abundance ^{1}H-^{15}N HMBC NMR characterization techniques (Scheme 5).[11] Unfortunately, crystallization attempts had failed to achieve so far.

4.2.2 Scope and challenge of the reaction

After confirming the structure of the new product, we then explored the substrate scope of the reaction. Gratifyingly, many phenols and phenothiazinimines were involved, varieties of functional groups on phenols were tolerated, such as alkyls, ketones, nitriles, CF_3, methoxys and halides. Alternatively, chloramine B could form the special imine with phenothiazines too and conduct the amination reaction with phenols in moderate yields (Scheme 6, **3ba**, **3bb**). Besides, the electron-rich phenols (**3aa**, **3ac**, and **3cj**) provided good yields as usual and the halo-phenol (**3ae**) showed less reactivity. To our delight, the non-functionalized phenol (**3ci**) was tolerated and gave a low yield of 40%, despite the failed purification of the minor isomer.

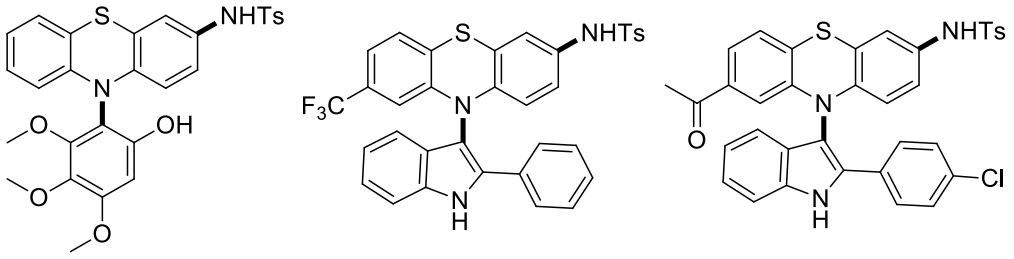


Scheme 6. Scope of imines and phenols [a] isolated yields, [b] 0.5 mmol scale, [c] 90 °C

reaction temperature, [d] very minor *para* isomer lost during purification, see also entry **3cl** for *ortho/para* relative reactivity/selectivity

Indeed, we obtained that the 3,5-dimethylphenol in coupling with phenothiazinimine induced a significant 2:1 regioisomeric ratio for the products **3cl** and **3cl'** in favor of the kinetic C2 position. Besides, the cyano- and chloro-phenothiazinimine performed the amination reaction very well with each two isomers. The regioisomeric ratio of the products between **3fa**(**3ga**) and **3fa'**(**3ga'**) was quite similar for the mixed phenothiazinimine reagents.

Furthermore, parts of interesting phenols and indoles were also investigated and furnished with those imines. Representatively, the 3,4,5-trimethoxylphenol (**3am**) smoothly conducted the amination reaction and gave the coupling product in a moderate yield of 44%. As expected, the indole reacted with phenothiazinimines and provided accepted to excellent yields of the designed C3-aminated products (Scheme 7, **3cn** and **3do**).



3am, 44% **3cn**, 90% **3do**, 30%[a]

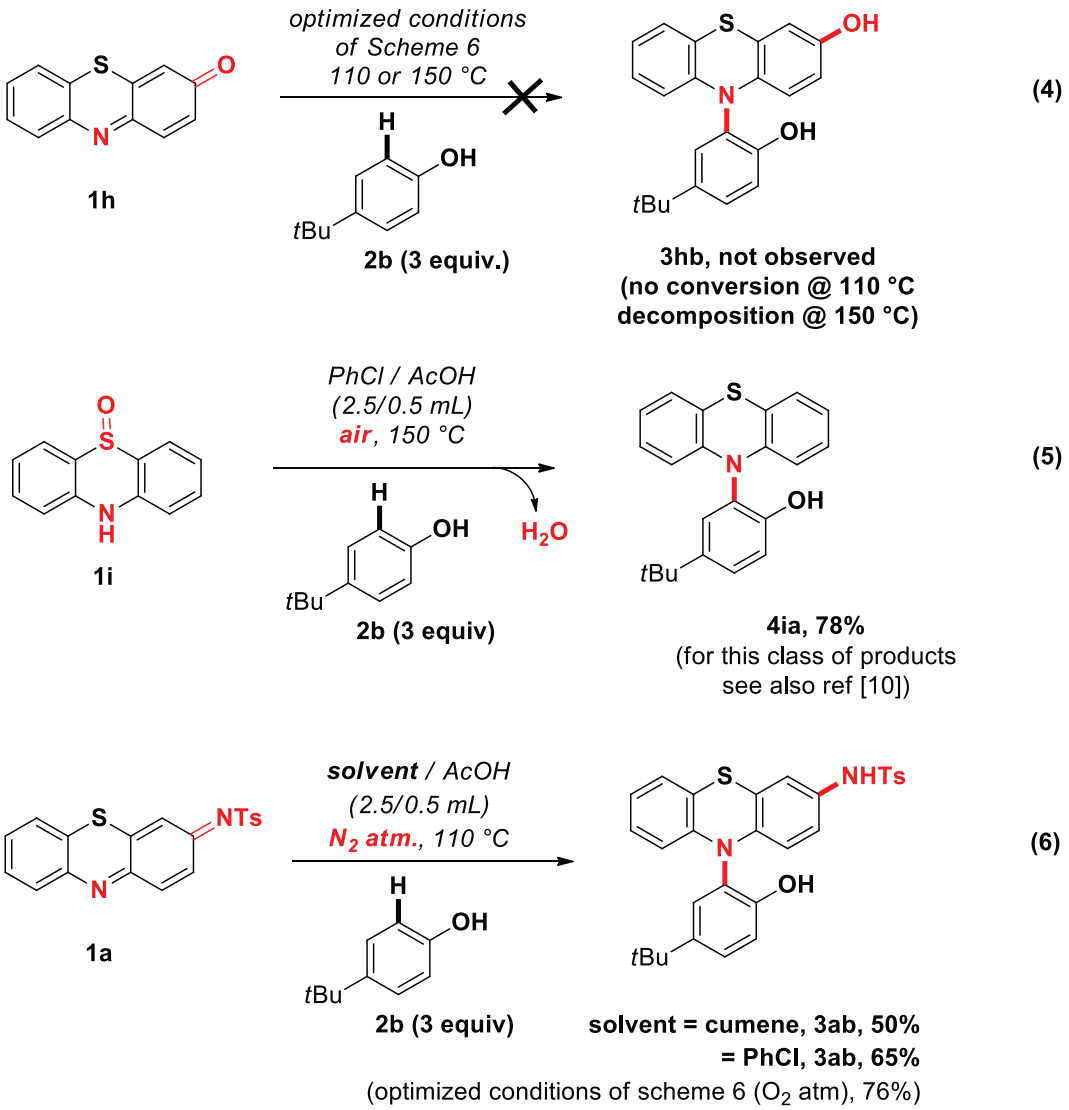
Scheme 7. Extended scope [a] ^{1}H NMR yield

4.2.3 Mechanistic studies and discussion

4.2.3.1 Mechanistic experiments and results

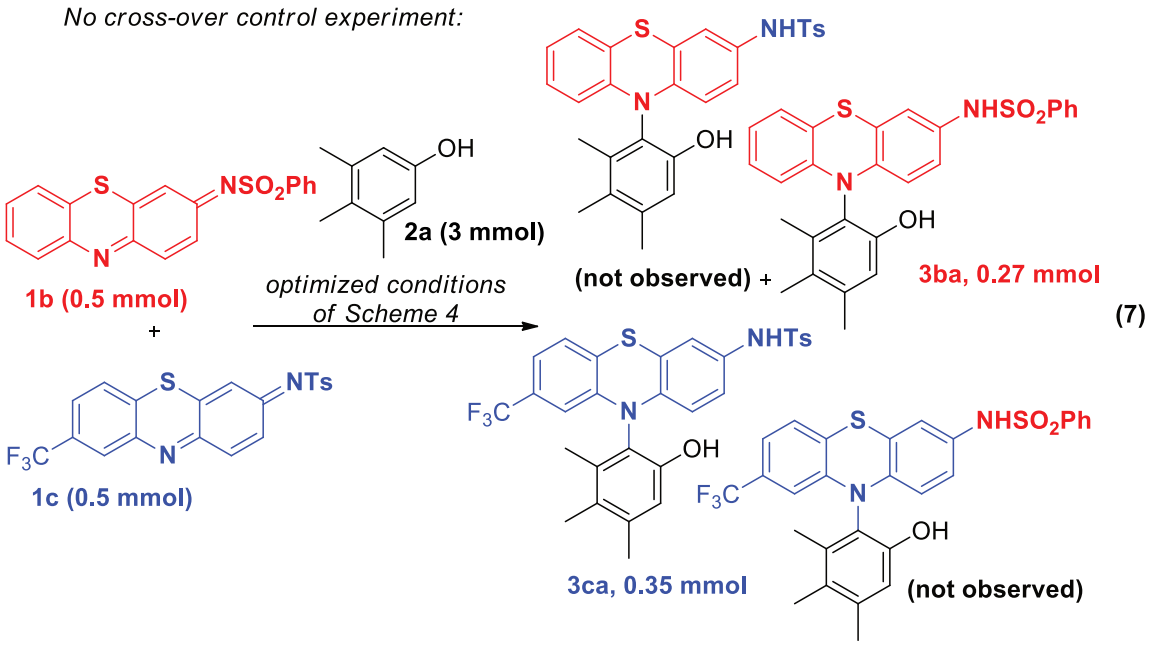
The broad scope indicated that those pre-synthesized phenothiazinimines were typically reactive. In order to gain an insight into the reaction mechanism, series of essential mechanistic experiments were performed. Based on the previous research of the amination pathways of phenothiazine and phenols, we prepared some interesting intermediates and then conducted experiments with phenol to reveal the plausible explanation of this amination reaction.

The first compound we synthesized was phenothiazine **1h** which was found in the literature.[12] The corresponding condensation product **3hb** could not be detected. Indeed, the reagents were recycled at 110 ^{o}C but they decomposed significantly at 150 ^{o}C (Eq. 4, Scheme 8).



Scheme 8. Mechanistic experiments

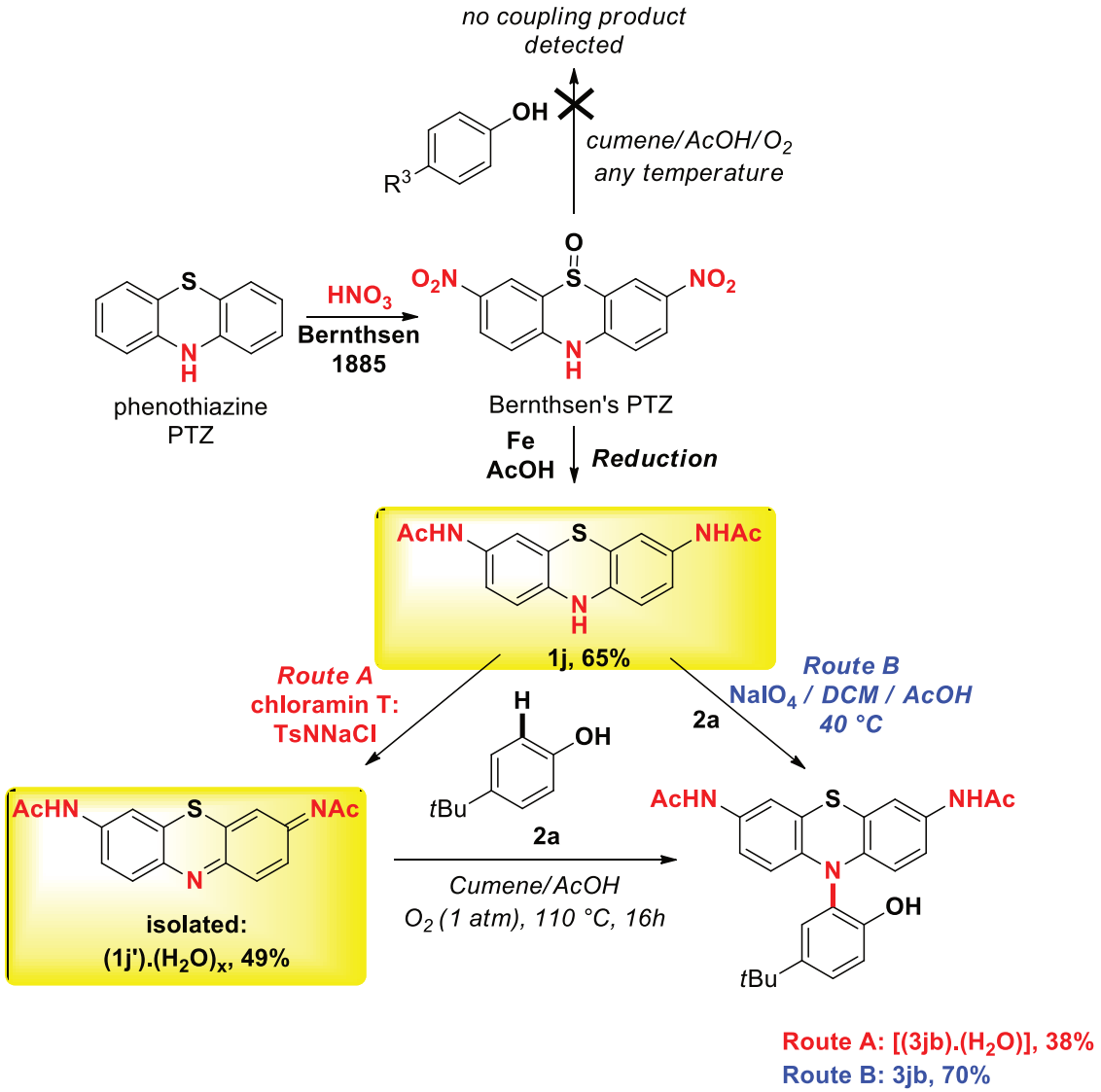
Then we prepared the parent S-oxide phenothiazine substrate **1i**, as an alternative compound.[13] In contrast, it typically performed the known C-N coupling product **4ia** in which the oxygen atom is not retained (H_2O as leaving group, internal oxidant concept, Eq. 5).[14,15] To investigate the internal oxidant character of phenothiazinimines, we then conducted the further control experiments (Eq. 6) in which showed that the reaction undergoes smoothly in a strict N_2 atmosphere condition, albeit with lower yields (50% in cumene and 65% in chlorobenzene). This reaction explained the reactivity of phenothiazinimines and an external oxidant was recommended to improve the conversion.



Scheme 9. Cross over control experiment

In addition, a cross over control experiment between **1b** and **1c**, based on two different PTZ backbones and two different chloramines, was performed (Eq. 7). Out of our predicted four potential products, only two non-crossed products **3ba** and **3ca** were obtained. Thus, there was no imine cross-over event occurs in this amination reaction, which arguably constitutes another argument against Shah's proposed structure but in favor of Gontar's. What's more, Shah's substrate would have involved a 1,4 nitrene sulfur-to-carbon migration, a relatively long distance migration which might therefore have been subject to cross-over scrambling.

In order to better apprehend and further confirm to Gontar phenothiazinimine structural interpretation, we envisioned a different synthetic route. We then tried to synthesize the Bernthsen's PTZ, which was known since 1885 and prepared by nitration of non-functionalized PTZ.[16] Unfortunately, we were so far unsuccessful at utilizing Bernthsen's PTZ as an effective electrophilic reagent of any kind. With a further reduction in the presence of Fe^0 and acetic acid, it afforded the corresponding bis-acetamidophenothiazine **1j** (Scheme 10). This phenothiazine could conduct with phenol under the periodate method to provide the designed aminated product **3jb** in 73%. Alternatively, it could also be oxidized with chloramine T to the corresponding acetylated phenothiazinimine **1j'**, and this compound was found to be a competent electrophilic amination reagent, albeit with moderate yield (**3jb**, 35%). Notably, the tosylonitrene moiety does not insert into the imine, and functions solely as an external oxidant.



Scheme 10. Control experiments of Bernthsen's PTZ

4.2.3.2 Discussion

According these control experiments above, we realized that the mechanism of this amination reaction might be theoretically complicated. The Bernthsen's PTZ could not undergo the pathway in the presence of cumene/AcOH/O_2 conditions which suggested that there was no radical intermediate formed during the whole reaction. In contrast, the reductive substrate **1j**, which either could be oxidized with chloramine T to the phenothiazinimine **1j'** and then did the amination step with phenol in radical cumene system, but also could provide the same amination product in one step with the strong oxidant such $NaIO_4$.[17] Further effort will focus on the mechanism research.

4.3 Conclusion and perspective

In summary, we solved the historical disputed structural assignment of phenothiazinimines and validated Gontar's proposal as the dominant species, in which the sulfur atom remains surprisingly un-oxidized. Except for phenothiazines, we discovered that phenothiazin-imine was an alternative and excellent electrophilic amination reagent towards phenol. We expected these novel reactive substrates to impact the field of phenothiazine relied material synthesis.[18] Meanwhile, we expected this C-N bond formation method to consolidate the intermolecular metal-free C-H oxidative amination toolbox. Finally, the overall redox neutral character of the C-N coupling reaction, allowing full atom efficiency, together with the catalyst free character, might perhaps made it a future candidate for click-like tethering technology.

In the near future, we will try to discover more elements of the reaction mechanism and enlarge the scope more than phenols and indoles. In the other side, we will keep trying some other simplified reaction conditions to get more close to the concept of click chemistry.

4.4 References

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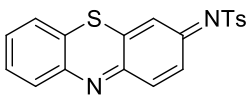
4.5 Experimental section

4.5.1 General Information

All reactions were carried out in dried reaction vessels with sealed Teflon screw caps under oxygen. NMR spectra were measured on a Bruker AMX 400 or on Bruker Avance 600 systems using $CDCl_3$ or $(CD_3)_2SO$ as solvents, with proton and carbon resonances at 400/600 MHz and 101/151 MHz, respectively. Coupling constants (*J*) are quoted in Hz. Flash chromatography was performed on silica gel (40-63 mesh) by standard technique. Substrates were purchased either from Sigma Aldrich, Alfa Aesar, TCI, or ABCR. HRMS data were determined on a WATERS GCT-Premier^{TM} mass spectrometer. The latter equipment was utilized for the HRMS characterization of about half of all entries. The other compounds, generally too polar and/or too poorly soluble, were characterized instead by Elementary Analysis.

4.5.2 Substrate synthesis

The phenothiazinimines were prepared according to the protocol of Shah.[S1] Typically, a 250 mL open flask is filled with phenothiazine (20.0 mmol), chloramine (30.0 mmol), ethanol (30 mL), distilled water (30.0 mL) and a magnetic stirring bar. All the steps were operated in open air and the flask is then heated up to 80 °C, and thereafter immediately cooled down to room temperature. After a filtration of the crude product, the precipitate is then washed by more than 500 mL hot water (90 °C). The precipitate is thereafter submitted to methanol (200 mL), heated up to 70 °C and cooled again to room temperature. The precipitate is then filtrated again and washed twice with fresh methanol. The product is then collected and dried. None of the following phenothiazinimine is soluble enough for intelligible NMR.



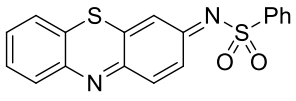
Chemical Formula: $C_{19}H_{14}N_2O_2S_2$
Exact Mass: 366.0497
Molecular Weight: 366.4567
m/z: 366.0497 (100.0%), 367.0530 (20.5%), 368.0455 (9.0%), 368.0564 (2.0%), 369.0488 (1.9%), 367.0491 (1.6%)
Elemental Analysis: C, 62.27; H, 3.85; N, 7.64; O, 8.73; S, 17.50

1a (FWP-922): According to the above mentioned procedure. Isolated yield: 71% (dark violet powder).

IR (neat, cm^{-1}): ν: 1616, 1587, 1554, 1517, 1494, 1466, 1434, 1356, 1282, 1241, 1143, 1117, 1077, 1037, 1017, 951, 918, 885, 853, 836, 820, 809, 764, 747, 719, 694, 680.

Elemental analysis theoretical : N 7.64%, C 62.27%, H 3.85%, S 17.50%.

Found : N 7.56%, C 62.73%, H 3.96%, S 17.47%.



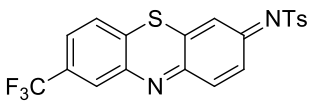
Chemical Formula: $C_{18}H_{12}N_2O_2S_2$
Exact Mass: 352.0340
Molecular Weight: 352.4301
m/z: 352.0340 (100.0%), 353.0374 (19.5%), 354.0298 (9.0%), 354.0407 (1.8%), 355.0332 (1.8%), 353.0334 (1.6%)
Elemental Analysis: C, 61.34; H, 3.43; N, 7.95; O, 9.08; S, 18.20

1b (JRW-487): According to the above mentioned procedure (with 50 mmol chloramine B). Isolated yield: 61% (dark black powder).

IR (neat, cm^{-1}): ν: 3056, 2229, 1614, 1587, 1553, 1518, 1505, 1462, 1433, 1413, 1361, 1296, 1283, 1243, 1145, 1120, 1077, 1035, 919, 887, 877, 836, 823, 774, 752, 716, 689, 672.

Elemental analysis theoretical : N 7.95%, C 61.34%, H 3.43%, S 18.20%.

Found : N 7.74%, C 61.82%, H 3.63%, S 18.02%.



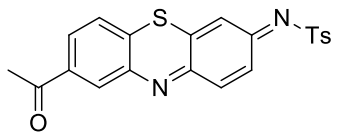
Chemical Formula: $C_{20}H_{13}F_3N_2O_2S_2$
Exact Mass: 434.0371
Molecular Weight: 434.4546
m/z: 434.0371 (100.0%), 435.0404 (21.6%), 436.0328 (9.0%), 436.0438 (2.2%), 437.0362 (2.0%), 435.0364 (1.6%)
Elemental Analysis: C, 55.29; H, 3.02; F, 13.12; N, 6.45; O, 7.37; S, 14.76

1c (FWP-936): According to the above mentioned procedure (with 40 mmol chloramine T). Isolated yield: 60% (dark brown-purple powder).

IR (neat, cm^{-1}): ν: 3054, 1606, 1561, 1523, 1509, 1482, 1448, 1361, 1332, 1310, 1279, 1238, 1212, 1182, 1128, 1092, 1081, 1059, 1040, 969, 935, 923, 900, 840, 810, 778, 760, 725, 699, 687, 665.

Elemental analysis theoretical : N 6.45%, C 55.29%, H 3.02%, S 14.76%.

Found : N 7.74%, C 61.82%, H 3.15%, S 14.73%.



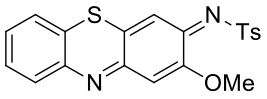
Chemical Formula: $C_{21}H_{16}N_2O_3S_2$
Exact Mass: 408.0602
Molecular Weight: 408.4933
m/z: 408.0602 (100.0%), 409.0636 (22.7%), 410.0560 (9.0%), 410.0669 (2.5%), 411.0594 (2.1%), 409.0596 (1.6%)
Elemental Analysis: C, 61.75; H, 3.95; N, 6.86; O, 11.75; S, 15.70

1d (CHB-185): According to the above mentioned procedure. Isolated yield: 67 % (dark brown solid).

IR (neat, cm^{-1}): ν: 2943, 1684, 1591, 1515, 1489, 1450, 1397, 1356, 1297, 1279, 1207, 1117, 1081, 1054, 1034, 919, 845, 831, 767, 736, 684.

Elemental analysis theoretical : N 6.86%, C 61.75%, H 3.95%, S 15.70%.

Found : N 6.44%, C 61.40%, H 4.15%, S 15.26%.



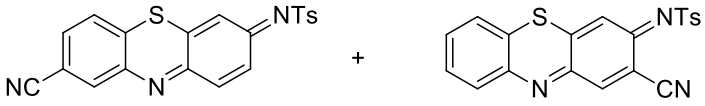
Chemical Formula: $C_{20}H_{16}N_2O_3S_2$
Exact Mass: 396.0602
Molecular Weight: 396.4826
m/z: 396.0602 (100.0%), 397.0636 (21.6%), 398.0560 (9.0%), 398.0669 (2.2%), 399.0594 (2.0%), 397.0596 (1.6%)
Elemental Analysis: C, 60.59; H, 4.07; N, 7.07; O, 12.11; S, 16.17

1e (CHB-180): According to the above mentioned procedure. Isolated yield: 57 % (deep purple solid).

IR (neat, cm^{-1}): ν: 3044, 2937, 1606, 1518, 1467, 1428, 1401, 1368, 1299, 1276, 1238, 1206, 1182, 1138, 1087, 1074, 1053, 996, 918, 851, 814, 755, 659, 682.

Elemental analysis theoretical : N 7.07%, C 60.59%, H 4.07%, S 16.17%.

Found : N 6.99%, C 61.04%, H 4.22%, S 16.08%.



1f +1f' (11:1)

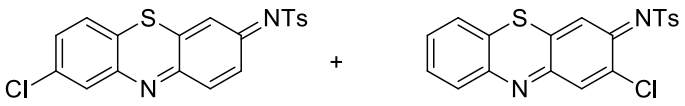
Chemical Formula: $C_{20}H_{13}N_3O_2S_2$
Exact Mass: 391.0449
Molecular Weight: 391.4661
m/z: 391.0449 (100.0%), 392.0483 (21.6%), 393.0407 (9.0%), 393.0516 (2.2%), 394.0441 (2.0%), 392.0443 (1.6%), 392.0420 (1.1%)
Elemental Analysis: C, 61.36; H, 3.35; N, 10.73; O, 8.17; S, 16.38

1f (JRW-484): According to the above mentioned procedure. Isolated yield: 54% (dark violet powder).

IR (neat, cm^{-1}): ν: 2229, 1614, 1592, 1550, 1516, 1469, 1441, 1361, 1280, 1244, 1141, 1074, 1037, 964, 914, 844, 810, 772, 742, 685, 673, 661.

Elemental analysis theoretical : N 10.73%, C 61.36%, H 3.35%, S 16.38%.

Found : N 10.82%, C 61.33%, H 3.46%, S 16.42%.



1g + 1g' (1.4:1)

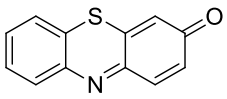
Chemical Formula: $C_{19}H_{13}ClN_2O_2S_2$
Exact Mass: 400.0107
Molecular Weight: 400.9017
m/z: 400.0107 (100.0%), 402.0077 (32.0%), 401.0141 (20.5%), 402.0065 (9.0%), 403.0111 (6.6%), 404.0035 (2.9%), 402.0174 (2.0%), 403.0098 (1.9%), 401.0101 (1.6%)
Elemental Analysis: C, 56.92; H, 3.27; Cl, 8.84; N, 6.99; O, 7.98; S, 16.00

1g (JRW-479): According to the above mentioned procedure. Isolated yield: 54% (dark black powder).

IR (neat, cm^{-1}): ν: 3068, 1597, 1547, 1527, 1436, 1434, 1385, 1354, 1285, 1250, 1232, 1213, 1139, 1122, 1080, 1036, 928, 908, 843, 817, 760, 722, 683, 670, 656.

Elemental analysis theoretical : N 6.99%, C 56.92%, H 3.27%, S 16.00%.

Found : N 6.79%, C 57.42%, H 3.35%, S 15.55%.



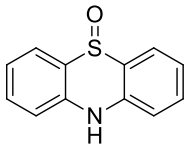
Chemical Formula: $C_{12}H_7NOS$
Exact Mass: 213.0248
Molecular Weight: 213.2551
m/z: 213.0248 (100.0%), 214.0282 (13.0%), 215.0206 (4.5%)
Elemental Analysis: C, 67.58; H, 3.31; N, 6.57; O, 7.50; S, 15.04

1h (CHB-120): This compound was previously described.[S2] The following analytical data is given in order to confirm the structure:

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.92 (m, 1H), 7.78 (m, 1H), 7.69 (~d, ^3J = 10.5 Hz, 1H), 7.60 (highly symmetrical multiplet comprising at least 11 lines, 1H), ~6.92 (~dd, ^3J = 10.5 Hz, ^4J = 2.3 Hz, 1H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 181.69 (s, C_{quat}), 146.07 (s, C_{quat}), 139.73 (s, CH), 138.44 (s, C_{quat}), 134.91 (s, CH), 133.42 (s, CH), 131.48 (s, CH), 128.28 (s, CH), 125.63 (s, CH), 123.23 (s, C_{quat}), 119.78 (s, CH). One Cquat line is overlapped.

IR (neat, cm^{-1}): ν: 3053, 2921, 2852, 1624, 1598, 1532, 1497, 1437, 1401, 1347, 1296, 1259, 1232, 1180, 1130, 1112, 1083, 1018, 983, 884, 814, 769, 758, 717, 691, 657.



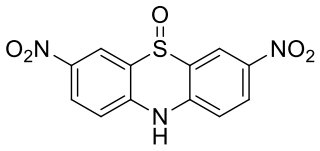
Chemical Formula: $C_{12}H_9NOS$
Exact Mass: 215.0405
Molecular Weight: 215.2710
m/z: 215.0405 (100.0%), 216.0438 (13.0%), 217.0363 (4.5%)
Elemental Analysis: C, 66.95; H, 4.21; N, 6.51; O, 7.43; S, 14.90

1i (CHB-87): This compound was previously described.[S3] The following analytical data is given in order to confirm the structure.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.96 (s, 1H), 7.90 (dd, ^3J = 7.8 Hz, ^4J = 1.3 Hz, 2H), 7.63-7.58 (m, 2H), 7.39 (dd, ^3J = 8.3 Hz, ^4J = 0.6 Hz, 2H), 7.21-7.17 (m, 2H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 136.85 (s, C_{quat}), 132.72 (s, CH), 131.16 (s, CH), 121.20 (s, CH), 120.84 (s, C_{quat}), 116.80 (s, CH).

IR (neat, cm^{-1}): ν: 3243, 3051, 1684, 1611, 1584, 1522, 1469, 1441, 1359, 1277, 1236, 1206, 1161, 1140, 1075, 1028, 970, 919, 891, 858, 799, 765, 739, 704, 682.



Chemical Formula: $C_{12}H_7N_3O_5S$
Exact Mass: 305.0106
Molecular Weight: 305.2661
m/z: 305.0106 (100.0%), 306.0140 (13.0%), 307.0064 (4.5%), 306.0077 (1.1%), 307.0149 (1.0%)
Elemental Analysis: C, 47.21; H, 2.31; N, 13.77; O, 26.21; S, 10.50

Bernthsen's PTZ (CHB-88): This compound was previously described.[S4] The following analytical data is given in order to confirm the structure.

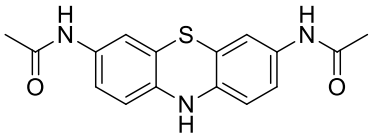
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.31 (s, 1H), 8.94 (d, ^4J = 2.5 Hz, 1H), 8.47 (dd, ^3J = 9.1 Hz, ^4J = 2.6 Hz, 2H), 7.58 (d, ^3J = 9.1 Hz, 2H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 141.67 (s, C_{quat}), 139.75 (s, C_{quat}), 128.15 (s, CH), 128.12 (s, CH), 121.43(s, C_{quat}), 118.75 (s, CH).

IR (neat, cm^{-1}): ν: 3270, 3075, 2625, 2456, 1947, 1616, 1595, 1581, 1505, 1474, 1317, 1279, 1233, 1120, 1035, 911, 899, 899, 835, 744, 721, 676.

Elemental analysis theoretical : N 13.77%, C 47.21%, H 2.31%, S 10.50%.

Found : N 13.76%, C 46.96%, H 2.50%, S 10.79%.



Chemical Formula: $C_{16}H_{15}N_3O_2S$
Exact Mass: 313.0885
Molecular Weight: 313.3742
m/z: 313.0885 (100.0%), 314.0919 (17.3%), 315.0843 (4.5%), 315.0952 (1.4%), 314.0855 (1.1%)
Elemental Analysis: C, 61.32; H, 4.82; N, 13.41; O, 10.21; S, 10.23

1j (WYR-2/ PAG-2): This compound is new. A mixture of Bernthsen's PTZ (3.05 g, 10.0 mmol) and iron (5.30 g, 9.50 mmol) in acetic acid (50 mL) was heated under reflux for 17 h. The reaction mixture was filtered over a plug of silica gel with ethyl acetate. After concentration, the crude product was purified by flash column chromatography in ethyl acetate/ MeOH (9:1). Isolated yield: 65% (grey solid).

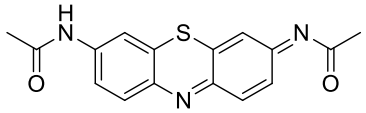
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.73 (s, 2H), 8.01 (s, 1H), 7.24 (d, ^{4}J = 2.3 Hz, 2H), 7.10 (dd, ^{3}J = 8.5 Hz, ^{4}J = 2.3 Hz, 2H), 6.59 (d, ^{3}J = 8.5 Hz, 2H), 1.97 (s, 6H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 167.69 (s, C_{quat}), 137.68 (s, C_{quat}), 133.61 (s, C_{quat}), 118.54 (s, CH), 116.96 (s, CH), 115.74 (s, C_{quat}), 114.17 (s, CH), 23.81 (s, CH_3).

IR (neat, cm^{-1}): ν: 3365, 3283, 3060, 1746, 1656, 1596, 1536, 1486, 1392, 1364, 1305, 1290, 1256, 1136, 1015, 976, 875, 816, 808, 701, 681.

Elemental analysis theoretical : N 13.41%, C 61.32%, H 4.82%, S 10.23%.

Found : N 13.39%, C 61.06%, H 4.95%, S 10.19%.



* $2H_2O$

Chemical Formula: $C_{16}H_{17}N_3O_4S$
Exact Mass: 347.0940
Molecular Weight: 347.3889
m/z: 347.0940 (100.0%), 348.0973 (17.3%), 349.0898 (4.5%), 349.1007 (1.4%), 348.0910 (1.1%)
Elemental Analysis: C, 55.32; H, 4.93; N, 12.10; O, 18.42; S, 9.23

1j' (CHB-182): Bis-acetamido-phenothiazine 1j (1.80 g, 5.74 mmol) and chloramin T trihydrate (1.96 g, 8.61 mmol) were dissolved in a 1:1 mixture of EtOH/ H_2O (50 mL). The reaction mixture was heated to 80 °C. As soon as it reached this temperature, heating was stopped and the mixture was allowed to cool to room temperature while being stirred. The precipitate was filtered and washed with hot water. The solid was thereafter stirred in boiling MeOH (50 mL) for 30 min. After cooling to room temperature, the solid was filtered, washed twice with MeOH, and dried in open air. Isolated yield: 54 % (light purple solid).

IR (neat, cm^{-1}): ν: 3509 (presumably water band), 3244 (NH band), 3065, 2941, 1669, 1598, 1515, 1467, 1429, 1399, 1275, 1238, 1205, 1138, 1073, 1052, 995, 917, 851, 832, 815, 756, 738, 703, 681, 660.

Elemental analysis theoretical : N 12.10%, C 56.32%, H 4.93%, S 9.23%.

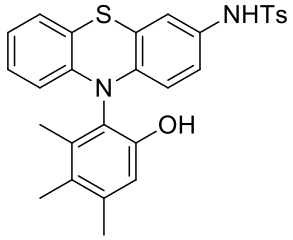
Found : N 12.03%, C 55.07%, H 4.94%, S 9.43%.

(Theoretical values are based on one molecule **1j'** with two molecules of water; found values are formed by the average of two measurements).

4.5.3 Experimental procedure

Typically, the phenothiazinimine (1 mmol), the phenol (3 mmol), cumene (2.5 mL) and acetic acid (0.5 mL) are united under air in a 170 mL reactor equipped with Teflon screw cap. The reactor is then flushed with oxygen atmosphere (1-2 min.), then sealed (tightly) and exposed to 110°C for 16 h. (magnetic stirring set to approx. 500 turns/min). The crude product is purified by column chromatography (SiO_2 gel).

4.5.4 Substrate characterization



Chemical Formula: $C_{28}H_{26}N_2O_3S_2$
Exact Mass: 502,1385
Molecular Weight: 502,6476
m/z: 502.1385 (100.0%), 503.1418 (30.3%), 504.1343 (9.0%), 504.1452 (4.4%), 505.1376 (2.7%), 503.1379 (1.6%)
Elemental Analysis: C, 66.91; H, 5.21; N, 5.57; O, 9.55; S, 12.76

3aa (FWP-934): The crude product was purified by flash column chromatography on silica gel, cyclohexane / ethyl acetate (7:3). Isolated yield: 81% (light green solid).

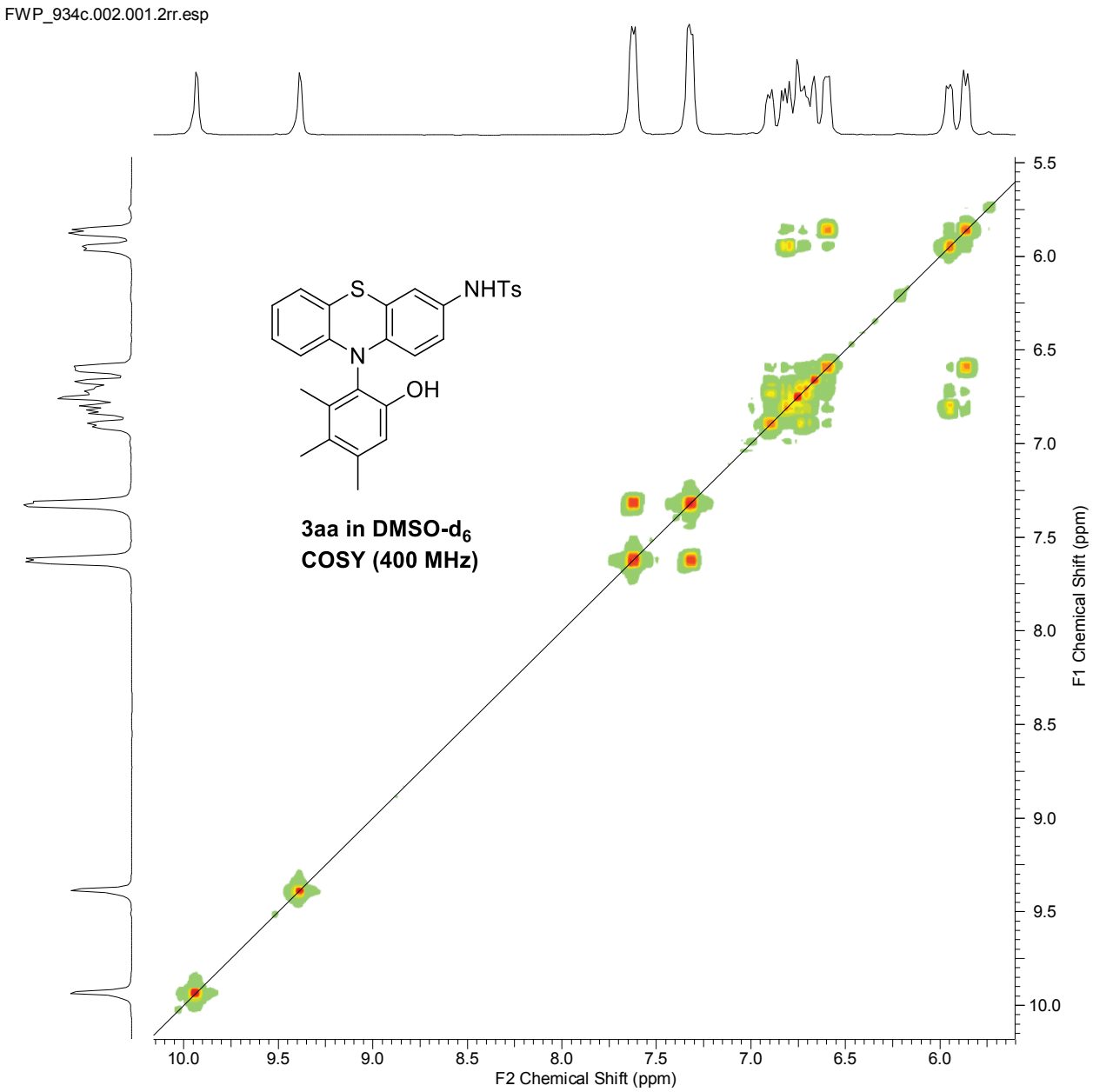
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.94 (s, 1H), 9.40 (s, 1H), 7.63 (2nd order d, ^{3}J ~ 8.4 Hz, 2H), 7.33 (2nd order d, ^{3}J ~ 8.4 Hz, 2H), 6.91 (dd, ^{3}J = 7.6 Hz, J = 1.0 Hz, 1H), 6.82 (td, ^{3}J ~ 8.3 Hz, ^{4}J = 1.2 Hz, 1H), 6.76 (s, 1H), 6.72 (broad t, ^{3}J = 7.3 Hz, 1H), 6.67 (d, ^{4}J = 2.3 Hz, 1H), 6.61 (dd, ^{3}J = 8.6 Hz, J = 2.3 Hz, 1H), 5.96 (broad d, ^{3}J = 8.1 Hz, 1H), 5.87 (d, ^{3}J = 8.8 Hz, 1H), 2.32 (s, 3H), 2.23 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6): δ (ppm): 152.58 (s, C_{quat}), 143.13 (s, C_{quat}), 141.95 (s, C_{quat}), 138.93 (s, C_{quat}), 137.31 (s, C_{quat}), 136.71 (s, C_{quat}), 135.76 (s, C_{quat}), 131.90 (s, C_{quat}), 129.63 (s, 2CH), 127.37 (s, CH), 126.67 (s, 2CH), 126.06 (s, CH), 122.96 (s, C_{quat}), 121.94 (s, CH), 120.04 (s, CH), 119.01 (s, C_{quat}), 118.69 (s, CH), 117.44 (s, C_{quat}), 115.45 (s, CH), 115.33 (s, CH), 114.97 (s, CH), 20.92 (s, CH_3), 20.48 (s, CH_3), 15.19 (s, CH_3), 14.10 (s, CH_3). One C_{quat} line is overlapped.

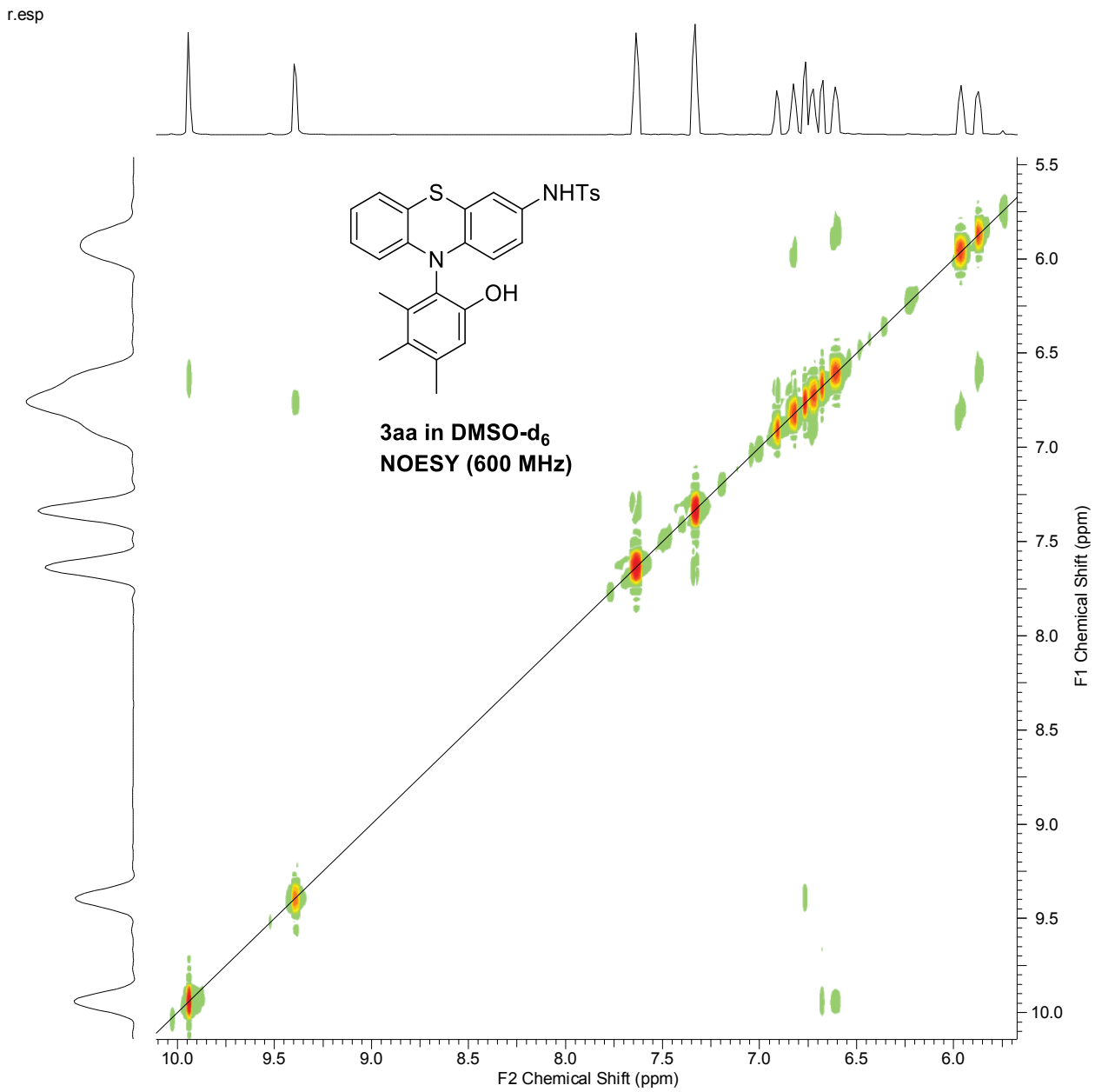
IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3505, 3301, 3250, 2919, 1598, 1495, 1464, 1443, 1376, 1313, 1275, 1251, 1218, 1185, 1155, 1091, 1038, 941, 917, 853, 808, 746, 691, 667, 655.

EI-HRMS: mass spectrometry: m/z calc. 502.1385 $[C_{28}H_{26}N_2O_3S_2]^{\bullet+}$, measured: 502.1560.

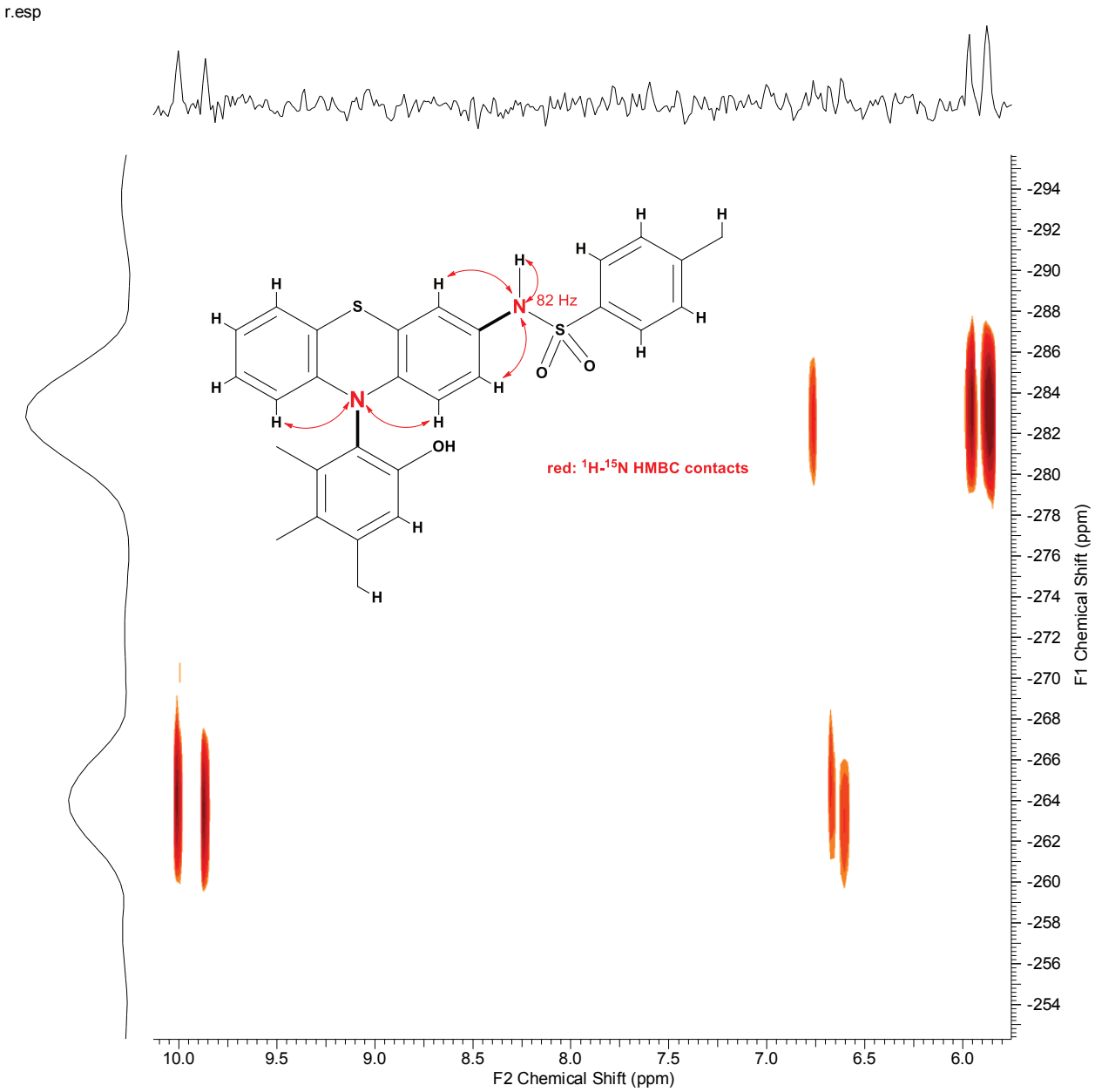
COSY (400 MHz) as well as NOESY and ^{1}H-^{15}N HMBC (600 MHz) are provided with spectra (Scheme 11, 12 and 13).



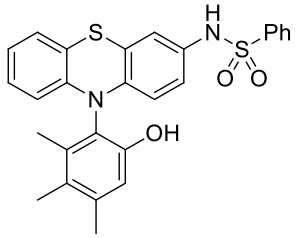
Scheme 11. COSY (400 MHz) NMR of **3aa** in DMSO-d_6



Scheme 12. NOESY (600 MHz) NMR of **3aa** in DMSO-d_6



Scheme 13. ^{1}H-^{15}N HMBC (600 MHz) NMR of **3aa** in DMSO-d_6



Chemical Formula: $C_{27}H_{24}N_2O_3S_2$
Exact Mass: 488,1228
Molecular Weight: 488,6211
m/z: 488.1228 (100.0%), 489.1262 (29.2%), 490.1186 (9.0%), 490.1295 (4.1%), 491.1220 (2.6%), 489.1222 (1.6%)
Elemental Analysis: C, 66.37; H, 4.95; N, 5.73; O, 9.82; S, 13.12

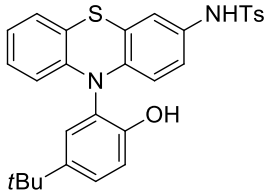
3ba (JRW-491): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 72% (coffee powder).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.99 (s, OH), 9.38 (s, CH), 7.74 (d, ^3J = 7.2 Hz, 1H), 7.58 (m, 3H), 6.92 (dd, ^3J = 7.6 Hz, J = 1.2 Hz, 1H), 6.83 (td, ^3J = 7.6 Hz, J = 1.4 Hz, 1H), 6.74 (m, 2H), 6.64 (d, J = 2.4 Hz, 1H), 6.59 (dd, ^3J = 8.8 Hz, J = 2.4 Hz, 1H), 5.95 (d, ^3J = 7.6 Hz, 1H), 5.86 (d, ^3J = 8.8 Hz, 1H), 2.24 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.57 (s, C_{quat}), 141.90 (s, C_{quat}), 139.53 (s, C_{quat}), 139.06 (s, C_{quat}), 137.32 (s, C_{quat}), 135.73 (s, C_{quat}), 132.81 (s, CH), 131.67 (s, C_{quat}), 129.21 (s, 2CH), 127.41 (s, CH), 126.67 (s, C_{quat}), 126.62 (s, 2CH), 126.07 (s, CH), 122.93 (s, C_{quat}), 121.97 (s, CH), 120.40 (s, CH), 119.00 (s, C_{quat}), 118.98 (s, CH), 117.40 (s, C_{quat}), 115.45 (s, CH), 115.31 (s, CH), 114.98 (s, CH), 20.50 (s, CH_3), 15.21 (s, CH_3), 14.11 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3382, 3254, 2925, 1599, 1493, 1463, 1442, 1427, 1313, 1297, 1250, 1157, 1091, 1073, 1038, 1001, 935, 914, 885, 855, 821, 742, 721, 688, 668.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{27}H_{24}N_2O_3S_2]^{\bullet+}$, 488.1228, found: 488.1261.



Chemical Formula: $C_{29}H_{28}N_2O_3S_2$
Exact Mass: 516,1541
Molecular Weight: 516,6742
m/z: 516.1541 (100.0%), 517.1575 (31.4%), 518.1499 (9.0%), 518.1608 (4.7%), 519.1533 (2.8%), 517.1535 (1.6%)
Elemental Analysis: C, 67.41; H, 5.46; N, 5.42; O, 9.29; S, 12.41

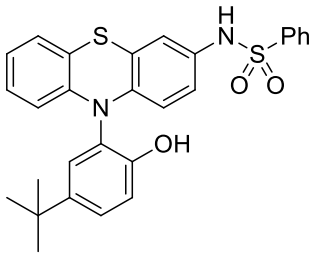
3ab (FWP-932): The crude product was purified by flash column chromatography on silica gel, cyclohexane / ethyl acetate (7:3). Isolated yield: 76% (light purple sticky solid).

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm): 7.69 (AA' half of AA'BB', 7.7073, 7.7022, 7.6985, 7.6865, 7.6814, 7.6770, 2H), 7.50 (dd, ^{3}J = 8.6 Hz, ^{4}J = 2.3 Hz, 1H), 7.39 (d, ^{4}J = 2.3 Hz, 1H), 7.29 (BB' of AA'BB', 2H), 7.17 (s, 1H), 7.15 (d, ^{3}J = 8.6 Hz, 1H), 7.05 (dd, ^{3}J = 7.3 Hz, ^{4}J = 1.8 Hz, 1H), 6.95 (td, ^{3}J = 7.3 Hz, ^{4}J = 1.8 Hz, 1H), 6.90 (broad d, ^{3}J = 7.3 Hz, 1H), 6.88 (d, ^{4}J = 2.5 Hz, 1H), 6.66 (dd, ^{3}J = 8.8 Hz, ^{4}J = 2.3 Hz, 1H), 6.35 (dd, ^{3}J = 8.1 Hz, ^{4}J = 1.0 Hz, 1H), 6.23 (d, ^{3}J = 8.8 Hz, 1H), 6.13 (s, 1H), 2.40 (s, 3H), 1.39 (s, 9H).

^{13}C {^{1}H} NMR (101 MHz, CD_2Cl_2 + DMSO-d_6): δ (ppm): 152.72 (s, C_{quat}), 143.70 (s, C_{quat}), 143.00 (s, C_{quat}), 142.85 (s, C_{quat}), 139.94 (s, C_{quat}), 136.72 (s, C_{quat}), 131.87 (s, C_{quat}), 129.15 (s, 2CH), 127.43 (s, CH), 126.77 (s, CH), 126.57 (s, 2CH), 126.44 (s, CH), 125.80 (s, CH), 125.51 (s, C_{quat}), 121.58 (s, CH), 119.78 (s, CH), 119.38 (s, C_{quat}), 118.88 (s, CH), 117.95 (s, C_{quat}), 116.51 (s, CH), 115.36 (s, CH), 115.12 (s, CH), 33.57 (s, C_{quat}), 30.95 (s, *t*Bu), 20.82 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = around 3400 (very broad), 3251, 2958, 1597, 1579, 1494, 1463, 1441, 1379, 1366, 1292, 1248, 1212, 1150, 1090, 1040, 1019, 948, 921, 862, 812, 744, 708, 661.

EI-HRMS: mass spectrometry: m/z calc. 516.1541 $[C_{29}H_{28}N_2O_3S_2]^{\bullet+}$, measured: 516.1566.



Chemical Formula: $C_{28}H_{26}N_2O_3S_2$
Exact Mass: 502,1385
Molecular Weight: 502,6476
m/z: 502.1385 (100.0%), 503.1418 (30.3%), 504.1343 (9.0%), 504.1452 (4.4%), 505.1376 (2.7%), 503.1379 (1.6%)
Elemental Analysis: C, 66.91; H, 5.21; N, 5.57; O, 9.55; S, 12.76

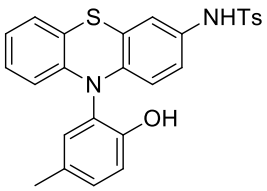
3bb (JRW-490): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 50% (violet powder).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.40 (s, OH), 9.72 (s, NH), 7.74 (m, 2H), 7.58 (m, 3H), 7.37 (dd, ^{3}J = 8.8 Hz, J = 2.4 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 7.04 (d, ^{3}J = 8.8 Hz, 1H), 6.97 (dd, ^{3}J = 7.6 Hz, J = 1.2 Hz, 1H), 6.89 (td, ^{3}J = 7.8 Hz, J = 1.2 Hz, 1H), 6.77 (td, ^{3}J = 7.4 Hz, J = 1.0 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.64 (dd, ^{3}J = 9.0 Hz, J = 2.6 Hz, 1H), 6.01 (dd, ^{3}J = 8.0 Hz, J = 0.8 Hz, 1H), 5.93 (d, ^{3}J = 8.8 Hz, 1H), 1.23 (s, 9H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.88 (s, C_{quat}), 143.67 (s, C_{quat}), 142.91 (s, C_{quat}), 139.97 (s, C_{quat}), 139.50 (s, C_{quat}), 132.83 (s, CH), 131.84 (s, C_{quat}), 129.25 (s, 2CH), 127.41 (s, CH), 127.34 (s, CH), 126.91 (s, CH), 126.62 (s, 2CH), 126.21 (s, CH), 125.48 (s, C_{quat}), 122.09 (s, CH), 120.29 (s, CH), 119.16 (s, C_{quat}), 118.92 (s, CH), 117.62 (s, C_{quat}), 116.68 (s, CH), 115.63 (s, CH), 115.30 (s, CH), 33.80 (s, C_{quat}), 31.27 (s, $3CH_3$).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3265, 2956, 1594, 1505, 1464, 1442, 1416, 1307, 1273, 1250, 1215, 1147, 1091, 1039, 948, 926, 866, 821, 736, 723, 685, 671.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{28}H_{26}N_2O_3S_2]^{\bullet+}$: 502.1385, found: 502.1428.



Chemical Formula: $C_{26}H_{22}N_2O_3S_2$
Exact Mass: 474,1072
Molecular Weight: 474,5945
m/z: 474.1072 (100.0%), 475.1105 (28.1%), 476.1030 (9.0%), 476.1139 (3.8%), 477.1063 (2.5%), 475.1066 (1.6%)
Elemental Analysis: C, 65.80; H, 4.67; N, 5.90; O, 10.11; S, 13.51

3ac (FWP-939): The crude product was purified by flash column chromatography on silica gel, cyclohexane / ethyl acetate (7:3). Isolated yield: 82% (light purple sticky solid).

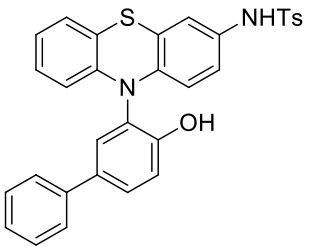
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): broad spectrum: the smaller couplings could not be solved: 10.00 (s, 1H), 9.72 (s, 1H), 7.64 (d, ^{3}J = 7.4 Hz, 2H), 7.33 (d, ^{3}J = 7.4 Hz, 2H), 7.15 (d, ^{3}J = 7.8 Hz, 1H), 7.02 (d, ^{3}J = 8.0 Hz, 1H), 6.97 (s, 1H), 6.95 (d, ^{3}J = 8.2 Hz, 1H), 6.86 (t, ^{3}J = 7.4 Hz, 1H), 6.76 (t, ^{3}J = 7.0 Hz, 1H), 6.74 (s, 1H), 6.66 (d, ^{3}J = 8.3 Hz, 1H), 6.05 (d, ^{3}J = 7.9 Hz, 1H), 5.96 (d, ^{3}J = 8.6 Hz, 1H), 2.31 (s, CH_3), 2.21 (s, CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6): δ (ppm): 153.05 (s, C_{quat}), 143.16 (s, C_{quat}), 142.73 (s, C_{quat}), 139.68 (s, C_{quat}), 136.61 (s, C_{quat}), 132.04 (s, C_{quat}), 131.19 (s, CH), 130.66 (s, CH),

129.96 (s, C_{quat}), 129.67 (s, 2CH), 127.30 (s, CH), 126.68 (s, 2CH), 126.15 (s, CH), 125.88 (s, C_{quat}), 122.05 (s, CH), 119.87 (s, CH), 119.17 (s, C_{quat}), 118.66 (s, CH), 117.59 (s, C_{quat}), 116.99 (s, CH), 115.67 (s, CH), 115.35 (s, CH), 20.92 (s, CH_3), 19.81 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3429, 3244, 2925, 1597, 1576, 1514, 1493, 1462, 1440, 1380, 1331, 1306, 1287, 1272, 1248, 1215, 1187, 1156, 1134, 1087, 1039, 1014, 936, 921, 897, 857, 823, 808, 775, 748, 727, 700, 669.

EI-HRMS: mass spectrometry: m/z calc. 474.1072 $[C_{26}H_{22}N_2O_3S_2]^{\bullet+}$, measured: 474.1091.



Chemical Formula: $C_{31}H_{24}N_2O_3S_2$
Exact Mass: 536,1228
Molecular Weight: 536,6639
m/z: 536.1228 (100.0%), 537.1262 (33.5%), 538.1186 (9.0%), 538.1295 (5.4%), 539.1220 (3.0%), 537.1222 (1.6%)
Elemental Analysis: C, 69.38; H, 4.51; N, 5.22; O, 8.94; S, 11.95

3ad (JRW-486): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 75% (turquoise powder).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): ~10.05 (s, OH and NH), 7.71 (dd, ^3J = 8.4 Hz, J = 2.0 Hz, 1H), 7.62 (m, 4H), 7.49 (d, J = 2.4 Hz, 1H), 7.38 (t, ^3J = 7.2 Hz, 2H), 7.33 (d, ^3J = 8.4 Hz, 2H), 7.28 (t, ^3J = 7.2 Hz, 1H), 7.20 (d, ^3J = 8.4 Hz, 1H), 6.98 (dd, ^3J = 7.6 Hz, J = 1.6 Hz, 1H), 6.89 (td, ^3J = 7.8 Hz, J = 1.6 Hz, 1H), 6.78 (td, ^3J = 7.6 Hz, J = 1.2 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.65 (dd, ^3J = 8.8 Hz, J = 2.4 Hz, 1H), 6.10 (dd, ^3J = 8.0 Hz, J = 0.8 Hz, 1H), 6.02 (d, ^3J = 8.8 Hz, 1H), 2.33 (s, 3H).

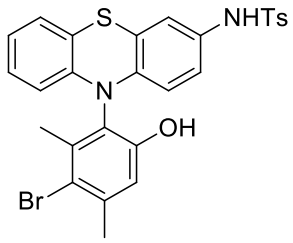
^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 155.26 (s, C_{quat}), 143.01 (s, C_{quat}), 142.73 (s, C_{quat}), 139.36 (s, C_{quat}), 138.84 (s, C_{quat}), 136.83 (s, C_{quat}), 132.84 (s, C_{quat}), 132.56 (s, C_{quat}), 129.64 (s, 2CH), 129.10 (s, CH), 128.83 (s, 2CH), 128.27 (s, CH), 127.40 (s, CH), 126.77 (s, CH), 126.72 (s, C_{quat}), 126.65 (s, 2CH), 126.22 (s, CH), 125.94 (s, 2CH), 122.09 (s, CH),

119.90 (s, CH), 119.06 (s, C_{quat}), 118.60 (s, CH), 117.87 (s, CH), 117.61 (s, C_{quat}), 115.70 (s, CH), 115.31 (s, CH), 20.93 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3252, 3033, 1597, 1577, 1514, 1486, 1463, 1377, 1293, 1213, 1150, 1119, 1088, 1042, 942, 923, 828, 810, 763, 745, 724, 696, 660.

Elemental analysis theoretical : N 5.22%, C 69.38%, H 4.51%, S 11.95%.

Found : N 5.06%, C 69.02%, H 4.70%, S 11.83%.



Chemical Formula: $C_{27}H_{23}BrN_2O_3S_2$
Exact Mass: 566,0333
Molecular Weight: 567,5171
m/z: 566.0333 (100.0%), 568.0313 (97.3%), 567.0367 (29.2%), 569.0347 (28.4%), 568.0291 (9.0%), 570.0271 (8.8%), 568.0401 (4.1%), 570.0380 (4.0%), 569.0325 (2.6%), 571.0305 (2.6%), 567.0327 (1.6%), 569.0307 (1.6%)
Elemental Analysis: C, 57.14; H, 4.08; Br, 14.08; N, 4.94; O, 8.46; S, 11.30

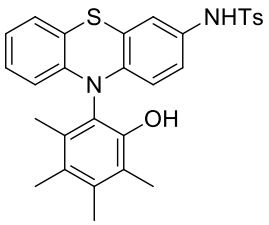
3ae (CHB-181): The crude product was purified by flash column chromatography on silica gel, cyclohexane / ethyl acetate (gradient 8:2 to 7:3). Isolated yield: 37 % (grey solid).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.01 (s, 1H), 9.96 (s, 1H), 7.60 (second order doublet, 2H), 7.34 (second order doublet, 2H), 6.96-6.94 (m, 2H), 6.87 (td, ^3J = 7.8 Hz, ^4J = 1.3 Hz, 1H), 6.77 (td, ^3J = 7.5 Hz, ^4J = 1.0 Hz, 1H), 6.66 (d, ^4J = 2.5 Hz, 1H), 6.60 (dd, ^3J = 8.9 Hz, ^4J = 2.6 Hz, 1H), 5.95 (d, ^3J = 8.1 Hz, 1H), 5.86 (d, ^3J = 8.8 Hz, 1H), 2.36 (s, 3H), 2.33 (s, 3H), 2.20 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6): δ (ppm) = 154.70 (s, C_{quat}), 143.26 (s, C_{quat}), 141.45 (s, C_{quat}), 139.15 (s, C_{quat}), 138.33 (s, C_{quat}), 137.84 (s, C_{quat}), 136.70 (s, C_{quat}), 132.34 (s, C_{quat}), 129.75 (s, CH), 127.63 (s, CH), 126.72 (s, CH), 126.34 (s, CH), 124.19 (s, C_{quat}), 122.43 (s, CH), 120.10 (s, C_{quat}), 119.26 (s, CH), 118.72 (s, CH), 117.68 (s, C_{quat}), 116.57 (s, C_{quat}), 116.50 (s, CH), 115.34 (s, CH), 114.89 (s, CH), 23.52 (s, CH_3), 20.76 (s, CH_3), 18.09 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3400, 3258, 2924, 1598, 1568, 1465, 1380, 1294, 1253, 1231, 1185, 1149, 1091, 1055, 994, 962, 921, 849, 811, 735, 703.

Elemental analysis: Theoretical:	N: 4.94 %	C: 57.14 %	H: 4.08 %	S: 11.30 %
Found:	N: 4.72 %	C: 57.16 %	H: 4.28 %	S: 11.04 %



Chemical Formula: $C_{29}H_{28}N_2O_3S_2$
Exact Mass: 516,1541
Molecular Weight: 516,6742
m/z: 516.1541 (100.0%), 517.1575 (31.4%), 518.1499 (9.0%), 518.1608 (4.7%), 519.1533 (2.8%), 517.1535 (1.6%)
Elemental Analysis: C, 67.41; H, 5.46; N, 5.42; O, 9.29; S, 12.41

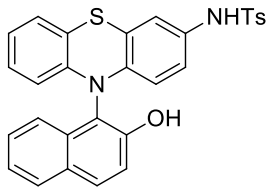
3af (FWP-944): half mmol scale. The crude product was purified by flash column chromatography on silica gel, cyclohexane / ethyl acetate (7:3). Isolated yield: 47% (light purple sticky solid).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.91 (s, 1H), 8.51 (s, 1H), 7.62 (2nd order d, ^{3}J ~ 8.2 Hz, 2H), 7.35 (2nd order d, ^{3}J ~ 8.2 Hz, 2H), 6.88 (dd, ^{3}J = 7.5 Hz, ^{4}J = 1.5 Hz, 1H), 6.81 (~td, ^{3}J ~ 7.8 Hz, ^{4}J ~ 1.6 Hz, 1H), 6.71 (td, ^{3}J = 7.4 Hz, ^{4}J = 1.2 Hz, 1H), 6.60 (d, ^{4}J = 2.4 Hz, 1H), 6.54 (dd, ^{3}J = 8.8 Hz, ^{4}J = 2.5 Hz, 1H), 5.85 (dd, ^{3}J = 8.2 Hz, ^{4}J = 1.0 Hz, 1H), 5.75 (d, ^{3}J = 8.8 Hz, 1H), 2.34 (s, CH_3), 2.20 (s, CH_3), 2.16 (s, CH_3), 2.11 (s, CH_3), 2.03 (s, CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6): δ (ppm): 150.55 (s, C_{quat}), 143.13 (s, C_{quat}), 141.62 (s, C_{quat}), 138.63 (s, C_{quat}), 136.74 (s, C_{quat}), 136.09 (s, C_{quat}), 131.84 (s, C_{quat}), 131.74 (s, C_{quat}), 129.64 (s, 2CH), 127.37 (s, CH), 126.92 (s, C_{quat}), 126.66 (s, 2CH), 125.90 (s, CH), 123.50 (s, C_{quat}), 121.88 (s, CH), 121.60 (s, C_{quat}), 119.99 (s, CH), 118.95 (s, C_{quat}), 118.52 (s, CH), 117.38 (s, C_{quat}), 115.31 (s, CH), 114.95 (s, CH), 20.93 (s, CH_3), 16.45 (s, CH_3), 15.99 (s, CH_3), 14.35 (s, CH_3), 12.91 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3491, 3250, 2920, 1599, 1579, 1494, 1463, 1442, 1379, 1300, 1216, 1185, 1154, 1085, 1053, 1018, 942, 915, 893, 851, 811, 744, 721, 704, 660.

EI-HRMS: mass spectrometry: m/z calc. 516.1541 $[C_{29}H_{28}N_2O_3S_2]^{\bullet+}$, measured: 516.1540.



Chemical Formula: $C_{29}H_{22}N_2O_3S_2$
Exact Mass: 510,1072
Molecular Weight: 510,6266
m/z: 510.1072 (100.0%), 511.1105 (31.4%), 512.1030 (9.0%), 512.1139 (4.7%), 513.1063 (2.8%), 511.1066 (1.6%)
Elemental Analysis: C, 68.21; H, 4.34; N, 5.49; O, 9.40; S, 12.56

3ag (JRW-489 and 493): Reaction temperature: 90 °C. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 82% (dark-green powder).

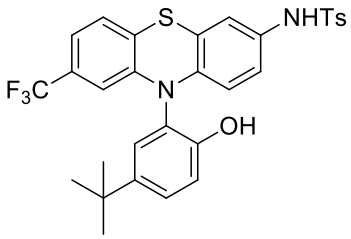
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.34 (s, OH), 9.98 (s, NH), 7.98 (d, J = 9.2 Hz, 1H), 7.90 (t, J = 8.8 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.43 (m, 2H), 7.34 (m, 3H), 7.01 (dd, ^3J = 7.2 Hz, J = 1.6 Hz, 1H), 6.78 (m, 3H), 6.56 (dd, ^3J = 9.0 Hz, J = 2.4 Hz, 1H), 5.98 (dd, ^3J = 8.0 Hz, J = 2.0 Hz, 1H), 5.90 (d, ^3J = 8.8 Hz, 1H), 2.32 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 153.79 (s, C_{quat}), 143.16 (s, C_{quat}), 142.04 (s, C_{quat}), 138.95 (s, C_{quat}), 136.65 (s, C_{quat}), 132.27 (s, C_{quat}), 131.52 (s, C_{quat}), 130.33 (s, CH), 129.68 (s, 2CH), 129.14 (s, C_{quat}), 128.42 (s, CH), 127.61 (s, CH), 127.51 (s, CH), 126.65 (s, 2CH), 126.30 (s, CH), 123.51 (s, CH), 122.32 (s, CH), 120.81 (s, CH), 119.99 (s, CH), 119.66 (s, C_{quat}), 118.94 (s, CH), 118.71 (s, CH), 118.12 (s, C_{quat}), 117.67 (s, C_{quat}), 115.67 (s, CH), 115.26 (s, CH), 20.94 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3250, 3057, 1625, 1599, 1492, 1463, 1441, 1381, 1301, 1271, 1206, 1146, 1089, 1039, 943, 917, 860, 810, 781, 743, 660.

Elemental analysis theoretical : N 5.49%, C 68.21%, H 4.34%, S 12.56%.

Found : N 5.22%, C 68.41%, H 4.55%, S 11.74%.



Chemical Formula: $C_{30}H_{27}F_3N_2O_3S_2$
Exact Mass: 584,1415
Molecular Weight: 584,6722
m/z: 584.1415 (100.0%), 585.1449 (32.4%), 586.1373 (9.0%), 586.1482 (5.1%), 587.1407 (2.9%), 585.1409 (1.6%)
Elemental Analysis: C, 61.63; H, 4.65; F, 9.75; N, 4.79; O, 8.21; S, 10.97

3cb (JRW-482): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 96% (seaweed powder).

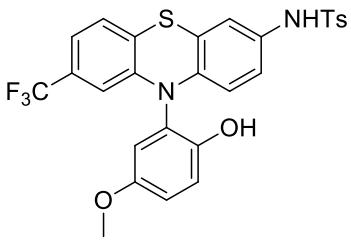
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.08 (s, OH), 9.90 (s, NH), 7.65 (d, ^3J = 8.0 Hz, 2H), 7.41 (dd, ^3J = 8.4 Hz, J = 2.4 Hz, 1H), 7.33 (d, ^3J = 8.0 Hz, 2H), 7.17 (m, 2H), 7.08 (m, 2H), 6.77 (d, J = 2.4 Hz, 1H), 6.69 (dd, ^3J = 8.0 Hz, J = 2.4 Hz, 1H), 6.18 (d, J = 1.6 Hz, 1H), 5.95 (d, ^3J = 8.8 Hz, 1H), 2.31 (s, 3H), 1.21 (s, 9H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.60 (s, C_{quat}), 143.93 (s, C_{quat}), 143.50 (s, C_{quat}), 143.20 (s, C_{quat}), 138.82 (s, C_{quat}), 136.61 (s, C_{quat}), 132.90 (s, C_{quat}), 129.69 (s, 2CH), 128.00 (q, ^3J = 31.8 Hz, C_{quat}), 127.32 (s, CH), 127.32 (s, CH), 127.27 (s, CH), 127.00 (s, CH), 126.68 (s, 2CH), 124.71 (s, C_{quat}), 123.80 (q, ^3J = 272.9 Hz, C_{quat}), 123.41 (s, C_{quat}), 120.05 (s, CH), 118.42 (q, ^3J = 5.5 Hz, CH), 118.29 (s, C_{quat}), 116.89 (s, CH), 116.11 (s, CH), 110.70 (q, ^3J = 3.8 Hz, CH), 33.80 (s, C_{quat}), 31.12 (s, $3CH_3$), 20.90 (s, CH_3).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.89 (s, CF_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3258, 2962, 1598, 1502, 1476, 1412, 1325, 1249, 1214, 1155, 1118, 1085, 971, 939, 871, 811, 668, 661.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{30}H_{27}F_3N_2O_3S_2]^{\bullet+}$: 584.1415, found: 584.1422.



Chemical Formula: $C_{27}H_{21}F_3N_2O_4S_2$
Exact Mass: 558,0895
Molecular Weight: 558,5918
m/z: 558.0895 (100.0%), 559.0928 (29.2%), 560.0853 (9.0%), 560.0962 (4.1%), 561.0886 (2.6%), 559.0889 (1.6%)
Elemental Analysis: C, 58.05; H, 3.79; F, 10.20; N, 5.02; O, 11.46; S, 11.48

3ch (JRW-495): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 68% (spring-green powder).

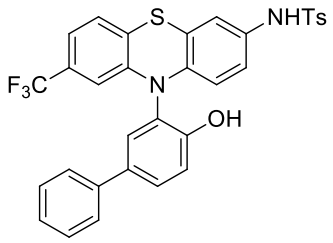
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.07 (s, OH), 9.63 (s, NH), 7.64 (d, ^{3}J = 8.4 Hz, 2H), 7.35 (d, ^{3}J = 8.4 Hz, 2H), 7.19 (d, ^{3}J = 8.0 Hz, 1H), 7.10 (m, 2H), 7.01 (dd, ^{3}J = 8.8 Hz, J = 2.8 Hz, 1H), 6.82 (d, J = 2.8 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.69 (dd, ^{3}J = 8.8 Hz, J = 2.4 Hz, 1H), 6.21 (d, J = 1.2 Hz, 1H), 5.97 (d, ^{3}J = 8.8 Hz, 1H), 3.68 (s, 3H), 2.33 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 153.55 (s, C_{quat}), 148.86 (s, C_{quat}), 143.24 (s, C_{quat}), 143.08 (s, C_{quat}), 138.55 (s, C_{quat}), 136.55 (s, C_{quat}), 132.93 (s, C_{quat}), 129.71 (s, 2CH), 128.00 (q, ^{3}J = 31.8 Hz, C_{quat}), 127.03 (s, CH), 126.68 (s, 2CH), 125.35 (s, C_{quat}), 123.83 (q, ^{3}J = 272.9 Hz, C_{quat}), 123.34 (s, C_{quat}), 120.03 (s, CH), 118.52 (q, ^{3}J = 3.8 Hz, CH), 118.46 (s, CH), 118.19 (s, C_{quat}), 117.89 (s, CH), 116.79 (s, CH), 116.16 (s, CH), 114.91 (s, CH), 110.68 (q, ^{3}J = 3.7 Hz, CH), 55.48 (s, CH_3), 20.92 (s, CH_3).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.74 (s, CF_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3250, 1738, 1598, 1502, 1476, 1412, 1325, 1277, 1220, 1152, 1115, 1086, 1033, 938, 870, 810, 768, 741, 688, 680.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{27}H_{21}F_3N_2O_4S_2]^{\bullet+}$: 558.0895, found: 558.0913.



Chemical Formula: $C_{32}H_{23}F_3N_2O_3S_2$
Exact Mass: 604,1102
Molecular Weight: 604,6618
m/z: 604.1102 (100.0%), 605.1136 (34.6%), 606.1060 (9.0%), 606.1169 (5.8%), 607.1094 (3.1%), 605.1096 (1.6%)
Elemental Analysis: C, 63.56; H, 3.83; F, 9.43; N, 4.63; O, 7.94; S, 10.61

3cd (JRW-494): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 93% (gray powder).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.32 (s, OH), 10.07 (s, NH), 7.77 (dd, ^3J = 8.4 Hz, J = 2.4 Hz, 1H), 7.63 (m, 5H), 7.36 (m, 4H), 7.28 (t, ^3J = 7.6 Hz, 1H), 7.23 (t, ^3J = 8.4 Hz, 2H), 7.12 (dd, ^3J = 8.0 Hz, J = 0.8 Hz, 1H), 6.76 (d, J = 2.4 Hz, 1H), 6.69 (dd, ^3J = 8.8 Hz, J = 2.4 Hz, 1H), 6.24 (d, J = 1.6 Hz, 1H), 6.02 (d, ^3J = 8.8 Hz, 1H), 2.33 (s, 3H).

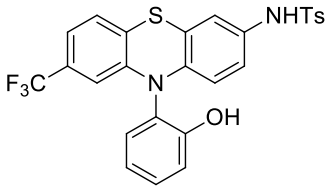
^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 154.76 (s, C_{quat}), 143.25 (s, C_{quat}), 143.21 (s, C_{quat}), 138.64 (s, C_{quat}), 138.56 (s, C_{quat}), 136.53 (s, C_{quat}), 133.25 (s, C_{quat}), 132.95 (s, C_{quat}), 129.72 (s, 2CH), 128.85 (s, 2CH), 128.79 (s, CH), 128.00 (q, ^3J = 31.9 Hz, C_{quat}), 127.12 (s, CH), 126.93 (s, CH), 126.67 (s, 2CH), 125.97 (s, 2CH), 125.85 (s, C_{quat}), 123.82 (q, ^3J = 272.9 Hz, C_{quat}), 123.47 (s, C_{quat}), 120.09 (s, CH), 118.58 (q, ^3J = 3.6 Hz, CH), 118.49 (s, CH), 118.28 (s, C_{quat}), 117.90 (s, CH), 116.20 (s, CH), 110.64 (q, ^3J = 4.1 Hz, CH), 20.93 (s, CH_3). (one CH is overlapped)

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.72 (s, CF_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3257, 3037, 1741, 1598, 1476, 1412, 1382, 1323, 1285, 1245, 1217, 1153, 1118, 1086, 963, 935, 869, 811, 762, 738, 697, 661.

Elemental analysis theoretical : N 4.63%, C 63.56%, H 3.83%, S 10.61%.

Found : N 4.40%, C 62.94%, H 4.14%, S 10.61%.



Chemical Formula: $C_{26}H_{19}F_3N_2O_3S_2$
Exact Mass: 528,0789
Molecular Weight: 528,5659
m/z: 528.0789 (100.0%), 529.0823 (28.1%), 530.0747 (9.0%), 530.0856 (3.8%), 531.0781 (2.5%), 529.0783 (1.6%)
Elemental Analysis: C, 59.08; H, 3.62; F, 10.78; N, 5.30; O, 9.08; S, 12.13

3ci (JRW-488): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 40% (pale violet-red powder).

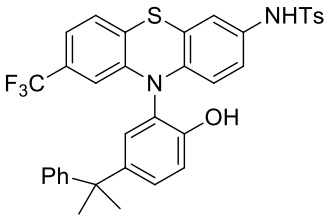
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.11 (s, OH), 10.05 (s, NH), 7.62 (d, ^3J = 8.4 Hz, 2H), 7.40 (td, ^3J = 7.8 Hz, J = 1.6 Hz, 1H), 7.35 (d, ^3J = 8.0 Hz, 2H), 7.23 (dd, ^3J = 8.0 Hz, J = 1.6 Hz, 1H), 7.20 (d, ^3J = 7.6 Hz, 1H), 7.14 (dd, ^3J = 8.4 Hz, J = 1.2 Hz, 1H), 7.11 (dd, ^3J = 8.0 Hz, J = 1.2 Hz, 1H), 7.02 (td, ^3J = 7.6 Hz, J = 1.2 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.66 (dd, ^3J = 9.0 Hz, J = 2.8 Hz, 1H), 6.13 (d, J = 1.2 Hz, 1H), 5.91 (d, ^3J = 8.8 Hz, 1H), 2.34 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 155.18 (s, C_{quat}), 143.25 (s, C_{quat}), 143.20 (s, C_{quat}), 138.59 (s, C_{quat}), 136.51 (s, C_{quat}), 132.87 (s, C_{quat}), 131.00 (s, CH), 130.87 (s, CH), 129.72 (s, 2CH), 128.07 (q, ^3J = 31.8 Hz, C_{quat}), 127.07 (s, CH), 126.66 (s, 2CH), 125.35 (s, C_{quat}), 123.80 (q, ^3J = 273.2 Hz, C_{quat}), 123.33 (s, C_{quat}), 121.30 (s, CH), 120.01 (s, CH), 118.52 (s, CH), 118.49 (s, CH), 118.14 (s, C_{quat}), 117.37 (s, CH), 116.05 (s, CH), 110.53 (q, ^3J = 3.9 Hz, CH), 20.94 (s, CH_3).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.80 (s, CF_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3251, 1599, 1509, 1498, 1476, 1458, 1414, 1329, 1313, 1302, 1253, 1217, 1164, 1126, 1106, 1088, 1020, 964, 948, 925, 864, 827, 812, 757, 708, 654.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{26}H_{19}F_3N_2O_3S_2]^{\bullet+}$: 528.0789, found: 528.0839.



Chemical Formula: $C_{35}H_{29}F_3N_2O_3S_2$
Exact Mass: 646,1572
Molecular Weight: 646,7416
m/z: 646.1572 (100.0%), 647.1605 (37.9%), 648.1530 (9.0%), 648.1639 (7.0%), 649.1563 (3.4%), 647.1566 (1.6%)
Elemental Analysis: C, 65.00; H, 4.52; F, 8.81; N, 4.33; O, 7.42; S, 9.92

3cj (JRW-498): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 82% (magenta powder).

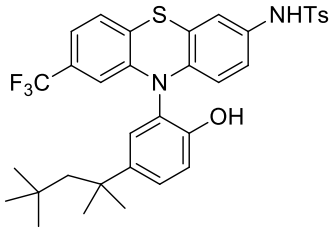
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.06 (s, OH), 9.95 (s, NH), 7.63 (d, ^3J = 8.0 Hz, 2H), 7.35 (d, ^3J = 8.0 Hz, 2H), 7.27 (dd, ^3J = 8.4 Hz, J = 2.4 Hz, 1H), 7.17 (m, 6H), 7.07 (d, ^3J = 8.4 Hz, 2H), 6.99 (d, J = 2.0 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.66 (dd, ^3J = 8.8 Hz, J = 2.4 Hz, 1H), 6.09 (d, J = 1.2 Hz, 1H), 5.94 (d, ^3J = 8.8 Hz, 1H), 2.34 (s, 3H), 1.60 (s, 6H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.66 (s, C_{quat}), 150.45 (s, C_{quat}), 143.34 (s, C_{quat}), 143.24 (s, C_{quat}), 138.45 (s, C_{quat}), 136.55 (s, C_{quat}), 132.83 (s, C_{quat}), 129.72 (s, 2CH), 129.06 (s, CH), 128.74 (s, CH), 128.06 (q, ^3J = 31.8 Hz, C_{quat}), 127.88 (s, 2CH), 126.97 (s, CH), 126.67 (s, 2CH), 126.23 (s, 2CH), 125.50 (s, CH), 124.59 (s, C_{quat}), 123.79 (q, ^3J = 272.8 Hz, C_{quat}), 123.17 (s, C_{quat}), 123.16 (s, C_{quat}), 119.97 (s, CH), 118.41 (q, J = 3.7 Hz, CH), 118.38 (s, CH), 117.96 (s, C_{quat}), 117.06 (s, CH), 115.94 (s, CH), 110.50 (q, J = 4.2 Hz, CH), 41.87(s, C_{quat}) , 30.36 (s, $2CH_3$), 20.94 (s, CH_3).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.95 (s, CF_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3255, 2970, 1739, 1598, 1500, 1476, 1411, 1383, 1326, 1258, 1154, 1119, 1086, 1030, 972, 940, 871, 811, 783, 764, 700, 666.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{35}H_{29}F_3N_2O_3S_2]^{\bullet+}$: 646.1572, found: 646.1612.



Chemical Formula: $C_{34}H_{35}F_3N_2O_3S_2$
Exact Mass: 640,2041
Molecular Weight: 640,7785
m/z: 640.2041 (100.0%), 641.2075 (36.8%), 642.1999 (9.0%), 642.2108 (6.6%), 643.2033 (3.3%), 641.2035 (1.6%)
Elemental Analysis: C, 63.73; H, 5.51; F, 8.89; N, 4.37; O, 7.49; S, 10.01

3ck (JRW-499): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 63% (light-gray powder).

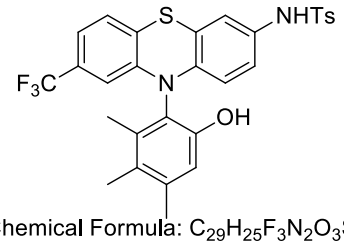
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.05 (s, OH), 9.85 (s, NH), 7.63 (d, ^{3}J = 8.0 Hz, 2H), 7.40 (dd, ^{3}J = 8.8 Hz, J = 2.4 Hz, 1H), 7.34 (d, ^{3}J = 8.0 Hz, 2H), 7.15 (m, 2H), 7.07 (dd, ^{3}J = 8.0 Hz, J = 1.2 Hz, 1H), 7.05 (d, ^{3}J = 8.4 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.62 (dd, ^{3}J = 9.2 Hz, J = 2.4 Hz, 1H), 6.16 (d, J = 1.2 Hz, 1H), 5.91 (d, ^{3}J = 8.8 Hz, 1H), 2.33 (s, 3H), 1.65 (s, 2H), 1.28 (s, 6H), 0.64 (s, 9H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.48 (s, C_{quat}), 143.34 (s, C_{quat}), 143.21 (s, C_{quat}), 142.45 (s, C_{quat}), 138.54 (s, C_{quat}), 136.54 (s, C_{quat}), 132.77 (s, C_{quat}), 129.69 (s, 2CH), 128.34 (s, CH), 128.29 (s, CH), 128.00 (q, ^{3}J = 31.8 Hz, C_{quat}), 126.91 (s, CH), 126.68 (s, 2CH), 126.19 (s, CH), 124.47 (s, C_{quat}), 123.77 (q, ^{3}J = 272.9 Hz, C_{quat}), 123.01 (s, C_{quat}), 119.87 (s, CH), 118.42 (s, CH), 118.33 (q, ^{3}J = 3.7 Hz, CH), 117.93 (s, C_{quat}), 116.64 (s, CH), 115.90 (s, CH), 110.70 (q, ^{3}J = 3.7 Hz, CH), 56.34 (s, CH_2), 37.57 (s, C_{quat}), 31.91 (s, C_{quat}), 31.44 (s, $3CH_3$), 20.93 (s, $2CH_3$).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.87 (s, CF_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3258, 2955, 1598, 1504, 1476, 1412, 1386, 1326, 1288, 1260, 1209, 1157, 1121, 1084, 971, 939, 872, 811, 693, 666.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{34}H_{35}F_3N_2O_3S_2]^{\bullet+}$: 640.2041, found: 640.2105.



Chemical Formula: $C_{29}H_{25}F_3N_2O_3S_2$
Exact Mass: 570,1259
Molecular Weight: 570,6456
m/z: 570.1259 (100.0%), 571.1292 (31.4%), 572.1217 (9.0%), 572.1326 (4.7%), 573.1250 (2.8%), 571.1253 (1.6%)
Elemental Analysis: C, 61.04; H, 4.42; F, 9.99; N, 4.91; O, 8.41; S, 11.24

3ca (JRW-483): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 87% (green-grey powder).

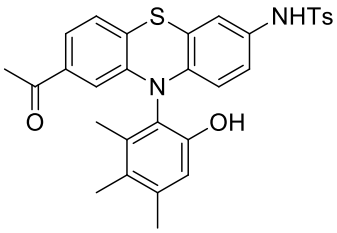
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.02 (s, OH), 9.59 (s, NH), 7.62 (d, ^3J = 8.0 Hz, 2H), 7.35 (d, ^3J = 8.0 Hz, 2H), 7.17 (d, ^3J = 8.0 Hz, 1H), 7.08 (dd, ^3J = 8.0 Hz, J = 0.8 Hz, 1H), 6.78 (s, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.63 (dd, ^3J = 8.8 Hz, J = 2.4 Hz, 1H), 6.14 (d, J = 1.2 Hz, 1H), 5.85 (d, ^3J = 8.8 Hz, 1H), 2.34 (s, 3H), 2.26 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.45 (s, C_{quat}), 143.23 (s, C_{quat}), 142.70 (s, C_{quat}), 138.04 (s, C_{quat}), 137.97 (s, C_{quat}), 136.59 (s, C_{quat}), 135.43 (s, C_{quat}), 132.80 (s, C_{quat}), 129.69 (s, 2CH), 128.00 (q, ^3J = 31.7 Hz, C_{quat}), 127.02 (s, CH), 126.99 (s, C_{quat}), 126.66 (s, 2CH), 123.84 (q, ^3J = 273.2 Hz, C_{quat}), 123.43 (s, C_{quat}), 122.16 (s, C_{quat}), 120.22 (s, CH), 118.56 (s, CH), 118.43 (q, ^3J = 4.1 Hz, CH), 118.40 (s, C_{quat}), 115.94 (s, CH), 115.41 (s, CH), 110.41 (q, ^3J = 3.9 Hz, CH), 20.93 (s, CH_3), 20.54 (s, CH_3), 15.23 (s, CH_3), 13.99 (s, CH_3).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.65 (s, CF_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3270, 2925, 1600, 1499, 1475, 1413, 1324, 1249, 1149, 1138, 1121, 1084, 1039, 952, 872, 850, 809, 771, 746, 705, 663.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{29}H_{25}F_3N_2O_3S_2]^{\bullet+}$: 570.1259, found: 570.1288.



Chemical Formula: $C_{30}H_{28}N_2O_4S_2$
Exact Mass: 544,1490
Molecular Weight: 544,6843
m/z: 544.1490 (100.0%), 545.1524 (32.4%), 546.1448 (9.0%), 546.1558 (5.1%), 547.1482 (2.9%), 545.1484 (1.6%)
Elemental Analysis: C, 66.15; H, 5.18; N, 5.14; O, 11.75; S, 11.77

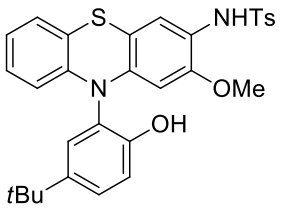
3da (CHB-188): The crude product was purified by flash column chromatography on silica gel, cyclohexane / ethyl acetate (7:3). Isolated yield: 60 % (yellow powder).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.97 (s, 1H), 9.47 (s, 1H), 7.61 (second order doublet, 2H), 7.38 (dd, ^{4}J = 1.6 Hz, ^{3}J = 8.0 Hz, 1H), 7.34 (second order doublet, 2H), 7.07 (d, ^{3}J = 8.0 Hz, 1H), 6.76 (s, 1 H), 6.66 (d, ^{4}J = 2.2 Hz, 1H), 6.59 (dd, ^{4}J = 2.4 Hz, ^{3}J = 8.8 Hz, 1H), 6.46 (d, ^{4}J = 1.5 Hz, 1H), 5.81 (d, ^{3}J = 8.9 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 2.25 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 196.82 (s, C_{quat}), 152.60 (s, C_{quat}), 143.26 (s, C_{quat}), 142.13 (s, C_{quat}), 138.33 (s, C_{quat}), 137.66 (s, C_{quat}), 136.69 (s, C_{quat}), 136.02 (s, C_{quat}), 135.56 (s, C_{quat}), 132.32 (s, C_{quat}), 129.49 (s, CH), 126.84 (s, C_{quat}), 126.71 (s, CH), 126.13 (s, CH), 124.79 (s, C_{quat}), 123.22 (s, CH), 122.61 (s, C_{quat}), 120.36 (s, CH), 118.64 (s, CH), 118.17 (s, C_{quat}), 115.75 (s, CH), 115.54 (s, CH), 112.71 (s, CH), 26.40 (s, CH_3), 21.00 (s, CH_3), 20.60 (s, CH_3), 15.29 (s, CH_3), 14.09 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3434, 3002, 2922, 2327, 1654, 1557, 1536, 1479, 1436, 1306, 1254, 1219, 120, 1183, 1140, 1092, 1034, 1005, 769, 753, 718, 701.

Elemental analysis:	Theoretical:	N: 5.14 %	C: 66.15 %	H: 5.18 %	S: 11.77 %
	Found:	N: 4.93 %	C: 65.92 %	H: 5.32 %	S: 11.67 %



Chemical Formula: $C_{30}H_{30}N_2O_4S_2$
Exact Mass: 546,1647
Molecular Weight: 546,7002
m/z: 546.1647 (100.0%), 547.1681 (32.4%), 548.1605 (9.0%), 548.1714 (5.1%), 549.1638 (2.9%), 547.1641 (1.6%)
Elemental Analysis: C, 65.91; H, 5.53; N, 5.12; O, 11.71; S, 11.73

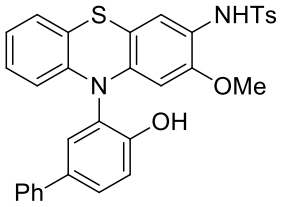
3eb (CHB-191): The crude product was purified by flash column chromatography on silica gel, cyclohexane / ethyl acetate (7:3). Isolated yield: 51 % (purple sticky solid).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.74 (s, 1H), 9.30 (s, 1H), 7.57 (second order doublet, 2H), 7.37 (dd, ^{3}J = 8.5 Hz, ^{4}J = 2.4 Hz, 1H), 7.31 (second order doublet, 2H), 7.16 (d, ^{4}J = 2.4 Hz, 1H), 7.05 (d, ^{3}J = 8.5 Hz, 1H), 6.99 (dd, ^{3}J = 7.5 Hz, ^{4}J = 1.4 Hz, 1H), 6.89 (td, ^{3}J = 7.8 Hz, ^{4}J = 1.5 Hz, 1H), 6.80 (td, ^{3}J = 7.4 Hz, ^{4}J = 0.9 Hz, 1H), 6.75 (s, 1H), 6.06 (d, ^{3}J = 8.0 Hz, 1H), 5.61 (s, 1H), 3.03 (s, 3H), 2.34 (s, 3H), 1.24 (s, 9H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6): δ (ppm) = 152.66 (s, C_{quat}), 152.61 (s, C_{quat}), 143.63 (s, C_{quat}), 142.66 (s, C_{quat}), 142.63 (s, C_{quat}), 142.43 (s, C_{quat}), 137.81 (s, C_{quat}), 129.17 (s, CH), 127.80 (s, CH), 127.26 (s, CH), 126.89 (s, CH), 126.74 (s, CH), 126.27 (s, CH), 125.54 (s, C_{quat}), 124.14 (s, CH), 122.38 (s, CH), 119.50 (s, C_{quat}), 118.50 (s, C_{quat}), 116.93 (s, CH), 115.51 (s, CH), 108.49 (s, C_{quat}), 100.29 (s, CH), 55.02 (s, CH_3), 33.67 (s, C_{quat}), 31.26 (s, CH_3), 20.96 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3435, 3100, 3053, 3007, 2922, 1653, 1556, 1537, 1479, 1452, 1436, 1307, 1254, 1218, 1199, 1190, 1182, 1167, 1144, 1123, 1092, 1035, 1008, 756, 718, 710.

Elemental analysis: Theoretical:	N: 5.12 %	C: 65.91 %	H: 5.53 %	S: 11.73 %
Found:	N: 4.84 %	C: 66.20 %	H: 5.78 %	S: 11.33 %



Chemical Formula: $C_{32}H_{26}N_2O_4S_2$
Exact Mass: 566,1334
Molecular Weight: 566,6898
m/z: 566.1334 (100.0%), 567.1368 (34.6%), 568.1292 (9.0%), 568.1401 (5.8%), 569.1325 (3.1%), 567.1328 (1.6%)
Elemental Analysis: C, 67.82; H, 4.62; N, 4.94; O, 11.29; S, 11.32

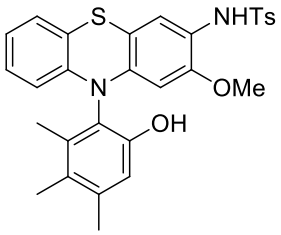
3ed (CHB-192): The crude product was purified by flash column chromatography on silica gel, cyclohexane / ethyl acetate (7:3). Isolated yield: 50 % (grey sticky solid).

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.20 (s, 1H), 9.33 (s, 1H), 7.72 (dd, ^3J = 8.5 Hz, ^4J = 2.4 Hz, 1H), 7.62 (d, ^3J = 7.8 Hz, 2H), 7.58 (d, ^3J = 8.2 Hz, 2H), 7.53 (d, ^4J = 1.5 Hz, 1H), 7.38 (t, ^3J = 7.5 Hz, 2H), 7.30 (d, ^3J = 8.4 Hz, 2H), 7.27 (t, ^3J = 7.3 Hz, 1H), 7.23 (d, ^3J = 8.5 Hz, 2H), 7.01 (d, ^3J = 7.4 Hz, 1H), 6.90 (t, ^3J = 7.4 Hz, 1H), 6.81 (t, ^3J = 7.7 Hz, 1H), 6.80 (s, 1H), 6.13 (d, ^3J = 8.3 Hz, 1H), 5.74 (s, 1H), 3.07 (s, 3H), 2.31 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6): δ (ppm) = 155.01 (s, C_{quat}), 152.69 (s, C_{quat}), 142.71 (s, C_{quat}), 142.60 (s, C_{quat}), 142.20 (s, C_{quat}), 138.76 (s, C_{quat}), 137.84 (s, C_{quat}), 133.06 (s, C_{quat}), 129.21 (s, CH), 129.14 (s, CH), 128.90 (s, CH), 128.48 (s, CH), 127.31 (s, CH), 126.90 (s, CH), 126.77 (s, C_{quat}), 126.73 (s, CH), 126.34 (s, CH), 125.98 (s, CH), 124.21 (s, CH), 122.53 (s, CH), 119.70 (s, C_{quat}), 118.71 (s, C_{quat}), 117.89 (s, CH), 115.63 (s, CH), 108.64 (s, C_{quat}), 110.42 (s, CH), 55.17 (s, CH_3), 20.96 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3308, 2931, 1592, 1486, 1467, 1442, 1380, 1332, 1289, 1262, 1215, 1187, 1151, 1090, 1064, 1042, 1001, 929, 898, 828, 813, 764, 745, 698.

Elemental analysis: Theoretical:	N: 4.94 %	C: 67.82 %	H: 4.62 %	S: 11.32 %
Found:	N: 4.59 %	C: 67.45 %	H: 4.91 %	S: 11.04 %



Chemical Formula: $C_{29}H_{28}N_2O_4S_2$
Exact Mass: 532,1490
Molecular Weight: 532,6736
m/z: 532.1490 (100.0%), 533.1524 (31.4%), 534.1448 (9.0%), 534.1558 (4.7%), 535.1482 (2.8%), 533.1484 (1.6%)
Elemental Analysis: C, 65.39; H, 5.30; N, 5.26; O, 12.01; S, 12.04

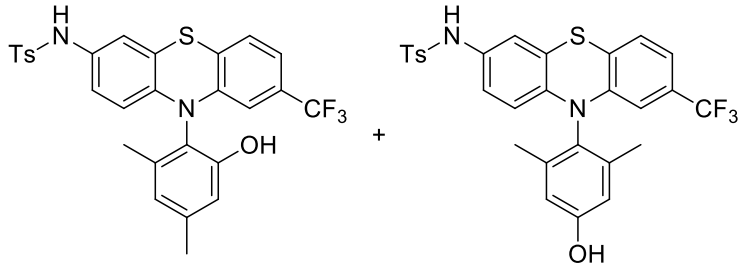
3ea (CHB-186): The crude product was purified by flash column chromatography on silica gel, cyclohexane / ethyl acetate (7:3). Isolated yield: 53 % (greenish-grey solid).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.46 (s, 1H), 9.28 (s, 1H), 7.58 (second order doublet, 2H), 7.30 (second order doublet, 2H), 6.96 (dd, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H), 6.85 (td, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H), 6.78 (td, ^3J = 7.1 Hz, ^4J = 0.9 Hz, 2H), 6.74 (s, 1H), 5.98 (dd, ^3J = 8.1 Hz, ^4J = 0.9 Hz, 1H), 5.64 (s, 1H), 3.06 (s, 3H), 2.32 (s, 3H), 2.23 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.82 (s, C_{quat}), 152.67 (s, C_{quat}), 142.69 (s, C_{quat}), 142.00 (s, C_{quat}), 141.71 (s, C_{quat}), 137.91 (s, C_{quat}), 137.51 (s, C_{quat}), 135.80 (s, C_{quat}), 129.19 (s, CH), 127.30 (s, CH), 126.80 (s, C_{quat}), 126.75 (s, CH), 126.23 (s, CH), 124.17 (s, CH), 123.14 (s, C_{quat}), 122.40 (s, CH), 119.50 (s, C_{quat}), 118.72 (s, C_{quat}), 115.46 (s, CH), 115.41 (s, CH), 108.66 (s, C_{quat}), 100.23 (s, CH), 55.24 (s, CH_3), 20.98 (s, CH_3), 20.61 (s, CH_3), 15.30 (s, CH_3), 14.25 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3435, 3100, 3053, 3007, 2922, 2166, 1968, 1653, 1556, 1536, 1451, 1436, 1307, 1254, 1218, 1199, 1190, 1182, 1167, 1144, 1123, 1092, 1035, 1008, 767, 756, 718, 710.

EI-HRMS: mass spectrometry: m/z for $[C_{29}H_{28}N_2O4S_2]^{\bullet+}$: 532.1490, found: 532.1497.



Chemical Formula: $C_{28}H_{23}F_3N_2O_3S_2$
Exact Mass: 556,1102
Molecular Weight: 556,6190
m/z: 556.1102 (100.0%), 557.1136 (30.3%), 558.1060 (9.0%), 558.1169 (4.4%), 559.1094 (2.7%), 557.1096 (1.6%)
Elemental Analysis: C, 60.42; H, 4.16; F, 10.24; N, 5.03; O, 8.62; S, 11.52

3cl + 3cl' (CHB-190): The crude product was purified by flash column chromatography on silica gel, cyclohexane / ethyl acetate (7:3). Isolated yield: 98 %.

Ortho-functionalized product (**3cl**): 64% isolated yield (dark purple sticky solid).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.02 (s, 1H), 9.85 (s, 1H), 7.62 (second order doublet, 2H), 7.33 (second order doublet, 2H), 7.15 (d, ^3J = 7.9 Hz, 1H), 7.06 (d, ^3J = 7.9 Hz, 1H), 6.75 (s, 1H), 6.71 (s, 1H), 6.64 (dd, ^4J = 2.3 Hz, ^3J = 8.8 Hz, 1H), 6.14 (s, 1H), 5.87 (d, ^3J = 8.9 Hz, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.03 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6): δ (ppm) = 155.07 (s, C_{quat}), 143.29 (s, C_{quat}), 142.45 (s, C_{quat}), 139.62 (s, C_{quat}), 137.74 (s, C_{quat}), 137.27 (s, C_{quat}), 136.63 (s, C_{quat}), 129.74 (s, CH), 128.08 (q, ^2J = 31.6 Hz, C_{quat}) 127.05 (s, CH), 126.72 (s, CH), 123.87 (q, ^1J = 272.6 Hz, C_{quat}), 123.42 (s, C_{quat}), 122.96 (s, CH), 121.92 (s, C_{quat}), 120.27 (s, CH), 118.62 (s, CH), 118.49 (q, ^3J = 3.6 Hz, CH), 118.38 (s, C_{quat}), 115.67 (s, CH), 115.06 (s, CH), 110.15 (q, ^3J = 4.3 Hz, CH), 21.00 (s, CH_3), 20.99 (s, CH_3), 16.82 (s, CH_3). (One C_{quat} signal is overlapped)

^{19}F {^{1}H} NMR (376 MHz, CD_2Cl_2): δ (ppm) = -61.76 (s, CF_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3254, 2924, 1740, 1596, 1500, 1476, 1412, 1325, 1248, 1210, 1154, 1120, 1087, 1051, 952, 912, 871, 838, 811, 706, 668.

EI-HRMS: mass spectrometry: m/z for $[C_{28}H_{23}F_3N_2O_3S_2]^{\bullet+}$: 556.1102, found: 556.1141.

Para-functionalized product (**3cl'**): 34% isolated yield (greenish-grey sticky solid).

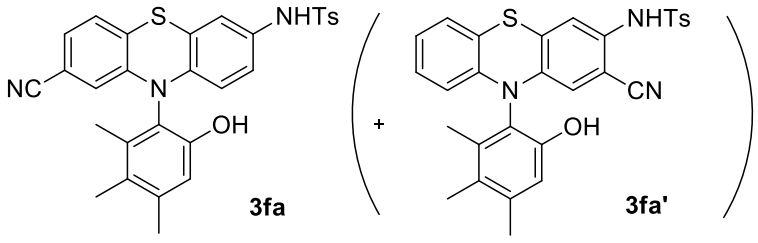
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.01 (s, 1H), 9.71 (s, 1H), 7.60 (second order doublet, 2H), 7.34 (second order doublet, 2H), 7.12 (d, ^{3}J = 7.9 Hz, 1H), 7.04 (d, ^{3}J = 8.0 Hz, 1H), 6.71 (s, 2H), 6.64 (d, ^{4}J = 2.4 Hz, 1H), 6.57 (dd, ^{3}J = 8.9 Hz, ^{4}J = 2.4 Hz, 1H), 5.88 (d, ^{4}J = 1.0 Hz, 1H), 5.74 (d, ^{3}J = 8.9 Hz, 1H), 2.34 (s, 3H), 1.96 (s, 6H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6): δ (ppm) = 157.35 (s, C_{quat}), 143.29 (s, C_{quat}), 141.75 (s, C_{quat}), 138.21 (s, C_{quat}), 136.82 (s, C_{quat}), 136.65 (s, C_{quat}), 132.93 (s, C_{quat}), 129.70 (s, CH), 128.21 (q, ^{2}J = 31.9 Hz, C_{quat}), 127.14 (s, CH), 127.06 (s, C_{quat}), 126.67 (s, CH), 123.69 (q, ^{1}J = 272.5 Hz, C_{quat}), 122.32 (s, C_{quat}), 120.34 (s, CH), 118.58 (s, CH), 118.52 (q, ^{3}J = 4.4 Hz, CH), 117.29 (s, C_{quat}), 116.29 (s, CH), 114.79 (s, CH), 108.75 (q, ^{3}J = 3.9 Hz, CH), 20.97 (s, CH_3), 17.36 (s, CH_3).

^{19}F {^{1}H} NMR (376 MHz, CD_2Cl_2): δ (ppm) = -62.00 (s, CF_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3470, 3433, 3007, 2926, 1656, 1556, 1536, 1479, 1436, 1307, 1255, 1191, 1183, 1167, 1145, 1129, 1098, 1038, 1009, 883, 754, 721, 709.

EI-HRMS: mass spectrometry: m/z for $[C_{28}H_{23}F_3N_2O_3S_2]^{\bullet+}$: 556.1102, found: 556.1157.



Chemical Formula: $C_{29}H_{25}N_3O_3S_2$
Exact Mass: 527,1337
Molecular Weight: 527,6571
m/z: 527.1337 (100.0%), 528.1371 (31.4%), 529.1295 (9.0%), 529.1404 (4.7%), 530.1329 (2.8%), 528.1331 (1.6%), 528.1308 (1.1%)
Elemental Analysis: C, 66.01; H, 4.78; N, 7.96; O, 9.10; S, 12.15

3fa (JRW-492): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 85% of **3fa** (lawngreen powder), and 8% of **3fa'**. Characterization of major product **3fa**:

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.03 (s, OH), 9.56 (s, NH), 7.62 (d, ^{3}J = 8.4 Hz, 2H), 7.35 (d, ^{3}J = 8.0 Hz, 2H), 7.15 (m, 2H), 6.78 (s, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.62 (dd, ^{3}J = 8.8 Hz, J = 2.4 Hz, 1H), 6.02 (d, J = 1.2 Hz, 1H), 5.83 (d, ^{3}J = 8.8 Hz, 1H), 2.34 (s, 3H), 2.26 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.18 (s, C_{quat}), 143.25 (s, C_{quat}), 142.57 (s, C_{quat}), 138.06 (s, C_{quat}), 137.54 (s, C_{quat}), 136.60 (s, C_{quat}), 135.48 (s, C_{quat}), 132.86 (s, C_{quat}), 129.70 (s, 2CH), 127.17 (s, CH), 127.12 (s, C_{quat}), 126.66 (s, 2CH), 125.50 (s, CH), 125.20 (s, C_{quat}), 121.90 (s, C_{quat}), 120.27 (s, CH), 118.64 (s, C_{quat}), 118.48 (s, CH), 117.91 (s, C_{quat}), 116.21 (s, CH), 115.91 (s, CH), 115.68 (s, CH), 109.65 (s, C_{quat}), 20.95 (s, CH_3), 20.55 (s, CH_3), 15.24 (s, CH_3), 13.99 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3250, 2925, 2227, 1740, 1598, 1557, 1466, 1400, 1302, 1206, 1153, 1089, 1040, 986, 939, 905, 854, 809, 770, 745, 721, 704, 660.

Elemental analysis theoretical : N 7.96%, C 66.01%, H 4.78%, S 12.15%.

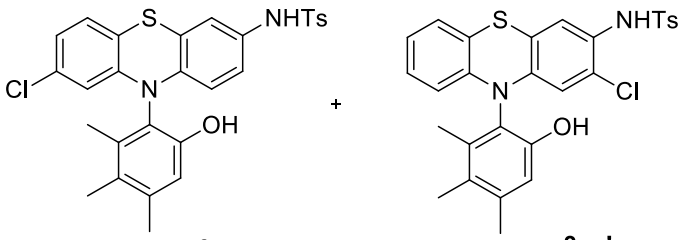
Found : N 7.86%, C 65.44%, H 4.88%, S 12.19%.

Characterization of minor product **3fa'** (8%):

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.18 (s, 1H) 9.61 (s, 1H), 7.61 (2nd order d, ^{3}J ~ 8.3 Hz, 2H), 7.40 (2nd order d, ^{3}J ~ 8.3 Hz, 2H), 6.95 (dd, ^{3}J = 7.3 Hz, ^{4}J = 1.5 Hz, 1H), 6.89 (~td, ^{3}J = 7.7 Hz, ^{4}J = 1.8 Hz, 1H), 6.81 (td, ^{3}J = 7.3 Hz, ^{4}J = 1.2 Hz, 1H), 6.80 (s, 1H), 6.52 (s, 1H), 5.95 (s, 1H), 5.93 (dd, ^{3}J = 8.3 Hz, ^{4}J = 1 Hz, 1H), 2.39 (s, CH_3), 2.26 (s, CH_3), 2.09 (s, CH_3), 2.08 (s, CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.11 (s, C_{quat}), 143.52 (s, C_{quat}), 140.98 (s, C_{quat}), 140.56 (s, C_{quat}), 138.17 (s, C_{quat}), 136.58 (s, C_{quat}), 135.43 (s, C_{quat}), 132.37 (s, C_{quat}), 129.73 (s, 2CH), 128.14 (s, CH), 127.18 (s, C_{quat}), 126.83 (s, 2CH), 126.36 (s, CH), 124.54 (s, CH), 123.10 (s, CH), 121.85 (s, C_{quat}), 116.91 (s, CH), 116.40 (s, C_{quat}), 116.36 (s, C_{quat}), 115.71 (s, CH), 115.47 (s, CH), 108.82 (s, C_{quat}), 21.00 (s, CH_3), 20.54 (s, CH_3), 15.22 (s, CH_3), 13.97 (s, CH_3).

Poorly regio-selective functional groups, the case of chloro-phenothiazine



3ga **3ga'**

Chemical Formula: $C_{28}H_{25}ClN_2O_3S_2$
Exact Mass: 536,0995
Molecular Weight: 537,0927
m/z: 536.0995 (100.0%), 538.0966 (32.0%), 537.1029 (30.3%), 539.0999 (9.7%), 538.0953 (9.0%), 538.1062 (4.4%), 540.0924 (2.9%), 539.0987 (2.7%), 537.0989 (1.6%), 540.1033 (1.4%)
Elemental Analysis: C, 62.61; H, 4.69; Cl, 6.60; N, 5.22; O, 8.94; S, 11.94

3ga (JRW-481): The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 93% (**3ga** + **3ga'**, 1.4/1, lime powder).

3ga: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.98 (s, OH), 9.52 (s, NH), 7.61 (d, ^3J = 8.0 Hz, 2H), 7.35 (d, ^3J = 8.0 Hz, 2H), 6.98 (d, ^3J = 8.0 Hz, 1H), 6.81 (dd, ^3J = 8.0 Hz, J = 2.0 Hz, 1H), 6.76 (s, 1H), 6.66 (s, 1H), 6.61 (dd, ^3J = 8.8 Hz, J = 2.4 Hz, 1H), 5.87 (d, J = 2.0 Hz, 1H), 5.85 (d, ^3J = 8.8 Hz, 1H), 2.34 (s, 3H), 2.25 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.34 (s, C_{quat}), 143.40 (s, C_{quat}), 143.21 ((s, C_{quat}), 138.01 (s, C_{quat}), 137.85 (s, C_{quat}), 136.62 (s, C_{quat}), 135.49 (s, C_{quat}), 132.56 (s, C_{quat}), 131.83 (s, C_{quat}), 129.69 (s, 2CH), 127.42 (s, CH), 126.97 (s, C_{quat}), 126.65 (s, 2CH), 122.37 (s, C_{quat}), 121.48 (s, CH), 119.99 (s, CH), 118.85 (s, C_{quat}), 118.50 (s, CH), 116.73 (s, C_{quat}), 115.82 (s, CH), 115.50 (s, CH), 114.26 (s, CH), 20.95 (s, CH_3), 20.54 (s, CH_3), 15.24 (s, CH_3), 14.02 (s, CH_3).

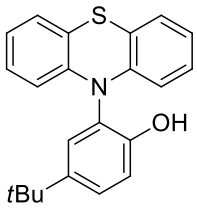
3ga': ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.73 (s, OH), 9.56 (s, NH), 7.59 (d, ^3J = 8.0 Hz, 2H), 7.36 (d, ^3J = 8.4 Hz, 2H), 6.98 (dd, ^3J = 7.6 Hz, J = 1.6 Hz, 1H), 6.89 (td, ^3J = 7.6 Hz, J = 1.6 Hz, 1H), 6.81 (td, ^3J = 7.6 Hz, J = 1.2 Hz, 1H), 6.77 (s, 1H), 6.74 (s, 1H), 5.97 (dd, ^3J = 8.0 Hz, J = 1.0 Hz, 1H), 5.85 (s, 1H), 2.37 (s, 3H), 2.25 (s, 3H), 2.08 (s, 6H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 152.30 (s, C_{quat}), 143.11 (s, C_{quat}), 141.53 (s, C_{quat}), 141.03 (s, C_{quat}), 137.92 (s, C_{quat}), 137.58 (s, C_{quat}), 135.45 (s, C_{quat}), 129.55 (s, 2CH), 128.76 (s, C_{quat}), 127.68 (s, CH), 127.16 (s, C_{quat}), 127.00 (s, C_{quat}), 126.70 (s, 2CH), 126.31 (s,

CH), 125.57 (s, CH), 122.82 (s, CH), 122.35 (s, C_{quat}), 117.92 (s, C_{quat}), 117.43 (s, C_{quat}), 115.52 (s, CH), 115.45 (s, CH), 114.87 (s, CH), 20.99 (s, CH_3), 20.53 (s, CH_3), 15.23 (s, CH_3), 14.03 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3252, 2922, 1598, 1572, 1492, 1461, 1390, 1299, 1246, 1185, 1153, 1090, 1038, 1019, 950, 939, 904, 849, 803, 766, 740, 660.

EI-HRMS: mass spectrometry: m/z calc. for $[C_{28}H_{25}ClN_2O_3S_2]^{\bullet+}$: 536.0995, found: 536.1042.

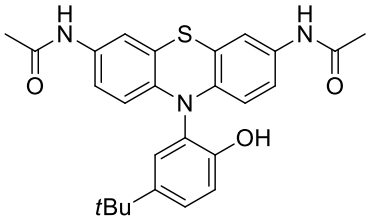


(control experiment)

Chemical Formula: $C_{22}H_{21}NOS$
Exact Mass: 347,1344
Molecular Weight: 347,4732
m/z: 347.1344 (100.0%), 348.1377 (23.8%), 349.1302 (4.5%), 349.1411 (2.7%), 350.1335 (1.1%)
Elemental Analysis: C, 76.04; H, 6.09; N, 4.03; O, 4.60; S, 9.23

4ia (CHB-92): Note: this compound was already characterized in a previous publication.[S5] Compound **1i** (1 mmol), *tert*-butyl phenol (3 mmol), PhCl (2.5 mL) and AcOH (0.5 mL) were united under air in a 170 mL screw cap reactor. The reaction mixture was heated to 150 °C for 24 h. the reaction mixture was directly purified by flash column chromatography on silica gel, pentane / ethyl acetate (gradient 9:1 to 4:1). Isolated yield: 78 %.

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.76 (s, 1H), 7.40 (dd, ^3J = 8.5 Hz, ^4J = 2.5 Hz, 2H), 7.16 (d, ^4J = 2.5 Hz, 1H), 7.07 (d, ^3J = 8.5 Hz, 1H), 6.99 (dd, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 2H), 6.89 (td, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 2H), 6.79 (td, ^3J = 7.4 Hz, ^4J = 1.1 Hz, 2H), 6.06 (dd, ^3J = 8.3 Hz, ^4J = 1.0 Hz, 2H), 1.25 (s, 9H).



Chemical Formula: $C_{26}H_{27}N_3O_3S$
Exact Mass: 461,1773
Molecular Weight: 461,5759
m/z: 461.1773 (100.0%), 462.1807 (28.1%), 463.1731 (4.5%), 463.1840 (3.8%), 464.1765 (1.3%), 462.1743 (1.1%)
Elemental Analysis: C, 67.65; H, 5.90; N, 9.10; O, 10.40; S, 6.95

3jb (CHB-193): The crude product was purified by flash column chromatography on silica gel, cyclohexane / ethyl acetate (7:3). Isolated yield: 35 % (green solid).

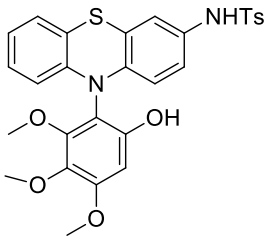
Route B for **3jb** (PAG-6): The reaction was conducted according to a recently reported protocol.[S6] The crude product was purified by flash column chromatography on silica gel with pure ethyl acetate. Isolated yield: 73 % (green solid).

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.77 (s, 2H), 9.70 (s, 1H), 7.38 (dd, ^3J = 8.6 Hz, ^4J = 2.4 Hz, 1H), 7.36 (d, ^4J = 2.4 Hz, 2H), 7.14 (d, ^4J = 2.4 Hz, 1H), 7.05 (d, ^3J = 8.5 Hz, 1H), 6.95 (dd, ^3J = 8.8 Hz, ^4J = 2.3 Hz, 1H), 5.96 (d, ^3J = 8.9 Hz, 1H), 1.97 (s, 6H), 1.25 (s, 9H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6): δ (ppm) = 167.83 (s, C_{quat}), 153.09 (s, C_{quat}), 143.64 (s, C_{quat}), 138.62 (s, C_{quat}), 133.86 (s, C_{quat}), 127.64 (s, CH), 126.79 (s, CH), 125.84 (s, C_{quat}), 118.15 (s, CH), 117.91 (s, C_{quat}), 116.90 (s, CH), 116.75 (s, CH), 115.15 (s, CH), 33.85 (s, C_{quat}), 31.35 (s, CH_3), 23.80 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3203, 2954, 1717, 1667, 1634, 1599, 1503, 1473, 1391, 1370, 1297, 1247, 1214, 1162, 1127, 1016, 972, 868, 804, 796.

Elemental analysis: Theoretical:	N: 9.10 %	C: 67.65 %	H: 5.90 %	S: 6.95 %
Found:	N: 8.17 %	C: 67.24 %	H: 6.30 %	S: 6.51 %



Chemical Formula: $C_{28}H_{26}N_2O_6S_2$
Exact Mass: 550.1232
Molecular Weight: 550.6458
m/z: 550.1232 (100.0%), 551.1266 (30.3%), 552.1190 (9.0%), 552.1299 (4.4%), 553.1224 (2.7%), 551.1226 (1.6%), 552.1275 (1.2%)
Elemental Analysis: C, 61.07; H, 4.76; N, 5.09; O, 17.43; S, 11.65

3am (JRW-485): Synthesized by N-p-tosyl-phenothiazinimine (1.0 mmol, 366 mg) and 3,4,5-trimethoxyl-phenol (3.0 mmol, 552 mg) in cumene (2.5 ml) and acetic acid (0.5 ml) under 110 °C in the oxygen atmosphere. The crude product was purified by flash column chromatography on silica gel with the solution of hexane/ethyl acetate 1/1. Isolated yield: 44% (moss-green oil liquid).

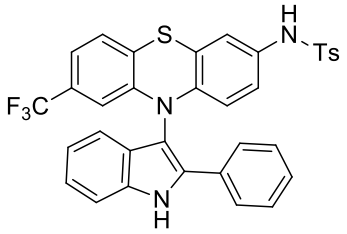
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.91 (s, OH), 9.72 (s, NH), 7.61 (d, ^{3}J = 8.4 Hz, 2H), 7.34 (d, ^{3}J = 8.0 Hz, 2H), 6.91 (m, 2H), 6.75 (td, ^{3}J = 7.6 Hz, J = 1.2 Hz, 1H), 6.62 (m, 2H), 6.48 (s, 1H), 6.06 (dd, ^{3}J = 8.4 Hz, J = 1.2 Hz, 1H), 5.96 (d, ^{3}J = 8.4 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 3.61 (s, 3H), 2.34 (s, 3H).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 153.73 (s, C_{quat}), 152.04 (s, C_{quat}), 151.17 (s, C_{quat}), 143.16 (s, C_{quat}), 142.57 (s, C_{quat}), 139.57 (s, C_{quat}), 136.55 (s, C_{quat}), 135.14 (s, C_{quat}), 131.90 (s, C_{quat}), 129.64 (s, 2CH), 127.33 (s, CH), 126.68 (s, 2CH), 126.03 (s, CH), 122.00 (s, CH), 120.01 (s, CH), 119.17 (s, C_{quat}), 118.61 (s, CH), 117.61 (s, C_{quat}), 115.55 (s, CH), 115.14 (s, CH), 112.40 (s, C_{quat}), 95.83 (s, CH), 60.72 (s, CH_3), 60.60 (s, CH_3), 55.56 (s, CH_3), 20.94 (s, CH_3).

IR (neat, cm^{-1}): U: 3247, 2929, 2852, 1694, 1644, 1595, 1491, 1463, 1416, 1377, 1309, 1221, 1154, 1091, 1037, 992, 947, 915, 809, 747, 703.

Elemental analysis theoretical : N 5.09%, C 61.07%, H 4.76%, S 11.65%.

Found : N 4.47%, C 60.30%, H 4.98%, S 10.63%.



Chemical Formula: $C_{34}H_{24}F_3N_3O_2S_2$
Exact Mass: 627.1262
Molecular Weight: 627.6985
m/z: 627.1262 (100.0%), 628.1296 (36.8%), 629.1220 (9.0%), 629.1329 (6.6%), 630.1254 (3.3%), 628.1256 (1.6%), 628.1232 (1.1%)
Elemental Analysis: C, 65.06; H, 3.85; F, 9.08; N, 6.69; O, 5.10; S, 10.22

3cn (CHB-202): Synthesized by 2-trifluoromethyl-N-p-tosyl-phenothiazinimine (1.0 mmol, 434 mg) and 2-phenylindole (3.0 mmol, 579 mg) in cumene (2.5 ml) and acetic acid (0.5 ml) under 110 °C in the oxygen atmosphere. The crude product was purified by flash column chromatography on silica gel with the solution of hexane / ethyl acetate 7/3. Isolated yield: 90% (dark purple).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.03 (s, NH from indole), 10.09 (s, NH from tosylamide), 7.85 (d, ^3J = 8.0 Hz, 2H), 7.59 (m, 3H), 7.44 (t, ^3J= 7.2 Hz, 2H), 7.21~7.35 (m, 7H), 7.09 (m, 2H), 6.84 (d, J = 2.8 Hz, 2H), 6.59 (dd, ^3J = 8.8 Hz, J = 2.4 Hz, 1H), 6.41 (s, 1H), 6.15 (d, ^3J = 8.8 Hz, 1H), 2.29 (s, CH_3).

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ (ppm): 143.84 (s, C_{quat}), 143.22 (s, C_{quat}), 139.09 (s, C_{quat}), 136.55 (s, C_{quat}), 135.04 (s, C_{quat}), 133.37 (s, C_{quat}), 133.21 (s, C_{quat}), 130.15 (s, C_{quat}), 129.65 (s, 2CH), 128.99 (s, 2CH), 128.39 (s, CH), 128.00 (q, ^3J = 31.7 Hz, C_{quat}), 127.48 (s, CH), 126.62 (s, 2CH), 126.09 (s, 2CH), 124.98 (s, C_{quat}), 123.80 (q, ^3J = 272.9 Hz, C_{quat}), 123.01 (s, CH), 122.24 (s, C_{quat}), 120.52 (s, CH), 120.19 (s, CH), 119.47 (s, C_{quat}), 119.08 (q, ^3J = 3.6 Hz, CH), 118.69 (s, CH), 117.51 (s, CH), 116.53 (s, CH), 112.58 (s, CH), 111.43 (s, C_{quat}), 110.97 (q, ^3J = 3.6 Hz, CH), 20.89 (s, CH_3).

^{19}F NMR (376.5 MHz, DMSO-d_6) δ (ppm): -61.85 (s, CF_3).

IR (neat, cm^{-1}): U: 3133, 3053, 2950, 1634, 1603, 1582, 1526, 1504, 1474, 1445, 1369, 1352, 1270, 1244, 1203, 1142, 1127, 1080, 1069, 1027, 936, 916, 800, 780, 749, 736, 718, 692.

Elemental analysis theoretical : N 6.69%, C 65.06%, H 3.85%, S 10.22%.

Found : N 6.54%, C 64.90%, H 4.00%, S 10.14%.

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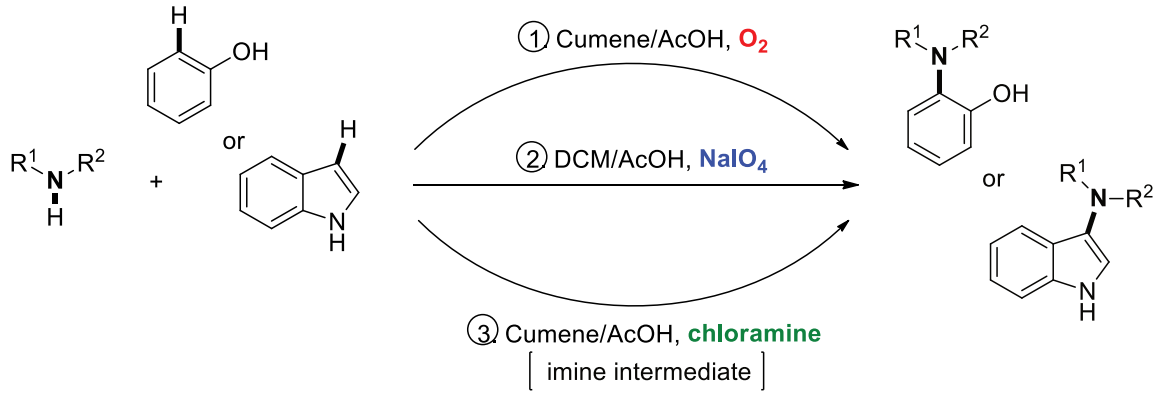
In summary, we've successfully developed series of novel simplified transition metal-free conditions for the typical C-N bond formation reactions. We also selected numerous efficient and challenging oxidants to conduct the amiantion reaction of phenols or indoles with phenothiazines or its derivatives.

From chapter II to chapter IV, we had mainly discussed these classical oxidant, the molecular oxygen, the hypervalent iodines, and the chloramine substrates. And for each of them, we discovered a suitable condition to smoothly perform the typical C-N bond formation reaction (Scheme 1).



Scheme 1. Summary of different oxidants in the transition metal-free amination reaction

Mechanistically, transition metal-free amination reactions performed particularly different pathways from the classical transition metal catalyzed cases. As significant examples, those novel C-N bond formation methodologies were conducted either in radical pathway, or in electrophilic aromatic substitution. So far, the study to the mechanism research was still under development. We would design some more control experiment to get close to it.

With respect to the CDC amination reactions, we expect to discover some more efficient and green oxidants which may have chance to overcome the scope limits of previous results.

Finally, we hope that the synthesized specifically reactive phenothiazinimine substrate will have a place in the synthetic toolbox in the near future.

7. Curriculum vitae

Personal Data

Name	Rongwei JIN
Nationality	Chinese

Education

08. 2014 - 12.2017	PhD in Organic Chemistry, TU Kaiserslautern, Germany, under the supervision of Prof. Dr. Frederic W. Patureau.
09. 2012 - 06. 2014	M.S. in Organometallic Chemistry, under the supervision of Prof. Dr. Pierre H. Dixneuf and Prof. Henri Doucet, University of Rennes 1, France, with a thesis entitled "*Regio-,monocontroled Palladium-Catalysed Direct Arylation at Carbon C2 of Pyrroles using Benzenesulfonyl Chlorides*".
09. 2008 - 06. 2012	B.A. in Chemistry College, Lanzhou University, China.
09. 2005 - 06. 2008	Yiwu High School, Zhejiang, China.

Personal Activities

03. 2017	3rd **IGCS**-Mitglied, 3rd **International Green Science Symposium & Advanced School for Green Chemistry**, Rennes, France.
05. 2015	Member of **HFMC Conference**, Heidelberg, Germany
07. 2014	Host and assistant, 2nd **International Symposium of C-H bond Activation**, Rennes, France.

Publications

2013-2014	Charles Beromeo Bheeter, **Rongwei Jin**, Jitendra K. Bera and Henri Doucet, *RSC. Adv.* **2013** (Impact factor: 3.708) (Palladium-catalysed direct heteroarylation of bromobenzenes bearing SO_2R substituents at C2 or C4)
	Charles Beromeo Bheeter, **Rongwei Jin**, Jitendra K.Bera, Pierre

H.Dixneuf, Henri Doucet, *Adv.Synth.Catal.* **2014** (Impact factor: 5.542)
(Intramolecular palladium-catalysed dehydrogenative sp3 C-H bonds functionalisation for the synthesis of unsaturated N-alkenyl sulfonamides)

Rongwei Jin, Charles Beromeo Bheeter, Henri Doucet, *Beilstein Journal of Organic Chemistry*, **2014** (Impact factor: 2.820)
(Hindered aryl bromides for regioselective palladium-catalysed direct arylation at less favourable C5 of 3-substituted thiophenes)

Rongwei Jin, Frederic W. Patureau, *ChemCatChem.* **2014** (Highlight, Impact factor: 5.044)
(Metal-free dehydrogenative isoquinolone synthesis)

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(Palladium-catalysed direct desulfitative arylation of pyrroles using benzenesulfonyl chlorides as alternative coupling partners)

2015-2017

Marie-L. Louiallt-Habermeyer, **Rongwei Jin**, Frederic W. Patureau, *Angew. Chem. Int. Ed.* **2015** (Impact factor: 11.26)
(O2-mediated dehydrogenative amination of phenols)

Rongwei Jin, Frederic W. Patureau, *Org. Lett.* **2016** (Impact factor: 6.579)
(Mild, periodate-mediated, dehydrogenative C−N bond formation with phenothiazines and phenols)

Rongwei Jin, Christina Bub, Frederic W. Patureau, *Org. Lett.* **2018**, *accepted*. (doi: 10.1021/acs.orglett.8b00914)
(Phenothiazinimides: atom-efficient electrophilic amination reagents)

Title: Phenothiazinimides: Atom-Efficient Electrophilic Amination Reagents

Author: Rongwei Jin, Christina L. Bub, Frederic W. Patureau

Publication: Organic Letters

Publisher: American Chemical Society

Date: Apr 1, 2018

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