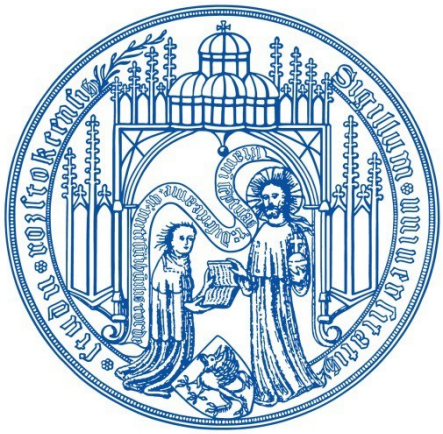
Leibniz-Institut für Katalyse e.V.
an der Universität Rostock

The development of new procedures for heterocycle synthesis under metal-free conditions



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Dedicated to my parents and on the occasion of my sister's 30th birthday!

Abstract

Universität Rostock

The development of new procedures for heterocycles synthesis under metal-free condition

Jian-Bo Feng

Leibniz-Institut für Katalyse e.V. an der Universität Rostock

This thesis mainly describes recent development in the synthesis of N- and O-containing heterocycles, which were conducted under transition-metal-free condition. During the past decades, numerous corresponding works were presented elegantly that could avoid and solve the intractable problems like metal residue, the use of toxic solvents and heavy metals. Against this background, a variety of works that employed the organic compounds as the catalyst, used ionic liquids as the solvent or under the microwave irradiation were well developed. In this case, due to the importance of heterocyclic compounds, a series of heterocycles like quinazolinones, quinazolinimines, quinazolinamines, aminoisoquinoline and dibenzoxazepinamines *etc.* were synthesized under transition-metal-free condition as presented in this thesis, which aims to provide a green, convenient and efficient methodology for the construction of the compounds bearing these units.

Diese Arbeit beschreibt vorwiegend die aktuellen Entwicklungen auf dem Gebiet der übergangsmetall-freien Synthese von stickstoff- und sauerstoffhaltigen Heterozyklen. Über die letzten Jahrzehnte wurden bereits Arbeiten veröffentlicht, welche die Probleme wie Schwermetallrückstände im Produkt oder die Verwendung von giftigen Lösungsmitteln, die durch den Gebrauch von Übergangsmetallen entstehen können, vermeiden. Vor diesem Hintergrund wurden im Rahmen dieser Arbeit chemische Reaktionsvorschriften entwickelt und untersucht, die diese Probleme durch den Einsatz von Organokatalysatoren, ionischen Flüssigkeiten oder Mikrowellenstrahlung umgehen. Somit wurden unterschiedliche Heterozyklen wie Quinazolinone, Quinazolinimine, Quinazolinamine, Aminoisoquinoline, Dibenzoxazepinamine und weitere unter übergangsmetall-freien Bedingungen synthetisiert. Die entwickelten Methoden könnten grüne, günstige und effiziente Alternativen für die Herstellung von Substanzen mit diesen genannten Struktureinheiten darstellen.

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List of Abbreviations

Ar	*Aryl*
Bn	*Benzyl*
Bu	*Butyl*
^{t}Bu	*Tert-butyl*
BHT	*2,6-bis(1,1-dimethylethyl)-4-methylphenol*
Cy	*Cyclohexyl*
Cat.	*Catalyst*
DPPP	*1,3-Bis(diphenylphosphino)propane*
DCC	*Dicyclohexylcarbodiimide*
DIPA	*Diisopropylamine*
DBU	*1,8-Diazabicycloundec-7-ene*
DMP	*Dess–Martin periodinane*
DMAD	*Dimethyl acetylenedicarboxylate*
DCM	*Dichloromethane*
DMF	*Dimethylformamide*
DHP	*Dihydropyran*
DABCO	*1,4-diazabicyclo[2.2.2]octane*
DMAP	*4-Dimethylaminopyridine*
DMSO	*Dimethyl sulfoxide*
DCDMH	*1,3-dichloro-5,5-dimethylhydantoin*
ee	*Enantiomeric excess*
etc.	*Et cetera*
et al.	*Et alii*
E	*Entgegen (describing the absolute stereochemistry of double bonds)*
EWG	*electron-withdrawing group*
EDDA	*Ethylenediamine-N,N'-diacetic acid*
h	*Hour*
iso	*Sum of branched products*
LDA	*Lithiumdiisopropylamide*

***m*-CPBA**	*meta-Chloroperoxybenzoic acid*
n	*normal*
Boc	*Butoxycarbonyl*
***N*-**	*Nitrogen substituted*
NMP	*N-Methylpyrrolidone*
NuH	*Nucleophile*
NHC	*N-Heterocyclic Carbene*
NCS	*N-Chlorosuccinimide*
NBS	*N-Bromosuccinimide*
OAc	*Acetate*
Me	*Methyl*
MOM	*Methoxymethyl acetal*
TBS	*tert-Butyldimethylsilyl*
PTSA	*p-Toluenesulfonic acid*
Ph	*Phenyl*
PIFA	*Iodosobenzene bis(trifluoroacetate)*
Ph	*Phenyl*
TMEDA	*Tetramethylethylenediamine*
TEMPO	*Transition metal*
TFAT	*Trifluoroacetic anhydride*
TFE	*Tetrafluoroethylene*
TBAF	*Tetrabutylammonium fluoride hydrate*
TMS	*Trimethylsilyl* **THF**
	Tetrahydrofuran
TFA	*Trifluoroacetic acid*
TFAA	*Trifluoroacetic anhydride*
X	*Leaving group, (pseudo)halide*
Z	*zusammen(describing the absolute stereochemistry of double bonds)*

1 Introduction

Heterocyclic compounds are highly important for their abundance in numerous natural products like vitamins,[1] alkaloids[2] and unique biological activities.[3] On the other hand, due to the extraordinary and excellent characters, the heterocycles act as an irreplaceable role not only in the pharmaceutical and medicine industry, but also in the functional materials such as OLEDs.[4] With the development of society, researches on the heterocycles synthesis seemed as a hot topic and numerous works have been developed elegantly and extensively.[5]

However, with the rapid development of the society, more and more people realized the severity of environmental problems. Paul Anastas, who directed the Green Chemistry Program and John C. Warner published a set of principles to guide the practice of green chemistry. The twelve principles addressed a range of ways to reduce the environmental and health impacts of chemical production. In Unite States, a famous and influential award named *Presidential Green Chemistry Challenge Awards*, aimed to promote the environmental and economic benefit of developing and using novel green chemistry. In Europe, the researchers of University of York contributed to the establishment of the Green Chemistry Network with the Royal Society of Chemistry and launched the journal *Green Chemistry*. In China, with the development of the industry and population explosion, the sustainable development including the environment to be bearable, sustainable and viable has been advocated by the government as a national strategy.

Recently, the transition-metal-catalyzed synthesis of heterocycles emerged as an attractive approach, which seemed to be more novel and efficient and attracted much attention in this filed. Nonetheless, the metals like Pd,[5a, b, 5e] Ag,[5d] Ru,[6] Rh,[7] Cu,[8] Co[9] *etc.* could bring the problems of metal pollution to the environment and affect the human lives ultimately. Besides, the metal residues seem to be an unavoidable problem that it is hard to remove the metals used as the catalyst or any additives in the reaction completely, which may affect the biological activities of corresponding compounds in pharmaceuticals or medicines. What is more, the metals accompanying the pharmaceuticals or the medicines would accumulate in the organisms and disturb or destroy the functions of some organs which could even lead to death.

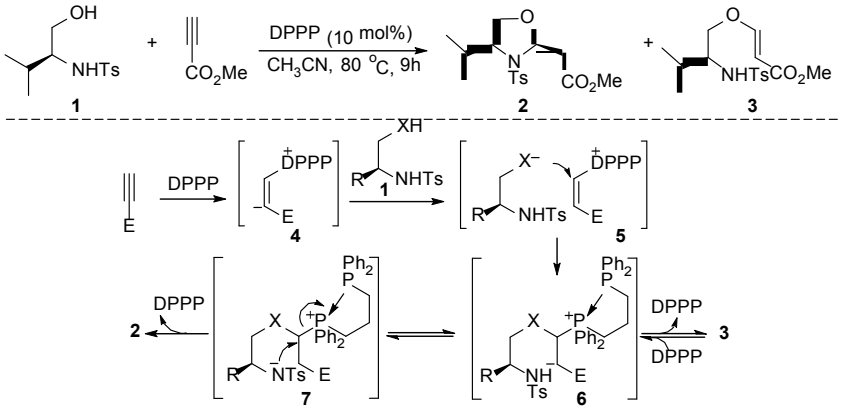
Hence, developing new methodologies of the reactions without transition metals, especial heavy and toxic metals but under transition-metal-free or organocatalytic reaction conditions seems to be as a green, environmentally favorable choice. During the past decades, a variety of methodologies for the synthesis of heterocycles were developed elegantly, such as the reactions conducted with organic catalysts, with the application of microwave irradiated technologies and the utilization of the ionic liquids instead of organic solvents. In this work, the achievements in the synthesis of 5-membered- and 6-membered-heterocycles containing O and N atom on these topics are presented selectively, which may furnish an alternate to synthesize heterocycles in considerable and ideal pathways.

2 The synthesis of *N* containing heterocycles

2.1 The synthesis of *N*-containing five-membered heterocycles

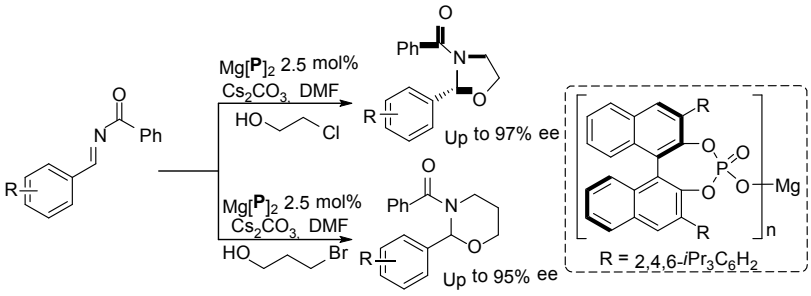
2.1.1 The synthesis of oxazolidines

In 2007, Kwon's group developed a convenient protocol for the synthesis of oxazolidines, thiozolidines, pyrrolidines and octahydroindoles *via* bisphosphine-catalyzed double Michael reactions (Scheme 1).[10] Various *β*-amino carbonyl azolidines derivatives were transformed in excellent yields with high diastereoselectivities. It was considered that the conjugated addition between DPPP and the electron-deficient acetylene could generate the vinyl anion **4**. Then, the first conjugated addition between **1** and **4** afforded the intermediate **6**. Subsequently, the *β*-elimination of the phosphine yielded the mono-Michael product **3**. However, in the presence of another phosphine moiety at an optimal distance, a S_N2 displacement would be taken place and gave the cyclized product **2** as shown in scheme 1.



Scheme. 1 DPPP-catalyzed synthesis of oxazolidine

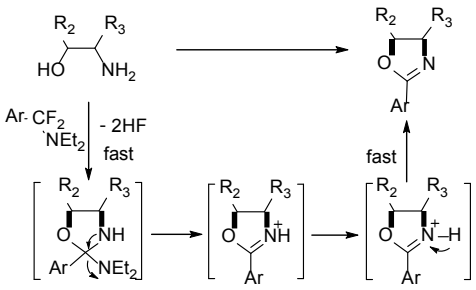
Recently, Antilla presented a highly efficient method for the enantioselective synthesis of 1.3-oxazolidines by the enantioselective addition of alcohols to imines, which was catalyzed by a chiral magnesium phosphate catalyst and followed by an intramolecular cyclization under basic condition (Scheme 2).[11] Under the optimal condition, a variety of substrates were converted to corresponding chiral heterocycles in good yields with excellent enantioselectives. Moreover, when 3-Cl- or 3-Br-propanol was used instead, the six-membered products could also be obtained in moderate to good enantioselectivies and high yields.



Scheme 2. The synthesis of 1,3-oxazolidines and 1,3-oxazinanes

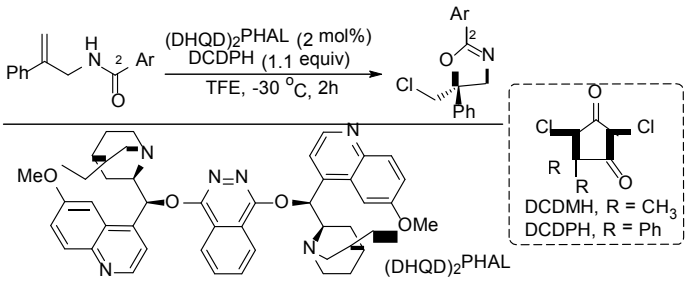
2.1.2 The synthesis of oxazolines

Amino alcohols react with benzaldehyde,[12] benzontrile[13] or the compound with a unsaturated moiety[14] to synthesis oxazolines has been reported extensively. The N and O atoms were utilized as the nucleophiles to react with unsaturated bond and the desired heterocycles were formed by an intramolecular cyclization. In addition, the Hara group found that the *α,α*-difluoroalkylamine could be used instead of these unsaturated compounds and reacted with the amino alcohols could also afford similar products. Hence, a variety of oxazolines, thiazolines and imidazolines were obtained from corresponding amino alcohols, amino thiols and diamines with α,α-difluoroalkylamine (Scheme 3).[15]



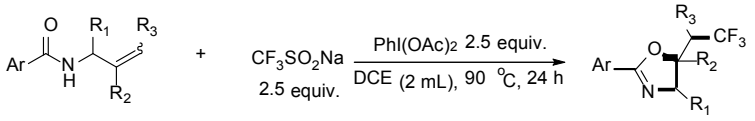
Scheme 3. The synthesis of oxazoline from amino alcohol and *α,α*-difluoroalkylamine

In 2011, Borhan and co-workers disclosed an efficient halocyclization of unsaturated amides to chiral heterocycles (Scheme 4).[16] Initially, in the presence of DCDMH, which acted as the chlorine source, $(DHQD)_2PHAL$ was tested as the best ligand and afforded the oxazoline in 57% *ee*. With further optimization, the TFE as the solvent and DCDPH as the chlorine source, the desired product could be afforded with 99% *ee* and in the excellent yields up to 97%. Interestingly, the *para* substituent on the C2 aryl ring was considered to be a crucial role in stereoselectivity. When there was a NO_2- , CH_3- or Br-, corresponding stereoselectivities were enhanced while the bulky *t*Bu group gave a lower *ee* value. In addition, it should be noted that the steric effect affected the stereoselectivity significantly. When there was a 2,4,6-triethylphenyl substituent group, the stereoselectivity was decreased dramatically.

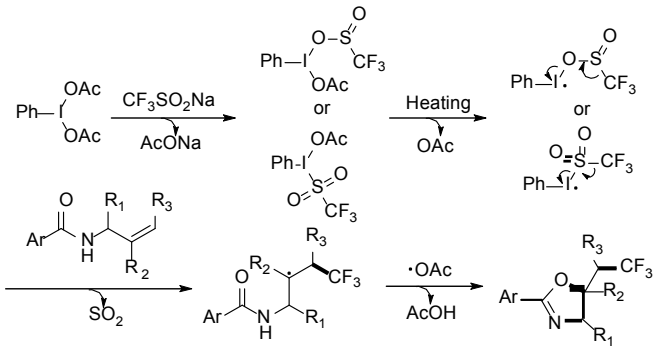


Scheme 4. Halocyclization of unsaturated amide mediated by $(DHQD)_2PHAL$

N-allylamide as the precursor to synthesize oxazolines was also presented by Fu in 2014.[17] It was the first example preparing CF_3-containing oxazolines with a sequential intermolecular trifluoromethylation and an intramolecular cyclization (Scheme 5). The CF_3-containing oxazolines were transformed from the sodium trifluoromethanesulfinate as the CF_3 source and iodobenzene diacetate as the oxidant. Under the optimal condition, all the target products were afforded in moderate to good yields and the F-, Cl-, Br- and NO_2-were tolerated well. There was no desired products could be detected when 2.5 equivalents of TEMPO was added, which seemed to be a radical intermediated procedure as illustrated in scheme 6.

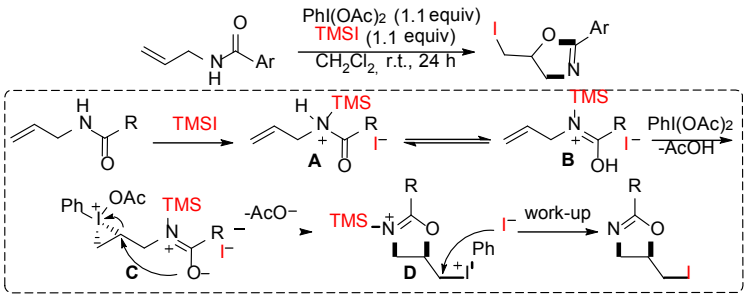


Scheme 5. Trifluoromethylation of *N*-allylamide with CF_3SO_2Na to CF_3-containing oxazoline



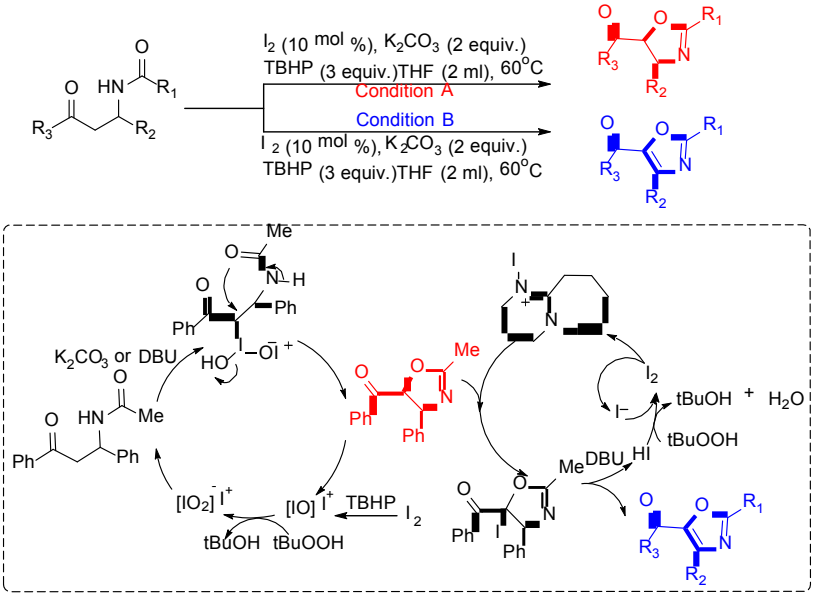
Scheme 6. The mechanism of the trifluoromethanylaiton of *N*-allylamide with CF_3SO_2Na

Later, the $PhI(OAc)_2$-promoted intramolecular cyclization of *N*-allylcarboxamide/*N*-allylcarbothioamide to synthesize oxazolines was also improved by Li's group.[18] PIDA was used as the reaction promotor and halotrimethylsilane as the halogen source. Throughout the text, the target product 5-haolomethyloxazolines/5-haolomethylthiazolines were afforded in good to excellent yields. Additionally, the TMSBr and TMSCl could also be used as the bromine and chlorine source with good yields, which could be used for the widespread application in the organic synthesis. However, the reaction pathway was completely different from the previous reports. In this protocol, it was considered that the interaction between the start material and TMSI produced intermediate **A**, which could be further tautomerized to **B**. Then the C=C bond was activated by PIDA and an intramolecular nucleophilic attack of oxygen on the iodinium three-membered ring. Subsequently, the intermediate **D** was generated followed by the formation of the final product (Scheme 7).



Scheme 7. PIDA-promoted intramolecular halooxygenation of *N*-allylbenzamide

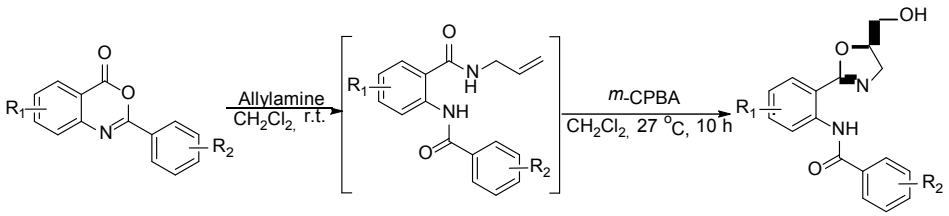
In 2015, the synthesis of oxazolines and oxazoles from *β*-acylamino ketones controlled by bases was presented by Gao and co-workers (Scheme 8).[19] TBHP was employed as the identical oxidant and I_2 as the catalyst. The difference was the base that when K_2CO_3 was used as the base, the oxazoline was given as the final product while the oxazole was generated instead in the presence of DBU. With several control experiments, it was considered that when DBU as the base, an active iodoimine intermediate could be formed and then reacted with the oxazoline. Subsequently, an *α*-iodo intermediate could be generated and was followed by an elimination in the presence of DBU, which yielded the oxazole as the final product. Certainly, within this facile method, corresponding oxazolines and oxazoles could be formed selectively and efficiently.



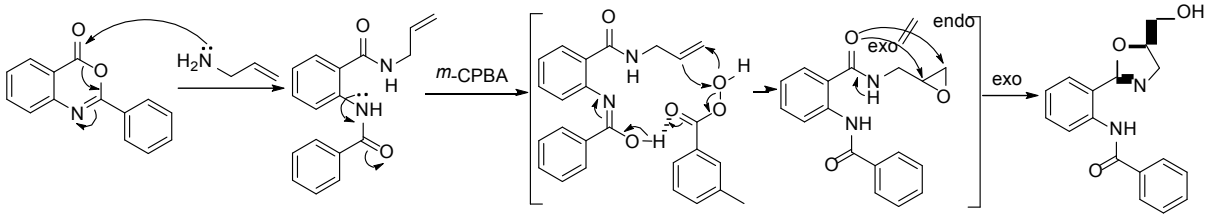
Scheme 8. I_2-catalyzed synthesis of oxazoline and oxazole controlled by base

Recently, Krishna *et al*. developed a tandem ring-opening/ring-closing strategy from benzoxazin-4-ones to oxazlines.[20] The initial hypothesis was the nonucleophilic ring-opening reaction of benzoxiazin-4-one with allylamine could lead to the *N*-allylbenzamide intermediate which could be ring-closed to form the

oxazoline in the presence of an approximate oxidant (Scheme 9). With the detailed optimization, several benzoxazin-4-ones were prepared and good to excellent yields of corresponding oxazolines were obtained. With several control experiments, the *ortho* amidic moiety which could be generated from the ring-opening seemed to be acted as an important role. When an *ortho N*-alkylated *N*-allylbenzamide (as the intermediate shown in scheme 9) was treated under the standard condition, no target product could be obtained while the *N*-actylated could afford the product in 78 % yield. Hence, a plausible mechanism was proposed that the amidic group was considered could facilitate the H-bonding with C=O of *m*-CPBA that increased the electrophilic character of *m*-CPBA on olefin to give the epoxide intermediate. Finally, the desired product was generated by the cyclization of epoxy amide (Scheme 10).



Scheme 9. The synthesis of oxazolines from benzoxazin-4-ones

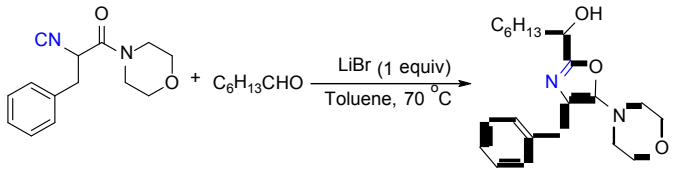


Scheme 10. The mechanism of the synthesis of oxazoline from benzoxazin-4-one

2.1.3 The synthesis of oxazoles

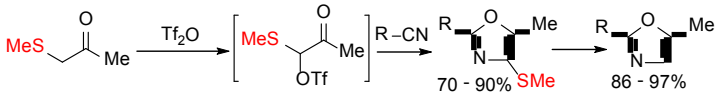
2.1.3.1 The synthesis of oxazoles based on –C≡N or -CNR_2

In 2004, the synthesis of 2,4,5-trisubstituted oxazoles from aldehyde and peptidic isocyanides was developed by Zhu (Scheme 11).[21] In the presence of lithium bromide, aldehydes and ketones with amides of *α*-isocyano-*β*-phenylpropionic acids could afford corresponding oxazoles in good to excellent yields. Due to the sparse solubility of LiBr in toluene, this reaction was considered to be catalytic in nature. The nucleophilic addition of isonitrile to *N,N*-dibenzylphenylalanal was investigated and found to be stereoselective to the *anti*-adduct. However, no stereoselectivities could be found between *N*-Boc phenylalanal and isonitrile.



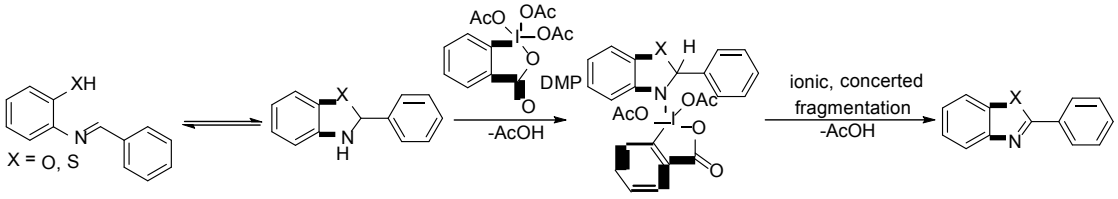
Scheme 11. The synthesis of polysubstituted oxazole from aldehyde and isonitrile

Later, Martínez-Alvarez and co-workers employed 1-(methylthio)actone and nitriles to synthesize 2,5-disubstituted and 2,4,5-trisubstituted 1,3-oxazoles in the presence of triflic anhydride.[22] The detailed control experiments indicated that the Tf_2O plays as an important role in the rate-determining step. The methylthio group at the C4 position could be removed easily with Raney nickel in good yield (Scheme 12).



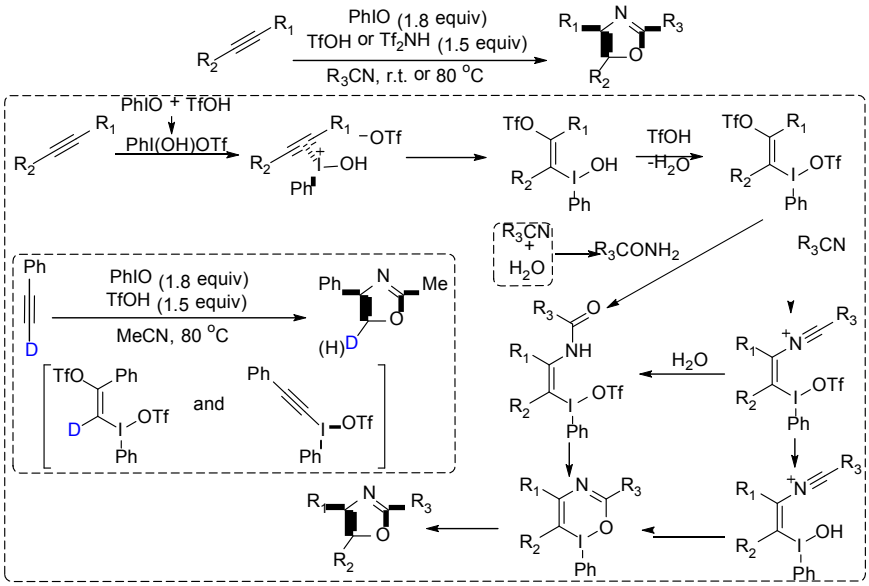
Scheme 12. The synthesis of oxazole from 1-(methylthio)actone and nitrile

Hypervalent iodine reagents as the oxidants have gained much attention for being eco-friendly. In 2007, Bose and Idrees disclosed a DMP-mediated intramolecular cyclization of azomethine to benzoxazole and benzothiazole.[23] The DMP (Dess-Martin periodinane) was a highly versatile hypervalent iodine(V) reagent. In the presence of DMP, the secondary amine followed by the cyclization could be oxidized and afforded corresponding benzoxazoles or benzothiazoles in high yields within 10-15 minutes (Scheme 13).



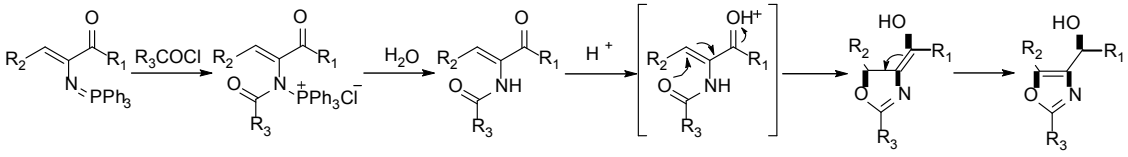
Scheme 13. The oxidative cyclization of azomethine to benzoxazole and benzothiazole by DMP

In 2013, Satio *et al* presented a [2+2+1] annulation of alkynes, nitriles and oxygen atoms to synthesize highly substituted oxazoles by the combination of PhIO with TfOH or Tf_2NH (Scheme 14). [24] The iodine(III) reagents PhI(OH)X used as a hypervalent iodine reagent, which could be formed *in situ* from iodosobenzene and a Brønsted acid. From the obtained results, both terminal and inner alkynes could give corresponding oxazoles in moderate to good yields. Moreover, a deuterium labeling experiment suggested that there exists an alkynyliodonium intermediate in the case of terminal alkyne substrate.



Scheme 14. The synthesis of oxazole from alkyne and nitrile with hypervalent iodine reagent

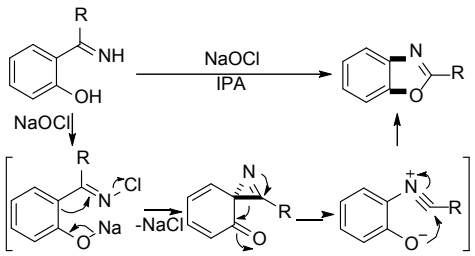
In 2012, Ding reported an approach to synthesize 2,4,5,-trisubstituted oxazole from vinyliminophosphorane, which *via* a tandem aza-Wittig/Michael/isomerization reaction.[25] Both aromatic and alkyl acyl chlorides could give corresponding oxazoles in good yields. The aza-Wittig reaction between iminophosphorane and acyl chloride could afford the amide after hydrolysis. Then an intermediate was generated by an intramolecular Michael addition under acid condition. Subsequently, the oxazole was formed as the final product with *via* isomerization, (Scheme 15).



Scheme 15. The synthesis of oxazole from vinyliminophosphorane

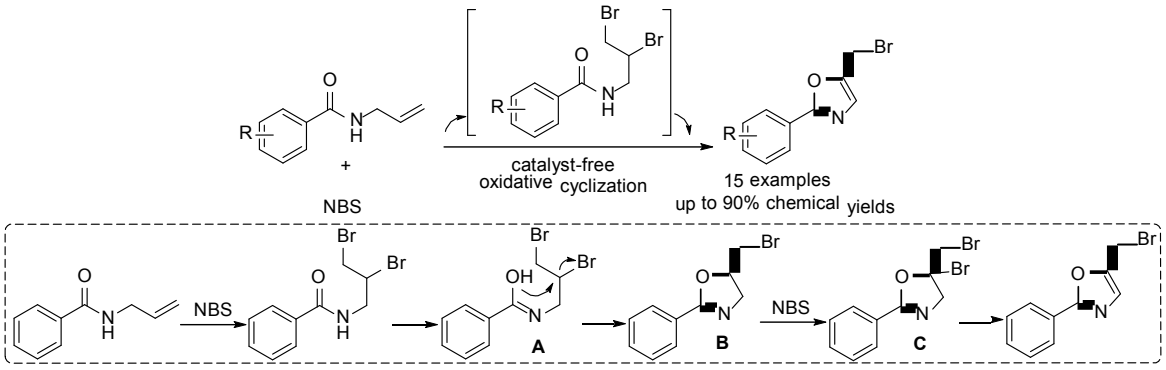
2.1.3.2 The synthesis of oxazoles based on –C=N or -CNHR

In 2011, the synthesis of 2-substituted benzoxazoles from *ortho*-hydroxyaryl N-H ketimines through a NaOCl mediated Beckmann-type rearrangement was described by the Chen group (Scheme 16).[26] In the presence of 3 equivalents of 10% aqueous NaOCl, various 2-substituted benzoxazoles were generated from corresponding *ortho*-hydroxyaryl ketimines in excellent yields. As the following depiction, the formation of benzoxazole within a Beckmann-type rearrangement *via* a spiro enone intermediate. The hydrogen bond to the phenoxide in aqueous media could weaken the nucleophilicity of the phenoxides. Hence, the species favored the [1,2]-aryl migration rearrangement and gave the oxazole as the product.



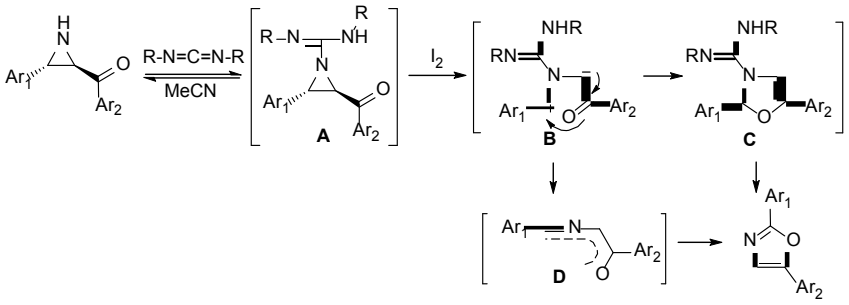
Scheme 16. The synthesis of 2-substituted benzoxazole from *ortho*-hydroxyaryl N-H ketamine

The next year, Pan and co-workers developed an efficient strategy to the synthesis of oxazole (Scheme 17).[27] In the presence of NBS, a catalyst-free intramolecular oxidative cyclization of *N*-allylbenzamide was converted to 2,5-substituted oxazole directly. The dibrominated compound was isolated, which was also used as the starting material and gave the target product in high yield under the same condition, which was considered as the intermediate or the captured intermediated of this oxidative cyclization procedure. As shown in scheme 17, the imidic tautomer **A** of the dibromindated intermediate may undergo an intramolecular nucleophilic substitution by the oxygen and formed the intermediate **B**. Then, the intermediate **C** was afforded by the bromination of **B** and the subsequent elimination gave oxazole as the final product.



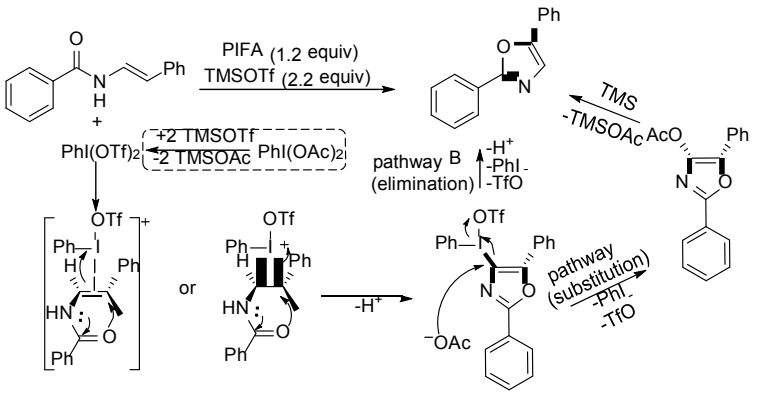
Scheme 17. Synthesis of 2,5-disubstituted oxazole from *N*-allylbenzamide

Later, 2,5-Diaryloxazoles formed by the ring expansion of keto aziridines in the presence of DCC and iodine was exhibited by Samimi.[28] The nature of Lewis acid seems to be as an important role that the oxazole was only obtained with I_2 while there were no corresponding products generated with BF_3, $Fe(NO_3)_3$ and $RuCl_3$. The I_2 was considered to promote the ring cleavage of the azirdine C-C bond resulting in the formation of intermediate **B**. In the meantime, the carbonyl group could stabilize the carbanionic center and the 3-aryl group could stabilize the benzylic cation thus generating the azomethine ylide. Finally, with the elimination of **C** or the ring closure of **D** following the formation of oxazole (Scheme 18).



Scheme 18. The synthesis of 2,5-diaryloxazole from keto aziridine

In 2013, Nachtsheim employed another hypervalent iodine reagent $PhI(OTf)_2$ in an intramolecular oxidative cyclization of *N*-styrylbenzamide to synthesize 2,5-disubstituted oxazole (Scheme 19).[29] In a remarkably short time, the 2,5-disubstituted oxazole was transformed in high yields *via* oxidative C-O bond forming reaction. To the reaction pathway, initially, the oxazoline was considered as the intermediate. However, with the relevant control experiments, the evidence indicated that this reaction favored the direct elimination rather than substitution. On the other hand, the trifluoroacetate is a much worse nucleophile than acetate. Hence, the pathway A can be neglected.

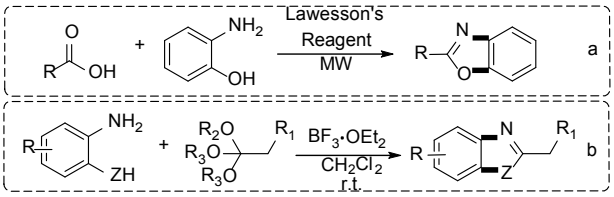


Scheme 19. Iodine(III)promoted synthesis of oxazole *via* oxidative cyclization of *N*-styrylbenzamide

2.1.3.3 The synthesis of oxazoles based on –C-NH_2

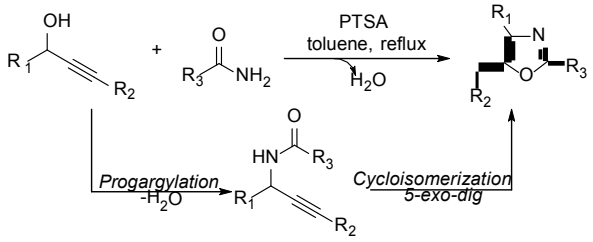
In 2007, Seijas developed a general method for the synthesis of 2-substituted benzoxazole and its derivatives from carbonxylic acids and different substituted 2-aminophenols (Scheme 20a).[30] The Lawesson's reagent acted as an efficient promotor in this solvent-free and microwave-assisted reaction. Moreover, the LR was considered to activate the carboxylic acid derivatives under microwave irradiation.[31] That being the reason why all the benzoic acids could be consumed and corresponding benzoxazoles were transformed in good yields while the thiobenzoic acid could not. Another synthesis of benzoxazoles was published by Markó in 2012 (Scheme 20b).[32] Aniline and its derivatives with

functionalized orthoesters were treated in the presence of $BF_3{\cdot}OEt_2$ under room temperature. Also, the benzothiazole and benzimidazole derivatives could also be formed in this protocol up to 95% yield. It should be noted that the orthoesters with a terminal alkene were also tolerated well, which could allow varying modifications for the further synthesis of other promising compounds.



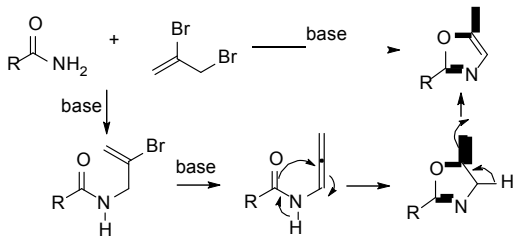
Scheme 20. The synthesis of benzoxazole from carboxylic acid and orthoester

In 2009, Zhan's group developed an efficient one-pot propargylation/cycloisomerization tandem process for the synthesis of oxazole derivatives (Scheme 21).[33] Initially, various Lewis acids were tested while the alkynylamide was afforded as the main product, which may due to the weak acidity. Several Brønsted acids like TFA, HCl, PTSA (*p*-toluenesulfonic acid monohydrate) were also screened and only PTSA seemed appropriately. In the presence of PTSA, the oxazole was obtained in 90% yield gratifyingly when propargylic alcohol and amide were reacted in toluene. Under the optimized reaction conditions, a variety of substituted oxazoles were transformed in good yields from corresponding propargylic alcohols and amides.



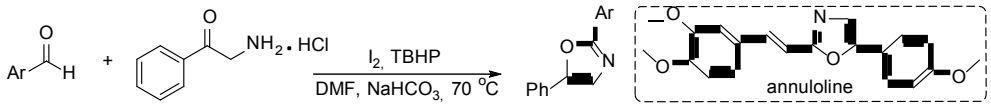
Scheme 21. The synthesis of oxazole from propargylic alcohol and amide

In the same year, Ray and Yasmin presented an efficient method for the synthesis of 2-aryl-5-alkyl-substituted oxazoles in one-pot (Scheme 22).[34] Various 2,5-disubstituted oxazoles were obtained by Cs_2CO_3-mediated reaction between aromatic amides and 2,3-dibromopropene.

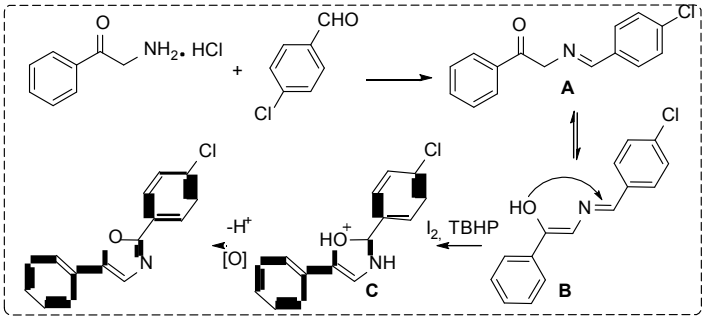


Scheme 22. Cs_2CO_3-mediated synthesis of oxazole from amide and 2,3-dibromopropene

In 2010, Wang and co-workers disclosed a practical synthesis of 2,5-disubstituted oxazoles *via* I_2-catalyzed tandem oxidative cyclization (Scheme 23).[35] Various aromatic aldehydes were treated with 2-amino-1-phenylethanone hydrochloride and afforded corresponding oxazoles in moderate to good yields when iodine was used as the sole catalyst and TBHP as the oxidant. In addition, this protocol has been applied to synthesize the natural product annuloline successfully with an isolated yield of 75%. To the mechanism, it was considered that the reaction of 2-amino-1-phenylethanone with benzaldehyde could formed **A** first. Then the enolizaiton of **A** afforded intermediate **B**. In the presence of I_2 and TBHP, the intermediate **C** was generated by an intramolecular attack of the oxygen atom to the C=N double bond. With further deprotonation and oxidation, the 2,5-disubstituted oxazole was afforded as the final product (Scheme 24).

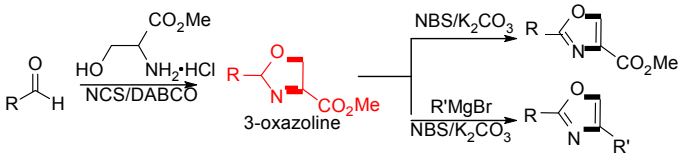


Scheme 23. I_2-catalyzed oxidative cyclization to the synthesis of 2,5-disubstituted oxazole



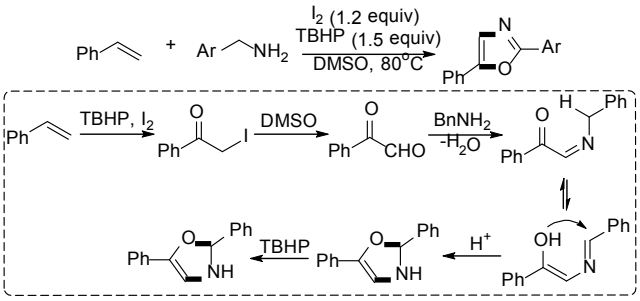
Scheme 24. Mechanism of I_2-catalyzed oxidative cyclization to 2,5-disubstituted oxazole

The preparation of oxazole and its derivatives from aldehyde was also developed by Fujioka *et al.*, which underwent a one-pot condensation-oxidation of aldehydes and serine or threonine methyl ester (Scheme 25).[36] The 3-xazoline-4-carboxylate was utilized as an intermediate which could be formed in the first step. In the presence of oxidant NBS and the base K_2CO_3, the oxazole-4-carboxylates were afforded in moderate to good yields. On the other hand, when the intermediate 3-oxazoline-4-carboxylate and derivatives were treated with Grignard reagent, corresponding 4-keto-oxazole derivatives could be obtained in excellent yields. Generally, various aldehydes could provide extensively synthetic options for the synthesis of oxazole derivatives bearing an oxazole unit. Moreover, with the Grignard reagents, a variety of 4-keto-oxazole derivatives could be generated as well.



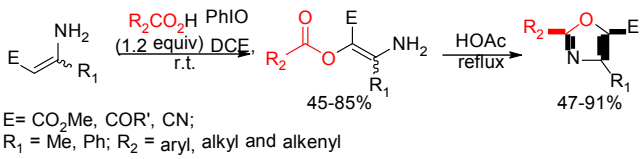
Scheme 25. The synthesis of oxazole-4-carboxylate and 4-ketone from aldehyde

I_2/TBHP-mediated synthesis of oxazoles from olefins and benzylic amines *via* a domino oxidative cyclization was also developed by Jiang (Scheme 26).[37] Under optimal reaction condition, a series of terminal aryl alkenes and benzylamine derivatives were converted to corresponding oxazoles in moderate to good yields. Unfortunately, the reaction with *n*-BuNH_2 failed. In addition, a plausible mechanism was presented as well suggesting that it could also form the same intermediate **B** as shown in scheme 24 and underwent the identical pathway.



Scheme 26. I_2/TBHP-mediated synthesis of oxazole from olefin and benzylic amine

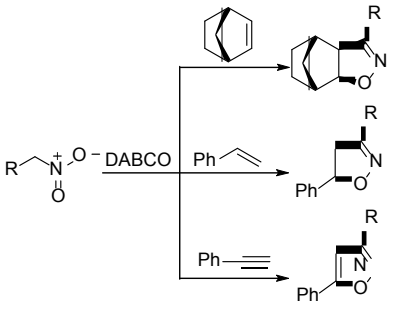
In 2012, Zhao and co-worker presented a direct *β*-acyloxyaltion of enamines *via* PhIO-mediated intermolecular oxidation to form the C-O bond and applied this to synthesize a series of oxazoles within two steps (Scheme 27).[38] The C(sp^2)-O bond could be formed between enamines and various carboxylic acids, including *N*-protected amino acids. In this protocol, a series of oxazole derivatives were afforded from the prepared *β*-acyloxyl enamines in acceptable to excellent yields *via* intramolecular condensation in boiling AcOH. Moreover, the *N*-protected amino acids were also examined. However, all the reactions need much time for the sluggish dehydration process. Nonetheless, all of them could give the corresponding oxazoles in moderate to good yields, which provided a practical and potential application in synthetic chemistry.



Scheme 27. The synthesis of oxazole based on the *β*-acyloxylation of enamine

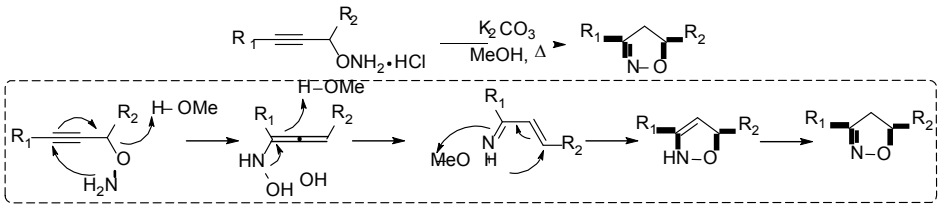
2.1.4 The synthesis of isoxazolines

In 2005, Machetti and co-workers found that the dehydration of primary nitro compounds could be performed in the presence of the bases and dipolarophiles.[39] They demonstrated that the tertiary diamine bases such as DABCO and TMEDA could promote the dehydration of the nitro compounds, which favored a thermodynamical process. However, the previous researches on the dehydration of nitro compounds were always undertaken by the combination of acylated agents and bases.[40] In the presence of the base DABCO, which was considered an efficient reagent,[41] a series of isoxazoline derivatives could be formed successfully (Scheme 28).



Scheme 28. DABCO-mediated synthesis of isoxazole derivatives from nitro compounds

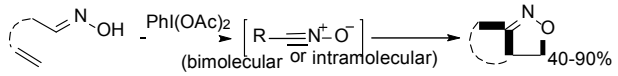
In 2006, Pennicott and Lindell described a tandem rearrangement-cyclization reaction to 2-isoxazolines from *o*-propargylic hydroxylamines (Scheme 29).[42] In the presence of K_2CO_3, various prepared *o*-propargylic hydroxylamine hydrochloride salts were converted to corresponding 2-isoxazolines in moderate to good yields. A possible pathway was proposed that the *N*-allenic hydroxylamine was generated *via* 2,3-sigmatropic rearrangement and an *α, β*-unsaturated oxime was followed by further rearrangement. Subsequently, 3-isoxazoline was afforded *via* a 5-*endo*-trig cyclization following an isomerization and gave the more stable 2-isoxazoline as the final product.



Scheme 29. The synthesis of 2-isoxazoline from *o*-propargylic hydroxylamines

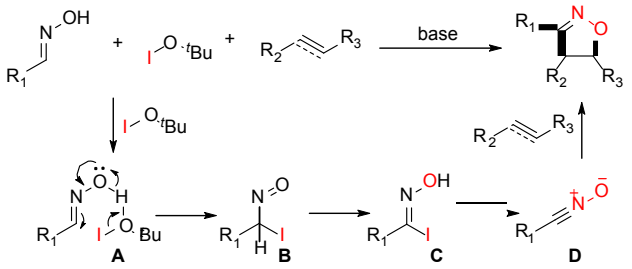
In 2009, Ciufolini *et al* developed an oxidative method to synthesize isoxazolines from oximes with hypervalent iodine reagents (Scheme 30).[43] The nitrile oxide was considered as an intermediate formed by the oxidation of oxime, which could be trapped *in situ* with olefin within an intermolecular or an

intramolecular cyclization. A series of oximes were examined with excess $PhI(OAc)_2$ in MeCN/TFE. Corresponding isoxazolines were furnished in good to excellent yields. However, when a terminal alkyne was used instead of an olefin, a fully aromatic oxazole was obtained with a lower yield in 50%.



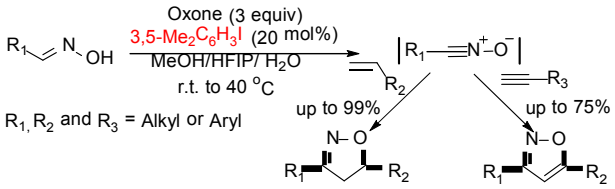
Scheme 30. $PhI(OAc)_2$-oxidation of oxime to isoxazoline.

Two years later, Minakata group presented a similar generation on nitrile oxides from oximes, a variety of isoxaolines and isoxazoles were formed with an intermolecular cycloaddition (Scheme 31).[44] The ^{t}BuOI was used as the sole oxidant which was prepared *in situ* from *tert*-butyl hypochlorite and sodium iodide. Under the optimal reaction condition, olefins with electron-deficient groups gave the desired isoxazolines in excellent yields and with complete regioselectivity. Moreover, a range of aldoximes treated with styrene or *N*-phenylmaleimide under the standard condition could afford corresponding isoxazoline derivatives in moderate to good yields as well. Based on the mechanism study, it was considered that the *α*-iodointroso intermediate **B** was transformed from the iodination and deprotonation of aldoxime with ^{t}BuOI. The tautomerization of **B** could generate intermediate **C** following the elimination of HI in the presence of the base and generated the nitrile oxide **D**. Subsequently, the cycloaddition between the intermediate **D** and an unsaturated bond afforded the isoxazoline or isoxazole as the final product.



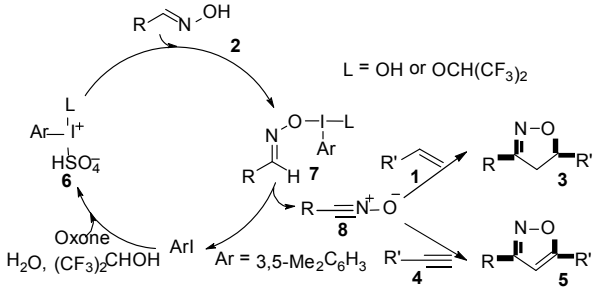
Scheme 31. The oxidative cycloaddition of oxime to isoxazoline with ^{t}BuOI

Compared with these two oxidative cycloaddition of oximes to isoxaozoles or isoxazoles, both of them used the equivalents of hypervalent iodine reagent. A hypervalent iodine catalyzed generation of nitrile oxides from oximes with alkene or alkynes to isoxazoline and isoxazole was developed by Yoshimura and co-workers (Scheme 32).[45] In the presence of hexafluoroisopropanol in methanol solution, the oxone was used as a terminal oxidant and activated the formation of hypervalent iodine species *in situ*. Similarly, under the optimal condition, corresponding isoxazolines and isoxazoles were afforded in moderate to good yields.



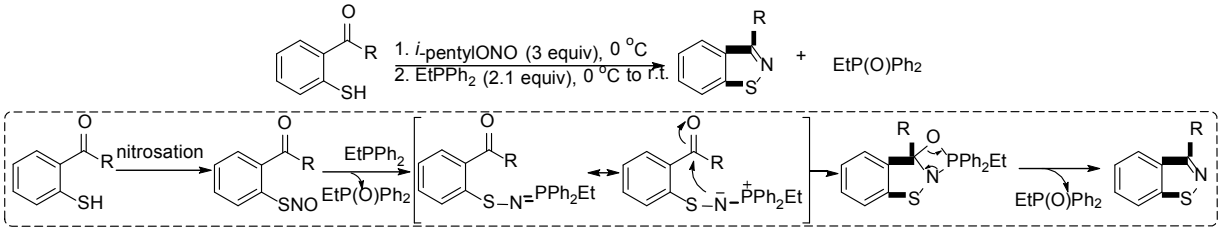
Scheme 32. Hypervalent iodine-catalyzed heterocyclization of aldoximes to isoxazolines and isoxazoles

It should be noted that there was a slight difference compared to the previous reports in mechanism. In this protocol, the activated hypervalent iodine species hydroxyl(aryl)iodonium ion $[ArI(OH)]^+$ **6** generated from ArI and oxone, which may react with aldoxime and gave the hypervalent alkoxy iodane **7** *via* ligand exchange. Consequently, the nitrile oxide **8** was formed by the reductive elimination of ArI and the regenerated ArI continued the next catalytic cycle. The procedure that the intermediate **8** reacted with alkene or alkyne to isoxazoline or isoxazole is the same as previous elaboration (Scheme 33).



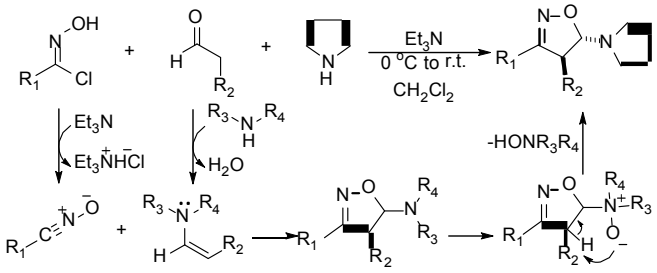
Scheme 33. The mechanism of cycloaddition of oxime to isoxazoline and isoxazole

In 2010, Xian developed a facile synthesis of 3-substituted benzisothiazoles from various *o*-mercaptoacylphenones with good yields.[46] Based on their previous works, the organophosphines were expected to react with *S*-nitrosothioles and form azaylide intermediates. Then the intermediate could undergo an intramolecular reaction with different electrophiles and generate various promising compounds. The *S*-nitrosothiol furnished by the nitrosation of *o*-mercaptoacylphenone could react with oranophosphine and form an azaylide intermediate. Then an intramolecular aza-Wittig reaction was occurred and generated the desired benzisothiazole (Scheme 34).



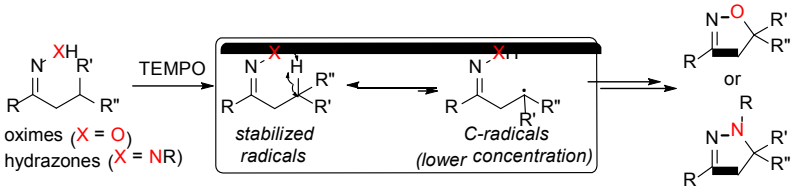
Scheme 34. The synthesis of 3-substituted benzisothiazole from *o*-mercaptoacylphenone

Later, in 2013, Wang and co-workers described an enamine-promoted [3+2]-cycloaddition to synthesize 3,4,5-trisubstituted isoxazolines under transition-metal-free condition, which provided a highly regiospecific method to synthesize 3,4-disubstituted isoxazoles (Scheme 35).[47] In the presence of trimethylamine, various aldehydes and *N*-hydroximidoyl chlorides were transformed to corresponding 3,4-disubstituted isoxazoles with Cope elimination of the cycloadduct 3,4,5-trisubstituted 5-(pyrrolidinyl)-4,5-dihydroisoxazoles.



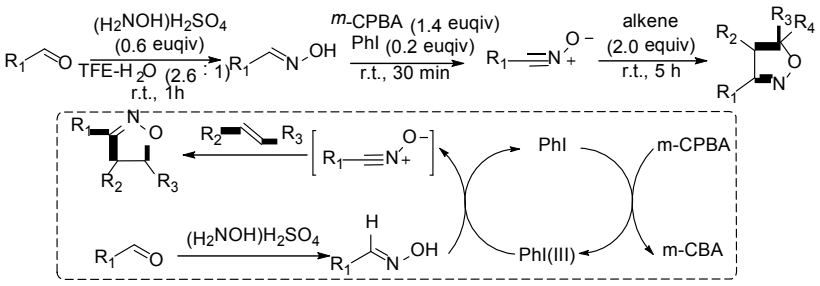
Scheme 35. The synthesis of 3,4,5-trisubstituted isoxazolines catalyzed by enamine

In the same year, Chiba's group disclosed a method for the synthesis of isoxazole and pyrazole *via* the aliphatic C-H oxidation of oximes and hydrazones, which underwent a 1,5-H radical shift of iminoxyl and hydrazonyl radicals generated from oxime and hydrazine in the presence of TEMPO, respectively (Scheme 36).[48]



Scheme 36. TEMPO-mediated aliphatic C-H oxidation with oximes and hydrazones

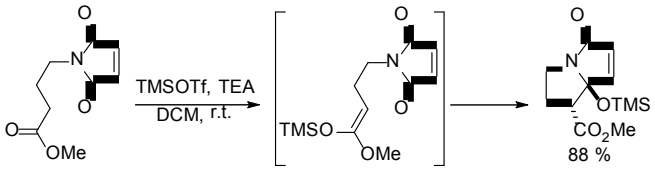
Yan presented a one-pot, three-step procedure for the synthesis of isoxazolines from aldehydes, which went through a catalytic cycloaddition between nitrile oxides and alkenes (Scheme 37).[49] Iodobenzene acted as the catalyst, which could generate a hypervalent iodine intermediate *in situ* in the presence of *m*-CPBA. During this procedure, the aldehydes and possessed could afford the aldoximes as the intermediate, which could be oxidized to nitrile oxides by the iodine intermediate. Subsequently, a 1,3-dipolar cycloaddition between the nitrile oxides and alkenes generated the desired isoxazolines as the final product.



Scheme 37. The synthesis of isoxazolines from aldehydes catalyzed by iodobenzene

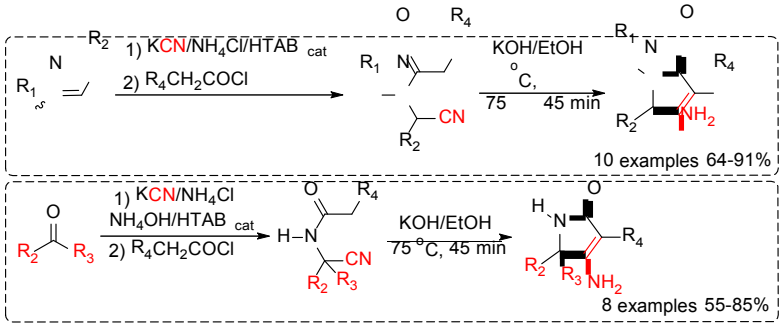
2.1.5 The synthesis of pyrrolones and pyrrolidineones

In 2006, Hoye reported a highly efficient and convenient approach for the silylative Dieckmann-like cyclization, which was applicable to ester/imide- and diester-containing substrates.[50] The nucleophilic ketene acetal in this procedure was considered as a key step during the transformation (Scheme 38).



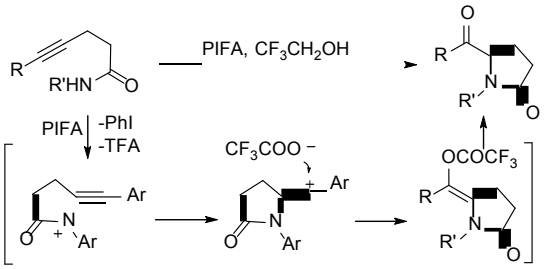
Scheme 38. Silylative Dieckmann-like cyclizations of ester-imides(diesters)

Later, Zali-Boeini and co-workers developed an efficient and novel procedure for the synthesis of fully substituted 4-aminopyrrolones from imines, ketones or *α*-bromophenyl acetonitriles (Scheme 39).[51] In ethanol, *α*-arylamino benzyl cyanides transformed from imines/ketones and KCN/NH_4Cl were converted to corresponding *α*-amino nitriles with a modified Strecker reaction. Subsequently, the *α*-amino nitrile precursors reacted with a suitable acyl halide and afforded the corresponding amides. In the presence of ethanolic KOH, the amides were transformed to the desired substituted 4-amino-1*H*-pyrrol-2(5*H*)-one in moderate to excellent yields.



Scheme 39. The synthesis of 4-amnio-1*H*-pyrrol-2(5*H*)-ones

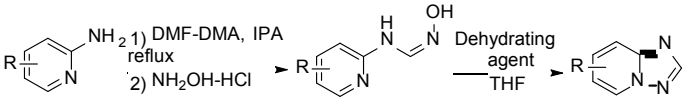
The synthesis of pyrrolidinone from alkynylamides, which took place in the presence of hypervalent iodine reagent PIFA by an intramolecular electrophilic cyclization was presented by Tellitu and co-workers in 2007 (Scheme 40).[52] A series of amides were treated with PIFA under optimized conditions and it was found that not only the *N*-aryl-substituted amide could afford the desired product, the *N*-methyl, *N*-allyl, *N*-benzyl and *N*-cyclohexylamides could also afford corresponding products in good yields. In addition, the alkynylcarboxylic acids with PIFA could be converted to the desired furanones under the same reaction conditions with moderate to good yields as well.



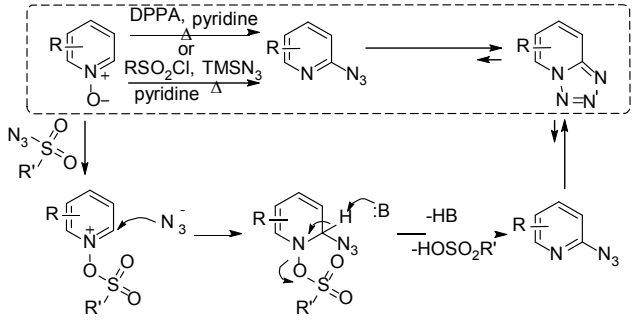
Scheme 40. Intramolecular PIFA-mediated alkyne amidation

2.1.6 The synthesis of imidazoles, triazoles and tetrazolos and derivatives

In 2005, Balselles and Huntsman synthesized a variety of [1,2,4]triazolo[1,5-*a*]pyridines from 2-aminopyridines *via* cyclization of *N*-(pyrid-2-yl)formamidoximes with trifluoroacetic anhydride (Scheme 41).[53] With inexpensive reagents and under mild reaction condition, various substituted triazoles were afforded in moderate to good yields. Later, Keith used the pyridine *N*-oxides and treated them with sulfonyl or phosphoryl azides, good to excellent yields of corresponding tetrazolo[1,5-*a*]pyridines were obtained in the presence of pyridine (Scheme 42).[54] With respect to the mechanism, the electrophile was considered to activate the *N*-oxide to nucleophilic attack and elimination. Moreover, under this solvent free condition, it is easily scaled up while without significantly diminishing the yield.

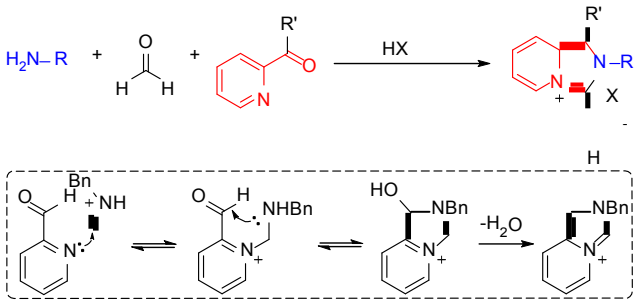


Scheme 41. Synthesis of triazoles from 2-aminopyridines



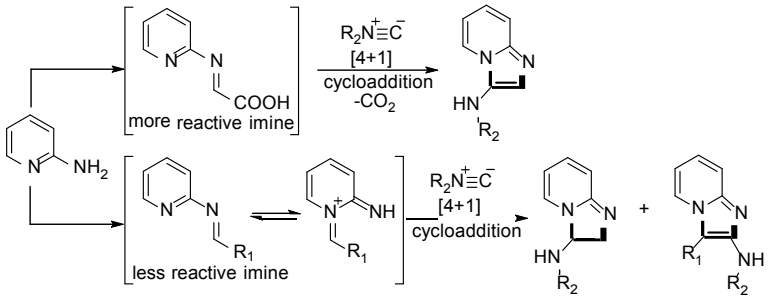
Scheme 42. One-step conversion of pyridine *N*-oxides to tetrazolo[1,5-*a*]pyridines

In 2011, Aron and Hutt developed a novel access to imidazo[1,5-*a*]pyridine *N*-heterocyclic carbene precursors (Scheme 43).[55] Three components coupling of substituted picolinaldehydes, amines and formaldehyde gave the corresponding imidazo[1,5-*a*]pyridinium ions in good yields, which provided an efficient method for the preparation of *N*-heterocyclic carbenes (NHCs). In addition, higher condensation was also described and provided an access to multidentate NHC ligands for various applications. To the mechanism, it was considered that the protonated Schiff base was attacked by picolinaldehyde and afforded a condensation intermediate, which was followed by the attack of the amine nitrogen to the aldehyde within an intramolecular cyclization. Finally, an irreversible dehydration led to the aromatic imidazo[1,5-*a*]pyridinium ion.



Scheme 43. The synthesis of imidazo[1,5-*a*]pyridine *N*-heterocyclic carbene precursors

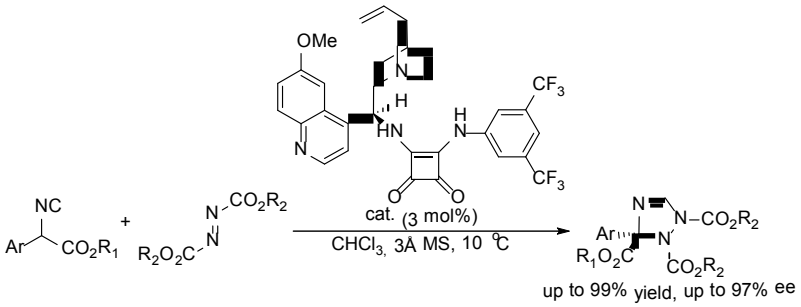
At the same year, Li and Sharma reported a regioselective and efficient method for the synthesis of 3-aminoimidazoazines, which employed glyoxylic acid as the formaldehyde source.[56] Generally, the formaldehydes would not perform well with Ugi-type multicomponent sequences. However, this methodology seemed to be superior to the previous methods in terms of yield and simplicity. It was considered that this may due to the glyoxylic acid derived imine is more reactive and can be cyclized before the isomerization resulting in a single regioisomer. On the other hand, imines derived from other aldehydes were not as active as formaldehydes that would isomerize, and afforded a mixture of regioisomers were obtained (Scheme 44).



Scheme 44. Formaldehyde-based Groebke-Blackburn-Bienaymé reaction to 3-aminoimidazoazines

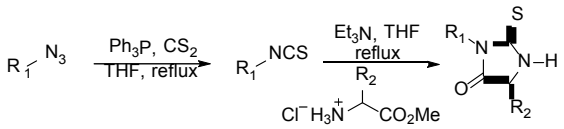
In 2013, Shi and co-workers presented a novel enantioselective hydrazination/cyclization cascade reaction of *α*-substituted isocyanoacetates with azodicarboxylates to the optically active 1,2,4-triazolines, which was catalyzed by Cinchona alkaloid derived squaramide catalysts (Scheme 45).[57] From the obtained results, it could find that the addition of 3 Å molecular sieves could slightly improve the

enantioselectivity. Also, under the optimal reaction condition, a variety of *α*-aryl isocyanoacetates and azodicarboxylates with different electronic and steric properties were well tolerated and afforded corresponding products in good to excellent yields.



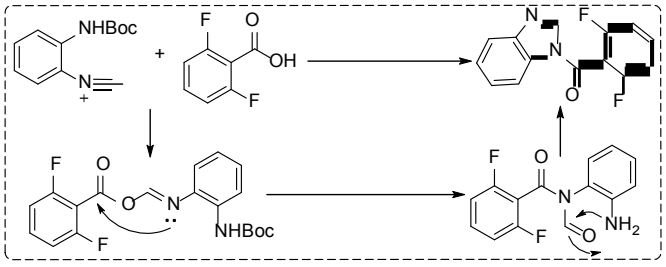
Scheme 45. *Cinchona* alkaloid squaramide catalyzed synthesis of 1,2,4-triazolines

In 2014, Tatibouët *et al* developed an efficient methodology to *N*-3-substituted 2-thiohydantoins from azide derivatives, which proceeded *via* the formation of iminophosphoranes and the condensation with carbon disulfide leading the isothiocyanates. Then the condensation with *α*-amino esters gave the *N*-3-substituted 2-thiohydantoins (Scheme 46).[58] From the obtained results, a variety of azide derivatives gave corresponding products in moderate to good yields. Moreover, it was found that this protocol was effective on primary and nonhindered azides.



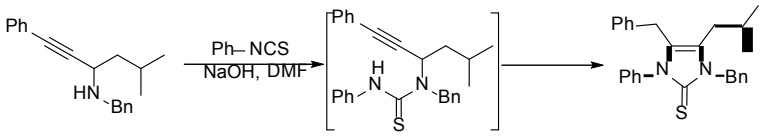
Scheme 46. Synthesis of *N*-3-substituted 2-thiohydantoins *via* Staudinger condensation

Later, Xu and co-workers disclosed a facile synthesis of benzimidazoles and quinoxalin-2(1*H*)one scaffolds *via* two-components coupling reaction involving a deprotection procedure and an intramolecular cyclization (Scheme 47).[59] The use of carboxylic and glyoxylic acids broadened the scope of the 2CC method and significantly extended the range of biologically active amides or peptides. A series of benzimidazoles were transformed in moderate to good yields in this convenient method and various structures in medicinal chemistry could be easily modified by changing the carboxylic acid.



Scheme 47. The synthesis of benzimidazole from 2-(*N*-Boc-amino)phenylisocyanide with carboxylic acids and glyoxylic acids

Recently, Dethe developed an atom-economic, regioselective intramolecular 5-*exo*-*dig* cycloisomerization for the synthesis of diverse substituted imidazole-2-thiones and spiro-cyclic imidazolidine-2-thiones, which was achieved by an intramolecular transition-metal-free condition, base-mediated hydroamination of propargylamine with isothiocyanates (Scheme 48).[60] From the control experiments, it was found that when the reaction was conducted in DMF without base, propargylthiourea could be isolated, which indicated that the base was unnecessary in the first step. However, the desired product could be obtained when the propargylthiourea was treated with the base in DMF. All these revealed that the base was not required for the formation of propargyl(thio)urea, but it was indispensable for the hydroamination of propargyo(thio)urea to form the imidazole-2-(thi)one. Various propargylamines were examined under the optimal reaction condition and gave corresponding imidazole-2-thiones in excellent yields.

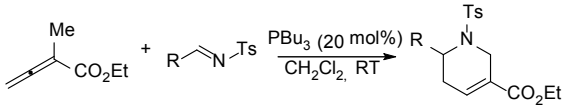


Scheme 48. One-pot synthesis of imidazolidine-2-thione

There is also ample elegant work focused on the synthesis of *N*-containing five-membered heterocycles, such as a radical cyclization of unsaturated sulfonamides to corresponding pyrrolidines and piperidines presented by Li and co-workers.[61] Xi developed a convenient method for the preparation of 1,3-benzothiazole-2-(3*H*)-thiones from *o*-haloaniline and carbon disulfide.[62] Interestingly, in 2012, Minakata reported a cyclizative atmospheric CO_2 fixation by unsaturated amines under mild reaction condition to cyclic carbamates with an iodomethyl group, which was conducted in the presence of hypervalent iodine ^{t}BuOI.[63] In addition, in 2013, Zhang described an iodine-mediated intramolecular amination of ketones to 2-acylindoles and 2-acylindolines.[64] However, due to the limited space, they are not described in detail here.

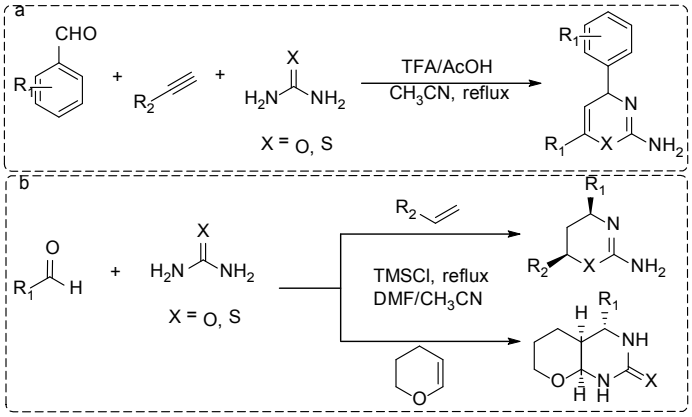
2.2 The synthesis of *N*-containing six-membered heterocycles

In 2003, Kwon *et al*. developed an [4+2] annulation reaction of *N*-tosylaldimines to tetrahydropyridine derivatives in excellent yields with complete regioselectivity and high diastereoselectivies.[65] A variety of ethyl 2-methyl-2,3-butadienoate and *N*-tosylaldimines were conducted in the presence of PBu_3 as the catalyst at room temperature (Scheme 49). However, from the obtained results, the salicyl and 2-pyrrolyl *N*-tosylmines gave no desired products while their *O*-TBS and *N*-Boc protected counterpart could undergo the annulation uneventfully and gave corresponding products in excellent yields, respectively.



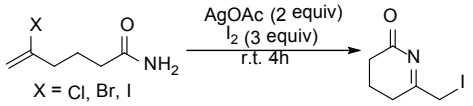
Scheme 49. The synthesis of tetrahydropyridines from ethyl 2-methyl-2,3-butadienonate and *N*-tosylaldimines

Later in 2005, Wu and Pan described a novel three-component one-pot reaction to synthesize 2-amino-4*H*-1,3-oxazines and 2-amino-4*H*-1,3-thiazines from alkynes, urea or thiourea and aldehydes (Scheme 50a).[66] The alkyne and aldehyde group were seemed to be flexible to prepare corresponding derivatives. A series of alkynes, aldehydes and urea or substituted ureas were examined and gave desired 2-amino-4*H*-1,3-oxazines in moderate to good yields. One year later, they developed another three-component reaction to synthesize 2-amino-5,6-dihydro-4*H*-1,3-thiazin-3-ium chloride salts and 2-amino-5,6-dihydro-4*H*-1,3-oxazin-3-ium chloride salts from aryl alkenes, urea or thioureas and aryl aldehydes (Scheme 50b).[67] The regioselectivity of both *N*-acyliminium ion and *N*-thioacyliminium processed with an alkene *via* the [4+2] cycloaddition and afforded all the target products as single *cis* diastereomers.



Scheme 50. Three-component reactions of alkynes, urea or thiourea and aldehydes or 3,4-dihydro-(2*H*)-pyran

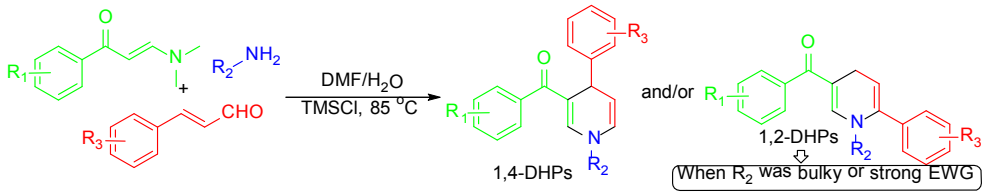
In 2007, Li and co-workers presented an electrophilic iodocyclization of unsaturated amides with an internal vinylic halogen substitution to cyclic iminoketones, which was speculated *via* exclusive *N*-attack or *O*-attack firstly (Scheme 51).[68] Based on the density functional calculation that indicated the iodocyclization procedure underwent the intramolecular indonium ion transfer from the amide nitrogen to the C=C double bond. The Cl-, Br- and I-substituted substrates could also give corresponding iminoketones in excellent yields when a series of substrates containing an internal vinylic halogen substitutent treated with $AgOAc/I_2$ under the optimal reaction condition.



Scheme 51. Halocyclization of unsaturated amides with vinylic halogen substitution

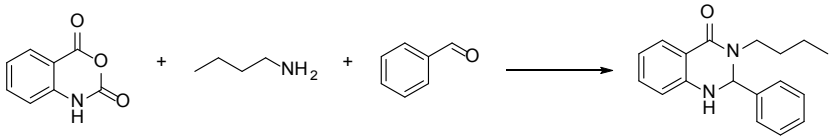
Two years later, Pan disclosed a three-component sequential reaction of *α, β*-unsaturated aldehydes, amines and enaminones to 1,3,4-trisubstituted 1,4-dihydropyridines (Scheme 52).[69] Moreover, the unexpected regioselective formation of 1,2-dihydropyridine was performed in this approach as well. In the

presence of TMSCl worked as a promoter, both aromatic and aliphatic amines were able to give moderate to good yields of corresponding 1,4-DHPs smoothly. Moreover, when sterically hindered aromatic amines or amines with strong electron withdrawing groups, the 1,2-DHP was afforded instead of 1,4-DHP, which was the first example of the regioselective synthesis of 1,2-DHPs.



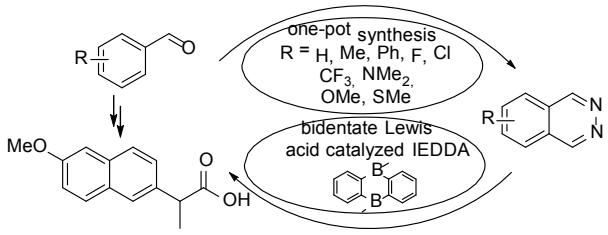
Scheme 52. The three-component cascade synthesis of 1,4- and 1,2-dihydropyridines

In 2012, Chauhan and co-workers described a green and energy-efficient synthesis of 2,3-dihydro/spiroquinazolin-4(1*H*)-ones *via* a three-component cyclocondensation from isotonic anhydride, amines and aldehydes/ketones (Scheme 53).[70] Compared to the previous methods, the convenient requirements and mild reaction conditions seemed to be improved significantly and it could be applied in large-scale reactions. Under the optimal reaction condition, aliphatic amines, aromatic mines, cyclic amines and hydroxyl amines were examined to be effective and gave corresponding products in excellent yields. Moreover, this methodology was further extended to cyclic ketones. From the obtained results, moderate to good yields of desire products could be generated, which provided an opportunity for the construction of diverse molecules bearing a quinazolinone unit.



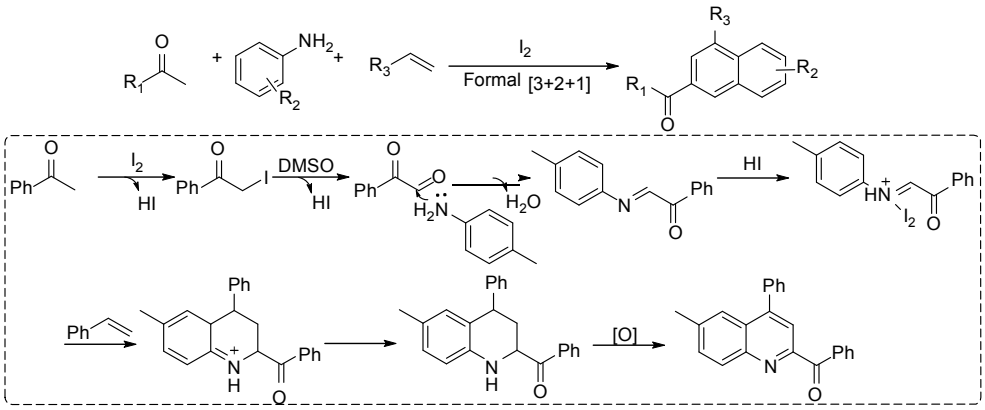
Scheme 53. The synthesis of 2,3-dihydroquinazolin-4(1*H*)-one *via* three-component reaction

At the same year, Wegner disclosed a one-pot strategy for the synthesis of phthalazines and pyridazino-aromatics from aromatic aldehydes.[71] Various substituents with electron-withdrawing or electron-donating groups were well tolerate and afforded desire 1,2-diazines in good to excellent yields. Additionally, what should be noted is that these products could be extended to synthesize substituted naphthalenes by the bidentate Lewis acid catalyzed inverse electron-demand Diels-Alder reaction (Scheme 54).



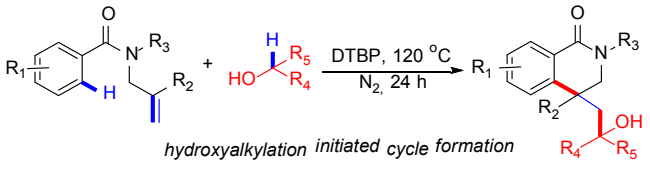
Scheme 54. The synthesis of phthalazines from aromatic aldehydes

In 2014, Wu group developed an efficient molecular iodine mediated formal [3+2+1] cycloaddition reaction for the synthesis of substituted quinolones from methyl ketones, arylamines and stryrenes (Scheme 55).[72] The methyl ketone presented unique reactiveness in the Povarov reaction and moderate to good yields of corresponding products could be formed. Based on the control experiments, a self-sequenced iodination/Kornblum oxidation/ Povarov/aromatization mechanism was proposed. The *α*-iodo ketone generated from the iodine and ketone, which could be converted to phenylglyoxal by a subsequent Kornblum oxidation. The C-acyl imine followed by the reaction between *p*-toluidine and aldehyde would react with HI and afforded the activated C-acyl imine ion. The activated species would be involved in the key step of the Povarov-type reaction and reacted smoothly with styrene to give the intermediate in the presence of excess or regenerated iodine. Subsequently, the intermediate would undergo sequential oxidation and aromatization to give the final product.



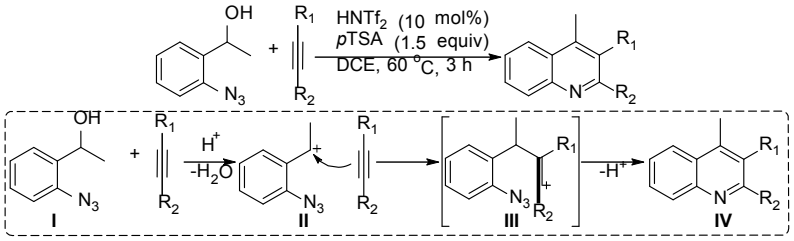
Scheme 55. The synthesis of quinolones by I_2-mediated formal [3+2+1] cycloaddition

Shortly after, Han *et al* described a metal-free hydroxyalkylation-initiated radical six-membered heterocycle formation of *N*-allylbenzamide, which proceeded through C(sp^3)-H bond cleavage, oxyalkylation of the double bond and intramolecular cyclization (Scheme 56).[73] Various *N*-allyl-*N*-methylbenzamide derivatives could afford the desired 4-(hydroxyalkyl)-3,4-dihydroisoquinolin-1(2*H*)-ones in moderate to good yields. Meanwhile, a series of alcohols were tested as well, but the yield seemed lower when the alkyl chain was increased. On the whole, this hydroxyalkylation-initiated radical cyclization of *N*-allylbenzamide showed excellent functional group tolerance and represented the atom-economic methodology to a six-membered heterocycle.



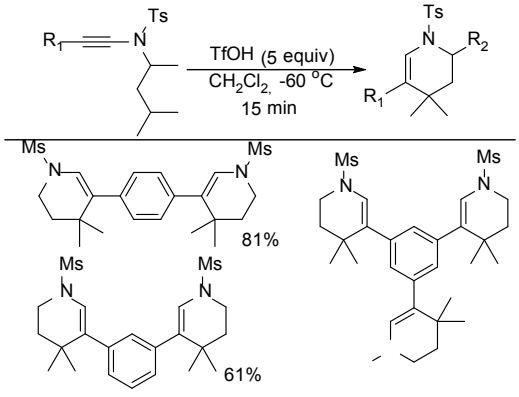
Scheme 56. Hydroxyalkylation-initiated radical cyclization of *N*-allylbenzamide to isoquinolinone

Recently, Niggemann employed a synergistic Brønsted acid catalytic system to synthesize highly substituted quinolines *via* metal-free carbonamination of unactivated alkynes, which successfully addressed the limitation of terminal or carboxylate activated alkynes in previous reports that used the alkynes as a building block (Scheme 57).[74] To the mechanism, the alcohol **I** was ionized to a benzylic carbocation **II**, which could react with the alkyne to form a vinylcation **III**. The loss of nitrogen was resulted from the nucleophilic addition of azide to the vinylcation. Subsequently, the desired product was generated by a simple deprotonation. In this reaction, expensive, sensitive and potentially toxic metal catalysts were unnecessary while a series of quinolines could be afforded in moderate to good yields.



Scheme 57. The carboamination of internal alkynes to polysubstituted quinolines

In 2016, Evano reported an efficient, modular and straightforward strategy to tetrahydropyridines and piperidines *via* a formal intramolecular hydroalkylation of yanamides (Scheme 58).[75] Under acidic condition, the yanamide could generate highly reactive keteniminium ion, which could be finely controlled to induce a remarkably efficient [1,5]-hydride shift from unactivated C-H bond and triggered a cationic cyclization. In the presence of triflic acid which was used to promote the reaction and avoid the trapping of the highly reactive ketenminium ion by the conjugated base, a series of ynamides were examined and smoothly converted to desired tetrahydropyridines in moderate to good yields. Indeed, this method was also applied to synthesis double and triple cyclized products under the same condition that delineated the potential of this keteniminium-triggered cyclization.



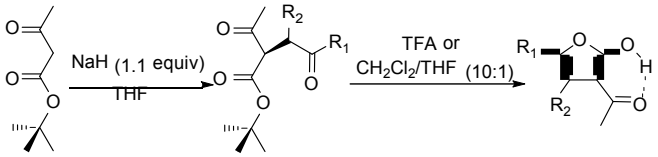
Scheme 58. Keteniminium-triggered intramolecular hydroalkylation of ynamides

3 The synthesis of *O*-containing heterocycles

3.1 The synthesis of *O*-containing five-membered heterocycles

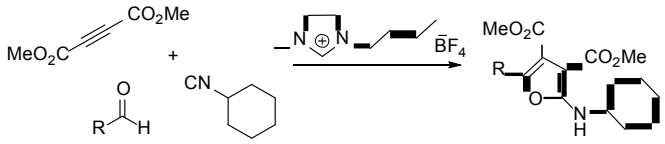
3.1.1 The synthesis of furan derivatives

In 2000, a variety of substituted 2-hydroxy-3-acetylfurans were synthesized by Neier, which proceeded *via* an alkylation between *tert*-butyl acetoacetate and *α*-haloketone (Scheme 59).[76] The alkylation of *tert*-butyl acetoacetate was realized by deprotonation with sodium hydride in THF and reacted with methyl 5-bromolevulinate, phenacyl bromide, chloroacetone and α-bromopropiophenone *et al*. to the racemic intermediate. With the treatment of TFA, a series of 3-acetyl-2-hydroxyfuran derivatives were afforded in good yields.



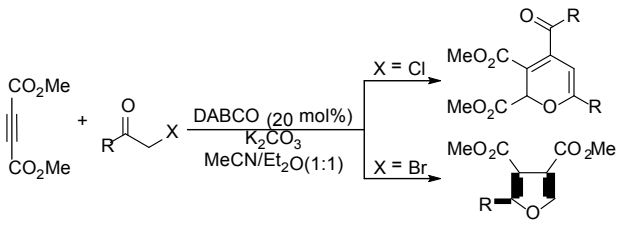
Scheme 59. Synthesis of tri- and tetrasubstituted furans catalyzed by TFA

In 2004, Yadav and co-workers developed a three-component coupling of aldehyde, dimethyl acetylenedicarboxylate (DMAD) and cyclohexyl isocyanide in [bmim]BF_4 to 2-aminofuran derivatives (Scheme 60).[77] The zwitterionic intermediate formed *in situ* from DMAD and isocyanide showed enhanced activity in ionic liquid that reduced the reaction time and improved the yields significantly. On the other hand, the ionic liquid could avoid the use of toxic and unfavorable benzene as solvent. Under the optimal reaction condition, the desired 2-aminofuran derivatives could also be transformed in good to excellent yields within less than 2 hours.



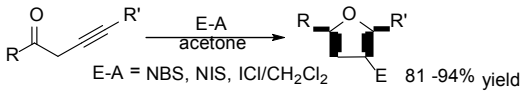
Scheme 60. Ionic liquids-promoted synthesis of 2-aminofuran derivatives

Later, Liang *et al*. employed the DMAD as the starting material as well and reacted with *α*-halo carbonyl compounds to synthesis polysubstituted furan, which was conducted in the presence of 20 mol% of DABCO as the catalyst (Scheme 61).[78] At room temperature, various *α*-chloroketones with DMAD were treated with anhydrous K_2CO_3. Unfortunately, the byproduct pyran turned out to be the major product while only acceptable to moderate yield of the desire furan was generated. On the contrary, when the *α*-bromoketones were treated under the same condition, there was trace of pyrans as the byproduct and the target product could be transformed in excellent yield.



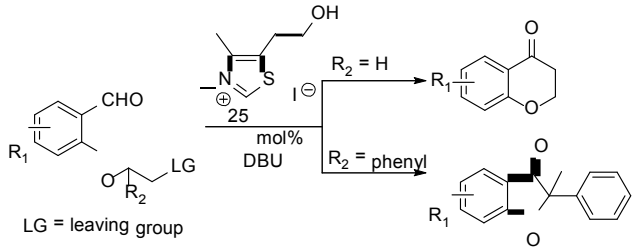
Scheme 61. DABCO-catalyzed *α*-halo carbonyl compounds with DMAD to furans

In 2015, Dembinski presented a regiocontrolled synthesis of 2,5-disubstituted 3-bromo- and 3-iodofurans *via* 5-Endo-Dig electrophilic cyclization of 1,4-disubstituted but-3-yn-1-ones (Scheme 62).[79] In the absence of the base and with the environmental friendly solvent acetone, a series of bromo- and iodo-furans were afforded in good to excellent yields with high atom economy. Moreover, the stronger electrophile iodine monochloride was also examined that when the reaction was treated with ICl in CH_2Cl_2, the desired iodofuran could also be obtained in good yield.



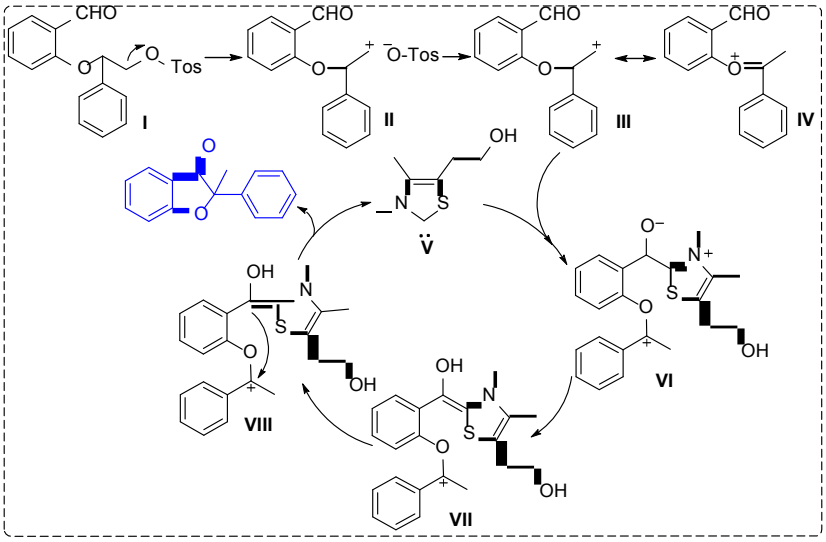
Scheme 62. Regiocontrolled synthesis of 2,5-disubstituted 3-Br- and 3-I-furans

Next year, She and co-workers developed a *N*-hetercyclic carbene catalyzed nucleophilic substitution reaction for the synthesis of benzofuranones (Scheme 63).[80] Interestingly, the benzopyrones were transformed when R_2 was H. While R_2 was a phenyl group, the cyclization process underwent isomerization and generated the benzofuranone as the final product. In the presence of NHC and DBU, various benzofuranones were afforded in moderate to good yields without any flavanones.



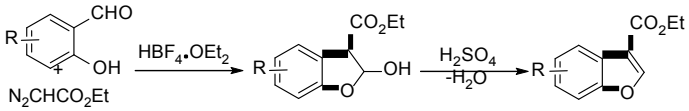
Scheme 63. NHC-catalyzed nucleophilic substitution to benzopyrone and benzofuranone

To the mechanism, the ion pair **II** may be formed under the reaction condition and the carbon cation rearranged to give the more stable intermediate **III**. Then the intermediate **VI** was formed by the reaction of carbene catalyst **V** and the intermediate **III**, which would undergo a deprotonation to the thiazole-enamine **VII**. Finally, the umploung aldehyde would attach to the electrophilic center resulting in the formation of benzofuranone and the regenerated catalyst went to the next catalytic cycle (Scheme 64).



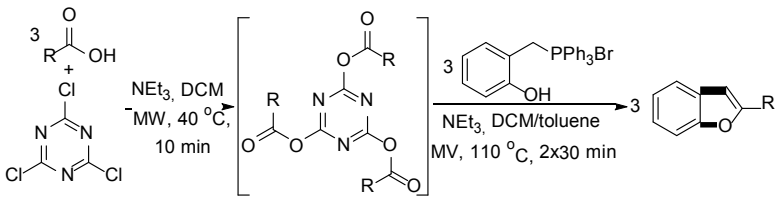
Scheme 64. Mechanism of NHC-catalyzed nucleophilic substitution to benzofuranone

In 2006, Hossain presented a convenient method for the synthesis of 3-ethoxycarbonylbenzofurans with two steps (Scheme 65). In the presence of $HBF_4 \cdot OEt_2$, a variety of corresponding products were afforded in excellent to quantitative yields from corresponding substituted salicylaldehydes and ethyl diazoacetates treated with sulfuric acid.



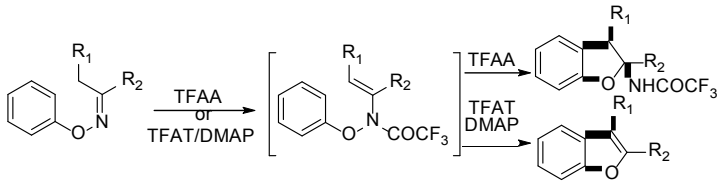
Scheme 65. The synthesis of benzofurans from salicylaldehydes and ethyl diazoacetate

In 2007, Giacomelli disclosed an efficient route to 2-substituted benzofurans from carboxylic acids directly (Scheme 66).[81] Under microwave irradiation, a series of carboxylic acids or the optically active *N*-Boc amino acid were converted to corresponding benzofurans in moderate to good yields. Moreover, based on this protocol, it was found that in the presence of TFA, the *N*-Boc derivatives could be deprotected and converted to corresponding *α*-alkyl 2-benzofuranmethanamines in DCM with quantitative yields.



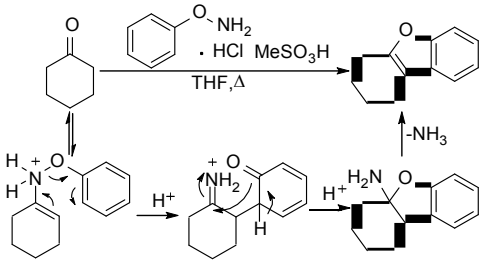
Scheme 66. The synthesis of 2-substituted benzofurans from carboxylic acids

The same year, Naito described a new synthetic method for the synthesis of benzofurans, which was triggered by acylation of oxime ethers resulting in the [3,3]-sigmatropic rearrangement of *N*-trifluoroacetyl-*ene*-hydroxylamines.[82] Moreover, the TFAT-DMAP system was found to be effective for the construction of various benzofurans (Scheme 67). To the DMAP, the effect was still unclear. Nonetheless, it may accelerate the first acylation step and trap a small amount of TFA and TfOH in commercial TFAT. Under the optimal reaction condition, a series of substituents was converted to corresponding products in good to excellent yields and several natural products were successfully accomplished in this reaction system with good yields.



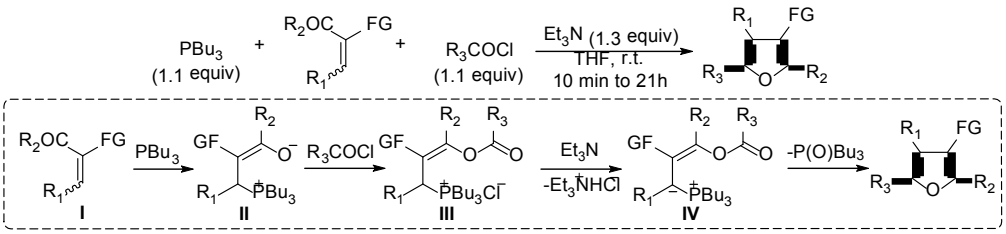
Scheme 67. The synthsis of benzofuran from oxime ethers with TFAA or TFAT-DMAP

Later, Tomkinson and co-workers synthesized a variety of benzofurans from *o*-arylhydroxylamines, which *via* a one-pot condensation-rearrangement-cyclization sequence. In the presence of methanesulfonic acid, corresponding benzofurans were afforded in moderate to good yields. Compared to the former reaction system, the initial oxime formation or trifluoroacetylation of the hydroxylamine nitrogen seemed to be unnecessary, which was considered as a mild procedure (Scheme 68).[83]



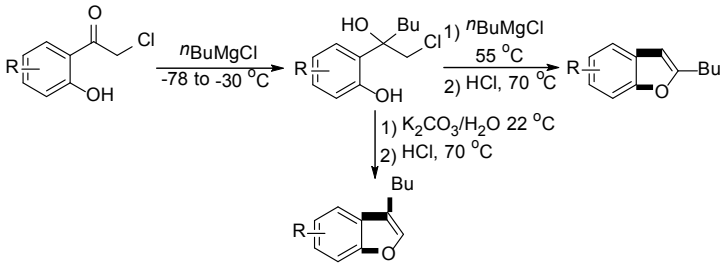
Scheme 68. The synthesis of benzofurans from *o*-arylhydroxylamines

In 2010, Lin and co-workers synthesized a variety of tetrasubstituted furans from the Michael acceptors, tributylphosphine and acyl chlorides *via* intramolecular Wittig reaction (Scheme 69).[84] The Michael acceptors bearing different ketones, ketone/ester or ketone/cyano were well studied and corresponding furans were generated in good to excellent yields. Based on the obtained results, it was considered that the Michael addition of Bu_3P to the starting material could give rise to the corresponding zwitterion, which would be acylated by an acid chloride leading to the formation of **III**. Subsequently, in the presence of Et_3N, the deprotonation of **III** generated the ylide **IV** and within an intramolecular Wittig reaction leading the target furan.



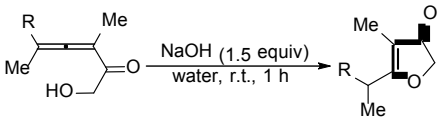
Scheme 69. The synthesis of furans from Michael acceptors and acid chlorides

Pei *et al*. developed a controlled regioselective synthesis of either C-2 or C-3 substituted benzo[*b*]furans from 1-(2-hydroxyphenyl)-2-chloroethanones (Scheme 70).[85] The alkoxide intermediate generated from Grignard reagent and *α*-chloro ketone, which could form either 2-substituted benzo[*b*]furan *via* a [1,2]-aryl migration or 3-substituted benzo[*b*]furan *via* a direct cyclization and dehydration sequence. From the obtained results, a variety of functionalized substrates were well tolerated and various Grignard reagents furnished corresponding furans in moderate to good yields.



Scheme 70. The regioselective synthesis of 2- and 3-substituted benzofurans

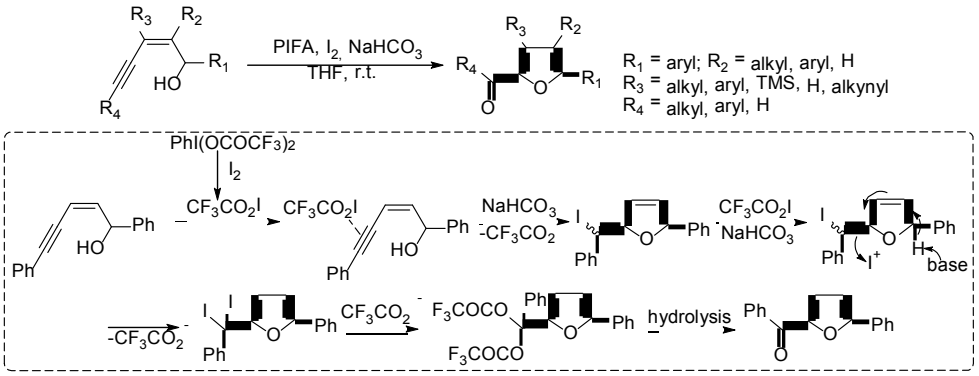
In 2011, Krause described a protocol for the synthesis of 3(2*H*)-furanones by cycloisomerization of allenic hydroxyketones, which was achieved in water without heating, cooling or any expensive and toxic metal catalysts (Scheme 71).[86] However, the prepared allenic hydroxyletones failed to give corresponding cycloisomerization products in the presence of gold or silver catalysts reported previously. Moreover, it could find that the furanone was only formed in a protic solvent. Under the optimal reaction condition, a series of furanones were transformed from corresponding allenic hydroxyletones in moderate to good yields.



Scheme 71. The synthesis of furanones from allenic hydroxyketones

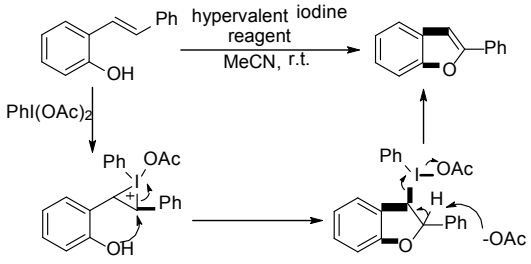
Another intramolecular cyclization to synthesize multisubstituted 2-acyl furans was presented by Liu and co-workers at the same year (Scheme 72).[87] With the combination of hypervalent iodine(III), molecular

iodine and the base, a series of 2-acyl furans with diverse substituted patterns were afforded in good yields. Under the mild reaction condition, the transformation was considered involving alkyne activation by trifluoroacetylhypoiodite generated *in suit* that the hypoiodite could coordinate with triple bond and enhanced the electrophilicity of the alkyne moiety. Then the 5-*exo*-*dig* nucleophilic attack of the hydroxyl group to the alkyne would form a 5-ylidene-2,5-dihydrofuran intermediate, which could undergo a further iodination leading a diiodide intermediate. Finally, the hydrolysis of the diiodide intermediate or the trifluo-substituted one afforded the furan as the desired product.



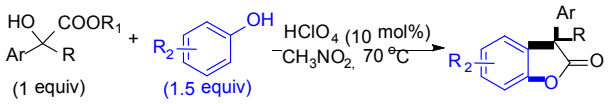
Scheme 72. The synthesis of multisubstituted 2-acyl furans from *cis*-enynols

Hypervalent iodine reagent was also employed by Wirth to synthesize 2-arylbenzofurans and 2-arylnaphthofurans from *ortho* hydroxystibenens (Scheme 73).[88] In the presence of (diacetoxyiodo)benzene [$PhI(OAc)_2$], good to excellent yields of various benzofurans were obtained within an intramolecular cyclization of corresponding *ortho* hydroxystilbenens. The substrates with electron-donating or electron-withdrawing groups were well tolerated. On the whole, the electron-donating substrates gave higher yields than electron-withdrawing groups. To the mechanism, the electrophilic iodine was considered to activate the double bond of stilbene and to form a three-membered iodonium intermediate The phenolic oxygen atom of the iodonium intermediate would undergo an intramolecular reaction and with the elimination of hypervalent iodine leading the 2-arylbenzofuran.



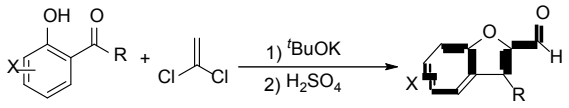
Scheme 73. Hypervalent iodoine mediated cyclization of *o*-hydroxystilbenes to benzofurans

In 2012, Zhou and co-workers developed a tandem Friedel-Crafts/lactonization reaction to benzofuranones from a variety of tertiary *α*-hydroxy acid esters and different substituted phenols (Scheme 74).[89] A series of cheap metals as powerful Lewis acids and Brønsted acids such as HOTf and $HClO_4$ were screened, while only $HClO_4$ could afforded the desired product efficiently in 85 % yield. Generally, in the presence of 10 mol% of $HClO_4$, electron-rich phenols could give the desired products in excellent yields. Nonetheless, the electronic effect was significant when the electron-rich substituents on the *ortho* or *para* position of the phenyl ring, the reaction proceeded smoothly and afforded corresponding products in high yield. On the contrary, even the electron-withdrawing groups could also give good yields, though the reactions were slow.



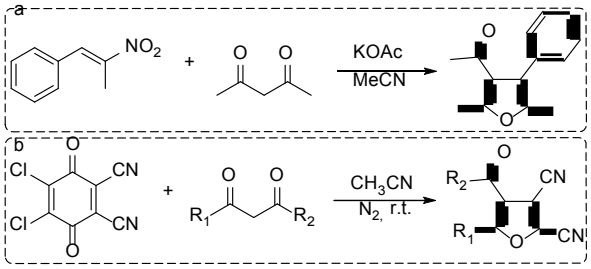
Scheme 74. The synthesis of benzofuranones from tertiary *α*-hydroxy acid esters and phenols

Markó described an efficient protocol to highly functionalized benzofurans from *o*-hydroxypheneones and dichloroethylene treated with the base ^{t}BuOK and underwent a facile rearrangement under mild acidic conditions (Scheme 75).[90] From the obtained results, it could find that this reaction was quite general, high yielding and proceeding efficiently with both alkyl- and aryl-substituted phenone. Various substituents such as halides were well tolerated. Moreover, when the base was used instead of LDA for the preparation of the chloroacetylene anion, the benzofuran-2-carbaldehyde could also be formed from the salicylaldehyde in 84% yield, which *via* a usual acid-catalyzed rearrangement.



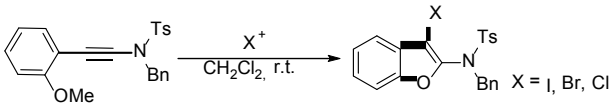
Scheme 75. The synthesis of benzofurans from *o*-hydroxypheneones and dichloroethylene

At the same year, Guan and co-workers presented a KOAc-promoted synthesis of substituted furans from nitroolefin and pentane-2,4-dione or *β*-ketoester (Scheme 76a).[91] Under the optimized condition, a wide range of functional groups were tolerated well and corresponding furans could be obtained in good yields. To the electronic effect, the electron-rich nitroolefins gave better reactivity and gave slightly higher yields than electron-deficient ones. Later, Deng *et al* developed an approach to 2,3-dicyanofuran by DDQ-mediated oxidative coupling, which employed the *β*-ketones or simple ketones/*β*-keto thiamides in one step to synthesize corresponding furans (Scheme 76b).[92] From the synthetic point of view, this protocol represented a powerful, simple and efficient approach to the construction of 2,3-dicyanofurans and thiophene units.



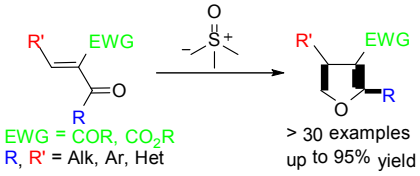
Scheme 76. The synthesis of multi-substituted furans from *β*-ketone and derivatives

In 2013, Cao developed a facile synthesis of 3-substituted 2-amidobenzofurans and 2-amidobenzothiophenes *via* an electrophilic cyclization of *o*-anisole- and *o*-thioanisole-substituted ynamides with I_2, NBS or NCS (Scheme 77).[93] Various ynamides were examined and moderate to good yields of corresponding 2-amidobenzothiophenes were constructed successfully. Moreover, all these products could be further transferred to 3-aryl-, 3-alkynyl- and 3-vinyl-2-amidobenzofurans *via* the Pd-catalyzed Suzuki-Miyaura, Sonogashira cross-coupling or Heck reaction in excellent yields, which furnished an alternative route to synthesize these bioactive molecules bearing a benzofuan skeleton.



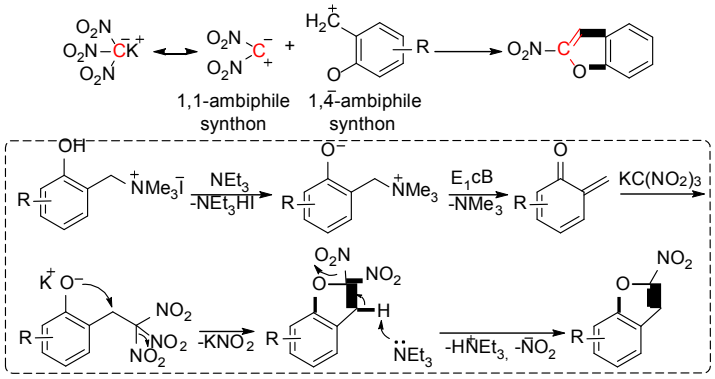
Scheme 77. The synthesis of 2-amidobenzofurans from *o*-anisole-substituted ynamides

In 2014, Budynina *et al* disclosed a straightforward, efficient and reliable approach to 2,3-dihydrofurans *via* a [4+1] annulation reaction between Corey ylide and *α,β*-unsaturated ketones (Scheme 78).[94] A broad series of 2-ylidene-1,3-diketones prepared from alkyl, alkenyl, aryl, hetaryl aldehydes, acetylacetone or other common 1,3-diketones were treated with Corey ylide. The obtained results indicated that there was no significant electronic effects on the benzene ring and corresponding 3,4,5-trisubstituted 2,3-dihydrofurans were afforded in good yields. To the diketone containing two different acyl groups, both carbonyl O-atoms were equally afforded the products and two isomeric dihydrofurans were obtained in an equimolar ratio. However, an electron-withdrawing group at the *α*-position of the ketones was found to be chemoselective when there was a *β*-alkyl or alkenyl-substituted *α*-acyl acrylate, the corresponding cyclopropanes were formed as side products.



Scheme 78. The synthesis of 2,3-dihydrofurans from *α,β*-unsaturated ketones

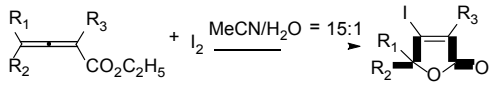
Recently, Osyanim employed the potassium trinitromethanide as a 1,1-ambiphilic synthon equivalent for the construction of benzofuran moiety (Scheme 79).[95] In the presence of trimethylamine, a variety of functional groups on the quaternary ammonium salts were well tolerated and afforded corresponding 2-nitrobenzofurans in moderate to good yields. To the mechanism, it seemed that an initial elimination of trimethylamine from the anion of the quaternary ammonium salt by an E_1cB mechanism could afford an electrophilic *o*-QM (*o*-quinone methides). With a sequence of Michael-type addition of trinitromethanide anion, intramolecular nucleophilic substitution and elimination of nitro groups, the 2-nitrobenzofuran was afforded as the final product.



Scheme 79. Potassium trinitromethanide as the 1,1-ambiphilic synthon to synthesis 2-nitroarenlfurans

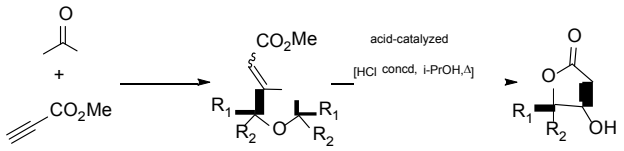
3.1.2 The synthesis of butenolide derivatives

In 2005, Ma synthesized a series of 4-iodofuran-2(5*H*)-ones by a facile iodolactonization of ethyl 2,3-allenoates (Scheme 80).[96] In the presence of I_2, the carbonyl oxygen atom which acted as an electrophile was added to the allene moiety regioselectively. With the iodolactonization of various 2,3-allenoates, corresponding 3-iodobutenolides could be obtained in good to excellent yields.



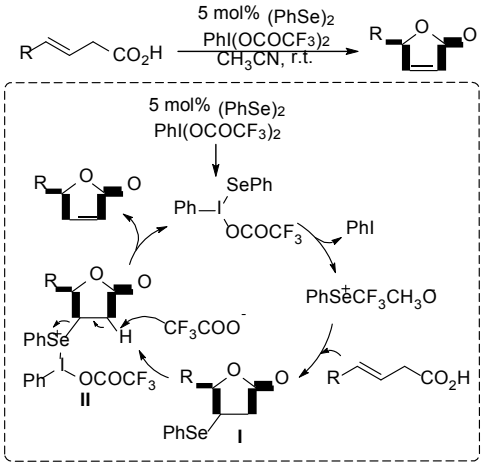
Scheme 80. Iodolactonization of 2,3-allenoates to 4-iodofuran-2(5*H*)-ones

Next year, García-Tellado described a one-pot and convenient access to 5-sp^2-substituted and 5,5-disubstituted tetronic acids, which involved a Michael addition of pyrrolidine on a secondary or tertiary *γ*-hydroxy-*α,β*-alkynl ester to give the enamine. Then, with an acid-catalyzed hydrolysis-Latonization, the tetronic acid was generated as the product (Scheme 81).[97]



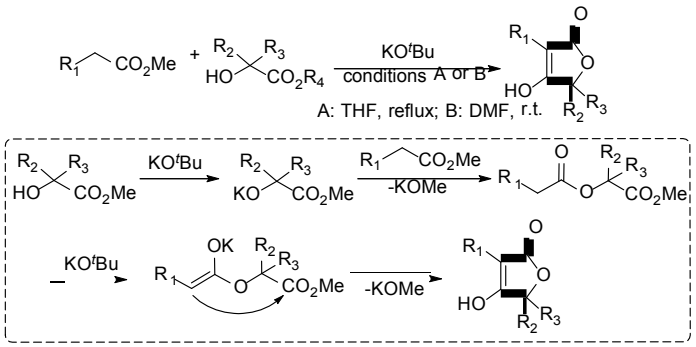
Scheme 81. Acid-catalyzed hydrolysis-lactonization to the synthesis of tetronic acids

Later, Wirth reported a convenient method for the synthesis of butenolides from a range of (*E*)-3-butennoic acids, which was catalyzed by 5 mol% of diphenyl diselenide (Scheme 82).[98] In the presence of the [bis(trifluorocaetoxy)iodo]benzene as the oxidant, the diphenyl diselenide was oxidized to phenylselenenyl trifluoroacetate, which could react with *β,γ*-unsaturated carboxylic acid and gave the intermediate **I**. Then the selenide in intermediate **I** may accelerate the elimination either by [bis(trifluorocaetoxy)iodo]benzene or phenylselenenyl trifluoroacetate and afforded the target product. However, from the obtained results, which may indicated that a fast elimination proceeded only with [bis(trifluoroacetoxy)iodo]benzene.



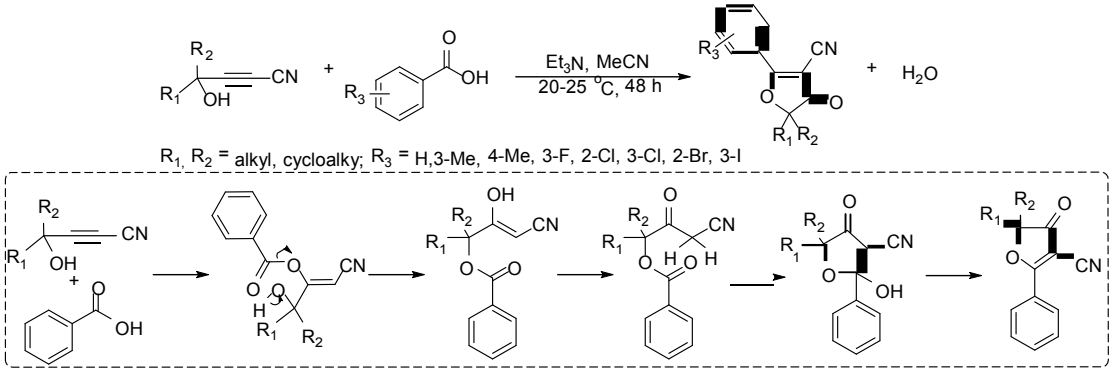
Scheme 82. The catalytic cyclization of (*E*)-4-phenylbut-3-enoic acids to butenolides

In 2008, Gall developed a tandem process involving a transesterification and a subsequent Dieckmann cyclization to synthesize tetronic acids from corresponding aryl- or heteroarylacetic acid esters and hydroxyacetic acid esters (Scheme 83).[99] All the tetronic acids were achieved in moderate to good yields either in THF at reflux condition or in DMF at room temperature. To the formation of tetronic acid, the transesterification of the alkoxide generated by the deprotonation of the hydroxyl ester and the methyl ester would afford a new ester as an intermediate, which would undergo a Dieckmann condensation and generated the tetronic acid as the final product.



Scheme 83. Tandem transesterification-Dieckmann cyclization of esters to tetronic acids

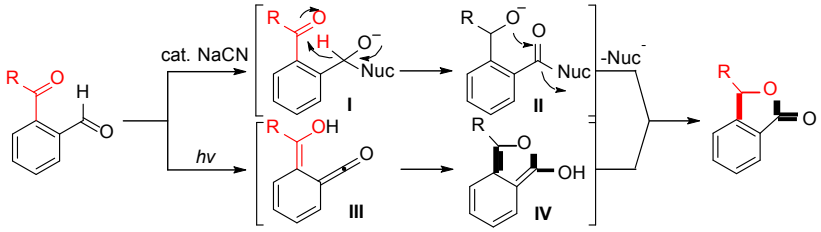
Two years later, Trofimov reported a domino reaction of *α,β*-acetylenic *γ*-hydroxyl nitriles with arenecarboxylic acids to 4-cyano-3(2*H*)-furanones, which was triggered by the addition of an arenecarboxylic acid to a triple bond followed by the domino reaction sequence: intramolecular transesterification-enol formation and Claisen condensation of the ketoacetonitrile tautomer with ester (Scheme 84).[100] In the presence of Et_3N, all the reactions proceeded smoothly and afforded corresponding 3(2*H*)-furanones in good yields. However, to the aliphatic carboxylic acids, under the optimal reaction condition, a mixture of the desired products and intermediate keto esters were formed with the ratio 1-2:1.



Scheme 84. The synthesis of 3(2*H*)-furanones from *α,β*-acetylenic *γ*-hydroxy nitriles with arenecarboxylic

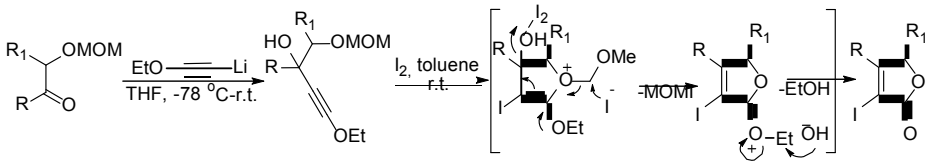
In 2012, Schmalz and co-workers disclosed a facile conversation (isomerization) of 2-formyl-arylketones into 3-substituted phthalides, which could be performed in either Cannizarro-Tishchenko-type reaction under nucleophile (NaCN) or under photo-catalyzed condition (DMSO, 350 nm) (Scheme 85).[101] In the presence of 10 mol% NaCN, which was considered as a convenient and inexpensive nucleophilic catalyst, a range of functional groups were well tolerated and the electronic properties of the substituents had little effect on the yields. On the other hand, when the reactions were conducted under the light-induce condition, the same substrates could furnish higher yields than the nucleophilic catalyzed process.

Certainly, to the mechanism, there was a significant difference between these two processes. The former one considered the attack of the nucleophilic catalyst at the aldehyde function of the substrate could give an intermediate, which would undergo an intramolecular hydride transfer to form an alkoxide intermediate. Subsequently, the lactone ring was established *via* a 5-*exo*-*trig* attack of the alkoxide at the carbonyl function with the release of nucleophilic catalyst. To the light-induced procedure, it would start with a Norrish **II** type reaction and a concomitant formation of an enol-ketene of type **III**. Then an intramolecular cyclic addition between the intermediate and the OH function could form the 1-hydroxyl-isobenzofurane, which would be tautomerized and generated the desired phthalide.



Scheme 85. Nucleophile- and light-induced synthesis of 3-substituted phthalides from 2-formylarylketones

In 2013, Reddy developed a convenient method to synthesize a range of 4,5-disubstituted 3-iodo-butenolides from various alkyne diols which *via* 5-*endo*-*dig* iodocyclization (Scheme 86)[102]. All the reactions were carried out with the using of I_2 in CH_2Cl_2 or toluene at room temperature. The oxygen in OMe and OMOM groups were utilized as an efficient nucleophile for the intramolecular cyclization. Various substrates with aliphatic substituents at C4 and C5 could afford the desired products in good yields. However, the aryl-substituted butenolides were obtained with a slightly diminished reactivity and the yields of corresponding products were decreased.

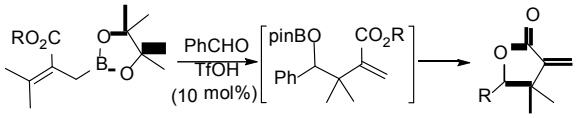


Scheme 86. The synthesis of 3-iodobutenolides *via* electrophilic iodocyclization of alkyne diols

3.1.3 The synthesis of lactones derivatives

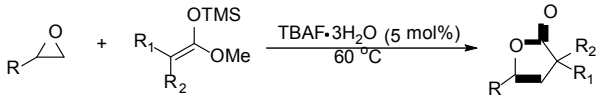
In 2007, Hall reported a triflic acid-catalyzed allylboration reaction between of 2-alkoxycarbonyl allylboronates and aldehydes to synthesize *β,γ*-disubstituted lactones with an *exo*-methylene at the *α*-position (Scheme 87).[103] Based on the detailed study on the reaction mechanism, it could find that the

nature of the aldehyde substrate was determinant for the stereochemistry of the lactone formation. The O-18 labeling was used to track the oxygen of aldehyde throughout the reaction sequence and indicated that none of the aldehyde oxygen was presented in the final products. Moreover, the control experiments indicated that there was a nucleophilic attack on the ester's alkoxy substituent. Nonetheless, there was no clear trend to find which one could give better results between *Z*- and *E*-substrates.



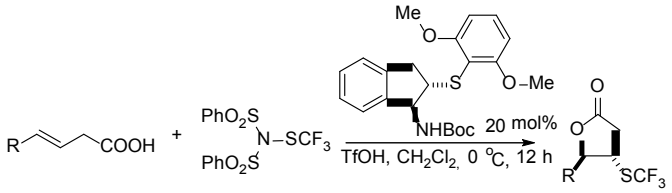
Scheme 87. Triflic acid-catalyzed addition of 2-alkoxycarbonyl allylboronates to aldehydes

In 2014, Vaccaro *et al* developed a catalytic approach to *γ*-lactones *via* a nucleophilic addition between silyl ketene acetals and epoxides (Scheme 88).[104] The tetrabutylammoniom fluoride was found to be efficient and employed as the catalyst loading to 5 mol%. Under the optimal reaction conditions, a variety of aryl and alkyl epoxides could afford corresponding *γ*-lactones in good yields and high regioselectivity.



Scheme 88. TBAF-catalyzed synthesis of *γ*-lactones from epoxides with ketene silyl acetals

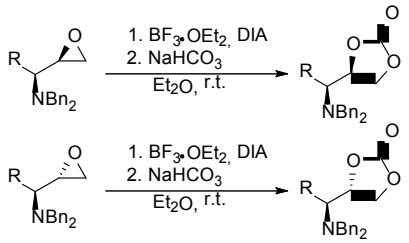
Recently, Zhao described an efficient approach for the enantioselective trifluoromethylthiolating lactonization by an indane-based bifunctional chiral sulfide catalyst and a shelf-stable electrophilic SCF_3 reagent (Scheme 89).[105] From the obtained results, the desired products could be formed with diastereoselectivities of >99:1 and good to excellent enantioselectivies. Besides, it could find that the electron-donating groups gave the lower enantioselectivity while the activities were not affected significantly. On the other hand, the electron-withdrawing groups just gave moderate yields, which seemed due to the incompletely consumption, but all of the products still kept high enantioselectives.



Scheme 89. Chiral sulfide-catalyzed enantioselective trifluoromethylthiolating lactonization

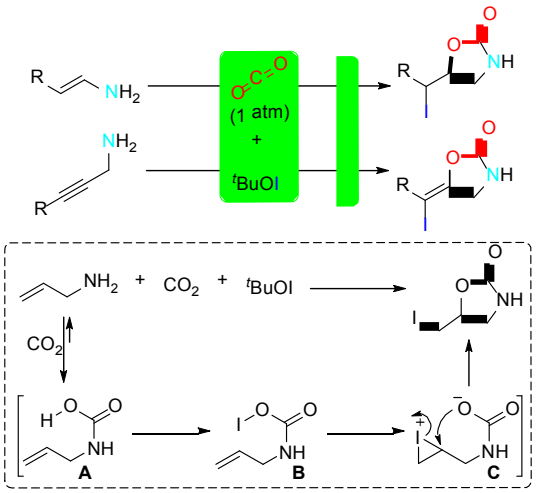
3.1.4 The synthesis of dioxolanones and oxazolidinones derivatives

In 2007, Concellón developed a totally selective reaction of CO_2 with enantiopure amino epoxides to synthesize (4*R*,1'*S*)- or (4*S*,1'*S*)-4-(1-amnoalkyl)-2-*oxo*-1,3-dioxolanes (Scheme 90).[106] Under the treatment with an aqueous solution of $NaHCO_3$ at room temperature, the enantiopure cyclic carbonates were furnished in good to excellent yields with total selectivity.



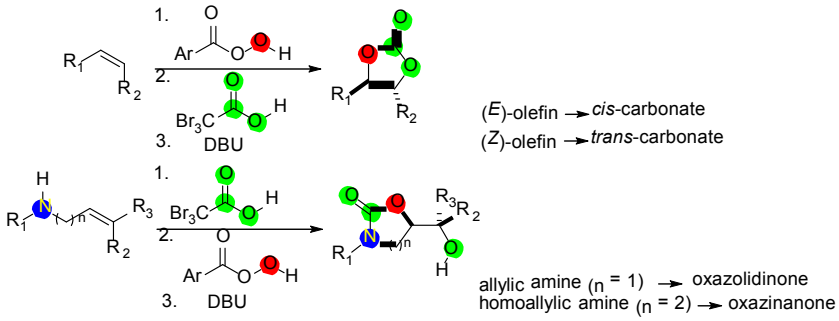
Scheme 90. The synthesis of dioxolanes from CO_2 and enantiopure amino epoxides

Later, Minakata employed the atmospheric CO_2 to build the cyclic carbamates skeletons with unsaturated amines (Scheme 91).[107] In the presence of ^{t}BuOI, a series of allyl and propargyl amines were converted to corresponding cyclic carbamates bearing a iodomethyl group in moderate to good yields. Several control experiments were well done and it seemed that the allyl carbamic acid **A** was formed by the amine and CO_2. In the presence of ^{t}BuOI, the proton-iodine process of **A** was taken place and generated an *O*-iodinated species **B**, which would serve as an iodonium source to form cyclic iodonium intermediate **C**. Subsequently, the cyclic carbamate was afforded with an intramolecular cyclization of **C** as the terminal product.



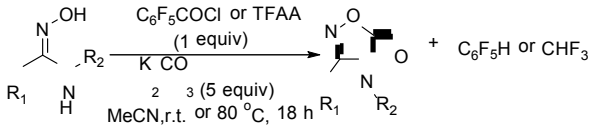
Scheme 91. The synthesis of cyclic carbamates from unsaturated amines with ^{t}BuOI

In 2010, Davies described an approach of olefins to cyclic carbonates and secondary allylic or homoallylic amines to cyclic carbamates, which *via* an initial epoxidation followed by S_N2-type epoxide ring opening by Br_3CCO_2H and subsequent base-promoted carbonate formation upon eliminiation of bromoform (Scheme 92).[108] With sequential treatment of 1,2-disubstituted olefins with *m*-CPBA, Br_3CCO_2H and DBU in one pot, corresponding disubstituted cyclic carbonates (1,3-dioxolan-2-ones) were afforded in good yields.



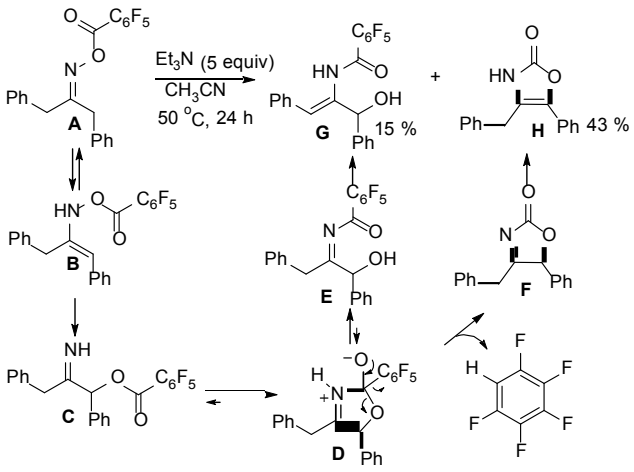
Scheme 92. The synthesis of cyclic carbonates/carbamates from olefins/allyic amines

Later, Zhu presented a novel synthesis of 1,2,4-oxadiazol-5-ones from amidoximes with pentafluorophenyl or trifluoromethyl anion which acted as a leaving group (Scheme 93).[109] Throughout this protocol, it could find that this unexpected C-C bond cleavage furnished an alternative methodology to synthesis a wide range of 1,2,4-oxadiazol-5-ones under the treatment with pentafluorobenzoyl chloride or trifluoroacetic anhydride (TFAA).



Scheme 93. The synthesis of 1,2,4-oxadiazol-5-ones from amidoximes

Several control experiments indicated that the tautomer of acyloxime would undergo a [3,3]-sigmatropic rearrangement to give **C**. The imine moiety would act as a nucleophile and attack to the carbonyl group leading to a tetrahedral intermediate **D**. At this stage, the reaction would be diverged to two directions. Fragmentation of the C-O bond would lead to the acyl-imine **E**, which upon isomerization would provide **G**. On the other hand, C-C bond cleavage would generate the pentafluorobenzene and **F**. The latter then could be tautomerized to the target product. Moreover, it could find that the yield of H was higher than **G**, which was considered that the C-C bond cleavage dominated over the alternative C-O bond scission (Scheme 94).

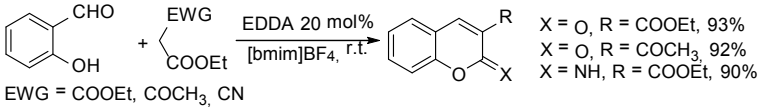


Scheme 94. The mechanism of amidoxine to 1,2,4-oxadiazol-5-one

3.2 The synthesis of *O*-containing six-membered heterocycles

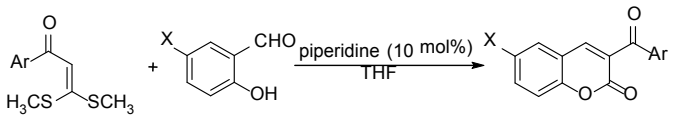
3.2.1 The synthesis of coumarins derivatives

In 2003, Chen and co-workers presented an ethylenediammonium diacetate (EDDA) catalyzed Knoevenagel condensation between aldehydes or ketones with active methylene in ionic liquid.[110] In this reaction, the ionic liquids, which was considered as 'green' recyclable alternatives to volatile organic solvents, with the catalyst EDDA recycled several times while no decreases in yields and reaction rates. In the case of 2-hydroxybenzaldehyde, the 3-substituted coumarins were furnished with high yields (Scheme 95). Later, Ranu employed the ionic liquid as the catalyst in a Knoevenagel condensation of aliphatic and aromatic carbonyl compounds as well.[111] In the presence of 20 mol% [bmlm]OH, a series of coumarins were afforded in excellent yields from corresponding 2-hydrobenzaldehydes and diethyl malonate or ethyl acetoacetate.



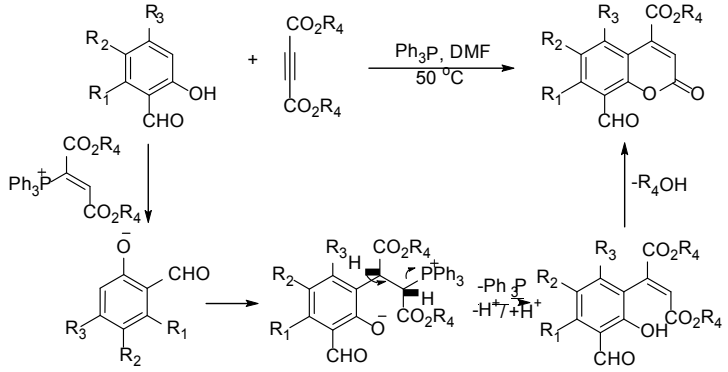
Scheme 95. EDDA catalyzed Knoevenagel condensation to synthesis of coumarins

3-Aroylcoumarins transformed from 2-Hydroxyaryladehydes and *α*-aroylketene dithioacetals were also developed by Rao *et al* in 2006 (Scheme 96).[112] In the presence of catalytic amount of piperidine in reflux THF, a series of salicylaldehydes and 2-hydroxy-1-naphthaldehydes were converted to corresponding coumarins in good to excellent yields.



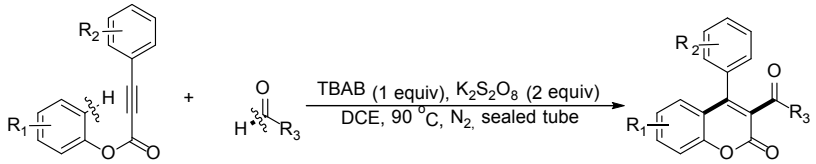
Scheme 96. The piperidine-catalyzed synthesis of 3-aroylcoumarins

In 2011, Majumdar and co-workers synthesized a variety of 4-carboxyalkyl-8-formyl coumarins from 2-hydroxybenzaldehydes *via* vinyltriphenylphosphonium salt mediated aromatic electrophilic substitution (Scheme 97).[113] A series of 2-hydroxybenaldehydes were tested and corresponding coumarins were obtained in moderate to good yields. The electron-donating groups in the *para* position of OH could present good yields while electron-withdrawing group gave relatively poor yields. To the mechanism, it was considered that the initial addition of triphenylphosphine to the acetylenic ester could give the vinyltriphenylphosphonium cation, which would attack to the aromatic ring at the *ortho* position of the salicylaldehyde anion and formed an intermediate. Subsequently, the formation of the desired coumarin was achieved by an intramolecular lactonization.



Scheme 97. Vinyltriphenylphosphonium salt mediated synthesis of 8-formyl coumarins

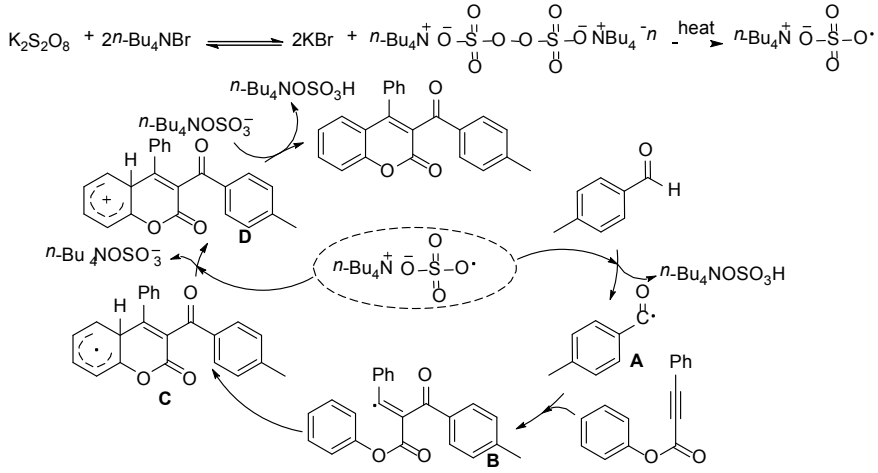
Recently, Wu *et al* developed an efficient tandem acylation/cyclization of alkynoates with aldehydes for the synthesis of 3-acyl-4-arylcoumarins, which was realized by the addition of acyl radical to alkynes and a C-H bond functionalization to form two new C-C bonds simultaneously (Scheme 98).[114]



Scheme 98. The synthesis of 3-acyl-4-arylcoumarins from alkynoates and aldehydes

Several control experiments indicated that the C-H bond cleavage was not the rate-limiting step and the addition of TEMPO or BHT revealed that it may involve a radical mechanism. Based on the obtained results, it was considered that the bis(tetrabutylammonium)peroxydisulfate transformed from peroxydisulfate and TBAB would be converted into the tetrabutylammonium sulfate radical anions at high

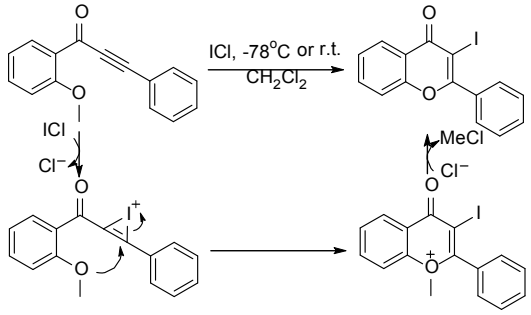
temperature. On the other hand, the radical **A**, generated from tetrabutylammonium sulfate radical and benzaldehyde, would attack to the *α*-position of C=O bond in alkynoate resulting the vinyl radical **B**. With an intramolecular cyclization, the radical intermediate **C** was formed from **B** and would undergo a single electron transfer leading cation **D**, which would be deprotonated by the sulfate dianion and gave the coumarin as the final product (Scheme 99).



Scheme 99. The mechanism of the synthesis of 3-acyl-4-arylcoumarins from alkynoates and aldehydes

3.2.2 The synthesis of chromanones, chromones and flavones derivatives

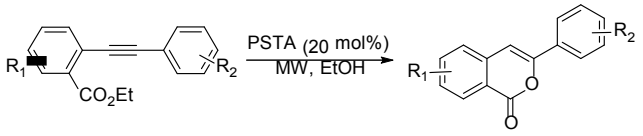
In 2006, Larock developed a ICl-induced cyclization of heteroatom-substituted alkynones to various 3-iodochromones and analogues (Scheme 100).[115] The scope of this reaction was quite general that varieties of functional groups were well tolerated and provided corresponding 3-iodochromones in good to excellent yields. Moreover, there was no limit to the synthesis of iodochromones, which could be further transformed by Pd-catalyzed coupling and furnished a wide range of functional substituted chromones, furans and ploycyclic compounds.



Scheme 100. ICl-induced cyclization to 3-iodochromones

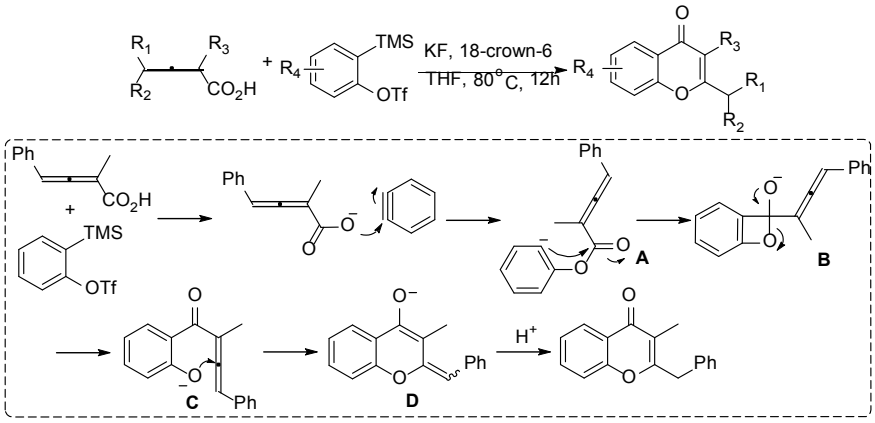
Two years later, Alami *et al* synthesized a series of 3-aryl-substituted isocoumarins in the presence of *p*-toluenesulfonic aicd (PTSA) as a mild acid catalyst (Scheme 101).[116] Under the microwave irradiation, a

variety of functionalized aromatic diarylalkynes were converted to corresponding isocoumarins in good yields. To the aliphatic arylalkynes, it could also be applied efficiently in this protocol.



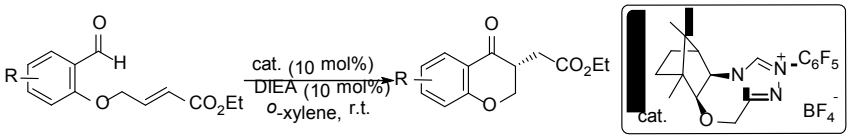
Scheme 101. PTSA-catalyzed synthesis of isocoumarins

In 2011, Ma described an efficient assembly of chromone skeleton from 2,3-allenoic aicd and benzyne (Scheme 102).[117] Various chromone derivatives were transformed in moderate to excellent yields under mild conditions. Instead of the cyclic conjugate addition of the intermediate formed by the nucleophilic addition of allenoic acid with benzyne, the intermediate **A** would undergo an 1,2-addition with the carbonyl group, which was followed by the ring opening, conjugate addition and the protonolysis resulting the formation of the chromone.



Scheme 102. The synthesis of chromones from 2,3-allenoic acids and benzynes

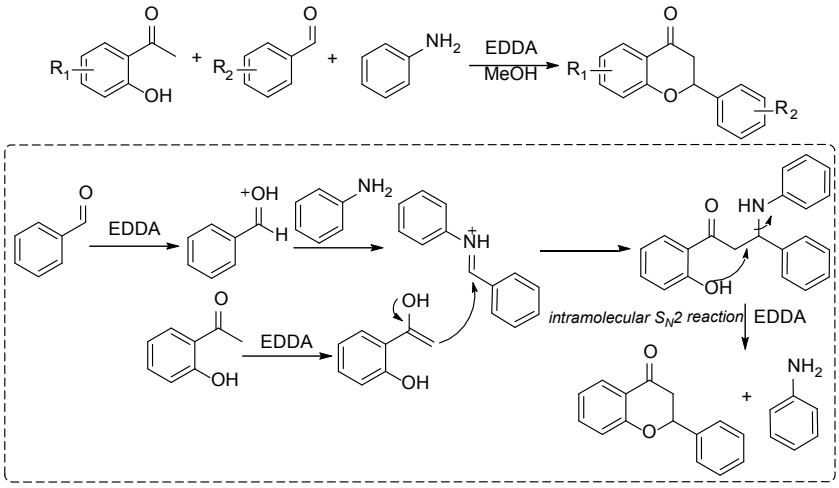
At the same year, You found that the chiral triazolium salts based on the camphor scaffold were seemed to be efficient for the asymmetric intramolecular Stetter reaction (Scheme 103).[118] With 10 mol% of the catalyst, a series of chromanones were obtained in excellent yields with up to 97% *ee*.



Scheme 103. NHCs-catalyzed synthesis of chromanones *via* an intramolecular Stetter reaction

Recently, in 2014, Lee and co-workers developed a mild and efficient one-pot synthesis of diverse flavanone derivatives from corresponding 2-hydroxyacetopheneones and aromatic aldehydes (Scheme 104).[119] In the presence of ethylenediamine diacetate (EDDA) as the catalyst, various flavanones were afforded in moderate to good yields. Several biological natural products bearing a flavanone moiety could also be performed well in this method. To the mechanism, the carbonyl group of benzaldehyde could be

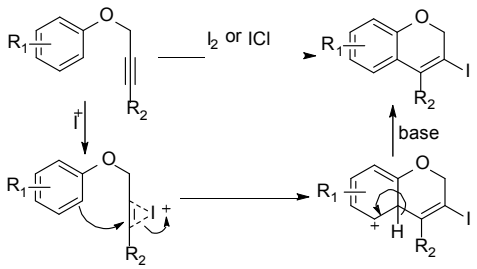
protonated by EDDA, which could facilitate the formation of an iminium **B**. The enol form **C**, generated from 2-hydroxyacetopheneone in the presence of EDDA, could attack the iminium ion to give intermediate **D**, which would undergo a cycloaddition to form the flavanone *via* an intramolecular S_N2 reaction.



Scheme 104. EDDA-catalzyed synthesis of flavanones *via* Mannich-type reaction

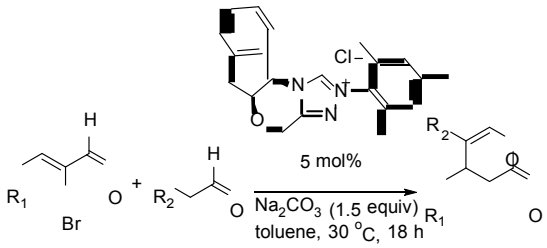
3.2.3 The synthesis of pyrans and pyranones derivatives

In 2007, Larock and co-workers developed a convenient method to the synthesis of 3,4-disubstituted 2*H*-benzopyran from substituted propargylic aryl ether, which *via* an electrophilic cyclization (Scheme 105).[120] In the presence of simple and inexpensive electrophiles I_2, ICl and PhSeBr, a wide range of functionalized propargylic aryl ethers including a simple phenyl or an alkenyl group were converted to corresponding iodo-substituted pyrans in moderate to good yields. However, the alkyl substituted on the alkyne terminus did not give the desired product with I_2 or ICl but worked with PhSeBr. To the mechanism, it was considered that the cyclization involving the initial formation of an iodonium or selenonium intermediate by the attack of electrophile on the triple bond followed the electrophilic attack on the electron cloud of the aromatic ring. With the losing of a proton, the 2*H*-benzopyran was generated as the final product.



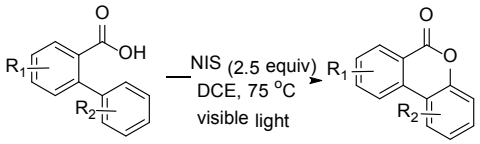
Scheme 105. Electrophilic cyclization of propargylic aryl ethers to 2*H*-benzopyrans

In 2013, Biju disclosed a NHC-catalyzed highly enantioselective lactonization of modified enals with enolizable aldehydes (Scheme 106).[121] Various 2-bromoenals and enolizable aldehydes were examined extensively. From the obtained results, all of them afforded corresponding pyranones in moderate to good yields with high enantioselectivity.



Scheme 106. NHC-catalyzed synthesis of pyranones from enals and aldehydes

Recently, Wei reported a NIS-mediated oxidative lactonization of 2-arylbenzoic acids for the synthesis of dibenzopyranones (Scheme 107).[122] A series of dibenzopyranones were performed from 2-arylbenzoic acids by a radical oxidative cyclization procedure mediate by *N*-iodosuccinimide (NIS). Compared to the substrates with electron-withdrawing substituents, the substrates with electron-donating substituents gave higher yields and the electron-rich substrates seemed to be more reactive in this reaction. Nonetheless, the steric hindrance acted as an important role, which may affect the coplanar formation and gave low yield of the target product.



Scheme 107. NIS-mediated oxidative lactonization of 2-arylbenzoic acids to dibenzopyranoness

4 Summery and perspective

Due to the space limit, it is impossible to present all of the corresponding works here in detail. This part summarized selectively about the recent development on the synthesis of 5-membered and 6-membered heterocycles containing O and N. From the literatures, it is obvious that various heterocycles could be performed without any transition metals while with the organocatalytic system, ionic liquids as the solvent or under the microwave irradiation condition. All these procedures seemed to be able to solve or release the problem of the metal residue, the pollution of heavy metal and the toxic solvents. With the deterioration of the environment and the development of human's life level, the research on these aspects would be paid more attention. Fortunately, throughout the investigations during the past decades, the organic catalyzed and promoted reactions have been attacked increasingly attention, which may act as a pivotal role in organic synthesis chemistry.

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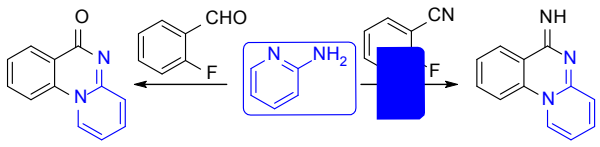
6 Objectives of this work

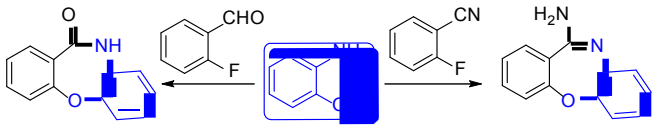
As described above, the synthesis of N- and O-containing heterocycles under transition-metal-free condition has been developed extensively and elegantly. In the case of the development of green chemistry and clean chemistry, we want to develop a new methodology to synthesize different kinds of heterocycles that have the biological activities or other functional application.

Due to the importance of quinazolinones, a variety of transition metal catalyzed syntheses of the quinazolinone and derivatives were presented extensively. Recently, our group developed a synthesis of linear and angular fused quinazolinones by a palladium-catalyzed carbonylation/nucleophilic aromatic substitution sequence. With the continuing interested in green chemistry and simple chemistry, we would like to develop a new method which seems to be green, convenient and efficient to synthesis these compounds without transition metals. On the other hand, it could solve the problem of metal residue, which may affect the application of corresponding bioactive compounds.

Hence, we envision that the quinazolinone and quinazolinimine could be transformed from 2-fluorobenzaldehyde and 2-fluorobenzonitrile with 2-amniopyridine under transition-metal-free condition, respectively. The F acts as a leaving group and the N atom of amniopyridine as the nucleophile with the sequential nucleophilic substitution and nucleophilic addition reaction to form the 6-membered heterocycles (Scheme 108; *J. Heterocyclic. Chem.*, **2015**, DOI 10.1002/jhet.2562; *Org. Biomol. Chem.*, **2015**, *13*, 10656-10662.). Moreover, it could find that when the 2-fluorobenzonitrile reacts with 2-aminophenol, it would afford the 7-membered heterocycle as well (Scheme 109; *Green Chem.*, **2015**, *17*, 4522-4526).



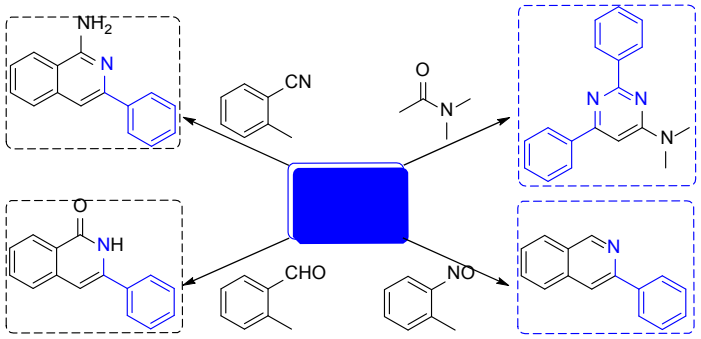
Scheme 108. The synthesis of quinazolinone and quinazolinimine



Scheme 109. The synthesis of dibenzo[*b,f*][1,4]oxazepin-11(10*H*)-one and dibenzo[*b,f*][1,4]oxazepin-11-amine

On the other hand, it could find that the unsaturated triple bond of benzonitrile could participate in the formation of various heterocycles *via* a nucleophilic addition. We assumed that the benzonitrile may react

with the carbanion which could undergo an intramolecular cyclization and generate corresponding heterocycles. Based on our previous study, we found that the DMAc and the 2-methylbenzontrile could afford the carbanion with the treatment of ^{t}BuOK, which would furnish an interesting route to synthesize the corresponding heterocycles (Scheme 110; *RSC Adv.*, **2015**, *5*, 106444-106447; *Adv. Synth. Catal.*, **2016**, *DOI: 10.1002/adsc.201600169*).



Scheme 110. The synthesis of 6-membered heterocycles based on benzonitrile

As shown above, most of the heterocycles may be performed without any transition metals while the base ^{t}BuOK employed as the sole promotor and/or *via* corresponding nucleophilic addiction and cyclization. All the procedures could be conducted without any special equipment or any other particular treatment, which may seem to be a convenient, efficient and economic commercial methodology to synthesize these heterocycles. Hence, we would like to develop, optimize and realize these meaningful reaction procedures, which may make a promising contribution to the development of the green and clean chemistry with our effort.

7 Publication

7.1 Base-promoted synthesis of dibenzoxazepinamines and quinazolinimines under metal-free conditions.

Jian-Bo Feng, Xiao-Feng Wu*

Green Chem., **2015**, *17*, 4522-4526.

Summary: An interesting base-promoted protocol for the synthesis of dibenzo[*b,f*][1,4]oxazepin-11-amines and quinazolinimines has been developed. Started from commercially available 2-fluorobenzonitriles, 2-aminophenols and 2-aminoethanol, good to excellent yields of the corresponding heterocycles can be achieved. Notably, only K_3PO_4 or K_2CO_3 was required as the promoter here and the reaction can be easily performed on a large scale.

Contribution: In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 80%.

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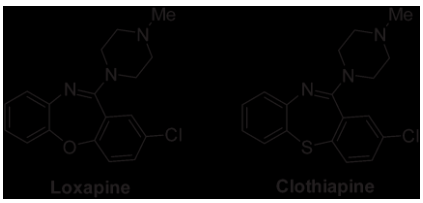
Base-promoted synthesis of dibenzoxazepinamines and quinazolinimines under metal-free conditions†

Jian-Bo Feng[a,b] and Xiao-Feng Wu*[a,b]

An interesting base-promoted protocol for the synthesis of dibenzo[b,f][1,4]oxazepin-11-amines and quinazolinimines has been developed. Started from commercially available 2-fluorobenzonitriles, 2-aminophenols and 2-aminoethanol, good to excellent yields of the corresponding heterocycles can be achieved. Notably, only K_3PO_4 or K_2CO_3 was required as the promoter here and the reaction can be easily performed on a large scale.

Dibenzo[b,f][1,4]oxazepin-11-amines and its derivatives are important moieties because they are pharmacologically active, for example, being anti-inflammatory,[1] antidepressant,[2] anti-oxidant,[3] having anti-tumor activities[4] etc. (Scheme 1).[5] To our surprise, despite the accepted importance of these compounds, there is still no general procedure that exists for their synthesis. Two examples were reported recently by Jiang and co-workers. They used 2-(2-bromophenoxy)aniline and isocyanides as the substrates with palladium as the catalyst, with the desired dibenzo[b,f][1,4]oxazepin-11-amines produced in good yields.[6] Therefore, research of general, convenient and practical strategies for the synthesis of these compounds is still of great importance and interest.



Scheme 1 Selected examples of pharmacologically active dibenzoxazepinamines.

Transition metal catalysts have already become a useful tool in modern organic synthesis, which has been verified by the Nobel Prize of Chemistry in 2001, 2005, and 2010.[7] These powerful catalysts have been applied to the preparation of heterocyclic compounds as expected. However, as one of the main interests in heterocycles is their biological activity, which is sensitive to the residual amount of metal catalyst in the final compounds, special attention has to be paid to the product purification and impurity detection. Hence, synthetic procedures without a metal catalyst or additive are needed by the synthetic community. Under all these backgrounds and our own research interests on heterocycle synthesis, we wish to report here a practical procedure for the synthesis of dibenzoxazepinamines and related analogues under metal-free conditions.[9] Only K_3PO_4 or K_2CO_3 was required as the promoter here and the reaction could be easily performed on a large scale.

Initially, the effect of the base was tested with 2-fluorobenzonitrile (1a) and 2-aminophenol (2a) as the model substrates in DMF at 100 °C under air (Table 1, entries 1–6). In all the tested organic and inorganic bases, K_3PO_4 gave the best results and 95% of the desired dibenzo[b,f][1,4]oxazepin-11-amine was isolated (Table 1, entry 4), while no product was detected with DBU as the base (Table 1, entry 6). Then the influence of the solvent on this transformation was checked. Compared with using DMF as a solvent, DMSO, DMAc, toluene and 1,4-dioxane showed decreased yields (Table 1, entries 7–10).[9] The temperature was considered as another possible variable for this method. However, no improvement appeared by either increasing the temperature to 130 °C or decreasing it to 70 °C (Table 1, entries 11–12). In order to exclude the possibility of air being involved in the reaction, a control reaction under an argon atmosphere was performed and no influence on the yield was observed.

With the optimal reaction conditions in hand, the generality and limitation testing was subsequently performed. A variety of substituted 2-aminophenols were examined at the

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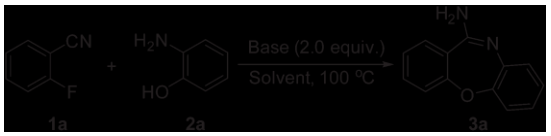
†Electronic supplementary information (ESI) available: Analytic data and NMR spectra. See DOI: 10.1039/c5gc01634g

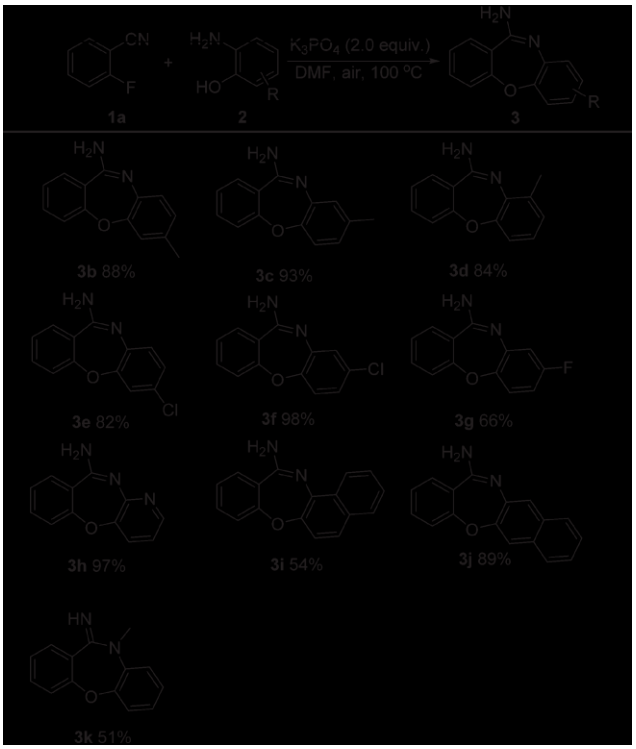
Table 1 Dibenzoxazepinamines synthesis: reaction conditions optimization[a]



Entry	Base	Solvent	T (°C)	Yield[b] (%)
1	Na_2CO_3	DMF	100	8
2	K_2CO_3	DMF	100	53
3	KOtBu	DMF	100	89
4	K_3PO_4	DMF	100	95
5	DABCO	DMF	100	30
6	DBU	DMF	100	0
7	K_3PO_4	DMSO	100	34
8	K_3PO_4	DMAc	100	81
9	K_3PO_4	Toluene	100	24
10	K_3PO_4	Dioxane	100	57
11	K_3PO_4	DMF	130	66
12	K_3PO_4	DMF	70	25

[a] Reaction conditions: 1 (1 mmol), 2 (1.5 mmol), base (2.0 equiv.), solvent (2 mL), 100 °C, air, 6 h. [b] Isolated yield.

Table 2 Dibenzoxazepinamines synthesis: substrate testing of 2-aminophenols[a]



[a] Reaction conditions: 1a (1 mmol), 2 (1.5 mmol), K_3PO_4 (2.0 equiv.), DMF (2 mL), 100 °C, air, 6 h, isolated yields.

first stage. As shown in Table 2, both electronic-donating and electronic-withdrawing groups substituted onto the substrates could give the desired products with 2-aminophenol in good yields. Additionally, 2-aminopyridin-3-ol could be applied as a substrate as well and gave the corresponding benzo[f]pyrido [3,2-b][1,4]oxazepin-10-amine (3h) in a 97% isolated yield. Furthermore, ortho-amino-substituted naphthalenols like 1-aminonaphthalen-2-ol and 3-aminonaphthalen-2-ol can also be used as suitable starting materials for this transformation and gave the corresponding products in good yields (3i, 3j). In the case of 2-(methylamino)phenol, 51% of 10-methyldibenzo[b,f] [1,4]oxazepin-11(10H)-imine (3k) was obtained as the desired product.

Next, various substituted 2-fluorobenzonitriles were tested with 2-aminophenol. As shown in Table 3, all the tested substrates provided moderate to good yields. This methodology showed good functional group tolerance, while the electronic-withdrawing functional groups showed a more positive effect than the electronic-donating group. From the obtained results, it can be seen that there are significant differences in the yields of the desired compounds (3n, 3o, 3s and 3p, 3q, 3r) when the same substituent is substituted in a different position. This phenomenon might be able to be explained by the electronic and the steric effects of the substituents on the nucleophilic substitution between the –OH and –F and the nucleophilic addition of the $–NH_2$ to the –CN. Only a trace of the desired product could be produced from 2-amino-6-fluorobenzonitrile and 2-aminophenol (3v), even with prolonging the reaction time and increasing the reaction temperature.

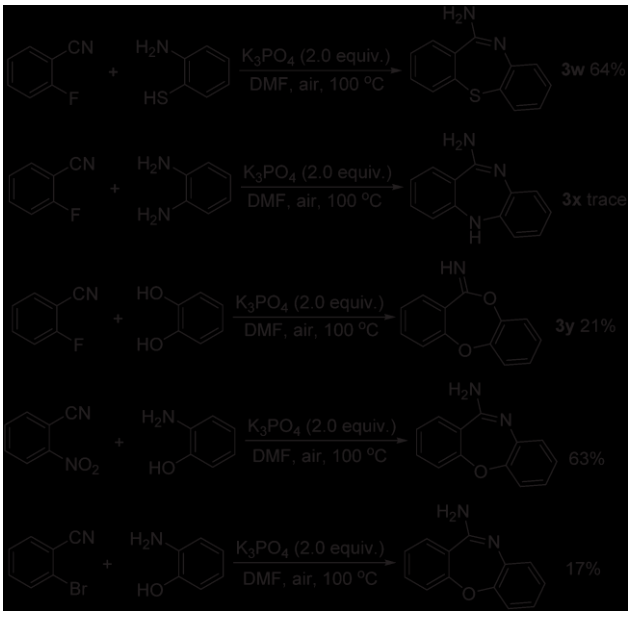
Encouraged by these results, we turned to testing analogues of the substrates (Scheme 2). Under the same reaction conditions, 64% of dibenzo[b,f][1,4]thiazepin-11-amine (3w) was isolated from the reaction between 2-fluorobenzonitrile and 2-aminobenzenethiol. However, only a trace of the desired product could be detected when using benzene-1,2-diamine as the reaction partner. In the case of pyrocatechol, 21% of 11H-dibenzo[b,e][1,4]dioxepin-11-imine was isolated together with a large amount of 2,2′-(1,2-phenylenebis(oxy))dibenzonitrile, which is a result of the reaction of two molecules of 2-fluorobenzonitrile with one molecule of pyrocatechol. Then 2-nitrobenzonitrile and 2-bromobenzonitrile were tested because of their similarity with 2-fluorobenzonitrile. As we expected, a moderate yield of the desired product could be produced from 2-nitrobenzonitrile and 2-aminophenol; while a 17% yield was obtained with 2-bromobenzonitrile, due to the differences in the leaving ability.

In order to prove the synthetic applicability of this procedure, we performed the reaction in a larger scale (Scheme 3). 5-Cholro-2-aminobenzonitrile was chosen as the substrate in an 8 mmol scale in 16 mL of DMF, 83% of the corresponding product could be isolated. Notably, 2-chlorodibenzo[b,f][1,4] oxazepin-11-amine is a key intermediate for the synthesis of the antidepressant drug Loxapine.[2,3]

Moreover, only a trace of the desired product was observed when 2-aminoethanol was applied as the substrate, together with a certain amount of 1,2-dihydro-9H-benzo[6,7][1,4]oxazepino[4,5-a]quinazolin-9-imine. After some further optimi-

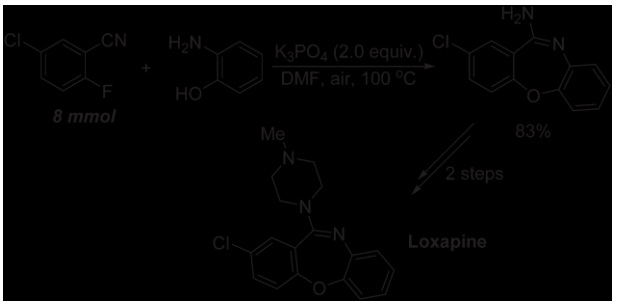
Table 3 Dibenzoxazepinamines synthesis: substrate testing of 2-fluorobenzonitriles[a]

[a] Reaction conditions: 1 (1 mmol), 2a (1.5 mmol), K_3PO_4 (2.0 equiv.), DMF (2 mL), 100 °C, air, 6 h, isolated yields.

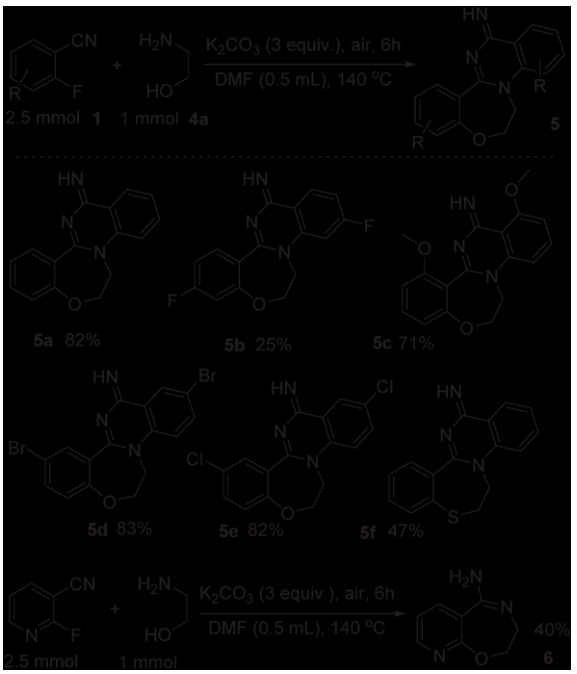


Scheme 2 Testing of substrate analogues.

zation, the yield of quinazolinimine could be improved to 82% by using 2.5 equiv. of 2-fluorobenzonitrile with K_2CO_3 as the base (Scheme 4, 5a). Some other 2-fluorobenzonitriles were



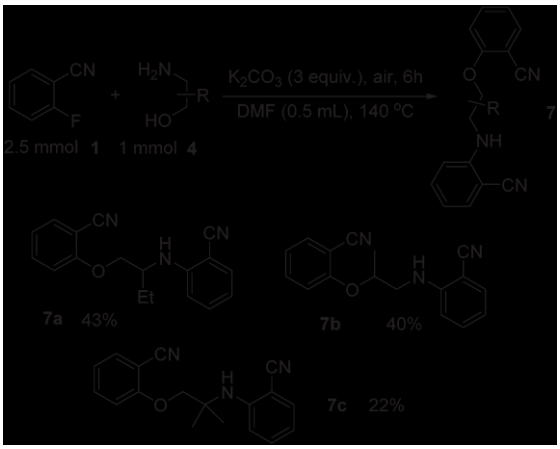
Scheme 3 Enlarged reaction.



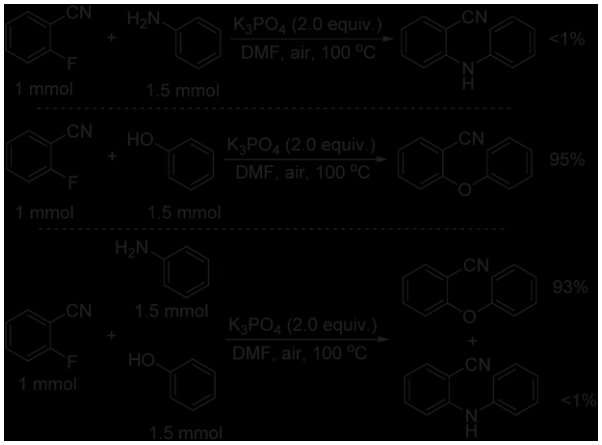
Scheme 4 Reaction of 2-aminoethanol with 2-fluorobenzonitriles.

tested as well, with moderate to good yields of the desired products being isolated to our delight (Scheme 4). Interestingly, 2,3-dihydropyrido[3,2-f][1,4]oxazepin-5-amine was isolated in a 40% yield when 2-fluoronicotinonitrile was used as the starting material (Scheme 4, 6). However, in the testing of the 2-aminoethanol derivatives, only non-cyclized products were detected (Scheme 5). Additionally, ethane-1,2-diol, ethane-1,2-diamine and 3-aminopropan-1-ol were tested with 2-fluorobenzonitrile as well. No desired product was observed in these cases.

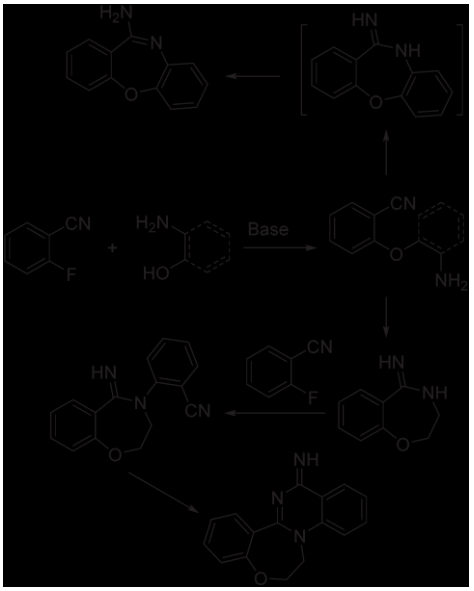
Based on these results and the control experiments (Scheme 6), a possible reaction pathway is proposed and shown in Scheme 7.[8,10] The reaction starts with the base-promoted nucleophilic substitution of 2-aminophenol/2-aminoethanol and 2-fluorobenzonitrile to give the corresponding aryl ether as the intermediate, followed by the addition of the amino group to the cyano group. In the case of 2-amino-



Scheme 5 Reaction of 2-aminoethanols with 2-fluorobenzonitrile.



Scheme 6 Control experiments.



Scheme 7 Proposed reaction mechanism.

phenol, the final product can be formed after rearrangement. When using 2-aminoethanol as the substrate, another molecule of 2-fluorobenzonitrile joins in the reaction and gives the final product after nucleophilic substitution and addition.

In conclusion, a practical and efficient methodology for the synthesis of dibenzo[b,f][1,4]oxazepin-11-amines has been developed. With 2-fluorobenzonitriles, 2-aminophenols and their analogues as the substrates, the corresponding products can be isolated in good to excellent yields under metal-free conditions. Additionally, this methodology can be performed on a large scale without any problems. Further, more complicated quinazolinimines can be produced when using 2-aminoethanol as the reaction partner.

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7.2 KO^{t}Bu-promoted synthesis of multi-substituted 4-aminopyrimidines from benzonitriles and aliphatic amides.

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Summary: Multi-substituted 4-aminopyrimidines have been prepared from commercially-available benzonitriles and aliphatic amides under transition-metal-free conditions. With KO^{t}Bu as the only promoter, the desired pyrimidines were isolated in moderate to excellent yields.

Contribution: In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 80%.

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KO^{t}Bu-promoted synthesis of multi-substituted 4-aminopyrimidines from benzonitriles and aliphatic amides†

Jian-Bo Feng[ab] and Xiao-Feng Wu*[ab]

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Multi-substituted 4-aminopyrimidines have been prepared from commercially-available benzonitriles and aliphatic amides under transition-metal-free conditions. With KO^{t}Bu as the only promoter, the desired pyrimidines were isolated in moderate to excellent yields.

Pyrimidine and its derivatives are ubiquitous in natural products, functional materials, etc.[1] Various biological activities, including anticonvulsant,[2] antitumor,[3] anticancer,[4] anti-inflammatory[5] and antimicrobial activities[6] have been reported. Representative examples of pharmaceuticals containing a pyrimidine moiety as the core structure, i.e. trimethoprim,[7] capecitabine[8] and imatinib,[9] are shown in Scheme 1.

Considering the importance of pyrimidines, a variety of elegant approaches have been developed.[10] Examples of transition metal catalyst-based procedures are gold-catalyzed cycloadditions of ynamides with two nitriles,[11] iron-catalyzed construction of 2-aminopyrimidines from alkynenitriles and cyanamides,[12] iridium-catalyzed multi-component synthesis of pyrimidines from amidines and alcohols[13] and niobium-catalyzed cycloaddition of alkynes and nitriles.[14] Transition metal-free procedures have also been developed.[15] Among these methodologies, the use of Tf_2O as a promoter to prepare pyrimidines from nitriles and methyl ketones has been established and applied. Here, we wish to report a new reaction pathway for the synthesis of pyrimidines from nitriles and amides. In our new procedure, KO^{t}Bu has been applied as the promoter. Various 4-aminopyrimidines were isolated in moderate to excellent yields.

Scheme 1 Selected examples of pharmaceuticals containing a pyrimidine core.

Table 1 Optimization of conditions for the synthesis of N,N-dimethyl-2,6-diphenylpyrimidin-4-amine[a]

Entry	Base (equiv.)	T (°C)	Yield[b] (%)
1	KO^{t}Bu (2)	100	68
2	NaO^{t}Bu (2)	100	0
3	K_2CO_3 (2)	100	0
4	K_3PO_4 (2)	100	0
5	KOH (2)	100	0
6	NaOMe (2)	100	5
7	KOAc (2)	100	0
8	KO^{t}Bu (1)	100	27
9	KO^{t}Bu (3)	100	60
10	KO^{t}Bu (2)	80	19
11	KO^{t}Bu (2)	110	86 (84)[c]
12	KO^{t}Bu (2)	120	73

[a] Reaction conditions: benzonitrile (3 equiv.), base, DMAc (2 mL), 16 h. [b] GC yield, with hexadecane used as the internal standard. [c] Isolated yield.

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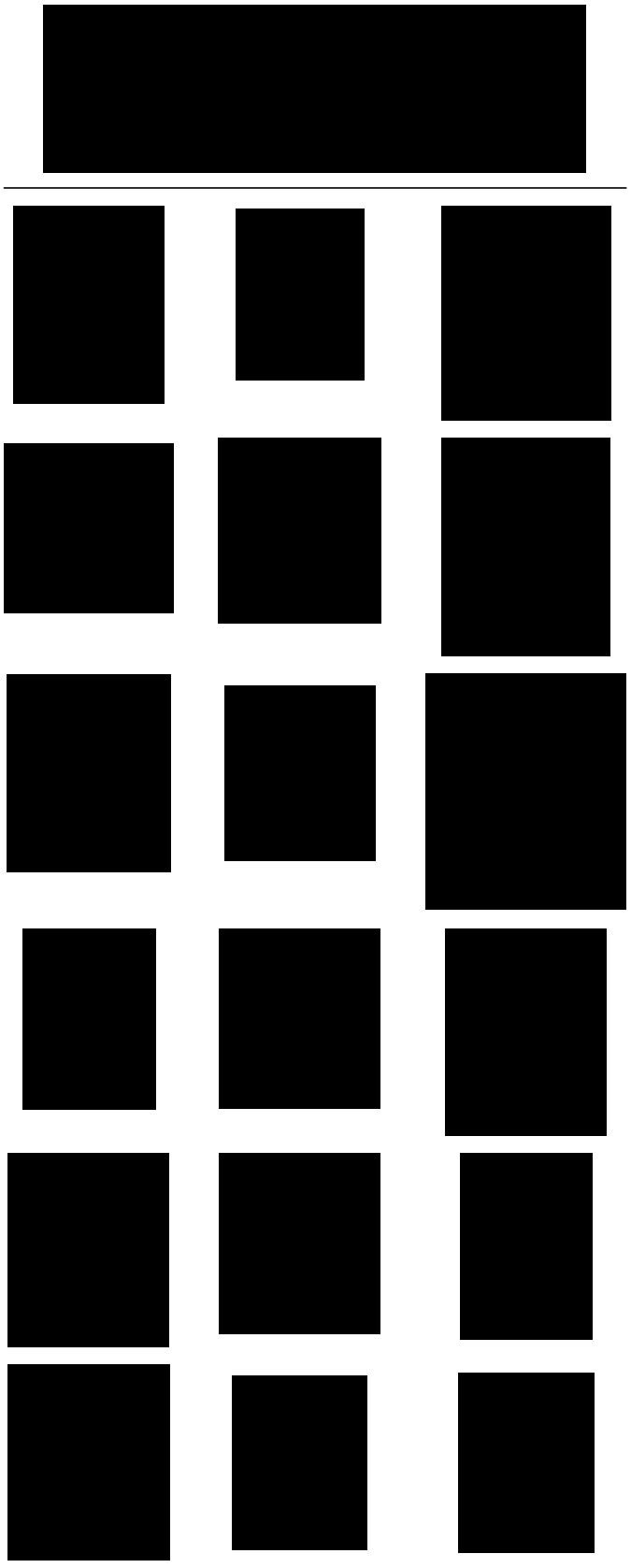
† Electronic supplementary information (ESI) available: General procedure, analytic data and NMR spectra. See DOI: 10.1039/c5ra24292d

Table 2 Synthesis of pyrimidines from benzonitriles and DMAc[a]



[a] Reaction conditions: 1 (3 equiv.), K^{t}OBu (2 equiv.), DMAc (2 mL), 110 °C, 16 h, isolated yield.

Initially, various inorganic bases were examined in 2 mL of DMAc with benzonitrile at 100 °C (Table 1, entries 1–7). To our delight, 68% of the target product was produced with KO^{t}Bu as the base (Table 1, entry 1). The other tested bases, which included NaO^{t}Bu, K_2CO_3, KOAc, K_3PO_4 and KOH, were ineffective here. No improvement in yield could be obtained when the amount of KO^{t}Bu was lowered or increased (Table 1, entries 8 and 9). However, 84% of the desired product was isolated when the reaction was conducted at 110 °C (Table 1, entry 11).

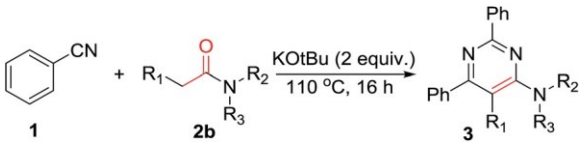
With the best reaction conditions in hand (Table 1, entry 11), we investigated the generality of this reaction. As shown in Table 2, electron-donating and electron-withdrawing substituents and even heterocyclic aromatic nitriles can be applied as the substrates in this new procedure. 71% of the desired pyrimidine (3ba) was produced from 4-methylbenzonitrile and DMAc. However, the yield decreased to 10% when the methyl group was substituted at the ortho position, which can be explained by steric hindrance. Ether and thioether groups can be well tolerated, and gave the corresponding pyrimidines in good to excellent yields (3da–3ga). Naphthonitriles were also tested under our conditions and gave the desired products in good yields (3ha–3ja). In the cases of halogen-substituted benzonitriles, the yields of the target pyrimidines decreased. This phenomenon can be explained by the nucleophilic substitution between the halogen groups and DMAc-decomposed N,N-dimethyl amine to give the corresponding N,N-dimethylaniline derivatives. To our delight, 90% of N,N-dimethyl-2,6-di(pyridin-3-yl)pyrimidin-4-amine (3ra) was isolated when nicotinonitrile was applied as the starting material. However, aliphatic nitriles failed here and no desired products could be obtained.

Subsequently, various DMAc derivatives were examined with benzonitrile. As illustrated in Table 3, moderate to good yields were achieved in all cases. A limitation of this procedure is that no primary and secondary amides can be applied. Additionally, besides amides, acetone, acetophenone, 2-phenylacetophenone, 1-cyclopropylethan-1-one, DMSO, etc. were tested as well. Rather than the desired pyrimidines, enaminones were obtained as the main products (3ai). From a synthetic point of view, it's interesting to prepare cross-cyclized pyrimidines. Hence, we applied 3-cyanopyridine (1.5 equiv.) and p-methylbenzonitrile (1.5 equiv.) as two different starting materials in DMAc under our best reaction conditions (Scheme 2). From the obtained results, we see that no selectivity could be achieved here.

Interestingly, when quinoline-3-carbonitrile was tested as substrate under our conditions, only 2-(3-cyanoquinolin-2-yl)-N,N-dimethylacetamide was formed and isolated. After further optimization, the yield was improved to 90% with 3 equiv. of KOtBu. Instead of DMAc, N,N-diethylacetamide and 1-morpholinoethan-1-one are suitable solvent and substrates as well (Scheme 3).

Based on the obtained results, a possible reaction pathway is proposed (Scheme 4). In the presence of KO^{t}Bu, the activated a-H of DMAc could be trapped and transformed into a carbon anion, I. Then, nucleophilic addition of the in situ-formed carbon anion to the nitrile group could take place and afford the intermediate enaminone, II. The amidine intermediate, III,

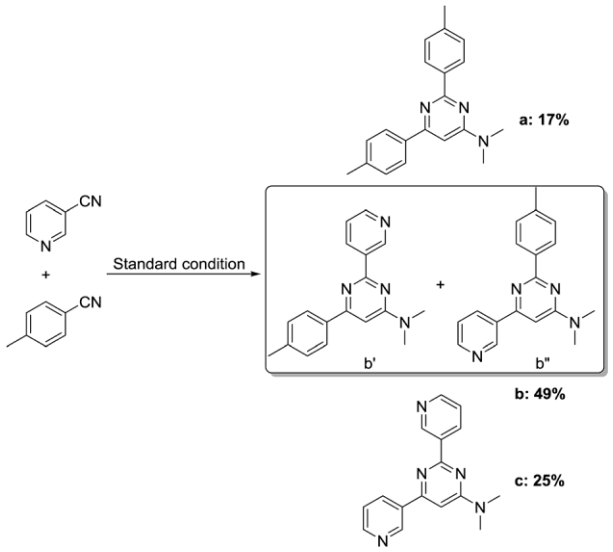
Table 3 Synthesis of pyrimidines from DMAc derivatives[a]



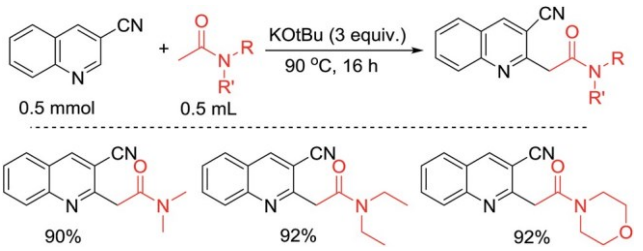
[redacted]

[a] Reaction conditions: 1 (3 equiv.), K^{t}OBu (2 equiv.), 2 (2 mL), 110 °C, 16 h, isolated yield.

could be formed after enaminone II reacts with another molecule of benzonitrile. The nitrogen anion in amidine intermediate III could then go through intramolecular nucleophilic addition to the carbonyl group to give the target molecule, through nucleophilic addition to the enol form of III.



Scheme 2 Synthesis of different 2,6-substituted pyrimidines.



Scheme 3 Direct functionalization of quinoline-3-carbonitrile.

[redacted]

Scheme 4 Proposed reaction mechanism.

Conclusions

In conclusion, we have presented a new pathway for the synthesis of pyrimidine derivatives. This procedure has advantages which include being highly economical, efficient and convenient. All the reactions were conducted in a one-pot, one-step manner, and without the addition of transition metal catalysts. The desired multi-substituted 4-aminopyrimidines were isolated in moderate to excellent yields from commercially-available benzonitriles and aliphatic amides, with KO^{t}Bu as the only promoter.

Acknowledgements

The authors thank the state of Mecklenburg-Vorpommern, the Bundesministerium für Bildung und Forschung (BMBF) and the Deutsche Forschungsgemeinschaft for financial support. In addition, the research leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking (CHEM21) under grant agreement no. 115360, resources of which are composed of a financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies in kind contribution. We also thank Dr C. Fischer, S. Schareina, and Dr W. Baumann for their excellent technical and analytical support. We also appreciate the general support from Prof. Matthias Beller.

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7.3 Synthesis of quinazolinimines and quinazolinamines from 2-fluorobenzonitriles under catalyst-free conditions.

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Summary: A convenient procedure for the synthesis of quinazolinimines and quinazolinamines from 2-fluorobenzonitriles has been developed. By using KO^{t}Bu as the promotor with 2-aminopyridines or amidines as the reaction partner, the desired heterocycles were produced in moderate to good yields under catalyst-free conditions.

Contribution: In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 80%.

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Synthesis of quinazolinimines and quinazolinamines from 2-fluorobenzonitriles under catalyst-free conditions†‡

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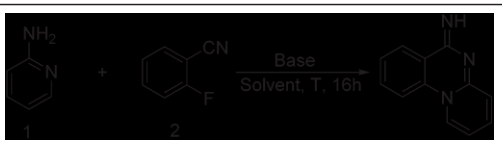
A convenient procedure for the synthesis of quinazolinimines and quinazolinamines from 2-fluorobenzonitriles has been developed. By using KO^{t}Bu as the promotor with 2-aminopyridines or amidines as the reaction partner, the desired heterocycles were produced in moderate to good yields under catalyst-free conditions.

The development of new procedures for the synthesis of heterocyclic compounds is one of the main areas in organic chemistry.[1] Heterocycles are present widely in naturally occurring compounds and also have numerous important applications in pharmaceuticals and so on. In the past few centuries, countless methodologies have been established as the importance of heterocycles was realized, such as the name reactions,[2] and the recently developed C–H activation procedures.[3] However, from the point of view of the pharmaceutical industry, the requirement of novel metal catalysts for these methods has limited their application on the industrial scale, mainly for two reasons: (1) the use of noble metal catalysts increases the cost of the procedure; (2) the biological activity of heterocycles is sensitive to the residual amount of metal catalyst in the final compounds, and hence special attention has to be paid to the product purification and impurity detection which further increase the cost. Hence, the development of synthetic procedures without the requirement of a metal catalyst or additive has become the aim of the synthetic community.[4] Gratifyingly, many transition metal-free procedures have been achieved, for example hypervalent iodine-catalyzed methods,[5] iodide-catalyzed oxidative pathways, etc.[6] Here, we wish to report our new results on the development of a new transition metal-free procedure for heterocycle synthesis.[7] By using KO^{t}Bu as the promotor, with 2-fluorobenzonitriles and 2-aminopyridines or amidines as the substrates via SNAr reactions,[4] biologically active quinazolinimines and quinazolinamines were produced in moderate to good yields.[8]

Initially, 2-fluorobenzonitrile and 2-aminopyridine were chosen as the model system to test the effects of solvents (Table 1, entries 1–6). In the presence of KO^{t}Bu at 100 °C, moderate to good yields can be achieved in all the tested cases. To our delight, 88% of 6H-pyrido[1,2-a]quinazolin-6-imine can be

Table 1 Optimization for the synthesis of quinazolinimine[a]



Entry	Base	Solvent	Temp.	Yield[b] (%)
1	^{t}BuOK	DMF	100	62
2	^{t}BuOK	DMAc	100	88
				64[c]
3	^{t}BuOK	DMSO	100	53
4	^{t}BuOK	Toluene	100	41
5	^{t}BuOK	1,4-Dioxane	100	44
6	^{t}BuOK	o-Xylene	100	43
7	^{t}BuONa	DMAc	100	0
8	K_2CO_3	DMAc	100	1
9	K_3PO_4	DMAc	100	6
10	KOH	DMAc	100	1
11	DBU	DMAc	100	0
12	NEt_3	DMAc	100	0
13	DABCO	DMAc	100	0
14	^{t}BuOK	DMAc	100	15[d]
15	^{t}BuOK	DMAc	120	31
16	^{t}BuOK	DMAc	80	61
17	^{t}BuOK	DMAc	100	59[e]
18	^{t}BuOK	DMAc	100	63[f]

[a] Reaction conditions: 2-aminopyridine (1 mmol), 2-fluorobenzonitrile (1.5 mmol), base (3 equiv.), solvent (2 mL), 100 °C, 16 h, air. [b] Isolated yields. [c] 12 h. [d] KO^{t}Bu (2 equiv.). [e] Solvent (4 mL). [f] Solvent (1 mL).

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†Dedicated to Professor Wen-Jing Xiao on the occasion of his 50th birthday.

‡Electronic supplementary information (ESI) available: NMR data and spectra. See DOI: 10.1039/c5ob01587a

Table 2 Synthesis of quinazolinimines with 2-fluorobenzonitriles[a]

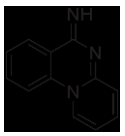
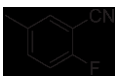
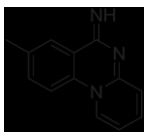
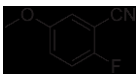
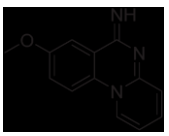
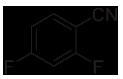
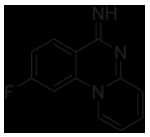
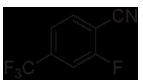
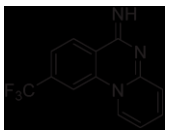
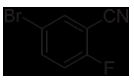
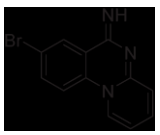
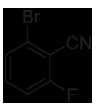
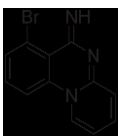
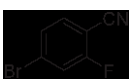
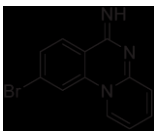
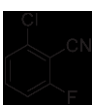
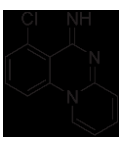
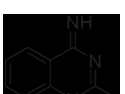
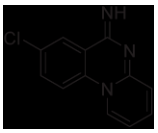
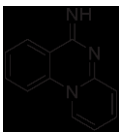
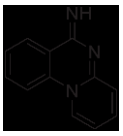
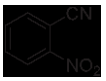
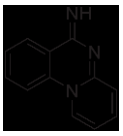
Entry	Substrate	Product	Yield
1			88%
2			79%
3			54%
4			57%
5			61%
6			33%
7			68%
8			48%
9			70%
10			68%

Table 2 (Contd.)

Entry	Substrate	Product	Yield
11			71%
12			55%
13			26%
14			8%

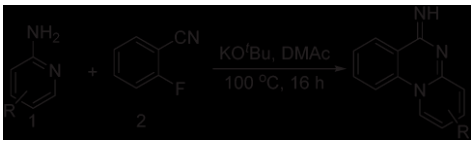
[a] Reaction conditions: 1 (1 mmol), 2 (1.5 mmol), ^{t}BuOK (3 equiv.), DMAc (2 mL), 100 °C, 16 h, air, isolated yield.

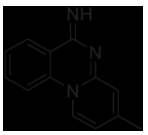
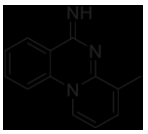
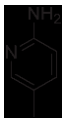
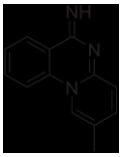
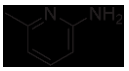
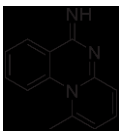
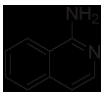
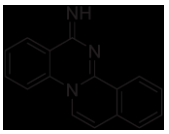
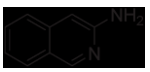
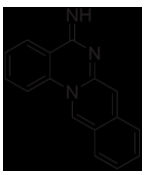
isolated from DMAc (Table 1, entry 2). Then we chose DMAc as the solvent to check the effect of bases, surprisingly no desired product was detected in the reactions with the other tested bases (Table 1, entries 1–13). Some tiny modifications were performed subsequently, however decreased yields were observed when the reaction time was shortened, the reaction temperature was decreased, the amount of promotor was lowered, and even when the concentration was changed (Table 1, entries 2, 14–18).

With the best reaction conditions in hand (KO^{t}Bu (3 equiv.), DMAc (2 mL), 100 °C, 16 h), the generality and limitation testing of this transition metal-free procedure was carried out. Firstly, various substituted 2-fluorobenzonitriles were tested with 2-aminopyridine. As shown in Table 2, moderate to good yields of the desired products can be achieved in all the cases. More specifically, both electron-donating and electron-withdrawing substituents can be tolerated. In addition to interesting fluoro and trifluoromethyl,[9] bromide and chloride can be tolerated as well which are ready for further modification in cross-coupling reactions.[10] Concerning the reaction mechanism, we believe the reaction starts with the deprotonation of 2-aminopyridine with ^{t}BuOK. Then the nitrogen atom of the pyridine ring attacks the carbon at which

the fluorine atom is substituted through S_NAr (nucleophilic

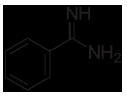
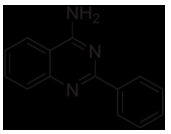
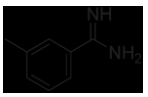
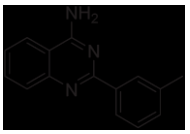
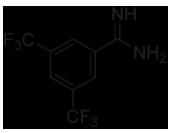
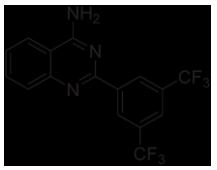
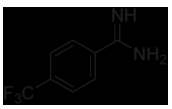
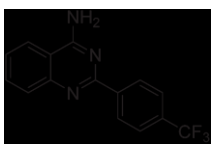
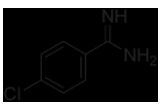
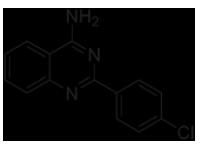
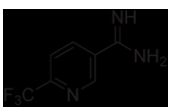
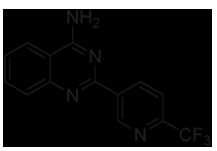
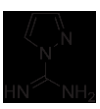
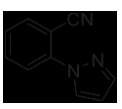
Table 3 Synthesis of quinazolinimines with aminopyridines[a]



Entry	Substrate	Product	Yield
1			78%
2			70%
3			46%
4			63%
5			7% 12%[b]
6			10%

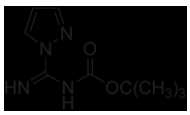
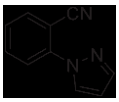
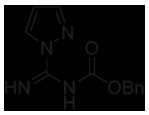
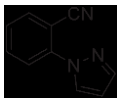
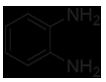
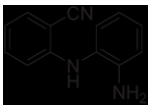
[a] Reaction conditions: 1 (1 mmol), 2 (1.5 mmol), ^{t}BuOK (3 equiv.), DMAc (2 mL), 100 °C, 16 h, air, isolated yield. [b] 140 °C.

Table 4 Synthesis of quinazolinamines[a]

Entry	Substrate	Product	Yield
1			70%
2			55%
3			20%
4			52%
5			20%
6			51%
7			36%

aromatic substitution) reaction followed by attacks of the nitrogen atom of the amino group on the cyano carbon. The final product can be produced after intramolecular rearrangement. In order to confirm that the cyclization proceeds via S_NAr, 2-halobenzonitriles and 2-nitrobenzonitrile were tested with 2-aminopyridine instead of 2-fluorobenzonitriles and the desired products could be formed as well (Table 2, entries 12–14). Then 2-aminopyridines were tested successively (Table 3). Moderate yields can be achieved except in the case of isoquinolinamines (Table 3, entries 5 and 6).

From the chemical structure of 2-aminopyridines, amidine is considered to be the same analogue. As shown in Table 4, amidines were selected to react with 2-fluorobenzonitriles.

8			77%
9			86%
10			31%[b]

70% of 2-phenylquinazolin-4-amine was produced from

[a] Reaction conditions: 1 (1 mmol), 2 (1.5 mmol), ^{t}BuOK (3 equiv.), DMAc (2 mL), 100 °C, 16 h, air, isolated yield. [b] ^{t}BuOK (5 equiv.).

benzamidine under the same reaction conditions (Table 4, entry 1). However, lower yields were obtained in the case of electron-withdrawing group substituted amidines (Table 4, entries 3–6) which may be due to the low stability of these amidines. When 1H-pyrazole-1-carboximidamides were tested with 2-fluorobenzonitriles, 2-(1H-pyrazol-1-yl)benzonitrile was produced in good yields (Table 4, entries 7–9). We believe 1H-pyrazole-1-carboximidamides decomposed in the reaction solution and gave pyrazole which then reacted with 2-fluorobenzonitrile to give the product. In the case of benzene-1,2-diamine, only 2-((2-aminophenyl)amino)benzonitrile was formed (Table 4, entry 10).

Conclusions

In conclusion, a convenient procedure for the synthesis of quinazolinimines and quinazolinamines from 2-fluorobenzonitriles and 2-aminopyridines or amidines has been developed. By using KO^{t}Bu as the promotor, the desired heterocycles were produced in moderate to good yields under catalyst-free conditions.

Experimental section

General procedure: under air, in a 25 mL reaction tube equipped with a stirring bar, 2-fluorobenzonitrile (1.5 mmol), 2-aminopyridine (1 mmol), ^{t}BuOK (3 equiv.) and DMAc (2 mL) were added. Then the tube was closed and heated up to 100 °C for 16 h, and the reaction mixture was cooled to room temperature when the reaction completed. The reaction solution was quenched with distilled water and extracted with ethyl acetate three times. The combined organic phases were washed with a saturated NaCl solution and dried over Na_2SO_4. The crude product was purified by column chromatography to give the pure product.

6H-Pyrido[1,2-a]quinazolin-6-imine

148 mg, 76%, yellow solid, 185 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 9.06 (dt, J = 7.5, 1.1 Hz, 1H), 7.89 (dt, J = 8.4, 0.9 Hz, 1H), 7.67–7.58 (m, 2H), 7.45–7.27 (m, 3H), 6.69 (ddd, J = 7.7, 6.3, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-d) δ 155.88, 148.04, 144.61, 134.68, 133.31, 128.15, 127.10, 125.65, 124.91, 124.16, 115.39, 111.53; GC-MS (EI, 70 eV: m/z(%) = 194 (M+, 100), 195 (65), 169 (51), 67 (11); HRMS(ESI): calcd for $[C_{13}H_{11}N_3 + H]^+$: 196.08692; found: 196.08706.

8-Methyl-6H-pyrido[1,2-a]quinazolin-6-imine

167 mg, 79%, yellow solid, 147 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 9.03 (ddd, J = 7.5, 1.6, 0.9 Hz, 1H), 7.68 (dt, J = 1.7, 0.9 Hz, 1H), 7.50–7.47 (m, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.55–7.51 (m, 1H), 7.49 (dd, J = 1.9, 0.5 Hz, 1H), 7.35 (ddd, J = 9.2, 6.2, 1.6 Hz, 1H), 7.28–7.20 (m, 1H), 6.65 (ddd, J = 7.7, 6.2, 1.6 Hz, 1H), 2.54–2.45 (m, 4H), 7.71–7.64 (m, 1H); ^{13}C NMR (75 MHz, chloroform-d) δ 155.83, 147.43, 142.73, 134.74, 133.81, 127.97, 127.09, 125.78, 123.52, 115.09, 111.11, 21.52; GC-MS (EI, 70 eV): m/z(%) = 210 (M+, 100), 211 (17), 209 (43), 181 (39); HRMS(ESI): calcd for $[C_{13}H_{11}N_3 + H]^+$: 210.10257; found: 210.10269.

7-Bromo-6H-pyrido[1,2-a]quinazolin-6-imine

188 mg, 68%, white solid, 177 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 8.39 (dd, J = 8.7, 0.9 Hz, 1H), 8.30 (ddd, J = 5.0, 1.9, 0.9 Hz, 1H), 7.62 (ddd, J = 8.4, 7.3, 1.9 Hz, 1H), 7.35 (dd, J = 8.7, 8.0 Hz, 1H), 7.19 (dd, J = 8.0, 0.9 Hz, 1H), 7.06 (s, 1H), 6.93 (ddd, J = 7.3, 5.0, 0.9 Hz, 1H), 6.88 (dt, J = 8.3, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-d) δ 153.53, 147.98, 145.90, 138.13, 134.28, 124.98, 124.62, 117.61, 116.55, 115.93, 111.99, 103.41; GC-MS (EI, 70 eV): m/z(%) = 275 (M+, 100), 276 (54), 273 (56), 272 (96), 249 (33), 247 (34), 193 (23); HRMS(ESI): calcd for $[C_{12}H_8BrN_3 + H]^+$: 273.99744; found: 273.99791.

10-Chloro-6H-pyrido[1,2-a]quinazolin-6-imine

156 mg, 68%, yellow solid, 206 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 9.06 (dt, J = 7.5, 1.2 Hz, 1H), 8.53–8.25 (m, 1H), 7.79 (ddd, J = 14.5, 7.9, 1.3 Hz, 2H), 7.63–7.35 (m, 2H), 7.39–7.12 (m, 1H), 6.76 (ddd, J = 7.6, 5.6, 2.3 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-d) δ 155.30, 148.45, 141.99, 134.86, 133.14, 131.32, 127.98, 126.41, 124.08, 122.84, 116.80, 111.90; GC-MS (EI, 70 eV): m/z(%) = 194 (M+, 100), 229 (14), 195 (13); HRMS(ESI): calcd for $[C_{12}H_8ClN_3 + H]^+$: 230.04795; found: 230.04834.

8-Bromo-6H-pyrido[1,2-a]quinazolin-6-imine

90 mg, 33%, yellow solid, 185 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 9.04 (ddd, J = 7.5, 1.6, 0.8 Hz, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.71 (dd, J = 8.8, 2.1 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.42 (ddd, J = 9.2, 6.4, 1.6 Hz, 1H), 7.31–7.21 (m, 2H), 6.71 (ddd, J = 7.6, 6.4, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-d) δ 154.62, 148.23, 143.86, 136.18, 134.73, 129.08, 128.06, 126.66, 125.81, 117.47, 116.79, 111.66; GC-MS (EI, 70 eV): m/z (%) = 272 (M+, 100), 273 (65), 274 (75), 274 (72), 249 (39), 247 (22), 193 (29), 249 (39); HRMS(ESI): calcd for $[C_{12}H_8BrN_3 + H]^+$: 273.99744; found: 273.99792.

8-Methoxy-6H-pyrido[1,2-a]quinazolin-6-imine

122 mg, 54%, yellow solid, 174 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 8.96 (ddd, J = 7.5, 1.6, 0.9 Hz, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.28–7.24 (m, 1H), 7.24–7.21 (m, 1H), 7.20–7.14 (m, 2H), 6.59 (ddd, J = 7.7, 6.2, 1.6 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 157.10, 155.55, 146.43, 139.46, 133.03, 129.03, 127.73, 125.86, 122.83, 115.81, 111.09, 104.64, 55.76; GC-MS (EI, 70 eV): m/z(%) = 225 (M+, 100), 226 (16), 224 (51), 210 (98), 211 (18), 199 (20), 182 (15), 182 (42); HRMS(ESI): calcd for $[C_{13}H_{11}N_3O + H]^+$: 226.09749; found: 226.09768.

7-Chloro-6H-pyrido[1,2-a]quinazolin-6-imine

160 mg, 70%, white solid, 156 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 8.35 (dd, J = 8.6, 0.9 Hz, 1H), 8.31 (ddd, J = 5.0, 2.0, 0.9 Hz, 1H), 7.63 (ddd, J = 8.3, 7.3, 1.9 Hz, 1H), 7.43 (dd, J = 8.7, 8.0 Hz, 1H), 7.03 (dd, J = 8.0, 0.9 Hz, 2H), 6.94 (ddd, J = 7.3, 5.0, 0.9 Hz, 1H), 6.88 (dt, J = 8.3, 0.9 Hz, 1H); ^{13}C NMR

(75 MHz, chloroform-d) δ 153.50, 147.98, 145.60, 138.16, 136.73, 134.11, 121.49, 117.61, 116.04, 114.73, 111.96, 99.99; GC-MS (EI, 70 eV): m/z(%) = 228 (M+, 100), 229 (55), 230 (39), 231 (18), 205 (10), 203 (37), 193 (10); HRMS(ESI): calcd for $[C_{12}H_8ClN_3 + H]^+$: 230.04795; found: 230.04827.

8-Chloro-6H-pyrido[1,2-a]quinazolin-6-imine

163 mg, 71%, yellow solid, 180 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 9.05 (ddd, J = 7.5, 1.6, 0.8 Hz, 1H), 7.85 (dd, J = 1.8, 0.9 Hz, 1H), 7.57 (t, J = 1.4 Hz, 2H), 7.43 (ddd, J = 9.2, 6.3, 1.6 Hz, 1H), 7.32–7.23 (m, 2H), 6.72 (ddd, J = 7.7, 6.3, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-d) δ 154.75, 148.11, 143.43, 134.75, 133.55, 130.06, 128.87, 128.05, 125.74, 123.55, 116.29, 111.73; GC-MS (EI, 70 eV): m/z(%) = 228 (M+, 100), 229 (67), 230 (42), 231 (23), 205 (12), 203 (37), 193 (14); HRMS(ESI): calcd for $[C_{12}H_8ClN_3 + H]^+$: 230.04795; found: 230.04827.

9-Bromo-6H-pyrido[1,2-a]quinazolin-6-imine

109 mg, 48%, yellow solid, 167 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 8.85 (ddd, J = 7.4, 1.5, 0.9 Hz, 1H), 8.27 (d, J = 8.7 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.53 (dd, J = 2.5, 1.7 Hz, 1H), 7.49 (ddd, J = 9.2, 1.7, 0.9 Hz, 1H), 6.90 (ddd, J = 7.6, 6.1, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-d) δ 158.57, 149.31, 148.47, 134.98, 130.14, 129.37, 128.75, 128.64, 126.81, 126.26, 114.89, 112.98; GC-MS (EI, 70 eV): m/z (%) = 226 (M+, 100), 227 (15); HRMS(ESI): calcd for $[C_{12}H_8BrN_3 + H]^+$: 273.99744; found: 273.99793.

9-(Trifluoromethyl)-6H-pyrido[1,2-a]quinazolin-6-imine

160 mg, 61%, yellow solid; ^{1}H NMR (300 MHz, chloroform-d) δ 9.10 (ddd, J = 7.5, 1.6, 0.8 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.90 (dd, J = 1.8, 0.9 Hz, 1H), 7.62–7.41 (m, 2H), 7.32 (ddd, J = 9.2, 1.5, 0.8 Hz, 1H), 6.78 (ddd, J = 7.7, 6.4, 1.5 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-d) δ 155.04, 148.80, 145.03, 135.25, 135.20–134.07 (m, J = 33.19 Hz), 128.06, 125.79, 125.20, 124.81 (q, J = 4.2 Hz), 122.20, 120.20 (q, J = 3.4 Hz), 117.40, 111.96; GC-MS (EI, 70 eV): m/z(%) = 262 (M+, 100), 263 (79), 242 (18), 237 (49), 67 (11); HRMS(ESI): calcd for $[C_{13}H_8F_3N_3 + H]^+$: 264.07431; found: 264.07458.

4-Methyl-6H-pyrido[1,2-a]quinazolin-6-imine

146 mg, 70%, yellow solid, 153 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 8.97 (ddd, J = 7.6, 1.7, 0.9 Hz, 1H), 8.01–7.83 (m, 1H), 7.75–7.55 (m, 2H), 7.33 (ddd, J = 8.2, 6.4, 1.9 Hz, 1H), 7.28–7.17 (m, 1H), 6.59 (t, J = 7.0 Hz, 1H), 2.49 (t, J = 0.9 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 156.52, 147.74, 144.73, 133.68, 132.79, 132.28, 127.84, 126.10, 124.57, 123.90, 115.24, 110.70, 18.71; GC-MS (EI, 70 eV): m/z(%) = 208 (M+, 100), 209 (65), 193 (10), 183 (36); HRMS(ESI): calcd for $[C_{13}H_{11}N_3 + H]^+$: 210.10257; found: 210.10272.

3-Methyl-6H-pyrido[1,2-a]quinazolin-6-imine

146 mg, 70%, yellow solid, 158 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 9.17 (d, J = 7.6 Hz, 1H), 8.08 (ddd, J = 8.1, 1.3, 0.6 Hz, 1H), 7.91–7.65 (m, 2H), 7.61–7.44 (m, 1H), 7.31–7.16 (m, 1H), 6.73 (dd, J = 7.6, 2.0 Hz, 1H), 2.55 (d, J = 1.2 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 155.87, 148.02, 145.75, 145.23, 132.94, 127.17, 127.01, 124.12, 123.95, 123.18, 115.12, 114.12, 21.24; GC-MS (EI, 70 eV): m/z(%) = 208 (M+, 100), 209 (58), 183 (38), 80 (10); HRMS(ESI): calcd for $[C_{13}H_{11}N_3 + H]^+$: 210.10257; found: 210.10272.

1-Methyl-6H-pyrido[1,2-a]quinazolin-6-imine

132 mg, 63%, yellow solid, 114 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 8.47–8.08 (m, 1H), 7.65–7.37 (m, 3H), 7.10–6.90 (m, 2H), 6.74 (ddd, J = 15.0, 7.9, 0.9 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 157.31, 153.28, 144.05, 138.33, 133.90, 132.78, 121.08, 118.19, 117.31, 116.44, 108.00, 100.55, 24.28; GC-MS (EI, 70 eV): m/z(%) = 208 (M+, 100), 209 (48), 183 (13); HRMS(ESI): calcd for $[C_{13}H_{11}N_3 + H]^+$: 210.10257; found: 210.10277.

2-Methyl-6H-pyrido[1,2-a]quinazolin-6-imine

96 mg, 46%, yellow oil; ^{1}H NMR (300 MHz, chloroform-d) δ 8.91–8.84 (m, 1H), 7.96–7.88 (m, 1H), 7.68–7.61 (m, 2H), 7.35 (ddd, J = 8.2, 6.0, 2.2 Hz, 1H), 7.30–7.25 (m, 2H), 2.30 (d, J = 1.3 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 155.94, 147.26, 144.95, 137.65, 132.94, 127.17, 125.33, 124.92, 124.51, 124.03, 121.01, 115.30, 18.18; GC-MS (EI, 70 eV): m/z(%) = 208 (M+, 100), 209 (59), 183 (39); HRMS(ESI): calcd for $[C_{13}H_{11}N_3 + H]^+$: 210.10257; found: 210.10290.

6H-Isoquinolino[2,1-a]quinazolin-6-imine

29 mg, 12%, yellow solid, 167 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 8.98 (ddt, J = 8.1, 1.4, 0.7 Hz, 1H), 8.84 (d, J = 7.9 Hz, 1H), 7.91 (dd, J = 8.1, 1.4 Hz, 1H), 7.74 (dd, J = 8.2, 1.3 Hz, 1H), 7.68 (ddt, J = 8.3, 7.0, 1.4 Hz, 2H), 7.62–7.54 (m, 2H), 7.39 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 6.89 (dd, J = 7.9, 0.7 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-d) δ 156.36, 146.32, 144.12, 133.31, 132.89, 131.92, 128.05 (d, J = 4.9 Hz), 127.81, 127.46, 127.24, 126.17, 125.34, 123.94, 123.39, 116.88, 111.55; GC-MS (EI, 70 eV): m/z(%) = 244 (M+, 100), 246 (15), 245 (93), 219 (32); HRMS(ESI): calcd for $[C_{16}H_{11}N_3 + H]^+$: 246.10257; found: 246.10285.

5H-Isoquinolino[2,3-a]quinazolin-5-imine

25 mg, 10%, yellow solid; ^{1}H NMR (300 MHz, chloroform-d) δ 8.97 (t, J = 0.9 Hz, 1H), 7.96–7.88 (m, 1H), 7.83 (dq, J = 8.3, 1.0 Hz, 1H), 7.65–7.58 (m, 1H), 7.57–7.40 (m, 3H), 7.35 (ddd, J = 8.1, 6.6, 1.4 Hz, 1H), 7.22–7.16 (m, 1H), 7.01 (s, 1H), 6.93 (td, J = 7.6, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-d) δ 151.97, 149.43, 144.59, 138.16, 133.93, 133.08, 130.94, 127.80, 125.55, 125.06, 124.98, 121.03, 117.32, 117.29, 103.81, 100.72; GC-MS (EI, 70 eV): m/z(%) = 245 (M+, 100), 246 (20), 244 (69), 205 (29), 219 (29), 213 (26), 117 (57); HRMS(ESI): calcd for $[C_{16}H_{11}N_3 + H]^+$: 246.10257; found: 246.10278.

2-Phenylquinazolin-4-amine

155 mg, 70%, white solid, 138 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 8.55–8.39 (m, 2H), 7.96 (ddd, J = 8.4, 1.2, 0.6 Hz, 1H), 7.79–7.65 (m, 2H), 7.54–7.43 (m, 3H), 7.39 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 6.03 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d)

δ 161.67, 161.00, 150.93, 138.61, 133.33, 130.21, 128.56–128.21 (m), 128.69, 128.46, 128.43, 125.78, 121.73, 113.07; GC-MS (EI, 70 eV): m/z(%) = 221 (M+, 100), 222 (17), 220 (16), 205 (29), 118 (21); HRMS(ESI): calcd for $[C_{16}H_{11}N_3 + H]^+$: 222.10257; found: 222.1028.

2-(4-Chlorophenyl)quinazolin-4-amine

52 mg, 20%, white solid, 149 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 8.50–8.41 (m, 2H), 7.94 (ddd, J = 8.5, 1.2, 0.6 Hz, 1H), 7.83–7.69 (m, 2H), 7.52–7.40 (m, 3H), 5.71 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d) δ 161.38, 159.76, 150.86, 136.92, 136.34, 133.41, 129.71, 128.80, 128.54, 125.97, 121.58, 112.99; GC-MS (EI, 70 eV): m/z(%) = 255 (M+, 100), 257 (38), 256 (17), 239 (29), 207 (18), 118 (19), 103 (10); HRMS(ESI): calcd for $[C_{14}H_{10}ClN_3 + H]^+$: 256.0636; found: 256.06383.

2-(3,5-Bis(trifluoromethyl)phenyl)quinazolin-4-amine

71 mg, 20%, yellow solid, 197 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 9.27–8.73 (m, 2H), 8.11–7.90 (m, 2H), 7.90–7.70 (m, 2H), 7.54 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 5.75 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d) δ 161.49, 157.60, 150.66, 140.50, 133.69, 131.58 (q, J = 33.4 Hz), 129.06, 128.97, 128.43 (d, J = 4.2 Hz), 126.67, 125.35, 123.84–123.17 (m), 121.74, 121.63, 118.13, 113.28; GC-MS (EI, 70 eV): m/z(%) = 357 (M+, 100), 358 (12), 356 (18), 341 (22), 338 (14); HRMS(ESI): calcd for $[C_{16}H_9F_6N_3 + H]^+$: 358.07734; found: 358.07789.

2-(6-(Trifluoromethyl)pyridin-3-yl)quinazolin-4-amine

148 mg, 51%, white solid, 205 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 9.85–9.74 (m, 1H), 8.96 (ddd, J = 8.3, 1.9, 0.8 Hz, 1H), 7.98 (dt, J = 8.4, 1.0 Hz, 1H), 7.90–7.71 (m, 3H), 7.54 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 5.81 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d) δ 161.50, 157.50, 150.71, 150.29, 136.98, 136.62, 133.68, 132.86, 129.10, 126.75, 121.66, 119.99 (q, J = 2.6 Hz), 113.35; GC-MS (EI, 70 eV): m/z(%) = 290 (M+, 100), 291 (17), 221 (32); HRMS(ESI): calcd for $[C_{15}H_{10}F_3N_3 + H]^+$: 291.08521; found: 291.08566.

2-(4-(Trifluoromethyl)phenyl)quinazolin-4-amine

150 mg, 52%, white solid, 170 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 8.70–8.51 (m, 2H), 8.02–7.91 (m, 1H), 7.85–7.66 (m, 4H), 7.49 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 5.86 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d) δ 161.57, 159.42, 150.88, 141.84, 133.68, 132.11, 131.68, 129.10, 128.76, 126.50, 126.22, 125.40 (q, J = 3.8 Hz), 122.61, 121.77, 113.28; GC-MS (EI, 70 eV): m/z (%) = 289 (M+, 100), 290 (18), 288 (18), 273 (26), 118 (10); HRMS(ESI): calcd for $[C_{15}H_{10}F_3N_3 + H]^+$: 290.08996; found: 290.09042.

2-(o-Tolyl)quinazolin-4-amine

129 mg, 55%, white solid, 134 °C; ^{1}H NMR (300 MHz, chloroform-d) δ 8.39–8.22 (m, 2H), 7.96 (ddd, J = 8.5, 1.2, 0.6 Hz, 1H), 7.80–7.61 (m, 2H), 7.38 (ddd, J = 8.3, 7.1, 1.4 Hz, 2H), 7.27 (ddt, J = 7.6, 1.6, 0.9 Hz, 1H), 6.01 (s, 2H), 2.44 (d, J = 0.9 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 161.61, 161.13, 150.94, 138.55, 138.00, 133.23, 130.97, 128.96, 128.66, 128.35, 125.6, 125.58, 121.71, 113.05, 21.55; GC-MS (EI, 70 eV): m/z(%) = 235 (M+, 100), 236 (17), 234 (19), 219 (20), 207 (10), 118 (17); HRMS(ESI): calcd for $[C_{15}H_{13}N_3 + H]^+$: 236.11822; found: 236.11853.

2-(1H-Pyrazol-1-yl)benzonitrile

145 mg, 86%, yellow oil; ^{1}H NMR (300 MHz, chloroform-d) δ 8.09 (t, J = 2.3 Hz, 1H), 7.81–7.69 (m, 3H), 7.69–7.59 (m, 1H), 7.38 (ddt, J = 9.2, 7.2, 1.7 Hz, 1 H), 6.50 (q, J = 2.2 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-d) δ 142.19, 141.92, 134.46, 134.02, 129.53, 127.28, 124.19, 117.02, 108.47, 105.32; GC-MS (EI, 70 eV): m/z(%) = 169 (M+, 100), 170 (12), 168 (10), 142 (47), 129 (15), 115 (23), 102 (27), 75 (14); HRMS(ESI): calcd for $[C_{10}H_7N_3 + H]^+$: 170.07127; found: 170.07124.

2-((2-Aminophenyl)amino)benzonitrile

65 mg, 31%, yellow oil; ^{1}H NMR (300 MHz, chloroform-d) δ 7.47 (ddd, J = 7.8, 1.6, 0.5 Hz, 1H), 7.36–7.27 (m, 1H), 7.21–7.05 (m, 2H), 6.96–6.64 (m, 3H), 6.57 (dt, J = 8.5, 0.7 Hz, 1H), 6.19–5.68 (m, 1H), 3.41 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d) δ 148.77, 143.15, 134.14, 132.64, 128.02, 127.64, 124.81, 119.21, 118.32, 117.70, 116.34, 113.40, 96.80; GC-MS (EI, 70 eV): m/z(%) = 209 (M+, 100), 210 (15), 208 (17), 182 (15), 181 (13).

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7.4 Oxidative synthesis of quinazolinones under metal-free conditions.

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Summary: A metal-free procedure for the synthesis of quinazolinones under oxidative conditions has been developed. In the presence of DABCO and TBHP, the desired products can be obtained in moderate yields with 2-fluorobenzaldehydes and 2-aminopyridines as the substrates.

Contribution: In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 80%.

Oxidative Synthesis of Quinazolinones under Metal-free Conditions

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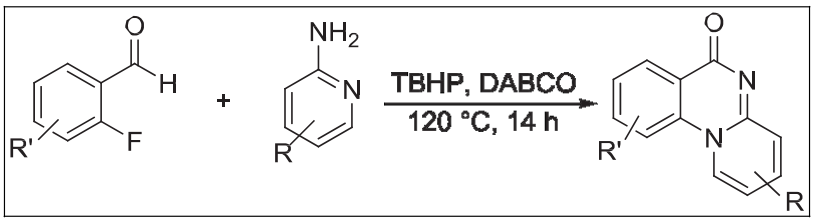

A metal-free procedure for the synthesis of quinazolinones under oxidative conditions has been developed. In the presence of DABCO and TBHP, the desired products can be obtained in moderate yields with 2-fluorobenzaldehydes and 2-aminopyridines as the substrates.

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INTRODUCTION

As the development of our society, the concept of "Sustainable Development" has been accepted and raises the demand of "Green Chemistry" [1]. Under this background, the establishment of metal-free synthetic procedures will be under current interests.

On the other hand, the syntheses of N-heterocyclic compounds have attracted general attention for their wide and distinct pharmaceutical activities [2]. Among the known N-heterocycles, quinazolinones is a class of representative example, which is reported with various activities including anticancer [3], anti-inflammation [4], antibacterial [5], and anti-diabetes [6]. Regarding the importance of quinazolinones, numerous elegant methods have been developed for their preparation [7]. In the transition metal-catalyzed methodologies, good to excellent yields of the desired products can be obtained with Pd, Ru, Ir, Cu, and Fe as the catalysts. However, besides the high costs of these catalytic systems, the heterocyclic products are usually contaminated by the metals. Furthermore, in the known oxidative procedures, oxidants like $KMnO_4$, N,N′-dicyclohexylcarbodiimide, and TBHP together with catalyst are usually required. In our group, we were succeeded in developing several new procedures for the synthesis of quinazolinones as well, such as palladium-catalyzed carbonylation of aryl bromides with 2-aminobenzamides [8] and metal-free procedures with aldehydes and 2-aminobenzamides and analogs as the substrates [9]. As our continuing interests on this topic, we wish to report our new results on the metal-free synthesis of quinazolinones from 2-fluorobenzaldehydes and 2-aminopyridines here.

EXPERIMENTAL

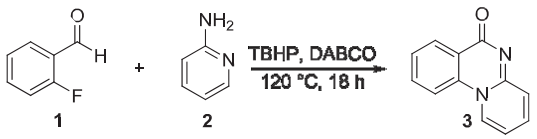
In a 25-mL pressure tube equipped with a stirring bar, 2-fluorobenzaldehyde (1 mmol), 2-aminopyridine (1.5 mmol), and DABCO (2 equiv.) were added in DMF (2 mL); then, TBHP (70 wt % in H_2O; 2 equiv.) was injected by syringe. After that, the tube was closed and heated up to 120 °C for 14 h. When the reaction is completed, cool the reaction mixture to room temperature. The reaction was quenched with distilled water, and the solution was extracted with ethyl acetate. The combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. The crude product was purified by column chromatography (ethyl acetate/pentane = 1:4).

RESULTS AND DISCUSSION

The first set of reactions was performed with solvents testing (Table 1, entries 1–4). We using 2-fluorobenzaldehyde and 2-aminopyridine as the model substrates; in the presence of TBHP and DABCO, different solvents were tested. Gratingly, 28% of the desired product was produced in DMF, while only low yield of the product was formed in the other tested solvents. To our surprise, the yield dropped dramatically when TBHP in decane was applied as the oxidant (Table 1, entry 5). In the other tested oxidants, cumene hydroperoxide gave similar yield of the desired product (Table 1, entry 6). Notably, full conversion of 2-fluorobenzaldehyde was detected in all the cases. 2-Fluorobenzoic acid, 2-Fluorobenzamide, and non-characterizable compounds are the by-products in general. Then the effects of bases were checked. Among all the tested

Table 1

Metal-free quinazolinones synthesis: optimization.[a]



1 2 3

Entry	Oxidant	Base	Solvent	Yield (%)[b]
1	TBHP	DABCO	DMF	28 (26)
2	TBHP	DABCO	DMSO	6
3	TBHP	DABCO	DMAc	7
4	TBHP	DABCO	1,4-Dioxane	9
5	TBHP	DABCO	DMF	3[d]
6	CHP	DABCO	DMF	26
7	DTBP	DABCO	DMF	Trace
8	BPO	DABCO	DMF	Trace
9	H_2O_2	DABCO	DMF	5
10	TBHP	DABCO	DMF	23[e]
11	TBHP	DABCO	DMF	83 (81)[c,f]
12	TBHP	DABCO	DMF	21[g]

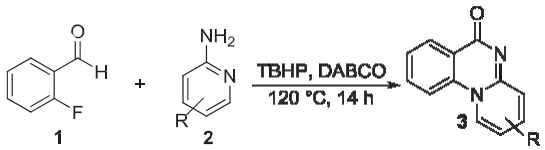
[a]Reaction conditions: 2-fluorobenzaldehyde (1, 1 mmol), 2-aminopyridine (2, 1.5 mmol), TBHP (70 wt % in H_2O; 2 equiv.), DABCO (3 equiv.), solvent (2 mL), 18 h.
[b]GC yield, using hexadecane as the internal standard.
[c]Isolated yield.
[d]5.5 M TBHP in decane.
[e]DABCO (2 equiv.), 10 h.
[f]DABCO (2 equiv.), 14 h.
[g]DABCO (2 equiv.), 24 h.

bases [K_2CO_3, K_3PO_4, KO^{t}Bu, DBU, 1,5-diazabicyclo[4.3.0] non-5-ene, and N,N-diisopropylethylamine (DIPEA)], DABCO was still proven to be the best base. Interestingly, the reaction time was found to be important for the outcome of this transformation. Shortened reaction time gave non-complete conversion, while the decomposition of the product was observed in the reaction with prolonged reaction time (Table 1, entries 10–12). Reaction temperatures were tested as well, but no better results can be obtained. At this stage, 81% of the product can be isolated in DMF, at 120 °C with DABCO (2 equiv.) as the base and TBHP (2 equiv.) as the oxidant (Table 1, entry 11).

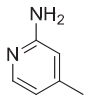
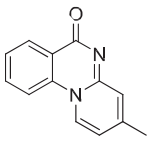
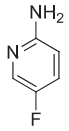
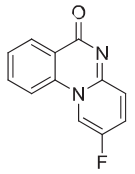
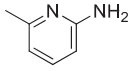
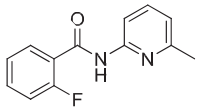
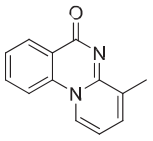
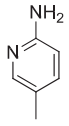
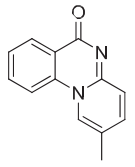
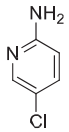
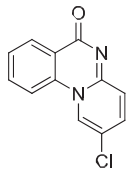
With the best reaction conditions in hand, we started the scope and limitation testing subsequently (Tables 2 and 3). Various functional group substituted 2-aminopyridines were tested at the beginning. Moderate yields of quinazolinones can be isolated from the corresponding 2-aminopyridines. Methyl, chloro, and fluoro are tolerable under this reaction conditions. However, 2-aminopyridine with functional groups like bromo, cyano and nitro can only give traces of the corresponding product under standard conditions. This phenomenon might be due to the reduced electron density on NH–Ar anion and subsequently decreased the ability of nucleophilic substitution with 2-F–Ar. This situation cannot be improved by varying the reaction temperature and time. On the other hand, steric effect acts as another important role for this transformation. Only the non-cyclized amide was isolated when 6-methylpyridin-2-amine was applied as the reaction

Table 2

Metal-free quinazolinones synthesis: 2-aminopyridines testing.[a]



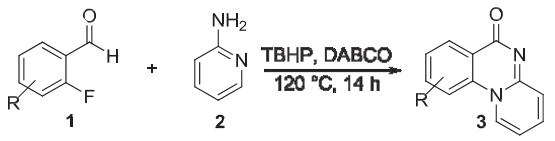
1 2 3

Entry	2	3	Yield[b]
1			48
2			52
3			48
4			52
5			38
6			30

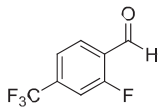
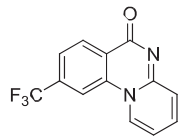
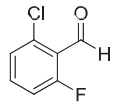
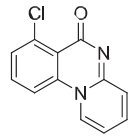
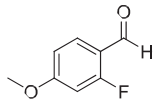
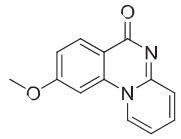
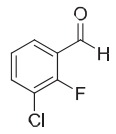
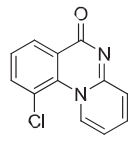
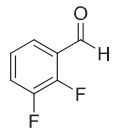
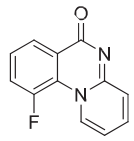
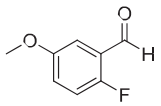
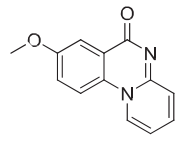
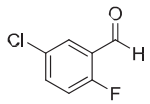
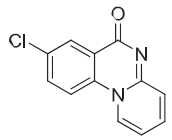
[a]Reaction conditions: 2-fluorobenzaldehyde (1, 1 mmol), 2-aminopyridine (2, 1.5 mmol), TBHP (2 equiv.), DABCO (2 equiv.), DMF (2 mL), 14 h, 120 °C.
[b]Isolated yield.

Table 3

Metal-free quinazolinones synthesis: 2-fluorobenzaldehydes testing.[a]



1 2 3

Entry	1	3	Yield
1			8
2			22
3			46
4			11
5			33
6			16
7			15

[a]Reaction conditions: 2-fluorobenzaldehyde (1, 1 mmol), 2-aminopyridine (2, 1.5 mmol), TBHP (2 equiv.), DABCO (2 equiv.), DMF (2 mL), 14 h.
[b]Isolated yield.

partner (Table 2, entry 3). Quinolin-2-amine was tested with 2-fluorobenzaldehyde as well, but only trace of the desired product was detected, which may due to the steric issue.

Then, different 2-fluorobenzaldehydes were reacted with 2-aminopyridine. As shown in Table 3, low to moderate of the corresponding quinazolinones were isolated. Compared with 2-fluorobenzaldehyde, the substituted substrates resulted decreased yields that can be explained as follows: (1) nucleophilic substitution can be favored by electron-withdrawing substituents, while this can lead the aldehyde to be activated and the trend to be oxidized to the acid; (2) electron-donating substituted aldehydes are more stable in oxidative conditions, but this can increase the difficulty in nucleophilic substitution.

Additionally, 2-bromobenzaldehyde and 2-nitrobenzaldehyde were tested as substrates with 2-aminopyridine under the same reaction conditions; 36% and 10% yields of the quinazolinone were produced (Scheme 1). Remarkably, no reaction occurred when 2-fluorobenzoic acid was applied as the starting material. By using 2-aminophenol as the reaction partner, good yield of the desired dibenzo[b,f][1,4]oxazepin-11(10H)-one can be achieved (Scheme 2). Based on these experiments, a possible reaction pathway has been proposed. As shown in Scheme 3, the reaction starts with amide formation via oxidative amidation. Then the rearrangement of the C¼N occurred and followed by nucleophilic substitution to give the final product.

CONCLUSIONS

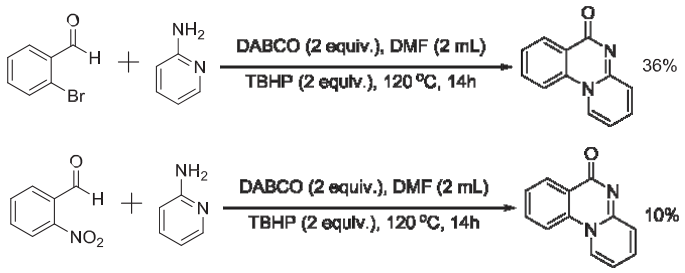
In summary, we have explored the possibility of using 2-aminopyridines and 2-fluorobenzaldehydes as starting materials for quinazolinone synthesis. In the neutral substrate, excellent yield can be achieved, while this transformation is very sensitive to the electron properties and steric character of the substrates.

EXPERIMENTAL

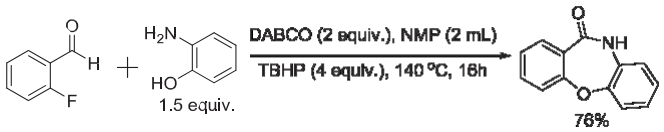
General comments. All reactions were carried out under air. Reactions were monitored by TLC analysis (precoated silica gel plates with fluorescent indicator UV254, 0.2 mm) and visualized with 254 nm ultraviolet light. Chemicals were purchased from Aldrich, Alfa-Aesar (Ward Hill, MA, USA) and, unless otherwise noted, were used without further purification. All compounds were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and recorded on Bruker AV 300 and AV 400 spectrometers. GC was performed on Agilent 6890 chromatograph with a 30-m HP5 column.

General procedure for the synthesis of quinazolinone. In a 25-mL pressure tube equipped with a stirring bar, 2-fluorobenzaldehyde (1 mmol), 2-aminopyridine (1.5 mmol), and DABCO (2 equiv.) were added in DMF (2 mL), then TBHP (70 wt % in H_2O; 2 equiv.) was injected by syringe.

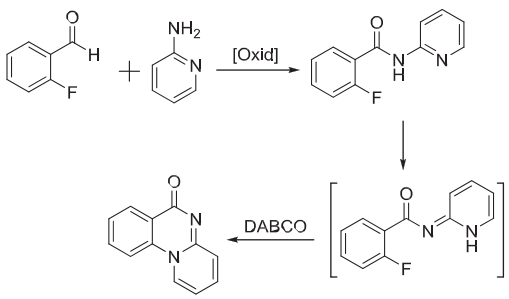
Scheme 1. Metal-free quinazolinones synthesis from 2-bromobenzaldehyde and 2-nitrobenzaldehyde.



Scheme 2. Oxidative synthesis of dibenzo[b,f][1,4]oxazepin-11(10H)-one.



Scheme 3. Proposed reaction mechanism.



After that, the tube was closed and heated up to 120 °C for 14 h. When the reaction was completed, cool the reaction mixture to room temperature. The reaction was quenched with distilled water, and the solution was extracted with ethyl acetate. The combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. The crude product was purified by column chromatography (ethyl acetate/pentane = 1:4).

6H-Pyrido[1–9]quinazolin-6-one [8b]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.80 (ddd, J = 7.3, 1.5, 0.9 Hz, 1H), 8.31 (ddd, J = 8.1, 1.6, 0.6 Hz, 1H), 7.91 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H), 7.82–7.62 (m, 2H), 7.59–7.43 (m, 2H), 7.07 (ddd, J = 7.6, 6.4, 1.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d^6) δ 158.25, 148.18, 147.35, 135.16, 135.00, 126.69, 126.42, 125.78, 124.94, 115.68, 113.19.

2-Fluoro-6H-pyrido[1,2-a]quinazolin-6-one [8b]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.74 (ddd, J = 5.3, 2.8, 0.7 Hz, 1H), 8.29 (ddd, J = 8.2, 1.7, 0.6 Hz, 1H), 7.99–7.79 (m, 2H), 7.76 (ddd, J = 8.5, 1.2, 0.6 Hz, 1H), 7.68–7.43 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d^6) δ 157.84 (d, J = 2.1 Hz), 153.40, 151.02, 147.74, 145.62, 134.98, 128.81–128.01 (m), 126.82, 126.48, 125.57, 115.06, 112.05, 111.63.

3-Methyl-6H-pyrido[1,2-a]quinazolin-6-one [7a]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.69 (dd, J = 7.4, 0.7 Hz, 1H), 8.26 (ddd, J = 8.2, 1.6, 0.6 Hz, 1H), 7.87 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H), 7.68 (ddd, J = 8.4, 1.2, 0.6 Hz, 1H), 7.46 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.29 (dt, J = 2.0, 1.1 Hz, 1H), 6.91 (dd, J = 7.5, 1.8 Hz, 1H), 2.38 (d, J = 1.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d^6) δ 158.19, 148.55, 147.35, 146.36, 134.89, 126.65, 126.52, 125.68, 127.47–126.16 (m), 124.45, 123.05, 115.95, 115.38, 20.78.

2-Fluoro-N-(6-methylpyridin-2-yl)benzamide [8b]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 10.69 (s, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.81–7.63 (m, 2H), 7.57 (dddd, J = 8.6, 7.2, 5.3, 1.8 Hz, 1H), 7.39–7.22 (m, 2H), 7.03 (dd, J = 7.5, 1.0 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d^6) δ 163.18, 160.38, 157.90, 156.66, 150.96, 138.54, 130.11 (d, J = 2.7 Hz), 126.68–121.90 (m), 119.22, 116.03 (d, J = 22.2 Hz), 110.99, 23.57.

4-Methyl-6H-pyrido[1,2-a]quinazolin-6-one [8b]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.98 (ddd, J = 7.5, 1.4, 0.7 Hz, 1H), 8.47 (dd, J = 8.6, 0.9 Hz, 1H), 8.26 (dd, J = 7.9, 1.7 Hz, 1H), 7.92 (ddd, J = 8.8, 7.2, 1.7 Hz, 1H), 7.82–7.58 (m, 2H), 6.97 (t, J = 7.0 Hz, 1H), 2.40–2.30 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d^6) δ 165.11, 151.55, 137.54, 136.01, 133.32, 132.15, 128.31, 127.86, 127.67, 121.02, 116.29, 112.37, 18.46.

2-Chloro-6H-pyrido[1,2-a]quinazolin-6-one [8b]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.78 (dd, J = 2.4, 0.7 Hz, 1H), 8.30 (ddd, J = 8.1, 1.7, 0.6 Hz, 1H), 7.93 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H), 7.82–7.69 (m, 2H), 7.62–7.48 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d^6) δ 157.45, 147.78, 145.75, 135.73, 135.22, 127.59, 126.89, 126.74, 125.66, 123.88, 120.18, 115.72.

9-(Trifluoromethyl)-6H-pyrido[1,2-a]quinazolin-6-one [7a]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.83 (ddd, J = 7.3, 1.5, 0.9 Hz, 1H), 8.48 (dt, J = 8.4, 0.8 Hz, 1H), 8.04 (dt, J = 1.7, 0.8 Hz, 1H), 7.90–7.66 (m, 2H), 7.58 (ddd, J = 9.2, 1.4, 0.8 Hz, 1H), 7.15 (ddd, J = 7.3, 6.5, 1.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d^6) δ 157.92, 148.45, 147.95, 136.34, 134.33 (d, J = 32.1 Hz), 128.76, 126.71, 125.80, 123.92 (d, J = 4.4 Hz), 119.83 (d, J = 3.6 Hz), 118.05, 113.99.

7-Chloro-6H-pyrido[1,2-a]quinazolin-6-one [7a]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.78 (ddd, J = 7.4, 1.6, 0.9 Hz, 1H), 7.85–7.71 (m, 2H), 7.65 (dd, J = 8.4, 1.2 Hz, 1H), 7.56–7.43 (m, 2H), 7.09 (ddd, J = 7.4, 6.5, 1.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d^6) δ 156.18, 150.54, 147.87, 136.14, 134.40, 132.76, 126.93, 126.55, 126.24, 125.51, 113.50, 112.68.

9-Methoxy-6H-pyrido[1,2-a]quinazolin-6-one [7a]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.78 (ddd, J = 7.3, 1.6, 0.8 Hz, 1H), 8.20 (dd, J = 8.8, 0.5 Hz, 1H), 7.72 (ddd, J = 9.2, 6.5, 1.6 Hz, 1H), 7.46 (dt, J = 9.2, 1.1 Hz, 1H), 7.22–6.92 (m, 3H), 3.93 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d^6) δ 164.62, 157.48, 150.62, 147.89, 135.45, 128.39, 126.52, 125.40, 116.20, 112.93, 109.45, 106.26, 55.74.

10-Chloro-6H-pyrido[1,2-a]quinazolin-6-one [7a]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.80 (ddd, J = 7.3, 1.6, 0.9 Hz, 1H), 8.25 (dd, J = 8.1, 1.5 Hz, 1H), 8.05 (dd, J = 7.6, 1.5 Hz, 1H), 7.79 (ddd, J = 9.2, 6.5, 1.6 Hz, 1H), 7.60 (ddd, J = 9.2, 1.4, 0.8 Hz, 1H), 7.45 (dd, J = 8.1, 7.6 Hz, 1H), 7.13 (ddd, J = 7.3, 6.5, 1.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d^6) δ 158.03, 147.76, 144.55, 136.15, 134.77, 129.90, 126.67, 126.06, 125.96, 124.69, 117.20, 113.90.

10-Fluoro-6H-pyrido[1,2-a]quinazolin-6-one [8b]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.82 (ddd, J = 7.3, 1.6, 0.9 Hz, 1H), 8.12 (dt, J = 8.2, 1.1 Hz, 1H), 7.87–7.71 (m, 2H), 7.65–7.58 (m, 1H), 7.48 (td, J = 8.0, 4.8 Hz, 1H), 7.13 (ddd, J = 7.6, 6.5, 1.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d^6) δ 158.44–157.42 (m), 154.33, 147.73, 138.13 (d, J = 12.8 Hz), 135.88, 126.61, 126.02, 124.47 (d, J = 7.6 Hz), 122.47 (d, J = 4.8 Hz), 119.54, 119.30, 117.63 (d, J = 2.6 Hz), 113.77.

8-Methoxy-6H-pyrido[1,2-a]quinazolin-6-one [7a]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.78 (ddd, J = 7.4, 1.5, 0.9 Hz, 1H), 7.73 (dd, J = 9.0, 0.5 Hz, 1H), 7.68–7.60 (m, 2H), 7.56 (dd, J = 9.0, 3.0 Hz, 1H), 7.50 (ddd, J = 9.2, 1.4, 0.9 Hz, 1H), 7.04 (ddd, J = 7.4, 6.4, 1.4 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d^6) δ 157.81, 156.60, 145.67, 143.21, 133.85, 128.61, 126.16, 126.07, 125.84, 116.24, 113.24, 104.97, 55.63.

8-Chloro-6H-pyrido[1,2-a]quinazolin-6-one [7a]. ^{1}H NMR (300 MHz, DMSO-d^6) δ 8.79 (ddd, J = 7.3, 1.6, 0.9 Hz, 1H), 8.23 (dd, J = 2.6, 0.5 Hz, 1H), 7.91 (dd, J = 8.9, 2.5 Hz, 1H), 7.84–7.68 (m, 2H), 7.54 (ddd, J = 9.2, 1.4, 0.9 Hz, 1H), 7.11 (ddd, J = 7.3, 6.4, 1.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d^6) δ 157.47, 147.63, 146.89, 135.66, 135.13, 129.03, 128.82, 126.53, 125.83, 125.30, 116.62, 113.73.

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7.5 Synthesis of *β*-Hydroxysulfides from Thiophenols and Disulfides with TBHP as the Oxidant and Reactant.

Jian-Bo Feng, Xiao-Feng Wu*

Chemistryopen, **2016**, *DOI: 10.1002/open.201600023*.

Summary: A new procedure for the synthesis of *β*-hydroxysulfides from thiophenols or diaryl disulfides with TBHP as the oxidant. In the presence of zinc iodide or potassium iodide, with TBHP as the oxidant and pre-reactant, thiophenols and diaryl disulfides reacted with the methyl group of ^{t}BuOH smoothly and selectivity to give the corresponding 2-methyl-1-(arylthio)propan-2-ols as the terminal products in moderate to good yields.

Contribution: In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 80%.

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Open Access ChemistryOPEN Communications

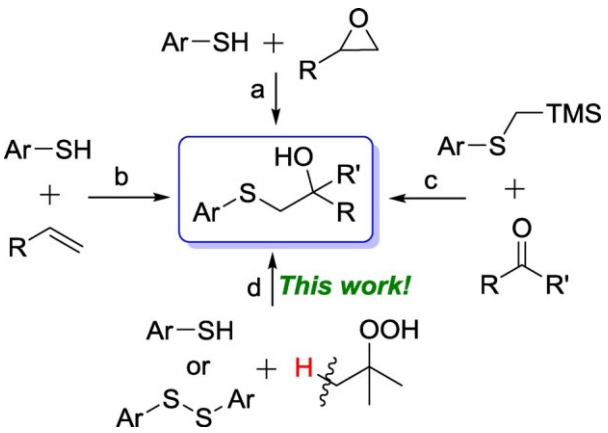
Synthesis of b-Hydroxysulfides from Thiophenols and Disulfides with tert-Butyl Hydroperoxide as the Oxidant and Reactant

Jian-Bo Feng[a, b] and Xiao-Feng Wu*[a, b]

In this Communication, we developed a new procedure for the synthesis of b-hydroxysulfides from thiophenols or diaryl disulfides with TBHP as the oxidant. In the presence of zinc iodide or potassium iodide, with TBHP as the oxidant and pre-reactant, thiophenols and diaryl disulfides reacted with the methyl group of tBuOH smoothly and selectivity to give the corresponding 2-methyl-1-(arylthio)propan-2-ols as the terminal products in moderate to good yields.

tert-Butyl hydroperoxide (TBHP) is one of the most commonly used organic oxidants in organic chemistry. tert-Butanol, the expected product after oxidation reactions, is usually considered as waste. From the view point of sustainable development, it will be interesting if there is a procedure can use tert-butanol as the reactant when using TBHP as the oxidant.

On the other hand, sulfur-containing compounds hold numerous important applications in various areas and many pharmaceutical, agrochemical, and naturally occurring products contain at least one sulfur atom in their core structures.[1] Among the plentiful sulfurated chemicals, b-hydroxysulfides represent a class of compounds with high interest and importance. They have been found to exist in pharmaceuticals and natural products.[2] In synthetic chemistry, b-hydroxysulfides are excellent substrates for the synthesis of allylic alcohols,[3] benzoxathiepines,[4] benzotiazepines,[5] a-thioketones,[6] a-substituted a,b-unsaturated enones,[7] and b-hydroxysulfoxides.[8] These procedures have also been applied in the synthesis of natural products. Based on the importance of b-hydroxysulfides, many synthetic methodologies have been developed for their preparation. The most explored procedure is the reaction of thiophenols with epoxides, but the selectivity is problematic (Scheme 1 a).[9] Alternatively, procedures based on the reaction between alkenes and thiophenols (Scheme 1 b)[10] or phenylthiomethyltrimethylsilane and carbonyl compounds (Scheme 1 c) have also been developed.[11] However, drawbacks include the availability and stability of substrates as well as low yield; in addition, the selectivity issue still needs to be solved. Using this background information, we developed a new procedure for b-hydroxysulfide preparation. With thiophenols and disulfides as the substrates, using TBHP as the oxidant and it's by-product as the reaction partner, the desired b-hydroxysulfides were synthesized in moderate to good yields (Scheme 1 d). The C_{sp^3}–H bond in the methyl group of tert-butanol, which is the by-product of the TBHP oxidant, was smoothly and selectivity cleaved.



Scheme 1. Procedures for the preparation of b-hydroxysulfides.

In the optimized reaction system, toluene was found to be the most suitable solvent for this reaction. This surprised us, as the reaction of thiophenols with toluene, using TBHP as the oxidant, has previously been explored.[12] However, neither the reaction of thiophenol with the solvent nor the further oxidation of the product was observed in our system. ZnI_2 was found to be the best catalyst here; lower yields were obtained when CuI, I_2, or TBAI were tested. No product could be detected with MeCN, cyclohexane, or iPrOH as the reaction media. During the substrate testing, as shown in Table 1, moderate to good isolated yields were generally obtained. Good yields can be achieved with electron-donating substituted thiophenols. Interestingly, the methylthio substituent can be tolerated and gives the corresponding 2-methyl-1-[(4-(methylthio)phenylth-

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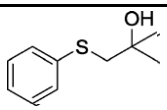
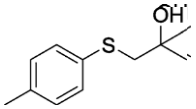
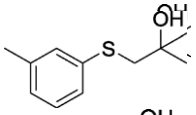
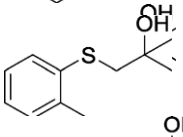
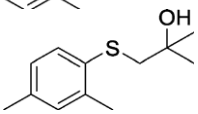
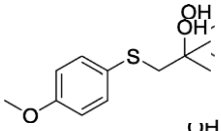
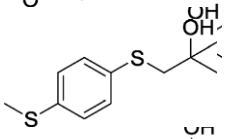
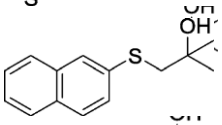
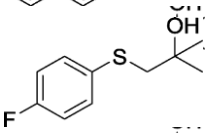
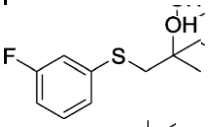
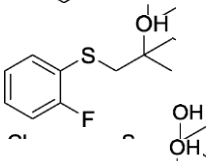
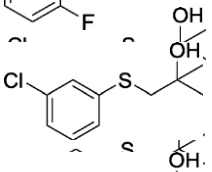
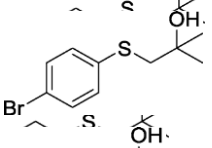
Table 1. Oxidative reactions of thiophenols with TBHP[a]

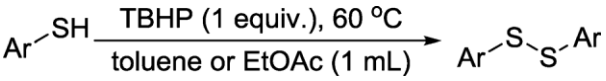
[redacted]

Entry	Product	Yield[b] [%]
1		78
2		64
3		74
4		77
5		77
6		62
7		58
8		43
9		63
10		75
11		89
12		35
13		31

[a] ArSH (1 mmol), ZnI_2 (20 mol %), TBHP (2 equiv; 70 % in water), toluene (1 mL), 80 8C, 28 h, argon. [b] Isolated yield.

io]propan-2-ol in 58 % yield (Table 1, entry 7). Fluoro-substituted b-hydroxysulfoxides can be synthesized in 63–89 % yields (Table 1, entries 9–11). Notably, chloro- and bromo-decorated products were obtained from the corresponding substrates under the same reaction conditions. These products are ready for further modification via cross-coupling methodologies (Table 1, entries 12 and 13). However, alkyl sulfide is not a suitable substrate here (Table 1, entry 14).

One main drawback of using thiophenols as substrates is their odor, which hampers their synthetic application. One solution for this problem is using the corresponding disulfides as the substrates, which can be produced from thiophenols and might also be the reaction intermediate. We found that diaryl disulfides can be produced in excellent yields by using TBHP as the oxidant with toluene or ethyl acetate as the solvent (Scheme 2).



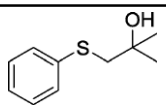
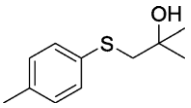
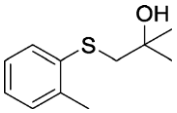
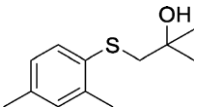
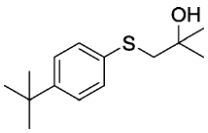
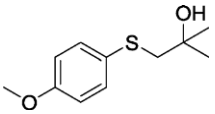
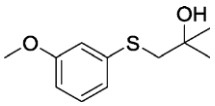
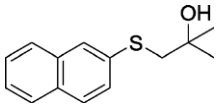
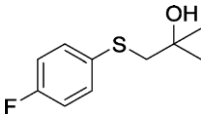
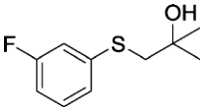
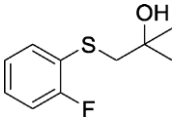
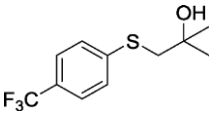
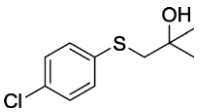
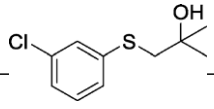
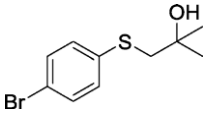
Scheme 2. Synthesis of disulfides from thiophenols.

Disulfides were then tested as substrates for this transformation. To our surprise, only a trace of the desired product could be detected when diphenyl disulfide was applied as the substrate under our former conditions. In our further optimization process, we found that I_2, MgI_2, and TBAI could all give the desired product, but in low yield. 76 % of 2-methyl-1-(phenylthio)propan-2-ol can be achieved when KI is used as the promotor (Table 2, entry 1). Of the various solvents, toluene proved to be the best reaction media, rather than MeCN, o-xylene, 1,4-dioxane, THF, DCE, tBuOH, or tert-amyl alcohol. Next, various diaryl disulfides were tested with KI as the catalyst. Compared with thiophenols as starting materials, similar functional group generality was observed and even better yields were obtained in some cases. The yield of 1-[(4-bromophenyl)thio]-2-methylpropan-2-ol could be improved to 72 % by using disulfide as the substrate (Table 1 entry 13 vs. Table 2 entry 15). The yields of chloro-substituted products were also increased (Table 2, entries 13 and 14). However, the nitro group could not be tolerated in either case, and no yield of the desired product was obtained.

Concerning the reaction mechanism, several control experiments were also performed. TEMPO (2 equiv) and BHT (2 equiv) were added to the reaction mixtures, and no desired product could be obtained in either case. Hence, we believe the reaction proceeded via a radical pathway. Based on our experimental results and knowledge, we propose that TBHP firstly reacted with the substrates and iodide to give tert-butyloxy and sulfur radicals. Then, the tert-butyloxy radical went through b-H transfer to give the corresponding methylene radical, which subsequently reacted with the sulfur radical to give the terminal product. To be clear, the methylene radical can also be formed through the radical exchange with thiol radical.

In conclusion, an interesting methodology for the synthesis of b-hydroxysulfoxides has been developed. With TBHP as the

Table 2. Oxidative reactions of disulfides with TBHP.[a]

Entry	Product	Yield[b] [%]
1		76
2		70
3		73
4		74
5		44
6		67
7		50
8		65
9		56
10		72
11		91
12		53
13		65
14		64
15		72

[a] ArSSAr (1 mmol), KI (40 mol%), TBHP (5 equiv; 70% in water), toluene (1 mL), 80 °C, 24 h, argon. [b] Isolated yield.

oxidant and reactant, 2-methyl-1-(arylthio)propan-2-ols were formed in moderate to good yields.

Experimental Section

General Procedure for Thiophenols

Thiophenol (1 mmol) and ZnI_2 (20 mol%) were added to a 15 mL tube equipped with a stirring bar. Then, the tube was flashed with argon and vacuum three times, and 1 mL of toluene and 2 equiv of TBHP (70% in water) were injected through a syringe. After that, the tube was closed and heated to 80 °C for 28 h. When the reaction was complete, the reaction mixture was cooled to room temperature. The reaction was quenched with distilled water and the solution was extracted with ethyl acetate. The crude product was purified by using column chromatography (ethyl acetate/pentane = 1:15).

General Procedure for Disulfides

1,2-Diphenyldisulfane (1 mmol) and KI (0.4 equiv) were added to a 25 mL Schlenk tube equipped with a stirring bar. Then, the tube was flashed with argon and vacuum three times, and 1 mL of toluene and 5 equiv of TBHP (70% in water) were injected through a syringe. After that, the tube was closed and heated to 80 °C for 24 h. When the reaction was complete, the reaction mixture was cooled to room temperature. The reaction was quenched with distilled water and the solution was extracted with ethyl acetate. The crude product was purified by using column chromatography (ethyl acetate/pentane = 1:15).

General Procedure for Disulfide Synthesis

A 15 mL tube equipped with a stirring bar, benzenethiol (1 mmol), EtOAc or toluene (1 mL), and TBHP (1 equiv; 70% in water) were added through the syringe. After that, the tube was closed and heated to 60 °C for 16 h. When the reaction was complete, the reaction mixture was cooled to room temperature. The reaction was quenched with distilled water and the solution was extracted with ethyl acetate. The crude product was purified by using column chromatography (pentane).

Acknowledgements

We appreciate the general support from Prof. Matthias Beller in LIKAT.

Keywords: cascade process · C–H activation · green chemistry · oxidation · b-hydroxysulfides

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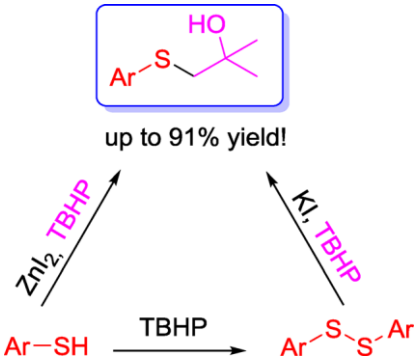
Quick to react: A procedure for the oxidative synthesis of b-hydroxysulfides is reported, in which thiophenols or diaryl disulfides are reacted with tert-butyl hydroperoxide (TBHP). In the presence of zinc iodide or potassium iodide, with TBHP as the oxidant and pre-reactant, thiophenols and diaryl disulfides react with the methyl group of tBuOH smoothly and selectivity to give the corresponding 2-methyl-1-(arylthio)propan-2-ols as the terminal products in moderate to good yields.



J.-B. Feng, X.-F. Wu*

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Synthesis of b-Hydroxysulfides from Thiophenols and Disulfides with tert-Butyl Hydroperoxide as the Oxidant and Reactant

7.6 Palladium-catalyzed carbonylative cyclization of arenes by C-H bond activation with DMF as the carbonyl source.

Jianbin Chen,[+] Jian-Bo Feng (equal first author),[+] Kishore Natte, Xiao-Feng Wu*

Chem. Eur. J. **2015**, *21*, 16370-16373

Summary: A novel palladium-catalyzed CO-gas- and autoclave-free protocol for the synthesis of 11H-pyrido[2,1-*b*]quinazolin-11-ones has been developed. Quinazolinones, the omnipresent motif in many pharmaceuticals and agrochemicals, were prepared in good yields by C-H bond activation and annulation using DMF as the CO surrogate. A ^{13}CO-labelled DMF control experiment demonstrated that CO gas was released from the carbonyl of DMF with acid as the promotor. The kinetic isotope effect (KIE) value indicated that the C-H activation step may not be involved in the rate-determining step. This methodology is operationally simple and showed a broad substrate scope with good to excellent yields.

Contribution: In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 40%.

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CHEMISTRY A European Journal Communication

& C–H Functionalization

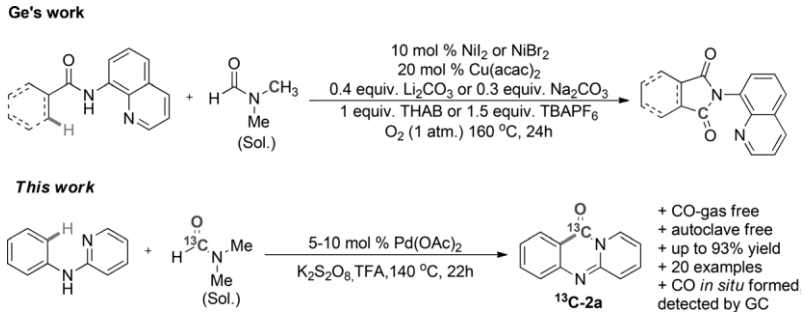
Palladium-Catalyzed Carbonylative Cyclization of Arenes by C–H Bond Activation with DMF as the Carbonyl Source

Jianbin Chen,[a] Jian-Bo Feng,[a, b] Kishore Natte,[a] and Xiao-Feng Wu*[a, b]

Dedicated to Professor Dr. Lutz F. Tietze on the occasion of his 75th birthday

Abstract: A novel palladium-catalyzed CO-gas- and autoclave-free protocol for the synthesis of 11H-pyrido[2,1-b]quinazolin-11-ones has been developed. Quinazolinones, which are omnipresent motif in many pharmaceuticals and agrochemicals, were prepared in good yields by C–H bond activation and annulation using DMF as the CO surrogate. A ^{13}CO-labelled DMF control experiment demonstrated that CO gas was released from the carbonyl of DMF with acid as the promotor. The kinetic isotope effect (KIE) value indicated that the C–H activation step may not be involved in the rate-determining step. This methodology is operationally simple and showed a broad substrate scope with good to excellent yields.

Carbonylation reactions continue to be of high interest for the chemists, since such reactions serve as a useful toolbox for the synthesis of carbonyl-containing products. Thus, many efforts have been made in the past decades on the development of transition-metal-catalyzed carbonylation reactions.[1] However, there are two main issues existing for most of the known carbonylative procedures: 1) they need ArX (X = I, Br, OTf, N_2BF_4, etc.) as their substrates;[1a,b,e] and 2) they rely on CO gas. The procedures based on ArX starting materials are not sustainable due to their pre-activation requirements, and over stoichiometric amounts of wastes that are generated after the reaction. In order to overcome such drawbacks, direct functionalization of the C–H bonds provides an ideal alternative pathway.[2] This concept has been accepted by organic chemists, and many carbonylative C–H activation procedures have been established.[1c,d, 3] For the CO-gas-based procedures, even though the use of CO gas holds significant advantages in industrial scale applications, its high toxicity character limits its application in laboratories. Hence, CO surrogate exploration is becoming an interesting topic.[4] Among the possible candidates, DMF solvent is an attractive CO surrogate because it is cheap and easily accessible.[5] In 2002, Alterman, Hallberg and their co-workers developed the first palladium-catalyzed aminocarbonylation of aryl bromides with DMF as the CO source.[4i] The desired amides were achieved in good yields at 180–190 8C in the presence of KOtBu under microwave conditions. Interestingly, in 2009 Chang and co-workers initially reported that DMF can also serve as an amine source in the decarbonylative amination of benzoxazoles with silver as the promoter,[6] and this transformation was further studied by several other groups.[7] Notably, Hiyama and Nozaki described an aminocarbonylation of aryl and alkenyl iodides by using DMF as the amide source with $POCl_3$ (phosphoryl chloride) as the promoter.[8] Later on, Bhanage and co-workers studied this transformation with Pd/C as well as $Pd(OAc)_2$/Xantphos as the catalytic systems, and provided broader substrate scope.[9] Remarkably, Ge and co-workers demonstrated that the methyl group from DMF can serve as a carbonyl source on nickel-catalyzed carbonylative C–H activation (Scheme 1).[10] Based on our continual interest on carbonylation reactions,[11] here we wish to report our new finding on using the carbonyl group of DMF as the CO source for palladium-catalyzed carbonylative C–H activation (Scheme 1).



Scheme 1. DMF as CO source in transition-metal-catalyzed carbonylation.

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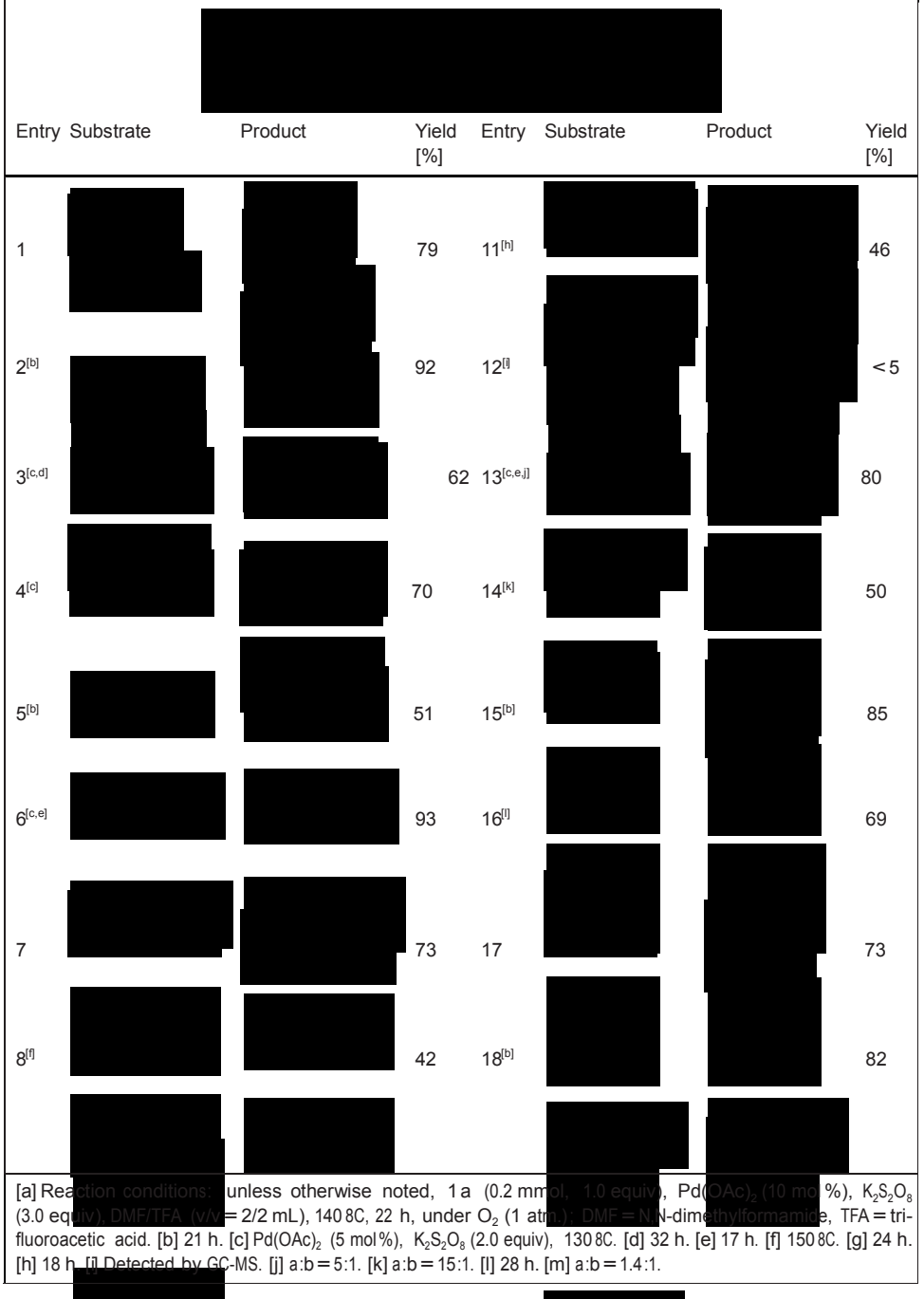
In our initial studies, we investigated the carbonylation of N-phenylpyridin-2-amine with DMF in the presence of $Pd(OAc)_2$ and using $K_2S_2O_8$ (potassium persulfate) as oxidant with HOAc as co-solvent. Unfortunately, no desired products was observed at 80 or 120 8C (see the Supporting Information). However, a trace of the desired product was obtained in the presence of FTA (trifluoroacetic acid) as the co-solvent at 100 8C and moderate yield were given at 120–130 8C. Changing the oxidant to $Na_2S_2S_8$ (sodium persulfate) led to lower efficiency. To our delight, the best conditions were achieved at 140 8C under oxygen atmosphere, which gave the desired product in 79% isolated yield.

Some analogues of DMF were tested next under our optimal conditions (see the Supporting Information for details). Moderate yields (21–57%) were achieved with N-methylformamide, N,N-diethylformamide, and N,N-dibutylformamide, while formamide and N-(2,6-diisopropylphenyl) formamide gave no result. Remarkably, 1-formylpiperidine gave the desired product in an excellent 85% GC yield, which is higher than DMF. It should be noted that some acetamides, such as DMAc (N,N-dimethylacetamide) and NMP (1-methylpyrrolidin-2-one), can also give trace of the products. This could be explained by the trace of iminium ion formation under oxygen atmosphere, which results in the generation of the carbonyl group from the methyl part of DMAc or NMP.[10]

DMF was chosen over 1-formylpiperidine as the CO source for the subsequent substrate scope study due to its easy accessibility. In general, both electron-rich or -poor substituted N-arylpyridin-2-amines (1) were transformed into valuable 11H-pyrido[2,1-b]quinazolin-11-one (2) scaffolds in moderate to good yields (Table 1). Benzene rings bearing methyl, phenyl and benzyloxy as the electron-donating groups at para positions were well tolerated and the corresponding products were obtained in good yields (Table 1, entries 2, 6 and 7). The halide substrates were also compatible, and gave their corresponding products in good yields (Table 1, entries 3–5). These products are useful intermediates for further reactions, such as transition-metal-catalyzed cross-coupling of C–X bonds.[12] Electron-withdrawing groups, such as trifluoromethoxy, and ketone were tolerated well (Table 1, entries 8 and 9). Coordinating N,N-dimethylamino and methylthio substituents also gave moderate yields, 65 and 46%, respectively (Table 1, entries 10 and 11). Furthermore, we did not observe any oxidation of the methylthio group under our conditions. Unfortunately, only a trace amount of the vinyl-substituted compound was observed by GC-MS (Table 1, entry 12). In the case of

Table 1. Pd-catalyzed carbonylative C–H bond cyclization with DMF as the CO surrogate.[a]



[a] Reaction conditions: unless otherwise noted, 1a (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (3.0 equiv), DMF/TFA (v/v = 2/2 mL), 140 8C, 22 h, under O_2 (1 atm); DMF = N,N-dimethylformamide, TFA = trifluoroacetic acid. [b] 21 h. [c] $Pd(OAc)_2$ (5 mol%), $K_2S_2O_8$ (2.0 equiv), 130 8C. [d] 32 h. [e] 17 h. [f] 150 8C. [g] 24 h. [h] 18 h. [i] Detected by GC-MS. [j] a:b = 5:1. [k] a:b = 15:1. [l] 28 h. [m] a:b = 1.4:1.

meta-methyl substituted starting material, the sterically less hindered regioisomer was formed preferentially (Table 1, entry 13); while meta-chloro substituted substrate was carbonylated at the sterically hindered position (Table 1, entry 14). Substrates with functional groups at the ortho-position on the arene proceeded well, and gave the desired products in good to excellent yields (Table 1, entries 15–17). Moreover, 1-naphthalene derived precursor was successfully transformed into the cyclized compound in 82% yield, while N-(naphthalen-2-yl)pyridin-2-amine derivative gave its corresponding product in 73% yield with 1.4:1 regioselectivity (Table 1, entries 18 and 19, respectively). The reaction also worked for the substrate containing a bromo substituent on the pyridyl ring, which gave 23% yield of the corresponding product (Table 1, entry 20).

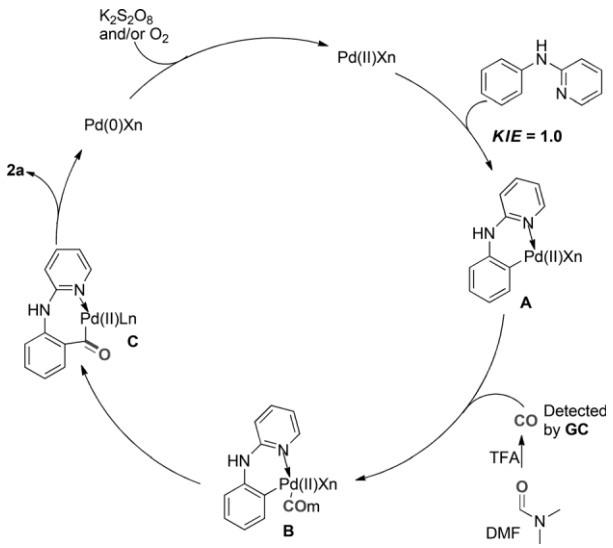
In order to gain some detail of this newly developed protocol, several control experiments of the benchmark reaction were performed. As shown in Scheme 2, ^{13}C-carbonyl labelled

Scheme 2. Control studies: ^{13}CO-DMF experiment and kinetic isotope effect (KIE).

DMF was tested in the reaction, and only ^{13}C-carbonyl-labelled product was detected in 20% GC yield [Eq. (1)]. Additionally, the kinetic isotope effect experiment was also performed, which indicated that C–H activation step might not be involved in the rate-determining step.

Based on the control experimental results, a preliminary mechanism for the carbonylative C–H cyclization of N-phenylpyridin-2-amine (1a) is proposed in Scheme 3. The coordination of Pd^{II} species to 1a, and the subsequent C–H activation step provides organometallic complex A. At elevated temperature, with the aid of an acid, CO is released from DMF in situ, which coordinates A to give an intermediate B. Then CO insertion into the Pd–C bond generates acylpalladium(II) C. Finally, the product is generated following reductive elimination, and the resulting Pd^0 is reoxidized to Pd^{II} by the oxidant.

In summary, we have developed the first general palladium-catalyzed carbonylative cyclization of N-arylpyridin-2-amines by C–H activation using DMF as the CO surrogate. A ^{13}CO-labelled DMF study, and other control experiments indicated that the carbonyl group of DMF is the CO source in this methodology.



Scheme 3. Proposed reaction mechanism.

Moreover, the KIE value suggested that C–H activation step might not be involved in the rate-determining step under our conditions. This methodology worked well for both electron-rich and -poor substrates, and gave the desired products in moderate to excellent yields.

Acknowledgements

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Keywords: carbonylation · C–H activation · DMF · heterocycles · palladium

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7.7 Potassium *tert*-butoxide-promoted synthesis of 1-aminoisoquinolines from 2-methylbenzonitriles and benzonitriles under catalyst-free conditions.

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Summary: A practical and efficient protocol for preparing a range of aminoisoquinolines is reported. Various aminoisoquinolines were prepared in moderate to good yields from the corresponding 2-methylbenzonitriles and benzonitriles upon treatment with potassium *tert*-butoxide.

Contribution: In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 75%.

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Advanced Synthesis & Catalysis

Potassium tert-Butoxide-Promoted Synthesis of 1-Aminoisoquinolines from 2-Methylbenzonitriles and Benzonitriles under Catalyst-Free Conditions

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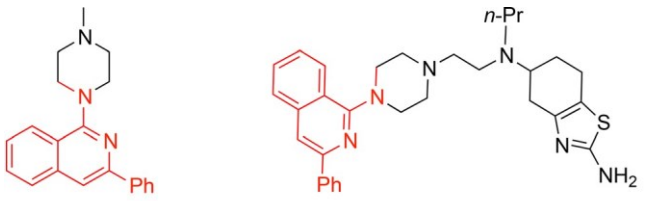
Abstract: Herein a practical and efficient protocol for preparing a range of aminoisoquinolines is reported. Various aminoisoquinolines were prepared in moderate to good yields from the corresponding 2-methylbenzonitriles and benzonitriles upon treatment with potassium tert-butoxide.

Keywords: 1-aminoisoquinolines; base-promoted reaction; benzonitriles; cascade reaction; metal-free conditions

The derivatives of amino-substituted isoquinolines are prevalent in natural products and functional materials. Additionally it has been reported that several examples in this family of compounds have been found to have activity in cancer,[1] tumor,[2] malaria[3] and Parkinson's disease cell lines (Scheme 1).[4] The isoquinoline backbone is apparent also in the skeleton of chiral ligands for asymmetric catalysts.[5] Given the important properties outlined, numerous preparation methods have been developed for aminoisoquinolines. A general protocol to obtain 1-aminoisoquinolines is via the direct amination of 1-haloisoquinolines.[6] In recent years, some alternative procedures have also been used. These methods include the domino electrophilic cyclization of 2-alkynylbenzamides or 2-alkynylbenzaldoximes[7,8] and the oxidative annulation of benzamidine derivatives with internal alkynes catalyzed by either rhodium, ruthenium or cobalt catalysts.[9] These newly developed procedures have a wider substrate scope as well as the benefit of needing mild reaction conditions. However, the necessity of either transition metal catalysts or preparing prefunctionalized substrates still remains. The involvement of transition metal catalysts not only raises the cost but also brings potential transition metal contamination into the heterocyclic products, which can be an issue with subsequent bioassay studies. In an effort to eliminate the above impediments and based on our continuing interest in developing new transition metal-free synthetic methodologies,[10] we intended to develop a simpler transition metal-free procedure for the preparation of 1-aminoisoquinolines from commercially available substrates. With t-BuOK as the only promoter, moderate to good yields of the desired aminoisoquinolines were achieved from the corresponding o-toluenenitriles and benzonitriles in a simple one-pot manner.



antitumor agent — potent *in vivo* activity in a Parkinson's disease animal model

Scheme 1. Selected examples of biologically active 1-aminoisoquinolines.

Initially, a variety of solvents was tested with o-toluenenitrile and benzonitrile as the model substrates, in the presence of t-BuOK at 1108C for 16 h (Table 1, entries 1–4). Encouragingly, 7% and 42% of the 3-phenylisoquinolin-1-amine were obtained in DMAc and toluene, respectively (Table 1, entries 1 and 4). Further reactions replacing t-BuOK with various inorganic bases only resulted in no desired product formation (Table 1, entries 5–10). To our delight the desired product was isolated in 81% yield when 2 equivalents of t-BuOK were employed (Table 1, entry 11) however further equivalents of t-BuOK were ineffective

Table 1. Optimization of the reaction conditions in the production of 3a.[a]

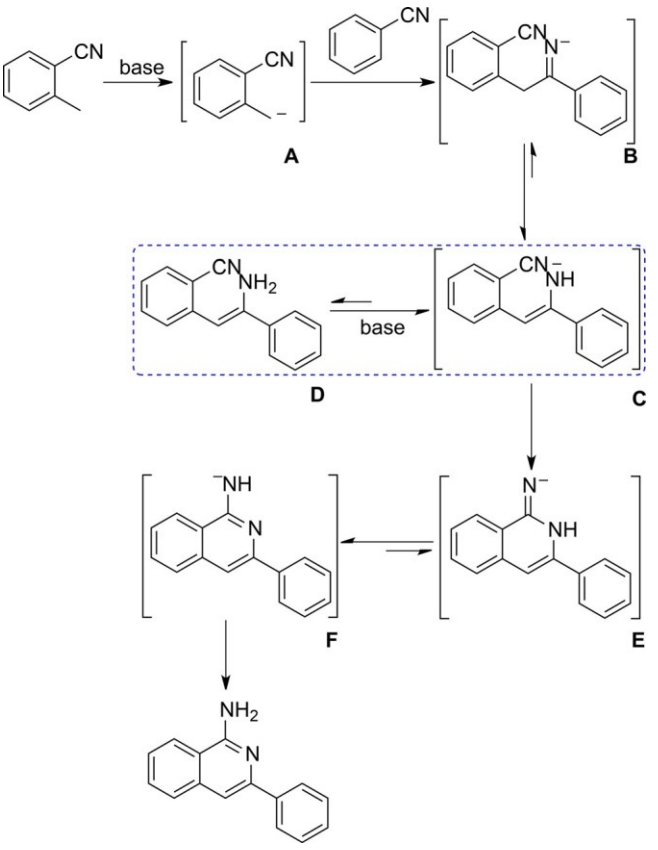
Entry	Base (equiv.)	Solvent	T [8C]	Yield [%]
1	t-BuOK (1)	DMAc	110	7
2	t-BuOK (1)	DMF	110	10
3	t-BuOK (1)	DMSO	110	4
4	t-BuOK (1)	toluene	110	42
5	t-BuOLi (2)	toluene	110	0
6	t-BuONa (2)	toluene	110	0
7	K_2CO_3 (2)	toluene	110	0
8	NaOAc (2)	toluene	110	0
9	NaOMe (2)	toluene	110	0
10	KOH (2)	toluene	110	0
11	t-BuOK (2)	toluene	110	81
12	t-BuOK (3)	toluene	110	75
13	t-BuOK (2)	toluene	90	47
14	t-BuOK (2)	toluene	130	73
15	t-BuOK (2)	toluene	110	66[b]
16	t-BuOK (2)	toluene	110	80[c]

[a] All reactions were performed under air, o-toluenenitrile (1 mmol), benzonitrile (1.5 equiv.), base (2 equiv.), solvent (1 mL), 80 8C, 16 h, isolated yield.
[b] Benzonitrile (1.0 equiv.).
[c] Benzonitrile (2.0 equiv.).

(Table 1, entry 12). Modifying either the reaction temperature or the ratio between benzonitrile and o-toluenenitrile did not further improve the yield (Table 1, entries 13–16).

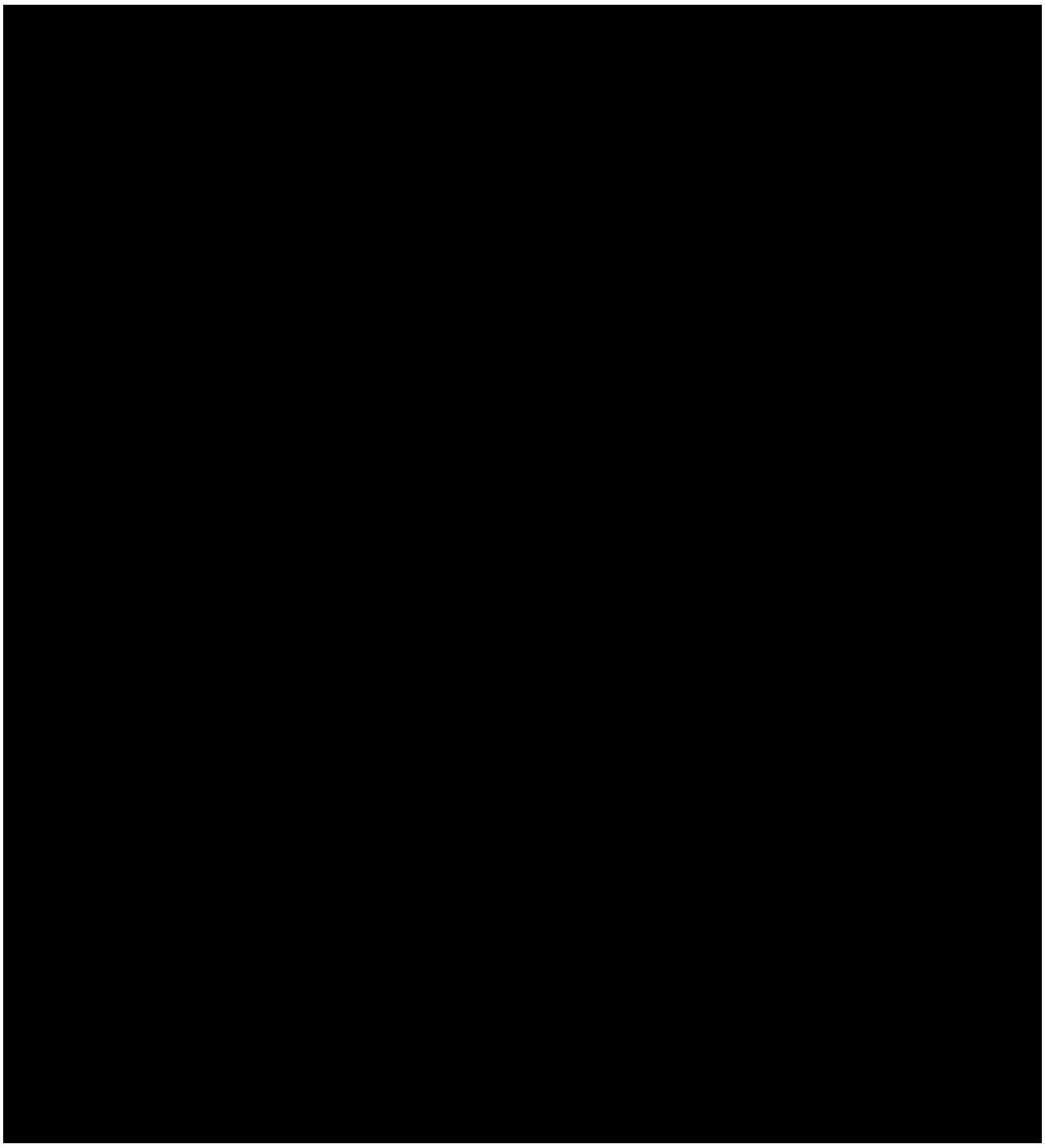
Following optimization of the reaction conditions, an investigation of the substrate scope was conducted (Table 2). When a methyl group was introduced into the 3- or 6-positon of o-toluenenitrile (Table 2, entries 2 and 3), a distinct substituent effect was observed where a moderate yield was first obtained for 2,6-dimethylbenzonitrile (Table 2, entry 2). Alternatively when the two methyl groups were adjacent to one another (Table 2, entry 3), the yield dramatically decreased. That may be due to the steric hindrance or the decreased activity of the methyl group. Halogen-derived substrates remained intact in the strong basic conditions and gave the corresponding products in good to moderate yields (Table 1, entries 5–9). Here, the obtained products could be used for a plethora of different reactions, in particular transformations through transition metal-catalyzed coupling reactions. In these cases, the decreased yields can be explained by the reaction of the halogens with t-BuOK to give the corresponding tert-butoxy ethers. As expected, the reaction between a primary amine and a benzonitrile occurred when both were present in the reaction mixture under our reaction conditions (Table 2, entry 10). For the strong electron-withdrawing groups like nitro and trifluoromethyl, no desired products could be detected (Table 2, entries 11 and 12). 2-Ethylbenzonitrile was investigated, but only trace amounts of the corresponding product were detected. This might due to the decreased reactivity resulting from the increased carbon chain length.

Afterwards, numerous substituted benzonitriles were tested with o-toluenenitriles under the standard reaction conditions (Table 3). Chloro-substituted benzonitriles could be used as the reaction partner and in these cases the corresponding products were isolated in moderate yields (Table 3, entries 1–3). However, for the fluoro-substituted starting materials such as 2-fluorobenzonitrile and 4-fluorobenzonitrile, only trace amounts of the target products could be detected by GC-MS. In these cases it was discovered that the corresponding tert-butoxy ether and amide were present. The same scenario was observed for Br-, I-, and NO_2-substituted benzonitriles, as these groups are good leaving groups in nucleophilic substitution processes. Benzonitriles with electron-donating groups afforded the corresponding products in moderate to good yields. In the case of methyl-substituted benzonitriles, o-methyl-derived compound 3r gave the product with



Scheme 2. A proposed mechanism for the synthesis of aminoisoquinolines.

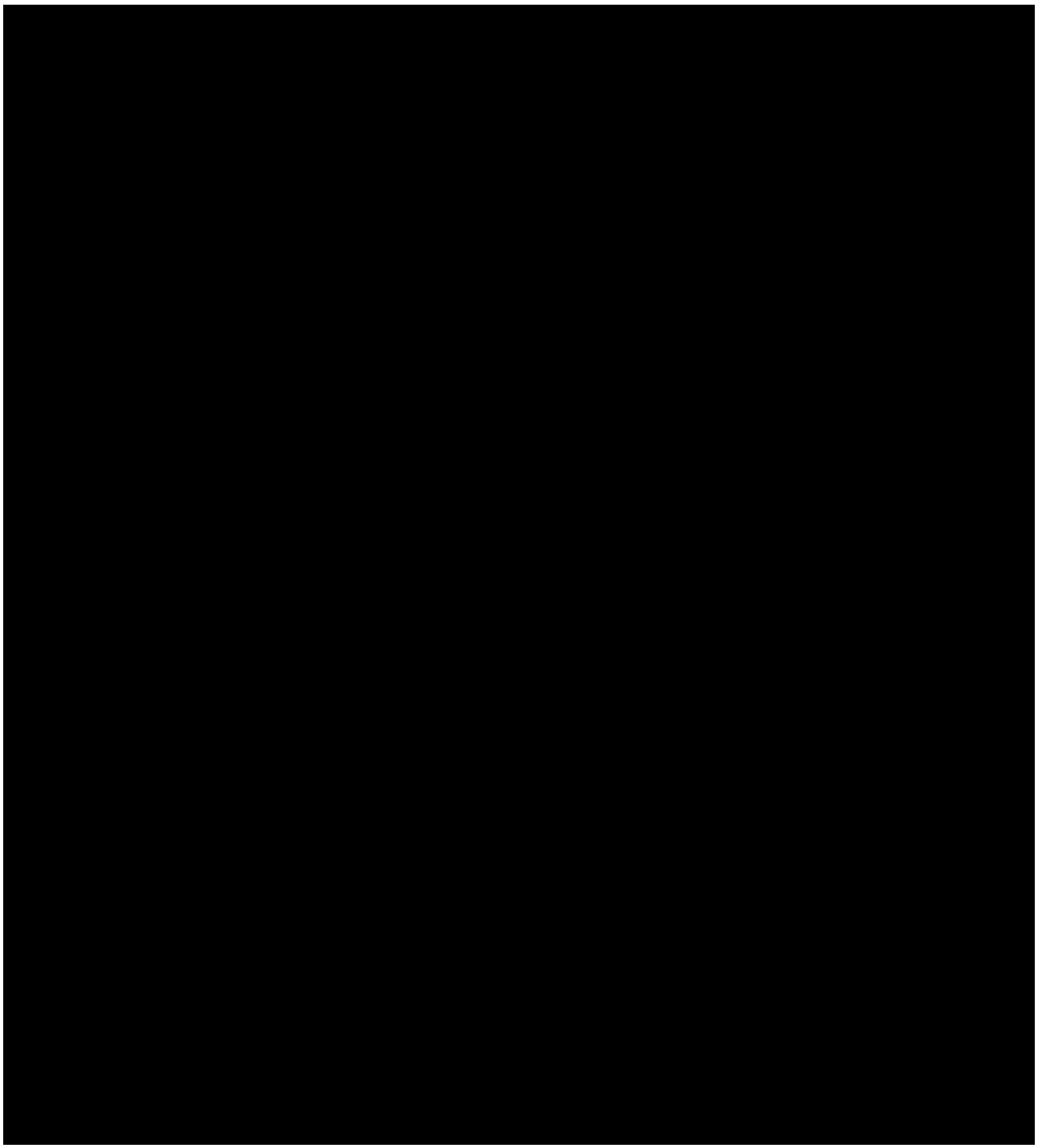
Table 2. Synthesis of aminoisoquinolines from benzonitrile and substituted o-toluenenitriles.[a]



[a] Reaction conditions: benzonitrile (1 mmol), o-toluenenitriles (1.5 equiv.), t-BuOK (2.0 equiv.), 110 8C, 16 h, isolated yield.

higher yield compared with the p-methyl-substituted case (Table 3, entries 5 and 6). It also should be mentioned that the undesired homo-coupled product between two molecules of o-toluenenitrile could be detected in all cases during the optimization process. However, the amount of homo-coupled product is much less pronounced in the presence of benzonitrile. Thus, using an excess of o-toluenenitrile in our protocol is necessary to avoid this undesired product. Through a highly concerted process, benzonitrile can quickly consume this intermediate and inhibit the generation of the undesired homo-coupled product. Good yields of the desired 1-aminoisoquinolines can be achieved from methoxy- or methylthio-substituted

Table 3. Synthesis aminoisoquinolines from o-toluenenitrile and benzonitriles.[a]



[a] Reaction conditions: benzonitriles (1 mmol), o-toluenenitrile (1.5 equiv.), t-BuOK (2.0 equiv.), 110 8C, 16 h, isolated yield.

benzonitriles without any further optimization (Table 3, entries 7–9). Moreover, the protocol can be applied with fused aromatic and heteroaromatic nitriles. The corresponding products 3v–3x were isolated in moderate yields (Table 3, entries 10–12). Unfortunately, no reaction occurred when aliphatic nitriles, such as acetonitrile, cyclohexanecarbonitrile, isobutyronitrile and 2-phenylacetonitrile were used as starting materials.

A possible reaction pathway has been derived for this new reaction process (Scheme 2). The reaction is proposed to begin with the generation of carbanion

A, generated from o-toluenenitrile in the presence of t-BuOK which will give intermediate B after reacting with benzonitrile. Intermediate C was considered as a more stable resonance structure of intermediate B. It should be noted that intermediate C can be used mechanistically to arrive at the protonated product D in the presence of a proton source. This process is reversible in the presence of base. Then nucleophilic addition of the nitrogen ion to the cyano of the o-toluenenitrile occurs and generates intermediate E, which can give the final product after rearrangement and protonation.

In conclusion, a practical and efficient methodology for the synthesis of 1-aminoisoquinolines has been developed. Moderate to good yields of the desired products can be obtained from the corresponding commercially available o-toluenenitriles and benzonitriles. The strong base t-BuOK was used as the only reaction promoter and no addition of any transition metal catalyst was required.

Experimental Section

General Procedure

Under an open atmosphere, a 25-mL pressure tube was charged with 1 mmol of o-toluenenitrile, 1.5 mmol of benzonitrile, 2 mmol of t-BuOK and 1 mL toluene. Then the tube was sealed and the mixture was heated under stirring at 110 8C for 16 h. After this time the mixture was cooled to room temperature and the mixture was concentrated under vacuum. The pure products were obtained after purification by column chromatography (ethyl acetate-pentane = 1:4).

3-Phenylisoquinolin-1-amine (3a): yield: 178 mg (81%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d = 8.19–7.99 (m, 2H), 7.82–7.71 (m, 2H), 7.61 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H), 7.56–7.35 (m, 5H), 5.35 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): d = 155.92, 149.49, 139.83, 138.12, 130.16, 128.51, 128.12, 127.45, 126.78, 125.82, 122.52, 116.87, 108.80; GC-MS (EI, 70 eV): m/z (%) = 220 (M^+, 100), 221 (17), 219 (30).

8-Methyl-3-phenylisoquinolin-1-amine (3b): yield: 145 mg (62%); light yellow solid; ^{1}H NMR (400 MHz, chloroform-d): d = 8.11–8.04 (m, 2H), 7.60–7.53 (m, 1H), 7.52–7.45 (m, 2H), 7.44 (s, 1H), 7.43–7.36 (m, 2H), 7.18 (dt, J = 7.1, 1.1 Hz, 1H), 5.49 (s, 1H), 2.91 (s, 3H); ^{13}C NMR (101 MHz, chloroform-d): d = 157.13, 148.69, 140.39, 139.45, 134.24, 129.45, 128.98, 128.44, 128.06, 126.61, 126.08, 117.69, 109.46, 24.45; GC-MS (EI, 70 eV): m/z (%) = 234 (M^+, 100), 235 (17), 233 (46), 77 (14).

5-Methyl-3-phenylisoquinolin-1-amine (3c): yield: 66 mg (28%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d = 8.18–8.02 (m, 2H), 7.64 (d, J = 8.3 Hz, 1H), 7.59 (s, 1H), 7.56–7.28 (m, 5H), 5.32 (s, 2H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d): d = 156.46, 149.52, 140.27, 137.39, 134.31, 130.61, 128.51, 128.08, 126.89, 125.26, 120.46, 116.67, 105.45, 19.30; GC-MS (EI, 70 eV): m/z (%) = 234 (M^+, 100), 235 (18), 233 (16), 104 (14), 195 (12), 168 (17), 167 (32).

6-Fluoro-3-phenylisoquinolin-1-amine (3d): yield: 83 mg (35%); light yellow solid); ^{1}H NMR (400 MHz, chloroform-d): d = 8.10–7.97 (m, 1H), 7.83–7.74 (m, 0H), 7.47 (tt, J = 6.9, 0.9 Hz, 1H), 7.43–7.32 (m, 1H), 7.18 (ddd, J = 9.0, 8.3, 2.6 Hz, 0H), 5.27 (s, 1H); ^{13}C NMR (101 MHz, chloroform-d): d = 163.43 (d, J = 250.7 Hz), 155.78, 150.85, 140.09 (d, J = 10.3 Hz), 139.45, 128.58, 128.47, 126.86, 125.49 (d, J = 9.8 Hz), 115.58 (d, J = 25.2 Hz), 113.87, 110.93 (d, J = 20.7 Hz), 108.52 (d, J = 4.4 Hz); GC-MS (EI, 70 eV): m/z (%) = 238 (M^+, 100), 239 (16), 237 (29), 212 (11), 195 (12), 168 (17), 167 (32).

7-Fluoro-3-phenylisoquinolin-1-amine (3e): yield: 95 mg (40%); light yellow solid; ^{1}H NMR (400 MHz, chloroform-d): d = 8.12–7.97 (m, 2H), 7.75 (ddd, J = 9.9, 4.6, 2.0 Hz, 1H), 7.57–7.33 (m, 6H), 5.21 (s, 2H); ^{13}C NMR (101 MHz, chloroform-d): d = 160.25 (d, J = 247.1 Hz), 161.84–161.03 (m), 159.43–157.71 (m), 155.40 (d, J = 4.9 Hz), 149.05 (d, J = 2.7 Hz), 139.56, 135.11, 129.89 (d, J = 8.3 Hz), 128.57, 128.22, 126.69, 120.22 (d, J = 24.6 Hz), 117.28 (d, J = 7.7 Hz), 108.43 (d, J = 1.6 Hz), 106.82 (d, J = 21.5 Hz); GC-MS (EI, 70 eV): m/z (%) = 238 (M^+, 100), 239 (17), 237 (26), 219 (13), 195 (12), 218 (25), 193 (13), 190 (17), 116 (10), 104 (11), 77 (10).

5-Chloro-3-phenylisoquinolin-1-amine (3 f): yield: 193 mg (76%); light yellow solid; ^{1}H NMR (400 MHz, chloroform-d): d = 8.17–8.04 (m, 2H), 7.85 (d, J = 1.0 Hz, 1H), 7.70 (ddd, J = 8.5, 7.4, 1.0 Hz, 2H), 7.53–7.45 (m, 2H), 7.43–7.38 (m, 1H), 7.35 (dd, J = 8.3, 7.5 Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (101 MHz, chloroform-d): d = 156.03, 150.85, 139.53, 136.11, 131.99, 130.35, 128.60, 126.99, 125.41, 121.49, 117.86, 105.09; GC-MS (EI, 70 eV): m/z (%) = 254 (M^+, 100), 256 (33), 255 (18), 219 (20), 218 (12), 190 (11), 96 (10).

6-Chloro-3-phenylisoquinolin-1-amine (3g): yield: 140 mg (55%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d = 8.06–7.99 (m, 2H), 7.71–7.68 (m, 1H), 7.65 (dt, J = 8.8, 0.7 Hz, 1H), 7.52–7.44 (m, 2H), 7.43–7.36 (m, 1H), 7.36–7.30 (m, 2H), 5.36 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): d = 155.83, 150.81, 139.35, 139.17, 136.26, 128.56, 128.47, 126.82, 126.41, 126.17, 124.27, 114.96, 107.81; GC-MS (EI, 70 eV): m/z (%) = 254 (M^+, 100), 256 (33), 255 (21), 218 (16), 193 (12), 190 (11), 109 (11), 95 (14), 77 (10).

7-Bromo-3-phenylisoquinolin-1-amine (3h): yield: 107 mg (36%); light yellow solid; ^{1}H NMR (400 MHz, chloroform-d): d = 8.08–7.97 (m, 2H), 7.90 (d, J = 2.0 Hz, 1H), 7.62 (dt, J = 8.8, 0.7 Hz, 1H), 7.54–7.43 (m, 3H), 7.42–7.38 (m, 1H), 7.36 (d, J = 0.9 Hz, 1H), 5.29 (s, 2H); ^{13}C NMR (101 MHz, chloroform-d): d = 155.86, 150.85, 139.57, 139.37, 129.56, 129.05, 128.59, 128.51, 126.83, 124.84, 124.29, 115.24, 107.73; GC-MS (EI, 70 eV): m/z (%) = 300 (M^+, 100), 301 (17), 299 (26), 298 (98), 218 (25), 218 (25), 193 (10).

6-Bromo-3-phenylisoquinolin-1-amine (3i): yield: 149 mg (50%); brown solid; ^{1}H NMR (400 MHz, chloroform-d): d = 8.11–7.98 (m, 2H), 7.92 (d, J = 1.9 Hz, 1H), 7.66 (dt, J = 8.8, 0.7 Hz, 1H), 7.53 (dd, J = 8.8, 1.9 Hz,1H), 7.50–7.43 (m, 2H), 7.42–7.35 (m, 2H), 5.27 (s, 2H); ^{13}C NMR (101 MHz, chloroform-d): d = 155.82, 150.82, 139.61, 139.31, 129.62, 129.14, 128.62, 128.56, 126.84, 124.92, 124.33, 115.28, 107.78; GC-MS (EI, 70 eV): m/z (%) = 298 (M^+, 100), 301 (17), 300 (98), 219 (13), 195 (12), 218 (25), 193 (13), 190 (17), 116 (10), 104 (11), 77 (10).

(Z)-N'-(3-Cyano-4-methylphenyl)benzimidamide (3j): yield: 146 mg (62%); white solid); ^{1}H NMR (300 MHz, chloroform-d): d = 7.88–7.74 (m, 2H), 7.53–7.39 (m, 3H),

7.34–7.24 (m, 1H), 7.19 (d, J=2.2 Hz, 1H), 7.10 (dd, J=8.1, 2.3 Hz, 1H), 4.84 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d): d=136.15, 131.46, 130.92, 128.63, 126.77 (d, J=2.6 Hz), 125.15, 118.13, 113.44, 19.76; GC-MS (EI, 70 eV): m/z (%) =235 (M^+, 100), 236 (16), 234 (80), 219 (35), 132 (52), 131 (29), 116 (15), 105 (13), 104 (92), 103 (16), 89 (36), 77 (53), 76 (11), 63 (11), 51 (21), 32 (11).

3-(2-Chlorophenyl)isoquinolin-1-amine (3m): yield: 117 mg (46%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d=7.82 (dd, J=8.3, 1.0 Hz, 1H), 7.78–7.74 (m, 1H), 7.68–7.60 (m, 2H), 7.56–7.45 (m, 2H), 7.41–7.27 (m, 3H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): d=155.72, 148.61, 139.63, 137.42, 132.40, 131.49, 130.29, 130.04, 128.91, 127.50, 126.75, 126.32, 122.50, 116.74, 113.15; GC-MS (EI, 70 eV): m/z (%) =254 (M^+, 100), 266 (30), 265 (18), 220 (18), 219 (63), 218 (21), 190 (14).

3-(3-Chlorophenyl)isoquinolin-1-amine (3n): yield: 137 mg (54%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d=8.18–8.04 (m, 1H), 7.93 (dt, J=7.3, 1.7 Hz, 1H), 7.83–7.72 (m, 2H), 7.63 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.54–7.44 (m, 2H), 7.44–7.28 (m, 2H), 5.28 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): d=155.90, 147.95, 141.65, 138.04, 134.58, 130.38, 129.72, 128.08, 127.62, 126.95, 126.27, 124.75, 122.55, 117.16, 109.12; GC-MS (EI, 70 eV): m/z (%) =254 (M^+, 100), 256 (34), 255 (21), 253 (10), 218 (18).

3-(4-Chlorophenyl)isoquinolin-1-amine (3o): yield: 130 mg (51%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d=8.06–7.95 (m, 2H), 7.85–7.73 (m, 2H), 7.63 (ddd, J=8.2, 6.9, 1.2 Hz, 1H), 7.55–7.38 (m, 4H), 5.30 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): d=155.86, 148.08, 138.09, 134.15, 130.47, 128.69, 128.02, 127.58, 126.20, 122.59, 116.99, 108.79; GC-MS (EI, 70 eV): m/z (%) =254 (M^+, 100), 256 (33), 255 (20), 253 (11), 218 (20).

3-(p-Tolyl)isoquinolin-1-amine (3q): yield: 133 mg (57%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d=8.10–7.91 (m, 2H), 7.85–7.69 (m, 2H), 7.60 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.51–7.35 (m, 2H), 7.35–7.20 (m, 2H), 5.28 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d): d=155.81, 149.56, 138.23, 137.99, 137.01, 130.11, 129.25, 127.41, 126.62, 125.64, 122.53, 116.78, 108.34, 21.24; GC-MS (EI, 70 eV): m/z (%) =234 (M^+, 100), 235 (15).

3-(o-Tolyl)isoquinolin-1-amine (3r): yield: 190 mg (81%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d=7.89–7.78 (m, 1H), 7.73 (ddt, J=8.3, 1.1, 0.5 Hz, 1H), 7.63 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.58–7.40 (m, 2H), 7.33–7.27 (m, 3H), 7.12 (d, J=0.9 Hz, 1H), 5.38 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d): d=155.46, 151.86, 140.77, 137.79, 135.96, 130.54, 130.20, 129.57, 127.78, 127.25, 125.88, 125.69, 122.54, 116.36, 112.08, 20.39; GC-MS (EI, 70 eV): m/z (%) =233 (M^+, 100), 234 (53), 216 (20), 116 (18).

3-(4-Methoxyphenyl)isoquinolin-1-amine (3s): yield: 200 mg (80%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d=8.11–7.97 (m, 2H), 7.82–7.68 (m, 2H), 7.59 (ddd, J=8.2, 6.9, 1.2 Hz, 1H), 7.50–7.37 (m, 2H), 7.08–6.87 (m, 2H), 5.25 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d): d=159.81, 155.77, 149.25, 138.31, 132.48, 130.12, 127.97, 127.33, 125.48, 122.54, 116.57, 113.91, 107.76, 55.31; GC-MS (EI, 70 eV): m/z (%) =250 (M^+, 100), 251 (16), 235 (25), 207 (23).

3-(3-Methoxyphenyl)isoquinolin-1-amine (3t): yield: 137 mg (55%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d=7.83–7.73 (m, 2H), 7.71–7.56 (m, 3H), 7.48 (dd, J=5.2, 1.0 Hz, 1H), 7.46–7.33 (m, 2H), 6.95 (ddd, J=8.2, 2.6, 1.0 Hz, 1H), 5.34 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d): d=159.98, 155.96, 149.39, 141.48, 138.22, 130.29, 129.59, 127.61, 126.01, 122.64, 119.31, 117.08, 114.24, 112.14, 109.07, 55.40; GC-MS (EI, 70 eV): m/z (%) =250 (M^+, 100), 251 (18), 249 (77), 221 (13), 220 (36), 219 (27), 205 (11), 204 (12), 190 (11), 220 (36), 219 (27), 205 (11).

3-[4-(Methylthio)phenyl]isoquinolin-1-amine (3u): yield: 192 mg (72%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d=8.08–7.91 (m, 2H), 7.82–7.69 (m, 2H), 7.59 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.49–7.38 (m, 2H), 7.38–7.29 (m, 2H), 5.32 (s, 2H), 2.53 (s, 1H); ^{13}C NMR (75 MHz, chloroform-d): d=155.86, 148.79, 138.52, 138.15, 136.57, 130.20, 127.41, 127.07, 126.46, 125.77, 122.55, 116.84, 108.24, 15.72.

3-(Naphthalen-2-yl)isoquinolin-1-amine (3v): yield: 127 mg (47%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d=8.60 (d, J=1.7 Hz, 1H), 8.19 (dd, J=8.6, 1.8 Hz, 1H), 8.01–7.76 (m, 5H), 7.70–7.58 (m, 2H), 7.48 (ddd, J=9.7, 6.1, 1.6 Hz, 3H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): d=155.92, 149.20, 138.26, 136.97, 133.64, 133.36, 130.36, 128.65, 128.13, 127.60, 126.05 (d, J=3.1 Hz), 125.97, 124.68, 122.62, 117.04, 109.28; GC-MS (EI, 70 eV): m/z (%) =270 (M^+, 100), 271 (23), 269 (27).

3-(Pyridin-4-yl)isoquinolin-1-amine (3w): yield: 119 mg (54%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d=8.85–8.57 (m, 2H), 8.08–7.89 (m, 2H), 7.90–7.75 (m, 2H), 7.66 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.61–7.42 (m, 2H), 5.41 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): d=156.20, 149.93, 147.04, 146.35, 137.71, 130.59, 127.83, 126.94, 122.64, 121.00, 117.78, 110.00; GC-MS (EI, 70 eV): m/z (%) =221 (M^+, 100), 222 (16), 220 (30), 193 (10).

3-(Pyridin-3-yl)isoquinolin-1-amine (3x): yield: 108 mg (49%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): d=9.77–8.95 (m, 1H), 8.60 (dd, J=4.8, 1.7 Hz, 1H), 8.36 (dt, J=8.0, 2.0 Hz, 1H), 7.98–7.72 (m, 2H), 7.65 (ddd, J=8.2, 6.9, 1.1 Hz, 1H), 7.55–7.44 (m, 2H), 7.41–7.31 (m, 1H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): d=156.22, 149.10, 148.28, 146.74, 138.01, 135.33, 134.19, 130.57, 127.67, 126.51, 123.45, 122.66, 117.25, 109.26; GC-MS (EI, 70 eV): m/z (%) =221 (M^+, 100), 222 (16), 220 (30), 193 (10).

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8 Potassium tert-Butoxide-Promoted Synthesis of 1-Aminoisoquinolines from 2-Methylbenzonitriles and Benzonitriles under Catalyst-Free Conditions

Adv. Synth. Catal. 2016, 358, 1 – 8

Jian-Bo Feng, Xiao-Feng Wu*

8 Miscellaneous

8.1 Curriculum vitae

Curriculum vitae

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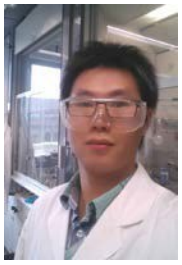

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8.2 Publication List

1. Jian-Bo Feng, Xiao-Feng Wu*, ^{t}BuOK-promoted synthesis of 3-substituted chromen-2-one from salicylaldehyde and phenylacetonitrile, **2016**, *submitted*.
2. Jian-Bo Feng, Xiao-Feng Wu*, A general Iodine-mediated synthesis of primary sulfonamides from thiols and aqueous ammonia, **2016**, *submitted*.
3. Jian-Bo Feng, Xiao-Feng Wu*, *Synthesis of β-Hydroxysulfides from thiophenols and disulfides with TBHP as the oxidant and reactant*. *Chemistryopen*, **2016**, *DOI: 10.1002/open.201600023*.
4. Jian-Bo Feng, Xiao-Feng Wu*, *Potassium tert-butoxide-promoted synthesis of 1-aminoisoquinolines from 2-methylbenzonitriles and benzonitriles under catalyst-free conditions*. *Adv. Synth. Catal*., **2016**, *DOI: 10.1002/adsc.201600169*.
5. Jian-Bo Feng, Xiao-Feng Wu*, *Base-promoted synthesis of dibenzoxazepinamines and quinazolinimines under metal-free conditions*. *Green Chem*., **2015**, *17*, 4522-4526.
6. Jian-Bo Feng, Xiao-Feng Wu*, *Synthesis of quinazolinimines and quinazolinamines from 2-fluorobenzonitriles under catalyst-free conditions*. *Org. Biomol. Chem*., **2015**, *13*, 10656-10662.
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Chapter

1. Ruthenium-Catalyzed Carbonylative Synthesis of Heterocycles. *Topics in Heterocyclic Chemistry*, DOI: 10.1007/7081_2015_149.
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