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Graphical Abstract

Efficient synthesis of quinazolines by the iron-catalyzed acceptorless dehydrogenative coupling of (2-aminophenyl)-methanols and benzamides

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[a] *College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, PR China.*

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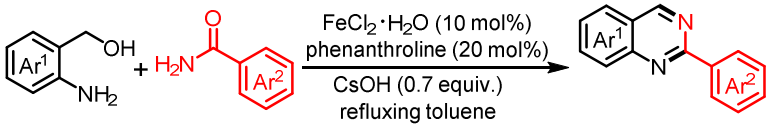

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ABSTRACT

The acceptorless dehydrogenation coupling (ADC) of (2-aminophenyl)methanols with benzamides was achieved with catalytic $FeCl_2 \cdot 4H_2O$ in an efficient synthesis of quinazolines. This simple catalytic system is atom-economical, environmentally benign and suited to a variety of substrates.

1. Introduction

The quinazoline moiety is at the core of numerous natural products, pharmacologically active molecules and organic functional materials [1-6], and much attention has focused on its synthesis and derivatization [7-13]. Typical methods for constructing 2-substituted quinazolines include (i) oxidative condensation of 2-aminobenzylamines with aldehydes [14-17], or alcohols [18-21], carboxylic acids [22], amines [23-25], α,α,α-trihalotoluenes [26], nitriles [27]; (ii) oxidative cyclization of 2-aminobenzophenones with benzylic amines [28-31], or nitriles [32], arylacetic acids [33]; (iii) oxidative cross-coupling of 2-aminoarylmethanols with nitriles [34, 35] or oxime ether [36]; (iv) Ullmann-type coupling and oxidation [37-39]; and (v) three-component oxidative coupling [40-47] (Scheme 1 (a)). These synthetic protocols often suffer from the use of stoichiometric or excessive amounts of inorganic oxidants, the production of large proportions of hazardous or toxic waste (low atom efficiency) and poor functional-group tolerance [48-51]. In recent years, some effective methodologies to overcome these drawbacks have been reported [52]. From the viewpoint of atom efficiency and safety, metal-catalyzed acceptorless dehydrogenative coupling (ADC) with the liberation of H_2O and H_2 as by-products is an attractive alternative for the synthesis of nitrogen-containing heteroaromatics [53]. The groups of Balaraman and Li have independently developed syntheses of quinazolines by ADC reaction of 2-aminobenzyl alcohols, or aldehydes with benzamides in the presence of $Mn(CO)_5Br$/NNN(NNN = N^1-(3-(dimethylamino)propyl)-N^3,N^3-dimethylpropane-1,3-diamine) [54] or [Cp*Ir(6,6'-$(OH)_2$bpy)$(H_2O)]^{2+}$ (6,6'-$(OH)_2$bpy = [2,2'-bipyridine]-6,6'-diol; bpy = 2,2-dipyridy) [55] as the catalyst. The groups of Zhang, Paul and Srimain have reported the synthesis of quinazolines via the ADC reaction of 2-aminobenzyl alcohol with nitriles catalyzed by $Ru_3(CO)_{12}$/Xantphos [56], [Ni(MeTAA)] (MeTAA = tetramethyltetraaza[14]annulene) [57] or [(NNS)$Mn(CO)_3$]Br (NNS = 2-(ethylthio)-N-(pyridin-2-ylmethyl)ethan-1-amine) [58] using t-BuOK as the base. Yi and co-authors demonstrated the ADC reaction of 2-aminophenyl ketones with amines to quinazolines catalyzed by $[(C_6H_6)(PCy_3)(CO)RuH]BF_4$/tbphOH (tbphOH = 4-(1,1-dimethylethyl)-1,2-benzenediol) at 140 °C [59] (Scheme 1 (b)). The reported ADC methodologies required the use of expensive organometallic precursors, toxic phosphine organic ligands, t-BuOK as the base, and/or relatively high temperatures [60-63]. Therefore, it is highly desirable to develop phosphine-free and inexpensive metal catalyzed reaction systems for synthesis of quinazolines under mild reaction conditions. Iron catalysts for ADC are attractive due to their abundance, low price and low toxicity [64]. Following on from our studies of the transition metal-catalysed ADC reaction [65-68], we herein report a cheap and environmentally friendly route to construct quinazolines via iron-catalysed coupling of (2-aminophenyl)methanols with benzamides with CsOH as the base in refluxing toluene.

2. Results and discussion

(2-Aminophenyl)methanol (**1a**) and benzamide (**2a**) were chosen as the model substrates to optimize reaction conditions (Table 1). Reaction of **1a** with **2a** (1.5 equiv.) in the presence of 10 mol% $FeCl_2 \cdot 4H_2O$, 20 mol% 1,10-phenanthroline (phen) and

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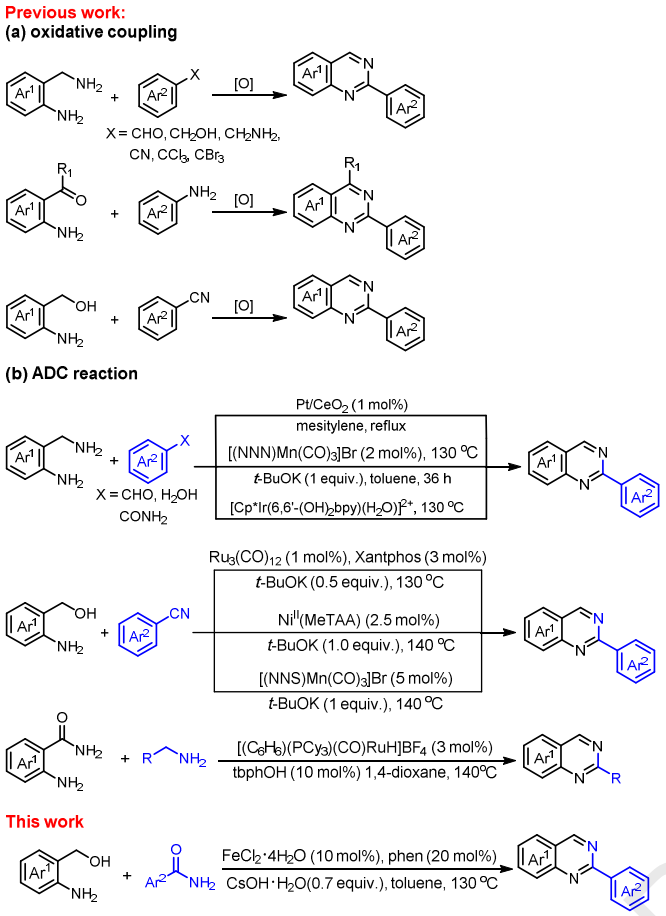
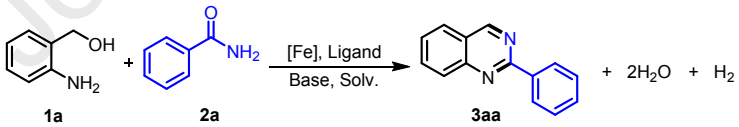


Scheme 1. Synthesis of 2-substituted quinazolines.

CsOH·H_2O (1 equiv.) in refluxing toluene (at 130 °C) for 24 h resulted in the formation of the desired product 2-phenylquinazoline (**3aa**) in high yield (91% by HPLC analysis, entry 1). Replacing $FeCl_2·4H_2O$ with $FeCl_3$, $FeSO_4·7H_2O$, $Fe(BF_4)_2·6H_2O$, $Fe(CH_3COO)_2$ or FeC_2O_4 generated **3aa** in 23-73% HPLC yields (entries 2-6). To our surprise, the reaction of **1a** with **2a** proceeded even without the addition of phen ligand, albeit providing the product in only 31% HPLC yield (entry 7). In the absence of $FeCl_2·4H_2O$ and phen, **3aa** was isolated in 30% yield (entry 8). Increasing the amount of $FeCl_2·4H_2O$ from 10 mol% to 15 mol% did not further promote the reaction. The yield of the product was decreased from 91% to 78% when the $FeCl_2·4H_2O$ loading was decreased from 10 mol% to 5 mol% (entries 9-10). Other similar N-heterocyclic organic ligands, such as 2,2'-bipyridine (bipy), N,N'-dimethylethane-1,2-diamine (dmeda), 4,7-diphenyl-1,10-phenanthroline (dphphen), 2,9-dimethyl-1,10-phenanthroline (dmphen), 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) provided the product **3aa** in lower yields (entries 11-15). A higher yield was not observed when the molar ratio of phen : $FeCl_2·4H_2O$ was changed from 2 : 1 to 3 : 1 (entry 16). While only 55% yield of **3aa** was obtained when the $FeCl_2·4H_2O$/phen ratio was 1 : 1 (entry 17). The screening of different bases revealed that t-BuOK also gave a good yield of **3aa** (entry 18). KOH, NaOH, $K_3PO_4·3H_2O$, and Cs_2CO_3 provided more moderate yields (entries 19-22). No coupling product was formed when weak base Na_2CO_3 or K_2CO_3 was employed (entries 23 and 24). The coupling reaction didn't proceed without base (entry 25). A decreased loading of CsOH·H_2O to 70 mol% did not affect the conversion, but reducing its loading to 0.5 equiv. decreased the yield of **3aa** to 54% (entries 26-27). The choice of solvent also played an important role. Toluene and xylene were the most suitable solvents at 130 °C (entries 1, 26 and 28). The same coupling cyclization gave a 75% yield in t-amyl-alcohol and 48% yield in 1,4-dioxane (entries 29-30). However, this model ADC reaction did not proceed at all in DMSO or DMF (entries 31-32). The product yield was decreased from 91% to 86% when the molar ratio **1a**/**2a** was changed from 1 : 1.5 to 1 : 1.2 (entry 33).

Table 1 Optimizing conditions for the dehydrogenative condensation/coupling reaction of (2-aminophenyl)methanols and benzamides.



Entry[a]	Cat.	Ligand	Base	Solvent	Yield of **3aa** (%)[b]
1	$FeCl_2·4H_2O$	phen	CsOH·H_2O	toluene	91%
2	$FeCl_3$	phen	CsOH·H_2O	toluene	69%
3	$FeSO_4·7H_2O$	phen	CsOH·H_2O	toluene	40%
4	$Fe(BF_4)_2·6H_2O$	phen	CsOH·H_2O	toluene	23%
5	$Fe(CH_3COO)_2$	phen	CsOH·H_2O	toluene	62%
6	FeC_2O_4	phen	CsOH·H_2O	toluene	73%
7	$FeCl_2·4H_2O$	-	CsOH·H_2O	toluene	31%
8	-	-	CsOH·H_2O	toluene	30%
9[b]	$FeCl_2·4H_2O$	phen	CsOH·H_2O	toluene	91%
10[c]	$FeCl_2·4H_2O$	phen	CsOH·H_2O	toluene	78%
11	$FeCl_2·4H_2O$	bipy	CsOH·H_2O	toluene	17%
12	$FeCl_2·4H_2O$	dmeda	CsOH·H_2O	toluene	38%
13	$FeCl_2·4H_2O$	dphphen	CsOH·H_2O	toluene	58%
14	$FeCl_2·4H_2O$	dmphen	CsOH·H_2O	toluene	85%
15	$FeCl_2·4H_2O$	tmphen	CsOH·H_2O	toluene	81%
16[d]	$FeCl_2·4H_2O$	phen	CsOH·H_2O	toluene	89%
17[e]	$FeCl_2·4H_2O$	phen	CsOH·H_2O	toluene	55%
18	$FeCl_2·4H_2O$	phen	t-BuOK	toluene	88%
19	$FeCl_2·4H_2O$	phen	KOH	toluene	66%

20	$FeCl_2 \cdot 4H_2O$	phen	NaOH	toluene	60%
21	$FeCl_2 \cdot 4H_2O$	phen	$K_3PO_4 \cdot 3H_2O$	toluene	72%
22	$FeCl_2 \cdot 4H_2O$	phen	Cs_2CO_3	toluene	76%
23	$FeCl_2 \cdot 4H_2O$	phen	Na_2CO_3	toluene	Trace
24	$FeCl_2 \cdot 4H_2O$	phen	K_2CO_3	toluene	Trace
25	$FeCl_2 \cdot 4H_2O$	phen	-	toluene	Trace
26[f]	$FeCl_2 \cdot 4H_2O$	phen	$CsOH \cdot H_2O$	toluene	91%
27[g]	$FeCl_2 \cdot 4H_2O$	phen	$CsOH \cdot H_2O$	toluene	54%
28	$FeCl_2 \cdot 4H_2O$	phen	$CsOH \cdot H_2O$	xylene	91%
29	$FeCl_2 \cdot 4H_2O$	phen	$CsOH \cdot H_2O$	t-amyl-alcohol	75%
30	$FeCl_2 \cdot 4H_2O$	phen	$CsOH \cdot H_2O$	1,4-dioxane	48%
31	$FeCl_2 \cdot 4H_2O$	phen	$CsOH \cdot H_2O$	DMSO	Trace
32	$FeCl_2 \cdot 4H_2O$	phen	$CsOH \cdot H_2O$	DMF	Trace
33[h]	$FeCl_2 \cdot 4H_2O$	phen	$CsOH \cdot H_2O$	toluene	86%

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), Fe catalyst (10 mol% of Fe), ligand (20 mol%), base (1.0 mmol), solvent (2 mL) reflux under N_2 in open system for 24 h, HPLC yields by using diphenyl as the internal standard.

[b] Using 15 mol% $FeCl_2 \cdot 4H_2O$ and 30 mol% phen.

[c] Using 5 mol% $FeCl_2 \cdot 4H_2O$ and 10 mol% phen.

[d] Using 30 mol% phen.

[e] Using 10 mol% phen.

[f] Using 0.7 equiv. $CsOH \cdot H_2O$.

[g] Using 0.5 equiv.$CsOH \cdot H_2O$.

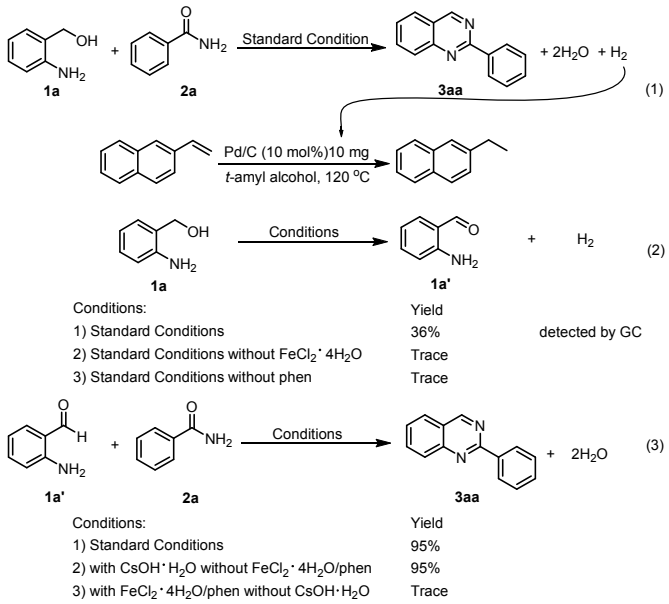
[h] Using **2a** (1.2 mmol).

Optimization of the reaction conditions revealed that the best yield was obtained with **1** (1 mmol), **2** (1.5 equiv.) and $CsOH \cdot H_2O$ (0.7 equiv.) in refluxing toluene for 24 h (Table 1, entry 26). The scope of possible substrates was next explored (Table 2). Arylamides **2a**-**2f** and **2j** bearing *para* electron donating substituents on phenyl rings were readily coupled with **1a** to give the corresponding quinazolines **3aa**-**3af** and **3aj** in 78-91% yield. The use of electron-withdrawing arylamides **2g**-**2i** (*para*) and **2j**-**2n** (*meta*) afforded the desired products **3ag**-**2ai**, **3aj**-**3an** in the lower yield range of 60–72%. Steric hindrance of the reactive functionality similarly had a detrimental influence on yield (Table 2, entries 15-16). 2-Methylbenzamide was reacted with **1a** to generate **3aq** in 71% yield. 2-Naphthamide was converted to the corresponding quinazoline **3ar** in a high yield of 92%. Heteroatom-containing substrates like nicotinamide also delivered the corresponding quinazolines **3as** and **3at** in moderate yields.

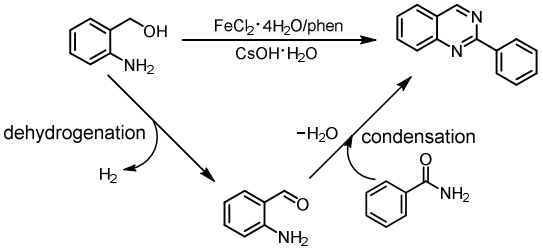
Next, the substrate scope of the partner 2-amino-benzyl was studied (Table 2, entries 21–26) and revealed that deactivating groups or steric hindrance similarly had a deleterious influence on yield. The dehydrogenative condensation/coupling reaction of 2-amino-5-methylbenzyl alcohol (**1b**) with **2a**, [1,1'-biphenyl]-4-carboxamide (**2f**), or 2-naphthamide (**2r**) gave the desired products **3ba**, **3bf** and **3br** in a good 76-81% yield. Chloro-substituted **1c** reacted less efficiently with **2a**, **2b** or **2r**, affording the respective products **3ca**, **3cb** and **3cr** in 54-69% yield. Sterically hindered 1-(2-aminophenyl)ethan-1-ol (**1d**) coupled with **2a** to afford the cyclized product **3da** in 43% isolated yield. This dehydrogenative condensation/coupling reaction of **1a** (1.11 g, 9 mmol) and **2a** (1.63 g, 13.5 mmol) also worked on the gram-scale to give **3aa** in 41% yield (0.76 g) under the optimized conditions.

Molecular hydrogen as by-product was identified by gas chromatography (GC) during the dehydrogenative condensation/coupling reaction of **1a** and **2a** to give **3aa** (see supporting information, Fig. S1). Likewise, when this model reaction was connected with a second reaction vessel containing 2-vinylnaphthalene and Pd/C, 2-ethylnaphthalene was formed (Fig. S2), confirming the generation of H_2 (eqn 1, Scheme 2). The reaction of only (2-aminophenyl)methanol with $FeCl_2 \cdot 4H_2O$, phen and $CsOH \cdot H_2O$ in refluxing toluene for 24 h afforded the dehydrogenated product 2-aminobenzaldehyde (**1a'**) in 36% isolated yield, together with H_2 (identified by GC analysis) (Fig. S1). This reaction did not proceed without the addition of $FeCl_2 \cdot 4H_2O$ or phen in refluxing toluene (eqn 2, Scheme 2). The condensation of 2-aminobenzaldehyde **1a'** with **2a** resulted in the formation of **3aa**. This reaction occurred in the absence of $FeCl_2 \cdot 4H_2O$ and phen, but did not proceed without CsOH (eqn 3, Scheme 2).

Based on the studies above and on relevant literature [54-62], we propose a mechanism for ADC transformation proceeding through a one-pot dehydrogenation of (2-aminophenyl)methanol to the corresponding aldehyde followed by base-promoted condensation with benzamide to form quinazoline (Scheme 3).



Scheme 2. Verification experiments

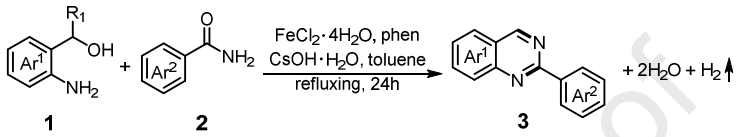


Scheme 3. Proposed mechanism

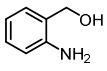
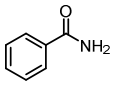
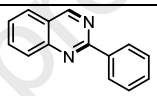
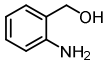
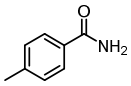
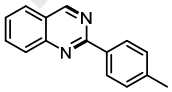
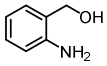
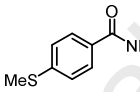
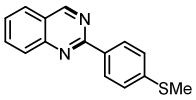
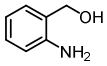
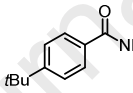
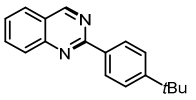
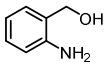
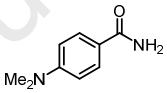
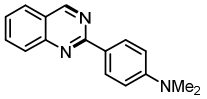
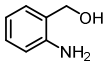
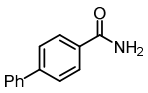
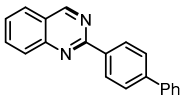
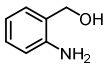
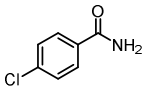
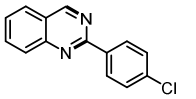
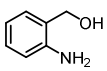
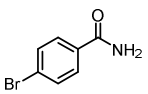
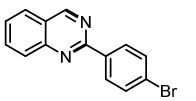
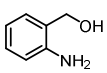
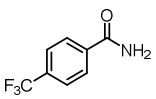
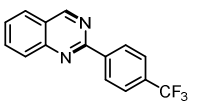
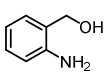
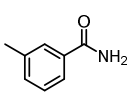
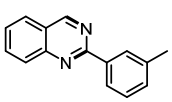
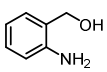
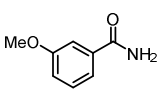
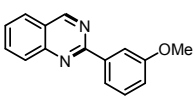
3. Conclusions

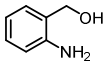
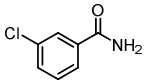
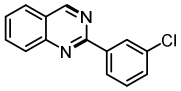
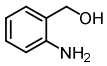
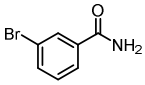
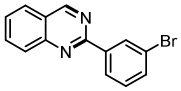
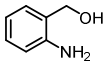
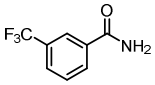
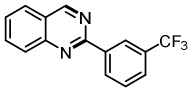
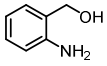
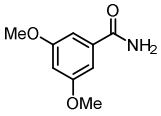
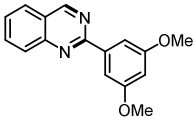
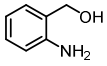
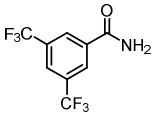
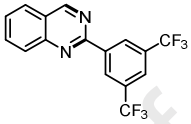
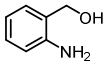
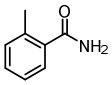
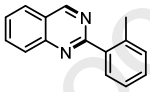
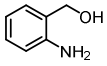
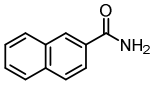
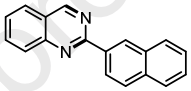
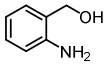
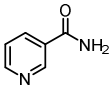
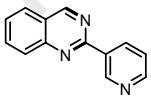
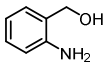
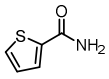
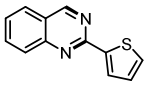
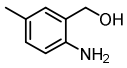
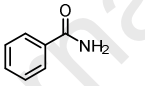
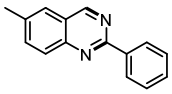
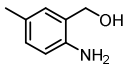
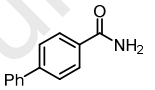
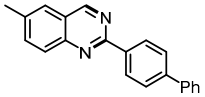
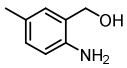
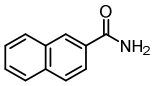
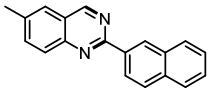
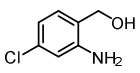
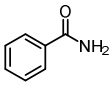
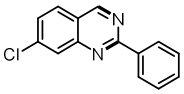
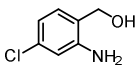
In summary, we have developed a sustainable and operationally simple method for synthesis of quinazoline derivatives via iron-catalysed acceptorless dehydrogenative condensation/coupling reaction of (2-aminophenyl)methanol with benzamides under mild reaction conditions. A series of substituted benzamides efficiently reacted with various (2-aminophenyl)methanols, furnishing the desired products and only H_2 and H_2O as by-products. This protocol had high functional group tolerance, did not require the use of toxic phosphine ligands, stoichiometric oxidants or t-BuOK as strong base. The construction of other heterocycles catalyzed by iron catalysts is undergoing in our lab.

Table 2 Synthesis of quinazolines.



1 2 3

Entry[a]	1		2		Product		Yield (%)[b]
1		**1a**		**2a**		**3aa**	87%
2		**1a**		**2b**		**3ab**	88%
3		**1a**		**2c**		**3ac**	78%
4		**1a**		**2d**		**3ad**	85%
5		**1a**		**2e**		**3ae**	91%
6		**1a**		**2f**		**3af**	89%
7		**1a**		**2g**		**3ag**	68%
8		**1a**		**2h**		**3ah**	72%
9		**1a**		**2i**		**3ai**	60%
10		**1a**		**2j**		**3aj**	84%
11		**1a**		**2k**		**3ak**	63%

12		**1a**		**2l**		**3al**	65%
13		**1a**		**2m**		**3am**	70%
14		**1a**		**2n**		**3an**	63%
15		**1a**		**2o**		**3ao**	56%
16		**1a**		**2p**		**3ap**	51%
17		**1a**		**2q**		**3aq**	71%
18		**1a**		**2r**		**3ar**	92%
19		**1a**		**2s**		**3as**	43%
20		**1a**		**2t**		**3at**	53%
21		**1b**		**2a**		**3ba**	76%
22		**1b**		**2f**		**3bf**	81%
23		**1b**		**2r**		**3br**	81%
24		**1c**		**2a**		**3ca**	54%
25		**1c**		**2b**		**3cb**	58%
26		**1c**		**2r**		**3cr**	69%
27		**1d**		**2a**		**3da**	43%

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), $FeCl_2 \cdot 4H_2O$ (10 mol%), phen (20 mol%) and $CsOH \cdot H_2O$ (0.7 mmol), refluxing in 2 mL toluene under N_2, 24 h.
[b] Isolated yield.

4. Experimental

4.1. General

All reagents were used as obtained from commercial sources without further purification. All solvents were obtained from commercial sources and were purified according to standard procedures. Column chromatography was performed on silica gel. ^{1}H (400 MHz), ^{13}C (101 MHz or 150 MHz) and ^{19}F (376 MHz) NMR spectra were recorded at ambient temperature on a Varian UNITY plus-400 spectrometer and Bruker Avance III HD spectrometer. HPLC was conducted on a LC-20A with MeCN and H_2O as the mobile phase. High resolution mass spectra (HRMS) were obtained with a MICRO TOF-Q III. IR spectra (KBr disk) were recorded on a Nicolet MagNa-IR550 FT-IR spectrometer (4000-400 cm^{-1}).

4.2. General procedure for synthesis of quinazolines

A 25 mL Schenk tube containing **1** (1.0 mmol), **2** (1.5 mmol), $FeCl_2 \cdot 4H_2O$ (10 mol%), phen (20 mol%) and $CsOH \cdot H_2O$ (0.7 mmol) was evacuated and flushed with nitrogen three times. Dried toluene (2 mL) was added under an N_2 atmosphere. The tube was then placed in an oil bath at 130 °C. The reaction was continued for 24 h under a slow and steady N_2 flow. After cooling to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using petroleum ether and ethyl acetate as eluent.

*4.2.1. 2-phenylquinazoline (**3aa**) [37]*

White solid (180 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.47 (s, 1H), 8.62 (d, J = 6.8 Hz, 2H), 8.10 (d, J = 8.3 Hz, 1H), 7.92 (t, J = 9.4 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.54 (d, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 161.0, 160.5, 150.7, 138.0, 134.1, 130.6, 128.6, 128.6, 127.2, 127.1, 123.6. HRMS (CI-TOF) *m/z* calcd for $C_{15}H_{12}N_2$ $[M + H]^+$ 207.0917, found 207.0928.

*4.2.2. 2-(p-tolyl)quinazoline (**3ab**) [37]*

White solid (195 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.45 (s, 1H), 8.52 (d, J = 7.9 Hz, 2H), 8.08 (d, J = 8.3 Hz, 1H), 7.89 (t, J = 8.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.34 (d, J = 7.9 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 161.1, 160.4, 150.7, 140.9, 135.2, 134.1, 129.4, 128.5, 128.5, 127.1, 127.0, 123.5, 21.5. HRMS (CI-TOF) m/z calcd for $C_{15}H_{12}N_2$ $[M + H]^+$ 221.1073, found 221.1079.

*4.2.3. 2-(4-(methylthio)phenyl)quinazoline (**3ac**) [56]*

Yellow solid (197 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.44 (s, 1H), 8.54 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.0 Hz, 1H), 7.91 (t, J = 8.0 Hz, 2H), 7.69 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 160.7, 160.4, 150.8, 142.0, 134.6, 134.1, 128.9, 128.5, 127.1, 127.0, 125.8, 123.5, 15.3. HRMS (CI-TOF) *m/z* calcd for $C_{15}H_{13}N_2S$ $[M + H]^+$ 253.0794; found: 253.0799.

*4.2.4. 2-(4-(tert-butyl)phenyl)quinazoline (**3ad**) [57]*

White solid (224 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.48 (s, 1H), 8.55 (d, J = 7.8 Hz, 2H), 8.15 (d, J = 8.0 Hz, 1H), 7.92 (t, J = 8.8 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.57 (d, J = 7.8 Hz, 2H), 1.39 (s, 10H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 160.9, 160.5, 154.2, 150.6, 134.9, 134.3, 128.5, 128.4, 127.2, 127.2, 125.7, 123.4, 34.9, 31.3. HRMS (CI-TOF) m/z calcd for $C_{18}H_{18}N_2$ $[M + H]^+$ 263.1543, found 263.1531.

*4.2.5. N,N-dimethyl-4-(quinazolin-2-yl)aniline (**3ae**) [56]*

Yellow solid (227 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.38 (s, 1H), 8.53 (d, J = 8.6 Hz, 2H), 8.05 (d, J = 7.3 Hz, 1H), 7.85 (t, J = 7.6 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 6.83 (d, J = 8.6 Hz, 2H), 3.08 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 161.4, 160.2, 152.2, 150.9, 133.8, 129.9, 128.1, 127.1, 126.1, 125.6, 123.0, 111.7, 40.2. HRMS (CI-TOF) *m/z* calcd for $C_{16}H_{15}N_3$ $[M + H]^+$ 250.1339, found 250.1321.

*4.2.6. 2-([1,1'-biphenyl]-4-yl)quinazoline (**3af**) [40]*

White solid (252 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.51 (s, 1H), 8.72 (d, J = 8.2 Hz, 2H), 8.16 (d, J = 8.3 Hz, 1H), 7.94 (t, J = 8.8 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 7.5 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 160.6, 150.5, 143.5, 140.5, 136.5, 134.4, 129.1, 128.8, 128.4, 127.7, 127.4, 127.4, 127.2, 127.2, 123.5. HRMS (CI-TOF) *m/z* calcd for $C_{20}H_{14}N_2$ $[M + H]^+$ 283.1230, found 283.1228.

*4.2.7. 2-(4-chlorophenyl)quinazoline (**3ag**) [57]*

White solid (164 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.47 (s, 1H), 8.59 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 8.4 Hz, 1H), 7.94 (t, J = 8.1 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 160.5, 159.9, 150.5, 137.0, 136.2, 134.4, 129.9, 128.8, 128.5, 127.6, 127.2, 123.6. HRMS (CI-TOF) *m/z* calcd for $C_{14}H_9ClN_2$ $[M + H]^+$ 241.0527, found 241.0544

*4.2.8. 2-(4-bromophenyl)quinazoline (**3ah**) [57]*

White solid (205 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.44 (s, 1H), 8.50 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.6 Hz, 1H), 7.91 (t, J = 7.4 Hz, 2H), 7.66 (s, 1H), 7.65–7.57 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 160.59, 160.0, 150.6, 136.8, 134.3, 131.8, 130.1, 128.6, 128.5, 127.5, 127.1, 125.4, 123.6. HRMS (CI-TOF) m/z calcd for $C_{14}H_9BrN_2$ $[M + H]^+$ 285.0022, found 284.9985.

*4.2.9. 2-(4-(trifluoromethyl)phenyl)quinazoline (**3ai**) [57]*

White solid (165 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.53 (s, 1H), 8.77 (d, J = 7.9 Hz, 2H), 8.24–8.11 (m, 1H), 7.98 (t, J = 8.1 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.69 (t, J = 7.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 160.6, 159.5, 150.6, 141.2, 134.5, 132.2 (d, J = 32 Hz), 128.9, 128.7, 128.0, 127.2, 125.6 (q, J = 3.8 Hz), 123.8. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -62.67. HRMS (CI-TOF) *m/z* calcd for $C_{15}H_9F_3N_2$ $[M + H]^+$ 275.0791, found 275.0788..

*4.2.10. 2-(m-tolyl)quinazoline **(3aj)** [57]*

White solid (186 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.47 (s, 1H), 8.42 (d, J = 10.4 Hz, 2H), 8.11 (d, J = 8.3 Hz, 1H), 7.91 (t, J = 8.1 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.33 (d, J = 7.2 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 161.1, 160.5, 150.7, 138.3, 137.8, 134.2, 131.5, 129.1, 128.6, 127.2, 127.1, 125.8, 123.6, 21.5. HRMS (CI-TOF) *m/z* calcd for $C_{15}H_{12}N_2$ $[M + H]^+$ 221.1073, found 221.1078.

*4.2.11. 2-(3-methoxyphenyl)quinazoline (**3ak**) [57]*

White solid (150 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.48 (s, 1H), 8.31–8.17 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H), 7.93 (t, J = 9.5 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (151

MHz, $CDCl_3$, ppm) δ 160.7, 160.4, 160.0, 150.6, 139.2, 134.2, 129.6, 128.6, 127.4, 127.1, 123.6, 121.2, 117.4, 113.0, 55.5. HRMS (CI-TOF) *m/z* calcd for $C_{15}H_{12}N_2O$ $[M + H]^+$ 237.1022, found 237.1021.

*4.2.12. 2-(3-chlorophenyl)quinazoline (**3al**) [57]*

White solid (157 mg, 65%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.50 (s, 1H), 8.65 (s, 1H), 8.54 (s, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.96 (t, *J* = 7.7 Hz, 2H), 7.67 (t, *J* = 7.3 Hz, 1H), 7.49 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 160.6, 159.4, 150.5, 139.4, 134.8, 134.6, 130.7, 129.9, 128.7, 128.5, 127.8, 127.2, 126.7, 123.7. HRMS (CI-TOF) *m/z* calcd for $C_{14}H_9ClN_2$ $[M + H]^+$ 241.0527, found 241.0526.

*4.2.13. 2-(3-bromophenyl)quinazoline (**3am**) [57]*

White solid (200 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.50 (s, 1H), 8.81 (s, 1H), 8.60 (d, *J* = 7.7 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.97 (t, *J* = 7.7 Hz, 2H), 7.67 (dd, *J* = 14.0, 7.2 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 160.5, 159.3, 150.5, 139.7, 134.6, 133.6, 131.6, 130.2, 128.5, 127.8, 127.2, 127.2, 123.7, 122.9. HRMS (CI-TOF) *m/z* calcd for $C_{14}H_9BrN_2$ $[M + H]^+$ 285.0022, found 284.9984

*4.2.14. 2-(3-(trifluoromethyl)phenyl)quinazoline (**3an**) [40]*

White solid (173 mg, 63%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.50 (s, 1H), 8.94 (s, 1H), 8.84 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.95 (t, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 160.7, 159.4, 150.6, 138.6, 134.6, 131.7, 131.3, 131.0, 129.1, 128.7, 127.9, 127.2 (dd, *J* =8.7, 5.0 Hz), 125.6 (q, *J* = 4.0 Hz), 123.8, 122.9. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -62.54. HRMS (CI-TOF) *m/z* calcd for $C_{15}H_9F_3N_2$ $[M + H]^+$ 275.0791, found 275.0809.

*4.2.15. 2-(3,5-dimethoxyphenyl)quinazoline (**3ao**)*

White solid (150 mg, 56%). Mp: 77.0–78.0 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.48 (s, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 7.94 (t, *J* = 7.7 Hz, 2H), 7.85 (s, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 6.65 (s, 1H), 3.94 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 161.1, 160.4, 150.4, 139.6, 134.4, 128.5, 127.5, 127.1, 123.6, 106.3, 104.1, 55.6. HRMS (CI-TOF) *m/z* calcd for $C_{16}H_{14}N_2O_2$ $[M + H]^+$ 267.1128, found 267.1099. IR (KBr disk, cm^{-1}): 3001 (w), 2833 (w), 2026 (m), 1575 (s), 1553 (m), 1489 (w), 1400 (m), 1348 (s), 1306 (m), 1045 (m), 728 (m), 717 (m).

*4.2.16. 2-(3,5-bis(trifluoromethyl)phenyl)quinazoline (**3ap**) [30]*

Yellow solid (175 mg, 51%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.49 (s, 1H), 9.13 (s, 2H), 8.14 (d, *J* = 8.6 Hz, 1H), 8.03–7.93 (m, 3H), 7.70 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 160.8, 157.9, 150.5, 134.0, 134.7, 132.0 (q, *J* = 33.5 Hz), 128.7, 128.6(d *J* = 2.8 Hz), 128.3, 127.2, 124.3, 124.0, 123.8(m), 122.5. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -62.76, -62.92. HRMS (CI-TOF) *m/z* calcd for $C_{16}H_8F_6N_2$ $[M + H]^+$ 343.0664, found 343.0653.

4.2.17. 2-(o-tolyl)quinazoline (3aq) [34]

White solid (157 mg, 71%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.52 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.02–7.86 (m, 3H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 6.6 Hz, 3H), 2.61 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 163.9, 160.0, 150.3, 138.3, 137.4, 134.2, 131.3, 130.6, 129.4, 128.5, 127.6, 127.1, 126.0, 122.9, 21.0. HRMS (CI-TOF) *m/z* calcd for $C_{15}H_{12}N_2$ $[M + H]^+$ 221.1073, found 221.1062.

*4.2.18. 2-(naphthalen-2-yl)quinazoline (**3ar**) [34]*

White solid (236 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.54 (s, 1H), 9.18 (s, 1H), 8.74 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 6.6 Hz, 1H), 8.03–7.88 (m, 4H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.60–7.45 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 160.8, 160.6, 150.6, 135.0, 134.7, 134.4, 133.4, 129.3, 129.1, 128.5, 128.3, 127.7, 127.4, 127.2, 127.2, 126.3, 125.4, 123.6. HRMS (CI-TOF) *m/z* calcd for $C_{18}H_{12}N_2$ $[M + H]^+$ 257.1073, found 257.1063.

*4.2.19. 2-(pyridin-3-yl)quinazoline (**3as**) [37]*

White solid (89 mg, 43%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.84 (s, 1H), 9.50 (s, 1H), 8.95 (d, *J* = 7.7 Hz, 1H), 8.75 (d, *J* = 3.5 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.97 (t, *J* = 8.5 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.61–7.43 (m, 1H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 160.7, 158.8, 150.6, 150.2, 149.4, 136.5, 134.5, 134.0, 128.7, 127.9, 127.2, 123.9, 123.7. HRMS (CI-TOF) *m/z* calcd for $C_{13}H_9N_3$ $[M + H]^+$ 208.0869, found 208.0865

*4.2.20. 2-(thiophen-2-yl)quinazoline (**3at**) [37]*

White solid (113 mg, 53%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.37 (s, 1H), 8.21 (d, *J* = 1.6 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.96–7.83 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 4.7 Hz, 1H), 7.21 (t, *J* = 4.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 160.7, 157.7, 150.3, 143.5, 134.5, 130.2, 129.5, 128.5, 128.0, 127.3, 127.1, 123.3. HRMS (CI-TOF) *m/z* calcd for $C_{12}H_8N_2S$ $[M + H]^+$ 213.0481, found 213.0455

*4.2.21. 6-methyl-2-phenylquinazoline (**3ba**) [56]*

Yellow solid (168 mg, 76%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.43 (s, 1H), 8.62 (d, *J* = 7.0 Hz, 2H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.72 (s, 1H), 7.62–7.48 (m, 3H), 2.59 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 159.8, 149.0, 137.9, 137.3, 137.0, 130.7, 128.7, 128.6, 128.0, 125.9, 123.5, 21.7. HRMS (CI-TOF) *m/z* calcd for $C_{15}H_{12}N_2$ $[M + H]^+$ 221.1073, found 221.1064

*4.2.22. 2-([1,1'-biphenyl]-4-yl)-6-methylquinazoline (**3bf**)*

White solid (241 mg, 81%). Mp: 159.9–160.9 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.40 (s, 1H), 8.68 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.76 (t, *J* = 8.1 Hz, 3H), 7.70 (d, *J* = 6.2 Hz, 3H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.1 Hz, 1H), 2.58 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 160.0, 159.8, 149.3, 143.1, 140.6, 137.5, 136.9, 136.5, 128.9, 128.8, 128.2, 127.6, 127.3, 127.2, 125.8, 123.6, 21.6. HRMS (CI-TOF) *m/z* calcd for $C_{21}H_{16}N_2$ $[M + H]^+$ 297.1386, found 297.1383. IR (KBr disk, cm^{-1}): 2831 (w), 2779 (w), 2026 (m), 1631 (s), 1597 (s), 1424 (m), 1367 (s), 1352 (s), 1060 (w), 829 (m), 756 (m), 734 (m).

*4.2.23. 6-methyl-2-(naphthalen-2-yl)quinazoline (**3br**)*

Yellow solid (220 mg, 81%). Mp: 179.3–180.3 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.43 (s, 1H), 9.14 (s, 1H), 8.72 (d, *J* = 8.5 Hz, 1H), 8.02 (dd, *J* = 25.5, 8.5 Hz, 3H), 7.90 (d, *J* = 5.4 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.71 (s, 1H), 7.59–7.45 (m, 2H), 7.26 (s, 1H), 2.58 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 160.2, 159.8, 149.3, 137.6, 136.6, 135.2, 134.6, 133.4, 129.2, 128.8, 128.2, 128.2, 127.7, 127.0, 126.2, 125.9, 125.3, 123.6, 21.7. HRMS (CI-TOF) *m/z* calcd for $C_{19}H_{14}N_2$ $[M + H]^+$ 271.1230, found 271.1235. IR (KBr disk, cm^{-1}): 2831 (w), 2779 (w), 2026 (w), 1631 (s), 1596 (s), 1555 (m), 1365 (s), 1354 (s), 1186 (m), 951 (w), 830 (m), 747 (m).

*4.2.24. 7-chloro-2-phenylquinazoline (**3ca**) [40]*

Yellow solid (130 mg, 54%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.43 (s, 1H), 8.60 (d, *J* = 5.2 Hz, 2H), 8.09 (s, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.64–7.42 (m, 4H). ^{13}C NMR (101 MHz,

$CDCl_3$, ppm) δ 161.9, 160.2, 151.3, 140.4, 137.6, 131.0, 128.7, 128.5, 128.4, 127.8, 122.0. HRMS (CI-TOF) *m/z* calcd for $C_{19}H_9ClN_2$ $[M + H]^+$ 240.0454, found 240.0451

*4.2.25. 7-chloro-2-(p-tolyl)quinazoline (**3cb**) [57]*

Yellow solid (147 mg, 58%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.43 (d, J = 17.5 Hz, 1H), 8.50 (t, J = 7.3 Hz, 2H), 8.08 (d, J = 8.2 Hz, 1H), 7.95–7.81 (m, 1H), 7.64–7.51 (m, 1H), 7.34 (d, J = 7.7 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 162.0, 161.2, 160.5, 160.1, 151.4, 150.8, 141.4, 140.9, 140.3, 135.3, 134.9, 134.1, 129.5, 129.4, 128.7, 128.5, 128.4, 128.2, 127.7, 127.1, 127.1, 123.5, 121.9, 21.6. HRMS (CI-TOF) *m/z* calcd for $C_{15}H_{11}ClN_2$ $[M + H]^+$ 254.0611, found 254.0618.

*4.2.26. 7-chloro-2-(naphthalen-2-yl)quinazoline (**3cr**)*

Yellow solid (200 mg, 69%). Mp: 192.3–193.3 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.48 (s, 1H), 9.15 (s, 1H), 8.70 (d, J = 8.6 Hz, 1H), 8.14 (s, 1H), 8.02 (dd, J = 19.3, 7.8 Hz, 2H), 7.89 (t, J = 7.7 Hz, 2H), 7.57 (d, J = 8.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 161.9, 160.2, 151.4, 140.5, 134.9, 133.4, 129.4, 129.3, 128.5, 128.5, 128.4, 127.8, 127.8, 127.3, 126.4, 125.3, 122.0. HRMS (CI-TOF) *m/z* calcd for $C_{18}H_{11}ClN_2$ $[M + H]^+$ 290.0611, found 290.0601. IR (KBr disk, cm^{-1}): 2831 (w), 2779 (w), 2026 (m), 1631 (s), 1598 (s), 1383 (m), 1364 (m), 1065 (m), 739 (w), 787 (m), 772 (m).

*4.2.27. 4-methyl-2-phenylquinazoline (**3da**) [57]*

White solid (91 mg, 41%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.07 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 10.4 Hz, 3H), 7.53 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 6.81 (t, J = 9.0 Hz, 2H), 2.75 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 158.8, 147.2, 146.5, 144.9, 130.2, 129.8, 129.3, 129.2, 126.5, 125.9, 123.5, 121.7, 121.1, 117.5, 117.3, 19.0. HRMS (CI-TOF) *m/z* calcd for $C_{15}H_{12}N_2$ $[M + H]^+$ 221.1073, found 221.1075.

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Supplementary data

The identification of molecular hydrogen by gas chromatography and ^1H and ^{13}C NMR spectra for the isolated products for this article can be found in online version at doi:

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Highlights

► The Fe-catalyzed acceptorless dehydrogenative coupling of (2-aminophenyl)methanols and benzamides produces quinazolines.

► This simple catalytic system is atom-economical, environmentally benign.

► This coupling reaction is suited to various substrates under mild conditions.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: