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Synthesis of 2-substituted quinazolines *via* iridium catalysis†

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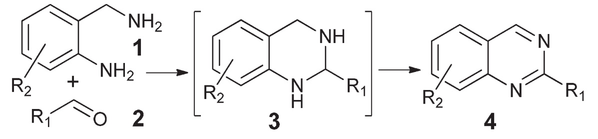
An iridium-catalyzed hydrogen transfer reaction was successfully applied in the synthesis of 2-substituted quinazolines in moderate yields starting from aldehydes or alcohols with 2-aminobenzylamines.

Quinazolines occur frequently in natural products and synthetic pharmaceuticals which exhibit important biological properties,[1] such as antidiabetic, antibacterial, anticonvulsant and anticancer activities. For example, prazosin was an effective medicine as α-adrenergic blockers for the treatment of high blood pressure, panic disorder and anxiety,[2] and lapatinib was used to treat solid tumor and breast cancer.[3]

Syntheses of substituted quinazolines have been widely explored,[4] and many efficient methods have been developed recently. As shown in Scheme 1, one of the synthetic methods to quinazolines utilizes condensations between aldehydes **2** and 2-aminobenzylamines **1** followed by oxidation of the aminal intermediate **3**. However, stoichiometric or large excess amounts of toxic oxidants were required for this oxidation; *e.g.*, DDQ, *p*-chloranil,[4c] NaClO[4k] and MnO_2 [4l] were used. In continuation of our work in the application of hydrogen transfer catalysis in the syntheses of quinazolinones,[5] we were interested to test if a hydrogen transfer catalyst[6] will catalyze the oxidation of aminal **3** to 2-substituted quinazoline **4** in one-pot as shown in Scheme 1.

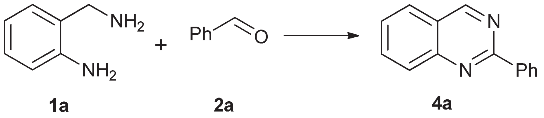


Scheme 1 One-pot synthesis of quinazolines.

Firstly, 2-aminobenzylamine **1a** with benzaldehyde **2a** was selected as the model substrate to test the one-pot reaction and the results are summarized in Table 1. We discovered that without a hydrogen acceptor, only 10% product **4a** was formed using $[Cp^*IrCl_2]_2$ (2.5 mol%) as the catalyst (Cp* = pentamethylcyclopentadienyl, entry 1). The major byproduct isolated was the *N*-benzylation product **5**[7] as shown in Scheme 2.

This byproduct formation could have originated from hydrogen transfer[8] to the imine intermediate **6**. Compound **5** could not be further transformed to the product quinazoline **4a** under hydrogen transfer catalysis, which accounted for the low yield of **4a** in this reaction. To improve the yields of **4a**, we decided to add a hydrogen acceptor to the reaction mixture. To our delight, the

Table 1 Optimization of conditions for the synthesis of quinazoline **4a** between **1a** and **2a**[a]



Entry	Catalyst	Additive	Acceptor	Solvent	Yield[b]
1	$[Cp^*IrCl_2]_2$	No	No	xylene	10%
2	$[Cp^*IrCl_2]_2$	No	styrene	xylene	66%[c]
3	$[Cp^*IrCl_2]_2$	No	*E*-crotonitrile	xylene	50%[c]
4	$[Cp^*IrCl_2]_2$	AcOH 0.2 eq.	styrene	xylene	43%
5	$[Cp^*IrCl_2]_2$	KOH 0.2 eq.	styrene	xylene	54%
6	$[Cp^*IrCl_2]_2$	*t*-BuONa 0.2 eq.	styrene	xylene	60%
7	$[Cp^*IrCl_2]_2$	K_2CO_3 0.2 eq.	styrene	xylene	46%
8	$[Cp^*IrCl_2]_2$	No	styrene	toluene	35%
9	$[Cp^*IrCl_2]_2$	No	styrene	DMF	50%
10	$[Cp^*IrI_2]_2$	No	styrene	xylene	57%
11	$RuCl_2(PPh_3)_3$	KOH 0.2 eq.	styrene	xylene	26%
12	$[Ru(p\text{-cymene})Cl_2]_2$[d]	KOH 0.2 eq.	styrene	xylene	52%

[a] Conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (2.5 mol%), styrene (4.0 eq.) in refluxing temperature of the solvent listed (1 mL) under N_2, 24 h. [b] H-NMR yield. [c] Isolated yield, 12% of byproduct **5** was also isolated in entry 2. [d] 2.5 mol% dppf was added.

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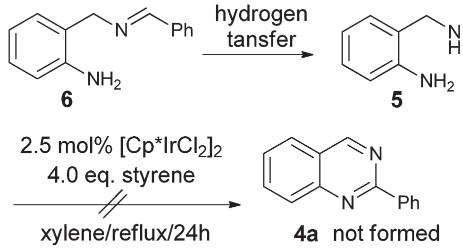
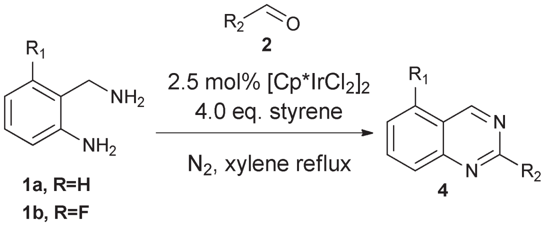


Scheme 2 Possible pathway to **5** from hydrogenation of imine **6** and reaction of **5** under hydrogen transfer conditions.

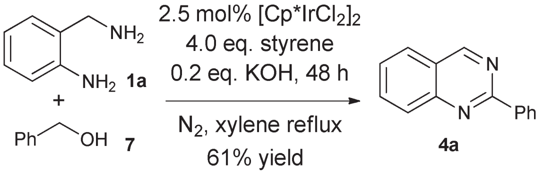
yields of **4a** were improved to 66% with addition of styrene (entry 2) and 50% with *E*-crotonitrile (entry 3). Further optimizations of the reaction by using acid or base additives were also tried (entries 4 to 7), but the best yield of 60% obtained by addition of NaOtBu (entry 6) was inferior to the results of 66% without such additives in entry 2. The effects of solvents (entries 8 and 9) and catalysts (entries 10 to 12) were also examined briefly with no increase of the yield of **4a.** After examining the reaction profiles, we decided to select the conditions of entry 2 (2.5 mol% [Cp*IrCl$_2$]$_2$ in refluxing xylene with addition of 4.0 eq. styrene) for our investigations of the substrate scope of the reaction.

Table 2 One-pot synthesis of quinazolines *via* Ir-catalyzed hydrogen transfers[a]



Entry	R_1	R_2	Yield[b]
1	H	C_6H_5	**4a** 66%
2	H	3–Cl–C_6H_4	**4b** 54%
3	H	3–Br–C_6H_4	**4c** 48%
4	H	3–NO_2–C_6H_4	**4d** 58%
5	H	3–Me–C_6H_4	**4e** 54%
6	H	3–OMe–C_6H_4	**4f** 51%
7	H	4–F–C_6H_4	**4g** 51%
8	H	4–Br–C_6H_4	**4h** 55%
9	H	4–NO_2–C_6H_4	**4i** 57%
10	H	4–Me–C_6H_4	**4j** 50%
11	H	Furyl	**4k** 55%
12	H	Benzyl	**4l** 49%
13	H	*n*-Pentanyl	**4m** 57%
14	F	C_6H_5	**4n** 56%
15	F	4–Br–C_6H_4	**4o** 60%
16	F	4–Me–C_6H_4	**4p** 62%
17	F	*n*-Pentanyl	**4q** 65%

[a] Conditions: Entries 1–13: **1a** (1.0 mmol), **2** (1.0 mmol), catalyst (2.5 mol%), styrene (4.0 eq.) in refluxing xylene (2 mL) under N_2, 24 h. Entries 14–17: **1b** (1.0 mmol), **2** (1.0 mmol), catalyst (2.5 mol%), styrene (4.0 eq.) in refluxing xylene (2 mL) under N_2, 24 h. [b] Isolated yield.

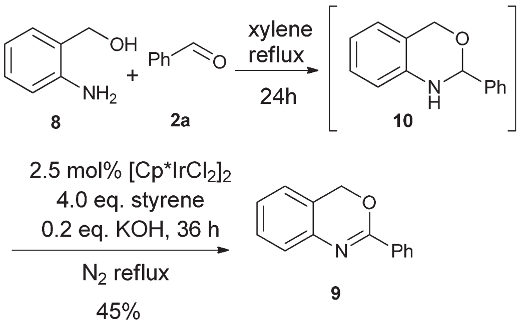


Scheme 3 One-pot synthesis of 2-phenylquinazoline starting with benzyl alcohol.

Subsequently, a variety of substituted quinazolines were synthesized using our optimized conditions. As shown in Table 2, both aliphatic and aromatic aldehydes reacted with 2-aminobenzylamines to give the corresponding quinazolines **4** in moderate yields. Reactions between **1a** and aromatic aldehydes with either electron-withdrawing or electron-donating groups (entries 2 to 10) showed that the yields were not affected significantly in the range of 48% to 58%. Furthermore, the reactions also performed well when 2-furyl aldehyde (55% yield, entry 11), 2-phenylacetaldehyde (49% yield, entry 12) and hexanal (57% yield, entry 13) were involed. Investigations of 2-(aminomethyl)-3-fluoroaniline **1b** with several aldehydes again gave substituted quinazolines **4n** to **4q** in moderate yields (56% to 65%, entries 14 to 17).

It was our next interest to test the employment of benzyl alcohol **7** instead of benzaldehyde **2a** in the synthesis of quinazoline **4a.** The above described conditions using benzaldehyde did not give a satisfactory yield of **4a** (only 10%) when benzylalcohol **7** was used. Some optimizations (see supporting information, ESI†) identified that the addition of base additives, such as KOH (0.2 eq.) was necessary to increase the yield of **4a** to 61% (Scheme 3).

When 2-aminobenzyl alcohol **8** was used, the condensation with benzaldehydes **2a** gave 2-phenyl-4*H*-benzo[d][1,3]oxazine **9** in 45% yield as shown in Scheme 4.[9] The optimized conditions also involved the use of KOH (2 eq.) to give a better yield (see supporting information, ESI†).



Scheme 4 One-pot synthesis of 2-phenyl-4*H*-benzo[d][1,3] oxazine between **8** and **2a**.

Conclusion

We have demonstrated a one-pot synthesis of 2-substituted quinazolines between 2-aminobenzylamines **1** and aldehydes **2** *via* iridium-catalyzed hydrogen transfers using styrene as a hydrogen acceptor. The use of benzyl alcohol **7** instead of benzyaldehyde also successfully gave a quinazoline product in moderate yield. Further extension for the synthesis of 4*H*-3,1-benzoxazine was also demonstrated by the example using 2-aminobenzyl alcohol **8**.

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7 Compound **5** was formed in 5% under these conditions; intermediates of **3** and **6** were also detactable in LC-MS.

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9 The assay yield of intermediate **10** is 62%, the rest of compound **8** decomposed under the reaction conditions, which accounted for the overall lower yield of compound **9**.