

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

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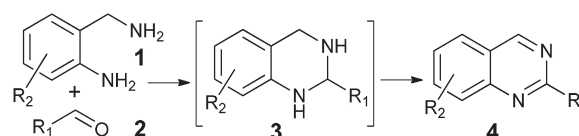
An iridium-catalyzed hydrogen transfer reaction was successfully applied in the synthesis of 2-substituted quinazolines in moderate yields starting from aldehydes or alcohols with 2-aminobenzylamines.

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 amina 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 MnO₂^{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 catalyst⁶ will catalyze the oxidation of amina **3** to 2-substituted quinazoline **4** in one-pot as shown in Scheme 1.

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*IrCl₂]₂ (2.5 mol%) as the catalyst (Cp* = pentamethylcyclopentadienyl, entry 1). The major byproduct isolated was the *N*-benzylolation product **5**⁷ as shown in Scheme 2.

This byproduct formation could have originated from hydrogen transfer⁸ to the imine intermediate **6**. Compound **5** could not be



Scheme 1 One-pot synthesis of quinazolines.

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

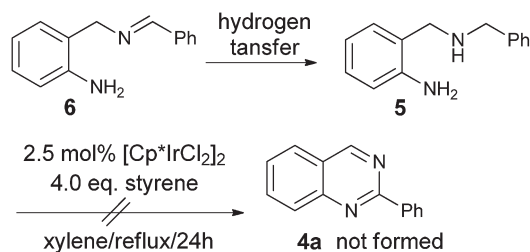
| Entry | Catalyst | Additive | Acceptor | Solvent | Yield ^b |
|-------|---|--|------------------------|---------|--------------------|
| 1 | [Cp*IrCl ₂] ₂ | No | No | xylene | 10% |
| 2 | [Cp*IrCl ₂] ₂ | No | styrene | xylene | 66% ^c |
| 3 | [Cp*IrCl ₂] ₂ | No | <i>E</i> -crotonitrile | xylene | 50% ^c |
| 4 | [Cp*IrCl ₂] ₂ | AcOH | styrene | xylene | 43% |
| 5 | [Cp*IrCl ₂] ₂ | 0.2 eq. KOH | styrene | xylene | 54% |
| 6 | [Cp*IrCl ₂] ₂ | 0.2 eq. <i>t</i> -BuONa | styrene | xylene | 60% |
| 7 | [Cp*IrCl ₂] ₂ | 0.2 eq. K ₂ CO ₃ | styrene | xylene | 46% |
| 8 | [Cp*IrCl ₂] ₂ | No | styrene | toluene | 35% |
| 9 | [Cp*IrCl ₂] ₂ | No | styrene | DMF | 50% |
| 10 | [Cp*IrCl ₂] ₂ | No | styrene | xylene | 57% |
| 11 | RuCl ₂ (PPh ₃) ₃ | KOH | styrene | xylene | 26% |
| 12 | [Ru(<i>p</i> -cymene)Cl ₂] ₂ ^d | 0.2 eq. KOH | 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 N₂, 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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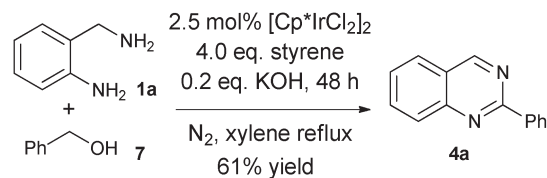
Scheme 2 Possible pathway to **5** from hydrogenation of imine **6** and reaction of **5** under hydrogen transfer conditions.

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% $[\text{Cp}^*\text{IrCl}_2]_2$ 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 | <i>n</i> -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 | <i>n</i> -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.

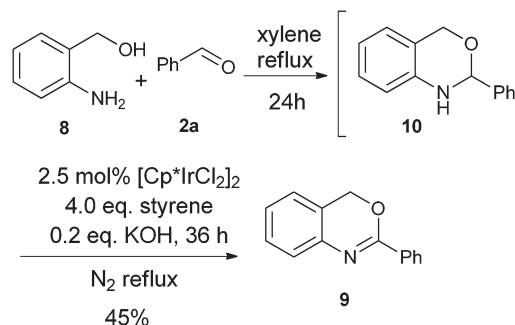


Scheme 3 One-pot synthesis of 2-phenylquinazoline starting with benzyl alcohol.

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 involved. Investigations of 2-(amino-methyl)-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 benzaldehyde 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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- Compound **5** was formed in 5% under these conditions; intermediates of **3** and **6** were also detectable in LC-MS.
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- 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**.