

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

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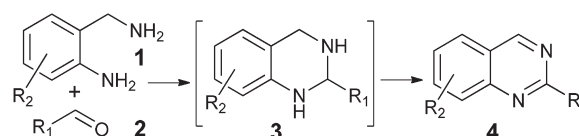
An iridium-catalyzed hydrogen transfer reaction was successfully applied in the synthesis of 2-substituted quinazolines in moderate yields starting from aldehydes or alcohols with 2-aminobenzylamines.

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

Syntheses of substituted quinazolines have been widely explored,<sup>4</sup> 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 amination intermediate **3**. However, stoichiometric or large excess amounts of toxic oxidants were required for this oxidation; e.g., DDQ, *p*-chloranil,<sup>4c</sup> NaClO<sup>4k</sup> and MnO<sub>2</sub><sup>4l</sup> were used. In continuation of our work in the application of hydrogen transfer catalysis in the syntheses of quinazolines,<sup>5</sup> we were interested to test if a hydrogen transfer catalyst<sup>6</sup> will catalyze the oxidation of amination **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\*IrCl<sub>2</sub>]<sub>2</sub> (2.5 mol%) as the catalyst (Cp\* = pentamethylcyclopentadienyl, entry 1). The major byproduct isolated was the *N*-benzoylation product **5**<sup>7</sup> as shown in Scheme 2.

This byproduct formation could have originated from hydrogen transfer<sup>8</sup> 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**<sup>a</sup>

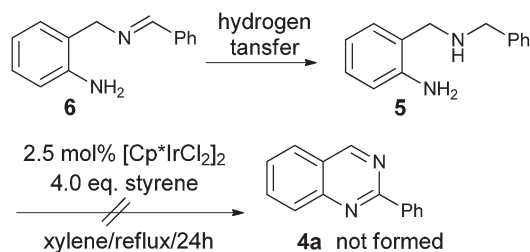
| Entry | Catalyst  | Additive                               | Acceptor               | Solvent | Yield <sup>b</sup> |
|-------|---|--|------------------------|---------|--------------------|
| 1     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                              | No                                     | No                     | xylene  | 10%                |
| 2     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                              | No                                     | styrene                | xylene  | 66% <sup>c</sup>   |
| 3     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                              | No                                     | <i>E</i> -crotonitrile | xylene  | 50% <sup>c</sup>   |
| 4     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                              | AcOH                                   | styrene                | xylene  | 43%                |
| 5     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                              | 0.2 eq. KOH                            | styrene                | xylene  | 54%                |
| 6     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                              | 0.2 eq. <i>t</i> -BuONa                | styrene                | xylene  | 60%                |
| 7     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                              | 0.2 eq. K <sub>2</sub> CO <sub>3</sub> | styrene                | xylene  | 46%                |
| 8     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                              | No                                     | styrene                | toluene | 35%                |
| 9     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                              | No                                     | styrene                | DMF     | 50%                |
| 10    | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                              | No                                     | styrene                | xylene  | 57%                |
| 11    | RuCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>3</sub>                | KOH                                    | styrene                | xylene  | 26%                |
| 12    | [Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> <sup>d</sup> | 0.2 eq. KOH                            | styrene                | xylene  | 52%                |

<sup>a</sup> 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<sub>2</sub>, 24 h. <sup>b</sup> H-NMR yield. <sup>c</sup> Isolated yield, 12% of byproduct **5** was also isolated in entry 2. <sup>d</sup> 2.5 mol% dppf was added.

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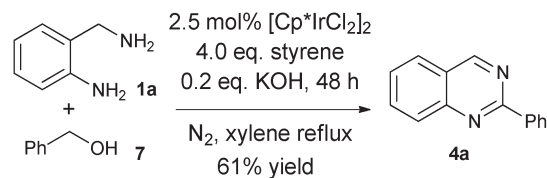
**Scheme 2** Possible pathway to **5** from hydrogenation of imine **6** and reaction of **5** under hydrogen transfer conditions.

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<sub>2</sub>]<sub>2</sub> 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<sup>a</sup>

| Entry | R <sub>1</sub> | R <sub>2</sub>                                   | Yield <sup>b</sup> |
|-------|----------------|--|--------------------|
| 1     | H              | C <sub>6</sub> H <sub>5</sub>                    | <b>4a</b> 66%      |
| 2     | H              | 3-Cl-C <sub>6</sub> H <sub>4</sub>               | <b>4b</b> 54%      |
| 3     | H              | 3-Br-C <sub>6</sub> H <sub>4</sub>               | <b>4c</b> 48%      |
| 4     | H              | 3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> | <b>4d</b> 58%      |
| 5     | H              | 3-Me-C <sub>6</sub> H <sub>4</sub>               | <b>4e</b> 54%      |
| 6     | H              | 3-OMe-C <sub>6</sub> H <sub>4</sub>              | <b>4f</b> 51%      |
| 7     | H              | 4-F-C <sub>6</sub> H <sub>4</sub>                | <b>4g</b> 51%      |
| 8     | H              | 4-Br-C <sub>6</sub> H <sub>4</sub>               | <b>4h</b> 55%      |
| 9     | H              | 4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> | <b>4i</b> 57%      |
| 10    | H              | 4-Me-C <sub>6</sub> H <sub>4</sub>               | <b>4j</b> 50%      |
| 11    | H              | Furyl  | <b>4k</b> 55%      |
| 12    | H              | Benzyl   | <b>4l</b> 49%      |
| 13    | H              | <i>n</i> -Pentanyl                               | <b>4m</b> 57%      |
| 14    | F              | C <sub>6</sub> H <sub>5</sub>                    | <b>4n</b> 56%      |
| 15    | F              | 4-Br-C <sub>6</sub> H <sub>4</sub>               | <b>4o</b> 60%      |
| 16    | F              | 4-Me-C <sub>6</sub> H <sub>4</sub>               | <b>4p</b> 62%      |
| 17    | F              | <i>n</i> -Pentanyl                               | <b>4q</b> 65%      |

<sup>a</sup> 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<sub>2</sub>, 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<sub>2</sub>, 24 h. <sup>b</sup> Isolated yield.

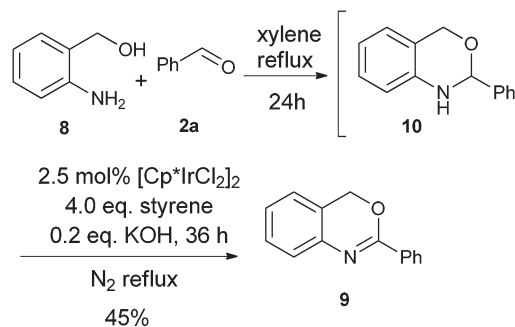


**Scheme 3** One-pot synthesis of 2-phenylquinazoline starting with benzyl alcohol.

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.<sup>9</sup> 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**.