

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

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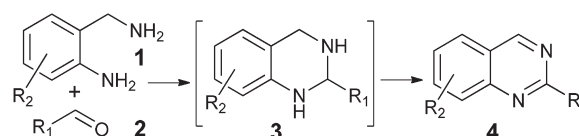
An iridium-catalyzed hydrogen transfer reaction was successfully applied in the synthesis of 2-substituted quinazolines in moderate yields starting from aldehydes or alcohols with 2-aminobenzylamines.

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*-benzylated 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>

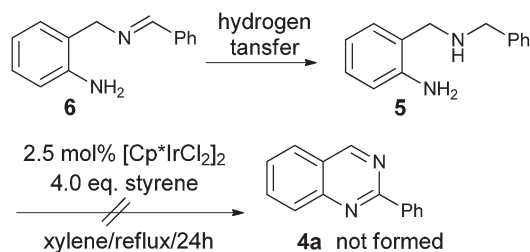
Entry	Catalyst	Additive	Acceptor	Solvent	Yield <sup>b</sup>
1	[Cp*IrCl <sub>2</sub> ] <sub>2</sub>	No	No	xylene	10%
2	[Cp*IrCl <sub>2</sub> ] <sub>2</sub>	No	styrene	xylene	66% <sup>c</sup>
3	[Cp*IrCl <sub>2</sub> ] <sub>2</sub>	No	<i>E</i> -crotonitrile	xylene	50% <sup>c</sup>
4	[Cp*IrCl <sub>2</sub> ] <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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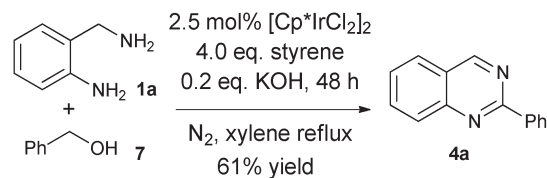
**Scheme 2** Possible pathway to **5** from hydrogenation of imine **6** and reaction of **5** under hydrogen transfer conditions.

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%  $[\text{Cp}^*\text{IrCl}_2]_2$  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<sup>a</sup>

Entry	$R_1$	$R_2$	Yield <sup>b</sup>
1	H	$\text{C}_6\text{H}_5$	<b>4a</b> 66%
2	H	3-Cl- $\text{C}_6\text{H}_4$	<b>4b</b> 54%
3	H	3-Br- $\text{C}_6\text{H}_4$	<b>4c</b> 48%
4	H	3- $\text{NO}_2$ - $\text{C}_6\text{H}_4$	<b>4d</b> 58%
5	H	3-Me- $\text{C}_6\text{H}_4$	<b>4e</b> 54%
6	H	3-OMe- $\text{C}_6\text{H}_4$	<b>4f</b> 51%
7	H	4-F- $\text{C}_6\text{H}_4$	<b>4g</b> 51%
8	H	4-Br- $\text{C}_6\text{H}_4$	<b>4h</b> 55%
9	H	4- $\text{NO}_2$ - $\text{C}_6\text{H}_4$	<b>4i</b> 57%
10	H	4-Me- $\text{C}_6\text{H}_4$	<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	$\text{C}_6\text{H}_5$	<b>4n</b> 56%
15	F	4-Br- $\text{C}_6\text{H}_4$	<b>4o</b> 60%
16	F	4-Me- $\text{C}_6\text{H}_4$	<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  $\text{N}_2$ , 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  $\text{N}_2$ , 24 h. <sup>b</sup> Isolated yield.

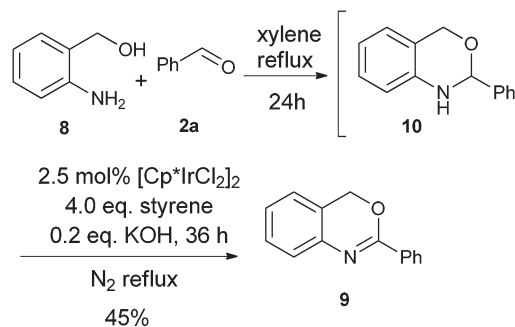


**Scheme 3** One-pot synthesis of 2-phenylquinazoline starting with benzyl alcohol.

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**.

## References

- (a) J. B. Hynes and J. M. Buck, *J. Med. Chem.*, 1975, **18**, 1191; (b) J. H. Chan, J. S. Hong, L. F. Kuyper, M. L. Jones, D. P. Baccanari, R. L. Tansik, C. M. Boytos, S. K. Rudolph and A. D. Brown, *J. Heterocycl. Chem.*, 1997, **34**, 145; (c) J. P. Michael, *Nat. Prod. Rep.*, 1999, **16**, 697; (d) B. A. Foster, H. A. Coffrey, M. J. Morin and F. Rastinejad, *Science*, 1999, **286**, 2507; (e) J. P. Michael, *Nat. Prod. Rep.*, 2002, **19**, 742; (f) J. P. Michael, *Nat. Prod. Rep.*, 2003, **20**, 476; (g) L. A. Doyle and D. D. Ross, *Oncogene*, 2003, **22**, 7340; (h) A. Lewerenz, S. Hentschel, Z. Vissiennon, S. Michael and K. Nieber, *Drug Dev. Res.*, 2003, **58**, 420; (i) A. Lüth and W. Löwe, *Eur. J. Med. Chem.*, 2008, **43**, 1478; (j) R. Gundla, R. Kazemi, R. Sanam, R. Muttineni, J. A. R. P. Sarma, R. Dayam and N. Neamati, *J. Med. Chem.*, 2008, **51**, 3367.
- J. F. Mendes da Silva, M. Walters, S. Al-Damluji and C. R. Ganellin, *Bioorg. Med. Chem.*, 2008, **16**, 7254.
- H. A. III. Burris, *Oncologist*, 2004, **9**, 10.
- For reviews:(a) A. Witt and J. Bergman, *Curr. Org. Chem.*, 2003, **7**, 659; (b) D. J. Connolly, D. Cusack, T. P. O'Sullivan and P. J. Guiry, *Tetrahedron*, 2005, **61**, 10153; (c) For examples: J. J. E. Vanden, J. Godin, A. Mayence, A. Maquestiau and E. Anders, *Synthesis*, 1993, 867; (d) T. Kitazume, F. Zulfiqar and G. Tanaka, *Green Chem.*, 2000, **2**, 133; (e) W. H. Correa, S. Papadopoulos, P. Radnidge, B. A. Roberts and J. L. Scott, *Green Chem.*, 2002, **4**, 245; (f) J. Sinkkonen, K. N. Zelenin, A. K. A. Potapov, I. V. Lagoda, V. V. Alekseyev and K. Pihlaja, *Tetrahedron*, 2003, **59**, 1939; (g) N. Coskun and M. Cetin, *Tetrahedron Lett.*, 2004, **45**, 8973; (h) N. Coskun and M. Cetin, *Tetrahedron*, 2007, **63**, 2966; (i) F. Portela-Cubillo, J. S. Scott and J. C. Walton, *Chem. Commun.*, 2008, **44**, 2935; (j) F. Portela-Cubillo, J. S. Scott and J. C. Walton, *J. Org. Chem.*, 2009, **74**, 4934; (k) Y. Peng, Y. Zeng, G. Qiu, L. Cai and V. W. Pike, *J. Heterocycl. Chem.*, 2010, **47**, 1240; (l) C. U. Maheswari, G. S. Kumar, M. Venkateshwar, R. A. Kumar, M. L. Kantam and K. R. Reddy, *Adv. Synth. Catal.*, 2010, **352**, 341; (m) C. Wang, S. Li, H. Liu, Y. Jiang and H. Fu, *J. Org. Chem.*, 2010, **75**, 7936; (n) J. Zhang, D. Zhu, C. Yu, C. Wan and Z. Wang, *Org. Lett.*, 2010, **12**, 2841; (o) B. Han, X. L. Yang, C. Wang, Y. W. Bai, T. C. Pan, X. Chen and W. Yu, *J. Org. Chem.*, 2012, **77**, 1136.
- (a) J. Zhou and J. Fang, *J. Org. Chem.*, 2011, **76**, 7730; (b) J. Fang and J. Zhou, *Org. Biomol. Chem.*, 2012, **10**, 2389.
- For reviews:(a) K. Fujita and R. Yamaguchi, *Synlett*, 2005, **4**, 560; (b) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, 753; (c) M. J. Krische, *Angew. Chem., Int. Ed.*, 2009, **48**, 34; (d) G. E. Debereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (e) T. Suzuki, *Chem. Rev.*, 2011, **111**, 1825; (f) J. Choi, A. H. R. MacArthur, M. Brookhart and A. S. Goldman, *Chem. Rev.*, 2011, **111**, 1761.
- Compound **5** was formed in 5% under these conditions; intermediates of **3** and **6** were also detectable in LC-MS.
- For hydrogen transfer in C–N bond formations:(a) R. Yamaguchi, K. Fujita and M. W. Zhu, *Heterocycles*, 2010, **81**, 1093; (b) A. J. Blacker, M. M. Farah, M. I. Hall, S. P. Marsden, O. Saidi and J. M. J. Williams, *Org. Lett.*, 2009, **11**, 2039; (c) W. X. Zhang, X. C. Dong and W. L. Zhao, *Org. Lett.*, 2011, **13**, 5386; (d) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853.
- 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**.