



Cite this: *RSC Adv.*, 2018, 8, 74

# A new and facile approach to 1,2-dihydroisoquinolin-3(4*H*)-imines by the Cu(I)-catalyzed reaction of 2-ethynylbenzyl methanesulfonates, sulfonyl azides and amines†

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Received 14th November 2017  
Accepted 11th December 2017

DOI: 10.1039/c7ra12412k

rsc.li/rsc-advances

A new, step-economical and operationally simple access to unsubstituted 1,2-dihydroisoquinolin-3(4*H*)-imines by Cu-catalyzed MCRs under mild conditions is described. In addition, selective hydrolysis of imines to the corresponding 1,2-dihydroisoquinolin-3(4*H*)-ones under refluxed conc. HCl has also been investigated.

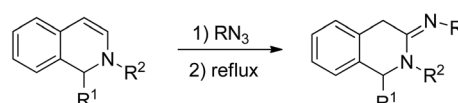
## Introduction

Heterocycle skeletons are popular scaffolds in various pharmaceuticals, biologically active compounds and functional materials.<sup>1</sup> Tetrahydroisoquinoline (THIQ), an important nitrogen-containing heterocycle skeleton, is also found frequently in naturally existing alkaloids which have been shown to have a wide range of interesting biological activities such as antitumor, antimicrobial activities, and other pharmacological properties.<sup>2</sup> Due to these advantages, great efforts have been made to develop various methodologies toward the synthesis of the THIQ skeleton and its derivatives. In general, traditional synthetic methods for the construction of this class of compounds are the Bischler–Napieralski cyclization/reduction,<sup>3</sup> the Pictet–Spengler reaction,<sup>3a,4</sup> the noble-transition metal-catalyzed asymmetric direct hydrogenation of isoquinoline or dihydroisoquinoline derivatives<sup>5</sup> and some other elegant reactions.<sup>6</sup> In recent years, in order to further expand the desirable molecular library of the THIQ alkaloids for the discovery of pharmaceutically active compounds, many excellent approaches by directly using THIQ precursors to their derivatives have also been developed. For example, currently, the most popular strategies to construct the THIQ skeleton-containing derivatives are the nucleophilic addition to the preformed C=N<sup>+</sup> bond of cyclic precursors offered from the substrate of tetrahydroisoquinoline *via* the oxidative cross-dehydrogenative coupling (CDC) reaction<sup>7</sup> or the redox-neutral reaction<sup>8</sup> and those associated with free radical intermediates.<sup>9</sup> Among the above-mentioned synthetic strategies, although all approaches can provide access to the THIQ

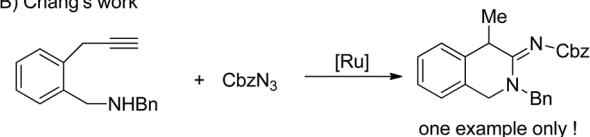
skeleton and their derivatives, the synthetic pathways towards 1,2-dihydroisoquinolin-3(4*H*)-imines, which are a class of important members of THIQ family and have been widely applied in material sciences and biological research,<sup>10</sup> are rarely reported in the literature. A more careful literature survey indicates that only Soufiaoui *et al.* in 1992 described their synthesis *via* the 1,3-dipolar cycloaddition of arylazides with 1,2-dihydroisoquinoline derivatives followed by splitting decomposition<sup>11</sup> under heating (Scheme 1A) and Chang's group

### Previous work

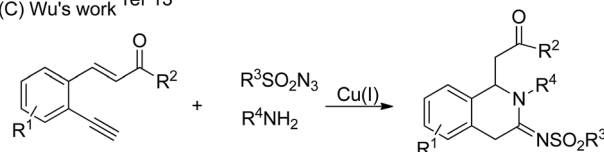
(A) Soufiaoui's work ref 11



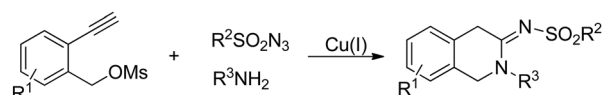
(B) Chang's work ref 12



(C) Wu's work ref 13



### This work

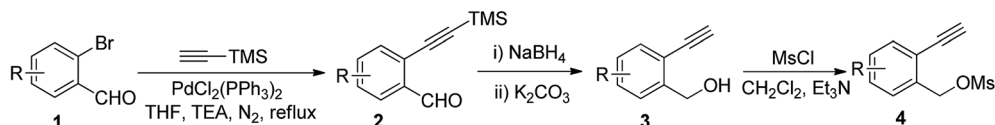


Scheme 1 Different strategies for the construction of 1,2-dihydroisoquinolin-3(4*H*)-imine.

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† Electronic supplementary information (ESI) available. CCDC 1574819. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra12412k



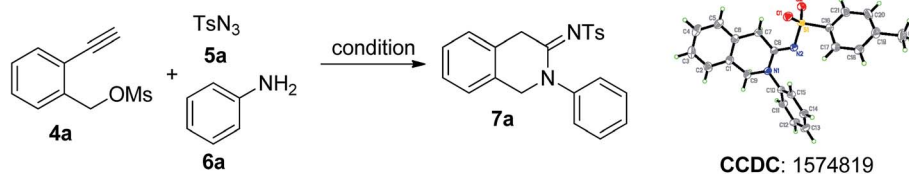


Scheme 2 Facile synthesis of 2-ethynylbenzyl methanesulfonates 4.

in 2006 reported a catalytic one-pot approach to the title product using aminoalkyne and azide as substrate under mild condition<sup>12</sup> (Scheme 1B). However, these methods to synthesize 1,2-dihydroisoquinolin-3(4*H*)-imine suffered from some disadvantages including multiple reaction steps,<sup>11</sup> harsh reaction conditions,<sup>11</sup> few scope of substrate (one example only!)<sup>12</sup> and the use of noble metal.<sup>12</sup> Therefore, the search for a step-economical, more convenient and efficient catalytic system with attractive features such as easily accessible starting materials, mild reaction conditions, and nontoxic side products to generate structural diversity of 1,2-dihydroisoquinolin-3(4*H*)-imine is of great value.

As an ideal synthetic tool, multicomponent reactions (MCRs) involving a tandem reaction process with three or more reagents in a single process under mild conditions have emerged as a powerful and attractive strategy for the synthesis of structurally diverse organic molecules. Recently, the

methodology is also applied in the synthesis of 1,2-dihydroisoquinolin-3(4*H*)-imines. For instance, Wu's group in 2011 presented one type of 1,2-dihydroisoquinolin-3(4*H*)-imines *via* MCRs using 2-ethynylphenyl-chalcones, sulfonyl azides and amines as substrates under Cu(I) catalyst (Scheme 1C),<sup>13</sup> in which the strategy may experience the reaction process with the active ketenimine intermediate investigated widely by the pioneers.<sup>14</sup> It is well known that the pharmacological and biological activity of molecule is shown to be dependent on the nature of substituents. However, most MCRs follow a single reaction route to afford only one substituted type of molecular skeleton and their derivatives. Therefore, development of novel MCRs for the selective formation of diverse substituted molecules containing the same molecular skeleton is a worthy and challenging goal. As a continuation of our interest in ketenimine chemistry and THIQ skeleton, we herein report a convenient and efficient synthetic strategy for the synthesis of 1,2-

Table 1 Optimization of the reaction conditions<sup>a</sup>

| Entry           | Catalyst          | Base                           | Solvent           | Temp. (°C) | Yield <sup>b</sup> (%) |
|-----------------|-------------------|--------------------------------|-------------------|------------|------------------------|
| 1 <sup>c</sup>  | CuI               | Et <sub>3</sub> N              | DCM               | rt         | 40                     |
| 2               | Cu <sub>2</sub> O | Et <sub>3</sub> N              | DCM               | rt         | nd                     |
| 3               | CuCl              | Et <sub>3</sub> N              | DCM               | rt         | 47                     |
| 4               | CuBr              | Et <sub>3</sub> N              | DCM               | rt         | 54                     |
| 5               | CuBr              | Et <sub>3</sub> N              | DCM               | 40         | 57                     |
| 6               | CuBr              | Et <sub>3</sub> N              | DCM               | 50         | 60                     |
| 7               | CuBr              | Et <sub>3</sub> N              | DCM               | 60         | 77                     |
| 8               | CuBr              | Et <sub>3</sub> N              | DCM               | 70         | 50                     |
| 9               | CuBr              | Et <sub>3</sub> N              | CHCl <sub>3</sub> | 60         | 64                     |
| 10              | CuBr              | Et <sub>3</sub> N              | MeCN              | 60         | 35                     |
| 11              | CuBr              | Et <sub>3</sub> N              | THF               | 60         | 67                     |
| 12              | CuBr              | Et <sub>3</sub> N              | Dioxane           | 60         | 50                     |
| 13              | CuBr              | Et <sub>3</sub> N              | DMF               | 60         | 35                     |
| 14              | CuBr              | K <sub>2</sub> CO <sub>3</sub> | DCM               | 60         | Trace                  |
| 15              | CuBr              | (iPr <sub>2</sub> )NEt         | DCM               | 60         | 70                     |
| 16              | CuBr              | DBU                            | DCM               | 60         | nd                     |
| 17              | CuBr              | DABCO                          | DCM               | 60         | 37                     |
| 18 <sup>d</sup> | CuBr              | Et <sub>3</sub> N              | DCM               | 60         | 82                     |
| 19 <sup>e</sup> | CuBr              | Et <sub>3</sub> N              | DCM               | 60         | 80                     |

<sup>a</sup> Reaction conditions: toluenesulfonyl azide (0.36 mmol), 2-ethynylbenzyl methanesulfonate (0.3 mmol), phenylamine (0.36 mmol), base (0.45 mmol), catalyst (0.03 mmol), solvent (1 mL). <sup>b</sup> Isolated yields. nd = not detected. <sup>c</sup> Reaction carried out for 12 h. <sup>d</sup> Reaction carried out for 0.5 h.

<sup>e</sup> Reaction carried out for 1 h.



dihydroisoquinolin-3(4*H*)-imines *via* novel MCRs from 2-ethynylbenzyl methanesulfonates, sulfonyl azides and amines (Scheme 1, this work).

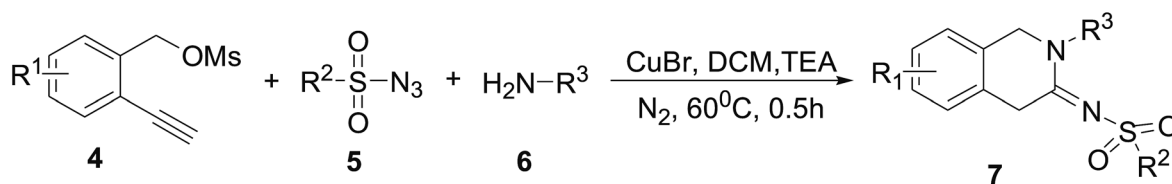
## Results and discussion

Our studies started with the synthesis of variously substituted 2-ethynylbenzyl methanesulfonates **4** from substituted 2-bromobenzaldehyde **1** according to the literature procedures<sup>15</sup> as indicated in Scheme 2.

And then, under N<sub>2</sub> and sealed tube, we carried out a model MCRs of 2-ethynylbenzyl methanesulfonate **4a** with TsN<sub>3</sub> **5a** and phenylamine **6a** in dichloromethane at room temperature in the presence of CuI and Et<sub>3</sub>N for 12 h (Table 1). To our delight, the desired product (entry 1), 2-dihydroisoquinolin-3(4*H*)-imine of **7a** was isolated in 40% yield, and its structure was further

conformed by X-ray crystallographic analysis (showed in Table 1). Inspired by the result of reaction, we continue to optimize the reaction condition of model reaction to improve the yield of **7a** to the highest. The results for various optimization experiments are summarized in Table 1. Subsequently, other copper salt were then screened under the reaction condition just mentioned. The results indicated that, in comparison to the potential copper catalyst, only CuBr was proven to be more effective one (54%), whereas Cu<sub>2</sub>O even can not lead to the formation of **7a** (entries 1–4). When the reaction temperature under CuBr as catalyst was gradually increased from rt to 60 °C, the yield of **7a** increases to 77%. However, it was found that further elevating the reaction temperature, in contrast, made the yield decrease (entries 5–8). We next examined the effect of solvent in the MCRs. The results revealed that dichloromethane (77%) was the most suitable solvent for the reaction (entry 7,

Table 2 Substrate scope of MCRs for the formation of **7<sup>a</sup>**



| Entry | R <sup>1</sup>                  | R <sup>2</sup>  | R <sup>3</sup>  | Product    | Yield <sup>b</sup> [%] |
|-------|---------------------------------|---|---|------------|------------------------|
| 1     | H( <b>4a</b> )                  | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>5a</b> )     | C <sub>6</sub> H <sub>5</sub> ( <b>6a</b> )                       | <b>7a</b>  | 82                     |
| 2     | <b>4a</b>                       | <b>5a</b>   | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>6b</b> )     | <b>7b</b>  | 78                     |
| 3     | <b>4a</b>                       | <b>5a</b>   | 4-FC <sub>6</sub> H <sub>4</sub> ( <b>6c</b> )                    | <b>7c</b>  | 84                     |
| 4     | <b>4a</b>                       | <b>5a</b>   | 4-ClC <sub>6</sub> H <sub>4</sub> ( <b>6d</b> )                   | <b>7d</b>  | 77                     |
| 5     | <b>4a</b>                       | <b>5a</b>   | 2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> ( <b>6e</b> )    | <b>7e</b>  | 68                     |
| 6     | <b>4a</b>                       | <b>5a</b>   | 2-FC <sub>6</sub> H <sub>4</sub> ( <b>6f</b> )                    | <b>7f</b>  | 76                     |
| 7     | <b>4a</b>                       | <b>5a</b>   | 2,6-EtC <sub>6</sub> H <sub>3</sub> ( <b>6g</b> )                 | <b>7g</b>  | 65                     |
| 8     | <b>4a</b>                       | <b>5a</b>   | 2,4,6-CH <sub>3</sub> C <sub>6</sub> H <sub>2</sub> ( <b>6h</b> ) | <b>7h</b>  | 74                     |
| 9     | <b>4a</b>                       | <b>5a</b>   | Bn( <b>6i</b> )   | <b>7i</b>  | 35                     |
| 10    | <b>4a</b>                       | <b>5a</b>   | <sup>t</sup> Bu( <b>6j</b> )                                      | <b>7j</b>  | 0                      |
| 11    | <b>4a</b>                       | C <sub>6</sub> H <sub>5</sub> ( <b>5b</b> )                       | <b>6a</b>   | <b>7k</b>  | 80                     |
| 12    | <b>4a</b>                       | <b>5b</b>   | <b>6e</b>   | <b>7l</b>  | 78                     |
| 13    | <b>4a</b>                       | <b>5b</b>   | <b>6h</b>   | <b>7m</b>  | 74                     |
| 14    | <b>4a</b>                       | 2,4,6-CH <sub>3</sub> C <sub>6</sub> H <sub>2</sub> ( <b>5c</b> ) | <b>6a</b>   | <b>7n</b>  | 85                     |
| 15    | <b>4a</b>                       | <b>5c</b>   | <b>6c</b>   | <b>7o</b>  | 84                     |
| 16    | 4-F( <b>4b</b> )                | <b>5a</b>   | <b>6a</b>   | <b>7p</b>  | 51                     |
| 17    | <b>4b</b>                       | <b>5a</b>   | <b>6c</b>   | <b>7q</b>  | 83                     |
| 18    | 5-F( <b>4c</b> )                | <b>5a</b>   | <b>6a</b>   | <b>7r</b>  | 89                     |
| 19    | <b>4c</b>                       | <b>5a</b>   | <b>6b</b>   | <b>7s</b>  | 77                     |
| 20    | <b>4c</b>                       | <b>5a</b>   | <b>6c</b>   | <b>7t</b>  | 84                     |
| 21    | <b>4c</b>                       | <b>5b</b>   | <b>6c</b>   | <b>7u</b>  | 81                     |
| 22    | <b>4c</b>                       | <b>5c</b>   | <b>6a</b>   | <b>7v</b>  | 80                     |
| 23    | 6-F( <b>4d</b> )                | <b>5a</b>   | <b>6a</b>   | <b>7w</b>  | 75                     |
| 24    | <b>4d</b>                       | <b>5a</b>   | <b>6c</b>   | <b>7x</b>  | 88                     |
| 25    | <b>4d</b>                       | <b>5b</b>   | <b>6a</b>   | <b>7y</b>  | 71                     |
| 26    | 4-Cl( <b>4e</b> )               | <b>5a</b>   | <b>6a</b>   | <b>7z</b>  | 77                     |
| 27    | <b>4e</b>                       | <b>5a</b>   | <b>6c</b>   | <b>7aa</b> | 87                     |
| 28    | <b>4e</b>                       | <b>5b</b>   | <b>6c</b>   | <b>7ab</b> | 72                     |
| 29    | 4-CH <sub>3</sub> ( <b>4f</b> ) | <b>5a</b>   | <b>6a</b>   | <b>7ac</b> | 77                     |
| 30    | <b>4f</b>                       | <b>5a</b>   | <b>6b</b>   | <b>7ad</b> | 73                     |
| 31    | <b>4f</b>                       | <b>5a</b>   | <b>6c</b>   | <b>7ae</b> | 51                     |

<sup>a</sup> Optimal reaction conditions: **4** (0.2 mmol), CuBr (0.02 mmol), Et<sub>3</sub>N (0.3 mmol) in DCM (1 mL), sealed and then heated at 60 °C for 0.5 h under N<sub>2</sub>.

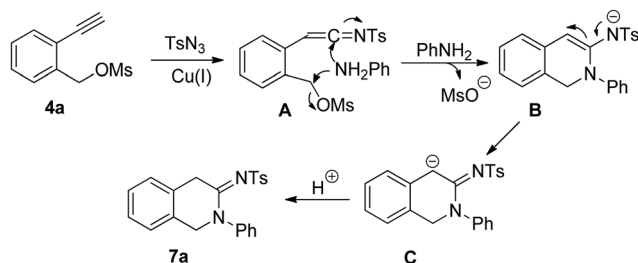
<sup>b</sup> Isolated yields are given.



entries 9–13). As showed in Table 1, different base also affected the final desired outcome. The reaction was carried out efficiently when triethylamine acted as the base, furnishing the desired product in 77% yield, and the corresponding product was not almost afforded in the presence of  $K_2CO_3$  or DBU (entry 7, entries 14–17). Additionally, it should be noted that the reaction time also played the important role in improving the yield of target product. The experimental results indicated the shorter reaction time would be beneficial to the formation of **7a** (entry 7, entries 18–19). Hence, after screening the reaction condition of MCRs, the optimized conditions to selectively obtain the desired product **7a**, under  $N_2$  and sealed tube, are identified as the employment of  $Et_3N$  as base and  $CuBr$  as catalyst in dichloromethane for 0.5 h at 60 °C.

With the optimized reaction conditions secured, we subsequently applied the optimized conditions for the formation of **7a** to explore the scope and generality of the MCRs. The results in this section, as summarized in Table 2, demonstrated that the present method is generally applicable in the formation of target products depending on the employment of the corresponding starting materials. It was found that all aromatic substrates bearing various substitution such as electron donating and withdrawing group underwent smoothly this transformation generating the corresponding products **7** with moderate to excellent yields. However, we also found that in addition to the substrates with withdrawing group such as F at the *para* position of phenyl ring giving the lower yields (51% in both) (entries 16, 31), the property of other substituents on phenyl ring showed no obvious impact on the yield of corresponding products. Intriguingly, when the substrates are aliphatic amines, the methodology only furnish either the low corresponding yield (entry 9, 35%) or no desired product (entry 10, 0%). The result may be caused by the fact that in contrast to aromatic amines, aliphatic amines with stronger nucleophilic have higher activity and lower selectivity. Therefore, when aliphatic amines reacted with other substrates, the product in a low or no yield will be achieved.

Based on the above results and the chemistry related to ketenimine, a plausible mechanism of this MCRs is proposed and shown in Scheme 3. Taking the formation of **7a** as an example, first, the ketenimine intermediate **A** is formed *via* the reaction of 2-ethynylbenzyl methanesulfonate (**4a**) with  $TsN_3$  under the optimized conditions. Subsequently, when the anilines added into the reaction, the double nucleophilic addition would happen to afford the intermediate **B**. And then, intermediate **B** will tautomerize into the intermediate **C**. Finally,



Scheme 3 Possible reaction mechanism for the formation of **7a**.

Table 3 Hydrolysis of imines **7** to 1,2-dihydroisoquinolin-3(4*H*)-ones **8**<sup>a</sup>

| Entry | R <sup>1</sup> | R <sup>2</sup>                                      | R <sup>3</sup>                                  | Product   | Yield <sup>b</sup> [%] |
|-------|----------------|---|---|-----------|------------------------|
| 1     | H(a)           | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> (b) | C <sub>6</sub> H <sub>5</sub>                   | <b>8a</b> | 66                     |
| 2     | a              | b   | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> | <b>8b</b> | 74                     |
| 3     | a              | b   | 4-FC <sub>6</sub> H <sub>4</sub>                | <b>8c</b> | 59                     |
| 4     | a              | b   | 4-ClC <sub>6</sub> H <sub>4</sub>               | <b>8d</b> | 69                     |

<sup>a</sup> Reaction conditions: **7** (0.5 mmol), conc HCl (10 mL), reactions refluxed for 12 h. <sup>b</sup> Isolated yields.

the intermediate **C**, which undergo sequential proton transfer, will transform into the desired product **7a**.

Subsequently, to further take advantage of the synthetic application of this methodology, we then explored the synthesis of 1,2-dihydroisoquinolin-3(4*H*)-ones **8** by hydrolysis of the resulting products **7**. To the best of our knowledge, **8** were considered as important building block in organic synthesis<sup>16</sup> and have good physiological activities in medicinal chemistry. For example, more recently, the researchers found that the compounds containing the skeleton of 1,2-dihydroisoquinolin-3(4*H*)-one were acetylcholinesterase and  $\beta$ -secretase dual inhibitors in treatment with alzheimer's disease.<sup>17</sup> Therefore, we proceeded to treat the dihydroisoquinolin-3(4*H*)-imines **7** with concentrated HCl under reflux for 12 h. To our delight, the corresponding title products **8** were achieved in good yields (Table 3). The results indicate that **7** can be considered as a class of important precursor of 1,2-dihydroisoquinolin-3(4*H*)-ones **8**.

In summary, a new and facile MCRs for the formation of unsubstituted 1,2-dihydroisoquinolin-3(4*H*)-imines in good yields has been developed under mild condition. The experimental results indicated that various aromatic substrates could be well tolerated in this reaction. Meanwhile, selective hydrolysis of imines to the corresponding 1,2-dihydroisoquinolin-3(4*H*)-ones has also been investigated under refluxed conc. HCl. In addition, some 2-ethynylbenzyl methanesulfonates that had not previously been reported were also synthesized and characterized. The methodology provides a step-economical and operationally simple access to functionalized desired product and can further enrich the compound library of 1,2-dihydroisoquinolin-3(4*H*)-imine.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We are grateful for financial support by the Science Foundation of Shanghai Institute of Technology (grant number YJ2013-61).



## Notes and references

- 1 (a) L. F. Tietze and A. Modi, *Med. Res. Rev.*, 2000, **20**, 304–322; (b) B. B. Touré and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439–4486; (c) S. Yu and S. Ma, *Angew. Chem., Int. Ed.*, 2012, **51**, 3074–3112; (d) K. S. Gudmundsson and B. A. Johns, *Org. Lett.*, 2003, **5**, 1369–1372; (e) C. Hamdouchi, B. Zhong, J. Mendoza, E. Collins, C. Jaramillo, J. Diego, D. Robertson, C. D. Spencer, B. D. Anderson, S. A. Watkins, F. Zhang and H. B. Brooks, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1943–1947.
- 2 For selected examples: (a) K. W. Bentley, *The Isoquinoline Alkaloids*, Hardwood Academic, Amsterdam, 1998, vol. 1; (b) J. D. Phillipson, M. F. Roberts and M. H. Zenk, *The Chemistry and Biology of Isoquinoline Alkaloids*, Springer Verlag, Berlin, 1985; (c) M. D. Rozwadowska, *Heterocycles*, 1994, **39**, 903–931; (d) D. Jack and R. Williams, *Chem. Rev.*, 2002, **102**, 1669–1730; (e) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341–3370; (f) P. Siengalewicz, U. Rinner and J. Mulzer, *Chem. Soc. Rev.*, 2008, **37**, 2676–2696; (g) B. Zhou, J. Guo and S. Danishefsky, *Org. Lett.*, 2002, **4**, 43–46; (h) A. Endo, A. Yanagisawa, M. Abe, S. Tohma, T. Kan and T. Fukuyama, *J. Am. Chem. Soc.*, 2002, **124**, 6552–6554; (i) K. W. Bentley, *Nat. Prod. Rep.*, 2006, **23**, 444–463; (j) X. Fang, Y. Yin, Y. Chen, L. Yao, B. Wang, M. Caneron, L. Lin, S. Khan, P. LoGrasso and Y. Feng, *J. Med. Chem.*, 2010, **53**, 5727–5737; (k) C. Razafindrabe, S. Aubry, B. Bourdon, M. Andriantsiferana, S. Pellet-Rostaing and M. Lemaire, *Tetrahedron*, 2010, **66**, 9061–9066.
- 3 (a) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341–3370; (b) B. S. Thyagarajan, *Chem. Rev.*, 1954, **54**, 1019–1064; (c) J. Gal, R. J. Wienkam and N. Castagnoli, *J. Org. Chem.*, 1974, **39**, 418–421.
- 4 J. Stöckigt, A. P. Antonchick, F. Wu and H. Waldmann, *Angew. Chem.*, 2011, **123**, 8692–8696; *Angew. Chem., Int. Ed.*, 2011, **50**, 8538–8564.
- 5 For selected examples of the asymmetric hydrogenation of isoquinolines, see: (a) Y. G. Zhou, *Acc. Chem. Res.*, 2007, **40**, 1357; (b) D. S. Wang, Q. A. Chen, S. M. Lu and Y. G. Zhou, *Chem. Rev.*, 2012, **112**, 2557–2590; (c) R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta and H. Takaya, *J. Am. Chem. Soc.*, 1986, **108**, 7117–7119; (d) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916–4917; (e) S. M. Lu, Y. Q. Wang, X. W. Han and Y. G. Zhou, *Angew. Chem.*, 2006, **118**, 2318–2321; *Angew. Chem., Int. Ed.*, 2006, **45**, 2260–2263; (f) C. Q. Li and J. L. Xiao, *J. Am. Chem. Soc.*, 2008, **130**, 13208–13209; (g) P. C. Yan, J. H. Xie, G. H. Hou, L. X. Wang and Q. L. Zhou, *Adv. Synth. Catal.*, 2009, **351**, 3243–3250; (h) L. E. Vanno, J. Ormala and P. M. Pihko, *Chem.–Eur. J.*, 2009, **15**, 12963–12967; (i) M. X. Chang, W. Li and X. M. Zhang, *Angew. Chem.*, 2011, **123**, 10867–10870; *Angew. Chem., Int. Ed.*, 2011, **50**, 10679–10681; (j) F. Berhal, Z. Wu, Z. G. Zhang, T. Ayad and V. Ratovelomanana-Vidal, *Org. Lett.*, 2012, **14**, 3308–3383; (k) A. Iimuro, K. Yamaji, S. Kandula, T. Nagano, Y. Kita and K. Mashima, *Angew. Chem.*, 2013, **125**, 2100–2104; *Angew. Chem., Int. Ed.*, 2013, **52**, 2046–2050; (l) Z. Wu, M. Perez, M. Scalone, T. Ayad and V. Ratovelomanana-Vidal, *Angew. Chem.*, 2013, **125**, 5025–5028; *Angew. Chem., Int. Ed.*, 2013, **52**, 4925–4928.
- 6 For other selected examples for the synthesis of THIQ skeleton and their derivatives: (a) A. Padwa, M. D. Danca, K. Hardcastle and M. McClure, *J. Org. Chem.*, 2003, **68**, 929–941; (b) A. Padwa and M. D. Danca, *Org. Lett.*, 2002, **4**, 715–717; (c) E. Garcia, E. Lete and N. Sotomayor, *J. Org. Chem.*, 2006, **71**, 6776–6784; (d) K. Shimizu, M. Takimoto and M. Mori, *Org. Lett.*, 2003, **5**, 2323–2325; (e) L. Evanno, J. Ormala and P. Pihko, *Chem.–Eur. J.*, 2009, **15**, 12963–12967.
- 7 For selected examples of oxidative cross-dehydrogenative coupling: (a) X. H. Liu, J. L. Zhang, S. X. Ma, Y. X. Ma and R. Wang, *Chem. Commun.*, 2014, **50**, 15714–15717; (b) S. Murarka, I. Deb, C. Zhang and D. Seidel, *J. Am. Chem. Soc.*, 2009, **131**, 13226–13227; (c) J. Xie, H. M. Li, J. C. Zhou, Y. X. Cheng and C. Zhu, *J. Angew. Chem.*, 2012, **124**, 1278–1281; *Angew. Chem., Int. Ed.*, 2012, **51**, 1252–1255; (d) J. M. Zhang, B. Tiwari, C. Xing, X. K. Chen and Y. R. Chi, *Angew. Chem.*, 2012, **124**, 3709–3712; *Angew. Chem., Int. Ed.*, 2012, **51**, 3649–3652; (e) G. Zhang, Y. X. Ma, S. L. Wang, Y. H. Zhang and R. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 12334–12337; (f) A. J. Neel, J. P. Hehn, P. F. Triplet and F. D. Toste, *J. Am. Chem. Soc.*, 2013, **135**, 14044–14047; (g) H. Ueda, K. Yoshida and H. Tokuyama, *Org. Lett.*, 2014, **16**, 4194–4197; (h) G. Zhang, Y. X. Ma, G. B. Cheng, D. B. Liu and R. Wang, *Org. Lett.*, 2014, **16**, 656–659; (i) H. M. Huang, Y. J. Li, Q. Ye, W. B. Yu, L. Han, J. H. Jia and J. R. Gao, *J. Org. Chem.*, 2014, **79**, 1084–1092.
- 8 For selected examples of redox-neutral reaction: (a) W. L. Lin, T. Cao, W. Fan, Y. L. Han, J. Q. Kuang, H. W. Luo, B. K. Y. Miao, X. J. Tang, Q. Yu, W. M. Yuan, J. S. Zhang, C. Zhu and S. M. Ma, *Angew. Chem., Int. Ed.*, 2014, **53**, 277–281; (b) Q. H. Zheng, W. Meng, G. J. Jiang and Z. X. Yu, *Org. Lett.*, 2013, **15**, 5928–5931; (c) M. T. Richers, M. Breugst, A. Y. Platonova, A. Ullrich, A. Dieckmann, K. N. Houk and D. Seidel, *J. Am. Chem. Soc.*, 2014, **136**, 6123–6135; (d) C. L. Jarvis, M. T. Richers, M. Breugst, K. N. Houk and D. Seidel, *Org. Lett.*, 2014, **16**, 3556–3559; (e) Z. B. Zhu and D. Seidel, *Org. Lett.*, 2017, **19**, 2841–2844; (f) K. L. Zheng, M. Q. You, W. M. Shu, Y. D. Wu and A. X. Wu, *Org. Lett.*, 2017, **19**, 2262–2265.
- 9 (a) W. T. Wei, X. J. Dong, S. Z. Nie, Y. Y. Chen, X. J. Zhang and M. Yan, *Org. Lett.*, 2013, **15**, 6018–6021; (b) Y. Y. Chen, X. J. Zhang, H. M. Yuan, W. T. Wei and M. Yan, *Chem. Commun.*, 2013, **49**, 10974–10976; (c) J. Xuan, T. T. Zeng, J. Feng, Q. H. Deng, J. R. Chen, L. Q. Lu, W. J. Xiao and H. Alper, *Angew. Chem., Int. Ed.*, 2015, **54**, 1625–1628.
- 10 For selected examples: (a) H. Li, J. L. Petersen and K. K. Wang, *J. Org. Chem.*, 2003, **68**, 5512–5518; (b) J. Qian, X. Qian and Y. Xu, *Chem.–Eur. J.*, 2009, **15**, 319–323; (c) M. Jaggi, C. Blum, N. Dupont, J. Grilj, S. X. Liu, J. Hauser, A. Hauser and S. Decurtins, *Org. Lett.*, 2009, **11**, 3096–3099; (d) H. Langhals and T. Pust, *Eur. J. Org. Chem.*, 2010, 3140–3145.



- 11 S. Kitane, L. Chraibi and M. Soufiaoui, *Tetrahedron*, 1992, **48**, 8935–8942.
- 12 S. Chang, M. J. Lee, D. Y. Jung, E. J. Yoo, S. H. Cho and S. K. Han, *J. Am. Chem. Soc.*, 2006, **128**, 12366–12367.
- 13 Z. Y. Chen, C. Ye, L. Gao and J. Wu, *Chem. Commun.*, 2011, **47**, 5623–5625.
- 14 For selected examples for ketenimine chemistry: (a) E. J. Yoo, I. Bae, S. H. Cho, H. Han and S. Chang, *Org. Lett.*, 2006, **8**, 1347–1350; (b) S. H. Cho and S. Chang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1897–1900; (c) S. H. Cho and S. Chang, *Angew. Chem., Int. Ed.*, 2008, **47**, 2836–2839; (d) E. J. Yoo, S. H. Park, S. H. Lee and S. Chang, *Org. Lett.*, 2009, **11**, 1155–1158; (e) I. Bae, H. Han and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 2038–2039; (f) Y. Shen, S. Cui, J. Wang, X. Chen, P. Lu and Y. G. Wang, *Adv. Synth. Catal.*, 2010, **352**, 1139–1144; (g) W. Yao, L. Pan, Y. Zhang, G. Wang, X. Wang and C. Ma, *Angew. Chem., Int. Ed.*, 2010, **49**, 9210–9214; (h) Y. Shang, K. Ju, X. He, J. Hu, S. Yu, M. Zhang, K. Liao, L. Wang and P. Zhang, *J. Org. Chem.*, 2010, **75**, 5743–5745; (i) I. Cano, E. Alvarez, M. C. Nicasio and P. J. Pérez, *J. Am. Chem. Soc.*, 2011, **133**, 191–193; (j) Y. Shang, X. He, J. Hu, J. Wu, M. Zhang, S. Yu and Q. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 2709–2713; (k) Z. Chen, D. Zheng and J. Wu, *Org. Lett.*, 2011, **13**, 848–851.
- 15 (a) P. C. Too and S. Chiba, *Chem. Commun.*, 2012, **48**, 7634–7636; (b) P. M. Poladura, E. Rubio and J. M. Gonzalez, *Angew. Chem., Int. Ed.*, 2015, **54**, 3052–3055; (c) H. J. Lu, C. Q. Li, H. L. Jiang, C. L. Lizardi and X. P. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 7028–7032.
- 16 (a) M. Hu, P. R. Guzzo, C. X. Zha, K. Nacro, Y. L. Yang, C. Hassler and S. Liu, *Tetrahedron Lett.*, 2012, **53**, 846–848; (b) R. A. J. Mook, K. Lackey and C. Bennett, *Tetrahedron Lett.*, 1995, **36**, 3969–3972; (c) A. Kamimura, Y. Ishihara, M. So and T. Hayashi, *Tetrahedron Lett.*, 2009, **50**, 1727–1730.
- 17 Y. C. Deng, Y. R. Jiang, X. J. Zhao and J. L. Wang, *J. Biomed. Sci.*, 2016, **4**, 112–113.

