DOI: 10.1002/adsc.201200155

Synthesis of Bi- and Tricyclic 1,2-Dihydroquinoline Derivatives from Arylamines and Alkynes by a Consecutive Zinc-Ammonium Salt Catalysis

Nibadita Purkait[a] and Siegfried Blechert[a,*]

[a] Institute of Chemistry, TU Berlin - Berlin Institute of Technology, Str. d. 17. Juni 135, 10623 Berlin, Germany
Fax: (+49)-30-3142-23619; e-mail: blechert@chem.tu-berlin.de

Received: February 23, 2012; Revised: May 2, 2012; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200155.

Abstract: A relay catalysis of a cationic zinc complex and *N*,*N*-dimethylaniline hydrotrifluoromethyl sulphonate induces a multiple C–C bond and C–N bond formation. The one-step synthesis make highly substituted bi- and tricyclic 1,2-dihydroquinoline derivatives easily available from simple starting materials. The high yielding process consists of several simultaneous operating steps.

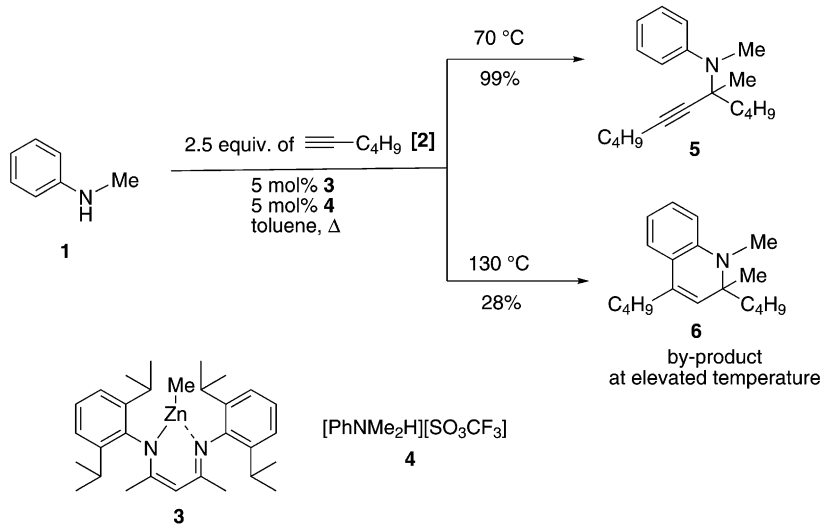
Keywords: 1,2-dihydroquinoline derivatives; domino reaction; hydroamination; sigmatropic rearrangement; zinc

Substituted hydroquinoline derivatives are important structural units in various natural products and pharmaceuticals.[1] Many heterocycles containing such units show biological activity and have potential therapeutic uses such as antibacterial,[2] anti-inflammatory,[3] inhibitors for lipid peroxidation,[4] HMG-CoA reductase,[5] and progesterone agonists[6] and antagonists.[7]

Many synthesis of hydroquinolines starting with aniline derivatives have been reported[8] such as Brønsted acid-catalyzed tandem reactions,[9] modified Skraup reactions,[10] Michael-aldol reactions,[11] metathesis[12] and tandem reactions of aromatic amines with alkynes.[13]

Hydroaminations of alkynes with aromatic amines followed by metal-catalyzed formation of the heterocycles have also been described. In 2005, Li and coworkers reported a domino route using 5 mol% $AgBF_4$ in diethyl ether at temperatures between 140 °C and 190 °C,[14] at the same time Yi and coworkers used 5 mol% of a ruthenium complex combining hydroamination and C–H bond activation in benzene at 95 °C.[15] Later Che et al. prepared 1,2-dihydroquinolines and quinolones by a tandem hydroamination–hydroarylation with 5 mol% of an Au(I)-NHC complex under microwave conditions at 150 °C.[16]

Herein we present a new domino process using a consecutive catalysis with 5 mol% of a Zn complex (**3**) as a cheap metal together with 15 mol% of an anilinium salt (**4**) as proton source. Domino reactions are highly attractive because several individual reactions are coupled yielding a product in a single process.[17] Another advantage of such cascade reactions in organic synthesis is often a high atom economy.[18] In context of our work on Zn-catalyzed hydroamination, we reported recently a new domino hydroamination–alkyne addition reaction giving access to functionalized propargylic amines.[19] The regioselective hydroamination of an alkyne with a cationic Zn complex led to an iminium salt followed by the Zn-catalyzed addition of monosubstituted acetylenes. In continuation of this work we observed in the case of arylamines, like *N*-methylaniline, at elevated temperatures as by-product the hydroquinoline derivative **6** (Scheme 1). The importance of such a type of heterocycles motivated us to unertake further studies on this reaction. A mixture of **1** with 2.5 equivalents of 1-hexyne was heated in toluene together with 5 mol% of a 1:1 mixture of precatalyst **3** and activator **4** for 24 h at 70 °C yielding 99% of the expected propargylic amine **5**. The same reaction at 130 °C gave under decomposition as only product which could be isolated by chromatography on silica gel the wanted 1,2-dihydroquinoline **6** in a yield of 28%. Similar results were obtained by heating the isolated **5** with 5 mol% of the 1:1 mixture of Zn complex and activator at 130 °C, thus indicating **5** as a precursor for the formation of **6**. However, the pure thermal reaction of **5** led only to decomposition, which demonstrates a catalytic reaction. The C–C bond formation between the arene and the triple bond could go *via* a direct metal-catalyzed cyclization. A similar copper-promoted reaction has been described.[20] Another pathway is the aromatic



Scheme 1.

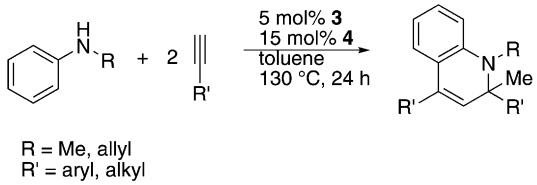
aza-Claisen rearrangement followed by cyclization of the resulting allene.[21] The thermal rearrangement of *N*-propargylanilines requires high temperatures which led to decomposition of the products.[22] The Lewis acid- or proton-catalyzed process is significantly milder.[9] Consequently we tested the influence of the anilinium salt **4** on the reaction **5**→**6**. We were pleased to see a complete conversion after 6 h at 130 °C yielding 98% of the wanted dihydroquinoline. We supposed that the low yield formation of **6** during the first attempt was caused by a small excess of the activator **4**. Thus heating *N*-methylaniline and 2.5 equivalents of 1-hexyne with 5 mol% Zn complex and 15 mol% **4** at 130 °C gave a clean formation of the wanted 1,2-dihydroquinoline with an excellent yield of 97%.

With these conditions in hand we tested the scope of this method. We synthesized first a series of substituted 1,2-dihydroquinolines starting from *N*-methyl- or *N*-allylaniline. The results are presented in Table 1. Besides 1-hexyne we used also 1-pentyne and 1-heptyne giving similar yields (**7** and **8**). Not surprisingly olefins are also tolerated (see **9**). Due to the weak Brønsted acid **4** the method tolerates the trityl-protected 4-pentynol, yielding **10** with an excellent overall yield of 92%. In this case the isolation of the product by chromatography on silica failed due to the lability of the trityl groups under such slightly acidic conditions. Using neutral alumina we could purify **10** without problems. We used also arylacetylenes. The simple phenyl-substituted case gave only moderate yields whereas the donor-substituted arenes yields 86% and 88% (see **11**–**13**). We tested also *N*-allylaniline. This substrate would give an *N*,*N*-allyl-propargylaniline as an intermediate which could undergo two different *N*-aryl-Claisen rearrangements. The sole product which could be isolated with 64% yield was again a quinoline derivative **14**, indicating the propargylic rearrangement at least as the predominant pathway. A by-product resulting from an allyl rearrangement could not be found, but such a reaction cannot be excluded, in particular in view of the different yields of **14** and **6**.

In order to extend the methodology also for the synthesis of tricyclic 1,2-dihydroquinoline derivatives we tested 2,3-dihydroindole and 1,2,3,4-tetrahydroquinoline. The results are presented in Table 2. The reactivity of the tetrahydroquinoline is comparable with that of *N*-methylaniline. The overall yields using alkyl- and aryl-substituted acetylenes are mostly excellent. Phenylacetylene gave a moderate yield of **17**, like in the case of **11**, whereas methyl- or methoxy-substituted phenylacetylenes worked much better. Dihydroindole is also a suitable substrate. The yields for the fused heterocycles **21**–**23** are in the range 53–61%. This means an average of 85–88% for each step of the domino process consisting of hydroamination, alkyne addition, rearrangement and cyclization.

Our hypothesis for the mechanism is summarized in Scheme 2. The reaction of the Zn complex **3** with the anilinium salt **4** gives the catalytically active cationic Zn species, which leads *via* Markovnikov hydroamination, protonation of the enamine, addition of the Zn acetylide and protonation to the propargylic ammonium salt **C**. This should undergo a proton-catalyzed 3,3-sigmatropic rearrangement. The resulting allene **D** can be trapped by protonation to an allyl cation which cyclizes to the final product **F**. A direct proton-catalyzed cyclization of this type of propargylic amines seems less likely to us, because such a synthesis of a 2,2-disubstituted 1,2-dihydroquinolines has to the best of our knowledge not been described. However, a clear proof of our proposal was not possible, since we could not obtain our propargylic amines with a quaternary carbon in an enantioenriched form. The yields of the sequence **C**→**F** are remarkable,

Table 1. Synthesis of bicyclic 1,2-dihydroquinoline derivatives.



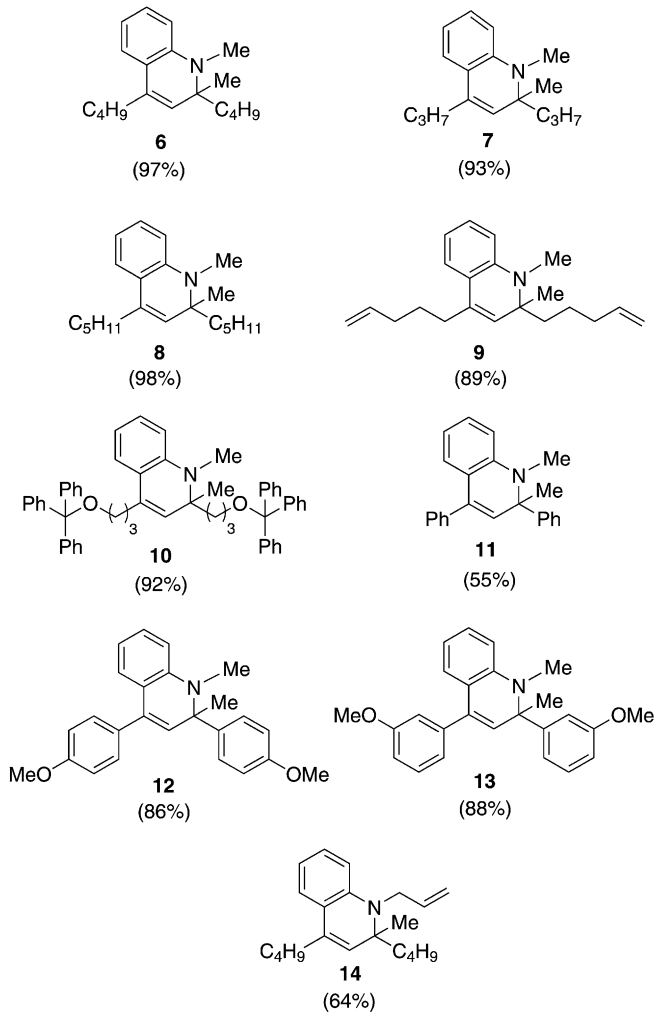
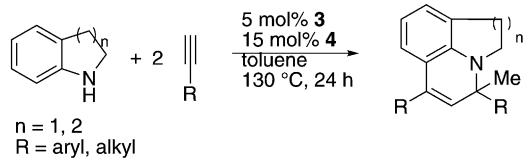
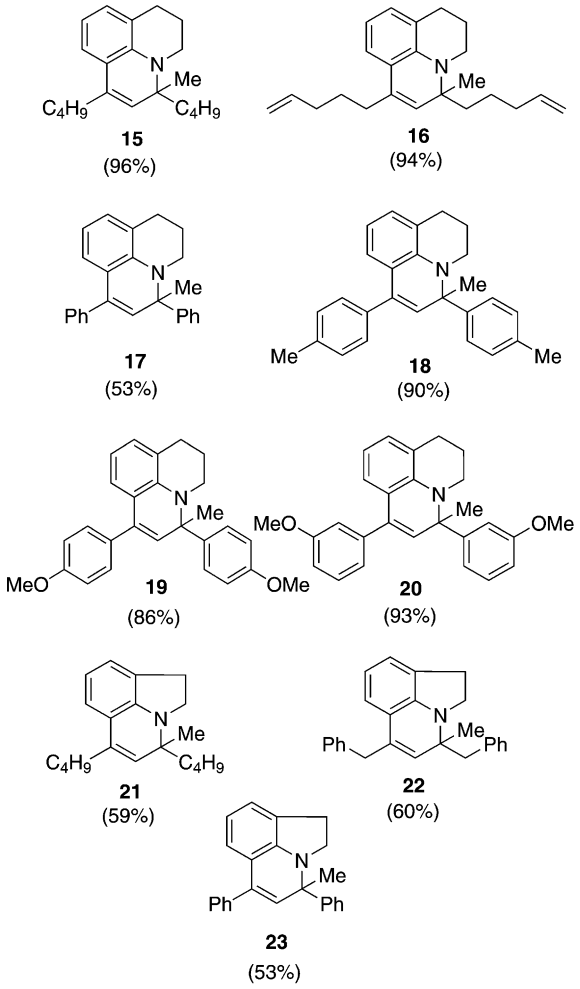


Table 2. Synthesis of tricyclic 1,2-dihydroquinoline derivatives.





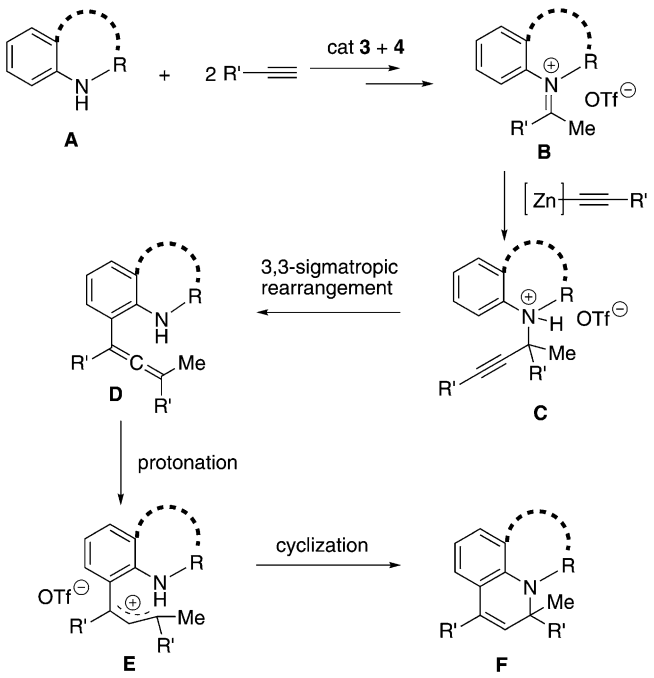
since many described propargylic aromatic *N*-Claisen rearrangements proceed less efficiently. Our studies clearly indicated the importance of the suitable proton source. The use of the catalyst **4** is not only crucial for the activation of the Zn catalyst, but also for the last proton-catalyzed steps. The reaction of propargylic amines with stronger acids like HCl gave no quinoline derivatives. Instead we observed elimination of the aniline substituent. A weak acid like BINOL-derived phosphoric acid, (*R*)-3,3′-bis(9-anthracenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate also works, but it cannot be used in combination with **3**.

In summary, we have developed an efficient consecutive process with two different catalysts working coexistent under the same reaction conditions, allowing a short synthesis of bi- and tricyclic substituted quinoline derivatives from simple starting materials.

Experimental Section

Typical Procedure for the Synthesis of 1,2-Dihydroquinoline Derivatives

Reactions were typically performed in reaction vials and prepared in an inert atmosphere. The precatalyst **3** (24.90 mg, 0.05 mmol) and the cocatalyst **4**



Scheme 2. Proposed mechanism.

$[PhNMe_2H][OTf]$ (40.20 mg, 0.15 mmol) were dissolved in toluene (2 mL). The substrate *N*-methylaniline (107 mg, 1 mmol) and *n*-hexyne (246.42 mg, 3 mmol) were added in the mixture. Subsequently, the mixture was injected into the reaction vial. The reaction mixture was then heated in an oil bath at 130 °C for 24 h. The reaction mixture was then cooled to room temperature and solvent was removed by evaporation. The crude mixture was purified by column chromatography with cyclohexane-DCM on silica giving **6**; yield: 97%.

Procedures and analytical data for all compounds are given in the Supporting Information.

Acknowledgements

We are thankful to the Berlin International Graduate School of Natural Science and Engineering (BIG-NSE) and Cluster of Excellence "Unifying Concepts in Catalysis" coordinated by the TU Berlin – Berlin Institute of Technology for the financial support.

References

[1] a) H. Takahash, Y. Bekkali, A. J. Capolino, T. Gilmore, S. E. Goldrick, P. V. Kaplita, L. Liu, R. M. Nelson, D. Terenzio, J. Wang, L. Zuvela-Jelaska, J. Proudfoot, G. Nabozny, D. Thomson, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5091; b) L. Zhi, C. M. Tegley, B. Pio, S. J. West, K. B. Marschke, D. E. Mais, T. K. Jones, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 415.

[2] J. V. Johnson, *J. Med. Chem.* **1989**, *32*, 1942.

[3] I. V. Ukrainets, L. V. Sidorenko, O. V. Gorokhova, N. A. Jaradat, *Chemistry of Heterocyclic Compounds*, **2006**, *42*, 475.

[4] B. Lockhart, N. Bonhomme, A. Roger, G. Dorey, P. Casara, P. Lestage, *Eur. J. Pharmacol.* **2001**, *416*, 59.

[5] T. K. Jones, D. T. Winn, L. Zhi, L. G. Hamann, C. M. Tegley, C. L. F. Pooley, U.S. Patent 5,688,808, **1997**.

[6] L. Zhi, Tegley, M. Christopher, K. B. Marschke, D. E. Mais, Jones, K. Todd, *J. Med. Chem.* **1999**, *42*, 1466.

[7] M. J. Coughlan, S. W. Elmore, M. E. Kort, P. R. Kym, J. L. Moore, J. K. Pratt, A. X. Wang, J. P. Edwards, T. K. Jones, *Patent* WO 9941256, **1999**.

[8] Microreview: T. Kitamura, *Eur. J. Org. Chem.* **2009**, 1111–1125; a) X. Y. Liu, C. M. Che, *Angew. Chem.* **2008**, *120*, 3865; *Angew. Chem. Int. Ed.* **2008**, *47*, 3805; b) M. Arisawa, C. Theeraladanon, A. Nishida, M. Nakagawa, *Tetrahedron Lett.* **2001**, *42*, 8029; c) K. A. Parker, T. L. Mindt, *Org. Lett.* **2002**, *4*, 4265; d) C. S. Yi, S. Y. Yun, I. A. Guzei, *J. Am. Chem. Soc.* **2005**, *127*, 5782; e) G. L. Lu, J. L. Portscheller, H. C. Malinakova, *Organometallics* **2005**, *24*, 945; f) R. Kamakshi, B. S. R. Reddy, *Catal. Commun.* **2007**, *8*, 825.

[9] X.-Y. Hua, J.-C. Zhang, W. Wie, J.-X. Ji, *Tetrahedron Lett.* **2011**, *52*, 2903–2905.

[10] a) S. Kamiguchi, I. Takahshi, H. Kurokawa, H. Miura, T. Chihara, *Appl. Catal. A* **2006**, *309*, 70; b) M. E. Theoclitou, L. A. Robinson, *Tetrahedron Lett.* **2002**, *43*, 3907.

[11] a) B. C. Ranu, A. Hajra, S. S. Dey, U. Jana, *Tetrahedron* **2003**, *59*, 813; b) K. Makino, O. Hara, Y. Takiguchi, T. Katano, Y. Asakawa, K. Hatano, Y. Hamada, *Tetrahedron Lett.* **2003**, *44*, 8925.

[12] a) P. Evans, R. Grigg, M. Monteith, *Tetrahedron Lett.* **1999**, *40*, 5247; b) M. Arisawa, C. Theeraladanon, A. Nishida, M. Nakagawa, *Tetrahedron Lett.* **2001**, *42*, 8029–8033.

[13] a) Y. M. Luo, Z. G. Li, C. J. Li, *Org. Lett.* **2005**, *7*, 2675; b) X. Y. Liu, P. Ding, J. S. Huang, C. M. Che, *Org. Lett.* **2007**, *9*, 2645; c) Y. Zhou, E. Feng, G. Liu, D. Ye, J. Li, H. Jiang, H. Liu, *J. Org. Chem.* **2009**, *74*, 7344–7348.

[14] Y. Luo, Z. Li, C-J. Li, *Org. Lett.* **2005**, *7*, 2675–2678.

[15] C.-S. Yi, S.-Y. Yun, I.-A. Guzei, *J. Am. Chem. Soc.* **2005**, *127*, 5782–5783.

[16] a) X.-Y. Liu, P. Ding, J.-S. Huang, C.-M. Che, *Org. Lett.* **2007**, *9*, 2645–2648; b) X.-Y. Liu, C.-M. Che, *Angew. Chem.* **2008**, *120*, 3865–3870; *Angew. Chem. Int. Ed.* **2008**, *47*, 3805–3810.

[17] For recent examples of relay domino sequences, see: a) Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, P.-F. Xu, D. J. Dixon, *Angew. Chem.* **2009**, *121*, 10018–10022; *Angew. Chem. Int. Ed.* **2009**, *48*, 9834–9838; b) Z.-Y. Han, H. Xiao, X.-H. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 14452–14453; c) S. Chercheja, T. Rothenbücher, P. Eilbracht, *Adv. Synth. Catal.* **2009**, *351*, 339–344; d) S. P. Lathrop, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628–13630; e) H. Rahaman, Á. Madarász, I. Pápai, P. M. Pihko, *Angew. Chem.* **2011**, *123*, 6247–6251; *Angew. Chem. Int. Ed.* **2011**, *50*, 6123–6127; f) P. Julien, B. Aicha, B. Gaelle, S. Jean, *Angew. Chem.* **2011**, *123*, 3343–3347; *Angew. Chem. Int. Ed.* 2011, 50, 3285–3289; g) B. M. Trost, N. Maulide, R. C. Livingston, *J. Am. Chem. Soc.* **2008**, *130*, 16502–16503;

h) L. F. Tietze, K. M. Sommer, J. Zinngrebe, F. Stecker, *Angew. Chem.* **2005**, *117*, 262–264; *Angew. Chem. Int. Ed.* **2005**, *44*, 257–259; i) S. A. A. El Bialy, H. Braun, L. F. Tietze, *Angew. Chem.* **2004**, *116*, 5505–5507; *Angew. Chem. Int. Ed.* **2004**, *43*, 5391–5393; j) K. C. Nicolaou, T. R. Wu, Q. Kang, D. Y.-K. Chen, *Angew. Chem.* **2009**, *121*, 3492–3495; *Angew. Chem. Int. Ed.* **2009**, *48*, 3440–3443; k) E. R. Strieter, A. Koglin, Z. D. Aron, C. T. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 2113–2115.

[18] T. K.-Y. Desmond, T.-G. Foo, F.-W. Yip, *Organometallics* **2011**, *30*, 4136–4143; B. Klaus, P. Oliver, *Angew. Chem.* **2011**, *123*, 6295–6298; *Angew. Chem. Int. Ed.* **2011**, *50*, 6171–6174; B. Amadeu, P.-U. Cristina, B. Carles, G. Henrik, F. Elena, *Angew. Chem.* **2011**, *123*, 7296–7299; *Angew. Chem. Int. Ed.* **2011**, *50*, 7158–7161.

[19] a) M. Biyikal, M. Porta, P. W. Roesky, S. Blechert, *Adv. Synth. Catal.* **2010**, *352*, 1870–1875. For other alkyne-imine addition reaction see: b) T. Zeng, L. Yang, R. Hudson, G. Song, A. R. Moores, C. J. Li, *Org. Lett.* **2011**, *13*, 442–445; c) S. Zhu, W. Yan, B. Mao, X. Jiang, R. Wang, *J. Org. Chem.* **2009**, *74*, 6980.

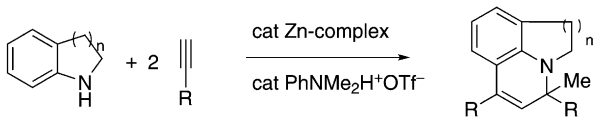
[20] a) R. D. Dillard, D. E. Pavey, D. N. Benslay, *J. Med. Chem.* **1973**, *16*, 251; b) U. K. Pomeranz, H. J. Hansen, H. Schmid, *Helv. Chim. Acta* **1973**, *56*, 2981; c) S. Jolidon, H.-J. Hansen, *Helv. Chim. Acta* **1977**, *60*, 978; d) R. D. Dillard, D. E. Pavey, D. N. Bensley, *J. Med. Chem.* **1973**, *16*, 251; e) M. A. Holman, N. M. Williamson, A. D. Ward, *Aust. J. Chem.* **2005**, *58*, 368.

[21] A. Saito, A. Kanno, Y. Hanzawa, *Angew. Chem.* **2007**, *119*, 4005; *Angew. Chem. Int. Ed.* **2007**, *46*, 3931. For further examples of aromatic Aza-Claisen rearrangements, see: M. Hiersemann, U. Nubbemeyer, *The Claisen Rearrangement: Methods and Applications*, Wiley-VCH, Weinheim, **2007**.

[22] H. Scheurer, J. Zsindely, H. Schmid, *Helv. Chim. Acta* **1973**, *56*, 478.

COMMUNICATIONS

6 Synthesis of Bi- and Tricyclic 1,2-Dihydroquinoline Derivatives from Arylamines and Alkynes by a Consecutive Zinc-Ammonium Salt Catalysis



Adv. Synth. Catal. **2012**, *354*, 1 – 6

Nibadita Purkait, Siegfried Blechert*

