Synthetic Methods

CBr₄-Mediated Cross-Dehydrogenative Coupling Reaction of Amines

Congde Huo,* Haisheng Xie, Mingxia Wu, Xiaodong Jia, Xicun Wang, Fengjuan Chen, and Jing Tang^[a]

Abstract: A novel CBr₄-mediated dehydrogenative Povarov/aromatization tandem reaction of glycine derivatives with alkenes, leading to complex quinoline derivatives, and a CBr₄-mediated dehydrogenative C–H functionalization of *N*-aryl tetrahydroisoquinolines with nucleophiles to form C–C and C–P bonds are reported. The reactions were performed under very simple and mild reaction conditions; only CBr₄ was used as a promoter. A plausible mechanism involving a radical process is proposed.

The imino Diels-Alder reaction was first discovered by Povarov in the 1960s.^[1] It consists of a formal [4+2] cycloaddition reaction of imines derived from aromatic amines with electron-rich alkenes to give tetrahydroquinolines. Since the pioneering study reported by Li in 2008,^[2] the oxidative dehydrogenative coupling of glycine derivatives has gained significant attention. This reaction relies on the oxidation of the secondary amine substrates to generate reactive imine intermediates.^[3] A onepot oxidative Povarov/aromatization tandem reaction of glycine derivatives with alkenes was first reported by García Mancheño et al. in 2011 (Scheme 1, A).^[4] A series of substituted quinolines were synthesized by using FeCl₃ as the catalyst and a 2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) oxoammonium salt as the oxidant. In 2012, Jia et al. developed the same tandem process under the catalysis of radical cation salts in the presence of InCl₃ under O₂ atmosphere (Scheme 1, B).^[5] In the same year, a similar approach between glycine derivatives and alkynes was developed by Hu et al. by using FeCl₃ as the catalyst and (tBuO)₂ as the oxidant.^[6] Although these examples represent notable progress in this area, metal reagents and complex catalyst systems were always required. Very recently, we discovered an unprecedented auto-oxidation coupling of glycine derivatives (Scheme 1, C).^[7] The reaction was performed in the absence of any redox-active catalyst and chemical oxidant under mild conditions; only organic solvents and an air atmosphere were required. However, under these autoxidation conditions, dehydrogenative Povarov/aromatization the

 [a] Dr. C. Huo, H. Xie, M. Wu, Dr. X. Jia, Dr. X. Wang, F. Chen, J. Tang College of Chemistry and Chemical Engineering Northwest Normal University, Lanzhou, Gansu 730070 (P. R. China) Fax: (+86)0931-7971989 E-mail: huocongde1978@hotmail.com
 Sunporting information for this article is quailable on the WMW university

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201500453. $\begin{array}{c} R^{1} \underbrace{ \left(\begin{array}{c} F^{3} \\ + \end{array} \right)^{2}}_{1} \underbrace{ \text{conditions } \mathbf{A} - \mathbf{D} \\ + \underbrace{ \left(\begin{array}{c} F^{3} \\ + \end{array} \right)^{2}}_{N} \underbrace{ \left(\begin{array}{c} F^{2} \\ + \end{array} \right)^{2}}_{N} \underbrace{$

Scheme 1. Dehydrogenative Povarov/aromatization tandem reaction.

tandem reaction of glycine derivatives with alkenes was limited to highly electron-rich alkenes. The quinoline products obtained by this tandem reaction are important structures that can be found in a number of biologically significant natural products and synthetic drugs.^[8] Therefore, the development of a more practical and metal-free method under simpler reaction conditions is still highly desired.

Carbon tetrabromide (CBr₄) has been used for several organic transformations;^[9] for example, it catalyzes the deprotection trialkylsilyl esters and β -(trimethylsilyl)ethoxymethyl ethers, $^{[9a,b]}$ esterifications, $^{[9c]}$ the formation of C–S bonds, $^{[9d]}$ the acetalization of aldehydes,^[9e] the tetrahydropyranylation of alcohols,^[9e] and the Friedel-Crafts alkylation of indoles with carbonyl compounds.^[9f] In this Communication, CBr₄ has been found to show good reactivity in cross-dehydrogenative coupling (CDC) reactions.^[10] Herein, we describe a novel, metalfree CBr₄-mediated dehydrogenative Povarov/aromatization tandem reaction of glycine derivatives with alkenes. Furthermore, we also developed an efficient CBr₄-promoted dehydrogenative C-H functionalization of N-aryl tetrahydroisoquinolines.^[11-13] To the best of our knowledge, no CBr₄-mediated CDC reaction of amines has been described yet. The use of CBr₄ instead of complex catalyst systems involving metals has many advantages, such as the low cost and easy handling.

These are not the final page numbers! **77**

Wiley Online Library

1

Chem. Eur. J. 2015, 21, 1-5





Recently, we observed the auto-oxidative coupling of glycine derivatives in acetonitrile (CH₃CN) and dichloroethane (DCE) as mixed reaction solvents. Further investigations revealed that DCE was crucial for this auto-oxidative progress.^[7] This information encouraged us to test other halogen-containing reagents. Initially, glycine ester 1 a and styrene 2 a were chosen as model substrates. Interestingly, ethyl 6-methyl-4-phenylquinoline-2carboxylate (3 aa) was produced in 55% yield when 1.0 equivalent of CBr₄ was used under air atmosphere (Table 1, entry 5). The most surprising finding was that the efficiency of this transformation was promoted when the reaction was carried out in an argon-filled Schlenk tube with an air balloon on the branch pipe (Table 1, entry 6, see the Supporting Information for experimental device). We believe the reason is that the formation of the side product ethyl 2-oxo-2-(p-tolylamino)acetate^[7] from self-oxidation can be avoided under these decreased oxygen concentration conditions. Further studies indicated that the yields decreased with lower CBr₄ loadings (Table 1, entries 9 and 10). In addition, both increasing and decreasing the temperature resulted in lower yields (Table 1, entries 11-13). The effect of different solvents was also surveyed, the best choice still being CH₃CN. All together it was discovered that 1.0 equivalent of CBr₄ in CH₃CN at room temperature were the optimized reaction conditions (81%, Table 1, entry 6).

Under the optimized conditions given above, the scope of the glycine derivatives 1 was investigated. Various glycine esters (Table 2, A) and glycine amides (Table 2, B) could be smoothly transformed into the desired products. In addition, a short peptide (1 k) was also tolerated in this transformation, generating 3 ka in 84% yield (Table 2, F). The scope of this

CBr₄-induced anaerobic CDC reaction leading to substituted quinolines was further expanded to a range of substituted styrenes (Table 2, D, E and F). The results demonstrate that styrenes with electron-donating or electron-withdrawing groups on the phenyl ring are suitable substrates in this transformation. It is worth noting that when indene was used, complex polycyclic quinolines were obtained (Table 2, C). To evaluate the practicability of our method, the reaction of 1a with 2a was performed on a 20 mmol scale in a single batch; no obvious loss of yield was observed (78% yield).

To develop a more general and useful method, we subsequently turned our attention to investigating the dehydrogenative coupling reaction of tertiary amines under the CBr₄-induced conditions. First, the sp³-sp² C-H coupling between N-aryl tetrahydroisoquinolines and indoles was successfully performed.[11] Different N-aryl tetrahydroisoguinolines (Table 3, A) and indoles with electron-donating or electron-withdrawing groups (Table 3, B) all worked well under the present reaction conditions. The coupling reaction between two sp³ C–H bonds is a very attractive but challenging area. CBr₄ was also demonstrated to be an efficient promoter for the dehydrogenative Mannich reaction of N-aryl tetrahydroisoquinolines and non-activated ketones under mild conditions

Chem. Eur. J. 2015 , 21, 1–5	www.chemeurj.org

www.chemeuri.org

2

ropean Journal ommunication



(Table 3, C).^[12] The combination of *N*-aryl tetrahydroisoguinolines and phosphites could also give the corresponding C-P coupling products (Table 3, D).^[13]

To probe the mechanism of this transformation, some control experiments were carried out. Firstly, the reaction of 1 a in the absence of styrene (2) under the standard reaction conditions was investigated. Imine 7a and its dimer 8a were ob-



© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **KR** These are not the final page numbers!





tained in a low yield (Scheme 2, rxn. 1). This result indicates that the imine is involved as an intermediate in this CBr₄-mediated process. Secondly, the reaction of **1a** and **2a** in the presence of 1.0 equivalent of CBr₄ (Scheme 2, rxn. 2), HCBr₃ (Scheme 2, rxn. 3), H₂CBr₂ (Scheme 2, rxn. 4), or HBr (Scheme 2, rxn. 5) was investigated. The desired product **3aa** was obtained in a very low yield in reaction 3 and not obtained in reactions 4 and 5. These results indicate that CBr₄ is crucial for this transformation and that only one bromine atom in CBr₄ is active for this transformation. Furthermore, the reaction of imine **7a** and styrene **2a** in the presence of 1.0 equivalent of CBr₄ (Scheme 2, rxn. 7), HCBr₃ (Scheme 2, rxn. 8), or HBr



Scheme 2. Control experiments.

Chem. Eur. J. 2015, 21, 1–5 www.chemeurj.org

These are not the final page numbers! 77

used, the desired product **3 aa** was detected, albeit in only 12% yield (rxn. 7), which is much lower than that of the model reaction (81%, Scheme 2, rxn. 2). However, when HBr was used, the desired product **3 aa** was obtained in a higher yield (56%, Scheme 2, rxn. 9). These results indicate that the in situ generated HBr is important for the subsequent [4+2] cycloaddition process. In addition, radical trapping experiments were conducted by employing TEMPO as a radical scavenger. No product was obtained in the standard reaction of **1 a** with **2 a** (Scheme 2, rxn. 6), but no inhibition was observed in the reaction of **7 a** with **2 a** (Scheme 2, rxn. 10). These results suggest that the oxidation step of the imine generation in the present reaction includes a radical process.

(Scheme 2, rxn. 9) was investigated. When CBr₄ was

Although the mechanism of this transformation is not fully clarified yet, a plausible mechanism based on the results described above is depicted in Scheme 3. Secondary amine 1 and CBr_4 initially react to form intermediate **A.** Then, a homolytic cleavage

of the weak N–Br bond occurs to form the radical cation intermediate ${f B}$ and a bromine radical. Next, after abstraction of



Scheme 3. Proposed mechanism.

3

a hydrogen atom by the Br radical, the radical intermediate **C** is formed. Intermediate **C** can react with dioxygen to provide the peroxide radical **D**, which then abstracts a hydrogen atom from substrate **1** to form the hydroperoxide **E** and radical **C**. Chain propagation continues until all substrate **1** is consumed. Subsequently, a Povarov reaction and the following aromatization result in the desired product **3**.

In summary, we have demonstrated a novel CBr_4 -mediated dehydrogenative Povarov/aromatization tandem reaction of glycine derivatives with alkenes, leading to complex quinoline derivatives, and a CBr_4 -mediated dehydrogenative C–H functionalization of *N*-aryl tetrahydroisoquinolines with nucleophiles to form C–C and C–P bonds. The starting materials and the promoter are commercial available or easily prepared. This



method is highly efficient and has a broad substrate scope. The reactions were performed under very simple and mild reaction conditions; only CBr_4 was used as a promoter. This work also presents a new way to initiate radical reactions under mild reaction conditions. Further applications of these CBr_4 -mediated methodologies will be reported shortly.

Experimental Section

General procedure for the CBr₄-mediated CDC reaction of glycine derivatives with alkenes

Glycine derivatives (1, 1.0 mmol), alkenes (1, 20 mmol), and CBr_4 (1.0 mmol) were dissolved in CH_3CN (30 mL). The reactions were performed in an argon-filled Schlenk tube with an air balloon on the branch pipe at ambient temperature and completed within 16 h. The products were isolated by column chromatographic separation.

General procedure for the CBr₄-mediated CDC reaction of *N*-aryl tetrahydroisoquinolines with nucleophiles

N-Aryl tetrahydroisoquinolines (**4**, 1.0 mmol), nucleophiles (**5**, 1.5 mmol), and CBr_4 (1.0 mmol) were dissolved in THF (40 mL). The reactions were performed in an argon-filled Schlenk tube with an oxygen balloon on the branch pipe at ambient temperature and completed within 48 h. The products were isolated by column chromatographic separation.

Acknowledgements

We thank the National Natural Science Foundation of China(21262029) and the Fok Ying Tong Education Foundation(141116) for financial support of this work.

Keywords: alkenes · carbon tetrabromide · dehydrogenation · glycine derivatives · quinolines · tetrahydroisoquinolines

- a) L. S. Povarov, B. M. Mikhailov, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* 1963, 953–956; b) L. S. Povarov, V. I. Grigos, B. M. Mikhailov, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* 1963, 2039–2041; c) L. S. Povarov, *Russian Chem. Rev.* 1967, *36*, 656–670.
- [2] L. Zhao, C.-J. Li, Angew. Chem. Int. Ed. 2008, 47, 7075-7078; Angew. Chem. 2008, 120, 7183-7186.
- [3] a) L. Zhao, O. Baslé, C.-J. Li, Proc. Natl. Acad. Sci. USA 2009, 106, 4106–4111; b) J. Xie, Z.-Z. Huang, Angew. Chem. Int. Ed. 2010, 49, 10181–10185; Angew. Chem. 2010, 122, 10379–10383; c) G. Zhang, Y. Zhang, R. Wang, Angew. Chem. Int. Ed. 2011, 50, 10429–10432; Angew. Chem. 2011, 123, 10613–10616; d) Z. Q. Wang, M. Hu, X. C. Huang, L. B. Gong, Y. X. Xie, J. H. Li, J. Org. Chem. 2012, 77, 8705–8711; e) W. Wei, R. Song, J. Li, Adv. Synth. Catal. 2014, 356, 1703–1707; f) P. Liu, Y. Li, H. Wang, Z. Wang, X. Hu, Tetrahedron Lett. 2012, 53, 6654–6656; g) S. Zhu, M. Ruep-

ing, Chem. Commun. 2012, 48, 11960–11962; h) C. Huo, C. Wang, M. Wu, X. Jia, H. Xie, Y. Yuan, Adv. Synth. Catal. 2014, 356, 411–415; j) C. Huo, C. Wang, C. Sun, X. Jia, X. Wang, W. Chang, M. Wu, Adv. Synth. Catal. 2013, 355, 1911–1916; j) W.-J. Yoo, A. Tanoue, S. Kobayashi, Asian. J. Org. Chem. 2014, 3, 1066–1069.

- [4] a) H. Richter, O. García Mancheño, Org. Lett. 2011, 13, 6066–6069; b) R.
 Rohlmann, T. Stopka, H. Richter, O. García Mancheño, J. Org. Chem. 2013, 78, 6050–6064.
- [5] a) X. Jia, F. Peng, C. Qing, C. Huo, X. Wang, Org. Lett. 2012, 14, 4030–4033; b) X. Jia, Y. Wang, F. Peng, C. Huo, L. Yu, J. Liu, X. Wang, J. Org. Chem. 2013, 78, 9450–9456.
- [6] P. Liu, Z. Wang, J. Lin, X. Hu, Eur. J. Org. Chem. 2012, 1583-1589.
- [7] C. Huo, Y. Yuan, M. Wu, X. Jia, X. Wang, F. Chen, J. Tang, Angew. Chem. Int. Ed. 2014, 53, 13544–13547.
- [8] a) V. V. Kouznetsov, *Tetrahedron* 2009, 65, 2721–2750; b) R. Musiol, M. Serda, S. Hensel-Bielowka, J. Polanski, *Curr. Med. Chem.* 2010, 17, 1960–1973.
- [9] a) M. Y. Chen, A. S.-Y. Lee, J. Org. Chem. 2002, 67, 1384–1387; b) A. S.-Y. Lee, F. Y. Su, Tetrahedron Lett. 2005, 46, 6305–6309; c) L. Zhang, Y. Luo, R. Fan, J. Wu, Green Chem. 2007, 9, 1022–1025; d) J. Tan, F. Liang, Y. Wang, X. Cheng, Q. Liu, H. Yuan, Org. Lett. 2008, 10, 2485–2488; e) C. Huo, C. Sun, C. Wang, X. Jia, W. Chang, ACS Sustainable Chem. Eng. 2013, 1, 549–553; f) C. Huo, T. H. Chan, Adv. Synth. Catal. 2009, 351, 1933–1938; g) T. Sugai, A. Itoh, Tetrahedron Lett. 2007, 48, 9096–9099; h) S. Hirashima, T. Nobuta, N. Tada, T. Miura, A. Itoh, Org. Lett. 2010, 12, 3645–3647; i) V. P. Srivastava, A. K. Yadav, L. D. S. Yadav, *RSC adv.* 2014, 4, 5815–5818.
- [10] For initial studies on the CDC reaction, see: a) Z. Li, C.-J. Li, J. Am. Chem. Soc. 2004, 126, 11810; b) Z. Li, C.-J. Li, Org. Lett. 2004, 6, 4997; c) S. Murahashi, N. Komiya, H. Terai, T. Nakae, J. Am. Chem. Soc. 2003, 125, 15312; for selective reviews on the CDC reaction, see: d) S. A. Girard, T. Knauber, C.-J. Li, Angew. Chem. Int. Ed. 2014, 53, 74–100; e) C. S. Yeung, V. M. Dong, Chem. Rev. 2011, 111, 1215–1292; f) M. Klussmann, D. Sureshkumar, Synthesis 2011, 353–369; g) C.-J. Li, Acc. Chem. Res. 2009, 42, 335–344; h) S. Murahashi, D. Zhang, Chem. Soc. Rev. 2008, 37, 1490–1501.
- [11] a) J. J. Zhong, Q. Y. Meng, G. X. Wang, Q. Liu, B. Chen, K. Feng, C. H. Tung, L. Z. Wu, *Chem. Eur. J.* **2013**, *19*, 6443–6450; b) P. Liu, C.-Y. Zhou, S. Xiang, C.-M. Che, *Chem. Commun.* **2010**, *46*, 2739–2741; c) C. Huo, C. Wang, M. Wu, X. Jia, X. Wang, Y. Yuan, H. Xie, *Org. Biomol. Chem.* **2014**, *12*, 3123–3128.
- [12] a) Y. M. Shen, M. Li, S. Z. Wang, T. G. Zhan, Z. Tan, C. C. Guo, *Chem. Commun.* 2009, 953–955; b) A. Sud, D. Sureshkumar, M. Klussmann, *Chem. Commun.* 2009, 3169–3171; c) Q. Xue, J. Xie, H. Jin, Y. Cheng, C. Zhu, *Org. Biomol. Chem.* 2013, *11*, 1606–1609; d) W. To, Y. Liu, T. Lau, C. Che, *Chem. Eur. J.* 2013, *19*, 5654–5664; e) J. Dhineshkumar, M. Lamani, K. Alagiri, R. Prabhu, *Org. Lett.* 2013, *15*, 1092–1095; f) T. Nobuta, N. Tada, A. Fujiya, A. Kariya, T. Miura, A. Itoh, *Org. Lett.* 2013, *15*, 574–577; g) C. Huo, M. Wu, X. Jia, H. Xie, Y. Yuan, J. Tang, *J. Org. Chem.* 2014, *79*, 9860–9864.
- [13] a) O. Baslé, C.-J. Li, *Chem. Commun.* 2009, 4124–4126; b) M. Rueping, S. Zhu, R. M. Koenigs, *Chem. Commun.* 2011, *47*, 8679–8681; c) D. P. Hari, B. Konig, *Org. Lett.* 2011, *13*, 3852–3855; d) J. Xie, H. Li, Q. Xue, Y. Cheng, C. Zhu, *Adv. Synth. Catal.* 2012, *354*, 1646–1650.

Received: February 4, 2015 Published online on ■■ ■, 0000

4



COMMUNICATION

Go tandem! A novel CBr₄-mediated dehydrogenative Povarov/aromatization tandem reaction of glycine derivatives with alkenes and CBr₄-mediated dehydrogenative C—H functionalization of *N*aryl tetrahydroisoquinolines is reported. The reactions were performed under simple and mild conditions, only CBr₄ and a solvent are required (see scheme). A plausible mechanism involving a radical process is also proposed.



Synthetic Methods

C. Huo,* H. Xie, M. Wu, X. Jia, X. Wang, F. Chen, J. Tang



CBr₄-Mediated Cross-Dehydrogenative 🖳 Coupling Reaction of Amines