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# Curtius-like Rearrangement of an Iron–Nitrenoid Complex and Application in Biomimetic Synthesis of Bisindolylmethanes

Dashan Li,[†,§] Ting Wu,[†,§] Kangjiang Liang,[†,§] and Chengfeng Xia*[,†,‡]

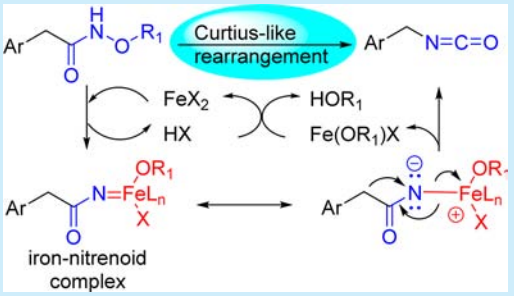
[†]State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, China

[‡]Key Laboratory of Medicinal Chemistry for Natural Resources, Ministry of Education, Yunnan University, Kunming 650091, China

[§]University of Chinese Academy of Sciences, Beijing 100049, China

Supporting Information

**ABSTRACT:** A Curtius-like rearrangement of hydroxamates to isocyanates was discovered. This reaction was initiated from an iron(II)–nitrenoid complex, which was generated by the iron(II)-catalyzed cleavage of N–O bonds of functionalized hydroxamates. To demonstrate the efficiency of this new Curtius-like rearrangement in synthetic chemistry, a biomimetic strategy for the one-pot preparation of bisindolylmethanes was developed.




Thermal or photochemical decomposition of acyl azides to corresponding isocyanates is known as the Curtius rearrangement.[1] Although nitrene intermediates are formed in the pyrolysis of most azido compounds, the mechanism of the Curtius rearrangement under thermal conditions most likely occurs via a concerted process.[2] In contrast, the photochemical Curtius rearrangement proceeds through the formation of nitrenes because the N–$N_2$ bond is easily broken by an energetic photon without alkyl or aryl participation.[3]

Bisindolylmethanes (BIMs), which have a basic skeleton consisting of two indole groups bridged by a single carbon at the 3 and 3′ positions, have been isolated from marine and terrestrial natural sources.[4] BIMs and their analogues exhibit a broad range of distinct biological activities.[5] Arundine **1**, which was isolated from the roots of *Arundo donax*,[4c] has been widely studied in cancer chemotherapy (Figure 1).[6] Arundine **1** suppresses ovarian cancer growth and potentiates the effect of cisplatin in tumor mouse models by targeting the signal transducer and activator of transcription 3[7] and induces apoptosis in prostate cancer.[8] Arundine **1** was also found to promote plant growth.[9] Synthetic BIM analogues, such as bis(5-methylindol-3-yl)methane (**3**), bis(5-bromoindol-3-yl) methane (**4**), and bis(6-chloroindol-3-yl) methane (**5**), have been shown to be inhibitors of the estrogen-induced growth of mammary tumors.[10]

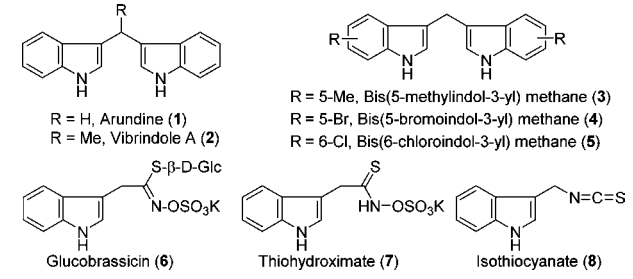



**Figure 1.** Examples of BIMs and biogenous intermediates.

BIMs are biosynthesized from glucobrassicin **6**, which has side chains derived from tryptophan and is among the most widely distributed glucosinolates in nature. After being hydrolyzed by myrosinase, **6** is converted to thiohydroximate **7** (Figure 1).[11] With some specific proteins (e.g., the epithiospecifier protein), the thiohydroxamate intermediate **7** is further converted to isothiocyanate **8** as the major product.[12] Isothiocyanate **8** is volatile and decomposes to the indolyl-3-methylene carbocation by losing one SCN.[13] In plants, the carbocation reacts with various nucleophiles, such as indoles, to yield BIMs. The activated acyl hydroxamates are known to undergo Lossen rearrangement under basic conditions to generate isocyanates.[14] A Lossen-like rearrangement was proposed to occur during the conversion of thiohydroximate to isothiocyanate in the presence of enzymes.[12] Herein, we report the Curtius-like rearrangement of iron–nitrenoid complexes via iron-catalyzed cleavage of the N–O bonds of functionalized heteroauxin hydroxamates and the biomimetic synthesis of BIMs.

Iron(II) was reported to be involved in the conversion of thiohydroximate to isothiocyanate with the epithiospecifier protein.[15] Iron(II) was also reported to cleave the N–O bond

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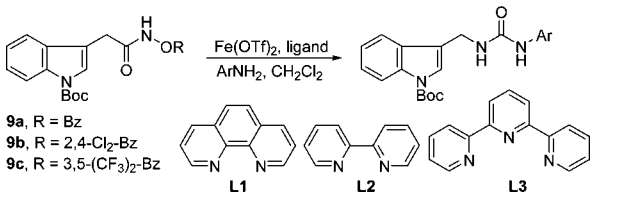
of functionalized hydroxamates or the N−N bond of acyl azides and generate an iron−nitrenoid complex for the aminohydroxylation or aminohalolation of olefins.[16] We proposed that the iron−nitrenoid complex could also undergo a Curtius-like rearrangement to generate the isocyanate.

To verify this hypothesis, the functionalized heteroauxin hydroxamates **9** were subjected to the proposed rearrangement with $Fe(OTf)_2$ as the catalyst. Aniline was added as a nucleophile to capture the unstable isocyanate intermediate and give the corresponding urea. In the presence of 1,10-phenanthroline (**L1**) as the ligand, we observed that substrate **9a** was consumed and that the urea **10** was generated in moderate yield (Table 1, entry 1, and Table S1 in the Supporting Information). Changing the functionalized group by incorporating electron-withdrawing substituents, such as 2,4-$Cl_2$ (**9b**) or 3,5-$(CF_3)_2$ (**9c**), distinctly improved the yield to 85% (entries 2 and 3). However, no reaction occurred in the absence of the catalyst $Fe(OTf)_2$ (entry 4). To verify whether the reaction proceeded through a Lewis acid promoted Lossen process,[17] both of the non-redox-active controls ($Zn(OTf)_2$ and $Sc(OTf)_3$) were performed and no rearrangements were observed (Table S2). These experimental results suggested that the formation of the iron−nitrenoid complex was necessary for the rearrangement. Therefore, this rearrangement proceeds as a Curtius-like rearrangement rather than a Lossen rearrangement. Other iron(II) catalysts, such as $FeCl_2$, $FeBr_2$, $Fe(OAc)_2$, and $FeSO_4$, also catalyzed the rearrangement, albeit in lower yields. However, trace amount of products were detected when $Fe(NTf_2)_2$ or $K_4Fe(CN)_6$ was used as the catalyst (Table S2). The ligand played an important role in the reaction. When no ligand was added, only a trace amount of urea was isolated. Changing the ligand to 2,2′-bipyridine (**L2**) resulted in a lower yield, whereas the reaction failed to proceed with 2,2′:6′,2″-terpyridine (**L3**) (entries 5−7). A variety of arylamines were evaluated under optimized conditions and gave the corresponding ureas in good yields (entries 8−15). In contrast, alkylamines removed the functionalized Bz groups by aminolysis and resulted in no reaction.

**Table 1. Optimization of the Reaction Conditions**

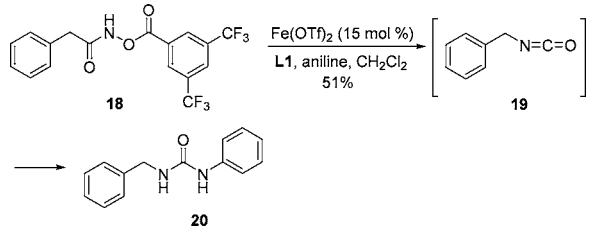



| entry[a] | substrate | $ArNH_2$ | ligand | product | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **9a** | aniline | **L1** | **10** | 63 |
| 2 | **9b** | aniline | **L1** | **10** | 72 |
| 3 | **9c** | aniline | **L1** | **10** | 85 |
| 4[c] | **9c** | aniline | **L1** | **10** | 0 |
| 5 | **9c** | aniline | | **10** | 5 |
| 6 | **9c** | aniline | **L2** | **10** | 50 |
| 7 | **9c** | aniline | **L3** | **10** | 0 |
| 8 | **9c** | *p*-toluidine | **L1** | **11** | 84 |
| 9 | **9c** | mesitylamine | **L1** | **12** | 78 |
| 10 | **9c** | *p*-anisidine | **L1** | **13** | 87 |
| 11 | **9c** | *p*-chloroaniline | **L1** | **14** | 81 |
| 12 | **9c** | *o*-bromoaniline | **L1** | **15** | 80 |
| 13 | **9c** | *o*-iodoaniline | **L1** | **16** | 77 |
| 14 | **9c** | *p*-carbomethoxy aniline | **L1** | **17** | 79 |

[a]The reaction was conducted with 15 mol % of iron(II) as a catalyst at room temperature. [b]Isolated yield. [c]No iron(II) catalyst was added.

To investigate if other acyl hydroxamates can also undergo the Curtius-like rearrangement, phenylacetyl hydroxamate **18** was subjected to the optimized reaction conditions with $Fe(OTf)_2$ as catalyst and **L1** as ligand. As shown in Scheme 1, urea **20** was isolated in 51% yield. Urea **20** was apparently generated from the isocyanate intermediate **19**, which was also formed by a Curtius-like rearrangement.

**Scheme 1. Curtius-like Rearrangement of Phenylacetyl Hydroxamate by an Iron(II) Catalyst**




Using the established iron(II)-catalyzed Curtius-like rearrangement, we attempted the biomimetic synthesis of BIMs. First, we demonstrated the method for the one-pot preparation of symmetric BIMs. A series of differently substituted heteroauxin hydroxamates with 3,5-$(CF_3)_2$-Bz as the functional group were used as substrates. The correspondingly substituted indoles were used as nucleophiles. As shown in Scheme 2, when unsubstituted heteroauxin hydroxamate and indole were subjected to the reaction, natural arundine **1** was obtained in 72% yield. For the synthesis of BIMs **3**, **4**, and **5**, which inhibit the estrogen-induced growth of mammary tumors, the methyl-, bromo-, or chloro-substituted substrates were used in the reactions, and the BIMs were obtained in 71, 73, and 75% yields, respectively. Since the heteroauxin also serves as a competitive nucleophile during the reaction, 2 equiv of indole was added to depress the side reaction.

This method also provides an efficient strategy for the preparation of unsymmetrical BIMs, which are reported less frequently than the symmetric BIMs.[18] After the N−O bond of the 3,5-$(CF_3)_2$-Bz-functionalized heteroauxin hydroxamate was cleaved by $Fe(OTf)_2$ and the indolyl iminium was formed, different indole derivatives coupled with the iminium to give BIMs. In addition to the electron-donating indole nucleophiles (**23** and **24**), the various halo-substituted indole nucleophiles also afforded good yields of compounds **25**−**29**. It should be noted that the electron-deficient indole derivatives, such as nitro or methyl carbonate, also smoothly produced the corresponding BIMs with acceptable yields (**30** and **31**). Moreover, when the *N*-methyl or *N*-benzyl indoles were subjected to this synthesis strategy, mono-N-substituted arundines **35** and **36** were obtained in good yield (75 and 73%).

The proposed iron(II)-catalyzed Curtius-like rearrangement mechanism is outlined in Scheme 3. The heteroauxin hydroxamate reacted with the iron(II) catalyst to give the iron−nitrenoid complex through cleavage of the N−O bond. Then, a Curtius-like rearrangement was triggered to afford the isocyanate intermediate. When there was an electron-with-



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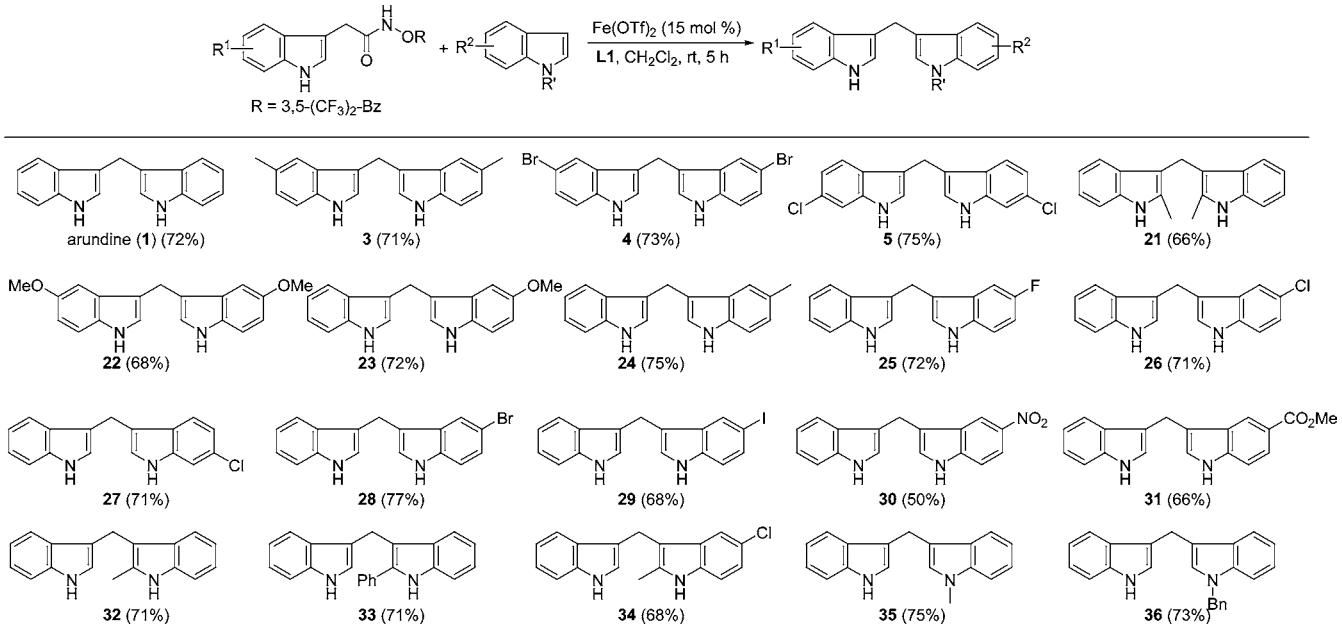
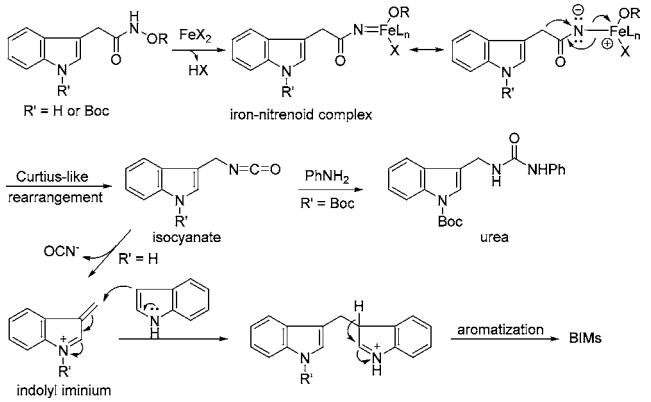
**Scheme 2. Biomimetic One-Pot Synthesis of BIMs via Curtius-like Rearrangement**




**Scheme 3. Proposed Mechanism of Biomimetic Synthesis of BIMs with Iron(II)-Catalyzed Curtius-like Rearrangement**




drawing group, such as a Boc protecting group, located on the N1 position, the nitrogen of the indole was electron-deficient and the isocyanate intermediate was stable enough and was added by aniline. If the indole was unprotected or protected with an electron-donating alkyl group, the lone pair electrons of nitrogen facilitate the quick loss of one OCN anion and biomimetically generate the indolyl iminium. Finally, an indole nucleophilic addition of the indolyl iminium affords the corresponding BIM.

In conclusion, an iron(II)-catalyzed Curtius-like rearrangement was discovered. The reaction proceeded via the decomposition of an iron−nitrenoid complex formed by cleavage of the N−O bonds of functionalized heteroauxin hydroxamates. The generated isocyanates were verified through capture by arylamines. This rearrangement reaction was successfully employed to biomimetically synthesize BIMs. The synthetic strategy featured an iron(II)-catalyzed cleavage of the N−O bonds of functionalized hydroxamates to form an iron−nitrenoid complex and the subsequent generation of indolyl isocyanate through Curtius-like rearrangement. After the spontaneously biomimetic loss of the isocyanate anion, the corresponding indolyl iminium reacted with indoles to afford BIMs in a one-pot manner.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00864.

Experimental procedures and compound characterization (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: xiachengfeng@mail.kib.ac.cn.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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