Sulfur(IV)-mediated umpolung \(\alpha\)-heterofunctionalization of 2-oxazolines†

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The \(\alpha\)-umpolung of carbonyl compounds significantly expands the boundaries of traditional carbonyl chemistry. Despite various umpolung methods available today, reversing the inherent reactivity of carbonyls still remains a substantial challenge. In this article, we report the first use of sulfonium salts, in lieu of well-established hypervalent iodoses, for the carbonyl umpolung event. The protocol enables the incorporation of a wide variety of heteroatom nucleophiles into the \(\alpha\)-carbon of 2-oxazolines. The success of this investigation hinges on the following factors: (1) the use of sulfoxides, which are abundant, structurally diverse and tunable, and easily accessible, ensures the identification of a superior oxidant namely phenoxathiin sulfoxide for the umpolung reaction; (2) the “assembly/deprotonation” protocol previously developed for rearrangement reactions in our laboratory was successfully applied here for the construction of \(\alpha\)-umpoled 2-oxazolines.

Introduction

The \(\alpha\)-functionalization of carbonyl compounds represents a fundamental process in synthetic chemistry.3 Due to its innate nucleophilicity, the \(\alpha\)-carbon of the carbonyl functionality reacts, typically as an enol/enolate intermediate, with electrophiles. In contrast, reversing the polarity of carbonyls with halogens, hypervalent iodoses, transition metals and other oxidative mediators provides them with unnatural electrophilic properties and consequently greatly expands the scope of coupling partners from electrophiles to nucleophiles.2 In this context, umpolung tactics using hypervalent iodine reagents enabling \(\alpha\)-functionalization of ketones with nucleophiles have gained enormous attention since their discovery in 1978 by Mizukami et al.3 In principle, there are two typical carbonyl sources used for iodine(III)-mediated umpolung reactions.4 First, ketones can be treated with nucleophile-substituted aryl iodoses to implement the umpolung event (Fig. 1a, eqn (1)).3 However, the need for the presynthesis of chemically stable and/or isolable nucleophile-substituted aryl iodoses often restricts the scope of nucleophiles. In contrast, the use of enol silyl ethers as a carbonyl source enables the carbonyl umpolung event mediated by simple aryl iodoses which significantly expands the scope of nucleophiles (eqn (2)).6 In addition, Maulide and co-workers developed an electrophilic-amide-
activation based umpolung protocol wherein the lutidine N-oxide as a nucleophile is used to trap the electrophilically activated amides thus enabling α-umpolung of amides (eqn (3)).

Similar to hypervalent iodine(III) reagents, sulfur(IV) reagents have also been extensively used to tune the reactivity of organic functionalities (Fig. 1b). As shown in Fig. 1b, a wide variety of unique sulfur(IV) reagents including alkyl, vinyl, aryl/heteroaryl and alkynyl sulfonium salts have been developed which often feature easy accessibility, structural variability, versatile reactivities and good functional group compatibility. However, to the best of our knowledge, there have been no reports on carbonyl umpolung by using sulfur(IV) reagents.

During the past years, we have devoted to the study of sulfonium or iodonium rearrangement reactions. In the program, we proposed an “assembly/deprotonation” protocol, the objective of which is to construct unprecedented unstable rearrangement precursors by dividing one reaction into multiple steps and finely tuning each step of the reaction. As a consequence, the tactic has enabled the development of [3,3]- and [5,5]-rearrangement of aryl sulfoxides and asymmetric rearrangement of aryl iodanes. Encouraged by the success of the “assembly/deprotonation” protocol in the rearrangement chemistry, we wondered if the

| Entry | Oxidant | Base | $T^1$, t$^1$ | $T^2$, t$^2$ | $T^3$, t$^3$ | Yield$^b$ |
|-------|---------|------|-------------|-------------|-------------|----------|
| 1     | 2a–2d, 2i | DBU | −40 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 0        |
| 2     | 2c–2h, 2j, 2k | DBU | −40 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 10 to 23 |
| 3     | 2i | DBU | −40 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 59       |
| 4     | 2m | DBU | −40 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 67       |
| 5     | 2n | DBU | −40 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 13       |
| 6     | 2o–2t | 2-Methylpyridine | −40 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | Trace$^c$ |
| 7     | 2m | NBu$_3$ | −40 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 66       |
| 8     | 2m | DPEA | −40 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 56       |
| 9     | 2m | DABCO | −40 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 18       |
| 10    | 2m | None | −40 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 0        |
| 11    | 2m | DBU | −60 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 57       |
| 12    | 2m | DBU | −20 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 84       |
| 13    | 2m | DBU | 0 °C, 3 h | −40 °C, 1 h | −40 °C, 12 h | 57       |
| 14    | 2m | DBU | −20 °C, 6 h | −40 °C, 1 h | −40 °C, 12 h | 68       |
| 15    | 2m | DBU | −20 °C, 10 min | −40 °C, 1 h | −40 °C, 12 h | 67       |
| 16    | 2m | DBU | −20 °C, 3 h | −60 °C, 1 h | −40 °C, 12 h | 64       |
| 17    | 2m | DBU | −20 °C, 3 h | −20 °C, 1 h | −40 °C, 12 h | 68       |
| 18    | 2m | DBU | −20 °C, 3 h | −40 °C, 3 h | −40 °C, 12 h | 60       |
| 19    | 2m | DBU | −20 °C, 3 h | −40 °C, 3 h | −40 °C, 12 h | 60       |
| 20    | 2m | DBU | −20 °C, 3 h | −40 °C, 10 min | −40 °C, 12 h | 63       |
| 21    | 2m | DBU | −20 °C, 3 h | −40 °C, 1 h | −60 °C, 12 h | 60       |
| 22    | 2m | DBU | −20 °C, 3 h | −40 °C, 1 h | −40 °C, 6 h | 30       |

$^a$ Reaction conditions: 2-oxazoline 1a (0.5 mmol), I(III)/S(IV) reagent 2 (1.0 equiv.), TFAA (1.5 equiv.), DCM (0.1 M), $T^4$ (h or min), $T^5$ (°C), base (3.0 equiv.), $T^5$ (h or min), $T^6$ (°C), $p$-anisidine (2.0 equiv.), $T^7$ (h or min), $T^8$ (°C). $^b$ Isolated yield. $^c$ TMSOTf, TMSOCOCF$_3$, or BF$_3$-Et$_2$O was used for activation of I(III) reagents wherein 2-methylpyridine was used as the base. For more details, see the ESI.
protocol could be further utilized for developing other transformations such as the umpolung reaction. Specifically, the “assembly” of an electrophile-activated sulfoxide with 2-oxazoline and subsequent “deprotonation” of in situ generated N-S(IV)2-oxazoline may lead to an umpoled 2-oxazoline (Fig. 1c). In lieu of a rearrangement process, the in situ generated sulfonium-enamine species may adopt an external nucleophile to achieve the umpolung α-functionalization of 2-oxazolines.

α-Heterofunctionalized 2-oxazolines are widely used as versatile synthetic intermediates to construct natural products, biologically active compounds and biomaterials.14 They also serve as useful ligands in transition metal catalysis.15 Moreover,

### Table 2  Reaction scope

| Reaction scope | 2-oxazolines | nucleophiles |
|----------------|--------------|--------------|
|               | ![Image](image1.png) | ![Image](image2.png) |

*a* Unless otherwise noted, the reaction was performed under the optimum conditions: 2-oxazoline 1 (0.5 mmol), 2m (1.0 equiv.), TFAA (1.5 equiv.), DCM (0.1 M), −20 °C for 3 h; then DBU (3.0 equiv.), −40 °C, 1 h; then nucleophile (2.0 equiv.), −40 °C, 12 h. b T1 = −40 °C, t1 = 3 h; T2 = −50 °C, t2 = 30 min. c n-BuNH2 (3.0 equiv.) was used. d Dibenzyl malonate was pretreated with NaH prior to be used in the reaction.
2-oxazoline as a masked carboxylic acid equivalent can be readily converted to other valuable functionalities such as acids, amides, ketones, polymers, etc. Despite their importance, the methods for the synthesis of \( \alpha \)-heterofunctionalized 2-oxazolines rely heavily on the derivatization of \( \alpha \)-heterofunctionalized carboxylic acids which are often not commercially available or difficult to synthesize. Therefore, the discovery of methods for direct \( \alpha \)-heterofunctionalization of 2-oxazolines is a useful endeavor.

Results and discussion

To verify our hypothesis, we first investigated the \( \alpha \)-amination of 2-oxazoline 1a with 4-methoxyaniline. According to the “assembly/deprotonation” protocol previously developed for rearrangement reactions in our laboratory, the optimization of the reaction conditions was conducted step by step in order to achieve a high efficiency of the whole process (Table 1). First, a wide variety of aryl sulfoxides and iodanes as oxidants were screened (entries 1–6). As a result, alkyl sulfoxides 2a–2c proved incompetent for the reaction since no desired product or extremely low yields were obtained in these cases (entries 1 and 2). In contrast, most of the aryl sulfoxides 2f–2n afforded the desired product 4a (entries 2–5). Among them, diaryl sulfoxides 2l and 2m were found to be the best two oxidants giving 4a in 59% and 67% yields, respectively (entries 3 and 4). The relatively higher efficiency of 2l and 2m could be attributed to their subtle electronic features that may not only meet the requirement of their electrophilic activation by anhydride but also possessed the durability in the system for the upcoming reaction sequences. In addition to aryl sulfoxides, the mostly used aryl iodanes 2o–2t are all ineffective for the reaction (entry 6). This is probably due to the compatibility issue of aryl iodanes when facing with the nucleophilic 4-methoxyaniline. Next, the choice of base was determined as another critical parameter for the reaction. DBU as base was superior to other tertiary amines and extremely low yields were obtained in these cases (entries 1 and 9). The necessity of base was also proved since 4-methoxyaniline failed to afford the desired product 4a albeit in a low yield (28%). To our pleasure, a set of susceptible groups, such as TBSO (4f), iodine (4g), nitrile (4i), Boc (4k), unsaturated carbyl group (4r), and thiophene group (4v) remained intact under the conditions. Impressively, even nucleophilic functional groups such as alkene (4h), alkynyl (4j) and indolyl groups (4o) that can be readily oxidized by hypervalent iodine reagents were also tolerated in the reaction. The functional groups tolerated in the reaction provide a versatile platform for further elaboration of the products.

Next, the scope of nucleophiles was studied under the optimum conditions (Table 2). To our delight, both alkyl and aryl amines (3a–3o) were proved to be suitable for the reaction. In addition to primary amines (3a–3h), secondary amines (3i–3o) also afforded the desired products (5a–5o) in good yields (48–77%). Gratifyingly, both alkyl and aryl thiols (3p–3y) were suitable for the reaction. As a result, a wide variety of \( \alpha \)-alkyl/
arylamo and \(\alpha\)-alkyl/arylthio 2-oxazolines were obtained with the protocol. The oxygen and carbon nucleophiles such as 4-methoxyphenol and dibenzyl malonate (3a and 3a’) were well adopted by the reaction. It should be noted that in the case of 3a’, dibenzyl malonate needs to be treated with NaH prior to submission to the reaction. Impressively, the practicality of the method was witnessed by the successful application of the method to a complex molecule namely ceritinib (LDK378), a novel ALK inhibitor for Non-Small Cell Lung Cancer (NSCLC), which bears multiple vulnerable functional groups such as aryl amines and pyrimidines. The limitations of the method were determined when using alkoxyl and carbon nucleophiles including sodium methoxide, ethanol, zinc reagents, indole, pyrrole and enol silyl ethers. These unsuccessful cases were probably due to the relatively weak nucleophilicity or the compatibility issues of nucleophiles towards the electrophilic 2-oxazoline to \(\alpha\)-S(IV)-enamine. Not surprisingly, the nucleophilic p-methoxyaniline attacks \(\alpha\)-S(IV)-sulfane 6a via \(\alpha\)-S(IV)-deprotonation of 2-oxazoline 1a by DBU, affording 2-oxazoline 1a via a facile stepwise process giving an intermediate \(\lambda^a\)-sulfane IM2 leading to IM4 wherein the acidity of the \(\alpha\)-proton of 2-oxazoline is dramatically increased. As a consequence, the \(\alpha\)-deprotonation of IM4 by DBU proceeds smoothly to afford \(N\)-(S(IV)) enamine IM5 which is now becoming an electrophile achieving the umpolung of 2-oxazoline. Not surprisingly, the nucleophilic \(p\)-methoxyaniline attacks \(\lambda^a\)-sulfane IM3 affording IM6 with C-N bond formation meanwhile releasing phenoxathiin as a side product. Finally, IM6 converts to product 4a via deprotonation by DBU. Overall, the nucleophilic attack of 2-oxazoline to \(\lambda^a\)-sulfane IM3 by crossing TS3 is the rate determining step of the whole transformation with an energy cost of 14.3 kcal mol\(^{-1}\) and the reaction is highly exergonic by 90.2 kcal mol\(^{-1}\). The energetic results are in good agreement with the experimental observations that the reaction proceeds readily at low temperature.

**Conclusions**

In summary, we have developed a sulfur(\(v\))-mediated umpolung strategy which enables \(\alpha\)-heterofunctionalization of 2-oxazolines. The success of the reaction relies on the choice of a subtle oxidant called phenoxathiin sulfoxide and the use of the “assembly/deprotonation” protocol for constructing umpoled 2-oxazoline species, presumably an N-S(\(v\))-enamine intermediate. Prominent features of the reaction include mild conditions, excellent functional group compatibility, and broad substrate scope for both coupling partners. In addition to the intermolecular reaction, the feasibility of the intramolecular version was proved as a potential approach for the synthesis of N-heterocycles. The whole reaction sequence consisting of five stages is supported by computational studies. Efforts to develop other sulfur(\(v\))-mediated umpolung reactions are currently underway in our laboratory.
Data availability

All experimental and characterization data, as well as DFT calculation data are available in the ESI.†

Author contributions

B. P. conceived the project and co-directed the project with P. D. Q. Z. developed the reaction and performed the experiments with Y. L., R. L., Z. H., L. K and P. D. Y. L. performed DFT calculations. B. P. prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

There are no conflicts to declare.

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The formation of \( \alpha\)-S(\(\pi\))-oxazoline in lieu of N-S(\(\pi\)) enamine \(\text{IM5}\) cannot be completely excluded. However, the barrier for the nucleophilic substitution of \(\alpha\)-S(\(\pi\))-oxazoline is calculated to be 24.3 kcal mol\(^{-1}\) which is much higher than the barrier of 13.3 kcal mol\(^{-1}\) for that of \(\text{IM5}\). Therefore, \(\text{IM5}\) is more likely to be the key umpoled intermediate.