Redox Catalysis Hot Paper

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A Brønsted Acid Catalyzed Redox Arylation**

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Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

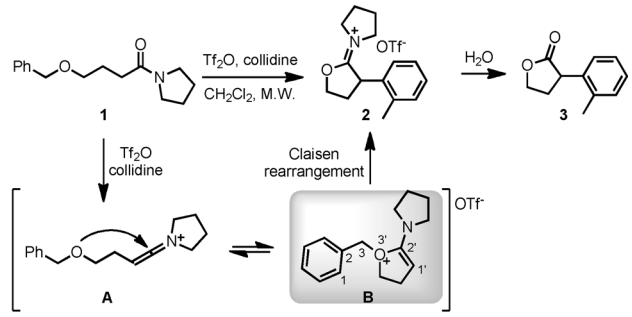
Abstract: *A Brønsted acid catalyzed redox arylation of ynamides that employs aryl sulfoxides as the arylating agents is reported. This metal-free transformation proceeds at room temperature and efficiently affords α-arylated oxazolidinones in a redox-neutral, atom-economic fashion.*

Redox-neutral reactions have recently emerged as conceptually appealing transformations in synthesis. The current interest in redox and atom economy as well as the continued advancement of green chemistry further stimulate the development of such reactions.[1,2] These processes, which do not always rely on transition-metal catalysis, often allow the functionalization of C–H bonds in organic molecules through mechanistically novel pathways.[1]

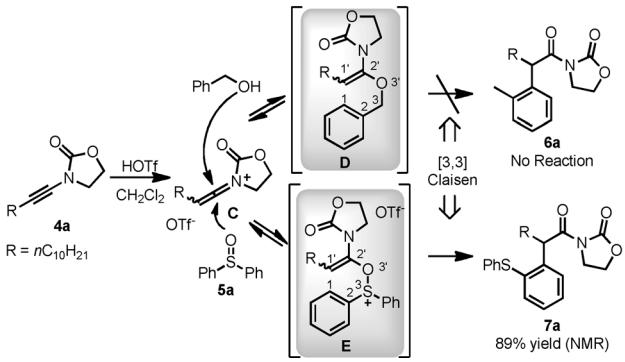
On the other hand, there has recently been considerable synthetic exploration of the electronic properties of ynamides.[3] Owing to their uniquely polarized triple bond, several exciting reactions were discovered; most of them involve one of the multiple modes of cycloaddition and rely on soft, alkynophilic transition-metal catalysts or promoters. Herein, we report a metal-free Brønsted acid catalyzed redox arylation reaction of ynamides through a [3,3]-sigmatropic rearrangement.

Our group has recently developed an α-arylative lactonization reaction by the electrophilic activation of amide substrates (Scheme 1a).[4] The treatment of amide **1** with triflic anhydride and 2,4,6-collidine generates keteniminium **A** in situ, its intramolecular nucleophilic capture leads to intermediate **B**. Claisen rearrangement and hydrolysis eventually afford the α-arylated lactone **3**. In practice, however, this transformation proceeded in modest to good yields and had a relatively narrow scope.[4a] These shortcomings were ascribed to the rather high energy penalty that is associated with the inevitable transient loss of aromaticity during the [3,3]-sigmatropic rearrangement step.

a) our previous work: α-arylation by an intramolecular Claisen rearrangement



b) hypotheses and attempts herein: intermolecular redox arylation



Scheme 1. Intramolecular α-arylation and intermolecular redox arylation.[8]

Inspired by this intramolecular α-arylation reaction,[5] we became curious whether an intermolecular version would be possible (Scheme 1b). Aware of the probable, deleterious competitive reaction of any added nucleophile with the Tf_2O activator (Tf = trifluoromethylsulfonyl), we sought to employ an ynamide such as **4a**[3] to generate the pivotal keteniminium **C** through protonation. Benzyl alcohol was the obvious choice of nucleophile, as we hoped that intermediate **D** would be formed to give arylated product **6a**. However, even though allylic and propargylic alcohols have been successfully employed in similar transformations before, no reaction was observed.[6] This failure of benzyl alcohol to serve as the aryl donor might again be attributed to the challenging transient loss of aromaticity upon [3,3]-sigmatropic rearrangement of **D**.

In contrast, the use of diphenyl sulfoxide **5a**[7] under otherwise identical conditions led to smooth conversion of the starting material. Strikingly, the desired α-arylated amide **7a**

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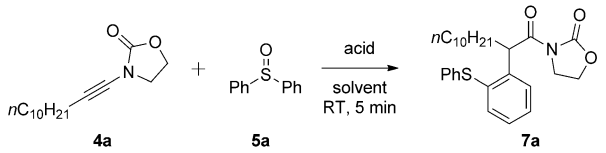
was generated in excellent yield at room temperature within only five minutes (Scheme 1b).[8]

Encouraged by this exciting preliminary result, we proceeded to further optimize the reaction conditions (Table 1). The use of two equivalents of the sulfoxide reagent was required for complete conversion (entry 4). Pleasingly, a catalytic amount of HOTf (10 mol%) was sufficient to promote the reaction under these conditions within a very short reaction time (entry 6).

Table 1: Optimization of the Brønsted acid catalyzed redox arylation.[a]



4a **5a** **7a**

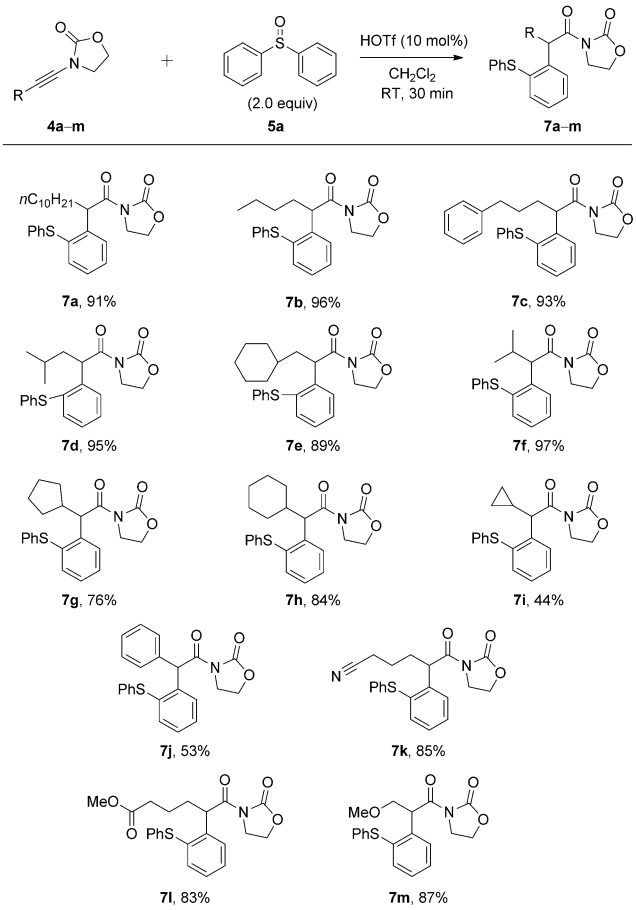
Entry	Acid (equiv)	Amount of **5a** [equiv]	Solvent	Yield[b] [%]
1	HOTf (1.0)	1.0	CH_2Cl_2	89
2	TFA (1.0)	1.0	CH_2Cl_2	–[c]
3	HOTf (0.2)	1.0	CH_2Cl_2	90
4	HOTf (1.0)	2.0	CH_2Cl_2	>95
5	HOTf (1.0)	1.0	toluene	74
6	HOTf (0.1)	2.0	CH_2Cl_2	>95

[a] Unless otherwise noted, all reactions were performed under argon atmosphere at room temperature for 5 min. [b] Determined by NMR spectroscopy using mesitylene as the internal standard. [c] No reaction was observed. TFA = trifluoroacetic acid.

With suitable reaction conditions in hand, we examined several ynamides **4a**–**m**. The reaction is applicable to a broad range of substrates, which generally afforded the α-arylated acyl oxazolidinones **7a**–**m** in good to excellent yields under mild conditions (Scheme 2). Substitution at the α- or β-position of the ynamide substrate (**4d**–**h**) does not have any detrimental influence on the yield. Remarkably, ynamides **4k** and **4l**, which bear functional groups, namely a nitrile and an ester moiety, respectively, are also compatible with the reaction conditions, thus allowing the α-arylation of a formal acyl oxazolidinone in the presence of other enolizable functional groups.

Subsequently, a broad range of aryl sulfoxides were submitted to this redox arylation reaction (Scheme 3). Both electron-donating and -withdrawing substituents were tolerated on the aryl ring. Importantly, the alkyl aryl sulfoxides **5f**–**l** also proved to be suitable reaction partners for this transformation, leading to smooth aryl transfer in typically excellent yields.

To gain more insight into the mechanism of this reaction, we conducted various labelling experiments. The use of DOTf as the acid catalyst led to the α-deuterated product [D_1]-**7a** (Scheme 4a). This supports the assumption that initial protonation of the ynamide triggers nucleophilic attack of the sulfoxide to the keteniminium intermediate. Another informative labelling experiment involved the competitive reaction of equimolar amounts of diphenyl sulfoxide (**5a**) and its deuterated analogue ([D_{10}]-**5a**; 80% deuteration; Scheme 4b). The reaction generated **7a** and [D_9]-**7a** in a 63:37 ratio.[9] Considering the degree of deuteration of [D_{10}]-**5a**, it



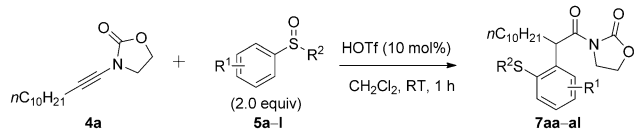
Scheme 2. Variation of the ynamide component of the Brønsted acid catalyzed redox arylation reaction.

can be concluded that C–H bond cleavage or formation is not involved in the rate-determining step of the overall process.

A control experiment was also performed with equimolar amounts of methylated sulfoxide **5b** and the chlorinated analogue **5c** (Scheme 5a). In this experiment, **7ab** and **7ac** were formed in a ratio of 72:28. Similarly, the use of unsymmetric diaryl sulfoxide **5m** led to the formation of two regioisomers in a 66:34 ratio (Scheme 5b). The observed clear preference for the more electron-rich aryl moiety during the crucial C–C bond forming event rules out an S_N-type mechanism at the *ortho* position of the sulfoxide.[7f,h]

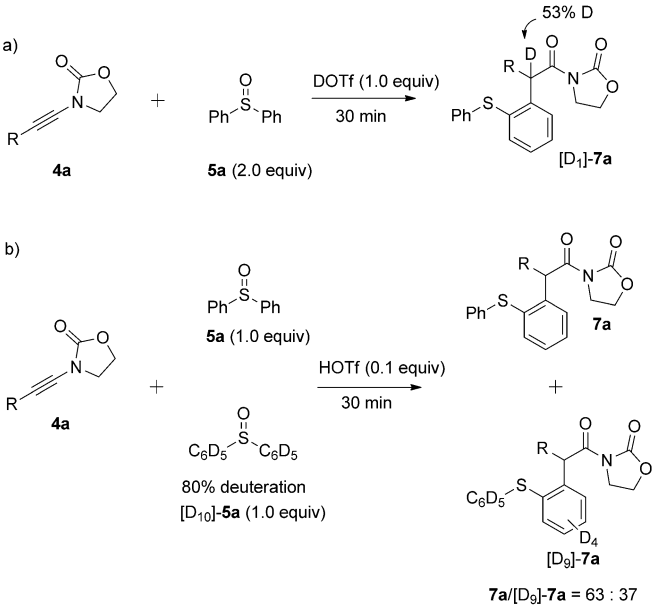
The presence of an oxazolidinone in both the substrates and the products renders the development of an asymmetric variant of this transformation possible (Scheme 6).[10] After a brief preliminary screen of chiral auxiliaries,[8] a promising diastereoselectivity of 75:25 was obtained with a *tert*-butyl-substituted oxazolidinone (Scheme 6), which demonstrated the feasibility of an asymmetric redox-neutral arylation reaction.

With this transformation, relevant heterocyclic cores may be easily prepared. For example, the use of the cyclic sulfoxide **5n** led to the α-arylated product **7an** in 72% yield, thus opening a practical alternative for the synthesis of functionalized dibenzothiophenes (Scheme 7).[11] Additionally, the aryl sulfanyl moiety can be easily removed under

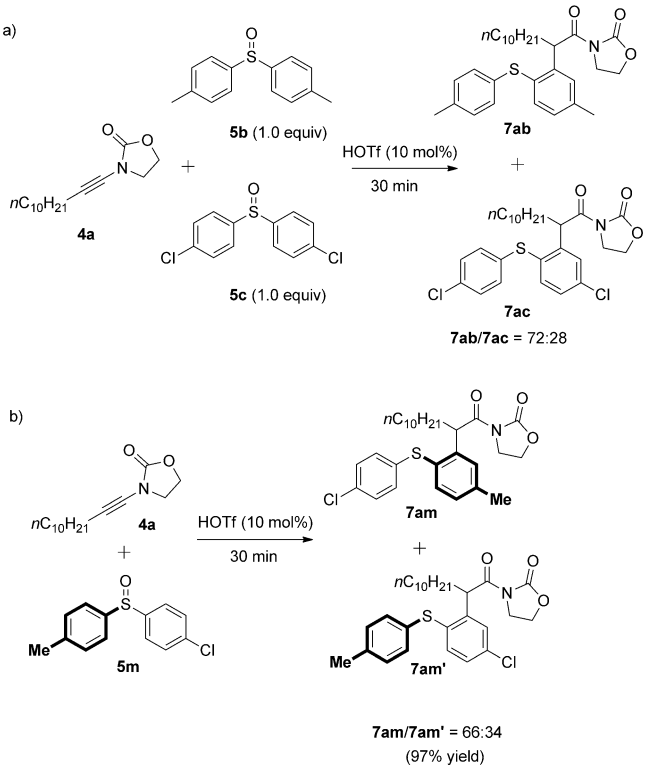


Nucleophile	Product, Yield	Nucleophile	Product, Yield
5a	**7a**, 91%[a]	5g	**7ag**, 90%
5b	**7ab**, 90%	5h	**7ah**, 94%
5c	**7ac**, 94%	5i	**7ai**, 81%
5d	**7ad**, 86%	5j	**7aj**, 37%
5e	**7ae**, 60%	5k	**7ak**, 96%
5f	**7af**, 86%	5l	**7al**, 79%

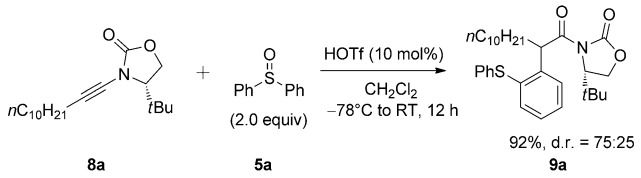
Scheme 3. Variation of the nucleophile of the Brønsted acid catalyzed redox arylation reaction. [a] Reaction time: 30 min. Bn = benzyl.



Scheme 4. Selected labelling experiments. R = $nC_{10}H_{21}$.



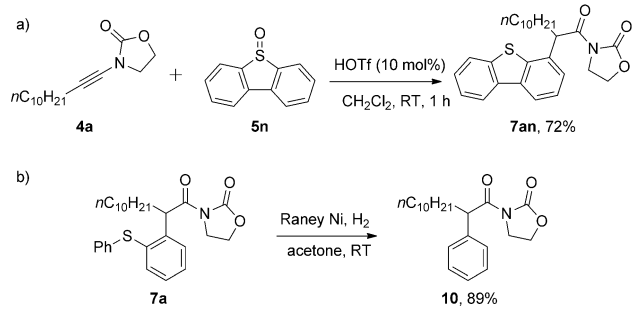
Scheme 5. Control experiments with **5b**, **5c**, and **5m**.



Scheme 6. Asymmetric Brønsted acid catalyzed redox arylation.

mild conditions to give the product of formal phenylation **10** in excellent yield.

In summary, we have developed a Brønsted acid catalyzed redox arylation of ynamides. This simple reaction is compatible with a broad range of functional groups and delivers α-arylated oxazolidinones in good to excellent yields under mild conditions. Further experiments focusing on asymmetric redox arylation reactions that rely on the use of suitable chiral auxiliaries or chiral counteranions are currently underway.[12]



Scheme 7. Synthesis of a dibenzothiophene and product elaboration.

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