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Z-Selective α-Arylation of α,β-Unsaturated Nitriles via [3,3]-Sigmatropic Rearrangement

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Dedication ((optional))

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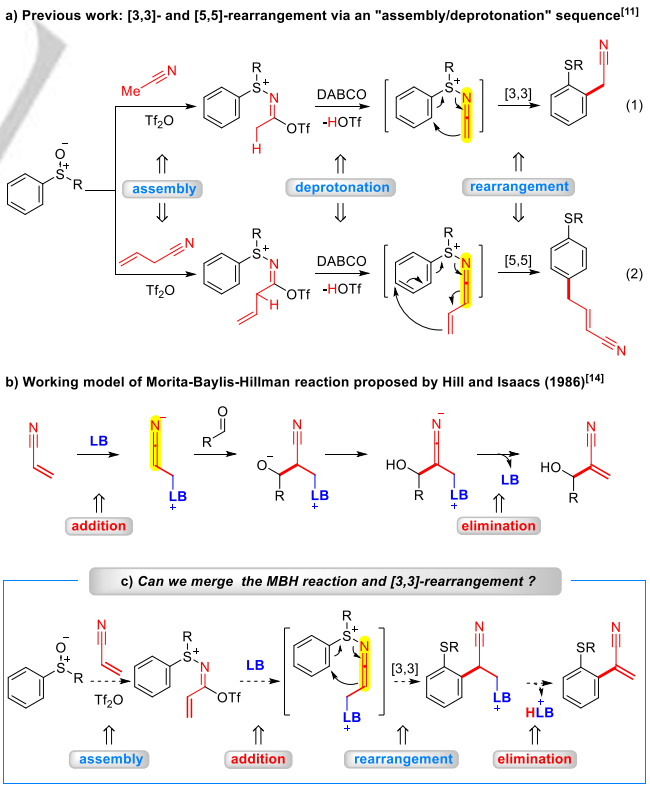
Abstract: Morita-Baylis-Hillman (MBH) reaction and [3, 3]-sigmatropic rearrangement are two paradigms in organic synthesis. By merging the two types of reactions, we herein describe [3,3]-rearrangement of aryl sulfoxides with α,β-unsaturated nitriles. The reaction was achieved by sequentially treating both coupling partners with electrophilic activator (Tf_2O) and base, offering an effective approach to prepare synthetically versatile α-aryl α,β-unsaturated nitriles with *Z*-selectivity through direct α-C-H arylation of unmodified α,β-unsaturated nitriles. The control experiments and DFT calculations support a four-stage reaction sequence including the assembly of Tf_2O activated aryl sulfoxide with α,β-unsaturated nitrile, MBH-like Lewis base addition, [3,3]-rearrangement, and E1cB-elimination. Among these stages, the Lewis base addition is diastereoselective and E1cB-elimination is *cis*-selective, which could account for the remarkable *Z*-selectivity of the reaction.

Introduction

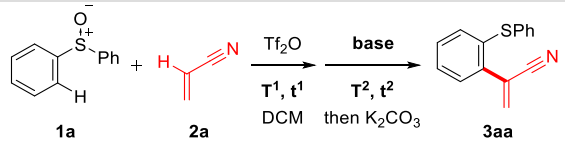
α-Aryl nitriles are an important family of target molecules that not only possess biological activities[1a-c] but also serve as useful intermediates for accessing other valuable compounds.[1d-f] Accordingly, considerable effort has been devoted to transition-metal catalyzed α-arylation of saturated nitriles.[2] In contrast, the methods for α-arylation of α,β-unsaturated nitriles (vinyl nitriles) has been rarely reported in the literatures.[3] The known protocols for the synthesis of α-aryl α,β-unsaturated nitriles rely on the cross-coupling of α-halogenated[3a] or metalated[3b] nitriles with aryl metals or aryl halides. To the best of our knowledge, there have been no examples of direct and stereospecific α-C-H arylation of unmodified α,β-unsaturated nitriles.

In the past few years, [3,3]-rearrangement of aryl sulfoxides have attracted great attentions from synthetic community.[4] With the rearrangement protocol, an array of nucleophiles such as allyl/propargyl silanes,[5,6] internal alkynes,[7] carbonyl compounds,[8] phenols,[9] stannyl nitriles[10] and alkyl nitriles[11] have been introduced into *ortho*-position of aryl sulfoxides. In this context, we have recently developed a [3,3]-rearrangement of aryl sulfoxides with alkyl nitriles using an "assembly/deprotonation" sequence that allows for *ortho*-C-H cyanoalkylation of aryl sulfoxides (Scheme 1a, eq 1).[11a] The "assembly/deprotonation" protocol also inspired us to develop a highly selective [5,5]-rearrangement of aryl sulfoxides with allyl nitriles that enables the remote *para*-C-H alkylation of aryl sulfoxides (eq 2).[11b] Mechanistic studies pointed out that the



Scheme 1. Previous work and design of the Morita-Baylis-Hillman-type [3,3]-rearrangement of aryl sulfoxides. Tf_2O = triflic anhydride. DABCO = triethylenediamine. LB = Lewis base.

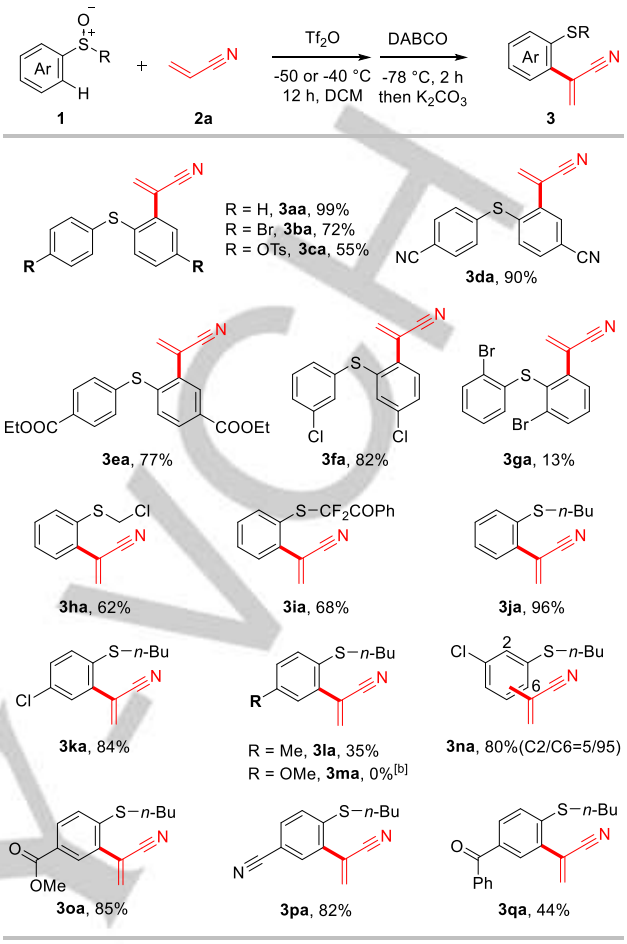
Table 1. Development of [3,3]-rearrangement of aryl sulfoxide **1a** with acrylonitrile[a]



1a **2a** **3aa**

entry	base	T^1, t^1	T^2, t^2	yield[b]
1	DABCO	-30 °C, 10 min	-30 °C, 10 min	45%
2	DABCO	-30 °C, 10 min	-78 °C, 10 min	61%
3	DABCO	-30 °C, 10 min	-78 °C, 2 h	83%
4	DABCO	-50 °C, 1 h	-78 °C, 2 h	54%
5	DABCO	-50 °C, 12 h	-78 °C, 2 h	99%
6	DABCO	-70 °C, 12 h	-78 °C, 2 h	27%
7	NEt_3	-50 °C, 12 h	-78 °C, 2 h	79%
8	DBU	-50 °C, 12 h	-78 °C, 2 h	97%
9	*i*-Pr_2EtN	-50 °C, 12 h	-78 °C, 2 h	92%
10	pyridine	-50 °C, 12 h	-78 °C, 2 h	59%
11	2-chloropyridine	-50 °C, 12 h	-78 °C, 2 h	84%
12	2-methylpyridine	-50 °C, 12 h	-78 °C, 2 h	82%
13	DABCO	-50 °C, 12 h	-78 °C, 2 h	99%[c]

[a] Reactions were performed on 0.5 mmol scale. Tf_2O was added at -78 °C, then the mixture was warmed to T^1. Base (2.0 equiv) and K_2CO_3 (10.0 equiv) were used. [b] Isolated yield. [c] 3.0 equiv of K_2CO_3 was used. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. For more details of reaction development, see the Supporting Information.



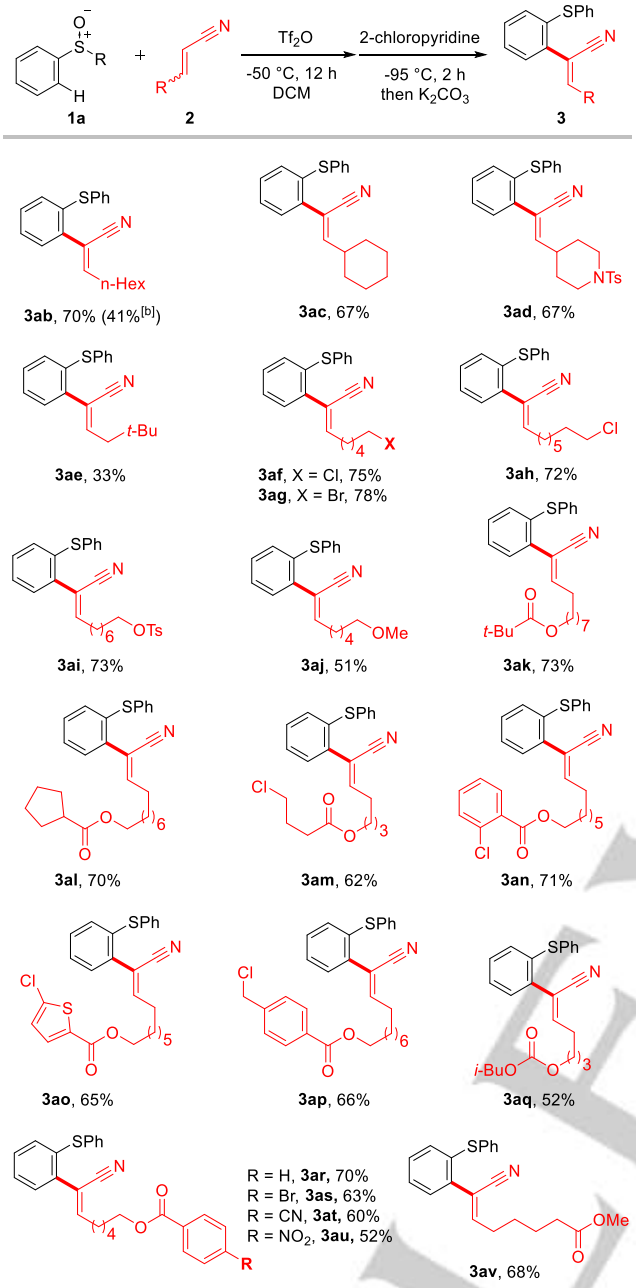
Scheme 2. Reaction scope of aryl sulfoxides. [a] Reactions were performed under optimum conditions. In cases of **3ia**-**3qa**, Tf_2O was added at -78 °C, then warmed to -40 °C. [b] Aryl sulfoxide **1m** deteriorated after the reaction.

key to the success of both reactions is the transient construction of the ketenimine-sulfoxonium intermediates highlighted in yellow that spontaneously undergo a rapid rearrangement to release the congestion of these ketenimine moieties. Triggered by this reaction pattern, we wondered whether new rearrangement reactions could be invented by seeking other methods for constructing the key ketenimine-sulfoxonium species.

The Morita-Baylis-Hillman (MBH) reaction constitutes one of the most powerful C-C bond forming reaction that involves the cross coupling of α-carbon of an activated alkene with electrophiles such aldehydes, imines and others.[12] A commonly accepted mechanism for MBH reaction was first proposed by Hoffmann[13] and further proved by Hill and Isaacs through their kinetic studies of the reaction of acrylonitrile and aldehyde.[14] As illustrated in Scheme 1b, the reaction consists of four steps including Michael addition, aldol addition, intramolecular proton transfer, and final β-elimination. The conjugate addition of a Lewis base (LB) to acrylonitrile affording a zwitterionic LB-ketenimine species attracted our attentions. This elegant protocol for transiently constructing ketenimine intermediates from readily available α,β-unsaturated nitriles inspired us to envision the possibility of combining the MBH reaction with [3,3]-rearrangement chemistry. Specifically, as depicted in Scheme 1c, the electrophilic assembly of aryl sulfoxide with acrylonitrile would give vinyl imine-sulfoxonium intermediate. The subsequent addition of a Lewis base to the intermediate would generate the desired LB-ketenimine-sulfoxonium species which we expected to undergo a rapid [3,3]-rearrangement to α-aryl β-LB nitrile. The LB appendage could be removed by base via β-elimination giving α-aryl acrylonitrile, thus providing a new protocol for direct α-C-H arylation of unmodified α,β-unsaturated nitriles.

Results and Discussion

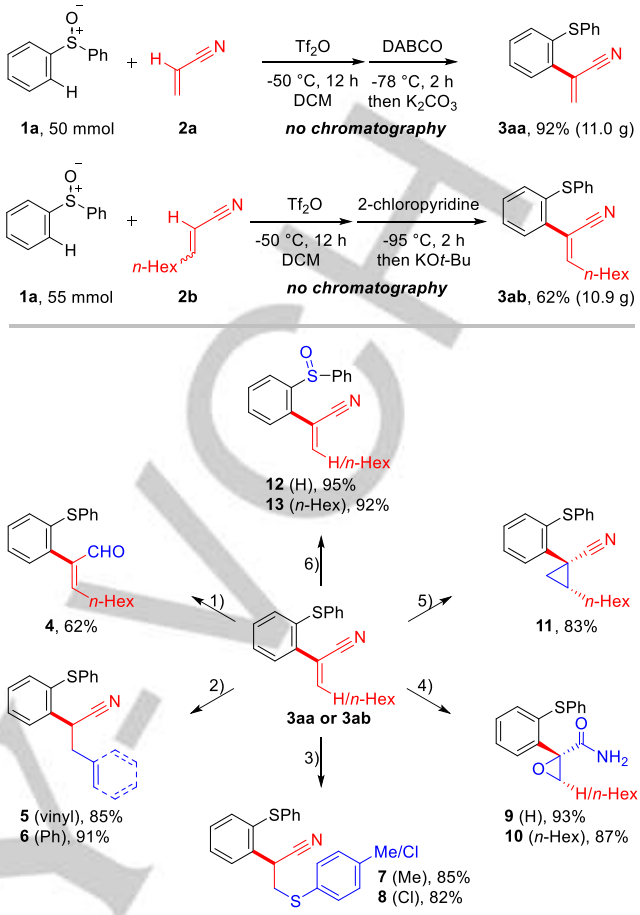
Reaction developments and applications: To verify our hypothesis, we first attempted to perform the reaction of diphenyl sulfoxide **1a** and acrylonitrile **2a** under the conditions (Tf_2O, -30 °C, 10 min; then DABCO, -30 °C, 10 min) that we have previously used for [3,3]-rearrangement of aryl sulfoxides with alkyl nitriles (Table 1, entry 1).[11a] Notably, DABCO is one of the most commonly used bases in Morita-Baylis-Hillman reaction.[12a] Excitingly, the reaction indeed furnished the desired α-aryl acrylonitrile **3aa** in a modest yield (45%). It is necessary to note that K_2CO_3 (10.0 equiv) was used for quenching the reaction mixture obtained after the addition of DABCO. Lowering the temperature (T^2) to -78 °C and prolonging the time (t^2) for the treatment with DABCO increased the yields significantly (entries 2 and 3). Surprisingly, further optimizing the temperature (T^1) and time (t^1) for the T_2O-initiated assembly process significantly improved the reaction efficiency producing **3aa** in a nearly



Scheme 3. Reaction scope of α,β-unsaturated nitriles. [a] Reactions were performed with aryl sulfoxide **1a** (0.5 mmol), *E*/*Z*-mixtures of α,β-unsaturated nitrile **2** (2.0 equiv), Tf_2O (1.5 equiv) and 2-chloropyridine (2.5 equiv). [b] DABCO was used as base.

quantitative yield (99%) (entry 5). Screening of bases revealed that DABCO was superior to other bases such as NEt_3, DBU, Hünig's base and pyridines (entries 7-12). Notably, most of these organic bases were proved to be suitable for the reaction with producing good yields of **3aa**. These results demonstrated an excellent base flexibility that can be beneficial for tuning the reaction in facing with different types of substrates. To our delight, decreasing the K_2CO_3 loading from 10.0 equiv to 3.0 equiv still afforded **3aa** with the best yield (99%) thus achieving the best conditions for the reaction (entry 13).

The reaction scope of aryl sulfoxides **1** is presented in Scheme 2. To our delight, both diaryl sulfoxides and aryl alkyl sulfoxides were all suitable for the reaction. *Para*- and *meta*-substituted diaryl sulfoxides (**1b**-**1f**) produced the expected



1) DIBAL-H, DCM; 2) CuI (10 mol%), $CH_2CHMgBr$ or C_6H_5MgBr, THF; 3) 4-chlorobenzenethiol or 4-methylbenzenethiol, DCM; 4) K_2CO_3, H_2O_2, DMSO; 5) trimethylsulfoxonium iodide, NaH, DMSO; 6) *m*-CPBA, DCM.

Scheme 4. Decagram-scale synthesis and elaboration of products **3aa** and **3ab**. DIBAL-H = diisobutylaluminium hydride. DMSO = dimethyl sulfoxide, *m*-CPBA = 3-Chloroperoxybenzoic acid.

products (**3ba-3fa**) in modest to good yields. However, *ortho*-bromo substituted diaryl sulfoxide **1g** suffering from steric hinderance furnished **3ga** in a low yield. To our delight, in addition to diaryl sulfoxides **1a**-**1q**, aryl alkyl sulfoxides **1h**-**1q** except **1m** were also suitable for the process. It is worthy of note that the reaction demonstrated excellent functional group compatibility. Functional groups (FGs) such as alkyl/aryl halides (**3ba**, **3fa**, **3ha**, **3ia**, **3ka** and **3na**) and pseudohalides (**3ca**), nitriles (**3da** and **3pa**), esters (**3ea** and **3oa**) and ketones (**3ia** and **3qa**) were well tolerated in the reaction. These functional groups could provide a versatile platform for further elaboration of products. Remarkably, *meta*-chloro substituted diaryl sulfoxide **1f** exclusively afforded the less hindered product **3fa** in good yield (82%). This is impressive since the related rearrangement of alkyl nitriles suffered from the poor regioselectivities.[11a] The excellent regio-selectivity could be attributed to the stereo effect raising from the DABCO moiety of the rearrangement precursor that enhanced the regiodiscrimination of [3,3]-rearrangement (Scheme 1c). One needs to be noted that electron rich aryl sulfoxides **1l** and **1m** were not suitable for the process. This is probably due to the less electrophilicity of Tf_2O-activated electron-donating group substituted aryl sulfoxides that impedes the assembly of aryl sulfoxides with nitrile **2a**.

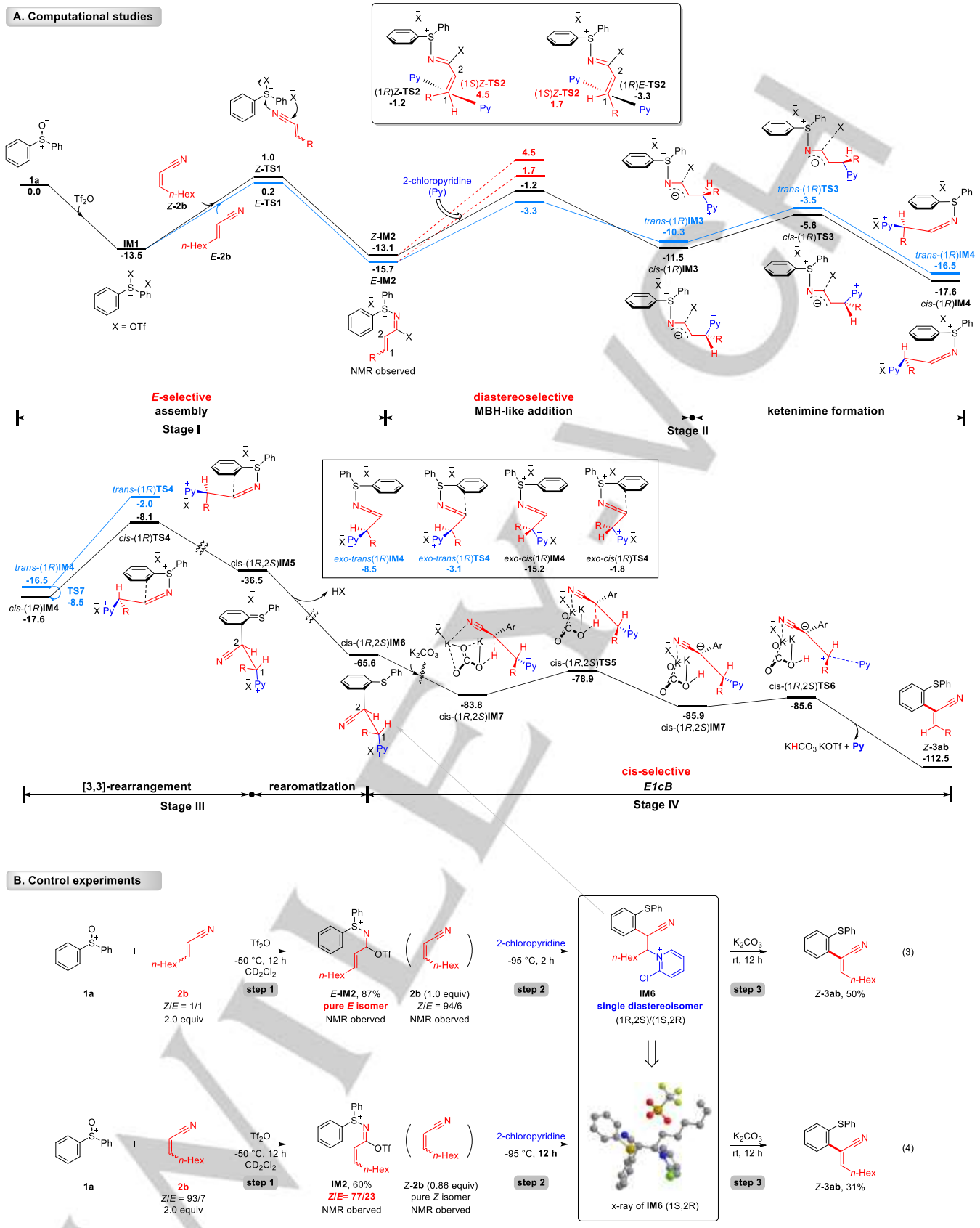


Figure 1. Mechanistic studies. (**A**) Computed energy profiles. Relative energies are given in kcal/mol. The ball-and-stick structures of the intermediates and transition states are given in Supporting Information. (**B**) Control experiments.

Furthermore, the scope of α,β-unsaturated nitriles **2** was investigated with current protocol (Scheme 3). To our delight, β-alkyl substituted alkenyl nitrile **2b** smoothly afforded the desired product **3ab** albeit in a modest yield (41%). Screening of bases identified 2-chloropyridine as the best base that significantly improved the yield of **3ab** (70%) (For optimization of the reaction of **1a** with **2b**, see the Supporting Information). Accordingly, 2-chloropyridine was used as a base in the following study. It is remarkable that the reaction exhibited excellent stereo-selectivity by giving the sole *Z*-olefin **3ab** from *E*/*Z* isomers of α,β-unsaturated nitrile **2b** (*E*/*Z* = 1/1) (Table 3). Impressively, in addition to linear alkyl groups, more bulky cyclohexyl group (**2c**) and piperidine group (**2d**) at β-positions were tolerated in the reaction. Excellent FG compatibility was also observed with the reaction of α,β-unsaturated nitriles **2**. FGs including Ts-protected amine (**3ad**), alkyl/aryl halides (**3af**-**3ah**, **3am**-**3ap** and **3as**) and pseudohalides (**3ai**), esters (**3ak**-**3ap** and **3ar**-**3av**), carbonates (**3aq**), nitriles (**3at**) and nitro groups (**3au**) and thiophenes (**3ao**) were all well tolerated in the reaction. Even highly electrophilic benzylic chloride (**3ap**) was found to be feasible for the process. The wide range of FGs tolerated in the reaction demonstrated the practicality of the methodology.

Impressively, the reactions of **2a** and **2b** performed on decagram-scale still produced desired product **3aa** in an excellent yield (92%, 11.0 g) and **3ab** in good yield with exclusive *Z*-selectivity (62%, 10.9 g)[15] , respectively (Scheme 4). It's worthy of note that chromatography was not necessary for purifying products that demonstrated the practicality of the protocol (For details, see the Supporting Information). Furthermore, the nitrile group of **3ab** could be reduced giving valuable (*Z*)-α,β-unsaturated aldehyde **4**. The double bond embodied in products could be simply elaborated to other valuable functionalities. For example, 1,4-addition of Grignard Reagents and thiophenols to **3aa** led to β-vinyl (**5**), phenyl (**6**) and heteroatom (**7** and **8**) substituted alkyl nitriles. The epoxidation and cyclopropanation of products gave α,β-epoxy amides (**9** and **10**) and cyclopropanes **11** with excellent stereoselectivity. Sulfides **3aa** and **3ab** could also be readily oxidized to corresponding sulfoxides (**12** and **13**). The versatile transformations of final products showcase the utility of the method.

Mechanistic studies: To support our envisioned reaction sequence (Scheme 1b) and understand the intriguing *Z*-selectivity of the reaction, we combined control experiments and DFT calculations to study a representative reaction (R = *n*-Hex, **2b**) in Table 3. The computational protocol is detailed in the Supporting Information. Figure 1A shows the free energy profile of the reaction to afford **3ab**, which can be divided into four stages. In stage I, Tf_2O activates **1a** to generate a salt **IM1**, followed by the addition of α,β-unsaturated nitrile **2b** to the salt via **TS1**, resulting in an imine-sulfonium intermediate **IM2** which corresponds to the activated alkene in MBH reaction. Attempts to locate transition states for a stepwise addition were unsuccessful. After the assembly, stage II forms the rearrangement precursor **IM4**. First, the Lewis base 2-cholorpyridine (**Py**) undergoes MBH-like addition to the alkene group of **IM2** via **TS2**. The resultant **IM3** then dissociates an OTf^- group to give ketenimine intermediate **IM4** as the rearrangement precursor. Stage III breaks S-N bond and forms a C-C bond via [3,3]-rearrangement followed by rearomatization. Finally, **IM6** undergoes E1cB-elimination with K_2CO_3 (see the Supporting Information), affording the final product **3ab** (stage IV). Overall, the reaction is highly exergonic by 112.6 kcal mol^{-1} and has a rate-determining barrier of 14.5/13.7 kcal mol^{-1} at *Z*-**2b**/*E*-**2b** addition. The feasible energetics explains why the reaction could take place smoothly and support our envisioned reaction sequence. In the following, we further characterize and corroborate our proposed mechanism in combination with control experiments (Figure 1B).

We first conducted control experiments to characterize the assembly process (stage I) to form **IM2** in the absence of **Py** and K_2CO_3 (Figure 1B). When 2.0 equiv of 1/1 mixture of *Z*-/*E*-**2b** was used, we observed pure *E*-**IM2** and a 94/6 mixture of *Z*-/*E*-**2b** (step1 in eq 3). When 2.0 equiv of 93/7 mixture of *Z*-/*E*-**2b** was used (for preparation of **2b** mixture, see the Supporting Information), we observed a 77/23 mixture of *Z*-/*E*-**IM2** and pure *Z*-**2b** (step 1 in eq 4). These control experiments indicate that **1a** is able to react with both *E*- and Z-**2b** but in favor of *E*-**2b**, which is in good agreement with our computed energetics; *E*-**2b** reacts with **1a** more favorably than *Z*-**2b** in terms of both kinetics (by 0.8 kcal mol^{-1}) and thermodynamics (by 2.6 kcal mol^{-1}). Therefore, the two competitive reactions, **IM1** with *E*-**2b** and *Z*-**2b**, respectively, preferentially give more stable *E*-**IM2** when *E*-**2b** is available and later gives *Z*-**IM2** when *E*-**2b** is consumed completely.

Next, we characterized stages II and III in the absence of K_2CO_3 (step 2 in eqs 3 and 4). Because **Py** addition to *E*-/*Z*-**IM2** can take place on the both sides of the alkene plane, there are four possible transition states (namely, (1*R*)*E*-**TS2**, (1*S*)*E*-**TS2,** (1*R*)*Z*-**TS2,** and (1*S*)*Z*-**TS2**, Figure 1A) with disparate energies for the addition. Note that the four transition states have their corresponding enantiomers which we do not need to consider because of the same energies of the enantiomers. As shown in Figure 1A, although the two pathways of stage II via (1*R*)*E*-**TS2** and (1*R*)*Z*-**TS2** result in two different conformations of **IM4**, respectively, stage III can only give (1*R,2S)***IM6**, because *trans*-(1*R*)**IM4** can easily convert to *cis*-(1*R*)**IM4** with a barrier (**TS6**) 6.5 kcal mol^{-1} lower than *trans*-(1*R*)**TS4.** We also considered the *exo*-isomers of **IM4** and **TS4** which can be obtained via rotation around S-N bond (see the inset in Figure 1A). Taken these isomers into account together, *cis*-(*1R*)**IM4** and *cis*-(*1R*)**TS4** are still the lowest rearrangement precursor and transition state, respectively.

Structurally, (1*S*)*E*-**TS2** and (1*S*)*Z*-**TS2** can lead to (*1S,2S*)**IM6** (Figure 1A). However, because (1*S*)*E*-**TS2** and (1*S*)*Z*-**TS2** are 5.0 and 5.7 kcal mol^{-1} higher than (1*R*)*E*-**TS2** and (1*R*)*Z*-**TS2**, respectively, the formation of (1*S,2S*)**IM6** is kinetically suppressed. Thus, the **Py** addition is diastereoselective, only affording (1*R,*2*S*)**IM6**. Intrigued by the predicted stereoselectivity, we preformed the additions of **Py** to *E*-**IM2** and *Z*-**IM2**, respectively (see step 2 in eqs 3 and 4). The NMR studies (for details, see Supporting Information) disclosed that both additions produced the same single diastereoisomer. **IM6** is stable in the absence of K_2CO_3, encouraging us to crystalize **IM6** for X-ray diffraction analysis. As shown in Figure 1B, the obtained X-ray structure corresponds to the (1*S,2R*)-enantiomer of our computed (1*R,2S*)**IM6**, rather than the (1*S,*2*S*)- or (1*R*,2*R*)-diastereomer. These experimental studies unambiguously demonstrate the diastereoselectivity of the **Py**

addition. In addition, (1*R*)*E*-**TS2** is 2.1 kcal mol^{-1} lower than (1*R*)*Z*-**TS2**, in agreement with the experimental observation that the **Py** addition (step 2 in eq 3) proceeded faster than that (step 2 in eq 4) (2h versus 12h).

A remarkable feature of the reaction is the exclusive *Z*-selectivity (Table 3). As detailed in Supporting Information, we attribute the *Z*-selectivity of the reaction to the diastereoselective **Py** addition and the *cis*-selective E1cB-elimination of **IM6**. With the caution of using monomeric K_2CO_3 to model K_2CO_3 base which may exist as aggregations in the solvent, we also tentatively analyzed the origins of the *Z*-selectivity of the reaction in the Supporting Information.

Conclusion

In summary, α-C-H arylation of α,β-unsaturated nitriles with aryl sulfoxides has been developed on the basis of a Morita-Baylis-Hillman-type addition triggered [3,3]-rearrangement. The reaction features high regio- and stereo-selectivity, excellent functional-group compatibility, and broad substrate scope for both coupling partners. The high efficiency of decagram-scale reaction highlights the practicability of the method. In a word, the protocol not only provides an efficient approach for the synthesis of valuable α-aryl α,β-unsaturated nitriles but also demonstrates the feasibility of merging MBH reaction into [3,3]-rearrangement process that is expected to inspire the development of new rearrangement reactions. The control experiments and DFT calculations support a reaction sequence including the assembly of Tf_2O activated aryl sulfoxide with α,β-unsaturated nitrile to give unsaturated imine-sulfoxonium salt, MBH-like 2-chloropyridine addition to give α-aryl β-ammonium nitrile, [3,3]-rearrangement to form C-C bond, and E1cB-elimination to give product. We tentatively attribute the *Z*-selectivity of the reaction to the diastereoselective 2-chloropyridine addition and the *cis*-selective E1cB-elimination.

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Keywords: [3,3]-sigmatropic rearrangement • Morita-Baylis-Hillman reaction • electrophilic activation • sulfoxide • arylation

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[15] In order to promote the finial elimination of β-ammonium nitrile salt, KO*t*-Bu in lieu of K_2CO_3 was used for the decagram-scale reaction.

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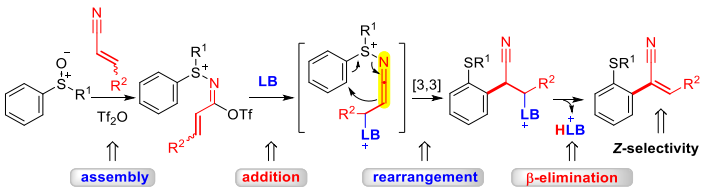

[3,3]-Sigmatropic rearrangement of aryl sulfoxides with α,β-unsaturated nitriles has been developed by merging Morita-Baylis-Hillman reaction into the S(IV)-mediated [3,3]-rearrangement process. The protocol enables the remarkable *Z*-selective synthesis of a wide variety of valuable α-aryl α,β-unsaturated nitriles that can be a challenge to traditional synthetic methods.