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Letter

Nucleophilic Vinylic Substitution (S_NV) of Trisubstituted Monofluoroalkenes for the Synthesis of Stereodefined Trisubstituted Alkenes and Divinyl Ethers

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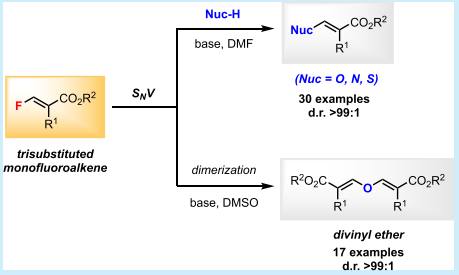
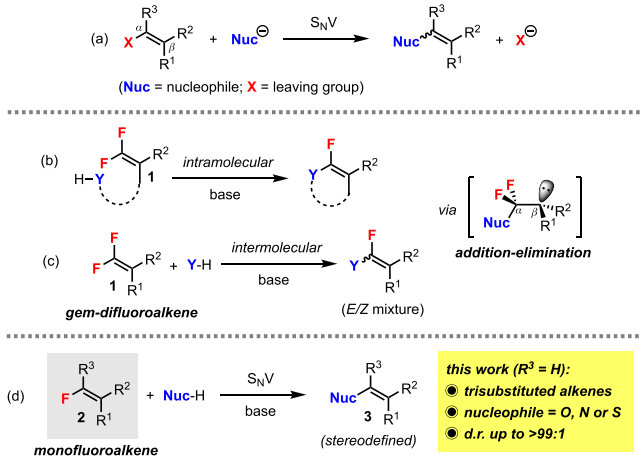
ABSTRACT: We herein describe a nucleophilic vinylic substitution (S_NV) of trisubstituted monofluoroalkenes with excellent stereocontrol (d.r. > 99:1). Starting from (*E*)-*β*-monofluoroacrylates, various trisubstituted (*E*)-alkenes containing O/N/S-substituent groups at the vinylic position can be obtained under simple conditions. Furthermore, (*E*,*E*)-divinyl ethers can be generated through dimerization of the monofluoroalkenes, triggered by adventitious water in the reaction mixture.



Nucleophilic vinylic substitution (S_NV) is a useful synthetic tool for directly generating compounds with multisubstituted C−C double bonds including vinyl ethers and enamines.[1] In S_NV, a leaving group (X) such as halogen is replaced by a nitrogen, oxygen, sulfur, or carbon nucleophile (Nuc) (Scheme 1a). The stereochemical outcome of the alkene product is of significance and the subject of much debate. Nucleophilic substitution of perfluorinated alkenes is a well-known process in organofluorine chemistry.[2] In particular, *gem*-difluoroalkenes **1** are susceptible to nucleophilic substitution of the vinylic F via an *addition−elimination* mechanism.[3] Ichikawa and co-workers pioneered the intramolecular S_NV of *gem*-difluoroalkenes through *5-endo-trig* cyclizations (Scheme 1b).[4] Cao and co-workers more recently contributed to the intermolecular version using various nucleophiles (Scheme 1c).[5] Mixtures of *E*/*Z* products were often obtained and the ratios depended on the substrate and nucleophile. The susceptibility of fluoroalkenes to nucleophilic substitution can be reasoned by the following:[3] (1) activation of the double bond by the electron-withdrawing inductive effect of fluorine; (2) *β*-anion stabilizing effect of fluorine through negative hyperconjugation; (3) repulsive interaction between fluorine lone pairs and *π*-electrons; (4) leaving group ability of the fluoride ion.

Scheme 1. Nucleophilic Vinylic Substitution (S_NV) of Fluoroalkenes



In comparison with difluoroalkenes, the S_NV reaction of *monofluoroalkenes* **2** has been much less studied.[5] The conversion of a vinylic carbon−fluorine bond into a carbon−heteroatom bond under simple conditions would be highly attractive for obtaining multisubstituted alkenes **3** (Scheme 1d), which is especially applicable because of various available stereoselective methods for preparing monofluoroalkenes **2**.[3,6] Moreover, this approach is complementary to conventional methods such as nucleophilic conjugate additions to activated alkynes[7a−c] and transition metal-catalyzed cross-couplings of vinyl halides.[7d,e]

One major challenge remains that monofluoroalkenes are intrinsically less reactive than difluoroalkenes toward nucleophilic substitution.[8] Also, the *E*/*Z* selectivity is unpredictable,

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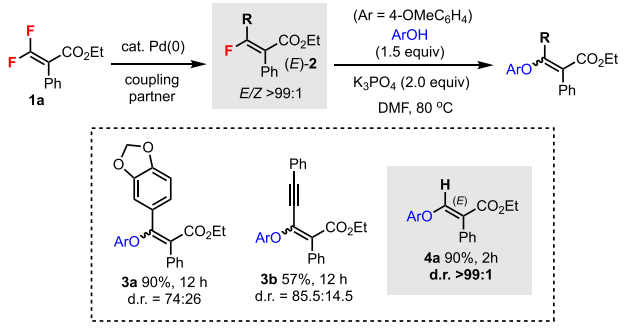
which can be influenced by the nature of nucleophiles, substrates, and reaction conditions.[1] For the method to be synthetically practical and useful, the reaction ought to be completely selective for generating stereodefined alkene product **3**.[9] We herein introduce a novel S_NV reaction of trisubstituted monofluoroalkenes using oxygen-, nitrogen-, or sulfur-containing nucleophiles to synthesize multifunctional trisubstituted alkenes with excellent diastereoselectivities.

Our group has recently reported a series of protocols for the synthesis of (*E*)-*β*-monofluoroacrylates **2** from tetrasubstituted *β*,*β*-difluoroacrylates **1a** via stereoselective Pd(0)-catalyzed C−F bond activation (Scheme 2).[10] We surmised that such type

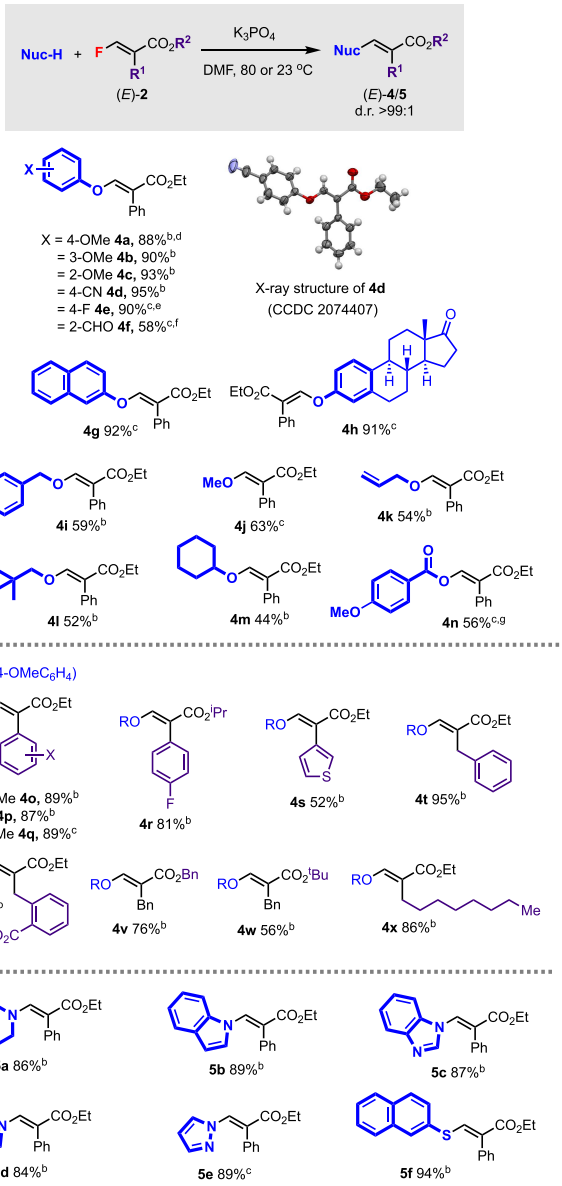
Scheme 2. Reactivity and Diastereoselectivity of (*E*)-*β*-Monofluoroacrylates in S_NV Reaction with 4-Methoxyphenol



of monofluoroalkenes could overcome the challenge of low reactivity in S_NV because of the activation of double bond by the ester substituent group. However, the diastereoselectivity in the product was not clear at the outset. Three representative monofluoroalkenes (*E*)-**2** bearing different substituent groups R, including aryl,[10c] alkynyl,[10a] and hydrogen,[10b] were prepared according to known procedures. They were subjected to the S_NV reaction using 4-methoxyphenol as a nucleophile and K_3PO_4 as a base in DMF at 80 °C.[5a] Reactions indeed took place with the isolation of the vinyl ether products **3a**, **3b**, and **4a** in moderate to good yields. The diastereoselectivities, on the other hand, depended heavily on the substituent group R. Whereas tetrasubstituted monofluoroalkenes yielded mixtures of diastereomers **3a** and **3b** in 74:26 to 85.5:14.5 ratios, the *trisubstituted* monofluoroalkene afforded product (*E*)-**4a**, *β*-phenoxyacrylate, as a single diastereomer. Its reactivity was also the highest, with complete conversion only after 2 h.

β-Aryloxy-/alkoxyacrylates and vinyl ethers in general are important structural motifs in natural products and versatile synthons in organic synthesis.[11] However, available methods for the synthesis of *trisubstituted* *β*-aryloxyacrylates resembling the structure of **4a** with well-defined alkene geometry are very limited.[12] The S_NV reaction of (*E*)-*β*-monofluoroacrylates **2** thus could offer a straightforward route to such class of compounds. The scope of the reaction was subsequently investigated (Scheme 3). Various substituted phenols afforded the *β*-aryloxyacrylates **4b**−**e** in good yields (90−95%), tolerating electron-donating and -withdrawing groups at different positions of the benzene ring. The reaction yield was consistent at a larger scale (1.0 mmol, 88% **4a**). Using salicylaldehyde as a nucleophile led to decreased yield (**4f**), whereas 2-naphthol was an effective nucleophile (**4g**). The human hormone estrone generated compound **4h** smoothly, demonstrating the feasibility of late-stage modification by

Scheme 3. S_NV Reaction of Monofluoroalkenes (*E*)-2 with O/N/S-Containing Nucleophiles for the Synthesis of Stereodefined Trisubstituted Alkenes (*E*)-4/5[a]



[a]General conditions: (*E*)-**2** (0.1 mmol, *E*/*Z* > 99:1), nucleophile (1.5 equiv.), K_3PO_4 (2.0 equiv.), DMF (0.2 M). Isolated yields. Unless specified otherwise, diastereomeric ratios (d.r.) of (*E*)-**4**/**5** were >99:1, determined by GC-MS and ^{1}H NMR analyses. [b]80 °C, [c]23 °C, [d]1.0 mmol scale, [e]d.r. = 97:3 and 89% yield at 80 °C, [f]d.r. = 96:4 and 62% yield at 80 °C, [g]d.r. = 97:3.

installing a tethered acrylate functionality onto a natural product core. Excellent diastereoselectivities were obtained (d.r. > 99:1) in these products, however, for some compounds (**4e** and **4f**), we observed the deterioration of d.r. (96:4 to 97:3) at 80 °C. The *E* configuration of the alkene was verified through the X-ray crystal structure of compound **4d** (CCDC 2074407).[13] Aliphatic alcohols including benzyl alcohol, methanol, allyl alcohol, neopentyl alcohol, and cyclohexanol were employed to synthesize *β*-alkoxyacrylates **4i**−**m**.[14] Full conversions and excellent diastereoselectivities were observed; however, the products were prone to decomposition by column chromatography, thus resulting in lower isolated yields.

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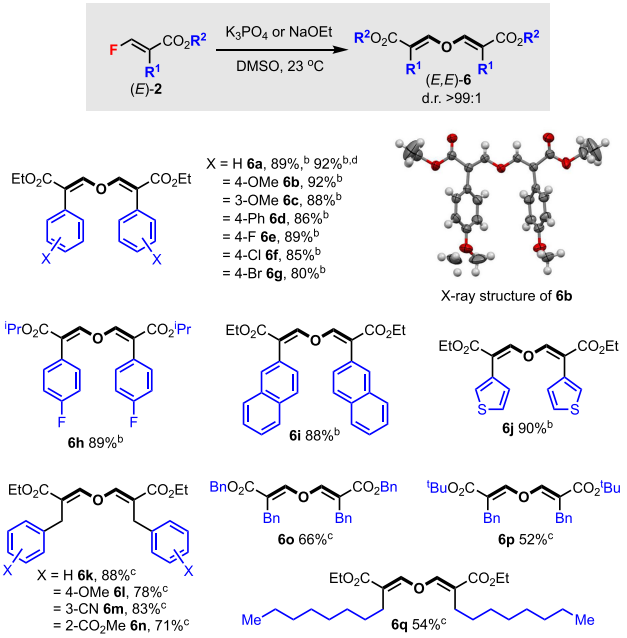
Using isopropanol and diethyl malonate failed to give the desired products because of byproduct formation at 80 °C. Even a carboxylic acid could be used as nucleophile leading to the vinyl acetate product **4n**, albeit in a lower d.r. (97:3).

Next, the effects of the substituent groups R^1 and R^2 of substrate **2** were investigated using 4-methoxyphenol. Electron-rich or -deficient α-aryl groups were tolerated (**4o**−**q**). Changing the ethyl ester group to bulkier isopropyl group did not affect the reaction (**4p** vs. **4r**). Heteroaromatic group such as 3-thienyl was tolerated (**4s**). Benzyl derivatives were high-yielding tolerating ortho substituent (**4t**−**u**). The structure of **4t** was verified by NOESY NMR experiments. Varying the ester group from ethyl to benzyl and *tert*-butyl decreased the yields (**4t** vs. **4v**−**w**). A long-chain alkyl group at α-position was also compatible (**4x**). Therefore, a modular synthesis of (*E*)-**4** was demonstrated where the nucleophile, α-substituent and ester group can be easily varied, which provides the advantage for SAR studies in drug discovery. More importantly, single diastereomers (*E*) were obtained for almost all of the products despite the steric and electronic differences in the nucleophiles and substrates. The reaction was not only limited to alcohols, various nitrogen- and sulfur-containing nucleophiles were also effective furnishing the S_NV products **5** in good yields and excellent diastereoselectivities. Morpholine afforded product **5a**, which belongs to the family of β-enamino esters that are versatile building blocks in organic synthesis.[15] Aromatic *N*-heterocycles are pharmaceutically important, they were suitable nucleophiles for generating indole (**5b**), benzimidazole (**5c**), imidazole (**5d**), and pyrazole (**5e**) derivatives. A vinyl sulfide compound **5f** was also obtained in high yield by using 2-naphthalenethiol as the nucleophile.

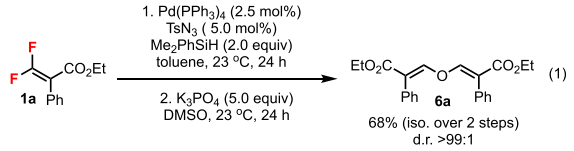
Interestingly, when subjecting monofluoroalkene **2a** to K_3PO_4 in DMF at room temperature *without* any nucleophile, an unexpected dimeric product divinyl ether **6a** was obtained in 84% yield (^{1}H NMR).[16] The yield was improved in DMSO and (*E,E*)-**6a** was isolated cleanly in good yields (89%, 92% at 1.0 mmol scale) as a single diastereomer (Scheme 4). Only a few reports have observed the formation of bis(*trans*-2-ethoxycarbonylvinyl)ether (i.e., compound **6**, R^1 = H, R^2 = Et),[17] to the best of our knowledge, synthesis of multi-substituted divinyl ethers such as **6a** was unprecedented. The reaction tolerated various aryl α-substituent group (R^1) containing electron-donating/-withdrawing groups and halogens (**6b**−**g**). The structure of the product was unambiguously confirmed through **6b** (CCDC 2074399) by X-ray crystallography.[13] Replacing the ethyl ester group by isopropyl did not affect the yield (compare **6e** and **6h**). Naphthyl and 3-thienyl groups were also compatible (**6i**−**j**). With the benzyl-substituted product **6k**, the conversion was poor using K_3PO_4.[16] A stronger base NaOEt was necessary to provide good yields of the benzylic compounds **6k**−**n** bearing different functional groups. The reaction yield decreased somewhat as the steric bulk of the ester group was increased (compare **6k**, **6o**, and **6p**). The compound containing a long-chain alkyl group (**6q**) was also furnished. In all cases, excellent diastereomeric ratios (>99:1) were obtained in the products. The modular synthesis of novel divinyl ethers **6** with well-defined alkene geometries (*E,E*) and tunable α-substituent group (R^1) and ester group (R^2) was therefore achieved through the base-mediated dimerization of monofluoroalkenes **2**.

Scheme 4. Synthesis of Stereodefined Divinyl Ether (*E,E*)-6 from Monofluoroalkenes (*E*)-2[a]



[a]General conditions: (*E*)-**2** (0.2 mmol, *E*/*Z* > 99:1), base, DMSO (0.2 M), 12−48 h. Isolated yields. Diastereomeric ratios (d.r.) of **6** were determined by ^{1}H NMR analysis. [b]K_3PO_4 (3.0 equiv.), [c]NaOEt (2.0 equiv.), [d]1.0 mmol scale.

Furthermore, a convenient two-step sequence to prepare the divinyl ether **6a** directly from *gem*-difluoroalkene **1a** without the isolation of **2a** was shown (eq 1). Following the Pd-catalyzed hydrodefluorination step,[10b] simply switching solvents and adding base allowed the isolation of (*E,E*)-**6a** in 68% yield over two steps.



Further studies were carried out to shed light on the reaction mechanisms (Scheme 5). Temperature effects on the diastereoselectiviy were investigated using 2-naphthol as a nucleophile with substrate **2a** (Scheme 5a). The reactions gave full conversions and were very selective at lower temperatures (60 °C and below), but showed decreased selectivity at higher temperatures. This effect was also observed with certain nucleophiles such as 4-fluorophenol and salicylaldehyde (cf. Scheme 3, **4e** and **4f**). Disubstituted monofluoroalkene (*Z*)-**7** was prepared according to literature procedures[18] and subjected to the standard conditions with 4-methoxyphenol (Scheme 5b). No S_NV reaction occurred, indicating the importance of the ester group for activating the double bond (compare with **4o**, Scheme 3). Tetrasubstituted monofluoroalkene **2t** with (*Z*)-configuration was employed in the standard S_NV conditions leading to a mixture of (*E/Z*)-products **3c** (Scheme 5c). This result was analogous to that using (*E*)-alkene as the substrate (compare with **3a**, Scheme 2), thus showing that the S_NV reaction of *tetrasubstituted* monofluoroalkenes was unselective regardless of the (*E*)- or (*Z*)-configuration. Substrate **2r** was unreactive in the standard conditions for generating divinyl ether products (Scheme 5d),

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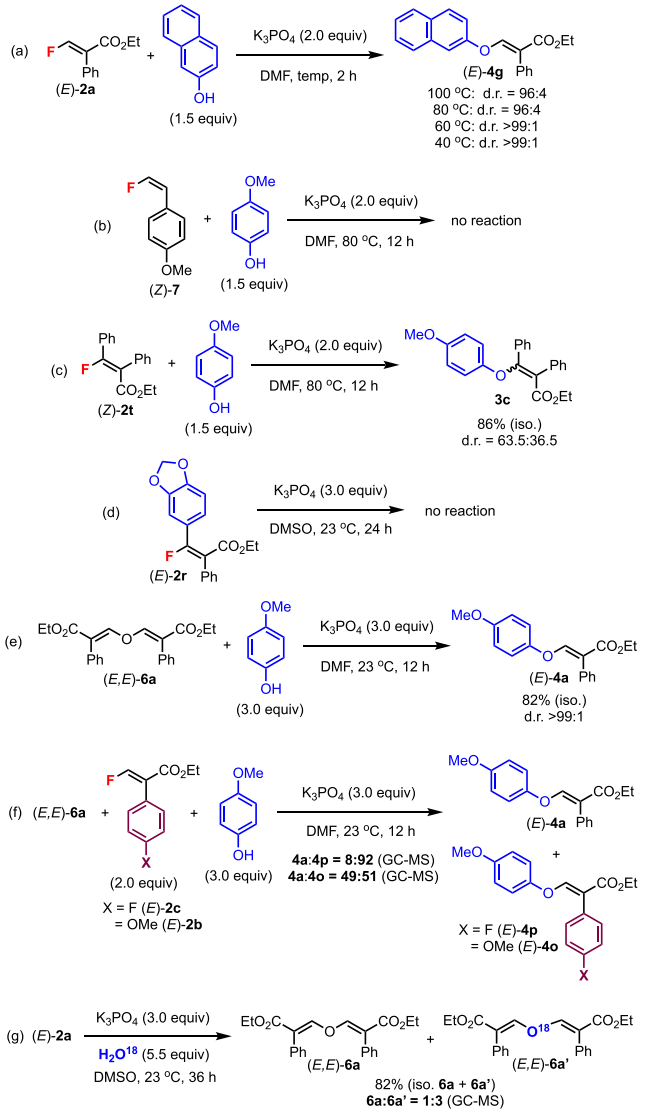
Scheme 5. Mechanistic Studies



despite its high yield in S_NV with a phenol (*cf.* Scheme 2), thereby demonstrating the superior reactivity of *trisubstituted* monofluoroalkenes for dimerization.

It is intriguing that the S_NV product **4a** could also be obtained from divinyl ether **6a**, instead of monofluoroalkene **2a**, in comparable yield and excellent diastereoselectivity (Scheme 5e). This implied the possible intermediacy of dimer **6**, although not exclusively, for product **4**, as similar conditions were employed for the S_NV reaction and dimerization (cf. Schemes 3 and 4).[16] Competition studies were carried out by mixing divinyl ether **6a** with monofluoroalkenes **2c** or **2b** bearing different α-aryl substituent groups, in the presence of the nucleophile (Scheme 5f). The results revealed an interesting distribution of the S_NV products (**4a** vs. **4p** or **4o**) depending on the substituent X. With an electron-withdrawing group (X = F), product **4p** predominated. With an electron-donating group (X = OMe), almost equal amounts of products **4a** and **4o** were obtained. Therefore, monofluoroalkenes **2** containing different α-substituent groups R^1 may have different reactivities in the S_NV reactions, and thus their mechanistic pathways may also differ, i.e., direct addition−elimination with **2** or through the divinyl ether intermediate **6**. To probe the mechanism for the formation of divinyl ethers **6**, we added H_2O^{18} to the standard conditions using **2a** (Scheme 5g). The O^{18}-labeled product **6a′** was obtained in significant amounts. On the basis of this evidence and literature report,[17a] the source of oxygen in **6** is likely from adventitious water in the reaction mixture, in which case, water acted as an effective nucleophile in the S_NV with **2**.

In summary, a nucleophilic vinylic substitution (S_NV) reaction has been developed for the synthesis of trisubstituted alkenes containing vinylic O/N/S-substituents from (*E*)-β-monofluoroacrylates. The stereocontrol of the alkene geometry is complete, affording (*E*)-products exclusively. Moreover, by omitting the nucleophile, novel (*E,E*)-divinyl ethers can be generated from the same substrates in high yields and >99:1 diastereomeric ratios. A plausible explanation for the excellent stereocontrol in the addition−elimination pathway is that the incipient ester enolate could participate in intramolecular hydrogen bonding with the β-hydrogen. As a result, the bond rotation is restricted until β-F elimination takes place affording the (*E*)-products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02359.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 2074399 and 2074407 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(13) Note the positional disorder of a methyl group in the structure of **6b**.

(14) For a silver-catalyzed method for the synthesis of *β*-methoxyacrylates including (*E*)-**4j**, see: Li, J.; Qian, B.; Huang, H. Silver-Catalyzed Olefination of Acetals and Ketals with Diazoesters to *β*-Alkoxyacrylates. *Org. Lett.* **2018**, *20*, 7090−7094.

(15) (a) Xin, D.; Burgess, K. A Chemoselective Route to *β*-Enamino Esters and Thioesters. *Org. Lett.* **2014**, *16*, 2108−2110. For a copper-catalyzed method for the generation of (*E*)-**5a**, see: (b) Pal, A.; Hussaini, S. R. Copper-Catalyzed Coupling of Thioamides and Donor/Acceptor-Substituted Carbenoids: Synthesis of Enamino Esters and Enaminones. *ACS Omega.* **2019**, *4*, 269−280.

(16) See the Supporting Information for full details.

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