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Direct Nucleophilic Acylation of Nitroalkenes Promoted by a Fluoride Anion/Thiourea Combination

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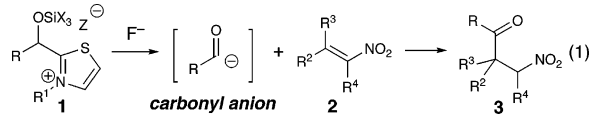
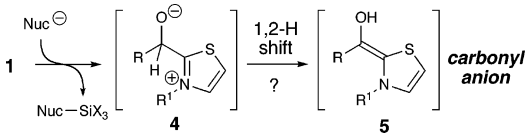
The ability to invert the reactivity of functional groups, or *Umpolung*, provides access to unconventional strategies for the synthesis of important target molecules.[1] A powerful tactic that accomplishes this goal converts a normally electrophilic carbonyl unit into a nucleophilic species with a subsequent bond-forming event. There are many established indirect stoichiometric methods to access this unusual reactivity, including metalated dithianes[2] and protected cyanohydrins.[3] These conventional approaches typically require strongly basic conditions and processing of the resulting products to unmask the carbonyl moiety. As part of our studies involving accessing new *Umpolung* bond-forming processes,[4] we wished to engage nitroalkenes as potential electrophiles with carbonyl anions. In general, conjugate additions to nitroalkenes afford highly useful compounds with diverse functionality for organic synthesis.[5] In this communication, we describe the first direct nucleophilic acylation of nitroalkenes (**2**) to produce β-nitro ketones (**3**) by the combination of a fluoride source with silylated thiazolium carbinols **1** (eq 1).



We began by surveying catalytic methods that installed carbonyl groups using aldehydes[6] or acylsilanes[7] as nucleophilic precursors. However, the heteroazolium-derived catalysts generated in situ for these processes typically require basic conditions, and our attempts with this approach afforded only low levels of β-nitro ketones (**3**), primarily due to rapid base-induced decomposition of the nitroalkene. Prompted by the paucity of efficient means to directly add carbonyl anions to this sensitive electrophile class, we hypothesized that accessing carbonyl anion reactivity without an amine base would be successful. In our previous studies with thiazolium-catalyzed additions of acylsilanes, we have observed that thiazolium carbinols, such as **1**, operate as storable and stoichiometric carbonyl anions when exposed to an amine base.[8] We reasoned that these easily prepared carbinols[9] might act as nucleophilic acyl reagents when exposed to a fluoride source, thereby selectively accessing carbonyl anions without amine bases (Scheme 1).

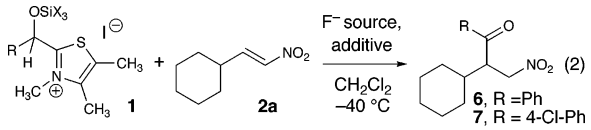
Scheme 1



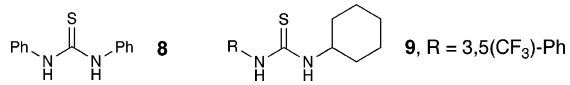
In this process, the resulting alkoxide **4** could undergo a 1,2-hydrogen shift to generate **5**, an intermediate described by Breslow in the benzoin reaction.[10] Alternatively, alkoxide **4** could also collapse to eject the thiazolium zwitterion and thus not undergo the desired addition reaction. Importantly, generating intermediate alkoxide **4** via addition of a deprotonated thiazolium salt to an aldehyde is untenable due to competing pathways, such as dimerization of the resulting thiazolium zwitterion.[11] Thus, accessing a pathway to produce nucleophile **5** cleanly *in the presence* of the nitroalkene is clearly a key requirement for success. To assess this approach, we began by examining the addition of thiazolium carbinols (**1**) to nitroalkene **2a** (Table 1).

Our initial investigations demonstrated that β-nitro ketone **6** could be isolated, using tetrabutylammonium triphenyl difluorosilicate to generate the carbonyl anion equivalent in situ at −40 °C (entry 1). Encouraged by the direct installation of a carbonyl unit at low temperature via this new process, the reaction was further enhanced by the addition of thiourea additive **9**. Our incorporation of a thiourea was based on the additions to nitroalkenes recently reported by Takemoto.[12] This unique fluoride/thiourea combination afforded an improved 66% yield of **6** (entry 2). Tetramethylammonium fluoride (TMAF)[13] was superior in terms of reaction times and simplicity of purification, but the yields remained unsatisfactory. To improve the process, silyl protecting groups were evaluated. Triethylsilyl (TES)-protected carbinols afforded increased yields of **6** compared to trimethylsilyl (TMS) variants, while more robust *tert*-butyldimethyl (TBS) analogues prevented the nitroalkene from being completely consumed. With the optimal fluoride source and protecting group in hand, placement of an electron-withdrawing group on the protected thiazolium carbinol increased the yield to 78% (entry 5). Finally, commercial thiocarbanilide (**8**) was a convenient additive and provided good yields of **7** (75%, entry 6).

Table 1. Fluoride Promoted Carbonyl Anion Additions to Nitroalkene **2a**



entry	R	X	fluoride source	additive	yield (%)
1	Ph	Me	$Bu_4N•Ph_3SiF_2$	none	33
2	Ph	Me	$Bu_4N•Ph_3SiF_2$	**9**	66
3	Ph	Me	$Me_4N•F$	**9**	53
4	Ph	Et	$Me_4N•F$	**9**	59
5	4-Cl−Ph	Et	$Me_4N•F$	**9**	78
6	4-Cl−Ph	Et	$Me_4N•F$	**8**	75



Investigation into the reaction scope was carried out with the optimal combination of fluoride source (TMAF) and thiourea **8** (Table 2, eq 3). Various nitroalkenes are competent substrates in the addition reaction, including branched and straight chain variants (entries 1−4). The nucleophilic acylation of a cyclic nitroalkene occurs smoothly with excellent diastereoselectivity to yield trans product **13** (20:1 dr, entry 5). Remarkably, formation of a quaternary

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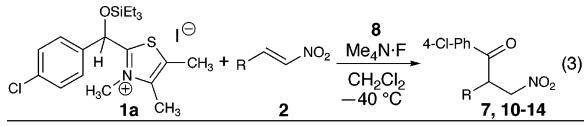
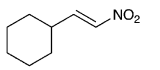
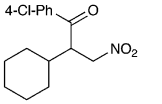
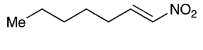
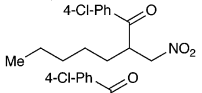
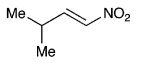
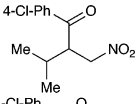
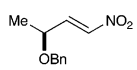
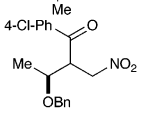
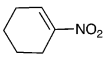
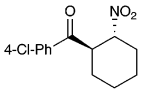
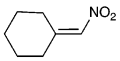
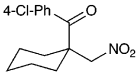
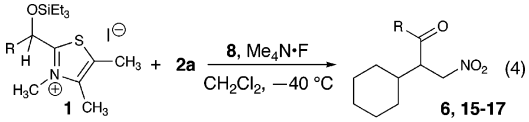
Table 2. Nucleophilic Acylation of Nitroalkenes with Protected Thiazolium Carbinols



entry	nitroalkene	product		Yield (%)
1			**7**	78%
2			**10**	65%
3			**11**	73%
4			**12** (1:1 dr)[a]	63%
5			**13** (20:1 dr)	80%
6			**14**	56%

[a] Diastereoselectivity = 6:1 when achiral thiourea **8** is replaced by **18**.

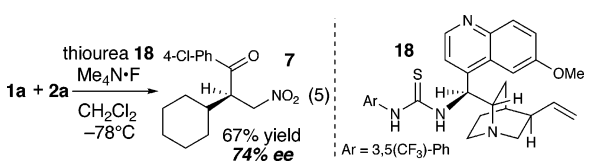
Table 3. Survey of Thiazolium Carbinols



entry	R	product	yield (%)
1	Ph (**1b**)	**6**	59
2	2-naphthyl (**1c**)	**15**	82
3	3-MeO−Ph (**1d**)	**16**	60
4	4-Br−Ph (**1e**)	**17**	81

center is possible by addition of the carbonyl anion equivalent to a β,β-disubstituted nitroalkene (entry 6).

Various protected thiazolium carbinols were also examined. The 2-naphthyl-derived carbinol was successfully added to nitroalkene **2a** (entry 2). In addition to electron-withdrawing groups, the reaction is also tolerant of an electron-donating substituent on the phenyl ring (entry 3). Currently, thiazolium carbinols derived from saturated aldehydes provide poor yields of desired product (<30%), underscoring the delicate balance between hydrogen transfer and unproductive reaction pathways.Our initial investigations indicate that this carbonyl addition process can be rendered stereoselective. The incorporation of chiral thiourea **18** derived from quinine[14] produces β-nitro ketone **7** in 67% yield and 74% ee (eq 5). Additionally, when thiourea **18** is used instead of **8** in the reaction that produces **12** (Table 2, entry 4), the diastereoselectivity improves to 6:1. These unoptimized results demonstrate the strong interaction between the nitroalkene and thiourea during the key carbonyl anion addition process and also provide a strong impetus to explore the potential of chiral thiourea catalysis on the title reaction.



In summary, the first direct nucleophilic addition of a carbonyl unit to nitroalkenes has been reported. In the presence of a fluoride anion, silyl-protected thiazolium carbinols do not undergo scission to an aldehyde and thiazolium zwitterion, but instead access carbonyl anion reactivity via a presumed 1,2-hydrogen shift. This distinct fluoride-activated acyl anion strategy is divergent from the typical combinations of heteroazolium salts and bases and thus allows for the use of reactive nitroalkenes as substrates. Additionally, newly formed stereocenters in this reaction can be controlled by a chiral thiourea. The enantioselective process implicates key interactions between thiourea and nitro functionality during carbon−carbon bond formation. Mechanistic investigations and the further exploration of these silyl-protected thiazolium carbinols as stoichiometric carbonyl anions will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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