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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record.

To be cited as: 10.1002/ange.201904530

Link to VoR: <https://doi.org/10.1002/ange.201904530>

Reductive C–C Coupling from α,β -Unsaturated Nitriles by Intercepting Keteniminates

Lillian V. A. Hale,[‡] N. Marianne Sikes,[‡] and Nathaniel K. Szymczak^{*[a]}

Abstract: We present a new atom economic strategy to catalytically generate and intercept nitrile anion equivalents using hydrogen transfer catalysis. Addition of α,β -unsaturated nitriles to a pincer-based Ru–H complex affords structurally characterized κ -N-coordinated keteniminates via selective 1,4-hydride transfer. When generated *in situ* under catalytic hydrogenation conditions, electrophilic addition to the keteniminate was achieved using anhydrides to afford α -cyanoacetates in high yields. This work represents a new application of hydrogen transfer catalysis for selective 1,4 addition to α,β -unsaturated nitriles.

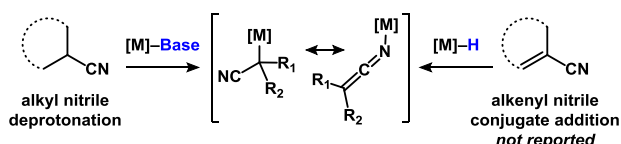
Nitrile anions are a diverse class of synthetic intermediates that provide access to highly functionalized products through nucleophilic addition and substitution reactions.^[1] Analogous to enolates, nitrile anions are ambident nucleophiles that can react either as carbanions to provide α -functionalized cyano products,^[1b-d] or as keteniminates to provide neutral ketenimines.^[1d;2] Each product class has further synthetic utility as building blocks for natural products and pharmaceuticals; while α -cyano groups are easily derivatized, ketenimines further undergo nucleophilic, electrophilic, and/or cyclization reactions. To access the diverse chemical space of these nitrogen containing compounds, new methods to generate and control the reactivity of nitrile anions are highly desirable.

The synthetic utility of nitrile anions is hindered by a lack of catalytic strategies available to generate them *in situ* from simple pro-nucleophiles.^[1b;1c;3] Alkyl nitriles are currently the major precursors to C- or N-metalated nitriles used in catalytic transformations (Scheme 1a, left).^[1c] Base-assisted deprotonation of alkyl nitriles with transition-metal catalysts has been successfully applied in a number of α -functionalization reactions; however, significant challenges remain. Methods that deliver products with all-carbon quaternary centers and/or occur with high stereoselectivities are rare.^[1b;1c;4] These challenges may be addressed by designing new catalytic methods using pro-nucleophiles with distinct modes of activation. α,β -Unsaturated nitriles can generate nitrile anions through conjugate addition (Scheme 1b, right) and are easily accessed from the corresponding ketone, aldehyde, or alkene in a single

step.^[5] Despite the potential for rapid multi-functionalization, this mode of activation is virtually unexplored for catalytic applications.

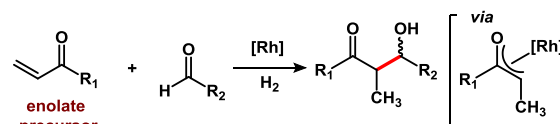
To contextualize the significance of expanding the pool of available pro-nucleophiles, it is useful to compare with well-established enolate chemistry; identifying new catalytic routes to form enolates or silyl enol ethers *in situ* has led to significant advances in selective reduction^[6] and reductive C–C bond forming reactions.^[7] In particular, Krische and co-workers have developed reductive C–C coupling reactions using hydrogen transfer catalysts and π -unsaturated substrates.^[7c;7e] They reported that under catalytic hydrogenation conditions, α,β -unsaturated ketones generate enolates capable of participating in aldol condensations (Scheme 1b).^[7b] Our current work parallels these discoveries based on α,β -unsaturated ketones and is the first example of using alkenyl nitriles as pro-nucleophiles for hydrogenative C–C bond forming reactions.

(a) metalated nitriles generated from alkyl and alkenyl nitrile pro-nucleophiles

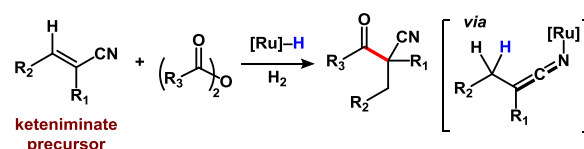


(b) hydrogenative C–C coupling using α,β -unsaturated pro-nucleophiles

prior art: reductive generation of enolates for aldol condensation



this work: reductive generation of keteniminates for α -cyanoalkylation



Scheme 1. (a) Formation of nitrile anions with alkyl nitrile or alkenyl nitrile pro-nucleophiles. (b) Hydrogen mediated reductive coupling using π -unsaturated substrates.

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Although nitriles may undergo insertion into metal-hydrides to afford imine type products,^[8] a second site of unsaturation may promote isomerization to form the resonance stabilized nitrile anion/keteniminate. We previously reported that

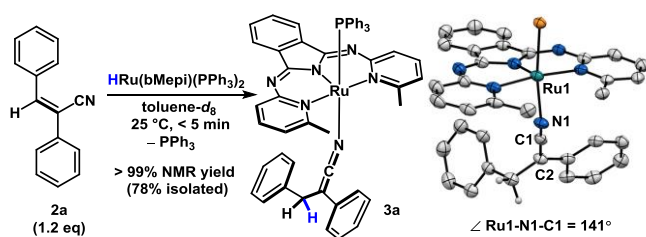
HRu(bMepi)(PPh₃)₂ (**1**, bMepi = 1,3-bis(6'-methyl-2'-pyridylimino)isoindoline)) is an excellent catalyst for reversible hydrogen transfer reactions of alcohols and amines.^[9] For nitrile substrates, hydride insertion readily occurs to form imine coordinated species, and the catalytically active Ru–H can be directly (re)generated from H₂. **1** exhibits unique reactivity with amines and nitriles, and has a high binding affinity for the intermediate imine.^[9d;10] We hypothesized that this reactivity would provide an entry point for evaluating hydrogenative C–C coupling with α,β -unsaturated nitriles.

We evaluated the insertion chemistry of α,β -unsaturated nitriles to Ru–H through stoichiometric addition of α -phenylcinnamionitrile (**2a**) to **1** (Scheme 2). When **2a** (1.2 equiv) was added to a toluene-*d*₈ solution of **1** at room temperature, quantitative conversion to a new species occurred within 5 minutes. ³¹P NMR spectroscopy confirmed the disappearance of **1** (51 ppm), concomitant with the appearance of free PPh₃ and a new resonance at 39 ppm. **1** was also absent in the ¹H NMR spectrum, with no detectable H₂ or hydride-containing byproducts, consistent with a hydride insertion reaction. A phase sensitive ¹H–¹³C correlation experiment (HSQC) revealed the presence of a –CH₂ group (¹H δ : 3.20; ¹³C δ : 34.7), consistent with hydride addition to the least substituted carbon of α -phenylcinnamionitrile (Figure S5).

X-ray diffraction of single crystals unambiguously confirmed the insertion product as the Ru-ketenimine complex **3a**. The *N*-coordinated ketenimine has an elongated C1–N1 bond of 1.190(7) Å and a shortened C1–C2 bond length of 1.369(7) Å. Analysis by IR spectroscopy revealed a bathochromic shift in the C–N stretching frequency between **2a** ($\nu_{\text{CN}} = 2218 \text{ cm}^{-1}$) and **3a** ($\nu_{\text{CN}} = 2210 \text{ cm}^{-1}$), consistent with C–N bond elongation upon formation of the C2=C1=N1 unit. These bond distances and IR frequencies are consistent with known metal-ketenimine complexes and reflect the electronic delocalization from the partially negative C2 atom into the adjacent C1–N1 group.^{[11][12][13]} A distinct feature of **3a** is the bent Ru–N1–C1 angle (= 141°), which is highly unusual for metalated ketenimines — only four structurally characterized ketenimine complexes exhibit M–N–C1 angles <145°.^{[14],[13;15]} Moreover, all reported κ -*N*-Ru-ketenimine complexes exhibit nearly linear coordination (Ru–N1–C1 Avg. 173°).^[16] In addition to a *base-free* route to form a ketenimine, the unique binding mode to Ru offers a new framework to develop subsequent reactivity.^[17]

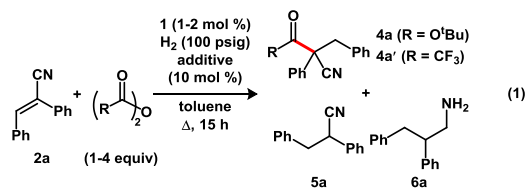
The linear geometry of substituted ketenimines allow for facile electrophilic additions to the C2 site, resulting in products with new all-carbon quaternary centers. Highly substituted carbons are desirable motifs for drug design and multi-step syntheses.^[18] When the electrophile is a carbonyl or acetate group, the resulting α -cyano compounds can be modified at either functional group to provide pharmaceutically relevant structural cores.^[19] The most common entry point into α -cyano carbonyl products are through lithiated alkyl nitriles; however, in most cases, stoichiometric addition of lithium diisopropylamide (LDA) or *n*-BuLi is required to unmask the nucleophilic carbon.^[4a;20] Silyl ketenimines are precursors to quaternary α -cyano carbonyl groups; however, stoichiometric base is also required.^[21] Interception of Ru-ketenimines with a carbonyl electrophile under hydrogenative reductive coupling conditions could provide α -functionalized cyano compounds while avoiding stoichiometric waste (eq 1).

The addition of carbonyl electrophiles to α,β -unsaturated nitriles in the presence of H₂ presents a key challenge: both C=C and C≡N groups are susceptible to hydrogenation using **1**. Prior to evaluating reductive coupling with **2a**, we interrogated hydrogenation reactivity using H₂ (100 psig) and **1** (1 mol %) (Table 1, entry 1). Complete hydrogenation of **2a** (0.25 mmol) to amine **6a** occurred at 80 °C.^[21] Reductive C–C coupling was evaluated using anhydrides based on the precedent for their electrophilic addition to α -cyano carbanions.^[2f;22] When di-*tert*-butyl dicarbonate (Boc₂O, 1 equiv) was added to the hydrogenation reaction above under analogous conditions (80 °C), acylation of **2a** occurred to provide **4a** in 29% yield and the remaining mixture (71%) was composed of hydrogenation products **5a** and **6a** (entry 2). Hydrogenative acylation was promoted with the addition of base, where 10 mol % LiO^{*t*}Bu at 80 °C increased the selectivity for **4a** over hydrogenation products (53:47; entry 3). Further optimization revealed that a higher temperature (100 °C), catalyst loading (2 mol % **1**) and concentration of Boc₂O (4 equiv) improved acylation selectivity, affording **4a** in 70% chemical yield (entry 4).



Scheme 2. Formation of Ru-ketenimine **3a** via selective 1,4-hydride transfer. The solid-state structure is displayed with 50% probability ellipsoids. PPh₃ phenyl groups and hydrogen atoms, except for the –CH₂ group, are omitted for clarity.

Table 1. Hydrogenative acylation of **2a** with **1**. Conversion and product ratios were determined by NMR analysis with PhSi(CH₃)₃ as an internal standard.



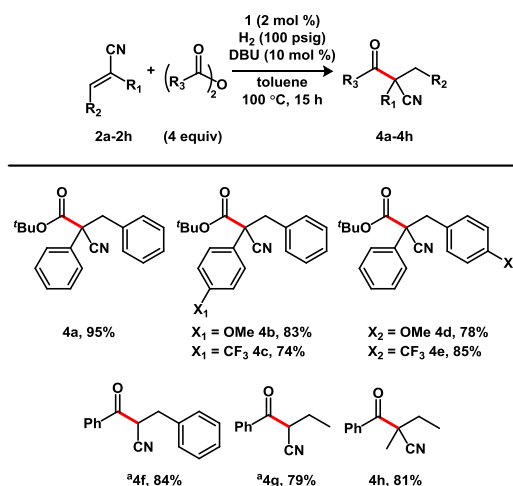
Entry	Temp (°C)	Additive (10 mol %)	Anhydride	% conv	4:5+6
1 ^a	80	None	None	>99	0:99
2 ^b	80	None	Boc ₂ O	>99	29:71
3 ^b	80	LiO ^t Bu	Boc ₂ O	>99	53:47
4 ^c	100	LiO ^t Bu	Boc ₂ O	>99	70:30
5 ^c	100	None	(CF ₃ CO) ₂ O	>99	93:7
6 ^c	100	DBU	Boc ₂ O	>99	95:5
7	100	DBU	Ac ₂ O	>99	89:11
8	100	DBU	(C ₆ H ₅ CO) ₂ O	>99	92:8

^areaction conditions: **1** (1 mol %), ^b reaction conditions: **1** (2 mol %), Boc₂O (2 equiv), ^creaction conditions: **1** (2 mol %), Boc₂O or (CF₃CO)₂O (4 equiv)

The improved selectivity toward acylation with the addition of LiO^tBu may be due to 1) base-assisted H₂ heterolysis, or 2) electrophilic activation of Boc₂O by Li⁺. To determine whether a more activated electrophile further improves the reaction selectivity, we evaluated trifluoroacetic anhydride (CF₃CO)₂O in place of Boc₂O. Under base-free conditions, (CF₃CO)₂O provided excellent selectivity for the acylated product **4a'** (93: 7, entry 5). Anhydride reagents with decreased reactivity (such as Boc₂O) may be further activated with an appropriate nucleophile to promote hydrogenative acylation. We previously identified 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a compatible base under hydrogenation conditions with **1**.^[23] When DBU was used in place of LiO^tBu to activate Boc₂O, the selectivity for **4a** dramatically improved (95:5, entry 6). These data indicate that the electrophilicity of the acylating agent influences reaction selectivity. Finally, the reductive acylation reaction is general to several representative anhydride reagents and, in addition to Boc₂O and (CF₃CO)₂O, we observed high yields using both acetic anhydride (89%, entry 7) and benzoic anhydride (92%, entry 8).^[24]

To assess the reaction scope and functional group compatibility, we examined α,β -unsaturated nitriles **2b-2h** with varying aryl and alkyl substitution (Scheme 3). Under optimized conditions with DBU and Boc₂O, diaryl α -cyanoacetates **4a-4e** were obtained in high isolated yields ranging from 78-95%. Alkyl substitution was also tolerated, although higher temperatures (150 °C) were required to obtain **4f** (84%) and **4g** (79%) from monoalkyl substituted alkenyl nitriles **2f** (R₁ = H, R₂ = C₆H₆) and

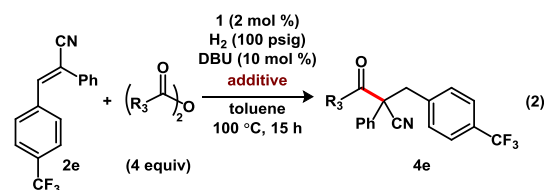
2g (R₁ = H, R₂ = CH₃) using DBU and (C₆H₅CO)₂O. In contrast, di-substituted 2,3-dimethylacrylonitrile (**2h**, R₁ = R₂ = CH₃) was reactive toward acylation with (C₆H₅CO)₂O at 100 °C to provide **4h** (81%).



Scheme 3. Synthesis of α -cyanoacetates **4a-4h** with Boc₂O or ((C₆H₅CO)₂O), DBU and **1**. Isolated yields following chromatography are reported. ^aReaction performed at 150 °C in mesitylene.

Finally, we examined the functional group compatibility of the hydrogenative acylation reaction using **1** in the presence of several common functional groups (eq 2, Table 2).^[25] Using **2e** and Boc₂O, the NMR yield of **4e** was assessed under standard conditions in the presence of potentially reactive additives. Notably, most additives tested did not decrease the yield of **4e** (entries 2-6). One limitation, however, was the incompatibility with hydrogen acceptors such as 2-vinylnaphthalene (entry 7), consistent with competitive hydrogenation by **1**.

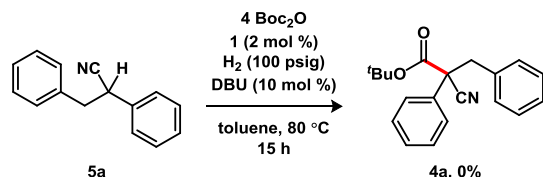
Table 2. Compatibility screening for hydrogenative acylation of **2e** in the presence of additives (1 equiv) containing common functional groups. R₃ = O^tBu. Yields were determined by NMR spectroscopy using PhSi(CH₃)₃ as an internal standard.



Entry	Additive (1 eq)	% conv	% yield
1	None	>99	86
2	N-benzylpyrrole	>99	88
3	2,4,6-collidine	>99	88
4	methyl benzoate	>99	86

5	N-methyl-N-phenylacetamide	>99	87
6	chlorobenzene	>99	86
7	2-vinylnaphthalene	57	0

Because saturated nitriles are products under hydrogenation conditions with **1** and α,β -unsaturated nitriles, a feasible pathway to α -cyanoacetate products may first involve C=C hydrogenation followed by deprotonation of the acidic α -C–H bond (by base or **1**) prior to acylation. To evaluate this possibility, we subjected saturated nitrile **5a** to our reaction conditions (Scheme 4). No **4a** was formed as assessed by NMR spectroscopy (see Figures S54–56). This suggests that **5a** does not undergo a base-assisted acylation. We attribute this result to competitive activation of the Boc₂O by DBU compared to deprotonation.^[26] We also found that stoichiometric reactions between **3a** and Boc₂O quantitatively affords **4a**, and that **3a** is a competent pre-catalyst. Under analogous conditions, **3a** provided identical yields of **4a** compared to reactions employing **1**, consistent with the intermediacy of **3a** during catalysis. Collectively, these results suggest that **1** provides a unique entry point to nitrile anions for catalysis, which is distinct from the previously reported deprotonation pathways of alkyl nitriles. Selective 1,4-hydride addition to α,β -unsaturated nitriles is a key step for generating catalytically competent keteniminate intermediates for hydrogenative C–C coupling reactions.



Scheme 4. Acylation of **5a** does not proceed under reductive C–C coupling conditions with **1** and DBU.

This work has introduced a new strategy to use catalytic hydrogen mediated reductive coupling to generate and intercept nitrile nucleophiles. Hydride transfer to α,β -unsaturated nitriles from **1** affords Ru-keteniminates that can be converted to α -cyanoacetate products under a H₂ atmosphere using catalytic DBU and **1**. Hydrogenative acylation enables the use of α,β -unsaturated nitriles as a new substrate class to access products containing all-carbon quaternary centers. Mechanistically distinct modes of nitrile activation are needed to discover new reactivity that parallels their oxygen containing counterparts. We predict that the diverse reactivity available to keteniminates and nitrile carbanions may be accessible following H[−] insertion by **1** to α,β -unsaturated nitriles. Current work is focused on exploring the scope in substrate and electrophile, as well as enantioselective acylation protocols.

Acknowledgments

This work was supported by the NSF (CHE-1350877 to N.K.S and CHE 1625543 for the X-ray diffractometers). L.V.A.H. and N.M.S acknowledge funding from a Rackham Graduate Student Research Grant. N.K.S. is a Camille and Henry Dreyfus Fellow.

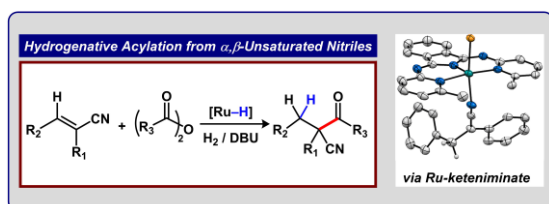
Keywords: keteniminate • ruthenium • α,β -unsaturated nitriles • hydrogenative acylation • catalytic reductive C–C coupling

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COMMUNICATION



We present a new application of hydrogen transfer catalysis to intercept ketenimine intermediates from α,β -unsaturated nitriles for a net hydrogenative acylation reaction.

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