Hydrogen Atom Transfer-Mediated Cyclisations of Nitriles

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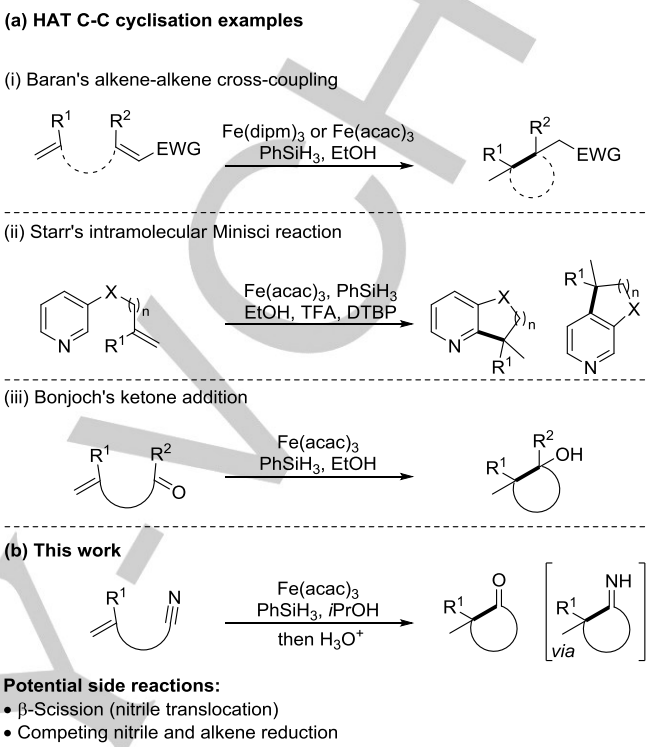
Abstract: Hydrogen atom transfer-mediated intramolecular C-C coupling reactions between alkenes and nitriles, using $PhSiH_3$ and catalytic $Fe(acac)_3$, are described. This introduces a new strategic bond disconnection for ring-closing reactions, forming ketones via imine intermediates. Of note is the scope of the reaction, including formation of sterically hindered ketones, spirocycles and fused cyclic systems.

In the early 1960s, Kwiatek and Seyler first reported the use of metal hydrides as catalysts in the hydrogenation of α,β-unsaturated compounds.[1,2] The discovery by Halpern,[3] later elegantly developed by Norton,[4] that metal-hydride hydrogen atom transfer (HAT) proceeded by a free-radical mechanism opened the door to a wide range of alkene hydrofunctionalisation reactions. But it was the pioneering work by Mukaiyama[5] on the catalytic hydration of alkenes, using $Co(acac)_2$ and oxygen, that sparked wider interest in the field of alkene hydrofunctionalisation. As a result, there now exists an extensive 'toolkit' for the addition of hydrogen and a functional group to an alkene with Markovnikov selectivity and high chemo-selectivity using cobalt, manganese and iron complexes.[6,7] Efforts have also been made to extend HAT methodologies to C-C bond formation, both in an intra- and intermolecular fashion: Baran's group developed a general C-C coupling reaction, utilising electron-deficient alkenes as capable radical acceptors (Scheme 1ai).[8–10] Hydropyridylation of alkenes by intramolecular Minisci reaction was recently demonstrated by Starr,[11] which allows for the formation of structures such as dihydropyranopyridines (Scheme 1aii). Furthermore, whilst conducting the work described in this paper, Bonjoch showed that ketones were able to undergo radical cyclisation to their tertiary alcohol counterparts (Scheme 1aiii).[12]

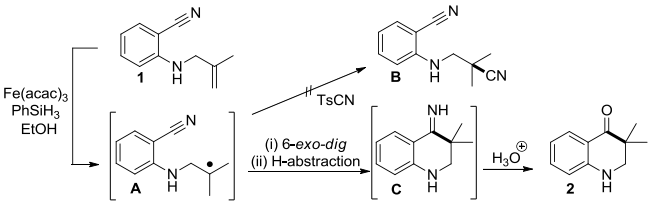
Yet, despite the use of radical acceptors such as acrylonitrile,[9] the HAT-initiated radical addition to nitriles has remained unreported. Whilst radical cyclisation onto a C≡N π-bond is feasible, it is about 50 times slower than its C=C and C≡C variants.[13] This is highlighted by the numerous reported failed attempts to cyclise onto a nitrile group;[14–16] although in isolated examples, radical cyclisations to nitriles have been achieved utilising tributyltin hydride,[17–19] titanium[20–22] and manganese[23] reagents.

In this work (Scheme 1b), we show that the scope of HAT-mediated cyclisation reactions can be expanded to exploit nitriles as radical acceptors, despite potential issues such as β-scission[24] and competing alkene/nitrile reduction pathways.[25]



Scheme 1. a) Previous examples of HAT-mediated C-C bond forming cyclisation reactions, b) the outline of this work and its challenges.

During studies of conventional hydrofunctionalisation chemistry with alkene-nitrile **1**, an interesting observation was made (Scheme 2). Rather than the radical intermediate **A** reacting with the electrophilic radicophile TsCN in an intermolecular fashion, leading to product **B**, the radical was trapped in an 6-*exo*-*dig* cyclisation to afford imine **C**. Dihydroquinolinone **2** was subsequently isolated from the reaction mixture upon treatment with aqueous acid (see below).



Scheme 2. Intramolecular HAT-mediated radical cyclisation onto the proximal nitrile *vs.* conventional hydrofunctionalisation reaction.

To explore the scope of the reaction, conditions were screened for conversion of test substrate **1** to ketone **2** (Table 1, see SI for further details). As oxygen might be needed for the regeneration of the catalyst, but could also potentially detrimentally intercept crucial organic radicals on our pathway, we performed experiments in sealed vials with a limited headspace of air (conditions A), or open to air (conditions B), or occasionally under inert gas (N_2) (conditions C), in all cases using solvents that

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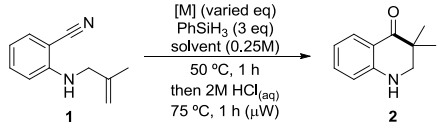
were not degassed. To access the ketone, it was found that hydrolysis of the imine intermediate was most effective under microwave conditions.

Examining firstly the catalyst, the reaction provided higher yields when using $Fe(acac)_3$ rather than $Mn(dpm)_3$ (entry 1 *vs.* entry 2). Switching from EtOH as solvent (see SI) to *i*PrOH caused no change in yields for reactions performed under similar conditions; however, *i*PrOH was preferred for reactions conducted open to the air because of its higher boiling point. Comparison of entries 3 and 4 showed that for small scale reactions, loading at 50 mol% of $Fe(acac)_3$ worked better than 20%, but when performed on larger (0.5 mmol) scale, conditions B with 20 mol% catalyst gave the best isolated yield of desired ketone **2** (94%) on a 0.5 mmol scale, after just 1 h at 50 ºC (*cf.* entry 5 vs 6).

Table 1 Screening of reaction conditions for conversion of **1** to **2**.



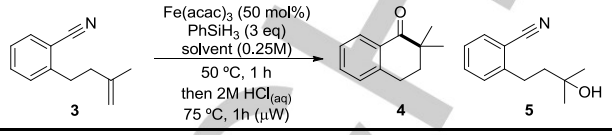
1 **2**

Entry[a]	*[M] (mol%)*	*Solvent*	*Conditions*[b]	*Yield (%)*	
				1	**2**
1	$Fe(acac)_3$ (50)	EtOH	A	3	81
2	$Mn(dpm)_3$ (50)	EtOH	A	14	66
3	$Fe(acac)_3$ (50)	*i*PrOH	B	<1	70
4	$Fe(acac)_3$ (20)	*i*PrOH	B	<1	57
5[c]	$Fe(acac)_3$ (20)	*i*PrOH	A	19	71
6[c]	**$Fe(acac)_3$ (20)**	***i*PrOH**	**B**	**-**	**94**

[a] HAT: 0.1 mmol; solution yield quoted, quantified by HPLC using an internal standard. [b] Conditions A, performed in a sealed vial with limited headspace of air; conditions B, performed in a vial open to air. [c] 0.5 mmol scale, isolated yields quoted.

We also optimised for conversion of substrate **3**, bearing an all-carbon side-chain, to ketone **4** (Table 2, see SI for further details), and discovered subtle differences compared to the N-linked substrate **1**. Substrate **3** performed moderately well (59% yield) on a small scale under the sealed conditions A (entry 1), with the competitive formation of oxidised side-product **5**, reflecting slower radical cyclisation kinetics than for substrate **1**. To enhance the kinetics, hexafluoroisopropanol (HFIP) was selected as a co-solvent. HFIP is a known Lewis acid[26] that might facilitate cyclisation onto the nitrile group. Addition of HFIP as a co-solvent with EtOH (1:1) increased the yield of desired product **4** to 77% (entry 2). This was increased yet further to 86% under conditions C (entry 3). Aerobic conditions on a 0.1 mmol scale (entry 4), were not beneficial, with the undesired tertiary alcohol **5** predominating at lower temperature (entry 5). However, on larger scale (0.5 mmol), aerobic conditions with 20 mol% catalyst (optimum for substrate **1**) gave a good yield of **4** (entry 6), although a superior yield (83%) was observed with EtOH:HFIP (N_2, entry 7). Conducting the reaction under conditions C in pure EtOH depleted the conversion (entry 8), highlighting the importance of HFIP for substrate **3** when the volume of air is limited. The beneficial effect of HFIP may be due to its Lewis acid character, although its benefits may extend beyond this - oxygen has a high solubility in fluorinated solvents,[27] which may facilitate catalyst turnover under sealed conditions (see SI, homogeneous solution for entry 7 vs. heterogeneous for entry 8).

Table 2. Screening of reaction conditions for conversion of **3** to **4**.



3 **4** **5**

Entry[a]	*Solvent*	*Conditions*	*Yield (%)*		
			(**3**)	(**4**)	(**5**)
1	EtOH	A	3	59	8
2	EtOH:HFIP	A	<1	77	5
3	EtOH:HFIP	C	4	86	3
4	*i*PrOH	B	<1	52	18
5[b]	*i*PrOH	B	21	11	51
6[c*]	*i*PrOH	B	–	74	–
7[c]	**EtOH:HFIP**	**C**	–	**83**	–
8[d*]	EtOH	C	–	33	–

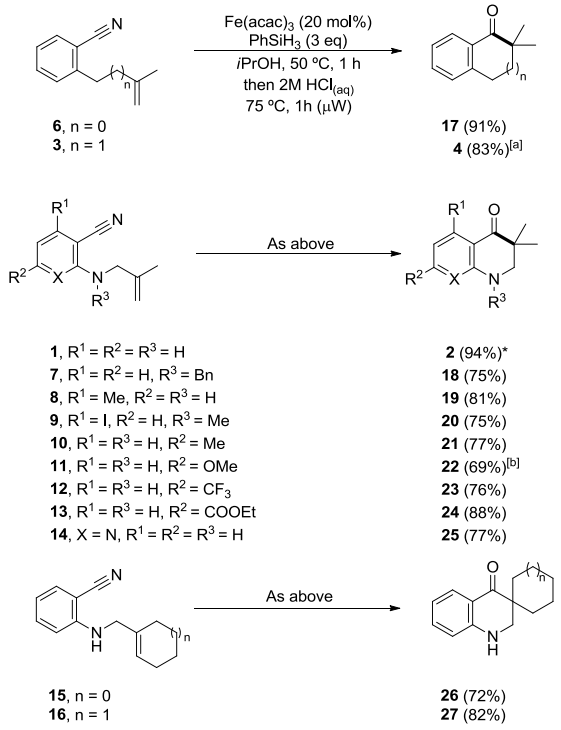
[a] HAT: 0.1 mmol; solution yield quoted, quantified by HPLC using an internal standard. [b] HAT conducted at RT. [c] 0.5 mmol scale, isolated yields quoted. *20 mol% $Fe(acac)_3$. [d] 0.5 mmol scale, NMR yield quoted as **3** and **4** co-elute during chromatography.

The optimised conditions (Table 1, entry 6) were applied to a range of aromatic substrates (Scheme 3). The 5-*exo*-*dig* cyclisation of alkene-nitrile **6** proceeded excellently under aerobic conditions (catalyst loading as low as 5 mol% also worked well; see SI), with only a slight drop in yield for the 6-*exo*-*dig* variant for substrate **3**. Benzyl protection of the tethering NH in **7** was well tolerated (although not necessary, *cf.* **1**) as was the inclusion of steric hindrance *ortho* to the nitrile in **8**. The presence of an iodide, (substrate **9**), was also well tolerated.

The amino-tethered substrate (**1**) outperforms its all-carbon variant (**3**), likely due to the planar N atom, positioning the two reacting groups in closer proximity resulting in faster cyclisation. Pleasingly, the HAT reaction of **1** to **2** was performed on a 1g scale without decrease in yield. Cyclisation proceeded smoothly with electron-donating aryl substituents *para* to the nitrile, operating either by inductive effect [**10** gave **21** (77%)] or mesomeric effect) [**11** gave **22** (69%)]. Similarly, electron-withdrawing groups (CF_3, **12**) (CO_2Et, **13**) produced successful cyclisations (76% and 88% respectively, as did heterocycle **14**. Facile access to spirocycles **26** and **27** was also achieved in good yields (72% and 82% respectively), providing a new entry to structurally complex scaffolds.

We next turned our attention to alkene-nitrile cyclisations in which the alkene and nitrile are not rigidly held by an aromatic ring (Scheme 4). Pleasingly, *cis*-fused aliphatic ring system **34** was formed in very good yield (73%) from **28**. Substrate **29**

Scheme 3. Aromatic substrate scope for the HAT-mediated cyclisation of alkene-nitriles.

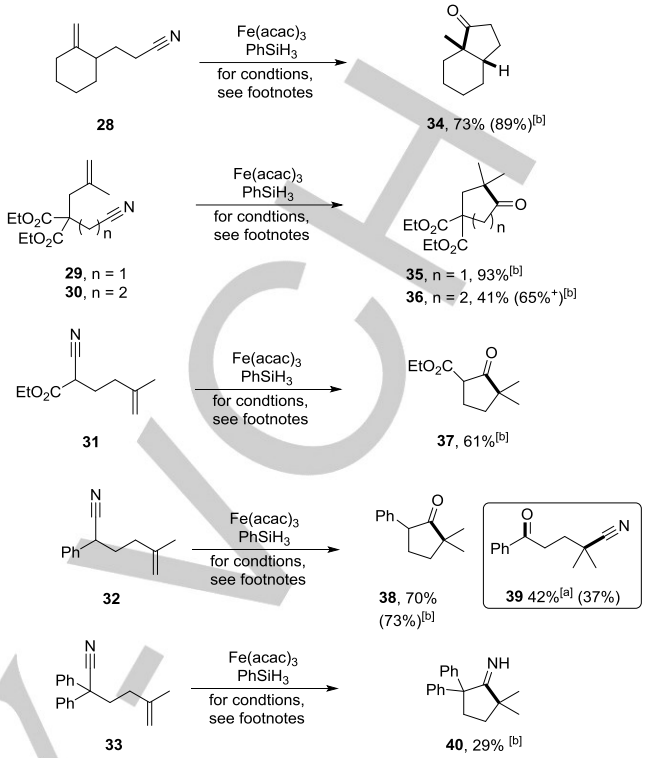


Isolated yields quoted. All reactions performed on a 0.5 mmol scale using conditions from Table 1 entry 6, unless otherwise stated. If 'X' is undefined, assume it is CH. [a] Conditions taken from entry 7, Table 2. [b] Hydrolysis for 5 h. *94% yield on 1g (5.8 mmol) scale.

derived from diethyl malonate cyclised in excellent yield (93%) to form 5-membered saturated ring **38** and the analogous 6-membered product **36** was obtained from **30**. Ethyl cyanoacetate-derived **31** was cyclised in good yield to form **37** (61%). Interestingly, substrate **32** underwent 5-*exo*-*dig*-cyclisation followed by reversible nitrile translocation. In aerobic conditions, the resulting benzyl radical is trapped by oxygen leading to the formation of benzoyl derivative **39**.[28] However, under conditions C, the iminyl radical was preferentially trapped and the resulting imine was hydrolysed on work-up to the expected ketone **38** (70%). The excellent selectivity shown likely reflects the strength of the Si-H bond, impeding abstraction by a stabilised benzylic radical; in contrast, the electrophilic iminyl radical may more rapidly abstract an H atom from the hydridic Si-H bond, due to polarity matching. Meanwhile, trapping of molecular oxygen occurs rapidly for the benzylic radical, while the electrophilic iminyl radical should be slow to form a weak N-O bond through coupling to O_2. The diphenyl variant **33** underwent cyclisation to yield the highly sterically hindered, and consequently hydrolytically stable, imine **40**.

We envisage a simplified mechanism[10] for coupling of alkenes to nitriles (Scheme 5). HAT from *in situ*-generated $HFe(acac)_2$ (**41**) to the alkene sets up the *exo*-*dig* cyclisation. We then considered the fate of the resulting iminyl radical. In the examples by Bonjoch[12] (alkoxyl radicals) and Baran[8–10] (radicals α- to an electron-withdrawing group), single electron transfer (SET), is proposed to convert the radicals to the

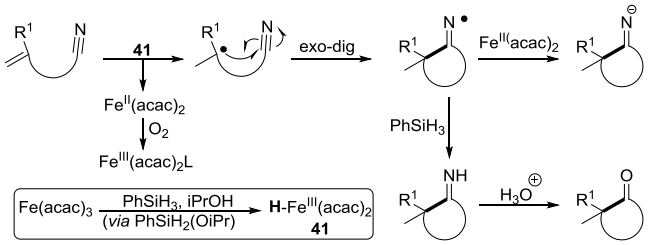
Scheme 4. Construction of aliphatic ring systems by HAT-mediated cyclisation of alkene-nitriles.



Isolated yield quoted, NMR yield determined with an internal standard given in parenthesis were applicable. [a] Aerobic conditions taken from Table 1, entry 6. [b] Inert conditions taken from Table 2, entry 7. * 30 mins reaction time and hydrolysis omitted, isolated product is impure. ^ 75 mol% $Fe(acac)_3$ and 4.5 eq $PhSiH_3$. +NMR yield, some fractions of **39** co-elute on silica with the hydrogenated starting material.

corresponding anions, with Fe^{II} being simultaneously oxidised to Fe^{III}. The iminyl radical present in our reactions may not be so easily reduced by electron transfer, and instead may abstract H from $PhSiH_3$ (supported by large drop off in yield when only 1.5eq of $PhSiH_3$ are used, see SI). The resulting imine is then hydrolysed *in situ* with aqueous acid to the corresponding ketone. The Fe^{II} species can be oxidised to Fe^{III} in the presence of oxygen to complete the catalytic cycle.

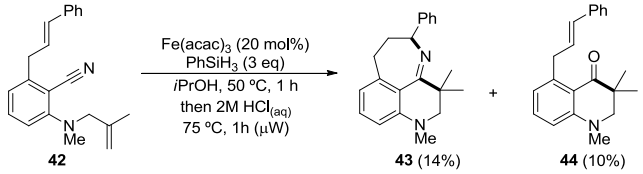
Scheme 5. Proposed mechanism for HAT-mediated alkene-nitrile cyclisation



If the iminyl radical intermediate is not being converted rapidly to the anion, then it should be possible to intercept the radical in a tandem cyclisation reaction (Scheme 6). To test this hypothesis, we designed substrate **42** (see **S2** in SI also), capable of undergoing a second cyclisation and subjected it to our standard reaction conditions (Scheme 6). The isolated tandem product was the 7-membered ring heterocycle **43** (14%), (rationalised in the SI file). The mono-cyclised product **44** was

also isolated (10%). This initial observation of tandem radical cyclisations supports our proposal that the lifetime of the iminyl radical is not negligible.

Scheme 6. HAT-mediated alkene-nitrile-alkene tandem cyclisation reaction.

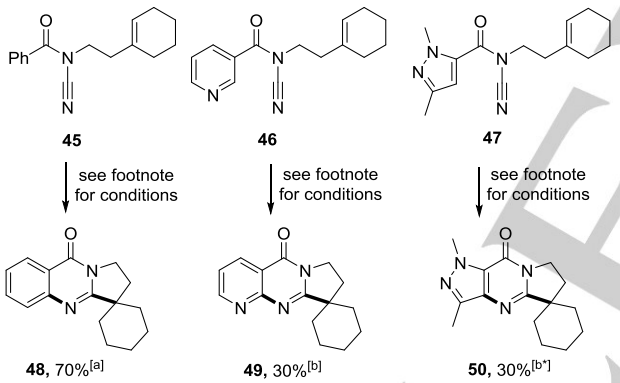


42 **43** (14%) **44** (10%)

NMR yields quoted were determined with an internal standard (products isolated by MDAP and characterised).

Encouraged by this result, we next applied our methodology to substrates bearing a cyanamide moiety that could undergo a tandem cyclisation with an (hetero)aromatic ring (Scheme 7). To our delight, benzamide **45** underwent the desired transformation in very good yield (70%) to form spiro-quinazolinone **48**. We also pursued challenging targets **49** and **50**, of direct relevance[29-31] to medicinal chemistry programmes. Nicotinic acid-derived substrate **46** gave **49** as the major product (30%), along with a small amount of 4-substituted regioisomer (5%); analogously, pyrazole **47** was converted to the complex fused heterocycle **50**, an otherwise challenging target.

Scheme 7. HAT-mediated alkene-cyanamide-(hetero)aryl tandem cyclisation reactions.



48, 70%[a] **49,** 30%[b] **50,** 30%[b*]

Isolated yields quoted. [a] Fe(acac)$_3$ 20 mol%, 1.05 eq PhSiH$_3$, *i*PrOH, 50 ºC, 1h, air. [b] Fe(acac)$_3$ 20 mol%, 1.5 eq PhSiH$_3$, 2 eq TFA, *i*PrOH, 80 ºC, 14h, air - note 5% 4-substituted regioisomer isolated also. * 24 h. Reduced yields for the nitrogen containing heterocycles is due to esterification of the starting cyanamide with isopropanol.

In summary, we have developed an iron-mediated HAT reaction between alkenes and nitriles. This work allows for the formation of hindered ketones, spirocycles and fused bicyclic systems. The reaction has been optimised to perform catalytically under air and has been shown to scale-up without significant loss of yield. Further investigations on cyanamides and other novel HAT substrates are currently ongoing.

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Keywords: HAT • nitriles • radical • cyclisation • Iron (III)

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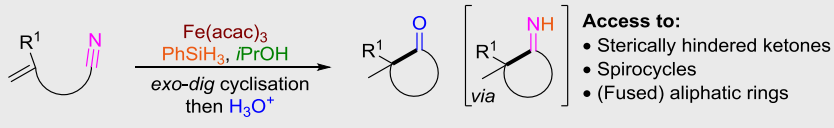

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