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Acyl hydrazines as precursors to acyl radicals

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Abstract—The use of acyl hydrazines (hydrazides) as precursors for the stoichiometric generation of acyl radicals is explored. Two classes of substrates are examined: unsubstituted acyl hydrazines and acyl hydrazines substituted with a leaving group (2-nitrobenzenesulfonyl or 'nosyl'). Both types are successfully converted to acyl radicals, and are then trapped by nitroxide radicals to give acyloxyamine products. Cyclization reactions are demonstrated for both classes of substrates. A low temperature modification of the McFayden–Stevens reaction is also developed.

1. Introduction

The use of acyl radical methodology as a tool for the formation of carbon–carbon bonds, and particularly in the construction of carbon ring systems has been an important development in modern synthetic organic chemistry.[1] Today a number of successful methods of generating acyl radicals have been developed, and have been utilized in organic synthesis. The most widely studied method is the stannane reduction of selenoesters,[2] based on a radical chain mechanism. Likewise, carbonylation of organohalides in a tin-mediated chain sequence has been developed by Ryu.[3] These methods suffer from toxicity and disposal issues associated with the use of organotin reagents and their resulting waste products. A number of techniques have been developed to circumvent these problems, including the use of tris(trimethylsilyl)silane,[4] water soluble tin hydride reagents,[5] fluorous tin hydride reagents,[6] and solid phase tin hydride reagents.[7] Other methods of generating acyl radicals have also been developed that avoid the use of organotin reagents altogether. Examples of these methods are the oxidation of aryl diazonium-tethered thioesters[8] and the photolysis of substrates such as thioxanthates,[9] acyl cobalt salen species,[10] and telluroesters.[11]

The alkyl or acyl hydrazine functional group is characterized by an N–N single bond connected to an alkyl carbon atom or a carbonyl group, respectively. Acyl hydrazines are also known as hydrazides, and the general class of carbon-substituted hydrazines are also referred to as carbohydrazines. Much is known about the structure and reactivity of carbohydrazines, and this class of functional groups has been reviewed.[12] Two distinct categories of carbohydrazines are considered in this discussion: unsubstituted ($R–NHNH_2$) and those substituted with a leaving group (R–NHNH–X or $R–NX–NH_2$).

The oxidative conversion of unsubstituted alkyl hydrazines to alkyl radicals was first demonstrated by Corey et al. in a strategy for preparing hindered optically active amines derived from borneol.[13] This method of generating radicals has been used extensively in our laboratory to study stereoselective trapping of nitroxides at prochiral carbon centers,[14] and has also been used in the synthesis of initiators for nitroxide-mediated 'living' free-radical polymerization.[15] Alkyl hydrazines substituted with leaving groups have also been shown to be precursors to alkyl radicals: Myers et al. have demonstrated that alkyl hydrazines substituted with a 2-nitrobenzenesulfonyl ('nosyl' or 'Ns') group spontaneously degrade to alkyl radicals.[16] The mechanism for the generation of alkyl radicals from unsubstituted and nosyl-substituted alkyl hydrazines involves the initial formation of a reactive alkyl diazene[17] intermediate (R–N=N–H) followed by degradation with loss of nitrogen to afford the carbon radical. There is evidence that acyl radicals generated from acyl hydrazines may play a part in the enzyme-mediated mechanism of action of isoniazid, a widely utilized antituberculosis drug.[18]

Herein the generation and utilization of acyl radicals from acyl hydrazine precursors is explored. Acyl hydrazines are attractive precursors to acyl radicals as they can be prepared easily from inexpensive reagents, and often exist as stable crystalline species. Reported here are results in the generation of acyl radicals from unsubstituted acyl hydrazines and from nosyl-substituted acyl hydrazines. Direct trapping of the acyl radicals is first demonstrated, followed by examples of cyclization reactions.

Keywords: acyl hydrazines; acyl radicals; McFayden–Stevens reaction.

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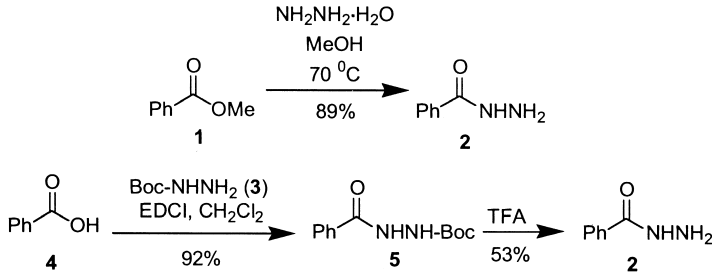


Scheme 1.

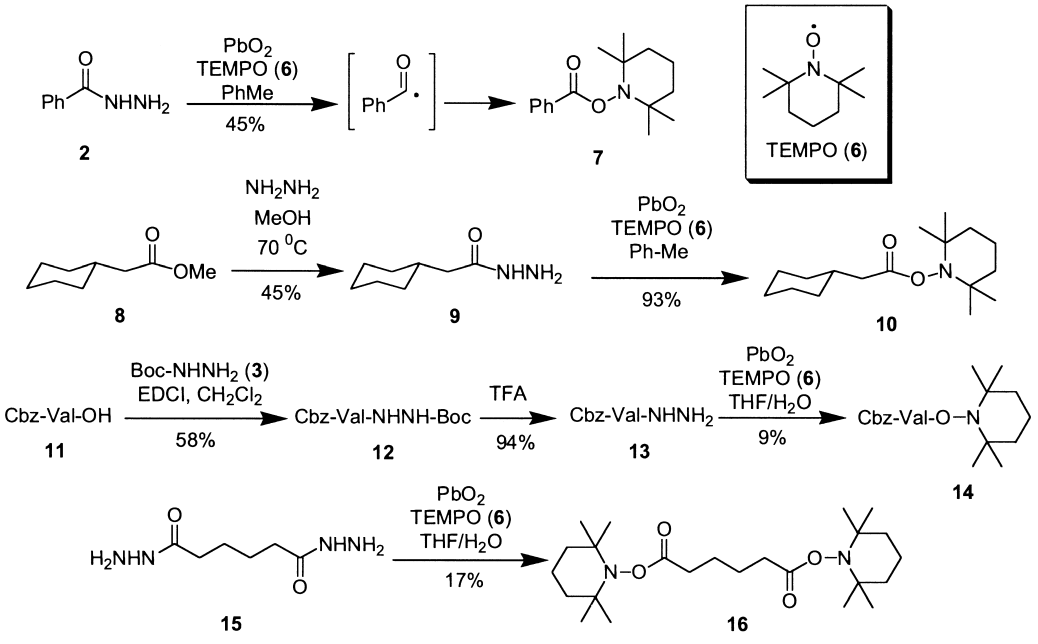
2. Results and discussion

2.1. Acyl radicals from unsubstituted acyl hydrazines

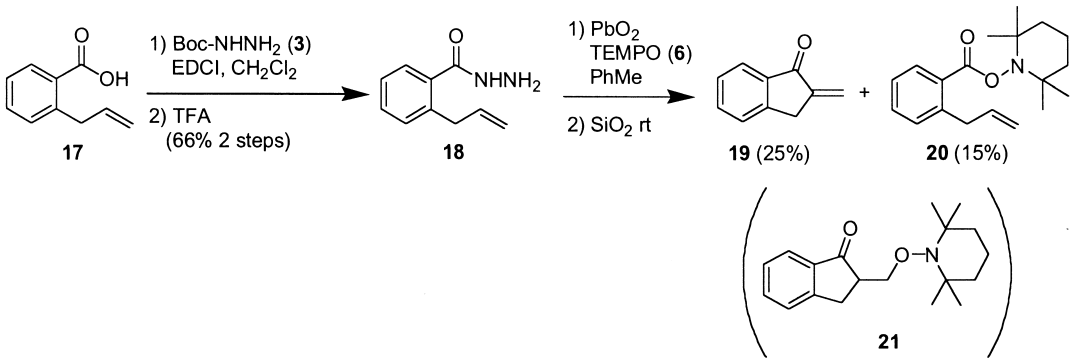
The first task at hand was the preparation of unsubstituted acyl hydrazine substrates. The most commonly reported method in the literature is the direct hydrazinolysis of methyl esters. For example, methyl benzoate (**1**) was reacted with hydrazine monohydrate to generate benzhydrazide (**2**) (Scheme 1). This method is unattractive due to the toxicity and explosiveness of hydrazine, and because a large excess is generally required. The use of hydrazine can be circumvented by using a two-step protocol[19] in which an acyl group is coupled with Boc-protected hydrazine (*tert*-butylcarbazate **3**), followed by deprotection. The alternative sequence is illustrated by the coupling of this reagent with benzoic acid (**4**) to generate Boc-protected acyl hydrazine **5**, which is then deprotected with trifluoroacetic acid (TFA) to yield benzhydrazide (**2**).

The generation of acyl radicals from benzhydrazide and other simple unsubstituted acyl hydrazines was then investigated (Scheme 2). The conditions employed were based on those utilized in the generation of alkyl radicals from alkyl hydrazines.[13–15] Thus benzhydrazide (**2**) was treated with lead oxide in the presence of the persistent nitroxide radical TEMPO (**6**) to afford acyloxyamine product **7**. This result demonstrated that unsubstituted acyl hydrazines could indeed be converted to acyl radicals, and spawned the examination of other substrates. Thus, methyl cyclohexylacetate (**8**) was cleanly converted to the corresponding unsubstituted acyl hydrazine (**9**) using the ester hydrazinolysis method, and was then treated with lead oxide and TEMPO to generate the trapped product (**10**) in excellent yield. Next, Cbz-protected valine (**11**) was converted to the corresponding Boc-protected acyl hydrazine (**12**), and was then deprotected to afford the unsubstituted acyl hydrazine (**13**). This compound was reacted with lead oxide and TEMPO to generate product **14**. Multiple chromatographic separations were required to obtain a pure sample, contributing to the low yield of this example. Lastly, commercially available adipic dihydrazide (**15**) was subjected to the same conditions to yield the diacyloxyamine product (**16**), albeit in low isolated yield.

Having demonstrated the simple trapping of acyl radicals derived from unsubstituted acyl hydrazines, more synthetically interesting acyl radical cyclization reactions were then explored. The first substrate examined was derived from 2-allylbenzoic acid[11c] (**17**), and sets the stage for a



Scheme 2.

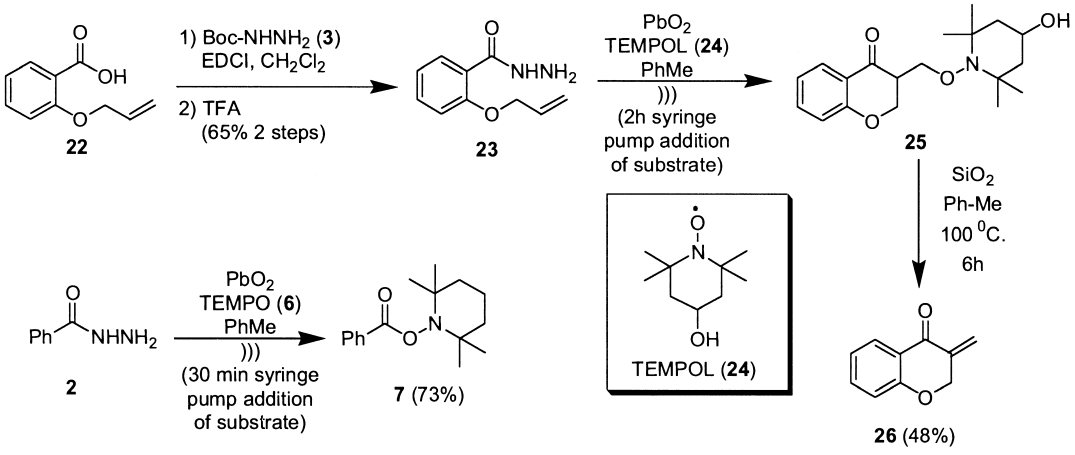


Scheme 3.

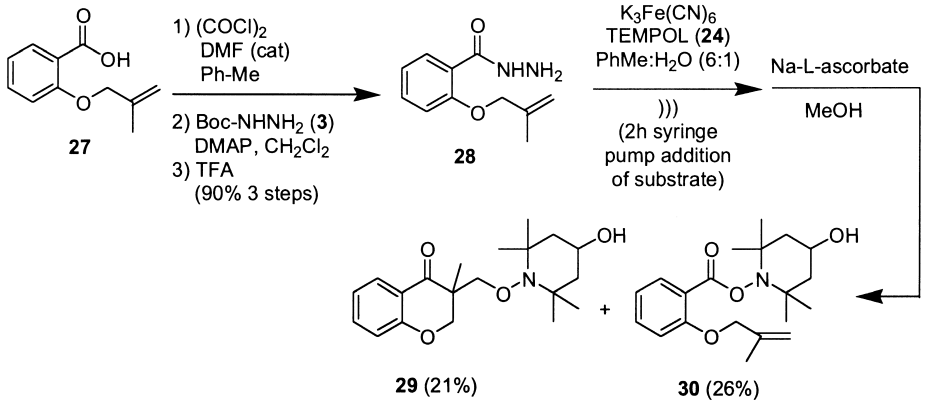
5-*exo-trig* radical cyclization. This material was prepared in a few steps by *ortho*-lithiation and alkylation[20] of a phenyl dimethyloxazoline precursor. The acid (**17**) was coupled to Boc-protected hydrazine (**3**) and then deprotected to afford the desired unsubstituted acyl hydrazine (**18**) (Scheme 3). Treatment of this substrate with lead oxide and TEMPO (**6**) followed by silica gel purification led to the isolation of two products: cyclized α,β-unsaturated ketone **19** and the undesired directly trapped product **20**. Compound **19** is derived from alkoxyamine product **21**, through silica-catalyzed elimination during purification.

The second substrate examined was derived from 2-allyloxybenzoic acid (**22**), which can be readily prepared in two steps from methyl salicylate,[11c] and was chosen as a precursor for 6-*exo-trig* cyclization. Through the standard sequence, the acid was coupled to Boc-protected hydrazine (**3**) and deprotected to yield substrate **23** (Scheme 4). Considerable effort was made to optimize the cyclization conditions for this substrate. It was found that slow addition of the substrate to a sonicated suspension of lead oxide and nitroxide trap (in this case TEMPOL, **24**) gave the greatest yield of cyclized product. The reasoning behind the use of these conditions will be addressed in the mechanistic discussion. After carrying out the cyclization, product **25** could not easily be separated from residual paramagnetic nitroxide, and this prevented ^{1}H NMR analysis. It was then discovered that the crude reaction mixture could be heated in the presence of silica gel to force elimination, allowing for the clean isolation of α,β-unsaturated ketone product **26**. The use of the nitroxide trap TEMPOL instead of less polar TEMPO was significant, as the latter was found to co-ellute with the eliminated product during the chromatographic purification. The optimization strategy developed for this cyclization substrate **23** was then extended for the prototypical acyl radical trapping reaction and found effective: when applied to benzhydrazide (**2**), the acyloxyamine product (**7**) was isolated in significantly higher yield (73%) than that previously obtained (45%).

The next cyclization substrate examined was derived from 2-(2-methallyloxy)-benzoic acid (**27**), also available from methyl salicylate.[11c] This was converted to the acyl chloride, coupled with Boc-protected hydrazine (**3**) and deprotected to give the corresponding unsubstituted acyl hydrazine substrate (**28**) (Scheme 5). Attempts at effecting cyclization of this substrate with lead oxide were unsuccessful, and led only to isolation of unreacted starting material. This could not be readily explained, but when other oxidants were screened, potassium ferricyanide was found to be satisfactory. Thus, treatment of the substrate with potassium ferricyanide and TEMPOL (**24**) was carried out. The crude reaction mixture was then treated with sodium L-ascorbate to reduce residual paramagnetic TEMPOL,[21] and the desired cyclized product (**29**) was then isolated, in addition to the product of direct acyl radical trapping (**30**). Interestingly, cyclization seems to have occurred exclusively in the 6-*exo-trig* mode on the hindered olefin: no evidence for the



Scheme 4.



Scheme 5.

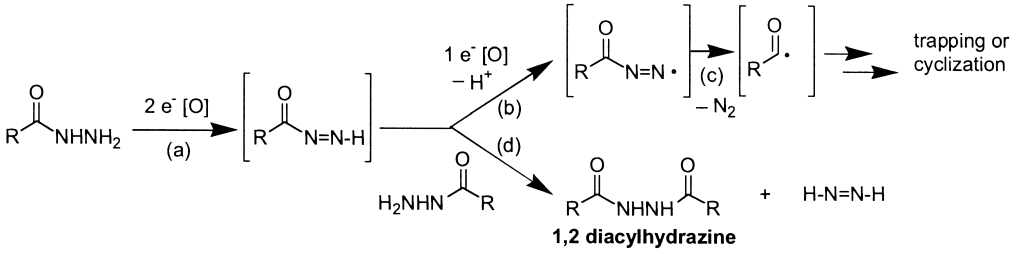
7-*endo-trig* product could be detected by ^{1}H NMR after treatment with sodium L-ascorbate. This is consistent with results obtained in the acyl radical cyclization of analogous selenoester,[2] aryl tethered thioester,[8] and telluroester[11] substrates. Attempts to cyclize an acyl radical onto a tethered aryl trap using 2-phenoxy benzhydrazide gave only a trace of the desired product under these oxidative conditions.

The oxidative generation of acyl radicals from unsubstituted acyl hydrazines is proposed to proceed through the mechanism shown in Scheme 6. The initial step proceeds via an overall two-electron oxidation of the substrate to generate an acyl diazene intermediate (step a). This intermediate can react via two different pathways. In the first, a one-electron oxidation occurs followed by loss of proton (step b) and liberation of dinitrogen (step c) to generate the acyl radical. In the second pathway, another equivalent of starting material can react through nucleophilic acyl substitution to generate a 1,2-diacylhydrazine byproduct (step d).[22] The addition of nucleophiles to acyl diazenes is a known reaction, and has been used in peptide synthesis.[23] The formation of the undesired 1,2-diacylhydrazine is particularly problematic as it consumes 2 equiv. of starting material. Two strategies for decreasing the occurrence of this side reaction were devised: (a) slow introduction of the substrate to minimize its concentration during the course of the reaction, and (b) increasing the rate of the oxidation events so that step b is enhanced over step d to minimize the formation of 1,2-diacylhydrazine. The first strategy is easily implemented by syringe pump addition of the substrate. The second strategy could be pursued by the use of stronger oxidizing agents. However, this is complicated by the fact that nitroxides can be oxidized to oxoammonium species.[24] Instead, sonication was performed to enhance interactions between the substrate (or acyl diazene) and the heterogeneous oxidizing agent.

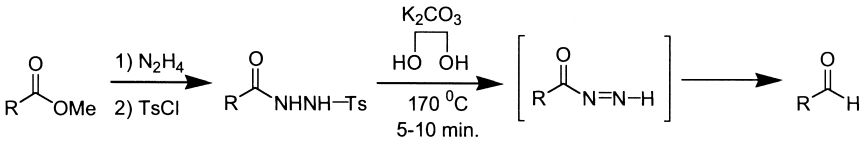
Another problematic side reaction is the formation of the acyl radical-nitroxide direct-trapped byproduct in the cyclization studies. The extremely fast rate constants with which nitroxides trap carbon radicals[25] makes it not surprising that direct-trapped material is generated in significant quantity. The use of a slower trap (diphenyl disulfide) was briefly investigated in a cyclization attempt with substrate **22**. Unfortunately the reaction produced a complicated mixture with only trace formation of the desired cyclized product, and recovery of the majority of the disulfide trap unreacted. This suggests that the nitroxide may be involved in the oxidative conversion of the acyl diazene to the acyl radical (Scheme 6, step b). This proposal is consistent with studies on alkyl diazenes, particularly kinetic evidence from Myers et al. on nosyl-substituted alkyl hydrazines which suggest that nitroxides accelerate the degradation of alkyl diazenes to alkyl radicals.[16b]

2.2. Acyl radicals from nosyl-substituted acyl hydrazines

The second method that was explored for the generation of acyl radicals utilizes acyl hydrazine substrates substituted with a leaving group. A key difference between the uses of unsubstituted acyl hydrazines and substituted acyl hydrazines lies in the mechanism for formation of the acyl diazene intermediate. In the case of the former, the substrate is oxidized in a two-electron manner to generate the acyl diazene. This contrasts with the latter, in which the substrate undergoes elimination to arrive at the same intermediate.



Scheme 6.



Scheme 7.

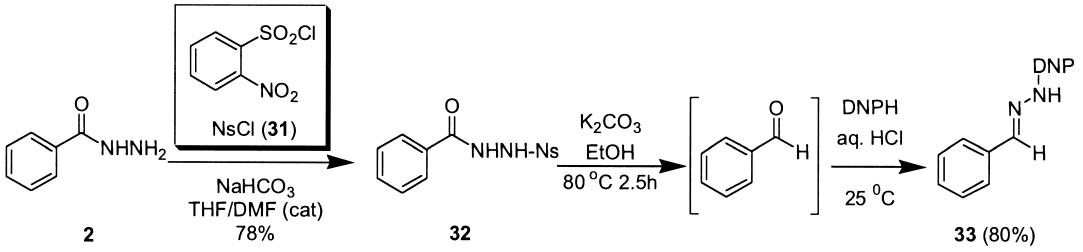
Methodology has been previously developed that utilizes substituted acyl hydrazines outside of the context of radical chemistry. The McFayden–Stevens reaction converts toluenesulfonyl ('tosyl')-substituted acyl hydrazines to aldehydes by brief thermolysis in the presence of base (Scheme 7).[26] This reaction effects a one-step reduction of carboxylic acid derivatives to aldehydes, and has been used as an alternative to hydride reducing agents such as diisobutylaluminum hydride (DIBAL) in natural products synthesis.[27,28] The McFayden–Stevens reaction most likely occurs through an acyl diazene intermediate,[26c] although a mechanism for the transformation of the diazene to the aldehyde has not been firmly established.

The ability to access acyl diazene intermediates by base catalyzed elimination might provide an alternative route to the generation of acyl radicals. However, the high temperatures employed in the traditional McFayden–Stevens reaction are unattractive in developing new methodology. Thus, two goals were established: (a) the development of lower temperature conditions for the McFayden–Stevens reaction, and (b) modification of these conditions to give access to acyl radical intermediates that could either be trapped or cyclized.

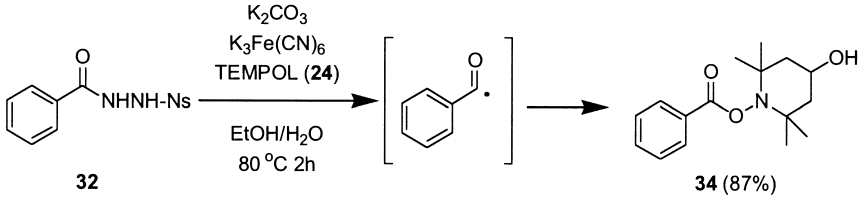
The first goal was pursued by selecting a better leaving group than the tosyl group normally used in the McFayden–Stevens reaction. In work by Myers et al. on generating alkyl diazenes (and alkyl radicals) from substituted alkyl hydrazines,[16] the nosyl group was found to be a highly effective choice. Indeed, precedent shows that electron-withdrawing aryl substituents accelerate the elimination of arylsulfonyl-substituted hydrazines.[29] Thus, a variant of the McFayden–Stevens reaction utilizing the nosyl group instead of tosyl was explored (Scheme 8). Benzhydrazide (**2**) was allowed to react with 2-nitrobenzenesulfonyl chloride (**31**) to generate the corresponding nosyl-substituted acyl hydrazine (**32**). In contrast with nosyl-substituted alkyl hydrazines, which degrade readily even at low temperature,[16] nosyl-substituted acyl hydrazines are surprisingly stable. To test the thermal stability of species **32**, it was dissolved in DMSO-d_6 and thermolyzed to 170°C without decomposition noted by ^{1}H NMR. This compound was then examined in the context of the normal McFayden–Stevens reaction. It was found that nosyl-substituted acyl hydrazine **32** could be converted to benzaldehyde by treatment with potassium carbonate at 80°C for 2.5 h, a much lower temperature than the traditional McFayden–Stevens reaction. The product was then isolated as the 2,4-dinitrophenylhydrazone (**33**).

The next goal was to modify these new conditions in a way that would give access to an acyl radical intermediate (Scheme 9). Assuming that an acyl diazene is formed transiently, the use of oxidizing conditions should allow the transformation of this intermediate to the desired acyl radical (see Scheme 6). Thus the newly developed McFayden–Stevens conditions were modified further by the addition of an oxidizing agent and a nitroxide radical trap. When applied to substrate **32**, these conditions produced the desired outcome: formation of acyloxyamine product **34** via a presumed acyl radical intermediate.

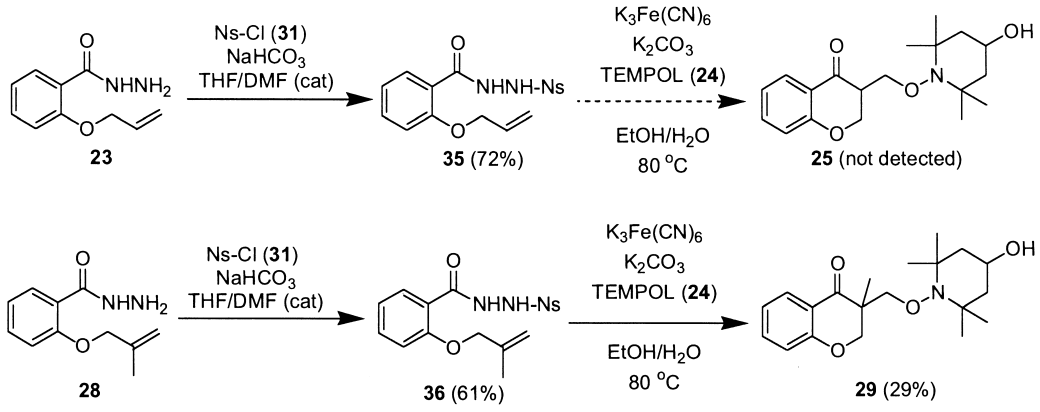
Having demonstrated the generation and simple trapping of acyl radicals derived from nosyl–substituted acyl hydrazines, the final objective was to use these conditions in the context of acyl radical cyclization (Scheme 10). Two of the previously utilized cyclization substrates were examined. In



Scheme 8.



Scheme 9.



Scheme 10.

the first case, compound **23** was cleanly transformed to the corresponding nosyl-substituted acyl hydrazine **35**. The cyclization of this substrate was attempted several times without success using the previously established conditions. It was suspected that the desired cyclized product **25** may have formed, but then immediately degraded under the reaction conditions. This is not unreasonable since a variety of reaction pathways can be envisioned for such a compound in refluxing alkali solution (e.g. base-catalyzed aldol chemistry). The next logical step was to utilize a substrate in which the product does not bear an α-hydrogen atom, to prevent enolization or elimination reactions of the product. Thus, unsubstituted acyl hydrazine **28** was converted to nosyl-substituted species **36**, and then subjected to the acyl radical generating conditions. The desired product **29** could be isolated cleanly, although the isolated yield was low. Very little (<3%) of the direct-trapped product (**30**) was isolated in this reaction. Unfortunately, attempts to optimize the yield of this reaction, or to characterize any side products were not successful.

3. Conclusion

In summary, a new method for the generation of acyl radicals has been developed that utilizes either unsubstituted acyl hydrazines or nosyl-substituted acyl hydrazines. With both classes of substrates, the simple generation of acyl radicals was demonstrated initially, followed by application to cyclization reactions. This method differs from seleno-ester, telluroester and carbonylation methodology, in that the acyl radical is generated in a stoichiometric fashion, and is trapped by a nitroxide rather than participating in a radical chain reaction. The use of lead oxide as oxidant was chosen for convenience in most cases, although the more environmentally friendly potassium ferricyanide was also demonstrated to be effective. In the development of these conditions, a lower-temperature variation of the McFayden–Stevens reaction was also developed.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon. Solvents for radical trapping experiments were degassed by passing argon through them for at least 15 min prior to use. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl. Sonication was carried out in a Fisher FS-14 cleaning bath. Slow reagent addition was performed using a Sage Instruments syringe pump (model 355) with gas tight Hamilton syringes. Analytical thin layer chromatography (TLC) was carried out using plastic plates coated with silica gel 60 F_{254}. The developed plates were visualized using short wave UV light (254 nm), and were typically stained in an iodine/silica chamber and/or using a staining dip (e.g. *p*-anisaldehyde or phosphomolybdic acid) followed by heating with a heat gun. Flash column chromatography was performed using Universal Scientific Inc. Silica Gel 63-200. NMR spectra were recorded on either a Bruker ACF dual probe 250 MHz or a Varian 500 MHz spectrometer with tetramethylsilane as an internal standard for proton and the $CDCl_3$ triplet as an internal standard for carbon. The following abbreviations are used to describe peak splitting when appropriate: br=broad, s=singlet, d=doublet, q=quartet, m=multiplet. IR spectra were recorded in $CDCl_3$ solution on a Perkin–Elmer 1600 FTIR spectrometer. High-resolution mass spectroscopy was obtained using FAB, CI, or EI on one of three systems: (a) a Finnegan 4000 spectrometer with the Super Incos Data System at the University of Illinois, (b) a VG ZAB-SE reverse geometry spectrometer with a VG 11/250 data system at the University of Illinois, or (c) a Mariner spectrometer from Applied Biosystems with TOF detection at the University of California at Santa Cruz. Melting points are uncorrected.

4.1.1. Benzoic hydrazide (2) by hydrazinolysis of methyl benzoate. General method A. To a solution of methyl benzoate (**1**) (0.2 ml, 1.6 mmol) in methanol (1.1 ml) was added hydrazine monohydrate (0.32 ml, 6.4 mmol), and the solution was refluxed for 6 h. TLC showed consumption of the ester starting material and formation of the product. Solvent was removed in vacuo and the residue was taken up in EtOAc (20 ml). This was washed with saturated aq. NaCl (20 ml) and then dried over $MgSO_4$. Solvent was removed in vacuo to afford a white crystalline solid (mp 109–113°C) (0.193 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.11 (bs, 2H), 7.34 (bs, 1H), 7.46 (dt, 2H, J=1.5, 9 Hz),

7.54 (dt, 1H, J=1.5, 9 Hz), 7.75 (dd, 2H, J=1.5, 9 Hz). The spectroscopic data of this compound matches that of the commercial material.

4.1.2. Benzoic hydrazide (2) by a two step coupling sequence from benzoic acid. General method B. To a solution of benzoic acid (**4**) (0.185 g, 1.51 mmol) in CH_2Cl_2 (15 ml) was added *tert*-butyl carbazate (**3**) (0.204 g, 1.54 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (aka EDCI or WSC-HCl) (0.297 g, 1.55 mmol), and the mixture was allowed to stir at rt overnight. TLC showed consumption of benzoic acid and formation of the product. CH_2Cl_2 was then added (15 ml) and the organic solution was washed sequentially with saturated aq. $NaHCO_3$ (3×15 ml) followed by saturated aq. NaCl (15 ml), and then dried over $MgSO_4$. Removal of solvent in vacuo yielded benzoic [*N*-(*tert*-butoxycarbonyl)]-hydrazide (**5**) as a white crystalline solid (mp 144–146°C) (0.329 g, 92%). This material was used in the next step without further purification or characterization.

Solid benzoic [*N*-(*tert*-butoxycarbonyl)]-hydrazide (**5**) (0.133 g, 0.56 mmol) was cooled to 0°C and trifluoroacetic acid was carefully added (1 ml). The mixture was allowed to stir from 0°C to rt, over 1 h. TLC showed consumption of the Boc-protected acyl hydrazine and formation of the product. Aq. saturated $NaHCO_3$ was added (5 ml) and the product was extracted with CH_2Cl_2 (3×10 ml). The organic layer was dried over $MgSO_4$, and then removal of solvent in vacuo yielded the product as a white crystalline material: mp 110–112°C (0.040 g, 53%). The spectroscopic data of this product matches that of the commercially available material.

4.1.3. (2,2,6,6-Tetramethyl-1-piperidinyloxy)-benzoate (7), using optimized conditions shown in Scheme 4. A mixture of benzhydrazide (**2**) (0.066 g, 0.485 mmol) in degassed toluene (1.6 ml) was prepared and a few drops of methanol was added to aid in solubility. This was then added slowly by syringe to a sonicated suspension of PbO_2 (0.541 g, 1.941 mmol) and 2,2,6,6-tetramethylpiperidinyloxy radical (TEMPO) (0.083 g, 0.534 mmol) in degassed toluene (1.6 ml), over a period of 30 min, and then the trace contents of the syringe were washed in with additional degassed toluene (1.6 ml). The suspension was allowed to sonicate an additional 30 min, and was then allowed to stir at rt overnight. The suspension was filtered through celite with CH_2Cl_2, and solvent was removed in vacuo to yield the product as a slightly yellow oil (0.092 g, 73%). TLC: 1:3 hexane/EtOAc, UV, I_2, ninhydrin stain, R_f=0.34. IR ($CDCl_3$): 1744 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.12 (s, 6H), 1.27 (s, 6H), 1.74–1.55 (m, 6H), 7.48 (t, J=7.5 Hz), 7.57 (t, J=7.5 Hz), 8.1 (d, J=5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, APT): δ 17.1 (CH_2), 21.0 (CH_3), 32.1 (CH_3), 39.2 (CH_2), 60.5 (C_{quat}), 128.7 (CH), 129.7 (CH), 129.9 (C_{quat}), 132.9 (CH), 166.5 (C_{quat}). HRMS calcd for $C_{16}H_{23}NO_2$ [M+H]=262.1807, found [M+H]=262.1795.

4.1.4. Cyclohexylacetic hydrazide (9). Using general method A, methyl cyclohexylacetate (**8**) (1.0 ml, 6.09 mmol) was converted to the title compound as a white crystalline material (mp 118–120°C) (0.428 g, 45%). TLC: 1:3 hexane/EtOAc, I_2, ninhydrin stain, R_f=0.34. IR ($CDCl_3$): 3450, 1671 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 0.90–1.29 (m, 6H), 1.68–1.82 (m, 5H), 2.00 (d, 2H, J=7.5 Hz), 3.91 (bs, 2H), 6.65 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$, APT): δ 26.1 (CH_2), 33.2 (CH_2), 35.2 (CH), 42.6 (CH_2), 173.3 (C_{quat}). LRMS (electrospray +): found [M+1]=157.

4.1.5. (2,2,6,6-Tetramethyl-1-piperidinyloxy)-cyclohexylacetate (10). General method C (unoptimized). A suspension of cyclohexylacetic hydrazide (**9**) in degassed toluene (0.3 ml) was added slowly by syringe to a stirred suspension of TEMPO (**6**) (0.048 g) and PbO_2 (0.297 g, 1.25 mmol) in degassed toluene (0.3 ml), and then the trace contents of the syringe were washed in with additional degassed toluene (0.3 ml). The suspension was allowed to stir at rt overnight, and then the product was filtered through celite with CH_2Cl_2, and solvent was removed in vacuo to yield the product as a slightly amber oil (0.081 g, 93%). TLC: 4:1 hexane/EtOAc, UV, I_2, PMA stain, R_f=0.77 (white by PMA). IR ($CDCl_3$): 1752 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 0.97–1.90 (m, 29H), 2.31 (d, 2H, J=6.5 Hz). ^{13}C NMR (63 MHz, $CDCl_3$, APT): δ 17.2 (CH_2), 20.7 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 32.2 (CH_3), 33.4 (CH_2), 34.8 (CH), 39.1 (CH_2), 40.9 (CH_2), 60.0 (C_{quat}), 172.7 (C_{quat}). HRMS calcd for $C_{17}H_{31}NO_2$ [M+H]=282.2433, found [M+H]=282.2433.

4.1.6. *N*-Carbobenzyloxy-L-valine hydrazide (13). Using general method B, *N*-carbobenzyloxy-L-valine (0.250 g, 0.995 mmol) was converted to the title compound as a white wax-like solid (0.096 g; 58% yield first step, 94% yield second step). ^1H NMR (250 MHz, $CDCl_3$): δ 0.83 (t, 6H, J=5 Hz), 1.93–1.82 (m, 1H), 2.50 (s, 3H), 3.34 (s, 3H), 3.73 (t, 1H, J=7.5 Hz), 4.23 (d, 2H), 5.01 (s, 2H), 7.4–7.22 (m, 9H), 9.13 (br s, 1H). The spectroscopic data of this compound matches the literature.[30]

4.1.7. *N*-(Carbobenzyloxy)-*O*-(2,2,6,6-tetramethyl-1-piperidinyl)-L-valine (14). Using general method C, *N*-carbobenzyloxy-L-valine hydrazide (**13**) (67 mg, 0.254 mmol) was converted to the crude product (42 mg, 43% yield). This was further purified by preparative TLC (4:1 hexane/EtOAc) to yield the title compound (0.009 g, 9%). TLC: 4:1 hexane/EtOAc, UV, R_f=0.5. IR ($CDCl_3$): 1758.5, 1721.2, 1224.9 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.96 (d, 6H, J=7 Hz), 1.06 (d, 6H, J=6.5 Hz), 1.16 (br s, 6H), 1.76–1.37 (m, 6H), 2.28–2.21 (m, 1H), 4.40 (dd, 2H, J=5, 10 Hz), 5.14 (s, 2H), 5.28 (d, 1H, J=10 Hz), 7.39–7.30 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$, APT): δ 17.0 (CH_2), 17.3 (CH_3), 19.8 (CH_3), 20.6 (CH_3), 20.8 (CH_3), 31.2 (CH), 32.1 (CH_2), 39.2 (CH_3), 39.4 (CH_3), 58.5 (CH), 60.3 (C_{quat}), 60.6 (C_{quat}), 67.1 (CH_2), 128.2 (CH), 128.3 (CH), 128.6 (CH), 136.4 (C_{quat}), 156.4 (C_{quat}), 171.9 (C_{quat}). HRMS calcd for $C_{22}H_{34}N_2O_4$ [M+H]=391.2597, found [M+H]=391.2600.

4.1.8. Bis-(2,2,6,6-tetramethyl-1-piperidinyloxy)-adipate (16). Using general method C, adipic dihydrazide (**15**) (239 mg, 1.37 mmol) was converted to the title compound as a slightly amber solid material (99 mg, 17% yield). IR ($CDCl_3$): 2975.3, 2940.8, 2232.2, 1753.8 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.06 (s, 12H), 1.15 (s, 12H), 1.75–1.38 (m, 12H), 1.78 (br s, 4H), 2.40 (br s, 4H). ^{13}C NMR

(125 MHz, $CDCl_3$, APT): δ 17.1 (CH_2), 20.7 (CH_3), 25.0 (CH_2), 31.1 (CH_3), 32.8 (CH_2), 39.1 (CH_2), 60.0 (C_{quat}), 172.9 (C_{quat}).

4.1.9. 2-Allylbenzhydrazide (18). Using general method B, 2-allylbenzoic acid[11c] (**17**) was converted to the title compound (66% over two steps) as white crystalline solid: mp 104–105°C. TLC: 1:3 hexane/EtOAc, UV, I_2, ninhydrin stain, R_f=0.2 (red by ninhydrin). IR ($CDCl_3$): 2950, 1794, 1670, 1476 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 3.47 (d, J=6.3 Hz), 4.26 (bs, 2H), 4.91–5.03 (m, 2H), 5.83–5.99 (m, 1H), 7.14–7.36 (m, 4H), 7.7 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 37.4 (CH_2), 116.1 (CH_2), 126.3 (CH), 127.4 (CH), 130.5 (CH), 134.0 (C_{quat}), 137.3 (CH), 138.2 (C_{quat}), 170.6 (C_{quat}). HRMS calcd for $C_{10}H_{12}N_2O$ [M]=176.0950, found [M]=176.0921.

4.1.10. 2-Methylene-1-indanone (19). To a suspension of 2-allylbenzhydrazide (**18**) (0.053 g, 0.301 mmol) in degassed toluene (30 ml) was added a few drops of *tert*-butanol to form a homogenous solution. TEMPO (**6**) was added (0.057 g, 0.365 mmol) followed by lead oxide (0.295 g, 1.234 mmol), and the reaction was allowed to stir at rt overnight. The product mixture was filtered through celite with CH_2Cl_2, and purified by preparative TLC (10:1 hexane/EtOAc) to yield the eliminated product, 2-methylene-1-indanone (**19**) (0.011 g, 25%) as slightly yellow oil. ^1H NMR (250 MHz, $CDCl_3$): δ 3.77 (s, 2H), 5.65 (s, 1H), 6.37 (s, 1H), 7.38–7.64 (m, 3H), 7.87 (d, 1H, J=7.5 Hz). The spectroscopic data of this compound matches the literature.[11c]

Also isolated by preparative TLC was the undesired direct-trapped product (2,2,6,6-tetramethyl-1-piperidinyloxy)-2-allylbenzoate (**20**) (0.014 g, 15%). IR ($CDCl_3$): 1730 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 0.90 (s, 6H), 1.14 (s, 6H), 1.46–1.77 (m, 6H), 3.75 (d, 2H, J=6.3 Hz), 4.96–5.07 (m, 2H), 5.96–6.02 (m, 1H), 7.25–7.40 (m, 2H), 7.44–7.47 (m, 1H), 7.84–7.88 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.2, 17.0, 20.9, 32.0, 38.1, 39.2, 60.3, 115.7, 125.8, 126.0, 129.7, 131.0, 131.8, 137.4, 141.9, 177.0.

4.1.11. 2-Allyloxybenzoic hydrazide (23). Using general method B, 2-allyloxybenzoic acid[11c] (**22**) (1.129 g, 6.33 mmol) was converted to the crude title compound as a slightly amber oil. This was crystallized with EtOAc/hexane in two batches to yield the product as white crystals: mp 54–56°C (1.181 g, 73% overall yield, 2 steps). TLC: 1:1 hexane/EtOAc, UV, I_2, R_f=0.1. IR ($CDCl_3$): 3421, 1794, 1653, 1480 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 4.17 (bs, 2H), 4.63 (d, 2H, J=5 Hz), 5.34–5.41 (m, 2H), 5.97–6.02 (m, 1H), 6.98–7.06 (m, 2H), 7.34–7.41 (m, 1H), 8.14 (d, 1H, J=7.5 Hz), 8.9 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$, APT): δ 69.8 (CH_2), 112.6 (CH_2), 119.2 (CH), 120.2 (C_{quat}), 121.5 (CH), 132.0 (CH), 132.1 (CH), 132.8 (CH), 156.4 (C_{quat}), 166.4 (C_{quat}). HRMS calcd for $C_{10}H_{12}N_2O_2$ [M]=192.0899, found [M]=192.0896.

4.1.12. 3-Methylenechroman-4-one (26). A solution of 2-allyloxybenzoic hydrazide (**23**) (0.114 g, 0.593 mmol) and 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy radical (TEMPOL) (**24**) (0.104 g, 0.604 mmol) in degassed toluene (6 ml) was prepared and added slowly by syringe to a sonicating suspension of lead oxide (0.856 g, 3.58 mmol) in degassed toluene (30 ml) over a period of 2 h. The trace contents of the syringe were then washed in with additional degassed toluene (6 ml). The suspension was allowed to stir at rt overnight. Silica was added (0.026 g) and the reaction mixture was heated to 100°C for 6 h. The product mixture was filtered through celite with CH_2Cl_2, and solvent was removed in vacuo to yield the crude product, which was then purified by flash column chromatography (10:1 hexane/EtOAc) to afford the eliminated product (0.046 g, 48%). ^1H NMR (250 MHz, $CDCl_3$): δ 4.99 (s, 2H), 5.56 (s, 1H), 6.30 (s, 1H), 6.99–7.07 (m, 2H), 7.47 (t, 1H, J=8.5 Hz), 7.99 (d, 1H, J=7.8 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 71.2, 118.0, 121.9, 122.1, 122.2, 127.9, 136.0, 139.0, 161.9, 181.9. The spectroscopic data of this compound matches the literature.[11c]

4.1.13. 2-(2-Methallyloxy)-benzoic hydrazide (28). To a solution of 2-(2-methallyloxy)-benzoic acid[11c] (**27**) (1.981 g, 10.30 mmol) in toluene (34 ml) was added oxalyl chloride (9 ml, 103 mmol, 10 equiv.) and DMF (three drops). The solution was allowed to stir 1 h, and then solvent was removed in vacuo to afford the crude acid chloride. The acid chloride was then dissolved in CH_2Cl_2 (34 ml) and cooled to 0°C. To this mixture was added DMAP (1.384 g, 10.96 mmol) followed by *tert*-butyl carbazate (**3**) (1.449 g, 10.96 mmol), and the solution was then allowed to stir at rt overnight. Solvent was removed in vacuo and the crude residue was then taken up in EtOAc (50 ml) and washed sequentially with 10% aq. HCl (2×50 ml) and 5% aq. $NaHCO_3$ (50 ml). The organic solution was dried over $MgSO_4$ and solvent was removed to yield the Boc-protected acyl hydrazine as white solid (mp 108–109°C) (2.924 g, 93%). This compound was used in the next step without further characterization.

Using the TFA-deprotection step described in general method B, 2-(2-methallyloxy)-benzoic [*N*-(*tert*-butoxycarbonyl)]-hydrazide (2.957 g, 9.65 mmol) was converted to the title compound (**28**) as white crystals: mp 78–80°C (1.926 g, 97% after recrystallization with EtOAc/hexane). IR ($CDCl_3$): 3155, 1794, 1654 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.76 (s, 3H), 4.65 (s, 2H), 4.97 (s, 1H), 5.06 (s, 1H), 7.05–7.08 (m, 1H), 7.14 (d, 1H, J=9 Hz), 7.49–7.52 (m, 1H), 7.67–7.70 (m, 1H), 10.05 (bs, 1H), 10.62 (bs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.0, 71.4, 112.7, 113.5, 120.5, 120.7, 130.2, 133.1, 140.2, 156.0, 164.7. HRMS calcd for $C_{11}H_{14}N_2O_2$ [M+H]=207.1134, found [M+H]=207.1136.

4.1.14. 3-[(4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy)methyl]-3-methylchromanone (29). A solution of 2-(2-methallyloxy)-benzoic hydrazide (**28**) (0.075 g, 0.36 mmol) in degassed toluene (1 ml+trace DMSO for solubility) was prepared and this was added slowly by syringe pump to a sonicating suspension of potassium ferricyanide (0.916 g, 3.83 mmol) and TEMPOL (**24**) (0.069 g, 0.400 mmol) in degassed 6:1 toluene/H_2O (18 ml), over a period of 2 h. Trace contents of the syringe were then washed in with approximately 1 ml of additional degassed toluene. The suspension was allowed to stir at rt overnight and then H_2O was added (20 ml) and the crude product mixture was extracted with CH_2Cl_2 (3×20 ml). Solvent

was removed in vacuo, and a suspension of sodium L-ascorbate (0.144 g, 0.727 mmol) in anhydrous MeOH (3.8 ml) was added and allowed to stir for 30 min. Solvent was removed again, and then the cyclized product (**29**) was isolated by flash column chromatography (2:1 hexane/EtOAc) as a colorless oil (0.027 g, 21%). IR ($CDCl_3$): 2978, 1686, 1607, 1479 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.05 (s, 3H), 1.14 (s, 3H), 1.17 (s, 3H), 1.21 (s, 3H), 1.26 (s, 3H), 1.43 (t, 2H, J=12 Hz), 1.63 (bs, 1H), 1.76 (dd, 2H, J=4, 12.5 Hz), 3.76 (d, 1H, J=9 Hz), 3.91 (m, 1H), 4.09 (d, 1H, J=9 Hz), 4.24 (d, 1H, J=12 Hz), 4.58 (d, 1H, J=12 Hz), 6.96 (d, 1H, J=8 Hz), 7.02 (dt, 1H, J=1, 8 Hz), 7.47 (dt, 1H, J=1, 8 Hz), 7.91 (dd, 1H, J=1, 8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.7, 21.2, 33.0, 46.0, 48.5, 60.6, 63.2, 73.8, 117.8, 120.4, 121.6, 127.8, 135.8, 161.5, 195.0. HRMS calcd for $C_{20}H_{29}NO_4$ [M+H]=348.2175, found [M+H]=348.2189.

Also isolated was the direct-trapped product (**30**) (0.033 g, 26%). IR ($CDCl_3$): 2979, 1734 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.17 (s, 6H), 1.21 (s, 6H), 1.77–1.82 (m, 5H), 1.86–1.88 (m, 2H), 3.99 (m, 1H), 4.53 (s, 2H), 4.98 (s, 1H), 5.14 (s, 1H), 6.92–6.98 (m, 2H), 7.38–7.42 (m, 1H), 7.72 (d, 1H, 7.5). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.5, 21.7, 32.1, 47.8, 60.7, 63.3, 72.2, 113.2, 120.3, 120.7, 131.0, 132.9, 140.3, 157.6, 167.0. HRMS calcd for $C_{20}H_{29}NO_4$ [M+H]=348.2175, found [M+H]=348.2122.

4.1.15. Benzoic [*N′*-(2-nitrobenzenesulfonyl)]-hydrazide (32). General method D. To a solution of benzhydrazide (**2**) (0.136 g, 1.0 mmol) in THF (3.3 ml) was added $NaHCO_3$ (0.848 g, 10.1 mmol) and 2-nitrobenzenesulfonyl chloride (**31**) (0.211 g, 0.95 mmol) and DMF (0.039 g, 0.53 mmol, 0.5 equiv.). This suspension was stirred at rt overnight. Next, H_2O was added (10 ml), and the product was extracted with CH_2Cl_2 (2×10 ml). The organic product layer was washed with 10% aq. HCl (10 ml), dried over $MgSO_4$, and then solvent was removed in vacuo to yield a yellowish solid (0.303 g, 99%). This material was recrystallized using CH_2Cl_2/hexane to yield the final product as a white crystalline solid: mp 156–158°C (0.239 g, 78%). TLC: 1:1 hexane/EtOAc, UV, I_2, R_f=0.5. IR ($CDCl_3$): 3155, 1794, 1475, 1383 cm^{-1}. ^1H NMR (500 MHz, MeOH-d_4): δ 7.41 (t, 2H, J=7.5 Hz), 7.52 (t, 1H, J=7.5 Hz), 7.68–7.73 (m, 3H), 7.79 (dt, 1H, J=1.5, 10 Hz), 7.90 (dd, 1H, J=1.5, 8 Hz), 8.11 (dd, 1H, J=1.5, 8 Hz). ^{13}C NMR (125 MHz, MeOH-d_4): δ 124.9 (CH), 127.2 (CH), 128.2 (CH), 131.2 (CH), 131.5 (C_{quat}), 132.0 (CH), 132.1 (CH), 134.3 (CH), 148.1 (C_{quat}), 167.5 (C_{quat}). HRMS calcd for $C_{13}H_{11}N_3O_5S$ [M+H]=322.0498, found [M+H]=322.0500.

4.1.16. Benzaldehyde 2,4-dinitrophenylhydrazone (33): low temperature McFayden–Stevens reaction conditions. A suspension of benzoic [*N*-(2-nitrobenzenesulfonyl)]-hydrazide (**32**) (0.112 g, 0.349 mmol) and freshly activated K_2CO_3 (0.372 g, 3.49 mmol) in 95% EtOH (3.5 ml) was heated at 80°C for 2.5 h. TLC showed only a trace presence of starting material. The reaction mixture was then filtered, and then added to a solution of 2,4-dinitrophenylhydrazine (0.172 g, 0.872 mmol) in 10% aq. HCl (8.7 ml), resulting in the immediate deposition of benzaldehyde 2,4-dinitrophenylhydrazone (**33**) as a yellow-orange solid. The solid was vacuum filtered, taken up in EtOAc, dried over $MgSO_4$, and solvent was removed in vacuo to yield the hydrazone as an orange crystalline solid (0.079 g, 80%): mp 230–233°C, lit 237°C. ^1H NMR (250 MHz, DMSO-d_6): δ 7.48–7.54 (m, 3H), 7.78–7.82 (m, 2H), 8.10 (d, 1H, J=11 Hz), 8.37 (dt, 1H, J=3, 11 Hz), 8.71 (s, 1H), 8.86 (d, 1H, J=3 Hz), 11.67 (bs, 1H). The spectroscopic data of this compound matches authentically prepared hydrazone from benzaldehyde.

4.1.17. (4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy)-benzoate (34). A solution of benzoic [*N*-(2-nitrobenzenesulfonyl)]-hydrazide (**32**) (0.070 g, 0.218 mmol) and TEMPOL (**24**) (0.043 g, 0.249 mmol) in THF (1 ml) was prepared, and this was added slowly by syringe pump to a refluxing (80°C) suspension of freshly activated K_2CO_3 (0.372 g, 2.69 mmol) and potassium ferricyanide (0.717 g, 2.18 mmol) in degassed 95% EtOH (3.5 ml), over a period of 1 h. Trace contents of the syringe were washed in with approximately 1 ml of additional degassed 95% EtOH, and the suspension was allowed to continue refluxing for an additional hour. H_2O was then added (20 ml) and the product was extracted with CH_2Cl_2 (3×20 ml). The organic layer was washed with saturated aq. NaCl (40 ml), dried over $MgSO_4$, and solvent was removed in vacuo to yield the product as a slightly amber-colored oil (0.052 g, 87%). IR ($CDCl_3$): 2944, 1747 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.32 (s, 3H), 1.78 (t, 2H, J=12 Hz), 1.95 (dt, 2H, J=4, 12 Hz), 4.10 (m, 1H), 7.46 (t, 2H, J=7.5 Hz), 7.57 (t, 1H, J=7.5 Hz), 8.05 (d, 2H, J=7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.9, 32.1, 47.7, 60.8, 63.1, 128.6, 129.5, 129.7, 133.1, 166.4. HRMS calcd for $C_{16}H_{23}NO_3$ [M+H]=278.1751, found [M+H]=278.1781.

4.1.18. 2-(2-Methallyloxy)-benzoic [*N′*-(2-nitrobenzenesulfonyl)]-hydrazide (36). Using general method E, 2-(2-methallyloxy)-benzoic hydrazide (**28**) (0.498 g, 2.41 mmol) was converted to the title compound as a slightly tan solid material: mp 108–110°C (0.513 g, 61% after recrystallization from CH_2Cl_2/hexane in two batches). IR ($CDCl_3$): 3382, 1665, 1602, 1544, 1480, 1400 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.95 (s, 3H), 4.67 (s, 2H), 5.16 (s, 1H), 5.18 (s, 1H), 7.01 (m, 2H), 7.46 (dt, 1H, J=2, 9 Hz), 7.64 (t, 1H, J=8 Hz), 7.76 (dt, 1H, J=1, 8 Hz), 7.84 (d, 1H, J=5 Hz), 8.04 (t, 2H, J=13 Hz), 8.73 (d, 1H, J=7 Hz), 9.84 (d, 1H, J=7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.6, 73.3, 112.9, 115.2, 118.4, 121.7, 126.4, 131.9, 132.4, 132.6, 133.0, 134.3, 134.5, 139.3, 147.9, 157.0, 164.4. HRMS calcd for $C_{17}H_{17}N_3O_6S$ [M+H]=392.0917, found [M+H]=392.0934.

4.1.19. 3-[(4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy)methyl]-3-methylchromanone (29) by cyclization of compound 36. A solution of 2-(2-methallyloxy)-benzoic [*N′*-(2-nitrobenzenesulfonyl)]-hydrazide (**36**) (0.104 g, 0.266 mmol) and TEMPOL (**24**) (0.050 g, 0.293 mmol) in THF (1 ml) was added slowly by syringe pump to a refluxing (80°C) suspension of freshly activated K_2CO_3 (0.368 g, 2.66 mmol) and potassium ferricyanide (0.875 g, 2.66 mmol) in degassed 95% EtOH (13 ml, 0.02 M), over a period of 2 h. Trace contents of the syringe were washed in with approximately 1 ml of additional degassed 95% EtOH, and the suspension was allowed to continue refluxing for an

hour. The majority of the solvent was then removed in vacuo. H_2O was then added (20 ml) and the product was extracted with CH_2Cl_2 (3×20 ml). The organic product layer was washed with saturated aq. NaCl (40 ml), dried over $MgSO_4$, and solvent was removed in vacuo to yield the crude product as a slightly amber-colored oil. The cyclized product (**29**) was isolated by flash column chromatography (2:1 hexane/EtOAc) as a colorless oil (0.027 g, 29%). Also isolated was direct-trapped product (**30**) (0.003 g, 3%). The spectroscopic properties of these compounds match those of the compounds isolated previously.

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