

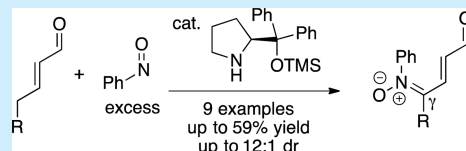
Dienamine-Catalyzed Nitron Formation via Redox Reaction

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S Supporting Information

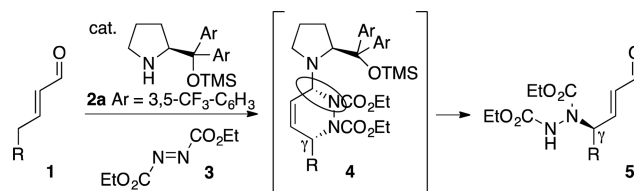
ABSTRACT: The first catalytic method to directly introduce nitron functionality onto aldehyde substrates is described. This reaction proceeds by an unprecedented organocatalytic redox mechanism in which an enal is oxidized to the γ -nitron via dienamine catalysis, thereby reducing an equivalent of nitrosobenzene. This reaction is a unique example of divergent reactivity of an enal, which represents a novel strategy for rapidly accessing small libraries of *N,O*-heterocycles. Alternatively, divergent reactivity can be suppressed simply by changing solvents.



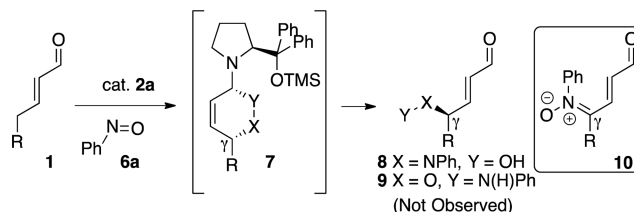
Aldehydes are one of the most versatile functional groups in organic chemistry, being readily transformable into other functionalities and indispensable in asymmetric reactions. Likewise, nitrones are useful reactive intermediates that are characteristically employed in dipolar cycloaddition reactions to generate heterocycles. However, direct methods to introduce nitron functionality in the presence of an aldehyde, to generate compounds with two handles for further functionalization, are exceedingly rare. This is most likely due to the incompatibility of the reactive aldehyde functional group with methods commonly used to generate nitrones, which include oxidation of amines, imines, or hydroxyl amines and C=N bond formation via condensation of hydroxyl amines with carbonyls.¹ In addition to a handful of examples of oxidation of pyridinecarboxaldehydes and quinolonecarboxaldehydes to the corresponding nitrones,² we identified only two methods in the literature for the direct introduction of a nitron in the presence of an aldehyde. There is one isolated example of reaction of a carbon–nitrogen ylide with 4-nitrosobenzaldehyde,³ and the other method entailed *N*-alkylation of aldoximes with enals.⁴ The latter strategy would be less amenable, however, to ketoximes, in which competitive *N*- and *O*-alkylation would be anticipated due to sterics.⁵ Herein we present our serendipitous discovery of a direct catalytic method to introduce nitron functionality to α,β -unsaturated aldehyde substrates via a novel C=N bond-forming strategy.

This discovery was made during investigations into dienamine-catalyzed reactions, which are a relatively underexplored mode of catalysis for chiral secondary amine organocatalysts. This is likely due to the challenges associated with controlling the regioselectivity of reactions with dienamines, which are nucleophilic at both their α - and γ -positions. Often, cyclic dienamines and/or steric bias are employed to influence the regioselectivity of dienamine-catalyzed intermolecular reactions.⁶ There is one example, however, of manipulating the reactivity of a linear dienamine (i.e., as a diene) in a [4 + 2] cycloaddition, with subsequent ring opening, to yield exclusively γ -functionalized α,β -unsaturated aldehydes (Scheme 1).⁷ The [4 + 2] mechanism accounts not only for the regioselectivity of this reaction but also for the high degree of stereocontrol despite the γ -position being remote from the chiral center of the catalyst.

Scheme 1. γ -Functionalization of Enals via Dienamine-Catalyzed [4 + 2] Cycloaddition Reaction⁷

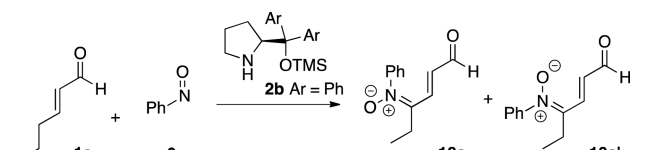


Scheme 2. Dienamine-Catalyzed Nitron Formation



We were curious to examine what other dienophiles could participate in a [4 + 2] cycloaddition with a dienamine to afford γ -functionalized α,β -unsaturated aldehydes, and we suspected that the labile bond (circled in 4, Scheme 1) might need to be a carbon–heteroatom bond. The electrophile selected for examination was nitrosobenzene (6a, Scheme 2) for two reasons.⁸ First, we were unsure whether γ -oxidation (7, X = O, Y = NPh) or γ -amination (7, X = NPh, Y = O) would occur. Second, when nitrosobenzene has been used as an electrophile in enamine-catalyzed α -functionalizations using related catalyst 2b (Ar = Ph),⁹ it has been shown that one can switch whether α -amination or α -oxygenation occurs simply via the addition or omission, respectively, of a carboxylic acid additive.^{8f,g} We were thus interested whether a similar reversal of regioselectivity might also be observed in γ -functionalizations. When this reaction was first attempted, however, neither 8 nor 9 was observed, but rather only nitron 10.

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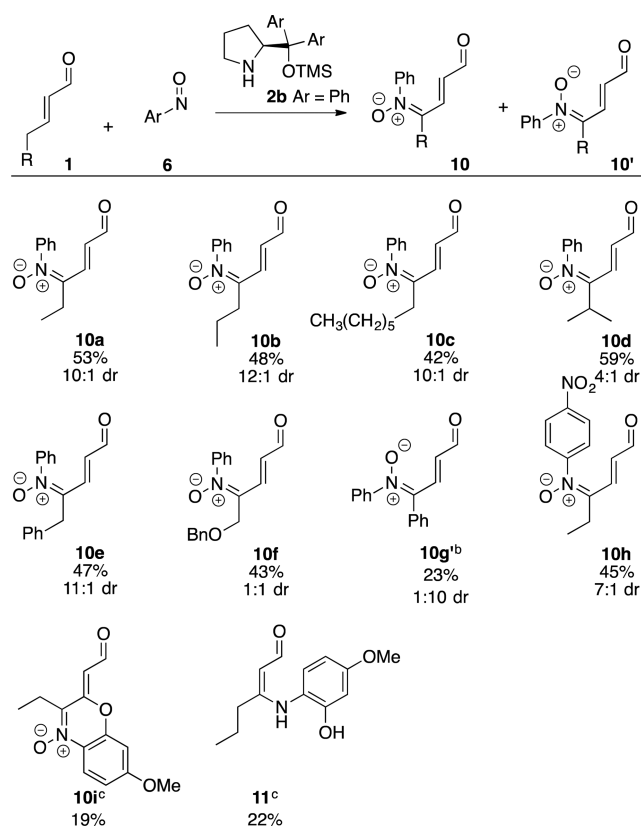
Table 1. Reaction Optimization^a


entry	6 (equiv)	additive	time (h)	temp (°C)	yield ^{b,c} (%)	dr ^d (10a/10a')
1 ^e	1	PhCO ₂ H	22	rt	24	12:1
2	1	PhCO ₂ H	4.25	rt	29	3:1
3	2	PhCO ₂ H	1	rt	31	3:1
4	2	PhCO ₂ H	65.5	−30	42	3:1
5	2	AcOH	14.5	−30	42 (2, 49)	4:1
6 ^f	2	AcOH	41	rt	40 (21, 23)	9:1
7 ^f	4	AcOH	41	rt	48	9:1
8 ^{f,g}	4	AcOH	39	rt	43	10:1
9 ^{f,h}	4	AcOH	144	rt	49	12:1
10 ^{f,i}	4	AcOH	15	rt	53	10:1
11 ^{f,i-j}	4	AcOH	15.5	rt	54	10:1

^aReaction conditions: **1a**, **6a**, **2b** (0.1 equiv), additive (0.1 equiv), toluene (1 M). ^bDetermined by ¹H NMR using 1,4-dioxane or cyclohexene as internal standard. ^cFirst number in parentheses is percentage of **1a** remaining, second number in parentheses is percentage of side product (vide infra) formed. ^dDetermined by ¹H NMR. ^eCatalyst **2a** used. ^f1,4-Dioxane is reaction solvent. ^gReaction concentration = 2 M. ^hReaction concentration = 0.5 M. ⁱ0.2 equiv of **2b** and of AcOH used. ^jReaction scaled 10-fold, using **1a** (2.5 mmol).

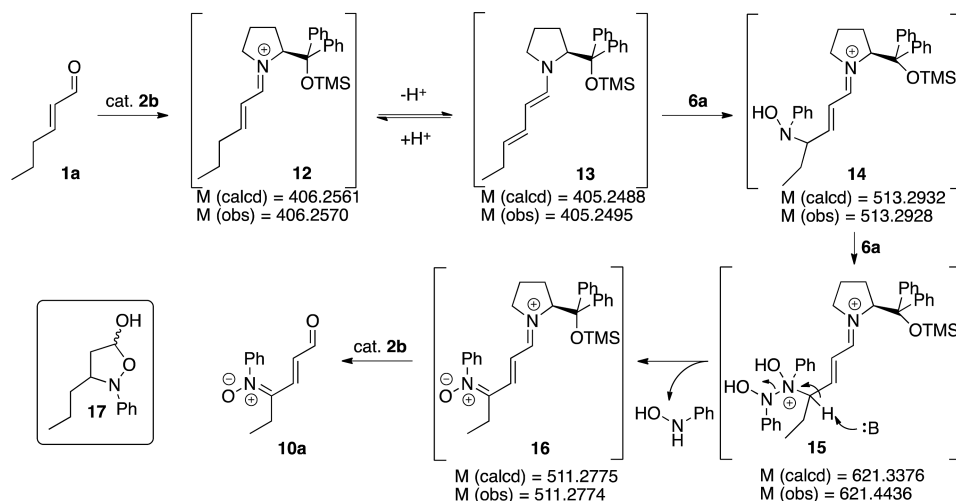
Seeking to optimize this transformation, and starting with conditions (i.e., catalyst **2a**, PhCO₂H additive) similar to those used for the dienamine-catalyzed γ -amination using diethyl azodicarboxylate (**3**),⁷ a 24% yield of the nitrone product was obtained with excellent diastereoselectivity (entry 1, Table 1). Switching to the more reactive catalyst **2b** shortened reaction times while improving reaction yield (entry 2). Increasing the ratio of **6a/1a** to 2:1 improved the yield slightly and further reduced reaction times (entry 3). Lowering the reaction temperature was found to have a big impact on yield (entry 4). Use of AcOH as the acid additive further shortened reaction times (entry 5). Under these conditions, however, when nitrosobenzene was completely consumed, only 2% of starting enal **1a** remained, while nearly all of the mass balance of the reaction could be accounted for by the formation of a side product (vide infra), which was generated in 49% yield. Switching the reaction solvent to 1,4-dioxane suppressed the formation of this side product significantly, and as a result, 21% of unreacted starting enal **1a** remained once nitrosobenzene was completely consumed (entry 6). Interestingly, in this solvent, the diastereoselectivity of this reaction was also significantly improved (entries 6–11). In an effort to drive the reaction toward completion, more equivalents of nitrosobenzene were used, which did further improve the yield of the nitrone product (entry 7). Increased or decreased reaction concentrations were not beneficial to this transformation (entries 8 and 9). Increasing the catalyst loading to 20 mol %, however, afforded the nitrone product in a still higher yield (entries 10 and 11). After exhaustive optimization,¹⁰ the conditions summarized in entry 10 provided the nitrone product in the highest attainable yield.

With optimized conditions in hand, the scope of this one-pot method was investigated (Scheme 3). Enals with alkyl R groups all afforded nitrone products (**10a–c**) in modest yield and outstanding dr. Notably, the sterically demanding isopropyl R group generated the corresponding nitrone product (**10d**) in the highest yield among all substrates examined. A δ -phenyl group and -heteroatom were tolerated, although the latter afforded no diastereoselectivity (**10e–f**). A γ -phenyl group furnished the nitrone product in low yield but, interestingly, favored formation

Scheme 3. Scope of Dienamine-Catalyzed Nitrone Formation Reaction^a

^aReaction conditions: **1**, **6** (4 equiv), **2b** (0.2 equiv), AcOH (0.2 equiv), 1,4-dioxane (1 M), rt, 14–18 h. Yield and dr determined by ¹H NMR using cyclohexene as internal standard. ^bReaction conditions: **1**, **6** (2 equiv), **2b** (0.1 equiv), AcOH (0.1 equiv), toluene (1 M), −30 °C. ^cReaction conditions: **1**, **6** (2 equiv), **2b** (0.1 equiv), CHCl₃ (0.5 M), rt.

Scheme 4. Proposed Mechanism

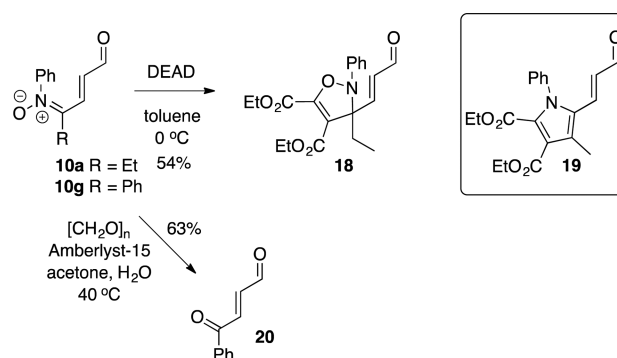


of the opposite diastereomer of the nitrone (**10g'**).¹¹ Other commercially available nitrosobenzenes were also examined in this transformation. The electron-poor *p*-nitronitrosobenzene provided the corresponding nitrone product in slightly reduced yield and dr compared to nitrosobenzene (**10h**). Use of the electron-rich 4-nitrosoresorcinol 1-monomethyl ether provided interesting results. The major diastereomer of the nitrone, with the aromatic ring *cis* to the enal moiety, evidently underwent a subsequent oxa-Michael addition and reoxidation to enal **10i**. The other major product, **11**, presumably arose from aza-Michael addition of *N*-arylhydroxylamine (vide infra), followed by dehydration to form an imine and tautomerization to the enamine.

Our working hypothesis for the mechanism of the reaction is illustrated in Scheme 4. Enal **1a** condenses with catalyst **2b** to form iminium ion **12**, which is in equilibrium with dienamine **13** via loss or gain of a proton. Both of these species were detected by HRMS analysis of the reaction mixture. Dienamine **13** reacts with 2 equiv of nitrosobenzene (**6a**) to generate **15**. The detection of iminium species **14** by HRMS suggests that dienamine **13** undergoes two successive reactions with a nitrosobenzene monomer, as opposed to reacting directly with the dimer of nitrosobenzene, which is known to be in equilibrium with the monomeric form in solution.¹² The reaction of **14** with nitrosobenzene must be very fast (i.e., faster than hydrolysis of the catalyst), as no aldehyde peak corresponding to the enal arising from hydrolysis of the catalyst in **14** (i.e., **8**) was observed in the ¹H NMR spectra of the crude reaction at any time point. It is still unclear whether a [4 + 2] cycloaddition and subsequent ring opening is, in fact, operative in the formation of **14**. We propose that deprotonation of **15** liberates the nitrone **10a**, along with 1 equiv of the product of reduction of nitrosobenzene, *N*-phenylhydroxylamine. Further evidence in support of this mechanism is the observation of **17** as the major byproduct of this reaction (vide supra). Compound **17** can be formed from the conjugate addition of *N*-phenylhydroxylamine to **1a** (via iminium **12**) followed by intramolecular hemiacetalization.¹³

This is, thus, a unique example of divergent reactivity of an enal in an organocatalyzed redox reaction. Under the conditions summarized in entry 5 in Table 1, 1 equiv of enal is oxidized to the γ -nitrone via dienamine catalysis, while a second equivalent of enal reacts with the reduced byproduct, *N*-phenylhydroxylamine, via iminium catalysis.

Scheme 5. Subsequent Elaboration of Nitrone Products



For medicinal chemists, this divergent reactivity may be useful, as it represents an interesting new means of rapidly accessing small libraries of medicinal compounds. In toluene, and using conditions summarized in entry 5 in Table 1, compounds **10a** and **17** are generated in an approximately 1:1 ratio and in a combined yield of 91% in one step.¹⁰ Both compounds are isolable, and each provides access to a structurally related *N,O*-heterocycle (i.e., **18** in Scheme 5 and **17**), which are compounds of importance in medicinal chemistry.¹⁴

For synthetic chemists, however, this divergent reactivity would be undesirable and, as mentioned previously, can be suppressed simply by switching the reaction solvent to 1,4-dioxane. It should be noted that, although the yields of nitrone products in 1,4-dioxane are moderate (Scheme 3), alternative strategies to synthesize compounds containing nitrone and aldehyde functionalities would necessitate the use of protecting groups and entail multiple steps, which may curtail the overall yield of desired product relative to this one step catalytic process.

In an effort to further hamper divergent reactivity, the possibility of oxidizing *N*-phenylhydroxylamine in situ to regenerate nitrosobenzene, thereby recycling this amine by-product and circumventing formation of byproduct **17**, was briefly examined. A preliminary screen of stoichiometric MnO₂ as well as catalytic conditions developed by Read de Alaniz and co-workers (CuCl₂, air, and pyridine) was undertaken.^{10,15} While the latter did completely suppress the formation of byproduct **17**, no improvement in the yield of **10a** was achieved.

Finally, subsequent transformations of **10** were investigated (Scheme 5). Under unoptimized conditions, a 1,3-dipolar

cycloaddition of **10a** with diethyl acetylenedicarboxylate (DEAD) at low temperature provided 2,3-dihydroisoxazole **18** in 54% yield. Interestingly, when this cycloaddition was run at higher temperatures, or when **18** was isolated, redissolved in toluene, and heated, pyrrole **19** was formed, albeit in extremely low yields ($\leq 12\%$). Formation of pyrroles from dipolarophilic alkynes and nitrones derived from ketones, under heating, isprecedented.¹⁶ Additionally, and also under unoptimized conditions, nitron **10g** was converted to ketone **20** in 63% yield.¹⁷ 2,3-Dihydroisoxazole **18**, pyrrole **19**, and ketone **20** all contain orthogonal aldehyde functionality that can be further manipulated.

In conclusion, we have developed the first catalytic method to directly introduce nitron functionality in the presence of an aldehyde. In this organocatalytic redox reaction, an enal is oxidized to the corresponding γ -nitron via dienamine catalysis, thereby reducing 1 equiv of nitrosobenzene to *N*-phenylhydroxylamine. When the reaction solvent is toluene, the *N*-phenylhydroxylamine reacts with unreacted enal to form 5-hydroxyisoxazolidines via iminium catalysis and subsequent intramolecular hemiacetalization. This is an unprecedented, and potentially useful, example of divergent reactivity of enals in an organocatalytic redox reaction. Alternatively, when the reaction solvent is 1,4-dioxane, this side reaction is suppressed and nitron products are obtained in higher yields. Importantly, the reaction products have two handles for further functionalization, and we have shown that the nitron can be manipulated orthogonally to the aldehyde. Further investigations into organocatalytic reactions using nitrosobenzene are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00770.

Synthetic procedures, optimizations, methods, configuration determination, mechanistic studies, and characterization data (PDF)

¹H, ¹³C, and INEPT NMR spectra (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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