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Citation: Sakai, Takeo, and Rick L. Danheiser. "Cyano Diels–Alder and Cyano Ene Reactions. Applications in a Formal [2 + 2 + 2] Cycloaddition Strategy for the Synthesis of Pyridines." *Journal of the American Chemical Society* 132.38 (2010): 13203-13205.

As Published: <http://dx.doi.org/10.1021/ja106901u>

Publisher: American Chemical Society

Persistent URL: <http://hdl.handle.net/1721.1/67720>

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

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Cyano Diels-Alder and Cyano Ene Reactions. Applications in a Formal [2 + 2 + 2] Cycloaddition Strategy for the Synthesis of Pyridines

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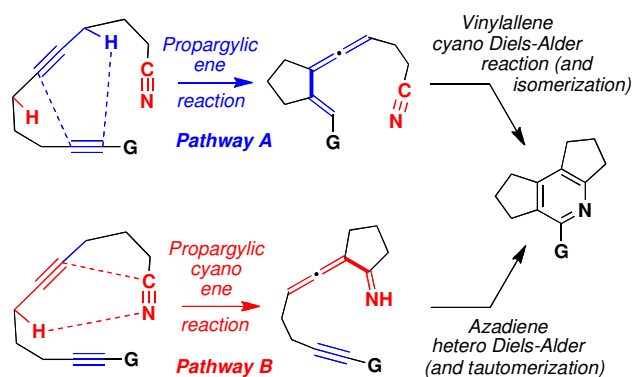
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Abstract: Two metal-free, formal [2 + 2 + 2] cycloaddition strategies for the construction of polycyclic pyridine derivatives are described that proceed via pericyclic cascade mechanisms featuring the participation of unactivated cyano groups as enophile and dienophile cycloaddition partners.

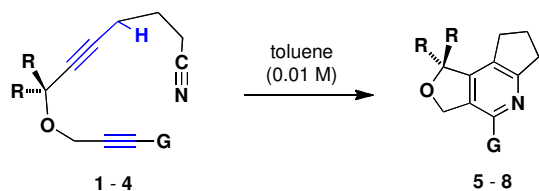
The nitrile functional group rarely participates as an enophile or dienophile in Alder ene and Diels-Alder cycloadditions.ⁱⁱⁱ Herein we describe two formal [2 + 2 + 2] strategies for the synthesis of substituted pyridines that proceed via pericyclic cascade processes involving the unusual reaction of *unactivated* nitriles as 2- π cycloaddition components. As outlined in Scheme 1, the first strategy begins with a propargylic ene reactionⁱⁱⁱ which is followed by an intramolecular Diels-Alder reaction in which an unactivated cyano group functions as the dienophile. When the initial propargylic ene step is blocked (e.g., by substitution at the appropriate propargylic carbon), then a second cascade sequence is operative which leads to the same pyridine products. This alternate pathway begins with an intramolecular propargylic ene reaction in which an unactivated cyano group serves as the enophilic π -bond. To our knowledge, the participation of an unactivated cyano group in a thermal ene reaction is unprecedented.^{iv,v} The resulting allenylimine then functions as a 1-azadiene in an intramolecular hetero Diels-Alder reaction^{vi} leading (after tautomerization) to the isolated pyridine product. Overall, these transformations provide strategies for achieving metal-free, formal [2 + 2 + 2] cycloadditions^{vii} that complement the well established transition-metal-catalyzed methodology^{viii} for the synthesis of this important heterocyclic ring system.^{ix}

Scheme 1. Synthesis of Pyridines via Pericyclic Cascade Strategies



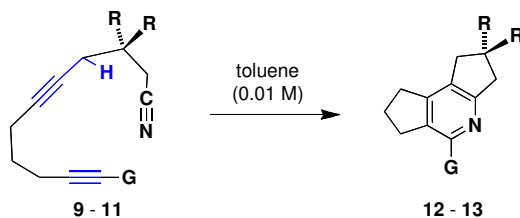
Tables 1 and 2 present examples of transformations leading to pyridines that proceed via the first pathway outlined in Scheme 1.^x In this pathway the first step involves a propargylic ene reaction in which the alkyne rather than cyano group functions as the enophile component. The observations summarized below suggest that this pathway is dominant even when both pathways are possible.

In the case of substrate **2**, substitution of two methyl groups at one propargylic carbon precludes cyano ene reaction as the first step in the cascade so that it is pathway A that must be operative. Comparison of the relative rates of reactions of substrates lacking *gem*-dimethyl substitution suggest that these transformations also proceed via the propargylic ene/cyano Diels-Alder mechanism. For example, activation of the terminal alkyne with an alkynyl substituent leads to a significant increase in the rate of disappearance of starting material (entries 1 and 4). This observation is consistent with an initial propargylic ene step, and would not be expected if the first step in the cascade were the cyano ene reaction. A similar trend is observed in the case of substrates **10** and **11** (Table 2) where the unactivated alkyne **11** (G = H) failed to react even at 200 °C and most of the starting material was recovered unchanged.

Table 1. Formal [2 + 2 + 2] Cycloadditions via Propargylic Ene/Cyano Diels-Alder Reactions

entry	R	G	conditions	product	yield (%) ^a	
1	1	H	160 °C, 21 h	5	71	
2	2	CH ₃	reflux, 66 h	6	96	
3	2	CH ₃	140 °C, 18 h	6	55	
4	3	H	C≡CSiMe ₃	reflux, 24 h	7	30
5	4	H	C≡CCH ₂ OSi <i>t</i> -BuMe ₂	reflux, 46 h	8	37

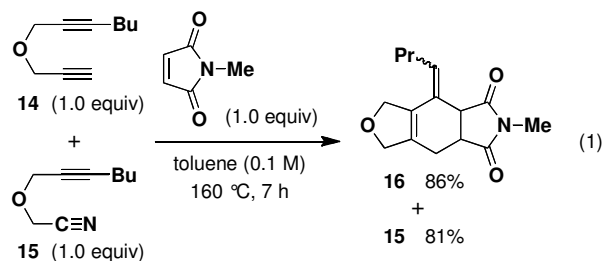
^aIsolated yield of products purified by chromatography.

Table 2. Formal [2 + 2 + 2] Cycloadditions via Propargylic Ene/Cyano Diels-Alder Reactions

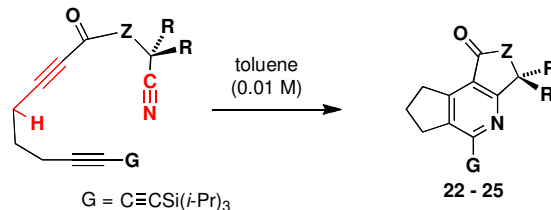
entry	R	G	conditions	product	yield (%) ^a
1	9	Et	C≡CSi(<i>i</i> -Pr) ₃	12	51
2	10	CO ₂ Et	C≡CSi(<i>i</i> -Pr) ₃	13	46
3	11	CO ₂ Et	H	–	0

^aIsolated yield of products purified by chromatography.

The following competition experiment provides further evidence for the greater enophilicity of alkynes compared to cyano groups in the propargylic ene reaction. Heating 1 equiv each of **14**, **15**, and *N*-methylmaleimide (NMM) at 160 °C led to the isolation of **16** in 86% yield and the recovery of most of nitrile **15** unchanged (eq 1). Thus, propargylic ene reaction of **14** (but not **15**) takes place under these conditions, generating a vinylallene that in this case is trapped in an intermolecular [4 + 2] cycloaddition with NMM to afford **16**. In summary, when both pathways in Scheme 1 are available, pathway A is favored. The relative facility of the cyano Diels-Alder reaction involving unactivated nitriles in this pathway is attributed to the entropic advantages associated with intramolecular cycloadditions and the high reactivity of the *s*-cis vinylallene as a Diels-Alder diene.^{xi}

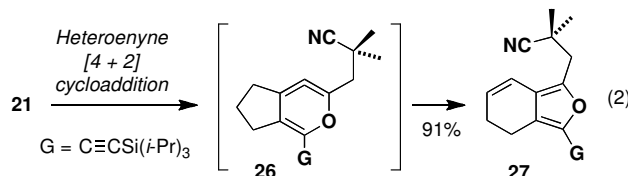


Interestingly, when the preferred pathway A is blocked, an alternate cascade sequence takes place that begins with a propargylic cyano ene reaction and which leads to the formation of the same type of pyridine products. Table 3 presents transformations involving substrates with amide, ester, and ketone tethers in which the position of the carbonyl group precludes the propargylic ene reaction with the alkyne participating as the enophile. Substrates incorporating *gem*-dimethyl substitution react at lower temperature, presumably due to the *gem*-dialkyl effect.^{xii} The reaction of nitriles **17** and **19** also proceed with the formation of fewer byproducts, since in these cases an α -proton is not available for tautomerization of the intermediate allenylimine prior to trapping in the hetero Diels-Alder step. Thermolysis of alkynone **21** failed to produce the desired pyridine and instead furnished the product of an “ynone” type [4 + 2] cycloaddition^{xiii} in high yield (eq 2).

Table 3. Formal [2 + 2 + 2] Cycloadditions via Propargylic Cyano Ene/Azadiene Diels-Alder Reactions

entry	Z	R	conditions	product	yield (%) ^a
1	17	MeN	CH ₃	22	74
2	18	MeN	H	23	58
3	19	O	CH ₃	24	62
4	20	O	H	25	35
5	21	CH ₂	CH ₃	–	0 ^b

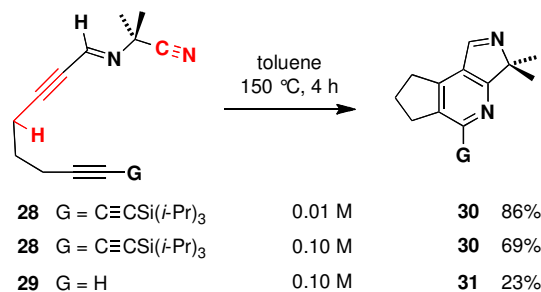
^aIsolated yield of products purified by chromatography. ^bYnone type [4 + 2] cycloadduct **27** was obtained in 91% yield (eq 2).



Further examples of the formation of pyridines via this alternate cascade pathway were observed when alkynylimine **28** was heated in toluene for several hours at 150 °C (Scheme 2). The tricyclic pyridine product **30** was obtained in 69% yield, and the yield improved to 86% when the reaction was carried out at higher dilution. This transformation can be explained as involving initial *E/Z* isomerization of the imine followed by sequential propargylic cyano ene and azadiene hetero Diels-Alder reactions as outlined in the lower pathway

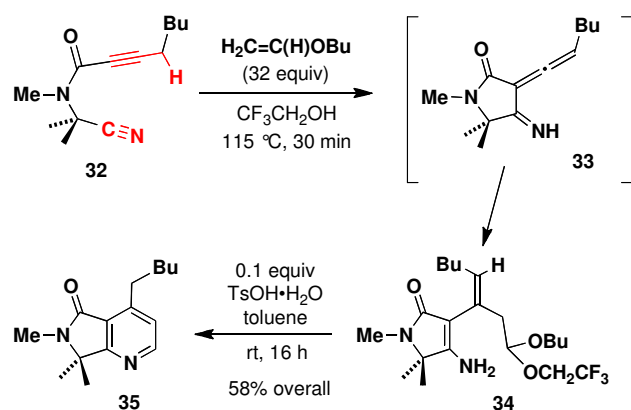
in Scheme 1. Consistent with this mechanism is the observation that the rate of disappearance of starting material was unchanged when a homologous compound bearing an additional methylene between the alkyne groups was subjected to thermolysis. The rate of the cyano ene reaction would not be expected to be affected in this case, while the rate of the hetero Diels-Alder reaction should be significantly slower. In fact, no pyridine products were obtained in the reaction of the homologous system, presumably because trapping of the reactive allenylimine intermediate is not competitive with dimerization and other alternative reaction pathways.

Scheme 2. Formal [2 + 2 + 2] Cycloadditions via Propargylic Cyano Ene/Azadiene Diels-Alder Reactions



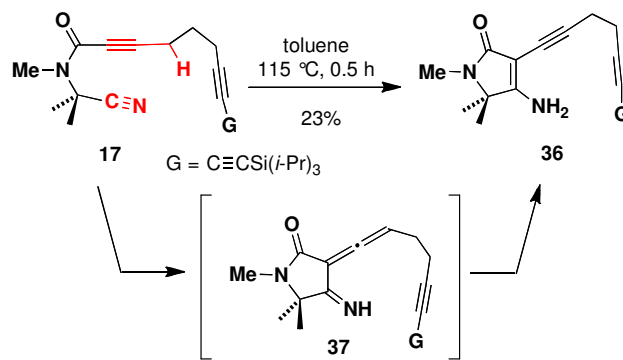
Schemes 3 and 4 provide further evidence in support of the proposal that the formation of the pyridine products in Table 3 begins with an intramolecular cyano ene reaction. Scheme 3 illustrates an alternate route to pyridines involving an inter-rather than intramolecular hetero Diels-Alder reaction. In this two-step approach, the intermediate allenylimine is trapped by an electron-rich alkene^{xiv} to afford an enamine (**34**) which is isolated and then converted to the desired pyridine upon exposure to acid.

Scheme 3. Stepwise [2 + 2 + 2] Cycloaddition via Propargylic Cyano Ene and Intermolecular Addition of Vinyl Ether

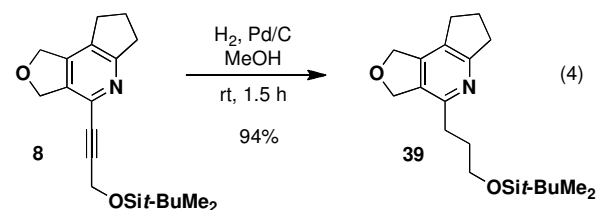
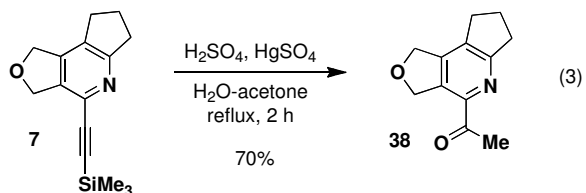


Further evidence for the cyano ene pathway was obtained when the thermolysis of nitrile **17** (Table 3, entry 1) was interrupted after only 30 min, allowing isolation of the unstable enamine **36** (Scheme 4). This compound is believed to form via tautomerization of the intermediate allenylimine **37** involved in the formation of pyridine **22**. Further heating transforms **36** to **22**, suggesting that **36** and **37** undergo interconversion at elevated temperature.

Scheme 4. Evidence for Propargylic Cyano Ene Reaction: Isolation of Enamine **36**



Throughout this study particular attention was focused on reactions of substrates with alkynyl G groups. These substituents were found not only to function as excellent activating groups for the propargylic ene and azadiene Diels-Alder reactions, but also can serve as synthetic equivalents for a variety of substituents on the pyridine ring. For example, hydration and hydrogenation of formal [2 + 2 + 2] cycloadducts **7** and **8** furnished **38** and **39**, respectively, in good yield (eq 3-4).



In summary, we have described two formal [2 + 2 + 2] cycloaddition strategies for the construction of polycyclic pyridine derivatives that proceed via unusual pericyclic cascade mechanisms featuring the participation of unactivated cyano groups as enophile and dienophile cycloaddition partners. Further studies are underway in our laboratory aimed at developing additional synthetically useful variants of this [2 + 2 + 2] strategy for the synthesis of pyridines.

Acknowledgment. We thank the National Institutes of Health (GM 28273), Merck Research Laboratories, and Boehringer Ingelheim Pharmaceuticals for generous financial support. T. S. was supported in part by a Research Fellowship of the Japan Society for the Promotion of Science (JSPS) for Young Scientists. We thank Dr. Michiko Sasaki for carrying out the competition experiment described in eq 1.

Supporting Information Available: Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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^v Murakami has recently reported intramolecular ene reactions of acyl nitriles promoted by carboxylic acids, see Shimizu, H.; Murakami, M. *Synlett* **2008**, 1817.

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^x For full details on the synthesis of cycloaddition substrates, see the Supporting Information.

^{xi} For a review of Diels-Alder reactions of vinylallenes, see Murakami, M.; Matsuda, T. Cycloadditions of Allenes. In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 727-815.

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^{xiv} Attempts to trap the intermediate allenylimine with the TMS enol ether derivative of cyclohexanone and with electron-deficient alkenes and alkynes were unsuccessful. Reaction with enamines proceeded in low yield.

TOC Template

(9 cm x 3-1/2 cm)

