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Photocatalyzed Site-Selective C–H to C–C Conversion of Aliphatic Nitriles

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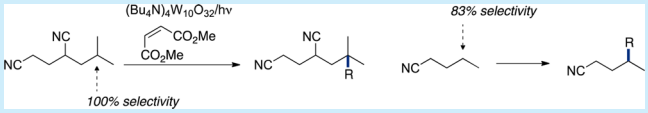
Supporting Information

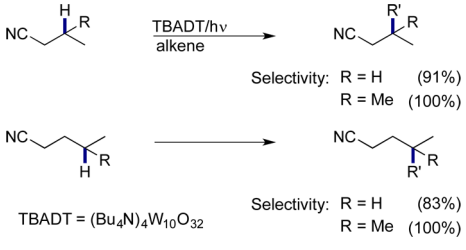
ABSTRACT: β- or γ-Site-selective C–H alkylation of aliphatic nitriles has been achieved using a decatungstate salt as the photocatalyst. The observed site selectivity was justified by a radical polar effect in transition states for hydrogen abstraction.



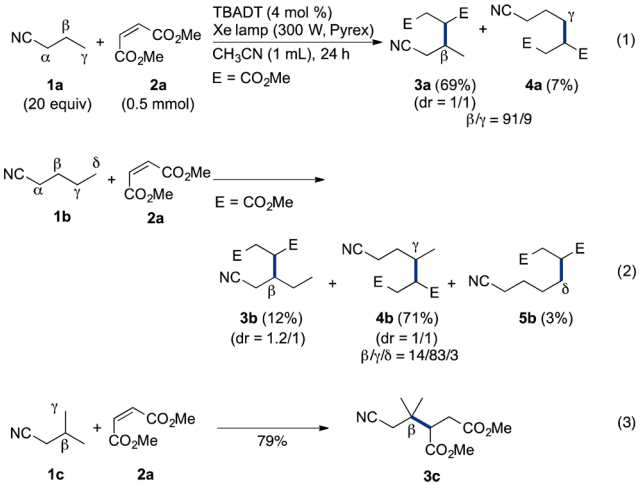
The site-selective functionalization of alkanes is currently one of the most important challenges in organic chemistry.[1] Aliphatic nitriles are potentially useful compounds, since they can be easily converted to a variety of functionalized compounds, such as carboxylic acids,[2] aldehydes,[3] esters,[4] amines,[5] and amides.[6] We theorized that functionalization of the C–H bonds in aliphatic nitriles would significantly widen the scope of accessible nitriles. Remarkably, site-selective C–H/C–C conversion in aliphatic nitriles is not readily achieved in any position other than α to the nitrile.[7,8] Recently, we reported that cyclopentanones could be regioselectively functionalized at the β-position using tetrabutylammonium decatungstate (TBADT)[9,10] as a photocatalyst, leading to highly selective C–H alkylation and acylation.[11] The polar effect[12] exerted in the S_H2 transition state of hydrogen abstraction by the excited decatungstate anion was invoked to explain the lack of reactivity at the usually activated α-position. In the present study, we report that this photocatalytic approach was highly effective for the β- and γ-site-selective alkylation of aliphatic nitriles by alkenes (Scheme 1).

As a model reaction, we chose to study the alkylation of butyronitrile **1a** by dimethyl maleate **2a** (Scheme 2). Thus, an acetonitrile (1 mL) solution of **1a** (20 equiv), **2a** (0.5 mmol), and TBADT (4 mol %) was irradiated using a Xe lamp (300 W) through a Pyrex tube for 24 h. Under these conditions, β-substituted butyronitrile **3a** was obtained in 69% isolated yield as a 1:1 mixture of diastereoisomers (Scheme 2, eq 1), while α-substituted butyronitrile was not observed, and γ-substituted butyronitrile **4a** was formed in only 7% yield. The complete avoidance of α-C–H activation can be accounted for by an unfavorable polar transition state for hydrogen abstraction α to the nitrile group (vide infra, Scheme 5, **TS-A** (R = H)). The preference for β-methylene activation rather than γ-methyl activation in **1a** reflects the weaker bond strength of the methylene C–H bond. Next, we examined the alkylation of valeronitrile **1b**, which has both β- and γ-methylene groups, with **2a** (Scheme 2, eq 2). The reaction yielded γ-substituted nitrile **4b** in a noteworthy preference to β-substituted nitrile **3b**

Scheme 1. Site-Selective Alkylation of Aliphatic Nitriles Presented in This Work



Scheme 2. Site Selectivity Observed in the TBADT Photocatalyzed C–H Alkylation of Butyronitrile 1a, Valeronitrile 1b, and Isovaleronitrile 1c by Dimethyl Maleate 2a



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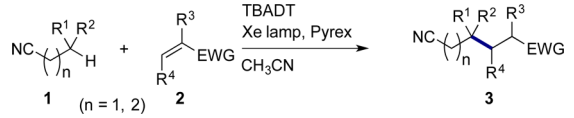
(γ/β = 83/14). In this reaction, products derived from C−H cleavage at the methyl position yielded only a trace amount of **5b**. The reaction of isovaleronitrile **1c**, bearing a methine carbon at the β-position, with **2a** gave the corresponding β-functionalized nitrile **3c** in 79% yield with complete site selectivity (Scheme 2, eq 3).

After obtaining promising results for the site-selective C−H functionalization of **1a**, **1b**, and **1c**, we next sought to assess the selectivity of a variety of aliphatic nitriles **1** in the reaction with electron-deficient alkenes **2**. The results are summarized in Table 1. In a similar manner, the reactions of **1c** with *tert*-butyl acrylate **2b**, methyl vinyl ketone **2c**, acrylonitrile **2d**, acrylamide **2e**, and phenyl vinyl sulfone **2f** all proceeded selectively at the β-position to give the corresponding β-alkylated nitriles **3d**−**3h** in good yields (Table 1, entries 1−5). The reaction of propionitrile **1d** with **2a** occurred selectively at the β-methyl, but it was very sluggish,[13] giving product **3i** in a low yield after 48 h (Table 1, entry 6). The alkylation of cyclopropyl cyanide **1e** with **2a** did not proceed (Table 1, entry 7). The reaction of isocapronitrile **1f** with **2a** proceeded selectively at the γ-methine to give **3k** in 79% yield (Table 1, entry 8). The reaction of **1f** with alkenes **2b**, **2c**, **2d**, and **2g** also gave the corresponding γ-alkylation products **3l**, **3m**, **3n**, and **3o**, respectively, in good yields (Table 1, entries 9−12). Notably, the formation of compound **3o** was likewise successful when the irradiation source was solar simulated light. The reaction of dinitriles was also examined. While the reaction of adiponitrile **1g** with **2a** proceeded selectively at the β-methylene carbon to give the β-alkylated product **3p** (Table 1, entry 13), the reaction of glutaronitrile **1h** with **2a** did not proceed (Table 1, entry 14). Dinitrile **1i**, which has six different C−H bonds including both nucleophilic and electrophilic methine groups, reacted with **2a** selectively at the only nucleophilic methine carbon to give **3r** in 52% yield (Table 1, entry 15). The direct sunlight-induced alkylation of aliphatic nitrile **1f** was also successful and gave γ-alkylated nitrile **3k** in a 62% yield (Table 1, entry 16).

To determine whether the key alkyl radical species would react with CO,[14] we examined a TBADT-catalyzed three-component coupling reaction comprising butyronitrile **1a**, CO, and dimethyl maleate **2a**. The reaction gave a mixture of β-acylated product **6a** and γ-acylated product **7a** in a 75/25 ratio under high CO pressures (Scheme 3). The decline of β-selectivity compared with alkylation using **2a** (β/γ = 91/9) may be ascribed to the stability of acyl radicals toward backward decarbonylation, since loss of CO from a secondary acyl radical is faster than that from a primary acyl radical.[14]

To gain insight into the mechanism, we carried out laser flash photolysis experiments. The reactive excited state of decatungstate shows a strong absorption in the red part of the visible spectrum and can be revealed at λ = 780 nm.[15] In the presence of hydrogen donors, a long-lived signal can be likewise observed and has been attributed to the reduced form of decatungstate ($H^+[W_{10}O_{32}]^{5-}$) that absorbs in the same region.[10e,15] The signal decay profiles resulting after laser excitation of the decatungstate anion were registered in acetonitrile, propionitrile, and butyronitrile. The signal lifetime was longer in acetonitrile (62 ns) compared to propionitrile (46 ns) and butyronitrile (39 ns; Figure 1 and Table S1). An opposite trend was observed for the long-lived signal, the intensity of which increased when shifting from acetonitrile to butyronitrile. Both spectral features are consistent with a more efficient hydrogen atom abstraction by excited dectungstate

Table 1. Site-Selective C−H Alkylation by Aliphatic Nitriles 1 Using TBADT as a Photocatalyst[a]



1 2 3

entry	nitrile 1	alkene 2	product 3	yield[b]
1	**1c**	**2b**	**3d**	82%
2	**1c**	**2c**	**3e**	86%
3	**1c**	**2d**	**3f**	73%
4[c]	**1c**	**2e**	**3g**	68%
5	**1c**	**2f**	**3h**	83%
6[d]	**1d**	**2a**	**3i**	31%
7	**1e**	**2a**	**3j**	n.d.[e]
8[f]	**1f**	**2a**	**3k**	79%
9[f]	**1f**	**2b**	**3l**	75%
10[f]	**1f**	**2c**	**3m**	60%
11[f]	**1f**	**2d**	**3n**	73%
12[g]	**1f**	**2g**	**3o**	54% (only *endo*)
13	**1g**	**2a**	**3p**	69%
14	**1h**	**2a**	**3q**	n.d.[e]
15	**1i**	**2a**	**3r**	52%
16[h]	**1f**	**2a**	**3k**	62%

[a] **1** (10 mmol), **2** (0.5 mmol), TBADT (4 mol %), acetonitrile (1 mL), irradiation by 300 W Xe lamp for 24 h. [b] Yields of product isolated after flash chromatography on SiO_2. If necessary, further purification was made by preparative HPLC. [c] 1 mL of acetonitrile/acetone (1/1) was used as the solvent. [d] 48 h. [e] Not detected. [f] Trace amount of β-alkylated nitrile was detected by ^{13}C NMR of the crude reaction mixture. [g] **1** (10 mmol), **2** (0.5 mmol), TBADT (4 mol %), acetonitrile (5 mL), irradiation by a SolarBox equipped with a 1.5 kW Xe lamp (500 Wm^{-2}) for 20 h. [h] Sunlight exposure for 56 h (7 days) in Osaka (autumn).

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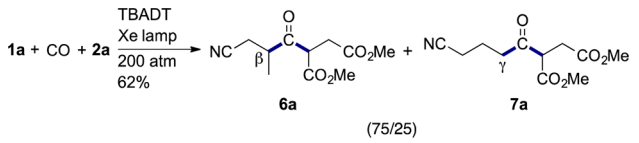
Scheme 3. Three-Component C−H Acylation of Butyronitrile 1a



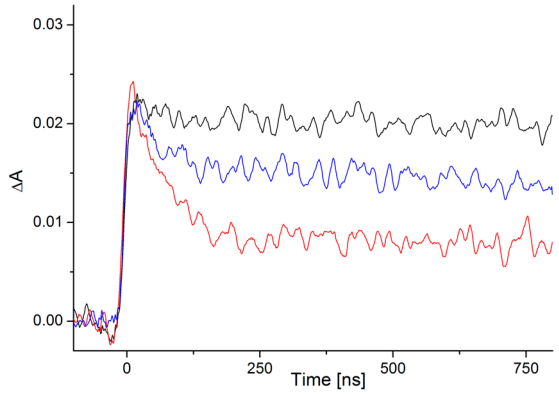
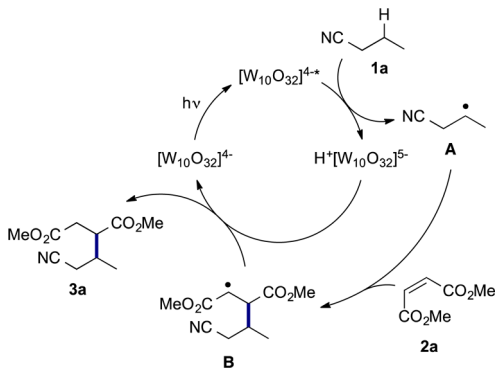


Figure 1. Nanosecond decays observed at 780 nm after 355 nm laser excitation of a 2×10^{-4} M TBADT solution in acetonitrile (red line), propionitrile (blue line), and butyronitrile (black line).

from butyronitrile than from acetonitrile, with propionitrile in between (see Supporting Information for further details).

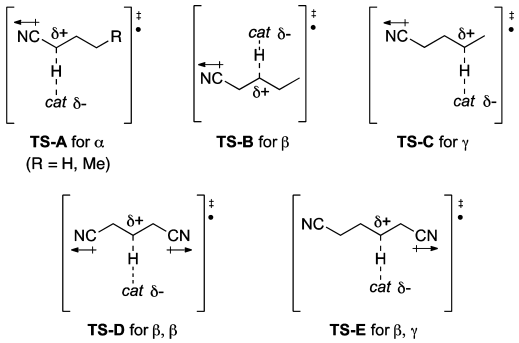
Scheme 4 illustrates a plausible reaction mechanism for the β-site-selective C−H alkylation of butyronitrile **1a** with

Scheme 4. Proposed Reaction Mechanism for the Photocatalyzed β−C-H Alkylation of Butyronitrile 1a with Dimethyl Maleate 2a



dimethyl maleate **2a**. The excited decatungstate anion abstracts a hydrogen from the β-C−H bond of **1a** to form the β-cyano radical **A**, which then combines with **2a** to form the adduct radical **B**. Back-hydrogen atom transfer from the reduced decatungstate anion gives the alkylated product **3a** and regenerates the starting decatungstate anion. The reluctant α-C−H functionalization of **1a** is rationalized by an unfavorable polar effect in the transition state **TS-A** (R = H; Scheme 5), in which a partial positive charge on the α-carbon is destabilized by the adjacent electronegative cyano group. The preference of β-methylene C−H to γ-methyl C−H may reasonably be ascribed to a weaker methylene C−H than the methyl C−H bond.[16] In the alkylation of valeronitrile **1b**, a preference for γ-methylene with respect to β-methylene functionalization was observed. This suggests that the inductive effect of a cyano

Scheme 5. Possible Polar S_H2 Transition States



group is persistent in **TS-B** for β-C−H cleavage but not in **TS-C** for γ-C−H cleavage, and in this regard it should be noted that a similar tendency for γ-functionalization was recognized in the radical chlorination of valeronitrile.[17−19] This assumption could explain the failure of the reaction of **1h**, in which double destabilization of the polar **TS-D** by two β-cyano groups is present. In the successful case of adiponitrile **1g**, the second cyano group that was located at the more remote γ-position exerted only a small effect, as shown in **TS-E**.

The present study used TBADT as a photocatalyst for the site-selective C−H to C−C conversion in aliphatic nitriles **1** with electron-deficient alkenes **2**. In all cases examined, no alkylation was observed at the weakest C−H bonds α to the cyano group, resulting in high β-site selectivity for alkylation of butyronitrile. When aliphatic nitriles bearing both β- and γ-methylene hydrogens are reacted, γ-functionalization was preferred. When both methine and methylene groups were available, selective methine C−H cleavage was observed. These site-selective C−H cleavages in aliphatic nitriles led to a new protocol for the synthesis of higher nitriles from lower nitriles. This *polar* radical approach could become a powerful and general tool for the site-selective C−H functionalization. The procedure is very straightforward and can be easily carried out by solar light irradiation. We are now applying this strategy to other systems.

■ ASSOCIATED CONTENT

Supporting Information

Typical experimental procedure and characterization for all products are present in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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