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Sequential Palladium-Catalyzed Allylic Alkylation/retro-Dieckmann Fragmentation Strategy for the Synthesis of α-Substituted Acrylonitriles

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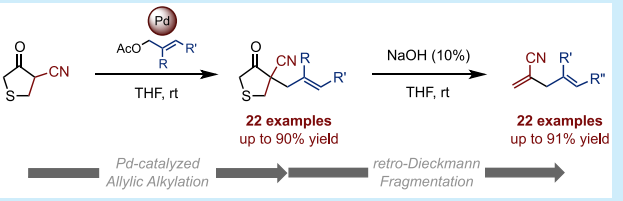
Supporting Information

ABSTRACT: A straightforward synthesis of α-substituted acrylonitriles is described using 4-cyano-3-oxotetrahydro-thiophene (c-THT) as an acrylonitrile surrogate. This unprecedented two-step sequence featuring a palladium-catalyzed allylic alkylation (Pd-AA) and a retro-Dieckmann fragmentation provides a general entry into diversely substituted 1,4-dienes.



Substituted acrylonitriles are valuable building blocks in synthetic organic chemistry. These double-headed warheads can indeed be engaged in a number of synthetic transformations; the nitrile moiety being a well-known precursor for other functional groups such as amines, acids, aldehydes, and alcohols,[1] while the alkene moiety can be involved in a variety of transformations including 1,4-additions,[2−5] Diels−Alder cycloadditions,[6] the Stetter reaction,[7] cross-couplings,[8−10] and cross-metatheses[11−13] just to name a few. Their use in material sciences and polymer chemistry is also unique; acrylonitrile remains one of the most useful monomers in the synthesis of plastics, acrylic fibers, and polyacrylonitrile.[14] Finally, the acrylonitrile motif can be found in a number of biologically active and structurally intriguing natural products such as calyculin A, benthocyanin C, ambiguinine G, cyanopuupehenone, or the tannins aleurinin A and B.[15,16] Interestingly, however, despite the plethora of applications, the methods allowing direct access to substituted acrylonitriles, particularly α-substituted acrylonitriles, remain rather scarce. Indeed, apart from the traditional syntheses employing hazardous hydrogen cyanide[17] or cyanogen halide as a cyanate source,[18] only a few efficient methods have been reported, and they usually rely on the cyanation of alkynes.[19−21]

With the aim of developing an alternative approach, we envisaged to tame the singular reactivity of 4-cyano-3-oxotetrahydrothiophene (c-THT, **1**) as an acrylonitrile surrogate[22] by subjecting it to a sequential palladium-catalyzed allylic alkylation[23]/retro-Dieckmann fragmentation (Figure 1).[22,24] Indeed, we envisioned that this two-step sequence would allow a straightforward, highly versatile and potentially scalable route to α-substituted acrylonitriles imbedded within a 1,4-diene scaffold.

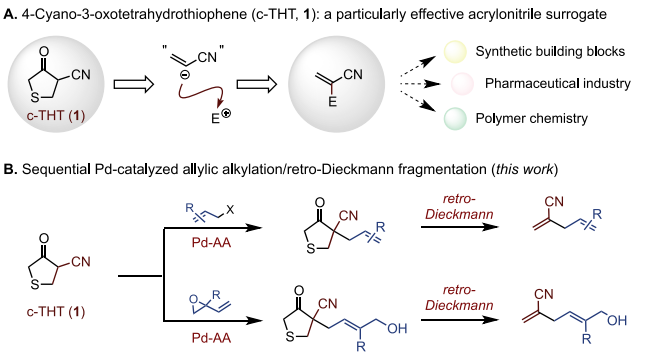


Figure 1. Use of 4-cyano-3-oxotetrahydrothiophene (c-THT, **1**) as an acrylonitrile surrogate for the synthesis of α-substituted acrylonitriles.

We initiated our study by optimizing the Pd-catalyzed allylic alkylation of 4-cyano-3-oxotetrahydrothiophene **1** using cinnamyl acetate **2a** as a model electrophilic allyl donor. The results are depicted in Table 1. A rapid screening of the reaction conditions (solvent and base) showed that running the reaction in THF at rt using 5 mol % of $Pd(PPh_4)_3$ and 1 equiv of K_2CO_3 led to a very satisfying 87% yield (Table 1, entries 1−10). Interestingly, the yield could be further improved by simply running the reaction in the absence of base under otherwise identical conditions (90%, Table 1, entry 11).

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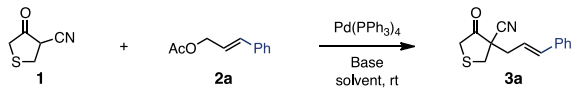
Table 1. Systematic study[a]



Entry	Solvent	Base	Yield[b] (%)
1	toluene	K_2CO_3	80
2	CH_3CN	K_2CO_3	80
3	CH_2Cl_2	K_2CO_3	83
4	Et_2O	K_2CO_3	76
5	DMF	K_2CO_3	70
6	THF	K_2CO_3	87
7	THF	NEt_3	82
8	THF	DBU	-
9	THF	Li_2CO_3	76
10	THF	NaOAc	86
11	**THF**	-	**90**

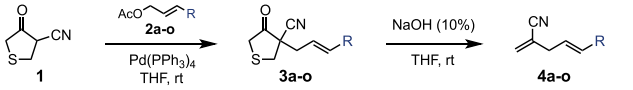
[a]All reactions were run on a 0.3 mmol scale using 1 equiv of cynammyl acetate and 5 mol % of $Pd(PPh_3)_4$. [b]Isolated yield.

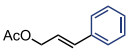
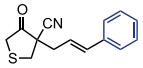
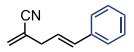
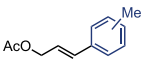
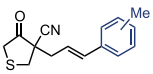
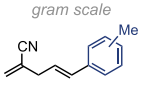
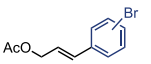
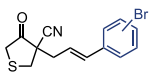
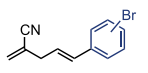
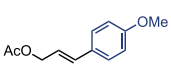
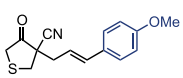
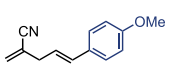
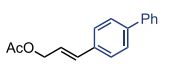
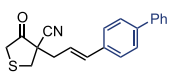
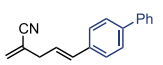
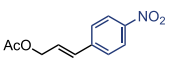
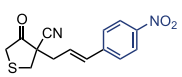
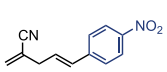
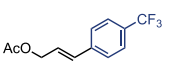
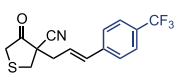
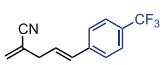
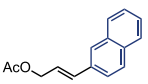
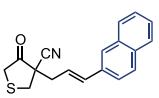
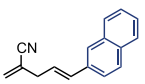
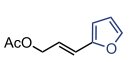
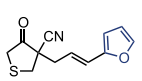
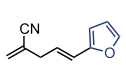
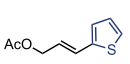
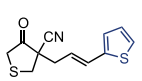
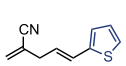
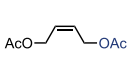
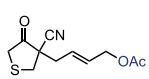
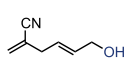
With these optimal conditions in hand [$Pd(PPh_4)_3$ (5 mol %), THF, rt], we rapidly aimed at evaluating the efficacy of this palladium-catalyzed allylic alkylation on a broad range of linear allyl acetates;[25,26] the results are depicted in Table 2.

Overall, the reaction appeared to be quite general. Indeed, with the exception of the *para*-nitro-substituted allyl acetate (**2j**), which only afforded the desired product in a moderate 55% isolated yield, the use of *para*-substituted cinnamyl acetates led to the corresponding allylated products **3d** and **3g−k** in good to excellent yields ranging from 64% to 90% (Table 2, entries 1−7). In the case of the *ortho*- and *meta*-substituted cinnamyl acetates **2b−c** and **2e−f**, good to excellent yields were obtained; however, a slightly lower reactivity was observed in the case of the *ortho*- and *meta*-bromo substituted derivatives (66% and 57%, respectively). Finally, the allylated products resulting from the naphthalene (**3l**, 78%), the furan (**3m**, 85%), and the thiophene (**3n**, 69%) precursors were obtained in good yields, whereas the use of *cis*-1,4-diacetoxy-2-butene (**2o**) afforded the corresponding allylated product **3o** in only 33% isolated yield.

As the allylation step showed great promise, we next evaluated the key retro-Dieckmann fragmentation, which would ultimately unveil the α-substituted acrylonitrile moiety. After screening various conditions, we rapidly discovered that exposing the *C*-allylated products to a 10% aqueous solution of NaOH at rt led to the best results. The retro-Dieckmann conditions were therefore applied to all the allylated products previously synthesized (**3a−o**). As a general trend, all the reactions afforded the desired α-substituted acrylonitrile in high yields independently of the substitution pattern on the olefin. Hence, with the exception of the *ortho*- and *para*-methyl substituted precursors **3b** and **3c**, which only afforded the corresponding 1,4-dienes **4b** and **4c** in 28% and 35% yield, respectively, all the other substrates were isolated in good to excellent yields ranging from 60% to 91% (Table 2, entries 1−7). This was also the case with the naphthalene (**4l**), the furan (**4m**), and the thiophene (**4n**) derivatives, which were isolated in 85%, 55%, and 83% yield, respectively. In the case of the allyl acetate precursor **3o**, the reaction logically provided the corresponding 1,4-diene **4o** with concomitant hydrolysis of the acetate (Table 2, entry 11). Most importantly, the entire sequence could be run on a gram scale without any noticeable

Table 2. Scope of the Method with Various Linear Allyl Acetates[a]



Entry	2a-o	3a-o	4a-o
1	 **2a**	 **3a** (90%[b], *E*/*Z*>20:1)	 **4a** (90%)[b], *E*/*Z*>20:1 *gram scale*
2	 **2b** (*o*) **2c** (*m*) **2d** (*p*)	 **3b** (o: 89%,[b] *E*/*Z*>20:1) **3c** (m: 89%,[b] *E*/*Z*>20:1) **3d** (p: 84%,[b] *E*/*Z*>20:1)	 **4b** (o, 28%,[b] *E*/*Z*>20:1) **4c** (m, 35%,[b] *E*/*Z*>20:1) **4d** (p, 77%,[b] *E*/*Z*>20:1)
3	 **2e** (*o*) **2f** (*m*) **2g** (*p*)	 **3e** (o: 66%,[b] *E*/*Z*>20:1) **3f** (m: 57%,[b] *E*/*Z*>20:1) **3g** (p: 84%,[b] *E*/*Z*>20:1)	 **4e** (o, 85%,[b] *E*/*Z*>20:1) **4f** (m, 91%,[b] *E*/*Z*>20:1) **4g** (p, 69%,[b] *E*/*Z*>20:1)
4	 **2h**	 **3h** (88%,[b] *E*/*Z*>20:1)	 **4h** (86%,[b] *E*/*Z*>20:1)
5	 **2i**	 **3i** (64%,[b] *E*/*Z*>20:1)	 **4i** (77%,[b] *E*/*Z*>20:1)
6	 **2j**	 **3j** (55%,[b] *E*/*Z*=4:1)	 **4j** (63%,[b] *E*/*Z*=4:1)
7	 **2k**	 **3k** (90%,[b] *E*/*Z*>20:1)	 **4k** (60%,[b] *E*/*Z*>20:1)
8	 **2l**	 **3l** (78%,[b] *E*/*Z*>20:1)	 **4l** (85%,[b] *E*/*Z*>20:1)
9	 **2m**	 **3m** (85%,[b] *E*/*Z*>20:1)	 **4m** (55%,[b] *E*/*Z*>20:1)
10	 **2n**	 **3n** (69%,[b] *E*/*Z*>20:1)	 **4n** (83%,[b] *E*/*Z*>20:1)
11	 **2o**	 **3o** (33%,[b] *E*/*Z*>20:1)	 **4o** (20%,[b] *E*/*Z*>20:1)

[a]All reactions were run on a 0.3 mmol scale using 1 equiv of allyl acetate **2a−o** and 5 mol % of $Pd(PPh_3)_4$. All retro-Dieckmann reactions were run on a 0.12 mmol scale using 1:1 mixture of THF and a 10% saturated aqueous solution of NaOH (2 mL). [b]Isolated yield.

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loss in yield and without ever observing the formation of the conjugated 1,3-diene (Table 2, entry 1).

Mechanistically, the retro-Dieckmann fragmentation proceeds through a 1,2-addition of a hydroxide ion onto the carbonyl moiety, which then rapidly undergoes elimination to form the stable α-substituted acrylonitrile with subsequent release of sodium thioglycolate. The reaction is fast (approximately 10 min) and affords the corresponding α-substituted α,β-unsaturated nitrile as a single *E* stereoisomer.

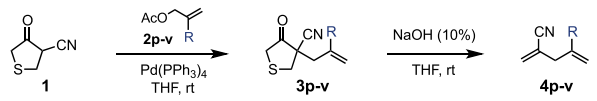
This two-step sequence was eventually applied to branched allyl acetates as well.[23g,h,27] Interestingly, replacing the hydrogen atom at the 2-position by a methyl (**2q**), a phenyl (**2r**), or a methyl ester (**2s**) did not hamper the reactivity of the Pd-AA and the yields remained satisfactory (Table 3, entries 1−4). A slight decrease in reactivity was observed in the case of the 2-chloro- and the 2-isopropyl-substituted allyl acetates **2t** and **2u** (Table 3, entries 5−6); however, the reactivity was regained with the 2-methyl carbinol substituted allyl acetate **2v**, which led to the corresponding allylated product **3v** in 89% yield despite the presence of the free OH (Table 3, entry 7). All of the resulting α-allylated products (**3p−v**) were eventually engaged in the retro-Dieckmann fragmentation step; all afforded the corresponding α-substituted acrylonitriles **4p−v** in yields ranging from 10% to 80% depending on the inherent volatility of the products.

To extend the scope of the method, we applied the same Pd-AA/retro-Dieckmann fragmentation sequence to methyl 4-oxotetrahydrothiophene-3-carboxylate **5**, used here as a methyl acrylate surrogate (Scheme 1). To our delight, the desired α-allylated product **7** was obtained in 64% yield over the two steps with no hydrolysis of the ester moiety. In addition, we also tested the method using vinyl epoxides instead of allyl acetates. Interestingly, in the presence of **8a** and **8b**, the linear products **9a** and **9b** were obtained thus confirming the known trend regarding the opening of epoxides in the presence of $Pd(PPh_3)_4$.[28] The latter were then engaged in the retro-Dieckmann fragmentation to form the corresponding 1,4-dienes **4o** and **10**, albeit in lower yields than usual due to a lower reactivity of the corresponding allylated intermediates.

To illustrate further the synthetic versatility of the method, a series of post-functionalizations were conducted on **4a** (Scheme 2) including both biocatalytic and chemical transformations. We first screened Almac's ERESK-9600 ene-reductase (ERED) enzyme kit for the stereoselective reduction of the acrylonitrile moiety. All of the reactions were performed utilizing the well-established coupled-enzyme approach, employing a glucose/GDH system to regenerate the required cofactor. Several hit enzymes were identified with ERED ER304 generating the desired saturated nitrile **11** in 42% yield and up to 92% ee at screening scale. We also screened a focused library of nine nitrile hydratases and 15 nitrilases from Almac's NESK-2400 nitrile manipulating enzyme kit for the mild and selective hydrolysis of the nitrile moiety. Among the 24 enzymes tested, enzyme NH103 led to the quasi-quantitative conversion of nitrile **4a** to amide **12** at screening scale. Work is ongoing to further establish the biotransformation utility and scope.

Some more traditional chemical transformations were also carried out. Hence, the selective reduction of the nitrile moiety using DIBAL-H afforded the corresponding aldehyde **13** in 79% yield. The selective reduction of the cyano-olefin in the presence of Stryker's reagent provided the corresponding saturated nitrile **11** in 57% yield. Meanwhile, the selective

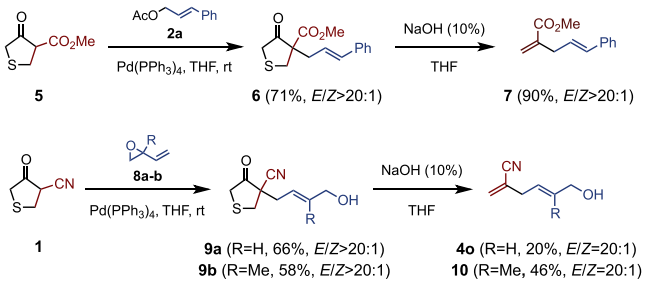
Table 3. Scope of the Method with Various Branched Allyl Acetates[a]



Entry	2p-v	3p-v	4p-v
1	**2p**	**3p** (76%[b])	**4p** (10%[b,c])
2	**2q**	**3q** (60%[b])	**4q** (15%[b,c])
3	**2r**	**3r** (67%[b])	**4r** (58%[b])
4	**2s**	**3s** (60%[b])	**4s** (15%[b,c])
5	**2t**	**3t** (31%[b])	**4t** (13%[b,c])
6	**2u**	**3u** (27%[b])	**4u** (69%[b])
7	**2v**	**3v** (89%[b])	**4v** (80%[b])

[a]All reactions were run on a 0.3 mmol scale using 1 equiv of allyl acetate **2p−v** and 5 mol % of $Pd(PPh_3)_4$. All retro-Dieckmann reactions were run on a 0.12 mmol scale using a 1:1 mixture of THF and a 10% saturated aqueous solution of NaOH (2 mL). [b]Isolated yield. [c]Highly volatile.

Scheme 1. Implementation of the Method[a]



[a]All Pd-AA reactions were run using 1 equiv of allyl acetate **2a** or epoxides **8a** and **8b** and 5 mol % of $Pd(PPh_3)_4$. All retro-Dieckmann reactions were run using a 1:1 mixture of THF and a 10% saturated aqueous solution of NaOH (2 mL).

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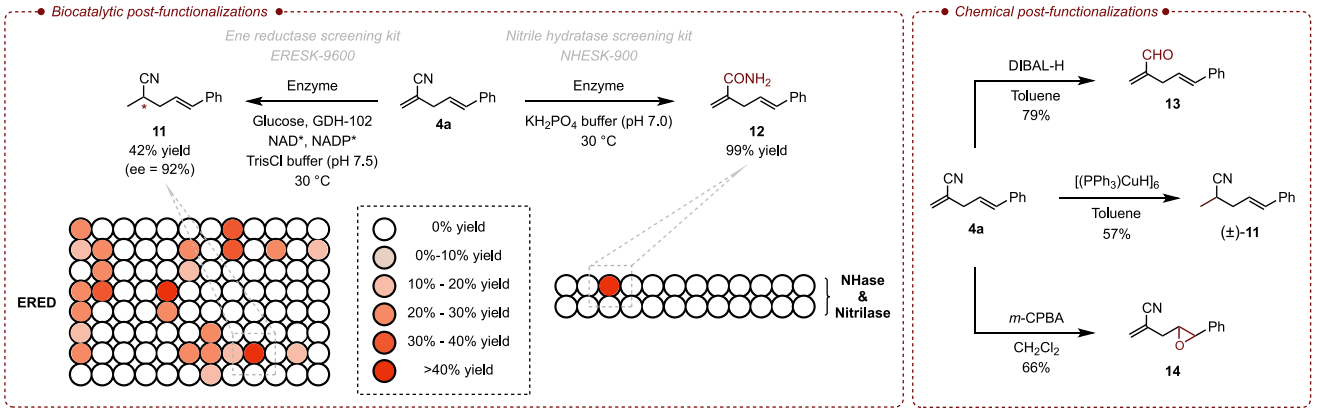
Scheme 2. Selective Post-functionalizations



oxidation of the styrene moiety was possible using *m*-CPBA, affording the corresponding epoxide **14** in 66% yield.

In summary, we have developed a highly straightforward and scalable route to α-substituted acrylonitriles through a sequential palladium-catalyzed allylic alkylation/retro-Dieckmann fragmentation of 4-cyano-3-oxotetrahydro-thiophene. The resulting 1,4-dienes bearing an acrylonitrile moiety were subsequently converted to various useful building blocks using biocatalytic and chemical transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03522.

Details of experimental procedures, ^{1}H and ^{13}C NMR spectra, and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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