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Site-selective olefinic C–H cyanation *via* alkenyl sulfonium salts†

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A chemo- and regioselective olefinic C–H cyanation strategy was developed through palladium-catalyzed C(sp^2)–S bond cleavage of stable alkenyl sulfonium salts with CuCN, efficiently affording multisubstituted alkenyl nitriles (acrylonitriles). This process features broad substrate scope, good chemo- and regioselectivities, and excellent functional group tolerance. The present protocol provides an alternative route to alkenyl nitriles from readily available functionalized alkenes by a site-selective interrupted Pummerer activation/palladium-catalyzed olefinic C(sp^2)–S cyanation sequence.

Introduction

Alkenes are some of the most useful building blocks in the chemical industry[1a] and useful partners in cross-coupling transformations,[1b] among which alkenyl nitriles (acrylonitriles) are considered as significant scaffolds,[2] and some of them act as the core structural motifs in biologically active molecules and natural products[3] (Fig. 1). For instance, CC-5079 has been found to be a potent antitumor agent,[3a] rilpivirine can be used as an *anti*-HIV reverse transcriptase inhibitor,[3b] and rhodiocyanoside A often exists in natural products.[3c] Alkenyl nitriles are characterized by the presence of a reactive olefin moiety and a nitrile group and have been applied as versatile reactants in organic synthesis.[4] Various methods have been established to access polyfunctionalized alkenyl nitriles, including direct approaches from alkenes and acrylonitriles or *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide under ruthenium[5a,b] and molybdenum[5c] or rhodium[5d] catalysis. Non-directed alkenyl C–H cyanation was realized with copper(II)/TMSCN[5e] or iodine(III)/TMSCN.[5f] The copper(I)-catalyzed vinylic Rosenmund–von Braun reaction of terminal alkenyl iodides with acetone cyanohydrin, sodium cyanide or potassium cyanide gave the corresponding acrylonitrile products.[6a] The same type of reaction with acetone cyanohydrin was also applied to terminal alkenyl bromides under palladium(0) catalysis.[6b] To date, general and straightforward methods to access multisubstituted alkenyl nitriles from readily available functionalized alkenes are still highly desirable.

Site-selective functionalization of arenes and alkenes is a great challenge in modern organic synthesis due to their multiple reactivities.[7] Recently, sulfonium salts have aroused much attention because of their diverse applications in carbon–carbon and carbon–heteroatom bond formation.[8] In this regard, aryl sulfonium salts have been extensively explored as coupling partners, and Ritter thianthrenation has been considered as a breakthrough to achieve highly site-selective aromatic C–H functionalization through interrupted Pummerer activation of aromatic C–H bonds by thianthrene (TT) or tetrafluorothianthrene (TFT) sulfoxide.[8,9] However, compared to aryl sulfonium salts alkenyl sulfonium salts have been paid much less attention in this area.[10] Although Liebeskind *et al.* reported the first palladium and nickel-catalyzed cross-coupling between aryl, heteroaryl, alkenyl and benzyl tetramethylenesulfonium salts with organometallic reagents,[10a] alkenyl sulfonium salts have only recently been applied for the elaboration of styrenes with organozinc compounds under nickel cat-

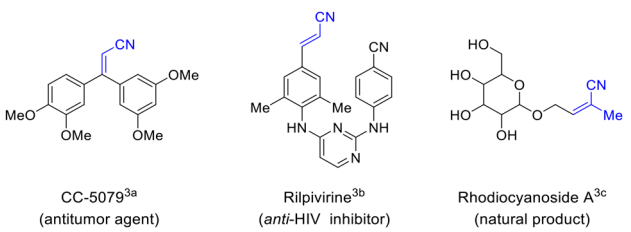

Fig. 1 Biologically active molecules with an alkenyl nitrile motif.

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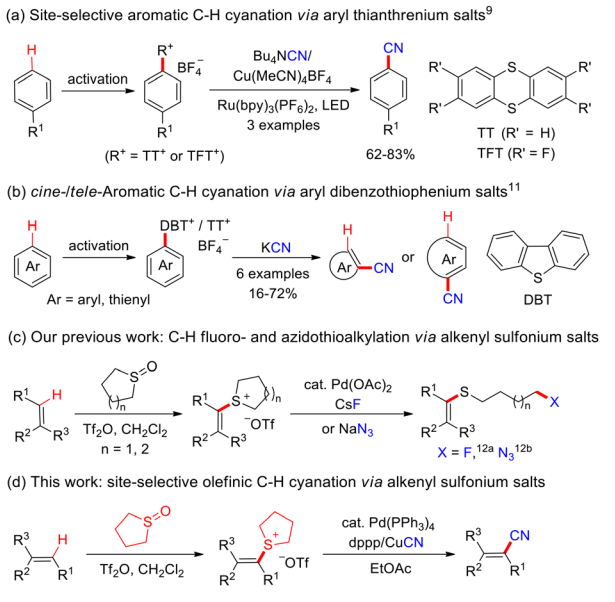
alysis,[10b] photocatalytic decarboxylative alkenylation of redox-active esters,[10c] palladium and ruthenium-catalyzed olefinic C–C and C–halogen bond formation,[10d] indirect functionalization of ethylene gas,[10e] copper-catalyzed silylation and borylation,[10f] germylation of styrenes,[10g] synthesis of *N*-vinylazoles,[10h] electrochemical route to allylic amines,[10i] and base-promoted amination and esterification.[10j] In the relevant case of constructing nitriles, aryl thianthrenium salts were found to be the potential coupling partners to generate aryl nitriles by means of a combination of Bu_4NCN and $Cu(MeCN)_4BF_4$ or Bu_4NCN and CuCN under photocatalysis, which was exemplified by three synthetic examples (62–83%) (Scheme 1a).[9] Substituted arenes and thiophenes underwent nucleophilic *cine*- or *tele*-aromatic C–H cyanation with extremely toxic KCN *via* their corresponding sulfonium salts, affording the target products in 16–72% yields with a limited scope of six examples (Scheme 1b).[11]

During our ongoing studies on functionalizing alkenes, we recently realized palladium-catalyzed olefinic C–H fluorothioalkylation[12a] and transition-metal-free azidothioalkylation[12b] *via* $C(sp^3)$–S bond cleavage of alkenyl sulfonium salts (Scheme 1c). Based upon the observation that the cleavage of the olefinic $C(sp^2)$–S bonds in alkenyl sulfonium salts sensitively depends on the reactivity of the selected coupling partners and the catalytic systems,[10] we envisioned that olefinic C–H cyanation might be achieved *via* an interrupted Pummerer activation/palladium-catalyzed olefinic $C(sp^2)$–S cyanation sequence. Herein, we disclose an efficient palladium-catalyzed site-selective protocol to access multisubstituted alkenyl nitriles (acrylonitriles) *via* alkenyl sulfonium salts (Scheme 1d).

The bench-stable alkenyl sulfonium salts were prepared through an interrupted Pummerer reaction by means of alkenes and tetrahydrothiophene *S*-oxide in the presence of triflic anhydride.[10b] Notably, a mixture of (*E*)/(*Z*)-alkene isomers usually gave a single (*E*)-alkenyl sulfonium salt which was confirmed by X-ray crystallographic structural determination of 1-(4-trifluoromethylphenyl)-2-(4-tolyl)vinyl sulfonium salt (**3m**) (see the ESI† for details). It should also be noted that the interrupted Pummerer reaction regioselectively occurred at the olefinic C–H site with less electron density among the two available adjacent internal olefinic C–H bonds, leading to site-selective desulfitative cyanation in our case.

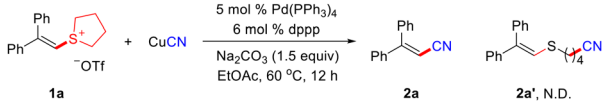


Scheme 1 C–H cyanation strategies using sulfonium salts.

Results and discussion

Initially, the reaction of 1-(2,2-diphenylvinyl)-tetrahydro-1*H*-thiophen-1-ium triflate (**1a**) and CuCN was conducted to optimize the reaction conditions (Table 1). After systematic studies, the optimal reaction conditions were identified (see the ESI†). In the presence of 5 mol% $Pd(PPh_3)_4$ as the catalyst, 6 mol% 1,3-bis(diphenylphosphino)propane (dppp) as the ligand, CuCN as the coupling partner, and Na_2CO_3 as the base in EtOAc under a nitrogen atmosphere, the reaction continued at 60 °C for 12 h to quantitatively form the target product 3,3-diphenylacrylonitrile (**2a**) in 98% isolated yield (Table 1, entry 1). The Pd(II) source $PdCl_2$ was ineffective, and dppp proved to be the most efficient ligand (Table 1, entries 2 and 3). In a poorly polar solvent such as toluene the reaction deteriorated, while the reaction efficiently proceeded in 1,2-dichloroethane (DCE) to reach 99% yield (Table 1, entries 4 and 5). TMSCN could act as a less effective cyanating reagent than CuCN giving **2a** in 58% yield (Table 1, entry 6), while $K_4[Fe(CN)_6]$

Table 1 Screening of reaction conditions[a]



Entry	Variation	Yield[b] of **2a** (%)
1	None	99 (98)[c]
2	$PdCl_2$ instead of $Pd(PPh_3)_4$	6
3	Xphos instead of dppp	39
4	Toluene instead of EtOAc	19
5	DCE instead of EtOAc	99
6	TMSCN instead of CuCN	58
7	$K_4[Fe(CN)_6]\cdot 3H_2O$ instead of CuCN	0
8	3 mol% $Pd(PPh_3)_4$	53
9	5 mol% dppp	63
10	1.0 equiv. CuCN	92
11	Without $Pd(PPh_3)_4$	0
12	Without dppp	22
13	Without Na_2CO_3	23
14	In air	0
15[d]	**None**	**99 (96)**[c]

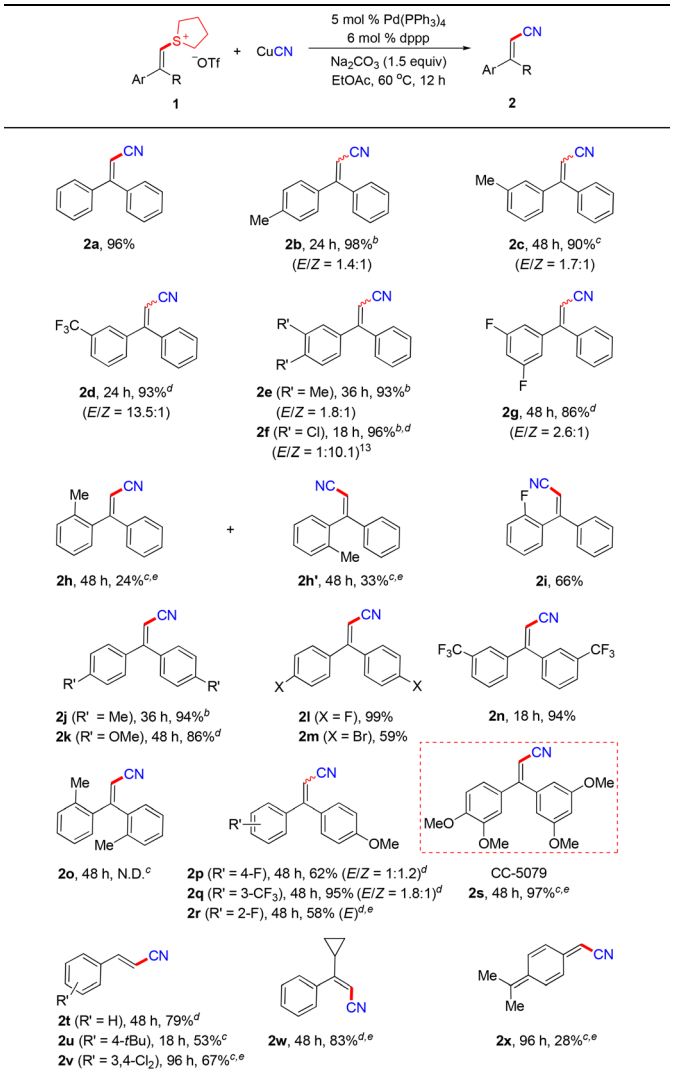
[a] Conditions: **1a** (0.2 mmol), CuCN (0.24 mmol), $Pd(PPh_3)_4$ (5 mol%), ligand (6 mol%), Na_2CO_3 (0.3 mmol), solvent (2 mL), 60 °C, N_2, 12 h. [b] Determined by ^1H NMR analysis of the crude product using $MeNO_2$ as the internal standard. [c] Isolated yields given in parentheses. [d] **1a** (0.3 mmol), CuCN (0.36 mmol), Na_2CO_3 (0.45 mmol). Xphos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. N.D. = not detected.

showed no reactivity (Table 1, entry 7). The use of suitable amounts of the catalyst, ligand and base is crucial for the desired cross-coupling reaction (Table 1, entries 8–13). The reaction could hardly take place in the absence of the $Pd(PPh_3)_4$ catalyst or in air (Table 1, entries 11 and 14). It is noteworthy that the ring-opening cyanation product **2a′** was not detected in the reaction mixture by proton NMR/HRMS analysis.

Under the optimal conditions, the scope of terminal alkenyl sulfonium salts (**1**) was investigated (Table 2). At 60 °C in EtOAc over a period of 12 h, unsubstituted 1,1-diphenylvinyl sulfonium salt (**1a**) reacted with CuCN and gave the target product **2a** in 96% yield. It was observed that the reactivity of substituted terminal alkenyl sulfonium salts of type **1** is very sensitive to the substituent(s) on the aryl group and the olefinic C═C backbone in the alkenyl sulfonium substrates. Thus, the reaction parameters were further modified to reach higher yields by elevating the temperature, extending the reaction time, using DCE as the reaction medium, and/or increasing the catalyst loading. When one aryl group in the 1,1-diaryl moiety is *para*- and *meta*-monosubstituted or 3,4- and 3,5-disubstituted, the target products **2b–2g** were obtained in excellent yields (86–98%),[13] and the electronic/steric properties of the substituents, that is, methyl, trifluoromethyl, chloro and fluoro, only slightly affected the reaction efficiency under the stated conditions. 2-Substituents such as 2-methyl and 2-fluoro exhibited an obvious steric impact on the formation of **2h**/**2h′** (57%) and **2i** (66%), respectively. It is noteworthy that (*E*)-**2h** (24%) and (*Z*)-**2h′** (33%) were isolated as two separable isomers, and **2i** was isolated as a single (*Z*)-isomer. When both aryls in the 1,1-diaryl moiety are substituted by the same 4- or 3-positioned groups such as 4-methyl, 4-methoxy, 4-fluoro, 4-bromo, and 3-trifluoromethyl, most of the target products, that is, **2j** (94%), **2k** (86%), **2l** (99%) and **2n** (94%), were formed in excellent yields, and only in the case of the 4,4′-dibromo-substituted product **2m** a moderate yield (59%) was obtained. Unexpectedly, 1,1-di(2-tolyl)vinyl sulfonium salt **1o** did not undergo the desired desulfitative cross-coupling to afford **2o** even at 80 °C, exhibiting a remarkable negative steric effect. When both of the aryls in the 1,1-diaryl moiety are substituted by various electron-donating/withdrawing substituents, multisubstituted acrylonitrile derivatives **2p** (62%), **2q** (95%), **2r** (58%) and **2s** (CC-5079, 97%) were synthesized in moderate to excellent yields. 2-F in **1r** and 3- and 5-OMe groups in **1s** demonstrated an obvious negative impact on their reactivity to interact with CuCN under the standard conditions. At 70 °C, **2r** was only formed in 30% yield, and increasing the catalyst loading to 10 mol% enhanced its yield to 58%. Notably, the potent antitumor agent CC-5079[3a] (**2s**) was prepared in 97% yield from such a concise process. It has been documented that copper(I)-catalyzed hydroarylation of 3-aryl-2-propyne-nitriles with arylboronic acids could give CC-5079 in good yields,[14a] and a 1,4-rhodium migration sequence could only give it in 12% yield from the reaction of *o*-(alkenyl)-substituted arylboronic acid and *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide.[14b] Styryl sulfonium salt **1t** showed good reactivity to CuCN at 70 °C, resulting in **2t** in 79% yield, whereas substituted styryl sulfonium salts exhibited a much lower reactivity to afford **2u** (53%) and **2v** (67%), respectively. 1-Phenyl-1-cyclopropylvinyl sulfonium salt (**1w**) reacted well to produce **2w** (83%) in the presence of 10 mol% catalyst. Unfortunately, the sulfonium salt generated from terpinene only exhibited poor reactivity to react with CuCN, forming **2x** in 28% yield over a period of 4 days at 80 °C.

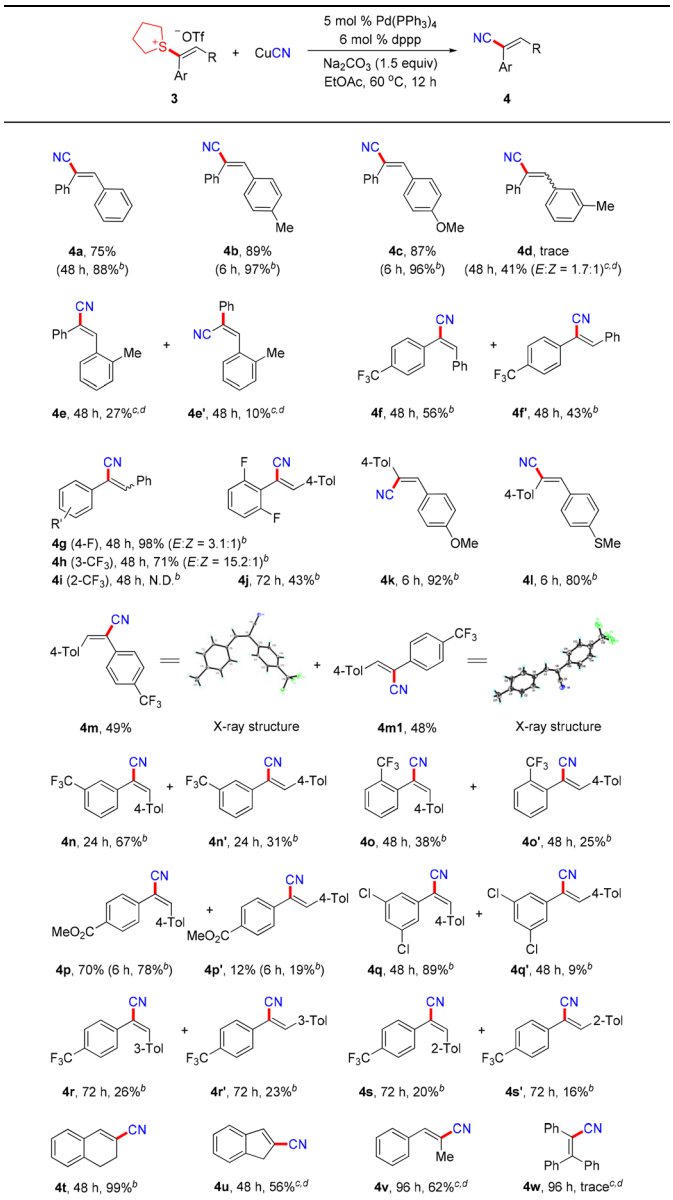
Next, the protocol generality was studied by conducting the reaction of internal alkenyl sulfonium salts **3** with CuCN (Table 3). The reaction of **3a–3d** with CuCN under the optimal conditions as shown in Table 2 (in EtOAc at 60 °C within 12 h) formed the target products **4a** (75%), **4b** (89%), **4c** (87%) and **4d** (trace), respectively. Elevating the temperature to 70–80 °C,

Table 2 Scope of terminal alkenyl sulfonium salts[a]



[a] Conditions: **1** (0.3 mmol), CuCN (0.36 mmol), $Pd(PPh_3)_4$ (5 mol%), dppp (6 mol%), Na_2CO_3 (0.45 mmol), EtOAc (2 mL), 60 °C, N_2, 12 h. Isolated yields. The molar ratio of (*E*)/(*Z*)-isomers was determined by ^{1}H NMR analysis. [b] In DCE. [c] 80 °C. [d] 70 °C. [e] Using $Pd(PPh_3)_4$ (10 mol%) and dppp (12 mol%).

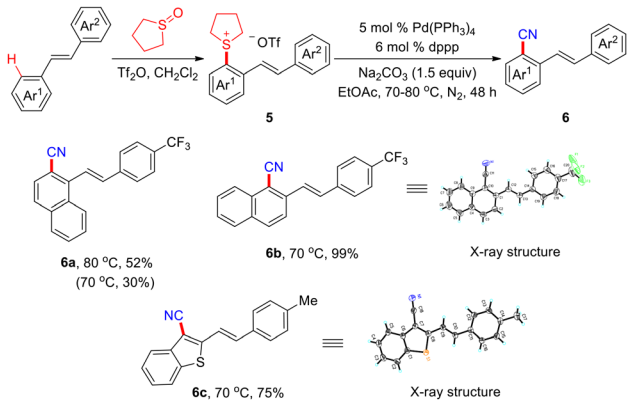
Table 3 Scope of internal alkenyl sulfonium salts[a]



[a] Conditions: **3** (0.3 mmol), CuCN (0.36 mmol), $Pd(PPh_3)_4$ (5 mol%), dppp (6 mol%), Na_2CO_3 (0.45 mmol), EtOAc (2 mL), 60 °C, N_2, 12 h. Isolated yields. The molar ratio of (*E*)/(*Z*)-isomers was determined by ^{1}H NMR analysis. [b] 70 °C. [c] 80 °C. [d] Using $Pd(PPh_3)_4$ (10 mol%) and dppp (12 mol%).

extending the reaction time and/or increasing the catalyst loading obviously enhanced the yields of **4a** (88%), **4b** (97%), **4c** (96%) and **4d** (41%). At 70 °C, the mono-substituted stilbenyl sulfonium salts with 4-methyl (**3b**) and 4-methoxy (**3c**) reacted more efficiently with CuCN than **3a**, giving **4b** (97%) and **4c** (96%) within 6 h, respectively. In these transformations, only (*E*)-products were obtained under the stated conditions. A 3-methyl substituent on one of the two aryl groups (in 3-tolyl) exhibited a remarkable negative steric impact on the reaction efficiency of alkenyl sulfonium salt **3d** to generate a mixture of two inseparable isomers of **4d** (41%, (*E*)/(*Z*) = 1.7 : 1). 2-Tolyl also exhibited an obvious negative steric effect on the reactivity of 1-phenyl-2-(2-tolyl)vinyl sulfonium salt (**3e**), leading to two separable isomeric products (*E*)-**4e** (27%) and (*Z*)-**4e′** (10%). 1-(4-Trifluoromethylphenyl)-2-phenylvinyl sulfonium salt (**3f**) efficiently reacted with CuCN to quantitatively afford the target product (*E*)-**4f** (56%)/(*Z*)-**4f′** (43%) as two separable isomers. In a similar manner, 1-(4-fluorophenyl)-2-phenylvinyl sulfonium salt (**3g**) gave a mixture of inseparable isomers as the product (**4g**, 98%, (*E*)/(*Z*) = 3 : 1). However, 3- and 2-CF_3 groups remarkably increased the negative steric effect on the formation of **4h** (71%) and **4i** (0%). 2,6-Difluoro functionality behaved similarly to affect the generation of **4j** (43%). 4-Tolyl-based di(substituted aryl)-functionalized alkenyl sulfonium salts reacted well with CuCN to give **4k** (92%), **4l** (80%), (*E*)-**4m** (49%)/(*Z*)-**4m1** (48%), and **4n** (67%)/**4n′** (31%), among which 3- and 4-CF_3 groups showed no steric effect on the formation of **4m**/**4m1** and **4n**/**4n′**, whereas a 2-CF_3 group led to much less efficient generation of **4o** (38%)/**4o′** (25%). It is noteworthy that a 4-methylthio group diminished the yield of **4l** to 80% compared to the 92% yield of the corresponding 4-methoxy-functionlized product **4k**, presumably due to the poisoning of the catalytically active palladium metal center by the alkylthio group during the reaction. Isomers **4m** and **4m1** were separately isolated and their (*E*) and (*Z*)-configurations were identified by X-ray crystallographic single crystal structure determinations (see the ESI†). Similar results (97–98% yields) were also obtained for compounds **4p** (78%)/**4p′** (19%) and **4q** (89%)/**4q′** (9%) with 4-CO_2Me and 3,5-Cl_2 as the substituents on one of the aryl groups. 3- and 2-tolyl moieties dramatically diminished the reactivity of alkenyl sulfonium salts **3r** and **3s**, resulting in the target products **4r** (26%)/**4r′** (23%) and **4s** (20%)/**4s′** (16%) in much lower yields. Under the stated conditions 1-(3,4-dihydronaphthalen-2-yl)sulfonium salt (**3t**) quantitatively formed **4t** (99%), while the sulfonium salt of indene (**3u**) underwent the reaction with CuCN less efficiently to give **4u** (56%) even under the relatively harsh conditions. 2-Methyl-3-phenylacrylonitrile (**4v**) was also accessed in a good yield (62%) from the 1-alkyl-1-phenyl-difunctionalized alkenyl sulfonium salt (**3v**). However, 1,1,2-triphenylvinyl sulfonium salt (**3w**) hardly underwent the reaction under the stated conditions due to the increased steric hindrance around the olefinic C(sp^2)–S site. It is noteworthy that the aliphatic, benzyl and N-heteroaromatic alkenyl sulfonium salts could not be successfully prepared through the interrupted Pummerer reaction by means of the corresponding alkenes and tetrahydrothiophene *S*-oxide in the presence of triflic anhydride.

The interrupted Pummerer activation strategy was tried to functionalize the internal olefinic C–H bonds in 1-naphthyl-2-aryl and 1-(2-benzothienyl)-2-aryl alkenes (Scheme 2). Instead, the interrupted Pummerer activation occurred at the 2-C–H site of the naphthyl moiety for 1-(1-naphthyl)-2-(4-CF_3-phenyl)-ethylene, at 1-C–H of the same aryl ring for 1-(2-naphthyl)-2-(4-CF_3-phenyl)ethylene and at the 3-C–H position of the thienyl ring for 1-(2-benzothienyl)-2-(4-tolyl)ethylene, respectively, giving the aryl and heteroaryl sulfonium salts of type **5**. Under the stated conditions, the desulfitative cross-coupling of sulfo-

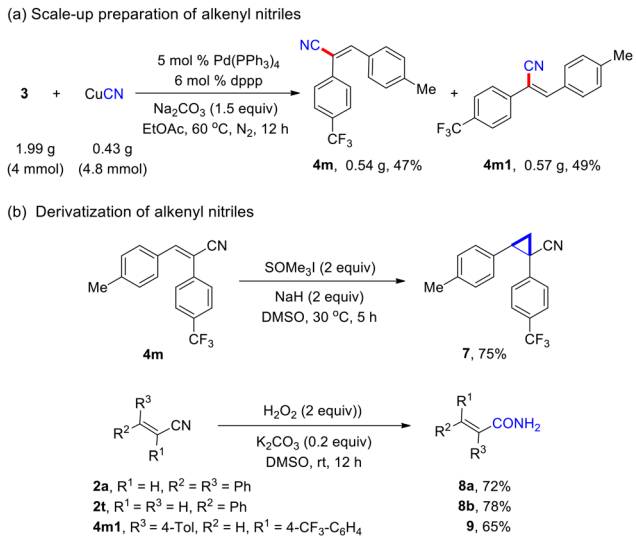


Scheme 2 Cyanation of alkenyl-functionalized naphthyl and benzothienyl sulfonium salts.

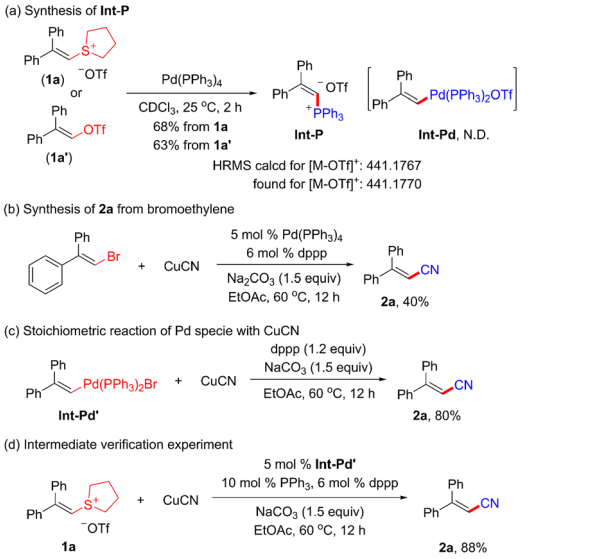
nium salts **5** was conducted with CuCN to afford the corresponding cyanation products **6** in 52–99% yields. Notably, 1-naphthyl sterically deteriorated the formation of **6a** (30% at 70 °C), while 2-naphthyl facilitated the production of **6b** (99%). 3-Cyanobenzothiophene (**6c**) was accessed in 75% yield in a similar fashion. These results have also revealed that condensed aromatic and heteroaromatic C–H bonds are more susceptible to the interrupted Pummerer activation conditions.[8–10] The molecular structures of aryl sulfonium salt **5b**, and nitriles **6b** and **6c** were further identified by X-ray crystallographic single crystal structural analysis (see the ESI†).

To explore the applicability of the present synthetic protocol, gram-scale preparation of **4m**/**4m1** was performed from the reaction of alkenyl sulfonium salt **3m** with CuCN under the standard conditions (Scheme 3a), affording two separable isomers **4m** (47%) and **4m1** (49%). Derivatization of the alkenyl nitrile products was exemplified by cyclopropanation of **4m** with $SOMe_3I$[15a] and oxidation of **2a**, **2t** and **4m1** with H_2O_2.[15b] The corresponding derivatization products **7–9** were thus accessed in 65–78% yields (Scheme 3b).

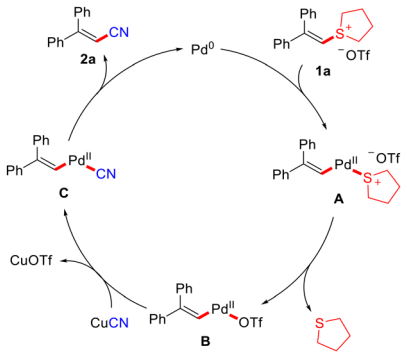
Control experiments were carried out to identify the catalytically active intermediates. A 1 : 1 molar ratio reaction of alkenyl sulfonium salt **1a** or alkenyl triflate **1a′**[16] with Pd$(PPh_3)_4$ was conducted in $CDCl_3$ at ambient temperature or 60 °C, giving no desired alkenylpalladium(II) complex **Int-Pd**. Instead, alkenyl-phosphonium triflate **Int-P** was isolated in 63–68% yields (Scheme 4a). Compound **Int-P** was structurally identified by ESI-TOF-MS (HRMS $[M-OTf]^+$ calcd for $C_{32}H_{26}P$: 441.1767; found 441.1770) and its NMR features (^{31}P NMR: 13.2 ppm) through comparison with that of its known tetrafluoroborate (^{31}P NMR: 9.9 ppm).[17a] Complex **Int-Pd** may be too unstable under the stated conditions to be detected and characterized.[17b] Thus, the analogue of **1a** and **1a′**, that is, 1,1-diphenyl-2-bromoethylene, was used for the mechanistic study. Under the standard conditions 1,1-diphenyl-2-bromoethylene reacted with CuCN to afford **2a** in 40% yield (Scheme 4b), and the stoichiometric reaction of alkenylpalladium(II) complex **Int-Pd′**,[18] a readily available stable analogue of complex **Int-Pd**, with CuCN formed **2a** in 80% yield (Scheme 4c). Under the conditions which are closer to the optimal conditions, as shown in Table 1, that is, in the presence of 5 mol% **Int-Pd′** as the catalyst, and 10 mol% PPh_3 and 6 mol% dppp as the ligands, the reaction of **1a** with CuCN formed the target product **2a** in 88% yield (Scheme 4d), suggesting that an alkenylpalladium(II) species of type **Int-Pd** may be involved in the present desulfitative cross-coupling process. The addition of 1,1-diphenylethylene and 2,6-di-*tert*-butyl-4-methylphenol (BHT) as radical inhibitors in the reaction mixture of **1a** and CuCN did not affect the reaction efficiency, excluding a radical pathway. The introduction of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) as a radical scavenger into the same reaction system led to **2a** in 26% yield (see the ESI†), which is presumably attributed to the possible



Scheme 3 Gram-scale preparation and derivatization of alkenyl nitriles.



Scheme 4 Mechanistic studies.



Scheme 5 Proposed mechanism.

Pd(0) catalyst deactivation by the oxidation of TEMPO, and is consistent with the observation of the model reaction conducted in air (Table 1, entry 14).

Based on the mechanistic studies and the previous work,[10b,17b] a plausible cyanation mechanism is proposed in Scheme 5. Initially, the oxidative addition of alkenyl sulfonium salt **1a** to palladium(0) occurs to form alkenyl palladium(II) complex **A**, followed by ligand exchange to generate alkenylpalladium(II) triflate complex **B** with the release of tetrahydrothiophene. Subsequently, species **B** is transmetalated with CuCN resulting in cyanated alkenylpalladium(II) complex **C**. Eventually, reductive elimination takes place to afford the final product **2a** and regenerates the catalytically active Pd(0) species to complete the catalytic cycle.

Conclusions

In conclusion, a highly efficient strategy to access diverse alkenyl nitriles has been developed through regio- and stereoselective interrupted Pummerer activation/palladium-catalyzed cyanation *via* alkenyl sulfonium salts. The present method was successfully applied for the stereoscopical synthesis of the potent antitumor agent CC-5079. The synthetic protocol features high chemo- and regioselectivities, broad substrate scope, and excellent functional group tolerance. The scale-up preparation and product derivatization applications have shown its potential practicality in organic synthesis.

Author contributions

J.M. started and performed the experiments and prepared the ESI.† J.L. and Z.L.H. partially analyzed and interpreted the results. P.W. synthesized some of the sulfonium salts. Y.-G.Z. supervised some of the experiments. Z.K.Y. conceived and directed the project and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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