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ARTICLE

From 1,2-difunctionalisation to cyanide-transfer cascades – Pd-catalysed cyanosulfenylation of internal (oligo)alkynes

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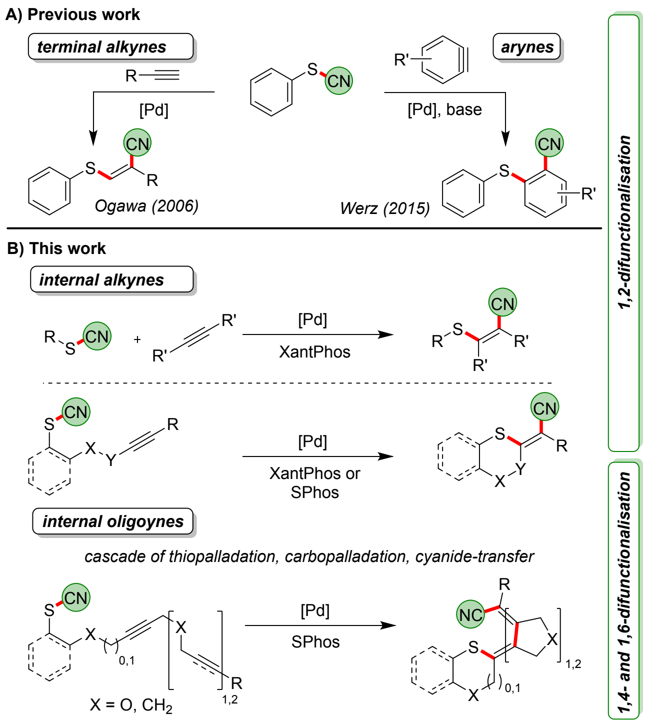
Internal alkynes substituted by aliphatic or aromatic moieties or by heteroatoms were converted into sulphur-substituted acrylonitrile derivatives. Key is the use of Pd catalysis, which allows the addition of aromatic and aliphatic thiocyanates in an intra- and intermolecular manner. Substrates with several alkyne units underwent further carbopalladation steps after the initial thiopalladation step, thus generating in a cascade-like fashion an oligoene unit with sulphur at one terminus and the cyano group at the other.

Introduction

An important method of accessing tetrasubstituted double bonds is the dual functionalisation of internal alkynes.[1] In its ideal and atom-economic way a substrate X-Y is attached to the C-C triple bond in a completely regio- and diastereoselective fashion. Depending on the type of substituents, either specially designed reagents are required or transition-metal catalysts are employed.[2-4] As prime example for the first scenario a *syn*-chlorocyanation using imidazolium thiocyanate in combination with BCl_3 was recently reported by Alcarazo *et al.*[2a] Morandi developed a Pd-catalysed intermolecular *syn*-aryliodination of internal alkynes[5] while Lautens and co-workers disclosed a series of intramolecular reactions leading to *syn*- and *anti*-carbohalogenations of triple bonds.[6] The key step of the latter reaction is a carbopalladation of the C-C triple bond followed by reductive elimination of the Pd to generate the carbon-halogen bond. Such a step is rare and can only be triggered by specific ligands.[5,6] The more common scenario is further reaction in a carbopalladation cascade[7] when other alkyne or alkene units are present.[8] In most cases a final elimination or cross-coupling reaction is employed to terminate the process. By such protocols, structures of astonishing complexity[9] such as fenestranes,[10] cyclooctatetraenes,[11] helicenes,[12] and several natural products[13] have been prepared from appropriately designed starting materials in just one synthetic step. The groups of Lautens, Cook and others have precisely designed intramolecular iodine-transfer reactions along these lines.[14] With other moieties such transfer reactions over several carbon atoms have only rarely been investigated.

Cyanosulfenylation reactions of terminal alkynes have been developed to access sulphur-substituted acrylonitrile derivatives starting from thiocyanates (Scheme 1A, left).[15] In these transformations the S-CN bond is broken and added across the C-C triple bond, which is comparable to reactions where O-CN or N-CN-bonds are activated to react with alkenes.[16] Later, we found that a similar Pd-catalysed process allows the reaction with arynes, which contain highly reactive formal triple bonds, leading to *o*-thiobenzonitriles (Scheme 1A, right).[17]



Scheme 1 Inter- and intramolecular cyanosulfenylation reactions.

Thus, we were first interested in seeking conditions to transform internal non-activated triple bonds to generate tetrasubstituted alkenes with sulphur and cyano in 1,2-position (Scheme 1B), and to determine whether this reaction might be also the starting point for a longer cascade involving – besides

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the thiopalladation step – carbopalladation steps of additional C-C triple bonds. The termination of the cascade was envisioned as a reductive elimination of the Pd catalyst to form the C-CN bond. Such an approach would lead to formal 1,4- and 1,6-cyanosulfenylation reactions (Scheme 1B).

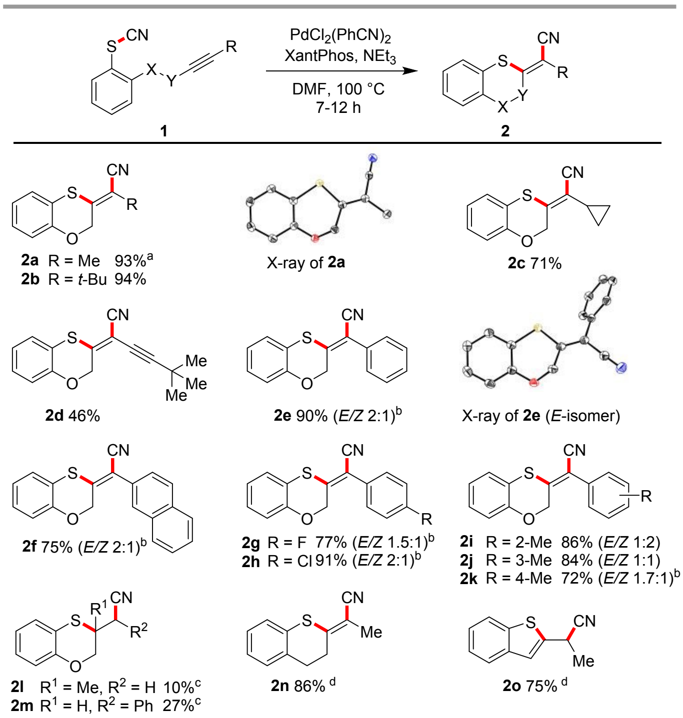
Results and Discussions

Optimisation of the reaction conditions

Initially, we explored the Pd-catalysed reaction of the aromatic thiocyanate unit across the C-C triple bond in **1a**. $PdCl_2(PhCN)_2$, tris(*t*-butyl)phosphine as ligand (derived from Fu' s salt[18]) and triethylamine in DMF at 100 °C generated the benzoxathiin **2a** in 4 h with 35% yield. Various other ligands gave no better results. A breakthrough was achieved using XantPhos, which led to an excellent yield of 93% (for full optimisation details, see Supporting Information).

Scope of aromatic thiocyanates

With these conditions in hand, we explored the scope and limitations of this transformation (Scheme 2).



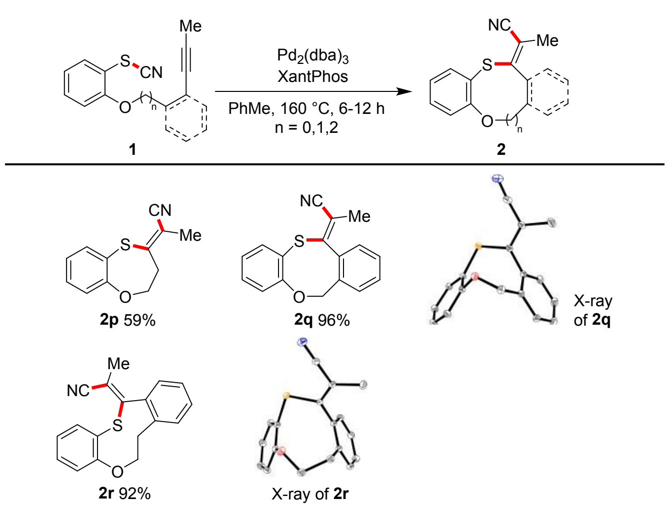
Scheme 2 Intramolecular cyanosulfenylation with aromatic thiocyanates. Reaction conditions: **1** (1.00 equiv.), $PdCl_2(PhCN)_2$ (10 mol%), XantPhos (20 mol%), NEt_3 (5.00 equiv.), DMF (20 mM), 100 °C, 7 h. [a] Large scale (1.5 mmol, 93%), $Pd(PPh_3)_4$ (5 mol%), SPhos (20 mol%), 160 °C, 3 h, PhMe (20 mM). [b] *Z*-isomer is shown also in case it is the minor isolated product because that is consistent with the plausible mechanism; *E*-isomer arises as result of a strong push-pull-system.[19] [c] $Pd(PPh_3)_4$ (5 mol%), SPhos (20 mol%), 160 °C, 6 h, DMF (20 mM). [d] $Pd(PPh_3)_4$ (5 mol%), SPhos (20 mol%), 110 °C, 3 h, DMF (20 mM). X = O, $(CH_2)_m$; Y = $(CH_2)_n$; m, n = 0,1,2.

Substrates with aliphatic termini were smoothly transformed and yielded products **2a**-**2c** in 71-94% yield. A 1,3-diyne unit reacted to enyne **2d** (46%). Differently substituted aromatic termini were tolerated and furnished products **2e**-**2k** in up to 91% yield. However, mixtures of *E*/*Z*-isomers were found because of the highly polarized character of the emerging tetrasubstituted olefin moiety. In these cases, the thioacrylonitrile moiety, as a strong push-pull-system, easily stabilizes a zwitterionic structure.[19] The positive charge is well stabilized at the sulphur and the negative charge next to the aryl substituent. This formal single bond character allows rotation leading to isomeric mixtures.[20]

Furthermore, **2l** (10%) and **2m** (34%) were synthesised from two alkenes as starting materials to demonstrate that also other π-systems can be employed in our protocol. To address smaller ring sizes the tether between the aromatic ring system and the C-C triple bond was shortened to afford substituted benzothiophene **2o** as the result of a subsequent isomerisation to the more stabilized aromatic system. A further shortening led not to an isolable four-membered ring benzothiete, but to a 3-cyano-substituted benzothiophene, as proved by X-ray crystallography.[21]

Seven- to nine-membered ring systems

We varied the ring size also in the opposite direction by increasing the tether length. In moderate to excellent yields the seven-membered ring **2p** (59%), the eight-membered oxathiocin **2q** (96%) and even the nine-membered oxathionin derivative **2r** (92%) were obtained. The structures of the latter two compounds were proved by X-ray crystallography (Scheme 3). The formation of a ten- and a twelve-membered ring system was unsuccessful.[22]



Scheme 3 Intramolecular cyanosulfenylation for large ring synthesis. Reaction conditions: **1** (1.00 equiv.), $Pd_2(dba)_3$ (10 mol%), XantPhos (20 mol%), PhMe (20 mM), 160 °C, 6-12 h.

Scope of aliphatic thiocyanates

Next, we focused on the scope with respect to aliphatic thiocyanates (Scheme 4). We realized that higher temperatures are required to enable the transformation. This observation might be traced back to a stronger S-CN bond (because of its non-conjugated nature) and/or the lack of preorganisation. Hence, a complete reoptimisation of the reaction conditions was necessary (see Supporting Information). Finally, $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ and the use of toluene as solvent and a reaction temperature of 160 °C proved to be the optimal choice. Under

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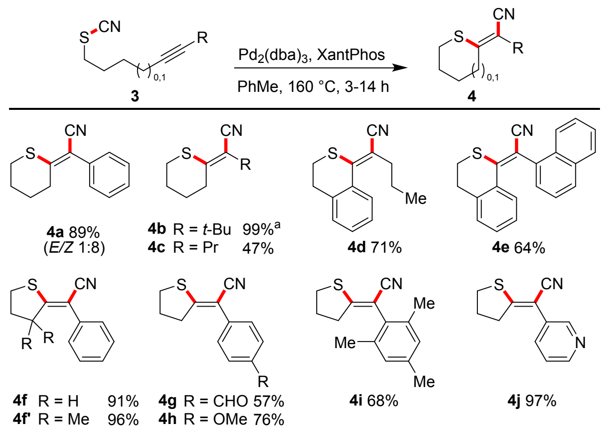
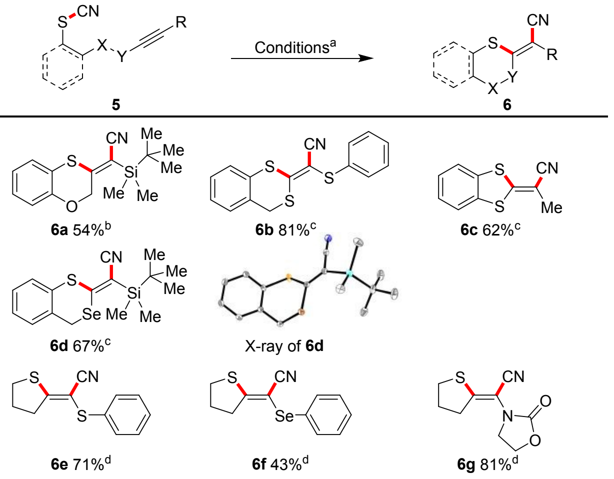
these conditions **4a** was obtained in 89% yield. The successful synthesis of products **4b**-**4d** shows that the reaction tolerates aliphatic termini, as well as a conjugated triple bond as exemplified in isothiochromene **4d**. The motif of a molecular switch was achieved with the synthesis of **4e** (64%). The generation of five-membered exocyclic thioenol ethers also proceeded smoothly. Electron-poor (**4g**), electron-rich (**4h**), sterically encumbered (**4i**), aromatic and heteroaromatic (**4j**) termini also permit the transformation. Compound **4f'** was prepared to investigate whether an acceleration of the reaction by a Thorpe-Ingold effect is be observed; the effect was small.[23]



Scheme 4 Intramolecular cyanosulfenylation with aliphatic thiocyanates. Reaction conditions: **3** (1.00 equiv.), Pd$_2$(dba)$_3$ (10 mol%), XantPhos (20 mol%), PhMe (20 mM), 160 °C, 3-14 h. [a] Pd(PPh$_3$)$_4$ (5 mol%), SPhos (20 mol%), 160 °C, 3 h, PhMe (20 mM).

Multiple heteroatom-substitution

Because we have a special interest in multiply hetero-substituted C-C double bonds, we subjected several α- and α,α'-(di)substituted triple bonds to the reaction conditions (Scheme 5).

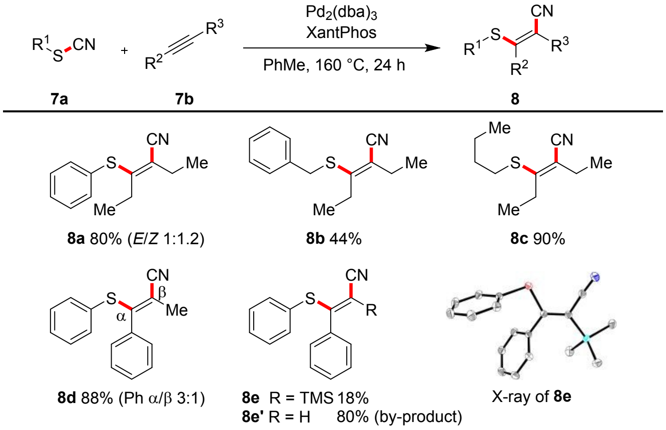


Scheme 5 Cyanosulfenylation of heterosubstituted triple bonds. [a] Reaction conditions: **5** (1.00 equiv.). [b] Pd(PPh$_3$)$_4$ (5 mol%), SPhos (20 mol%), 110 °C, 3 h, DMF (20 mM). [c] PdCl$_2$(PhCN)$_2$ (10 mol%), XantPhos (20 mol%), NEt$_3$ (5.00 equiv.), DMF (20 mM), 100 °C, 3-7 h. [d] Pd$_2$(dba)$_3$ (10 mol%), XantPhos (20 mol%), 160 °C, 3 h, PhMe (20 mM).

This allowed a diastereoselective access to the corresponding doubly or triply heterosubstituted olefin moieties in moderate to good yields. TBS-substituted triple bonds (e.g. **6a**, **6d**), and also the very electron-rich mono- or bis-substituted triple bonds with sulphur (**6b**, **6c**, **6e**) and selenium (**6d**, **6f**) were successfully transformed. An ynamide furnished the sulphur/nitrogen-substituted (*E*)-alkene **6g** in 81%.

Intermolecular cyanosulfenylation

All the transformations described so far proceeded in an intra-molecular manner. With an excess of alkyne (2.0 equiv.) and the catalytic system of Pd$_2$(dba)$_3$ and Xantphos in toluene at 160 °C we were able to realize an intermolecular variant (Scheme 6). 3-Hexyne was converted in yields of 44-90% into the tetrasubstituted alkenes **8a-8c**. The attack to methylphenyl acetylene afforded in 88% a regioisomeric mixture (3:1); the steric and electronic differentiation of the two acetylenic carbons seems not high enough to lead to a clear preference of the thiopalladation step. In contrast, with phenyl trimethylsilyl acetylene only one regioisomeric product **8e** was formed (compare also X-ray crystal structure); however, as the major product desilylated trisubstituted olefin **8e'** was found.



Scheme 6 Intermolecular cyanosulfenylation with different thiocyanates. Reaction conditions: **7a** (1.00 equiv.), **7b** (2.00 equiv.), Pd$_2$(dba)$_3$ (10 mol%), XantPhos (20 mol%), PhMe (20 mM), 160 °C, 24 h.

Thiopalladation-carbopalladation cascade with cyanide transfer

Our ultimate goal was to extend the sequence that starts with the thiopalladation by further carbopalladation steps. The reductive elimination of the Pd should then occur as the final step, generating a C-CN bond. Such an approach using oligoalkynes would lead to a formal 1,4- or 1,6-cyano-sulfenylation with a conjugated double bond system in between (Scheme 7). To successfully perform such a cascade, the carbo-palladation step must be faster than the reductive elimination of Pd forming the C-CN bond. Initial experiments using model compound **9a** and trimethylphosphine as ligand for Pd showed that a thiopalladation-carbopalladation sequence is possible. However, as final step a protodepalladation occurred and thus the cyano moiety was not found in the product (for X-

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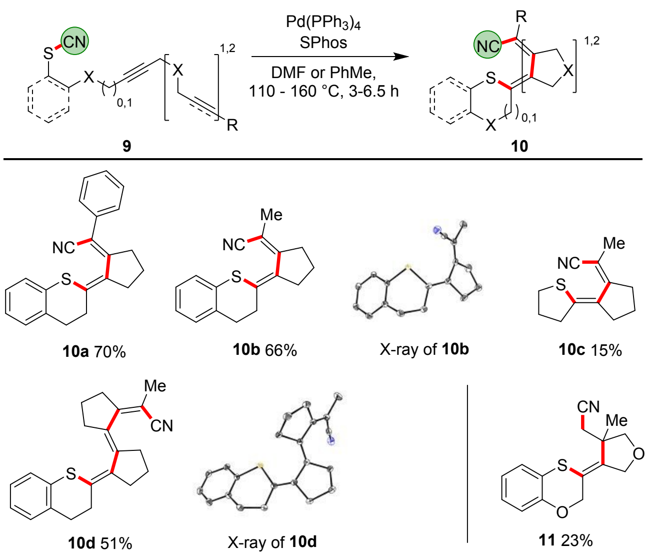
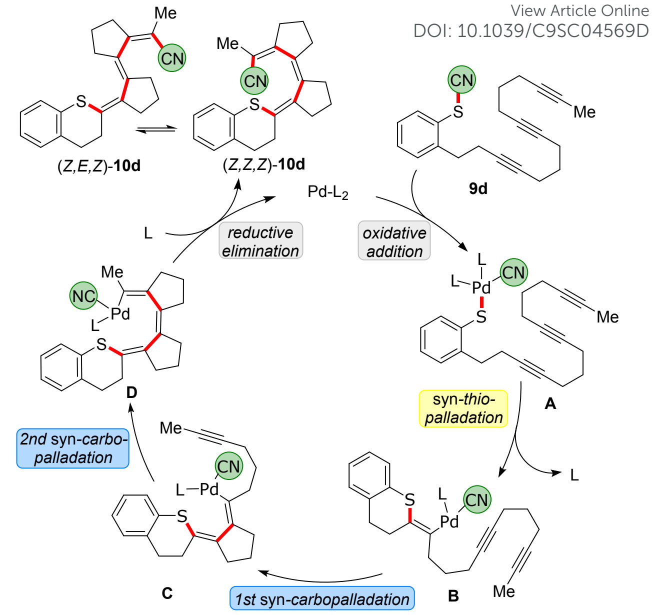


Scheme 7 Thiopalladation/carbopalladation/(carbopalladation)/cyanide transfer cascades with translocation of the CN group over four or six atoms. Product **9** uses an enyne as starting material. Conditions: **7** (1.00 eqiuv.), $Pd(PPh_3)_4$ (5 mol%), SPhos (20 mol%), 110 - 160 °C, 3-7 h, DMF or PhMe (20 mM).

ray analysis of this undesired product **10a'**, see Supporting Information). Reoptimisation studies revealed that the best results are obtained with SPhos and $Pd(PPh_3)_4$ as Pd source. The 1,4-cyanosulfenylation products **10a** and **10b** were obtained in yields of 66-70%. Because the conditions had been optimised for aryl thiocyanates, we expected a much lower yield for cascades starting with alkyl thiocyanates. Indeed, compound **10c** was obtained in only 15% yield. The thiopalladation-carbopalladation-carbopalladation cascade, generating one C-S and three C-C bonds in one step, yielded push-pull-substituted triene **10d** in 51% yield. X-ray crystallography unequivocally showed the translocation of the cyano group; the central double bond has isomerized to avoid a helical arrangement.[24] First unoptimised experiments with an alkyne-alkene system, furnishing **11**, demonstrated that, after formation of the tetrasubstituted double bond, the subsequent carbopalladation also allows the generation of an C(sp^3)-CN bond.[25]

Proposed mechanism

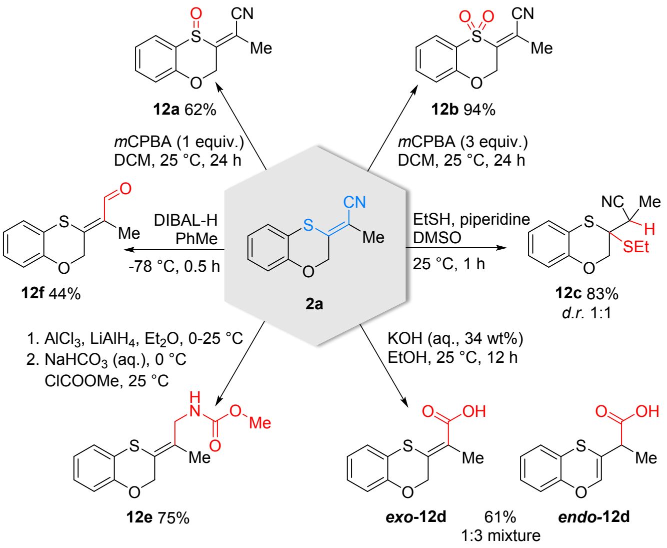
A plausible mechanism of the thiopalladation/carbopalladation/carbopalladation/cyanide transfer cascade to **10d**, based on our additional experimental results[26] (such as protodepalladation) and previously reported carbopalladation cascades,[10-12] is depicted in Scheme 8. After the oxidative addition of the Pd catalyst into the S-CN bond of **9d**, a thiopalladation occurs (**A** → **B**). Instead of delivering the CN group via reductive elimination of the Pd to the emerging double bond, the sequence continues by a first *syn*-carbopalladation to yield **C**. A repetition with another triple bond affords **D**. As terminating step, the C(sp^2)-CN bond is formed by reductive elimination of the Pd to furnish **E**. Because a strongly push-pull-substituted oligoene is formed, the double bonds are much weaker than in non-push-pull-substituted oligoenes; thus, isomerisation from (*Z,Z,Z*)-**10d** to (*Z,E,Z*)-**10d** might happen relatively easily.



Scheme 8 Proposed mechanism of the thiopalladation/carbopalladation/carbopalladation/cyanide transfer cascade.

Follow-up chemistry

To demonstrate the versatility of the thioacrylonitrile moiety, some postsynthetic functionalisations with **2a** were performed (Scheme 9). Depending on the amount of *m*CPBA, we were able to prepare either sulfoxide **12a** or sulfone **12b** in good to excellent yields, thus transforming the strongly polarized olefin into very electron-poor olefins. A Michael addition with ethanethiol led to a diastereomeric mixture of **12c** in 83% yield. Furthermore, the hydrolysis of the nitrile with aqueous KOH gave access to the carboxylic acids ***exo*-12d** and ***endo*-12d**. The partial reduction of the Michael system trapped by methyl chloroformate lead to carbamate **12e** in a good yield of 75%. Reaction of **2a** with DIBAL-H furnished the aldehyde **12f** in a moderate yield.



Scheme 9 Follow-up chemistry.

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Conclusions

In conclusion, we have developed a Pd-catalysed *syn*-1,2-cyanosulfenylation of internal alkynes to access tetra-substituted double bonds with sulphur and cyano in adjacent positions. Both aromatic and aliphatic thiocyanates undergo the reaction. Various substitution patterns of the C-C triple bond are tolerated, such as aliphatic and aromatic residues, but also heteroatoms such as sulphur, selenium, silicon and nitrogen. Our methodology facilitates access to tetrasubstituted olefins with four different elements as substituents of the double bond. The reaction works in an intramolecular manner paving the way to five-, six-, seven-, eight, and nine-membered ring systems, but also in an intermolecular way leading to acyclic compounds. By offering further alkyne moieties the transformation was extended to a thiopalladation/carbopalladation/(carbopalladation) cascade with translocation of the cyano group over four or six carbon atoms, generating up to four new bonds in one step.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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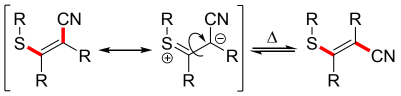

20 The configurational stability of *E*- and *Z*-isomers of **2e** was investigated in additional experiments under the reaction conditions. The *E*-configured starting material shows the generation of the *Z*-configured counterpart and *vice versa*. For more information, see Supporting Information.
21 CCDC 1948156 (**2a**), 1948157 (**2e**), 1969697 (**2q**), 1969698 (**2r**) 1948158 (**6d**), 1996969 **(8e)**1948159 (**10b**), 1948160 (**10d**), 1948161 (**2s**, SI) and 1948162 (**10a'**, SI) contain the supplementary crystallographic data for this paper.
22 For the synthesis of the starting material for larger rings, see Supporting Information.
23 For respective GC experiments, see Supporting Information.
24 An HPLC experiment directly after the reaction showed the existence of (*Z,Z,Z*)-**8d**, which slowly isomerizes to (*Z,E,Z*)-**8d**. For results of thermal and photochemical experiments, see Supporting Information.
25 The formation of a product from an alkene-alkene system was observed only in traces in GC-MS. For the synthesis of starting material, see Supporting information.
26 Experiments in the presence of TEMPO did not significantly decrease the yield (77% of **2a**); thus, we rule out the involvement of any radical intermediates.

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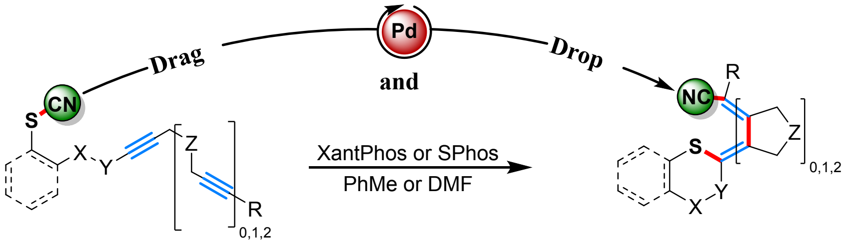

- ✓ 45 examples, yields of up to 99%
- ✓ intra- and intermolecular version
- ✓ broad functional group tolerance
- ✓ up to four new bonds in one step
- ✓ multi-substituted double bonds with up to four different elements

The intra- and intermoleculart Pd-catalysed cyanosulfenylation of internal alkynes enables the formation of tetrasubstituted thioacrylonitriles with up to four different elements as substituents and is extended to oligoyne systems leading to conjugated oligoenes and a cyanide transfer over four or six atoms.