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An Interrupted Pummerer/Nickel-Catalysed Cross-Coupling Sequence

Miles H. Aukland,^[a] Fabien J. T. Talbot,^[a] José A. Fernández-Salas,^[a] Matthew Ball,^[b] Alexander P. Pulis,^[a] and David J. Procter^{*[a]}

Abstract: An interrupted Pummerer/Ni-catalysed cross-coupling strategy has been developed and used in the elaboration of styrenes. The operationally simple method can be carried out in one-pot, involves the direct formation of stable alkenyl sulfonium salt intermediates, utilises a commercially available sulfoxide, catalyst and ligand, operates at ambient temperature, accommodates sp , sp^2 and sp^3 -hybridised organozinc coupling partners, and delivers functionalised styrene products in high yields over two-steps. An interrupted Pummerer/cyclisation approach has also been used to access carbo- and heterocyclic alkenyl sulfonium salts for the cross-coupling.

Transition metal-catalysed cross-couplings are an indispensable tool for the construction of carbon-carbon bonds.¹ In addition to traditional electrophilic partners used in such couplings (e.g. halogens, triflates, etc.), sulfur-based partners have, somewhat surprisingly given their reputation as catalyst poisons,² emerged as willing participants in such transformations and are highly valuable, alternative feedstocks.^{3–6} Recent developments have shown that couplings can be achieved using thiols, sulfides, sulfoxides, sulfones, and sulphonamides.³ By comparison, sulfonium salts have been greatly underexploited as coupling partners.^{4–6} In the majority of cases, sulfonium cross-couplings are carried out using palladium catalysts. As the need to move towards the use of inexpensive first row transition metals is now well-appreciated, nickel is an ideal candidate for many metal-catalysed processes due to its low cost and high natural abundance.⁷ Unfortunately, only three isolated examples describe the use of nickel catalysts for the cross-coupling of sulfonium salts (Scheme 1A).^{4a,6g} In these cases, sulfonium salts are typically accessed from sulfur-containing substrates by alkylation of sulfur.^{4a,6g}

Activated sulfoxides are excellent electrophiles and can be used selectively to generate functionality at the expense of C–H bonds in aromatic systems via interrupted Pummerer processes.^{8,9} In contrast, analogous interrupted Pummerer reactions of alkenes, that generate alkenyl sulfonium salts, have rarely been exploited in synthesis.^{10,11} We envisaged that, upon treatment with an activated sulfoxide, styrene derivatives would undergo an interrupted-Pummerer process to selectively form alkenyl sulfonium salts and that these crystalline, bench-stable

intermediates could then be employed as electrophilic coupling partners in base metal-catalysed carbon-carbon bond formation. Styrene derivatives are prevalent in a wide variety of pharmaceutical compounds and are ubiquitous in nature (Scheme 1B).¹² The synthesis of stilbenes is typically achieved through Mizoroki–Heck couplings using palladium catalysts¹³ and the few nickel catalysed processes¹⁴ require elevated temperatures or specialised catalysts.¹⁵ Alternatively, substituted stilbenes can be accessed via styrenyl halides¹⁶ but these can be hard to access^{17,18} and unstable.

A. Previous work: Metal-catalysed cross-coupling of sulfonium electrophiles

Pd cat. ■ few examples ■ aryl & benzyl salts

Ni cat. ■ only three isolated examples ■ benzyl & alkenyl salts

■ Underexploited sulfonium salts
■ Salts typically formed in a stepwise-fashion from sulfur-containing substrates

B. The importance of the styrene motif in target synthesis

C. This work: Interrupted Pummerer/Ni-catalysed sulfonium cross-coupling

Scheme 1. A. Underexploited sulfonium salts in metal-catalysed cross-coupling. B. Selected bioactive natural and non-natural styrene-containing compounds. C. An interrupted Pummerer/Ni-catalysed cross-coupling strategy.

Herein we report an operationally simple, interrupted Pummerer/Ni-catalysed cross-coupling strategy and its application in the elaboration of styrenes. The sequence has broad scope, exploits bench-stable alkenyl sulfonium salt intermediates formed directly from non-sulfur containing substrates, utilises commercial sulfoxide, catalyst and ligand, and can be carried out in one-pot at ambient temperature (Scheme 1C). An interrupted Pummerer sulfenylation/cyclisation approach has also been developed to access carbo- and heterocyclic alkenyl sulfonium salts for cross-coupling.

We began our studies by investigating the interrupted Pummerer reaction of styrene **1a**. Gratifyingly, when **1a** was

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treated with either dimethyl sulfoxide (DMSO) or commercial tetrahydrothiophene-S-oxide (THTSO), in combination with triflic anhydride, the corresponding sulfonium salts were formed quantitatively (by ^1H NMR), isolated in excellent yields, and their structures confirmed by X-ray crystallographic analysis (Scheme 2).¹⁹

Scheme 2. Direct, convenient and high yielding access to bench stable sulfonium salts: Interrupted Pummerer reactions of styrene with activated sulfoxides. [a] Using DMSO. [b] Using tetrahydrothiophene-S-oxide.

After optimisation of the interrupted Pummerer/Ni-catalysed cross-coupling (see supporting information), a one-pot version of the process was trialled on a variety of styrene derivatives **1a-q** and in all cases the coupling products **3a-q** were isolated in moderate to excellent yield (Scheme 3). To illustrate the scalability of the process, **3a** was prepared on a gram scale in 82% overall yield. Substrates bearing alkyl (**3b**), thiomethyl (**3d**), halogen (**3e-g**), trifluoromethyl (**3h** and **3i**), and ester (**3c** and **3j**) functional groups all underwent smooth sulfenylation and Ni-catalysed coupling with *p*-methoxyphenylzinc chloride. *ortho*-Substituents did not hinder the efficiency of the process and **3g** and **3h** were formed in good overall yield. Di-substituted styrenes could also be employed and gave the corresponding tri-substituted alkene products in good yields (**3k-m**). Pleasingly, the sulfonium salt Negishi cross-coupling occurred selectively even when the substrate contained an alternative pinacolato boron coupling handle (formation of **3n**). Vinyl ferrocene reacted selectively to give **3o** in 75% isolated yield: Ferrocene-substituted olefins have been investigated for their anticancer activity.²⁰ The interrupted Pummerer/Ni-catalysed coupling process can be used to *derivatise* stilbenes (preparation of **3l**) as well as simply to prepare them. Interestingly, upon exposure to the standard conditions, a mixture of *E/Z* stilbene isomers converges to give a single *E*-sulfonium salt²¹ that then undergoes stereoretentive coupling to give *E*-**3l**. Finally, the one-pot interrupted Pummerer/Ni-catalysed coupling was used to manipulate complex, biologically-relevant scaffolds: the methyl ester of Bexarotene, an FDA approved antineoplastic agent,²² and the complex olefin derived from estrone, underwent the one-pot process to give tri-substituted alkene **3p** (58% isolated yield, 81% brsm)²³ and **3q** (44% isolated yield), respectively. The use of *p*-methoxystyrene led to side-products from acid-mediated decomposition.

Scheme 3. Scope of the styrene coupling partner in a one-pot, interrupted Pummerer/Ni-catalysed cross-coupling. Yields determined by ^1H -NMR using MeNO_2 as internal standard. Isolated yields in parentheses.

Using *para*-fluorostyrene, we next assessed the scope of the interrupted Pummerer/Ni-catalysed coupling from the perspective of the nucleophilic organozinc coupling partner (Scheme 4). *Ortho*-, *meta*-, and *para*-substituted arylzinc reagents were all successfully coupled to give products **3r-y** in good to excellent yield. The presence of sensitive functionalities did not hamper the reaction; for example, nitrile **3v** and heteroaryl products **3ab** and **3ac** were obtained in good yield. In addition to aryl organozinc reagents, sp^3 -hybridised organozincs proved to be competent coupling partners; the use of primary and secondary alkylzincs delivered the expected coupling products in good overall yield (**3z**, **3ad** and **3ae**). Similarly, alkynylzinc reagents were shown to be effective partners (**3af** and **3ag**) and their use enabled convenient access to conjugated enyne motifs; structures of interest due to their presence in various bioactive marine natural products.²⁴

Scheme 4. Scope of the organozinc coupling partner in a one-pot, interrupted Pummerer/Ni-catalysed cross-coupling. Yields determined by ^1H NMR using MeNO_2 internal standard. Isolated yields in parentheses. [a] 10 mol% $\text{Ni}(\text{PCy}_3)_2\text{Cl}_2$ used.

Metal-free activation of the alkenes proceeds *via* an interrupted Pummerer pathway in which the styrenyl double bond acts as a nucleophile and attacks the activated sulfoxides at sulfur.⁹ Subsequent deprotonation of the cationic intermediates **A** generates bench stable, crystalline alkenyl sulfonium salts (Scheme 5A). The cross-coupling likely involves *in situ* formation of a low-valent nickel species and oxidative addition into the C–S bond to give Ni(II) intermediates **B**.^{25,26} Following transmetalation, reductive elimination from intermediate **C** delivers the coupling product (Scheme 5B).

Scheme 5. Mechanistic proposal for the two stages of the interrupted Pummerer/Ni-catalysed cross-coupling sequence.

We have carried out preliminary studies on extending the approach to alternative π -nucleophiles. Arene **4** underwent regioselective sulfenylation and Ni-catalysed cross-coupling of the resultant aryl sulfonium salt **5** with *p*-methoxyphenylzinc

chloride gave **6** in 62% overall yield. Similarly, phenylacetylene **7** underwent interrupted Pummerer/Ni-catalysed cross-coupling to give **9** in moderate yield via alkenyl sulfonium salt **8** (Scheme 6).²⁷

Scheme 6. Extension of the interrupted Pummerer/Ni-catalysed cross-coupling strategy to arene and alkyne coupling partners. [a] 2.2 equiv. K_2CO_3 used.

Finally, subjecting aryl-containing alkyne **10a** to the interrupted Pummerer conditions triggered cyclisation²⁸ and alkenyl sulfonium salt **11a** was obtained in 84% isolated yield. Due to the greater steric encumbrance of the C–S bond in trisubstituted **12a**, a short optimisation study was required to identify conditions for the Ni-catalysed cross-coupling of these salts with aryl zinc reagents (see supporting information): The combination of nickel(II) chloride and JohnPhos proved optimal for the coupling and tetra-substituted olefin **12a** was isolated in 80% yield.

Scheme 8. Scope of the interrupted Pummerer/cyclisation/Ni-catalysed cross-coupling sequence. Yields determined by ^1H -NMR using a MeNO_2 internal standard. Isolated yields in parentheses.

Bench stable alkenylsulfonium salts **11b–e** were next prepared from the corresponding alkynes **10b–e** and utilised in the Ni-catalysed cross-coupling to give products **12b–e** in moderate to high overall, isolated yield. The structure of sulfonium salt **11d** was confirmed by X-ray crystallographic analysis. Both electron-donating and electron-withdrawing substituents were tolerated (formation of **12b** and **12c**), as were heteroatoms in the tether between alkyne and arene: The later

substrates delivered heterocyclic products **12d** and **12e** in good yield.

In summary, an interrupted Pummerer process, using a readily available sulfoxide, activates styrenes under metal-free conditions. The resulting bench stable alkenyl sulfonium salts undergo Ni-catalysed Negishi cross-coupling with commercial ligands and catalysts to give high value products. The versatile sequence can be carried out in one-pot, embraces a range of organozinc partners, and can form di-, tri-, and tetra-substituted alkene products. Finally, interrupted Pummerer activation and sulfonium salt formation can be extended to arenes and alkynes, and in the later case, has been used to simultaneously trigger cyclisation.

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Keywords: Pummerer • sulfoxide • sulfonium salt • nickel catalysis • cross-coupling

- [1] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085.
- [2] a) J. Dunleavy, *Platinum Metals Rev.* **2006**, *50*, 110-110; b) N. S. Nasri, J. M. Jones, V. A. Dupont, A. Williams, *Energy & Fuels* **1998**, *12*, 1130-1134; c) X. Tiancun, A. Lidun, *Catal. Lett.* **1992**, *12*, 287-296.
- [3] a) Z.-Y. Tian, Y.-T. Hu, H.-B. Teng, C.-P. Zhang, *Tetrahedron Lett.* **2018**, *59*, 299-309; b) F. Pan, Z.-J. Shi, *ACS Catal.* **2014**, *4*, 280-288; c) L. Wang, W. He, Z. Yu, *Chem. Soc. Rev.* **2013**, *42*, 599-621; d) S. G. Modha, V. P. Mehtaz, E. V. Van der Eycken, *Chem. Soc. Rev.* **2013**, *42*, 5042-5055; e) S. R. Dubbaka, P. Vogel, *Angew. Chem. Int. Ed.* **2005**, *44*, 7674-7684; f) T.-Y. Luh, Z.-J. Ni, *Synthesis* **1990**, 89-103.
- [4] a) S. Zhang, D. Marshall, L. S. Liebeskind, *J. Org. Chem.* **1999**, *64*, 2796-2804; b) J. Srogl, G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1997**, *119*, 12376-12377.
- [5] a) H. Minami, S. Otsuka, K. Nogi, H. Yorimitsu, *ACS Catal.* **2018**, *8*, 579-583; b) H. Kawashima, T. Yanagi, C.-C. Wu, K. Nogi, H. Yorimitsu, *Org. Lett.* **2017**, *19*, 4552-4555; c) D. Vasu, H. Yorimitsu, A. Osuka, *Synthesis* **2015**, *47*, 3286-3291; d) D. Vasu, H. Yorimitsu, A. Osuka, *Angew. Chem. Int. Ed.* **2015**, *54*, 7162-7166.
- [6] a) Z.-Y. Tian, S.-M. Wang, S.-J. Jia, H.-X. Song, C.-P. Zhang, *Org. Lett.* **2017**, *19*, 5454-5457; b) S.-M. Wang, X.-Y. Wang, H.-L. Qin, C.-P. Zhang, *Chem. - Eur. J.* **2016**, *22*, 6542-6546; c) X.-Y. Wang, H.-X. Song, S.-M. Wang, J. Yang, H.-L. Qin, X. Jiang, C.-P. Zhang, *Tetrahedron* **2016**, *72*, 7606-7612; d) S.-M. Wang, H.-X. Song, X.-Y. Wang, N. Liu, H.-L. Qin, C.-P. Zhang, *Chem. Commun.* **2016**, *52*, 11893-11896; e) P. Cowper, Y. Jin, M. D. Turton, G. Kociok-Köhn, S. E. Lewis, *Angew. Chem. Int. Ed.* **2016**, *55*, 2564-2568; f) P. Cowper, A. Pockett, G. Kociok-Köhn, P. J. Cameron, S. E. Lewis, *Tetrahedron* **2018**, *74*, 2775-2786; g) J. F. Hooper, A. B. Chaplin, C. González-Rodríguez, A. L. Thompson, A. S. Weiler, M. C. Willis, *J. Am. Chem. Soc.* **2012**, *134*, 2906-2909; h) H. Lin, X. Dong, Y. Li, Q. Shen, L. Lu, *Eur. J. Org. Chem.* **2012**, 4675-4679; i) C. Vanier, F. Lorgé, A. Wagner, C. Mioskowski, *Angew. Chem. Int. Ed.* **2000**, *39*, 1679-1683.
- [7] S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299-309.
- [8] a) N. E. Shevchenko, V. G. Nenajdenko, E. S. Balenkova, *Synthesis* **2003**, *8*, 1191-1200; b) N. E. Shevchenko, A. S. Karpov, E. P. Zakurdaev, V. G. Nenajdenko, E. S. Balenkova, *Chem. Heterocycl. Compd.* **2000**, *36*, 137-143; c) V. G. Nenajdenko, P. V. Verteletzkiy, E. S. Balenkova, *Sulfur Lett.* **1996**, *20*, 75-84.
- [9] a) H. Yorimitsu, *Chem. Rec.* **2017**, *17*, 1-13; b) A. P. Pulis, D. J. Procter, *Angew. Chem. Int. Ed.* **2016**, *55*, 9842-9860; c) L. H. S. Smith, S. C. Coote, H. F. Sneddon, D. J. Procter, *Angew. Chem. Int. Ed.* **2010**, *49*, 5832-5844.
- [10] a) V. G. Nenajdenko, P. V. Verteletzkiy, I. D. Gridnev, N. E. Shevchenko, E. S. Balenkova, *Tetrahedron* **1997**, *53*, 8173-8180; b) J.-I. Matsuo, H. Yamanaka, A. Kawana, T. Mukaiyama, *Chemistry Lett.* **2003**, *32*, 392-393; For the interrupted Pummerer reaction of an alkene to give an allylsulfonium salt, see: c) G. Hu, J. Xu, P. Li, *Org. Lett.* **2014**, *16*, 6036-6039; d) V. V. Veselovsky, V. A. Dragan, A. M. Moiseenkov, *Tetrahedron Lett.* **1988**, *29*, 6637-6639; e) B. B. Snider, N. J. Hrib, L. Fuzesi, *J. Am. Chem. Soc.* **1976**, *98*, 7115-7117.
- [11] For the synthetic exploitation of aryl sulfonium salts, see: a) D. Kaldre, B. Maryasin, D. Kaiser, O. Gajsek, L. González, N. Maulide, *Angew. Chem. Int. Ed.* **2017**, *56*, 2212-2215; b) T. Stopka, M. Niggemann, N. Maulide, *Angew. Chem. Int. Ed.* **2017**, *56*, 13270-13274; c) D. Kaiser, L. F. Veiros, N. Maulide, *Adv. Synth. Catal.* **2017**, *359*, 64-77; d) H. J. Shrivies, J. A. Fernández-Salas, C. Hedtke, A. P. Pulis, D. J. Procter, *Nat. Commun.* **2017**, *8*, 14801-14808; e) T. Yanagi, S. Otsuka, Y. Kasuga, K. Fujimoto, K. Murakami, K. Nogi, H. Yorimitsu, A. Osuka, *J. Am. Chem. Soc.* **2016**, *138*, 14582-14585; f) D. Kaiser, L. F. Veiros, N. Maulide, *Chem. - Eur. J.* **2016**, *22*, 4727-4732; g) J. A. Fernández-Salas, A. J. Eberhart, D. J. Procter, *J. Am. Chem. Soc.* **2016**, *138*, 790-793; h) J. A. Fernández-Salas, A. P. Pulis, D. J. Procter, *Chem. Commun.* **2016**, *52*, 12364-12367; i) A. J. Eberhart, H. J. Shrivies, E. Alvarez, A. Carrer, Y. Zhang, D. J. Procter, *Chem. - Eur. J.* **2015**, *21*, 7428-7434; j) B. Peng, D. Geerdink, C. Farès, N. Maulide, *Angew. Chem. Int. Ed.* **2014**, *53*, 5462-5466; k) B. Peng, X. Huang, L.-G. Xie, N. Maulide, *Angew. Chem. Int. Ed.* **2014**, *53*, 8718-8721; l) X. Huang, M. Patil, C. Farès, W. Thiel, N. Maulide, *J. Am. Chem. Soc.* **2013**, *135*, 7312-7323; m) A. J. Eberhart, D. J. Procter, *Angew. Chem. Int. Ed.* **2013**, *52*, 4008-4011; n) A. J. Eberhart, C. Cicoira, D. J. Procter, *Org. Lett.* **2013**, *15*, 3994-3997; o) X. Huang, S. Klimczyk, N. Maulide, *Synthesis* **2012**, *44*, 175-183; p) X. Huang, N. Maulide, *J. Am. Chem. Soc.* **2011**, *133*, 8510-8513; q) A. J. Eberhart, J. E. Imbriglio, D. J. Procter, *Org. Lett.* **2011**, *13*, 5882-5885.
- [12] a) S. Bradamante, L. Barengi, A. Villa, *Cardiovasc. Drug Rev.* **2004**, *22*, 169-188; b) B. B. Aggarwal, A. Bhardwaj, R. S. Aggarwal, N. P. Seeram, S. Shishodia, Y. Takada, *Anticancer Res.* **2004**, *24*, 2783-2840.
- [13] a) F.-X. Felpin, L. Nassar-Hardy, F. Le Callonnec, Eric Fouquet, *Tetrahedron* **2011**, *67*, 2815-2831; b) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009-3066.
- [14] B. Lin, L. Liu, Y. Fu, S.-W. Luo, Q. Chen, Q.-X. Guo, *Organometallics* **2004**, *23*, 2114-2123.
- [15] a) N. Nowrouzi, M. Zarei, *Tetrahedron* **2015**, *71*, 7847-7852; b) P. K. Suganthya, R. N. Prabhub, V. S. Sridevi, *Tetrahedron Lett.* **2013**, *54*, 5695-5698; c) A. R. Ehle, Q. Zhou, M. P. Watson, *Org. Lett.* **2012**, *14*, 1202-1205; d) Z. Xi, B. Liu, W. Chen, *J. Org. Chem.* **2008**, *73*, 3954-3957; e) S. Ma, H. Wang, K. Gao, F. Zhao, *J. Mol. Catal. A: Chem.* **2006**, *248*, 17-20.
- [16] For an example of a Negishi coupling of styrenyl bromide, see: A. Gavryushin, C. Kofink, G. Manolikakes, P. Knochel, *Tetrahedron* **2006**, *62*, 7521-7533.
- [17] a) M. J. Koh, T. T. Nguyen, H. Zhang, R. R. Schrock, A. H. Hoveyda, *Nature* **2016**, *531*, 459-465; b) P. Pawluć, G. Hreczycho, J. Szudkowska, M. Kubicki, B. Marciniak, *Org. Lett.* **2009**, *11*, 3390-3393; c) C. Morrill, R. H. Grubbs, *J. Org. Chem.* **2003**, *68*, 6031-6034; d) K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410.
- [18] M. R. Kuszpit, M. B. Giletto, C. L. Jones, T. K. Bethel, J. J. Tepe, *J. Org. Chem.* **2015**, *80*, 1440-1445.

- [19] CCDC 1832461 (**2a**), 1832460 (**2b**), 1832454 (**3o**), 1832463 (**E-3p**), 1832462 (**11a**), 1836658 (**11d**) and 1836657 (**11c**).
- [20] a) A. Nguyen, S. Top, P. Pigeon, A. Vessieres, E. A. Hillard, M-A. Plamont, M. Huche, C. Rigamonti, G. Jaouen, *Chem. - Eur. J.* **2009**, *15*, 684-696; b) Y. Leng K. Tan, P. Pigeon, E. A. Hillard, S. Top, M-A. Plamont, A. Vessieres, M. J. McGlinchey, H. Muller-Bunzb, G. Jaouen, *Dalton Trans.* **2009**, 10871-10881; c) O. Buriez, J. M. Heldt, E. Labbe, A. Vessieres, G. Jaouen, C. Amatore, *Chem. - Eur. J.* **2008**, *14*, 8195-8203.
- [21] Stereochemistry of the alkene was confirmed by NMR analysis and nOe studies.
- [22] R. Gniadecki, C. Assaf, M. Bagot, R. Dummer, M. Duvic, R. Knobler, A. Ranki, P. Schwandt, S. Whittaker, *Brit. J. Dermatol.* **2007**, *157*, 433-440.
- [23] Confirmed by NMR and X-ray crystallographic analysis.
- [24] D. J. Faulkner, *Nat. Prod. Rep.* **1999**, *16*, 155-198.
- [25] E. Wenkert, M. E. Shepard, A. T. McPhail, *J. Chem. Soc., Chem. Commun.* **1986**, 1390-1391.
- [26] M. R. Grochowski, T. Li, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2010**, *132*, 12412-12421.
- [27] V. G. Nenajdenko, P. V. Vertelezkij, E. S. Balenkova, *Synthesis* **1997**, 351-355.
- [28] Intramolecular carbosulfenylation of alkenes: a) Z. Tao, K. A. Robb, K. Zhao, S. E. Denmark, *J. Am. Chem. Soc.* **2018**, *140*, 3569-3573; b) F. T. Schevenels, M. Shen, S. A. Snyder, *Org. Lett.* **2017**, *19*, 2-5.

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**An Interrupted Pummerer/Nickel-
Catalysed Cross-Coupling Sequence
for the Elaboration of Styrenes**

Styrenes are activated under metal-free conditions using an interrupted Pummerer process. The resulting, stable alkenyl sulfonium salts undergo Ni-catalysed cross-coupling under simple, mild conditions. The versatile sequence can be carried out in one-pot, embraces a range of organozinc partners, and can form di-, tri-, and tetra-substituted alkene products. Interrupted Pummerer activation of alkynes can also trigger cyclisation and the formation of carbo- and heterocyclic alkenyl sulfonium salts for cross-coupling.