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Synthesis of nitrodienes, nitrostyrenes, and nitrobiaryls through palladium-catalyzed couplings of β-nitrovinyl and *o*-nitroaryl thioethers†

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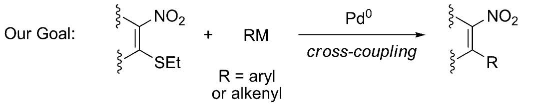
A highly efficient, base-free, mild protocol for the palladium-catalyzed, copper-activated desulfitative couplings of vinyl and aryl β-nitrothioethers generates a wide variety of conjugated nitroorganics. Orthogonality to traditional Suzuki–Miyaura coupling is demonstrated, as well as synthetic utility, through reductive Cadogan cyclization, for the formation of indoles, carbazoles, and pyrroles.

Transition metal-catalyzed cross-couplings are some of the most dependable and effectual methods for forming carbon–carbon bonds.[1] Notwithstanding this, a great challenge remains to develop increasingly chemoselective coupling protocols that operate under mild and neutral conditions. In our burgeoning program investigating the reactivity of conjugated nitroorganics,[2] our endeavours were initially encumbered by the lack of a general, systematic synthesis of 1-nitro-1,3-dienes, with a number of desired substrates apparently synthetically inaccessible. A careful survey of the literature revealed methods that rely on harsh acidic and oxidizing nitration conditions,[3] the Henry reaction of nitromethane with unsaturated carbonyls—a transformation that is severely limited in scope and efficiency,[4] and the addition of zinc cuprates with 1-ethylthio-2-nitroolefins—a process that we found to be similarly limited in terms of the scope of both the electrophile and cuprate.[5] To the best of our knowledge, the literature is devoid of flexible and convergent coupling strategies for the synthesis of conjugated nitroorganics, especially nitrodienes.[6] Thus, we set out to assess the potential for a palladium-catalyzed cross-coupling reaction of a suitably functionalized nitroalkene or nitroarene under neutral conditions, ideally with high chemoselectivity and a broad substrate scope (Scheme 1).



Scheme 1 Desulfitative cross-coupling.

While designing a suitable substrate for the transition metal-catalyzed β-functionalization of nitroalkenes, we were drawn to the recently developed Liebeskind–Srogl cross-coupling of thioesters and boronic acids to form ketones.[7] Whereas the stereoselective formation of β-thioethyl nitroalkenes from α-nitro ketones or *via* oxidation of β-thioethyl nitroalkanes has many precedents,[8] general methods for forming β-triflato or β-halo nitroalkenes are rare.[9] In addition, vinyl sulfides appear to be robust functional groups—in the absence of thiophilic activation. Prior to this present investigation, the literature featured no examples of metal-catalyzed cross-couplings of vinyl thioethers,[10] with the exception of the nickel-catalyzed Kumada coupling of simple vinyl sulfides.[11] The use of Grignard reagents, however, is undesirable because strongly basic nucleophiles readily reduce nitro groups.[12] Our hypothesis was that a highly electron-withdrawing nitro group would sufficiently activate the C(sp^2)–S bond for oxidative addition by palladium(0). In addition, there is a notable absence of examples of Liebeskind–Srogl couplings of alkylthiobenzenes, despite the multitude of known electron-poor 2-alkylthio-*N*-heterocycles.[13] We envisaged that an *ortho*-nitro substituent would similarly activate the aryl thioether for oxidative addition. If successful, ready access to traditional substrates for the Cadogan reductive cyclization would be possible, as would the preparation of non-traditional substrates (*vide infra*).

Initial experiments, based on typical desulfitative coupling conditions[7] for the reaction of *o*-ethylthionitrobenzene (**1a**) with (*E*)-1-hexenylboronic acid (**2a**), were moderately successful (Table 1, entry 1).[14] Gratifyingly, coupling proceeded well at room temperature—that is, without the typical need for heating. The catalyst turnover increased upon varying the solvent from DCM, through benzene and DMF, to methanol (entries 2–5), with the latter resulting in an 86% isolated yield of 1-hexenyl-2-nitrobenzene (**3aa**). Catalyst turnover was the limiting factor (entries 6–8); attempts at minimizing the catalyst loading with additional boronic acid (entry 9) or copper

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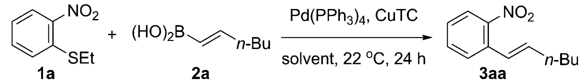
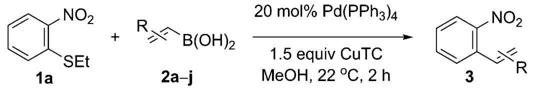
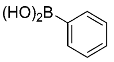
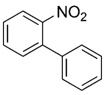
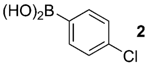
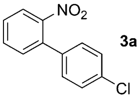
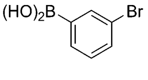
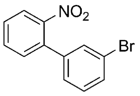
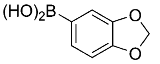
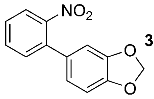
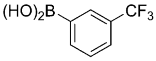
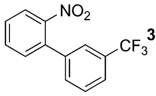
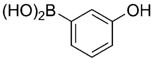
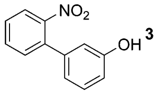
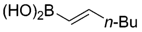
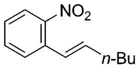
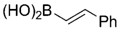
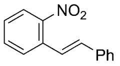
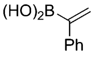
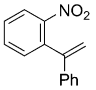
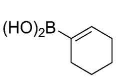
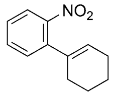
Table 1 Optimization of the coupling for the least-reactive thioether



Entry	$Pd(PPh_3)_4$ [mol%]	CuTC [equiv.]	**2a** [equiv.]	Solvent	Isolated yield [%]
1	20	1.5	3.0	THF	38
2	20	1.5	3.0	CH_2Cl_2	48
3	20	1.5	3.0	Benzene	53
4	20	1.5	3.0	DMF	63
5	20	1.5	3.0	MeOH	86
6	5	1.5	3.0	MeOH	23
7	10	1.5	3.0	MeOH	60
8	15	1.5	3.0	MeOH	67
9	10	1.5	6.0	MeOH	55
10	10	3.0	3.0	MeOH	64
11	10	4.5	3.0	MeOH	64
12	20	1.5	1.5	MeOH	79

Table 2 Cross-couplings of the *o*-nitroaryl thioether **1a** with aryl and vinyl boronic acids



Entry	$RB(OH)_2$	Product	Isolated yield [%][a]
1	 **2b**	 **3ab**	99
2	 **2c**	 **3ac**	96[b]
3	 **2d**	 **3ad**	94[b]
4	 **2e**	 **3ae**	99
5	 **2f**	 **3af**	88
6	 **2g**	 **3ag**	91
7	 **2a**	 **3aa**	86
8	 **2h**	 **3ah**	99
9	 **2i**	 **3ai**	53
10	 **2j**	 **3aj**	83

[a] Isolated yield. [b] No protodehalogenation or halide-coupling observed.

thiophenecarboxylate (CuTC: entries 10 and 11) did not result in exhaustive conversion. Finally, decreasing the content of boronic acid decreased the isolated yield, albeit to only a small extent (entry 12).

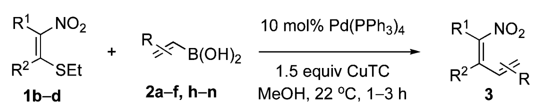
Next, we employed *o*-ethylthionitrobenzene (**1a**) for the synthesis of various *o*-nitrobiaryls and *o*-nitrostyrenes (Table 2). Desulfitative cross-coupling with phenylboronic acid resulted in quantitative conversion to the *o*-nitrobiaryl **3ab** (entry 1). Couplings with both 4-chlorophenylboronic acid and 3-bromophenylboronic acid proceeded with equally high efficiency to yield the biaryl halides **3ac** and **3ad**, respectively (entries 2 and 3). These results are particularly striking because these aryl halides are typical substrates for Suzuki–Miyaura cross-couplings, demonstrating the orthogonal reactivity of aryl sulfides with aromatic halides under base-free cuprous activation. In addition, both electron-rich 2,3-methylenedioxyphenylboronic acid and electron-poor 3-trifluoromethylphenylboronic acid underwent cross-couplings in excellent yields (entries 4 and 5, respectively). The presence of free phenolic protons did not interfere with the transformation, as evidenced by a notable isolated yield (91%) of the biaryl **3ag** (entry 6).

In addition to arylboronic acids, vinylboronic acids were also suitable partners for the coupling reaction. Both (*E*)-hexenylboronic acid (**2a**) and (*E*)-β-styrenylboronic acid (**2h**) underwent smooth couplings to form their expected nitrostyrenes (entries 7 and 8, respectively). α-Styrenylboronic acid underwent coupling, with diminished efficiency, to form the *gem*-diarylethene **3ai** (entry 9). Finally, cyclohexenylboronic acid was also compatible with the coupling protocol (entry 10). Therefore, a wide variety of boronic acids are suitable for the desulfitative couplings of *o*-ethylthionitrobenzene, generating both *o*-nitrobiaryls and *o*-nitrostyrenes in excellent yields.

To further expand the scope of compatible sp^2-hybridized thioether coupling partners, we explored the couplings of the β-nitrovinyl thioethers **1b–d** with both aryl and vinylboronic acids (Table 3). Desulfitative coupling of the vinyl thioethers proceeded rapidly at room temperature, with complete conversion observed at a lower catalyst loading (10 mol%). The cross-couplings of both electron-rich and -poor arylboronic acids proceeded with very high yields (entries 1–5). Heteroarylboronic acids were tolerated as well, as evidenced by the smooth coupling of 3-pyridylboronic acid in 94% yield, although mild heating was required in this case to ensure full conversion (entry 6). An *ortho*-substituted phenylboronic acid underwent cross-coupling with relatively moderate efficiency, presumably due to greater steric hindrance (entry 7).

Cross-couplings of vinyl thioethers with vinylboronic acids provided corresponding 1-nitro-1,3-dienes in good to excellent

Table 3 Cross-couplings of the β-nitrovinyl thioethers **1b–d** with various boronic acids



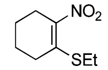
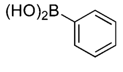
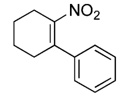
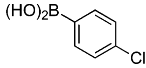
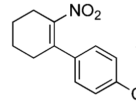
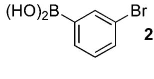
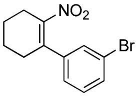
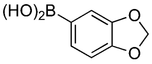
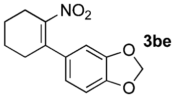
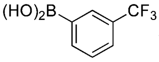
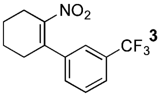
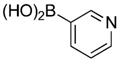
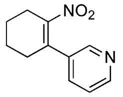
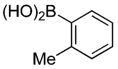
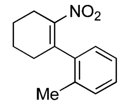
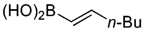
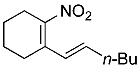
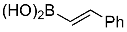
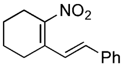
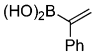
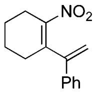
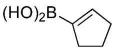
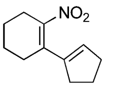
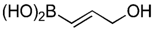
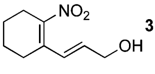
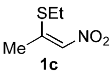
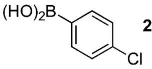
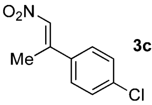
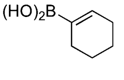
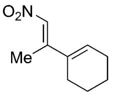
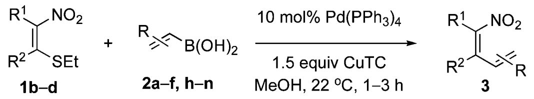
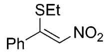
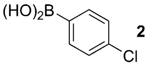
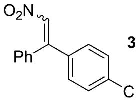
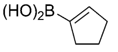
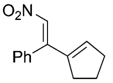
Entry	Thioether	RB(OH)$_2$	Product	Isolated yield [%][a]
1	 **1b**	 **2b**	 **3bb**	99
2	**1b**	 **2c**	 **3bc**	90
3	**1b**	 **2d**	 **3bd**	99
4	**1b**	 **2e**	 **3be**	99
5	**1b**	 **2f**	 **3bf**	96
6[b]	**1b**	 **2k**	 **3bk**	94
7	**1b**	 **2l**	 **3bl**	81
8	**1b**	 **2a**	 **3ba**	86
9	**1b**	 **2h**	 **3bh**	99
10	**1b**	 **2i**	 **3bi**	84
11	**1b**	 **2m**	 **3bm**	82
12	**1b**	 **2n**	 **3bn**	68
13	 **1c**	 **2c**	 **3cc**	90[c]
14	**1c**	 **2j**	 **3cj**	90[c]

Table 3 (*Contd.*)

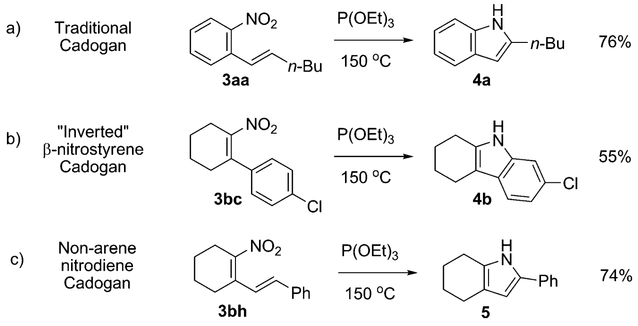


Entry	Thioether	RB(OH)$_2$	Product	Isolated yield [%][a]
15	 **1d**	 **2c**	 **3dc**	94[d]
16	**1d**	 **2m**	 **3dm**	84[c]

[a] Isolated yield. [b] Reaction was performed under reflux. [c] Stereochemistry determined through NOESY-NMR spectroscopic analysis (see the ESI†). [d] Diastereoisomeric ratio was not determined.

yields in short order (Table 3, entries 8–12). Application of the desulfitative cross-coupling protocol to the acyclic β-nitrovinyl thioethers **1c** and **1d** also proved successful (entries 13–16), but, conspicuously, with the loss of the stereochemical integrity of the nitroalkene.[15] Despite isomerization, we isolated the nitrodienes **3cc**, **3cj**, and **3dm** each as a single diastereoisomer, presumably due to sufficient steric bias toward one of the two β-substituents. Notwithstanding, the β-nitrovinyl thioethers underwent facile desulfitative couplings with aryl and vinylboronic acids, with exemplary yields, under mild conditions at room temperature.

o-Nitrostyrenes and *o*-nitrobiaryl compounds are traditional substrates for Cadogan reductive cyclizations to form indoles and carbazoles (Scheme 2a);[16] this lesser-utilized process for indole formation is comparable with the Leimgruber–Batcho indole synthesis, but without the need to prepare β-dimethylamino-2-nitrostyrenes or dinitrostyrenes prior to reduction.[17] Although the Cadogan reductive cyclization has been applied only sparingly in organic synthesis, it has been used widely in the synthesis of polycarbazole and heteroacene electronic materials.[18,19] With ready access to traditional *o*-nitrostyrene substrates, we treated **3aa** with triethyl phosphite to obtain the

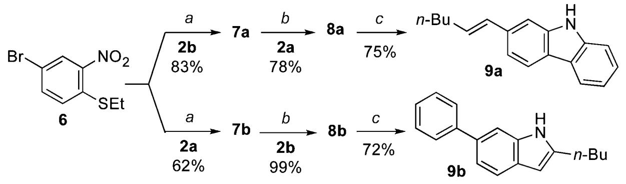


Scheme 2 Cadogan reductive cyclization.

indole **4a** in 76% yield.[20,21] "Inverted" substrates, such as β-nitrostyrene, have previously provided Cadogan products in only a few isolated instances,[22] yet here we found that the β-nitrostyrene **3bc** is a viable substrate for reductive cyclization, generating the indole **4b** (Scheme 2b). The corresponding non-arene reductive Cadogan cyclizations, to generate pyrroles, have not been disclosed previously, perhaps due in part to the lack of reliable methods for forming 1-nitro-1,3-dienes. We found that nitrodienes, such as **3bh**, are amenable to Cadogan conditions, in this case realizing the pyrrole **5** in good yield (Scheme 2c). The cross-couplings of β-ethylthionitroolefins and *o*-ethylthionitrobenzenes described herein provide rapid access to functionalized nitrodienes, nitrostyrenes, and nitrobiaryls, all of which are readily converted into valuable *N*-heteroaromatics.

To fully delineate the inherent power of orthogonal cross-coupling protocols, we prepared the *o*-ethylthionitrobenzene substrate **6** featuring an aryl bromide handle for Suzuki–Miyaura cross-coupling (Scheme 3). Under the desulfitative coupling conditions, substrate **6** reacted with both phenylboronic acid (**2b**) and hexenylboronic acid (**2a**) to generate the biaryl **7a** and the nitrostyrene **7b**, respectively. In each case, neither coupling nor protodebromination occurred at the aryl bromide. Subsequently, we subjected the aryl bromides **7a** and **7b** to Suzuki–Miyaura cross-couplings with the crossed boronic acids. Finally, we subjected the nitroarenes **8a** and **8b** to Cadogan reductive cyclizations to generate the functionalized carbazole **9a** and the 2,6-disubstituted indole **9b**, respectively. Accordingly, chemoselective, orthogonal cross-coupling protocols can be used in tandem to rapidly generate substituted aromatic *N*-heterocycles.

In summary, we have developed a general protocol for the coupling of β-nitrovinyl and *o*-nitroaryl thioethers with boronic acids under chemoselective, mild, base-free conditions. The reaction typically proceeds with high efficiency, generating nitrodienes, nitrostyrenes, and nitrobiaryls of high synthetic value. In particular, otherwise synthetically inaccessible 1-nitro-1,3-dienes can be prepared in excellent yields. Subjecting the reaction products to the conditions of Cadogan reductive cyclization provided rapid access to functionalized indoles, carbazoles, and pyrroles; notably, the use of Cadogan cyclization to form pyrroles had not been reported previously. In addition, the palladium-catalyzed desulfitative coupling is orthogonal to traditional Suzuki–Miyaura conditions, with no observed aryl halide coupling or protodehalogenation. Therefore, this coupling protocol constitutes a substantial advancement in the synthesis of conjugated nitroorganics.



Scheme 3 Orthogonal cross-couplings and Cadogan cyclizations. [a] 20 mol% $Pd(PPh_3)_4$, 1.5 equiv. CuTC, 3 equiv. $RB(OH)_2$, MeOH; [b] 10 mol% $Pd(PPh_3)_4$, K_2CO_3, $RB(OH)_2$, toluene–EtOH–H_2O, reflux; [c] $P(OEt)_3$, reflux.

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