DOI: 10.1002/adsc.201300678

Stereoselective Heck Reactions with Vinyl Sulfoxides, Sulfides and Sulfones

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Received: July 30, 2013; Revised: October 7, 2013; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300678.

Abstract: We report the Heck cross-coupling of notoriously unreactive, but synthetically valuable olefins: vinyl sulfoxides, vinyl sulfones, and vinyl sulfides. Key findings include the importance of the sterically hindered (tri-*tert*-butyl)phosphine ligand and the unique effectiveness of triethylamine as the base. The method is general, *E*-selective, and can be used to synthesize disubstituted or trisubstituted olefins through simple adjustments of stoichiometry.

Keywords: cross-coupling; Heck reaction; palladium; sulfoxides

Although the Heck reaction has become an essential component of the organic chemist's playbook,[1] strongly coordinating substrates are conspicuously absent from most methodology studies, likely because they interfere with the catalytic cycle. Olefins containing a sulfur substituent in any oxidation state (sulfide, sulfoxide, or sulfone) are particularly problematic, and only a handful of successful cross-coupling reactions are known.[2] Coordination of sulfoxides to Pd(II) is in fact well-established, and this interaction has even been employed to control the reactivity of palladium(II) in a number of reactions.[3] We report here that the bulky phosphine complex Pd[P(t-Bu)$_3$]$_2$ in combination with triethylamine as the base delivers an exceptionally active catalyst that can couple a broad-range of sulfur-bearing substrates.

The poor behavior of sulfur-substituted olefins in Heck couplings is unfortunate since the products of these reactions are synthetically versatile. Our interest in this area stemmed from a need to create an optically enriched vinyl sulfoxide to employ in an enantioselective synthesis of the kinamycin core. Vinyl sulfoxides and sulfones are veritable chemical chameleons: they are electrophilic at the β-position[4] and can be rendered electrophilic or nucleophilic at the α-position,[5] they can be interchanged with halides,[6] or reductively cleaved;[2a,4a,b] they can be transformed to sulfur ylides[7] or exploited in the various flavors of Pummerer-type chemistry.[8] Furthermore, the chirality of the sulfur atom in sulfoxides has been used as a stereochemical control element in numerous processes.[9] The current limiting factor in the synthetic value of vinyl sulfoxides is not their synthetic potential, but rather the lack of efficient and general ways to create them. A classic method is the *E*- or *Z*-selective reduction of alkynyl sulfoxides but only a few simple examples have been described.[10] The more recent Horner–Wittig approach leads to predominately *E*-configured products, but these are always contaminated with some *Z*-products (98:2 ratio in the best cases).[11] The sole reports of vinyl sulfoxide cross-couplings are by Carretero and co-workers[2a] and Doucet, Santelli and co-workers.[2b] The Doucet/Santelli procedure features an interesting tetradentate ligand concept, but the forcing conditions (130 °C) and the complexity of the ligand have likely hindered the adoption of this approach by the synthetic community. The Carretero work represents the most general approach to date, but there remain unmet challenges since their conditions employ excess aryl iodides and silver salts. Herein we describe our findings on the chemistry of vinyl sulfoxide, vinyl sulfide, and vinyl sulfone cross-couplings.

We began our investigations by testing Carretero's conditions – optimized for aryl iodides – on our model system **1** (see header of Table 1);[2a] these conditions, however, failed to deliver any product (entry 1) and also did not lead to oxidative addition into the Ar–Br bond. While conditions with Pd(PPh$_3$)$_4$ (entry 2) also failed to yield any desired coupling, a first hint of success was achieved with the Pd[P(t-Bu)$_3$]$_2$/Cs$_2$CO$_3$/DMF combination (entry 3).[12] Buchwald and Fu have shown that the hindered amine base NCy$_2$Me can have a dramatic accelerating effect on Heck couplings.[13] As seen in entry 6,

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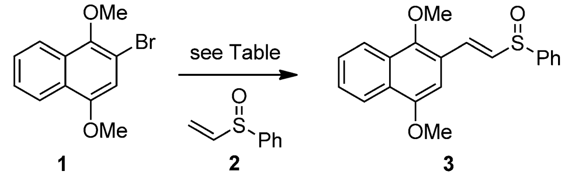
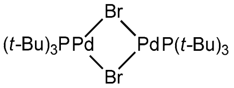
Table 1. Optimization of the catalyst system.

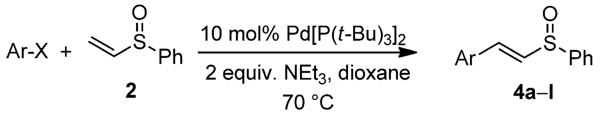


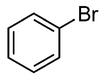
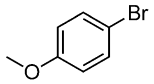
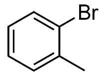
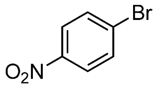
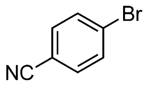
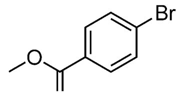
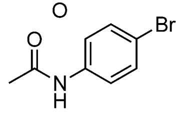
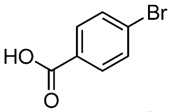
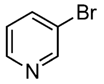
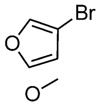
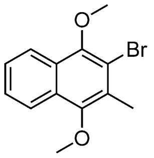
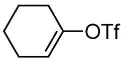
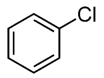
Entry	Catalyst	Base[a]	Solvent	Yield [%]
1	$Pd(OAc)_2$	Ag_2CO_3	DMF	0
2	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	0
3	$Pd[P(t\text{-}Bu)_3]_2$	Cs_2CO_3	DMF	11
4	$Pd[P(t\text{-}Bu)_3]_2$	Ag_2CO_3	DMF	0
5	$Pd[P(t\text{-}Bu)_3]_2$	Cs_2CO_3	dioxane	0
6	$Pd[P(t\text{-}Bu)_3]_2$	NCy_2Me	dioxane	60[b]
7	$Pd[P(t\text{-}Bu)_3]_2$	$N(i\text{-}Pr)_2Et$	dioxane	20[b]
8	$Pd[P(t\text{-}Bu)_3]_2$	DBU	dioxane	0[b]
9	$Pd[P(t\text{-}Bu)_3]_2$	pyridine	dioxane	15[b]
10	**$Pd[P(t\text{-}Bu)_3]_2$**	**NEt_3**	**dioxane**	**93**
11		NEt_3	dioxane	0[b]

[a] The main observable product with inorganic bases was dehalogenation.

[b] Represents % conversion according to ^{1}H NMR; an isolated yield was not determined in these cases.

Table 2. Scope of the Heck reaction with phenyl vinyl sulfoxide.



Entry	Ar-X	t [h]	Conv. [%]	Yield [%] / Product
1a)		0.5	>98	82 / **4a**
2		2	>98	73 / **4b**
3[a]		2	>98	80 / **4c**
4		1	90	76 / **4d**
5		2	>98	80 / **4e**
6		4	>98	88 / **4f**
7		2	>98	80 / **4g**
8[b]		2	>98	58 / **4h**
9		40	>98	88 / **4i**
10		24	40	37 / **4j**
11		1	>98	69 / **4k**
12		6	>98	23 / **4l**
13		32	<2	-

[a] 5 mol% $Pd[P(t\text{-}Bu)_3]_2$.

[b] 4 equiv NEt_3.

NCy_2Me was also superior to inorganic bases in sulfoxide cross-coupling but still did not deliver complete conversion. A screen of other common amine bases led to even lower conversions (entries 7–9). Triethylamine was the sole exception, proving uniquely effective for efficient coupling (entry 10: >98% conversion, 93% isolated yield). Curiously the palladium(I) dimer complex that has proven so active as a precatalyst in other forms of cross-coupling,[14] was completely unreactive with vinyl sulfoxides (entry 11).

With an effective catalyst system identified we explored the scope of the reaction with electronically and sterically diverse aryl bromides (Table 2). Phenyl bromide underwent complete vinylation in 30 min, delivering an 82% isolated yield. Electron-rich systems such as *p*-methoxybromobenzene or *o*-bromotoluene were successfully converted in good yield (73%, 80% respectively). It is noteworthy that unfunctionalized aryl bromides (entry 1) or those with only aliphatic functionalization (entry 3) can be run with 5 mol% catalyst, but heteroatom-substituted systems required 10 mol% catalyst loading to reach full conversion in a reasonable time.

Electron-poor substrates (entries 4–8) furnished the desired products in good yields as well: *p*-cyano-, *p*-methanoato- and *p*-acetamidobromobenzene underwent the transformation with full conversions and yields of 80% and above (see entries 5–7). Reaction of nitro-substituted aryl bromide was sluggish, reaching only 90% conversion under the standard conditions (entry 4). *p*-Bromobenzoic acid underwent full

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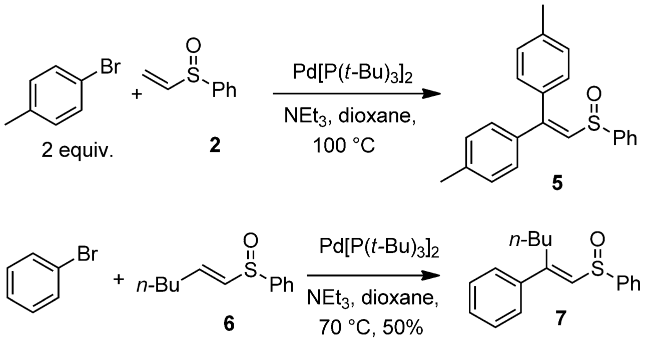
conversion, although four equivalents of triethylamine were needed to cope with the additional acidic protons.

More challenging heterocyclic aryl bromides as well as sterically encumbered substrates were also tolerated. 3-Bromopyridine (entry 9) was converted into the desired product with 88% yield, although forty hours were required for complete conversion. 3-Bromofuran was the most poorly accepted bromide substrate, delivering only 40% conversion and 37% yield after 24 h. Entry 11 represents a challenging substrate in terms of steric and electronic factors, and yet full conversion and 69% yield were attained.

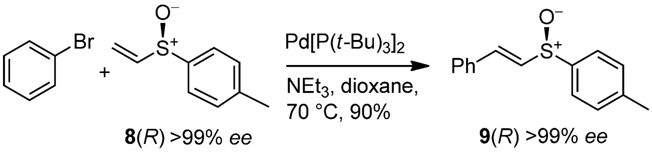
Entry 12 indicates that triflates are also viable cross-coupling partners. In this case the vinyl triflate was fully consumed but unreacted sulfoxide was still present. Although this suggests that some of the triflate decomposed during the reaction, 23% yield was still achieved. To our surprise phenyl chloride failed to react, although examples with aryl chlorides and different Heck acceptors are known with $Pd[P(t\text{-}Bu)_3]_2$.[13a] We therefore compared the known Heck coupling of 4-chloroacetophenone with styrene[13a] and found that the presence of phenyl vinyl sulfoxide inhibits the normal Heck coupling. This result suggests that one of the steps in the catalytic cycle with aryl chlorides is perturbed in the presence of sulfoxides.

The cross-coupling system is exceptionally active with aryl bromides and allows the formation of symmetrical and unsymmetrical trisubstituted olefins (see Scheme 1). For symmetrical olefins simply employing 2 equivalents of the aryl bromide at elevated temperature affords the desired product in good yield (see top line in Scheme 1). The ability to select between the single or double Heck products by simply adjusting the stoichiometry should prove of considerable synthetic value.

To obtain an unsymmetrically trisubstituted olefin sulfoxide **6**[15] was employed. After 21 h under the standard conditions with 5 mol% catalyst, the reaction proceeded to 80% conversion and delivered a 50% yield of **7** as the expected *E*-adduct exclusively – a result that not only demonstrates the catalysts potency, but also establishes alkyl-substituted vinyl sulfoxides as substrates.



Scheme 1. Synthesis of symmetrical (*top*) and unsymmetrical (*bottom*) trisubstituted olefins.



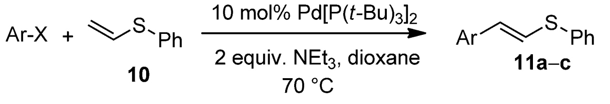
Scheme 2. Sulfoxide stereocenters are unaffected in the Heck coupling.

The cross-coupling conditions are compatible with sulfoxide stereocenters since enantiopure *R*-tolyl vinyl sulfoxide **8**(*R*) leads to enantiopure product **9**(*R*) (see Scheme 2). This result bodes well for using the coupling method to introduce sulfoxide-based chiral auxiliaries.

Although vinyl sulfoxides were our primary interest, we were aware that sulfones and sulfides are also poorly tolerated in Heck coupling. For example, vinyl sulfides in particular have only been employed in two cases that we could find.[2c,16] Nevertheless employing the conditions we identified led to complete conversion of phenyl vinyl sulfide **10** in two cases and 90% conversion in the case of nitrobromobenzene (Table 3, entry 3), delivering the products **11a–c** in 68–73% yield (see Table 3). It is noteworthy, that product **11c** was the first and only example where not only *E*- but also small amounts of the *Z*-isomer were observed.

Interestingly, the system developed by Yoshida[2c] for pyrimidine-directed Heck coupling of vinyl sulfides is almost identical to the system we describe here and yet they required aryl iodides to achieve cross-coupling. It is not clear why in Yoshida's case

Table 3. Vinyl sulfides are viable substrates.



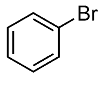
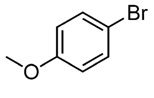
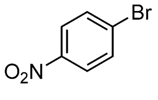
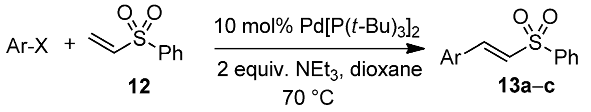
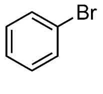
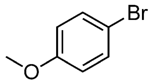
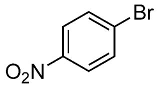
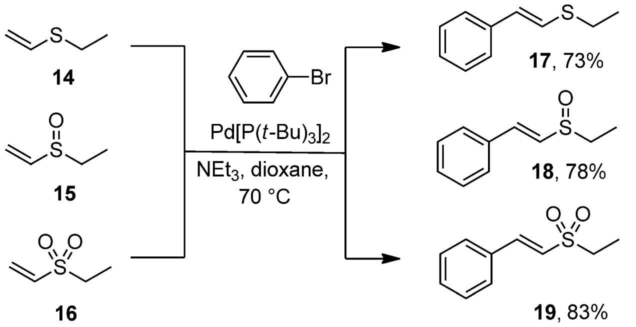
Entry	Ar-X	*t* [h]	Conv. [%]	Yield [%] / Product
1		3	>98	73 / **11a**
2		2	>98	68 / **11b**
3		4	90	68 / **11c**

Table 4. Additions to vinyl sulfones are also efficient.



Entry	Ar-X	*t* [h]	Conv. [%]	Yield [%] / Product
1		3	>98	88 / **13a**
2		2	>98	92 / **13b**
3		4	>98	74 / **13c**



Scheme 3. Additions to ethyl vinyl sulfide, sulfoxide and sulfone.

the ostensibly more reactive iodides also require a directing group to activate the olefin substrate, whereas we see that less reactive aryl bromides can be efficiently cross-coupled to vinyl sulfides lacking a directing group. It could be that although aryl iodides are superior in oxidative addition, the iodide anion generated in the process is deleterious to other steps of the catalytic cycle. Solvent effects may also be a factor as they used toluene and we used dioxane; but Fu has shown that with aryl chlorides there is a marginal difference between these two solvents in Heck reactions.[12]

If phenyl vinyl sulfone were accepted as a cross-coupling partner, then olefins bearing the whole set of sulfur oxidation states would be accessible through one unified protocol. Indeed phenyl vinyl sulfone **12** was efficiently coupled under the optimized conditions to deliver the sulfones **13a–c** in 74–92% yield (Table 4). In order to broaden the scope of the described methodology even further, we employed the catalyst system to ethyl vinyl sulfide/sulfoxide/sulfone (**14–16**); these substrates bear acidic alpha protons that could interfere with the catalytic reaction. In all three cases the desired product was furnished in good yield (Scheme 3) with 5 mol% catalyst.

Vinyl sulfur compounds in their various oxidation states are challenging substrates for Heck cross-couplings. The generality of the Pd[P(t-Bu)$_3$]$_2$/NEt$_3$ system opens up this class of molecules for further synthetic exploitation. Some practical points merit mention: the catalyst is commercially available, the procedure is operationally simple, and reaction times are shorter than with other catalyst systems (typically 2 h *vs.* 24 h with other catalysts). A disadvantage is the relatively high catalyst loading required (5–10%) for complete conversion. We are currently working to understand the catalyst decomposition pathways in the hope that it will support efforts to reduce the catalyst loading. Even with low turn-over numbers, however, the present catalyst system fills a void in Heck cross-coupling chemistry and should find broad applicability in the synthetic community.

Experimental Section

General Procedure for the Heck Vinylation

An oven-dried, nitrogen-flushed, two-necked, round-bottom flask was charged with 5 mL of dioxane. The bromide (0.63 mmol, 1.00 equiv.), the sulfoxide/sulfone/sulfide (0.63 mmol, 1.00 equiv.), NEt$_3$ (1.27 mmol, 2.00 equiv.) and Pd[P(t-Bu)$_3$]$_2$ (5–10 mol%, see the Supporting Information) were added and the mixture was immersed into a preheated oil bath at 70 °C. The pale yellow to dark brown solution was stirred under a nitrogen atmosphere and the reaction was followed by NMR. As soon as conversion stopped the solution was cooled to room temperature before removing the solvent under reduced pressure. The residue was dissolved in DCM and silica was added. After subsequent removal of the solvent, the product-laden silica was dry-loaded on a column for flash chromatography.

Acknowledgements

The Swiss National Science Foundation (Grant # 200021-134770), and the University of Basel are gratefully acknowledged for support of this work.

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6 Stereoselective Heck Reactions with Vinyl Sulfoxides, Sulfides and Sulfones

Adv. Synth. Catal. **2013**, *355*, 1 – 6

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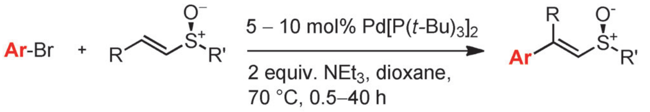

- R = H, alkyl, Ar
- R' = Ph, Et
- retention of configuration
- works with vinyl sulfides and vinyl sulfones

- 25 examples
- 23–93% yield