Palladium-catalyzed synthesis of bis-substituted sulfoxonium ylides

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ABSTRACT: The lack of general access to bis-substituted sulfoxonium ylides is addressed by developing a palladium-catalyzed C–H cross-coupling of α-ester sulfoxonium ylides with (hetero)aryl iodides, bromides and triflates. Three different catalysts have been evaluated. This method is amenable to the late stage functionalization of active pharmaceutical ingredients.

Sulfoxonium ylides have recently gained prominence as potentially safer surrogates of diazo compounds in metal-catalyzed reactions. Thus, the iridium-catalyzed formation of carbon-heteroatom bonds from mono-substituted α-carbonyl sulfoxonium ylides has been optimized in industry for the multikilogram synthesis of drug candidates,[1,2] and similar transformations can be promoted by other metal catalysts on smaller scale.[3–7] In addition, α-ketone sulfoxonium ylides can be used in rhodium-catalyzed functionalization reactions of carbon-hydrogen bonds of non-nucleophilic substrates,[8–21] and similar cross-couplings have been developed with ruthenium[22,23] and cobalt complexes,[24] whereas the C–H functionalization of nucleophilic α,β-unsaturated β-amino-esters has been described with an iridium catalyst.[25] Finally, the cross-dimerization of sulfoxonium ylides and diazo acetate derivatives has been reported recently.[26]

The superior thermal stability of sulfoxonium ylides over the parent diazo compounds is easily illustrated with compounds **1** and **2** (Scheme 1). Thus, the decomposition of diazo compound **1** occurs at 115 °C and liberates 706 J/g[27] whilst sulfoxonium ylide **2** undergoes decomposition at 172 °C, which liberates only 435 J/g. Accordingly, it would be desirable to develop a general access to (hetero)aryl-substituted sulfoxonium ylides like **2** that do not rely on the synthesis and use of donor-acceptor diazo compounds like **1**, in contrast to the current state-of-the-art.[4] Although iodoniums have also been reported as precursors of sulfoxonium ylides,[28] the optimized conditions are not suitable for the synthesis of ylides that are substituted by both an electron-acceptor and an electron-donor like in **2**. Moreover, it is possible to conduct the heteroarylation of dimethylsulfoxonium methylide followed by an acylation to obtain bis-substituted sulfoxonium ylides, but the direct nucleophilic aromatic substitution is limited to reactive heterocycles.[29] An alternative approach relies on the reaction of α-carbonyl sulfoxonium ylides with arynes,[30] but the structural variation of the precursors of these intermediates will be limited by the required multi-step synthesis, and the regioselectivity will remain in many cases an issue that is inherent to aryne chemistry.[31] Inspired by the palladium-catalyzed cross-coupling of aryl iodides with ethyl diazoacetate,[32] we assumed that a similar C–H functionalization of simple and stable α-ester sulfoxoniums could proceed efficiently. Whereas the conditions described previously for the synthesis of donor-acceptor diazocompounds by C–H functionalization[32-36] failed to deliver the expected sulfoxonium ylides in respectable amounts during our preliminary investigations, we report herein the successful deployment of this strategy after identification of novel conditions that are applicable to a wide set of substrates. To the best of our knowledge, the reaction described in this communication is the first example of a palladium-catalyzed transformation of sulfoxonium ylides.[37]

We began our study with model substrate **3** and iodobenzene (Table 1). A rapid survey of bases (entries 1–6) showed the most promising results when Cs_2CO_3 was used. Among the solvents examined (entries 4, 7–12), acetonitrile appeared optimal. Increasing the ratio of **3** to iodobenzene had a positive effect on the yield of product **4** (entry 13). Remarkably, in contrast to the reactivity described for ethyl diazoacetate,[2] the reaction of **3** with bromobenzene gave a better result than that obtained with

iodobenzene (entry 14), whereas benzene triflate also gave an excellent yield (entry 15). We could decrease the amount of base to 1.1 equiv without negative effects (entry 16). These results were therefore encouraging. However, polar product **4** was always obtained with small amounts of triphenylphosphine oxide after flash chromatography. Presumably, this side product is formed by the oxidation of free triphenylphosphine by dimethylsulfoxide.[38] Although compound **4** could be obtained in pure form after recrystallisation in 73% yield, we decided to identify alternative conditions before embarking on the exploration of the scope of this reaction. We thus examined the combination of $Pd_2(dba)_3$ (5 mol %) either with a reduced amount of PPh_3 (entry 17), or with other ligands (entries 18–21).

The choice of these alternative ligands was based on the assumption that the reductive elimination from **III** might be the rate-limiting step of the catalytic cycle (Scheme 2). Whilst further studies of the mechanism would be required to demonstrate our hypothesis, two observations support it. First, the better results obtained with bromobenzene as compared to iodobenzene (Table 1, entries 13 *vs* 14) indeed suggest that the oxidative addition of the catalyst into the carbon-halogen bond to give **I** is not rate-limiting. Second, using Ag_2CO_3 as base instead of Cs_2CO_3 did not promote the formation of **4**, which suggest that attempting to accelerate the transmetallation of **I** to **II** by forming a cationic palladium intermediate is not a favorable strategy. To the extent that the deprotonation of **II** into **III** is facile, the reductive elimination from **III** would therefore be the rate limiting step, and either sterically demanding or electron-poor ligands should accelerate that step.

We found that reducing the amount of PPh_3 did not prevent the formation of its oxide as side product (entry 17). Using electron-poor phosphites **L2** and **L3** did not give any product (entries 18 and 19). Gratifyingly, bulky phosphines **L4** and **L5** gave **4** in high yield after purification by flash chromatography without need for recrystallization (entries 20 and 21). Overall, we have thus identified three suitable catalysts: $Pd(PPh_3)_4$ (method A), $Pd_2(dba)_3$ + 4 **L4** (method B), and $Pd_2(dba)_3$ + 4 **L5** (method C). Although method A required further recrystallisation of compound **4**, we envisioned that less polar products might be more easily separated from triphenylphosphine oxide, and we decided to evaluate the three methods on a set of commercially available (hetero)aryl bromides.

As envisioned after the optimization study, methods B and C performed generally better than method A (Figure 1). Indeed, compounds **5**, **6**, **8–10**, **13**, **16**, and **18–22** were obtained in superior yields when using these two methods. However, method A is not without merits, and compounds **7**, **12**, **15** and **17** could be obtained in high yields and in pure form by this method after flash chromatography without recourse to further purification by recrystallization. Moreover, method A gave only mono-functionalized compound **14** from 1,3-dibromobenzene, even in the presence of an excess of reagent **3**, whereas methods B and C led to an intractable mixture of mono- and bis-functionalized products. In general, electron-poor or electron-neutral aryl bromides led to excellent conversion (**5–10**, **12–14**), whereas *para*-methoxybenzene bromide failed to deliver **11**, which is in agreement with our hypothesis that the reductive elimination might be the rate-limiting step in the catalytic cycle. Ortho substitution in the aryl bromide was tolerated in the case of cyano (**15**) and nitro (**16**) groups, but *ortho*-bromotoluene failed to deliver the expected product in either of the methods. The reactions of heteroaryl bromides are exemplified with a 3-pyridyl (**17**), a 2-quinolyl (**18**), and a 3-thiophenyl (**19**) group. Besides the reaction of ethyl ester **3**, other sulfoxonium ylides bearing an alkyl or aryl group also underwent the cross-coupling to give the expected products (**2**, **20–22**) in excellent yields. The synthesis of **4** could be performed on the gram scale in 83% yield according to method C, and decreasing the amount of $Pd_2(dba)_3$ to 2.5 mol% on that scale still afforded **4** in 69% yield.

As observed in our optimization study, aryl triflates are also convenient substrates of the cross-coupling with sulfoxonium ylides. Indeed, we could couple chromene derivative **23** and ylide **3** according to method B and obtain compound **24** in 77% yield (Equation 1).

Moreover, we could also couple structurally complex active pharmaceutical ingredients (API) in high yields by following method C, illustrating the good functional group tolerance of this reaction and its

synthetic utility (Scheme 3). We used the API either directly, as in the case of nicergoline, or its triflate, as in the case of estrone, and compounds **25** and **26** were obtained in very good yields

Sulfoxonium ylides are amenable to a wide array of tranformations.[37,39] For example, **4** and *para*-hydroxythiophenol reacted smoothly to give **27** (Scheme 4),[6] a precursor of a fatty acid synthase inhibitor.[40] Therefore, the shelf-stable white solid **4** that is now conveniently available by our method, also offers a valuable alternative feedstock to ethyl α-bromophenylacetate, a lacrymator that was used previously for the synthesis of this bioactive compound.[40] Finally, the ease of access to α-ester bis-substituted sulfoxonium ylides, as enabled by the cross-coupling described herein, could allow a full exploration of the scope of these ylides in the iridium-catalyzed N–H insertion reaction pioneered by Merck,[4a] as illustrated with the reaction of **10** leading to **28**.

In conclusion, we have described the first palladium-catalyzed cross-coupling of sulfoxonium ylides for the rapid synthesis of bis-substituted α-ester-α-(hetero)aryl sulfoxonium ylides from easily available (hetero)aryl bromides and triflates. This method provides a valuable alternative to the metal-catlyzed decomposition of diazo precursors that have a high thermal potential.[4] Moreover, this work expands the scope of metal-catalyzed cross-coupling of carbene precursors.[41] Further studies to generalize this reaction to other coupling partners are on-going in our laboratories.[42]

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Scheme 1. General access to (hetero)aryl-substituted sulfoxonium ylides by palladium-catalyzed C–H cross-coupling.

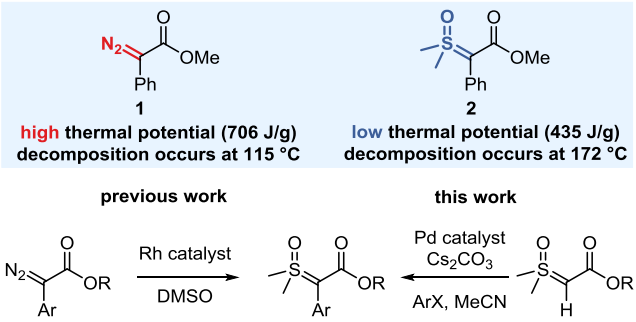
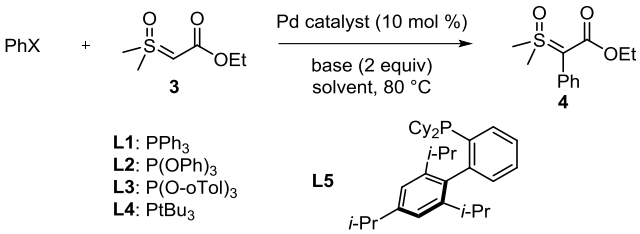


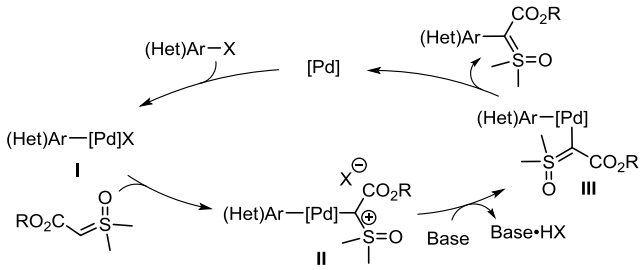
Table 1. Optimization of the reaction conditions[a]



entry	X	catalyst	base[b]	solvent	yield
1	I	$Pd(PPh_3)_4$	DBU	MeCN	2%[c]
2	I	$Pd(PPh_3)_4$	Et_3N	MeCN	2%[c]
3	I	$Pd(PPh_3)_4$	*t*-BuOK	MeCN	2%[c]
4	I	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	45%[c]
5	I	$Pd(PPh_3)_4$	K_2CO_3	MeCN	5%[c]
6	I	$Pd(PPh_3)_4$	Li_2CO_3	MeCN	2%[c]
7	I	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	29%[c]
8	I	$Pd(PPh_3)_4$	Cs_2CO_3	dioxane	25%[c]
9	I	$Pd(PPh_3)_4$	Cs_2CO_3	1,2-DCE	18%[c]
10	I	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	22%[c]
11	I	$Pd(PPh_3)_4$	Cs_2CO_3	EtOH	14%[c]
12	I	$Pd(PPh_3)_4$	Cs_2CO_3	THF	24%[c]
13	I	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	63%[d]
14	Br	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	80%[d]
15	OTf	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	87%[d]
16	Br	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	73%[e]
17[f]	Br	$Pd_2(dba)_3$ + 4 **L1**	Cs_2CO_3	MeCN	64%[d]
18[f]	Br	$Pd_2(dba)_3$ + 4 **L2**	Cs_2CO_3	MeCN	0%[c]
19[f]	Br	$Pd_2(dba)_3$ + 4 **L3**	Cs_2CO_3	MeCN	0%[c]
20[f]	Br	$Pd_2(dba)_3$ + 4 **L4**	Cs_2CO_3	MeCN	80%[e]
21[f]	Br	$Pd_2(dba)_3$ + 4 **L5**	Cs_2CO_3	MeCN	86%[e]

[a] The PhX/3 ratio is 1.15:1 in entries 1–12 and 1:2.5 in entries 13–21. [b] 2 equiv (entries 1–15) or 1.1 equiv (entries 16–21). [c] Yield determined by HPLC after 4 h. [d] Yield of isolated product after 16 h; the product contains 5–10 mol % of triphenylphosphine oxide. [e] Yield of pure isolated product after 16 h. [f] 5 mol % of $Pd_2(dba)_3$ + 20 mol % of L1–L5. 1,2-DCE: 1,2-dichloroethane; DMF: dimethylformamide; THF: tetrahydrofuran.

Scheme 2. Plausible mechanism of the cross-coupling (ligands are omitted for clarity).



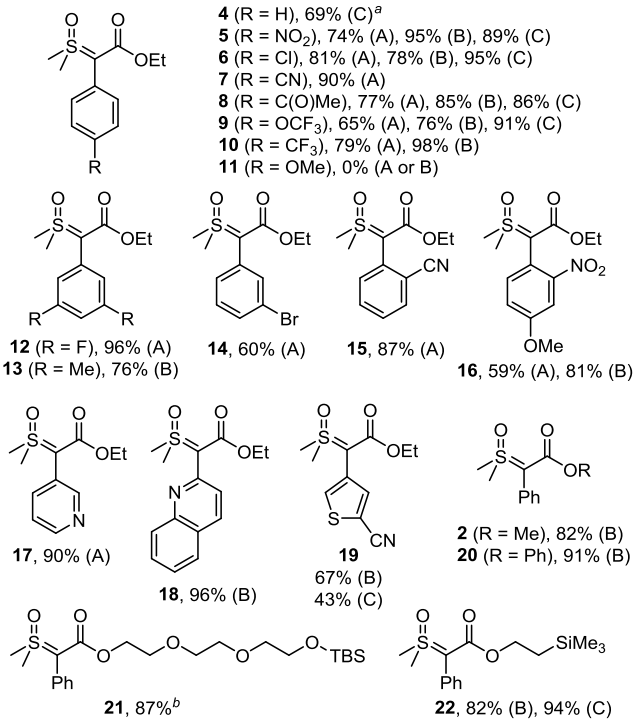
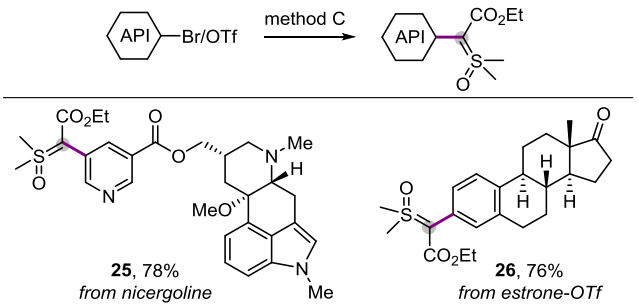


Figure 1. Scope of cross-coupling products obtained from (het-ero)aryl bromides and unsubstituted α-ester sulfoxonium ylides. Yields of pure isolated products from the reactions of (hetero)aryl bromides (0.20 mmol, 1 equiv), unsubstituted α-ester sulfoxonium ylides (0.50 mmol, 2.5 equiv), Cs_2CO_3 (0.22 mmol, 1.1 equiv) in MeCN (2 mL) at 80 °C for 14–16 hours in the presence of either $Pd(PPh_3)_4$ (0.02 mmol, 0.1 equiv) (method A), $Pd_2(dba)_3$ (0.01 mmol, 0.05 equiv) and L4 (0.04 mmol, 0.2 equiv) (method B) or $Pd_2(dba)_3$ (0.01 mmol, 0.05 equiv) and L5 (0.04 mmol, 0.2 equiv) (method C). [a] Phenylbromide (7 mmol, 1 equiv), $Pd_2(dba)_3$ (0.18 mmol, 0.025 equiv) and L5 (0.7 mmol, 0.1 equiv) were used. [b] $Pd(P\textit{t}\text{-}Bu_3)_2$ (0.02 mmol, 0.1 equiv) was used.

Scheme 3. Late-stage modification of API.



Scheme 4. Utility of α-ester bis-substituted sulfoxonium ylides for the synthesis of drug candidates and for further functionalization.