Palladium-Catalyzed Synthesis of α-Carbonyl-α'-(Hetero)aryl Sulfoxonium Ylides: Scope and Insight into the Mechanism

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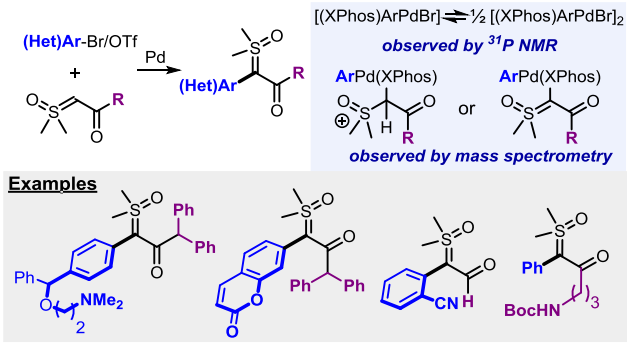
ABSTRACT. Despite recent advances, a general method for the synthesis of α-carbonyl-α'-(hetero)aryl sulfoxonium ylides is needed to benefit more greatly from the potential safety advantages offered by these compounds over the parent diazo compounds. Herein, we report the palladium-catalyzed cross-coupling of aryl bromides and triflates with α-carbonyl sulfoxonium ylides. We also report the use of this method for the modification of an active pharmaceutical ingredient and to the synthesis of a key precursor of antagonists of the neurokinin-1 receptor. In

addition, the mechanism of the reaction was inferred from several observations. Thus, the oxidative addition complex [(XPhos)PhPdBr] and its dimer were observed by $^{31}P\{^{1}H\}$ NMR and these complexes were shown to be catalytically and kinetically competent. Moreover, a complex resulting from the transmetallation of [(XPhos)ArPdBr] (Ar = *p*-CF_3-C_6H_4) with a model sulfoxonium ylide was observed by mass spectrometry. Finally, the partial rate law suggests that the transmetallation of and the subsequent deprotonation are rate-determining in the catalytic cycle.

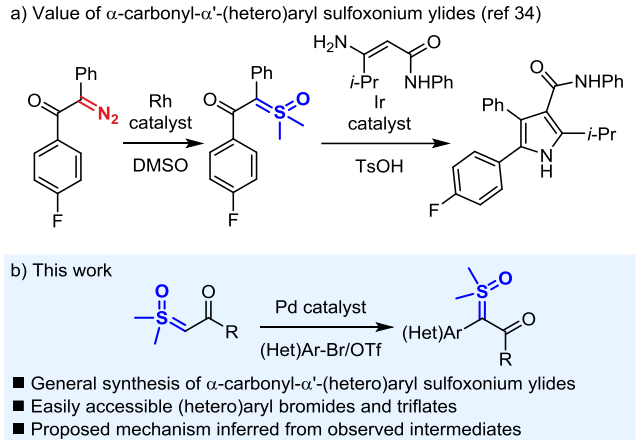
TOC graphic



INTRODUCTION

Metal-catalyzed reactions of sulfoxonium ylides have recently enjoyed a renaissance[1–5] that is encouraged by the potential utility of these methods for the multi-kilogram synthesis of drug candidates.[6] Hence, intensive efforts have been recently directed to the development of catalytic methods for the formation of carbon-carbon[7–28] and carbon-heteroatom[29–36] bonds from these ylides. Moreover, comparison of the energy released in differential scanning calorimetry studies clearly demonstrates the potential safety advantages offered by α-carbonyl sulfoxonium ylides over the parent diazo compounds.[7,8]

Scheme 1. Synthetic utility of α-carbonyl-α'-(hetero)aryl sulfoxonium ylides and their preparation by palladium-catalyzed cross-coupling.



Significantly, most of these methods involve the use of α-carbonyl sulfoxonium ylides that have only one substituent attached to the ylide carbon atom. A notable exception is the use of a bis-substituted α-carbonyl-α'-aryl sulfoxonium ylide in the synthesis of an advanced pyrrole precursor of atorvastatin (Scheme 1a),[34] an anti-cholesterol top-selling drug.

However, the preparation of bis-substituted α-carbonyl-α'-(hetero)aryl sulfoxonium ylides remains challenging and therefore limits their wider application in synthesis despite their significant potential utility. Thus, the sulfoxonium ylide depicted in Scheme 1a was prepared by the decomposition of an α-carbonyl-α'-aryl diazo compound in the presence of rhodium(II) acetate under harsh conditions that are not compatible with the high thermal potential of diazo compounds.[31,37,38] Although simple α-carbonyl-α'-(hetero)aryl sulfoxonium ylides can be prepared by reaction of arynes and α-carbonyl sulfoxonium ylides,[39] this approach does not enable easy structural variations of the (hetero)aryl group because of the necessary multi-step synthesis of the aryne precursors and the potential regioselectivity issues typical of many intermolecular reactions of unsymmetrical arynes.[40] Moreover, although iodoniums can serve as precursors of

sulfoxonium ylides,[41] the reported method is not suitable for the synthesis of ylides bearing both an electron-acceptor substituent and a (hetero)aryl group. As an alternative, one could consider a two-step sequence beginning with the nucleophilic aromatic substitution of reactive heterocycles with dimethylsulfoxonium methylide followed by an acylation,[42] but it cannot be applied to the introduction of simple aryl halides of decreased electrophilic character. Finally, the palladium-catalyzed carbonylative arylation of α-carbonyl sulfoxonium ylides has been described with aryl iodides, but it has not been described with less expensive aryl bromides or for the preparation of sulfoxonium ylides that bear only one electron-withdrawing group.[43] Accordingly, a general method for the preparation of α-carbonyl-α'-(hetero)aryl sulfoxonium ylides from easily available precursors remains needed.

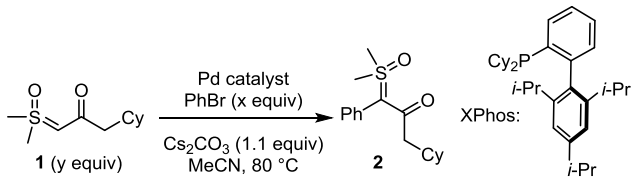
Herein, we now report the palladium-catalyzed cross-coupling of aryl bromides and triflates with α-carbonyl sulfoxonium ylides (Scheme 1b). The synthetic utility of the method is illustrated with the modification of an active pharmaceutical ingredient and by the synthesis of a key precursor of antagonists of the neurokinin-1 receptor. A mechanism is proposed on the basis of control experiments.

RESULTS AND DISCUSSION

Optimization and scope of the reaction. During our study of the palladium-catalyzed cross-coupling of α-ester sulfoxonium ylides and aryl bromides,[7] initial tests of the reactivity of α-ketone sulfoxonium ylide **1** led us to believe that no reaction occurred because ylides **1** and **2** were not distinguishable by thin layer chromatography. However, examination of the crude mixture by ^{1}H NMR confirmed that modest conversion was achieved (Table 1, entry 1). It is noteworthy that α-ketone sulfoxonium ylides are far less reactive than the corresponding esters in this palladium-catalyzed reaction. Nevertheless, by switching the ligand to XPhos and changing the stoichiometry

(entry 2) and concentration (entry 3) of the reaction, we managed to reach full conversion of ylide **1** and isolate pure **2** in good yield. Moreover, it is remarkable that sulfoxonium ylide **1** was recovered unchanged when mixed with either iodobenzene or bromobenzene and treated under the conditions that catalyze the cross-coupling of aryl iodides with α-diazo ketones.[44] Sulfoxonium ylides and diazo compounds have therefore a very distinct reactivity in palladium-catalyzed reactions.

Table 1. **Optimization of the reaction conditions**



entry	Pd catalyst	x/y	concentration	yield
1	10 mol % $Pd(PPh_3)_4$	1:1.5	0.1 M	24%[a]
2	5 mol % $Pd_2(dba)_3$ + 20 mol % XPhos	2.5:1	0.1 M	81%[b]
3	5 mol % $Pd_2(dba)_3$ + 20 mol % XPhos	2.5:1	0.5 M	83%[c]

[a] Yield determined from ^{1}H NMR of the crude mixture. [b] Isolated as two fractions, one of them containing 8% of recovered starting material **1**. [c] Yield of isolated pure product. Cy = cyclohexyl.

Scope of the reaction. Although the reaction conditions were at this stage not completely optimized with respect to the stoichiometry of reactants, we were eager to rapidly establish their generality. We found that varying the sulfoxonium fragment was well tolerated as illustrated with functionalized alkyl groups bearing for example an indole, a pyrrole, an ether, and Boc-protected primary and secondary amines (Figure 1, **3**–**7**), whereby the yields remained high throughout. Whereas primary (**3**–**6**) and secondary (**7**, **8**) alkyl groups were compatible, attempts for which the R group was a tertiary alkyl group (e.g. adamantyl) led to no conversion. On the other hand, sulfoxonium ylides bearing electron-poor (**9**) or electron-rich (**10**) aryl groups, as well as heteroaryls (**11** and **12**) groups, underwent the cross-coupling in high yields. Similarly, the aryl

bromides could be varied to give cross-coupled products **13**–**20** (Figure 2), although *para*-bromoanisole gave **15** in a lower yield due to the decomposition of the product under the reaction conditions. Thus, in that case, an optimal result was obtained by stopping the reaction after 2 hours. Moreover, the coupling of heteroaryl bromides gave **21** and **22**, and that of aryl triflates gave examples **23** and **24**. Finally, it is noteworthy that this protocol afforded formyl derivatives **25** and **26** in excellent yields.

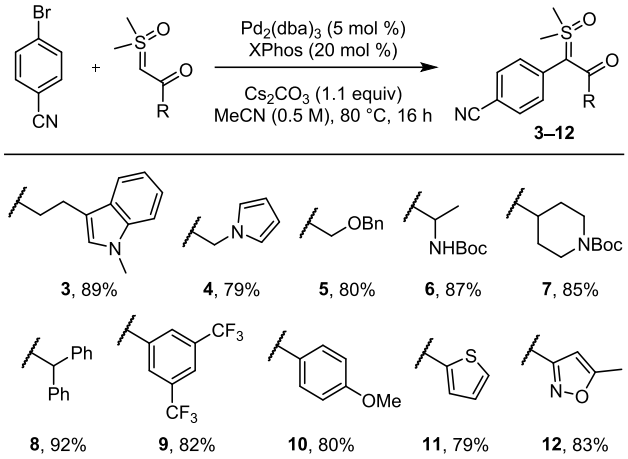


Figure 1. Scope of α-ketone sulfoxonium ylides. Yields of pure isolated products from the reactions of aryl bromide (1 mmol, 2.5 equiv), α-ketone sulfoxonium ylides (0.4 mmol, 1.0 equiv), Cs_2CO_3 (0.44 mmol, 1.1 equiv) in MeCN (0.8 mL).

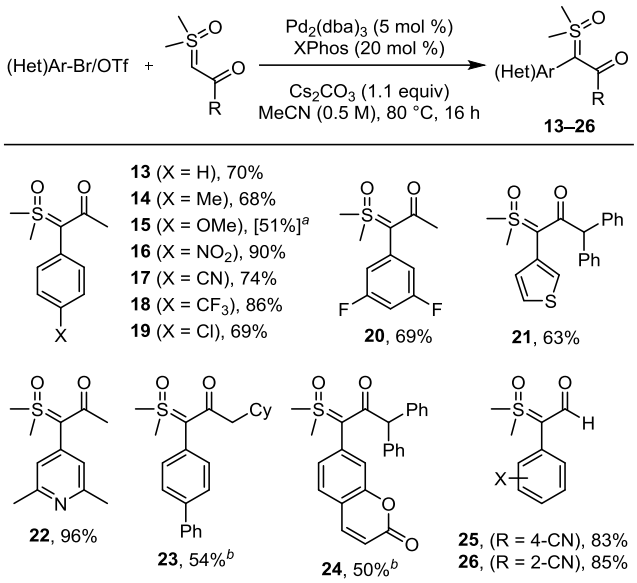
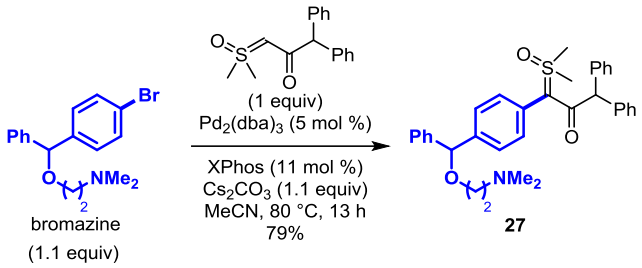


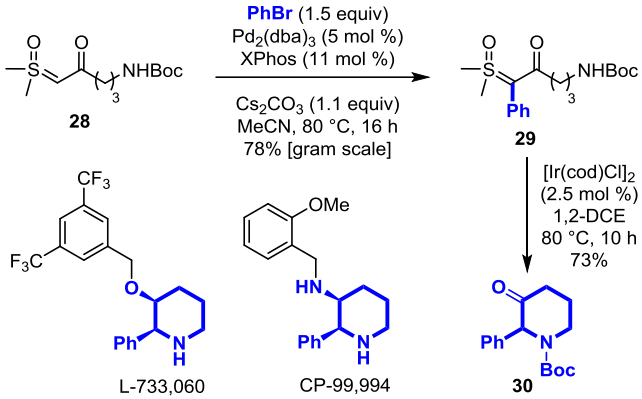
Figure 2. Scope of (hetero)aryl bromides. Yields of pure isolated products from the reactions of aryl bromides (1 mmol, 2.5 equiv), α-carbonyl sulfoxonium ylides (0.4 mmol, 1.0 equiv), Cs_2CO_3 (0.44 mmol, 1.1 equiv) in MeCN (0.8 mL). *a* ^{1}H NMR yield. *b* From triflate.

Importantly, further optimization of the reaction conditions enabled us to decrease the loading of aryl bromide and of XPhos. Decreasing the amount of aryl bromide is particularly relevant for the late-stage modification of more precious material, as for example the antihistamine drug bromazine.[45] Cross-coupling product **27** could thus be obtained in 79% yield by using only 1.1 equivalent of bromazine and 11 mol % of XPhos (Scheme 2). Moreover, reducing the excess of aryl bromide and XPhos is also relevant for gram-scale applications, as for example the reaction of sulfoxonium ylide **28** with bromobenzene that gave **29** without decrease of the yield (Scheme 3). By using an iridium catalyst,[31] this intermediate could then be converted in good yield into piperidinone **30**, a common precursor of L-733,060 and CP-99,994, two drugs developed as antagonists of the neurokinin-1 receptor.[46,47] It is noteworthy that the cyclization of **29** to give **30** is the first of its kind on a *bis-substituted* α-ketone-α'-(hetero)aryl sulfoxonium ylide.

Scheme 2. Late-stage modification of bromazine.

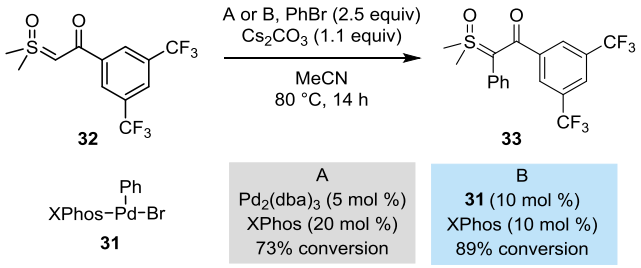


Scheme 3. Gram-scale synthesis of a drug precursor.



Study of the mechanism. To gain an insight into the mechanism of this reaction, we started our study by preparing the known oxidative addition complex **31**.[48] We observed that this complex was catalytically competent in the cross-coupling of **32** with bromobenzene (Scheme 4), and its use actually led to a higher yield of product **33** as compared to what was obtained under the conditions used to establish the scope described in figures 1 and 2. Importantly, the kinetic competence of **31** was also established in the conversion of **32** into **33** and no difference of initial rate was observed when compared to that obtained by using the combination of $Pd_2(dba)_3$ and XPhos.

Scheme 4. Catalytic competence of oxidative addition complex 31.



Moreover, complex **31** was also observed by ^{31}P NMR of the crude mixture resulting from the coupling of ylide **34** and bromobenzene into product **13** (Figure 3). Thus, besides resonances for XPhos and its oxide, we observed only a broad resonance at δ = 27.2 ppm and a sharper one at δ = 55.6 ppm (Figure S1, Supporting Information) in an approximately equimolar ratio, which we attribute to the monomer solvate complex [**31**•MeCN] and the solvent-free dimer [(XPhos)PhPdBr]$_2$, respectively. The attribution of these resonances is in a good agreement with the findings recently reported by Hii and co-workers in their study of related mono-phosphines complexes.[49]

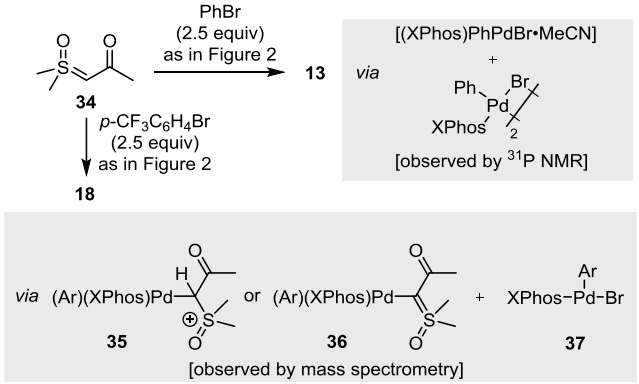


Figure 3. Observation of a dimer of the oxidative addition intermediate by ^{31}P NMR and possible structures of transmetalation intermediates detected by mass spectrometry. Ar = *p*-$CF_3C_6H_4$**.**

Having established that the oxidative addition complexes [(XPhos)ArPdBr] are catalytically and kinetically competent, we attempted to isolate a transmetalation complex that would result from

the reaction of **31** and sulfoxonium ylides, but this endeavor remained unsuccessful. However, the mass spectrum of the crude supernatant of the reaction between ylide **34** and *p*-$CF_3C_6H_4Br$, carried out under the catalytic conditions described in figure 2, showed minor peaks corresponding to a transmetalation complex with the correct isotope distribution, which would correspond to either **35** ([**35**]$^+$) or **36** ([**36** + H]$^+$) (Figure 4). The formation of such intermediates would be consistent with an earlier report of a palladium complex resulting from the stoichiometric transmetalation of Pd(II) salts with an α-ketone sulfoxonium ylide.[50] Besides these minor peaks, the most abundant peaks we could identity were those of the product **18** ([**18** + H]$^+$) and of a fragment of the oxidative addition complex **37** ([**37** – Br]$^+$), as well as those of XPhos and its oxide (Figure S2, Supporting Information). The interpretation of this data was confirmed by the independent synthesis of complex **37** that was characterized by X-ray crystallography as a dimer in the solid state (Figure 4). Analysis of pure **37** by mass spectrometry gave the same molecular peaks corresponding to the fragment [**37**– Br]$^+$.

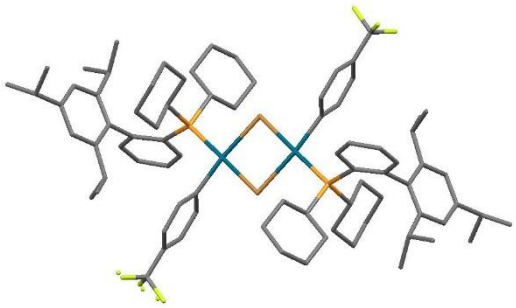
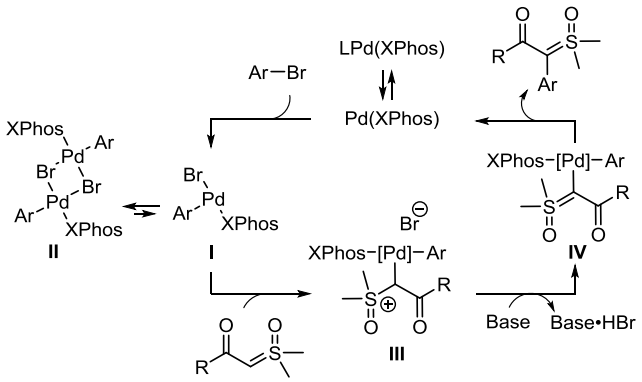


Figure 4. Crystal structure of oxidative addition complex 37 in the solid state.

Scheme 5. Proposed mechanism.



In view of the data collected in our study, we propose a mechanism (Scheme 5), by which rapid ligand exchange between dba and XPhos would generate an active catalyst (L = dba or MeCN).[51] Then, oxidative addition would give intermediate **I** that is in equilibrium with an off-cycle inactive dimer **II**, which is the resting state of the catalyst. We propose that **I** would undergo transmetalation to **III** upon reaction with the ylide, which would be followed by deprotonation to give **IV**, whose reductive elimination would regenerate the active catalyst and liberate the observed cross-coupling products.

Further support for the proposed mechanism was obtained by determining the rate law of the reaction conducted between model substrates *p*-$CF_3C_6H_4Br$ and sulfoxonium ylide **34**. Varying the initial concentrations of aryl bromide (0.30 – 1.25 M), ylide **34** (0.1 – 1.5 M), XPhos (0.06 – 0.50 M), and $Pd_2(dba)_3$ (0.006 – 0.038 M). We found that the initial rate ($rate_i$) obeyed the equation $rate_i = k_{obs}[ylide]^{0.6}[Pd_{tot}]^{0.5}$, whereas the order in aryl bromide and ligand was zero. These results confirmed several aspects of the mechanism of this reaction. First, the half-order in palladium is consistent with an equilibrium between inactive dimer **II** and the kinetically and catalytically competent oxidative addition intermediate **I**.[52] Second, the partial order in ylide observed in the rate law also suggests that the transmetalation is in the rate-determining zone of the catalytic cycle.[53] Third, the Lineweaver-Burk plots of the reciprocal of the initial rate as a function of the reciprocal of the individual concentration of ylide (Figure 5) gave a good linear correlation with

non-zero y intercept, which confirmed that one molecule of ylide is involved in the transmetalation. Fourth, although Cs_2CO_3 is not soluble under the reaction conditions, we observed a linear increase of the initial rate when increasing the amount of base from 0.44 to 2.0 equivalents (See supporting information). This effect suggests that the deprotonation step should also be included in the rate-determining zone, even if the order dependence in the concentration of base could not be rigorously established.[54]

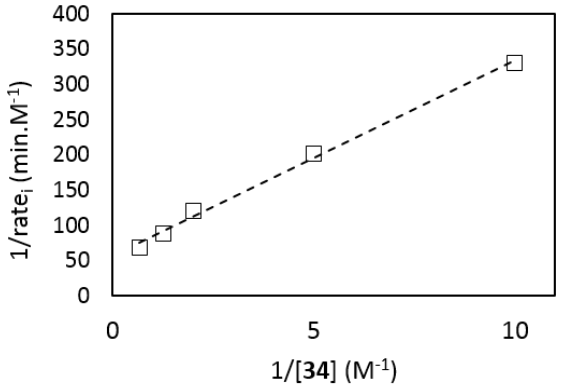


Figure 5. Lineweaver-Burk plots of the reaction of model sulfoxonium ylide 34 and *p*-$CF_3C_6H_4Br$. $1/rate_i = 56.8 \pm 4.4 + (27.9 \pm 0.9)/[\mathbf{34}]$ ($R^2 = 0.99$). Data from duplicate experiments**.** Error bars omitted for clarity.

Overall, these results highlight a remarkable contrast between α-ketone sulfoxonium ylides and α-diazoketones. Hence, our findings indicate that the transmetalation and deprotonation steps of the palladium-catalyzed cross-couplings of aryl bromides with α-carbonyl sulfoxonium ylides are rate-determining, whereas theoretical study of the palladium-catalyzed cross-coupling of α-diazo ketones and aryl iodides suggested these two steps occurred without kinetic barrier.[44] As mentioned previously, it is noteworthy that the model α-carbonyl sulfoxonium ylide used in the optimization of the reaction conditions was recovered unchanged when mixed with either

iodobenzene or bromobenzene and treated under the conditions that catalyze the cross-coupling of aryl iodides with α-diazo ketones,[44] which could point to a less pronounced nucleophilic character of sulfoxonium ylides as compared to their diazo counterpart in these reactions.

CONCLUSION

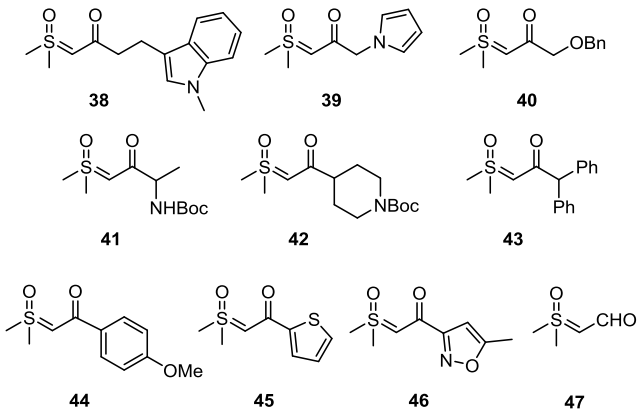
In conclusion, we have reported a general palladium-catalyzed cross-coupling for the preparation of α-carbonyl-α'-(hetero)aryl sulfoxonium ylides from easily available (hetero)aryl bromides and triflates. The procedure shows excellent functional group tolerance and is amenable to the modification of active pharmaceutical ingredients and to the synthesis of an advanced precursor of drug candidates. We anticipate that the method of preparation of α-carbonyl-α'-(hetero)aryl sulfoxonium ylides reported herein will enable the development of numerous reactions based on these valuable and safe reagents. Finally, our findings suggest that the transmetallation of an (hetero)aryl-palladium(II) intermediate by sulfoxonium ylides and the subsequent deprotonation steps are rate-determining, in sharp contrast to comparable reactions of α-diazoketones.

EXPERIMENTAL SECTION

Otherwise noted, all reactions were carried out in flame-dried glassware under dry nitrogen atmosphere. All commercially available reagents were used as received. THF was used after passage through Innovative Technology PureSolv MD system. Acetonitrile was purchased as dry solvent. $Pd_2(dba)_3$ was purchased from Strem. XPhos was purchased from FluoroChem: the original container was stored in an argon-filled glovebox at room temperature and samples of approximately 1 g were taken out of the glove box as needed and stored in a Schlenck tube that was flushed with argon. Cesium carbonate (99.9%) was purchased from Sigma Aldrich. Flash chromatography: Merck silica gel 60 (230-400 mesh). NMR: the ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ spectra were recorded on a Bruker DRX 500. The $^{19}F\{^{1}H\}$ spectra were recorded on a Bruker Avance 400

spectrometer. chemical shifts (δ) are given in ppm. The solvent signals were used as references for ^{1}H and $^{13}C\{^{1}H\}$ spectra ($CDCl_3$: $\delta = 77.0$; residual $CHCl_3$ in $CDCl_3$: $\delta = 7.26$). The $^{31}P\{^{1}H\}$ spectra were calibrated with an external standard ($P(OPh)_3$, $\delta = 128.0$ in $CDCl_3$). The $^{19}F\{^{1}H\}$ spectra were calibrated with an external standard ((trifluoromethyl)benzene, δ = -62.8). IR spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer, and the wavenumbers ($\tilde{\nu}$) are given in cm^{-1}. HRMS determined at the University of Liverpool on Agilent 6540A Accurate-Mass Q-ToF MS with Agilent Jetstream Source (ES+). Melting points were measured on a Griffin melting point apparatus (not corrected).

Mono-substituted α-carbonyl sulfoxonium ylides (1, 28, 32, 34, 38–47). Compounds **1**,[9] **28**,[30] **34**,[9] **38**,[8] **39**,[8] **40**,[55] **41**,[39] **42**,[9] **43**,[8] **44**,[33] **45**,[1] and **47**[17] were prepared by the reported procedures. The ^{1}H NMR chemical shifts of these compounds were in agreement with the literature values. Compounds **32** and **46** were prepared as described below.



1-(3,5-Bis(trifluoromethyl)phenyl)-2-(dimethyl(oxo)-λ⁶-sulfaneylidene)ethan-1-one (32). Under nitrogen, trimethylsulfoxonium iodide (5.28 g, 24 mmol, 3.0 equiv) was suspended in dry THF (50 mL) in a flame-dried round bottom flask that was protected from light with aluminium foil. Potassium *tert*-butoxide (2.69 g, 24 mmol, 3.0 equiv) was added and the mixture was stirred at reflux for 2 hours. After cooling to 0 °C, from 3,5-bis(trifluoromethyl)benzoyl chloride (5.4 mL,

8.0 mmol, 1 equiv) in THF (16 mL) was added dropwise to the mixture via a dropping funnel. After stirring at room temperature for 1 hour, the mixture was filtered through a plug of celite (elution CH_2Cl_2). After evaporation of all volatiles, purification by flash chromatography (silica gel, petroleum ether/ethyl acetate = 3:7 to 1:9) and recrystallization from ethyl acetate/hexane gave compound **32** (7.86 g, 79%). White solid; m.p.: 152–154 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (s, 2H), 7.93 (s, 1H), 5.06 (s, 1H), 3.85 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 178.2, 140.9, 131.6 (q, J = 33.3 Hz, 2C), 126.78, 126.75, 124.0 (hept, J = 3.7 Hz), 123.2 (q, J = 271.3 Hz, 2C), 70.0, 42.2 (2C). ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.9. IR (neat): $\tilde{\nu}$ = 3103 (w), 3025 (w), 3005 (w), 2921 (w), 1627 (w), 1548 (m), 1451 (w), 1406 (w), 1354 (m), 1311 (m), 1278 (s), 1191 (m), 1166 (s), 1132 (s), 1106 (s0, 1027 (s), 996 (m), 956 (m), 924 (w), 909 (m), 900 (m), 859 (m), 844 (m), 767 (w), 753 (w), 698 (w), 682 (w), 670 (w). HRMS (ESI): *m/z* calcd for $C_{12}H_{11}F_6O_2S$ [M + H]$^+$: 333.0378; found: 333.0382.

2-(Dimethyl(oxo)-λ^6-sulfaneylidene)-1-(5-methylisoxazol-3-yl)ethan-1-one (46). This compound (259 mg, 38%, white solid) was obtained from 5-methylisoxazole-3-carbonyl chloride (0.49 g, 3.4 mmol, 1 equiv) according to the method described for the preparation of **32** and after purification by flash chromatography (silica gel, CH_2Cl_2/MeOH = 98:2): 259 mg, 38%. White solid; m.p.: 117–119 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.30 (q, J = 0.9 Hz, 1H), 5.33 (s, 1H), 3.50 (s, 6H), 2.43 (d, J = 0.9 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 173.4, 170.0, 163.1, 100.3, 70.7, 42.1, 12.3. IR (neat): $\tilde{\nu}$ = 3140 (w), 3097 (w), 3009 (w), 2922 (w), 1599 (w), 1547 (s), 1465 (w), 1449 (s), 1344 (s), 1318 (w), 1295 (w), 1245 (w), 1182 (s), 1133 (w), 1073 (w), 1020 (s), 1008 (m), 996 (m), 979 (m), 941 (w), 901 (m), 848 (s), 827 (m), 813 (w), 768 (w), 753 (w), 689 (w), 658 (w). HRMS (ESI): *m/z* calcd for $C_8H_{12}NO_3S$ [M + H]$^+$: 202.0532; found: 202.0530.

Representative procedure for the palladium-catalyzed cross-coupling of α-carbonyl sulfoxonium ylides. Under nitrogen, a J-Young Schlenck tube was charged with XPhos (38 mg, 0.08 mmol, 0.2 equiv), Pd_2dba_3 (18 mg, 0.02 mmol, 0.05 equiv) and Cs_2CO_3 (143.4 mg, 0.44 mmol, 1.1 equiv). Acetonitrile (0.4 mL) was then added and the mixture was stirred at room temperature for 10 minutes. Then, bromobenzene (160 μL, 2.5 mmol, 2.5 equiv) was added followed by sulfoxonium ylide **1** (87 mg, 0.4 mmol, 1 equiv). The inner wall of the Schlenck tube was rinsed with acetonitrile (0.4 mL) and the tube was then sealed, placed in a preheated oil bath set at 80 °C and stirred for 15 hours. The crude was then filtered over celite at room temperature using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles under vacuum, purification by flash chromatography (silica gel; ethyl acetate/methanol: 9:1) afforded compound **2** (97 mg, 83%).

3-Cyclohexyl-1-(dimethyl(oxo)-λ^6-sulfaneylidene)-1-phenylpropan-2-one (2). Off-white solid; m.p.: 109-112 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.27 (m, 3H), 7.25-7.21 (m, 2H), 3.47 (s, 6H), 2.01 (d, J = 7.3 Hz, 2H), 1.84-1.71 (m, 1H), 1.67-1.52 (m, 5H), 1.27-1.14 (m, 2H), 1.11-0.97 (m, 1H), 0.77 (q, J = 13.3 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 188.6, 134.8 (2C), 132.1, 128.4, (2C), 127.7, 86.7, 45.4, 43.1 (2C), 35.2, 33.2 (2C), 26.3, 26.2 (2C). IR (neat): $\tilde{\nu}$ = 3675 (w), 3063 (w), 3014 (w), 2943 (w), 2916 (m), 2848 (w), 1534 (s), 1490 (w), 1439 (w), 1375 (s), 1312 (w), 1294 (w), 1272 (w), 1225 (m), 1182 (s), 1112 (w), 1073 (w), 1007 (m), 994 (m), 965 (m), 939 (m), 916 (w), 888 (w), 848 (w), 795 (w), 760 (w), 742 (m), 701 (s); HRMS (ESI): *m/z* calcd for $C_{17}H_{25}O_2S$ $[M + H]^+$: 293.1570; found: 293.1578.

4-(1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-4-(1-methyl-1H-indol-3-yl)-2-oxobutyl)benzonitrile (3). Obtained from **38** (111 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography

(silica gel; ethyl acetate/methanol = 9:1): 135 mg, 89%. Off-white solid; m.p.: 127–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (dt, *J* = 8.3, 2.1 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.19 (dd, *J* = 6.9, 0.8 Hz, 1H), 7.05-7.00 (m, 3H), 6.70 (s, 1H), 3.68 (s, 3H), 3.44 (s, 6H), 3.02 (t, *J* = 7.4 Hz, 2H), 2.56 (t, *J* = 7.4 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 188.0, 137.0, 136.6, 134.1 (2C), 131.4 (2C), 127.5, 126.0, 121.3, 118.7, 118.7, 188.3, 113.9, 109.9, 108.9, 85.0, 43.1 (2C), 38.9, 32.3, 21.2. IR (neat): $\tilde{\nu}$ = 3082 (w), 3038 (w), 3013 (w), 2967 (w), 2926 (w), 2855 (w), 2226 (m), 1600 (w), 1560 (s), 1497 (w), 1485 (w), 1474 (w), 1450 (w), 1434 (w), 1419 (w), 1395 (w), 1377 (w), 1343 (m), 1329 (m), 1321 (m), 1279 (w), 1264 (w), 1248 (w), 1223 (m), 1205 (m), 1172 (s), 1119 (w), 1065 (m), 1036 (m), 1008 (w), 976 (w), 934 (m), 915 (w), 847 (w), 800 (w), 748 (s), 735 (m), 697 (m), 656 (w). HRMS (ESI): *m/z* calcd for $C_{22}H_{23}N_2O_2S$ $[M + H]^+$: 379.1475; found: 379.1479.

4-(1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-2-oxo-3-(1H-pyrrol-1-yl)propyl)benzonitrile (4). Obtained from **39** (80 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel; ethyl acetate/methanol = 97:3 to 93:7): 95 mg, 79%. Light-brown solid; m.p: 123–125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.64 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 6.52 (t, *J* = 2.1 Hz, 2H), 6.11 (t, *J* = 2.1 Hz, 2H), 4.46 (s, 2H), 3.51 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): *δ* 180.9, 135.6, 134.4 (2C), 132.1 (2C), 121.4 (2C), 118.5, 111.2, 108.3 (2C), 83.9, 54.2, 42.9 (2C); IR (neat): $\tilde{\nu}$ = 3094 (w), 3012 (w), 2915 (w), 2228 (m), 1603 (w), 1541 (s), 1500 (m), 1432 (w), 1391 (w), 1382 (w), 1329 (w), 1296 (w), 1280 (w), 1226 (w), 1195 (s), 1183 (s), 1116 (w), 1095 (w), 1070 (w), 1056 (w), 1013 (m), 986 (w), 969 (m), 955 (M), 932 (w), 908 (w), 888 (w), 847 (w), 836 (w), 807 (w), 774 (w), 731 (s), 738 (s), 688 (w), 654 (w). HRMS (ESI): *m/z* calcd for $C_{16}H_{16}N_2NaO_2S$ $[M + Na]^+$: 323.0825; found: 323.0823.

4-(3-(Benzyloxy)-1-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-oxopropyl)benzonitrile (5). Obtained from **40** (96 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel; ethyl acetate/methanol = 9:1): 112 mg, 82%. Orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (dt, J = 8.4, 1.9 Hz, 2H), 7.35-7.21 (m, 7H), 4.52 (s, 2H), 4.00 (s, 2H), 3.57 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 183.2, 137.4, 135.8, 133.8 (o, 2C), 131.6 (o, 2C), 128.1 (o, 2C), 127.7 (o, 2C), 127.5 (o), 118.6 (e), 110.4 (e), 84.1 (e), 73.1 (e), 71.8 (e), 42.9 (o, 2C). IR (neat): $\tilde{\nu}$ = 3006 (w), 2919 (w), 2858 (w), 2224 (m), 1542 (s), 1499 (m), 1454 (w), 1404 (m), 1328 (m), 1307 (m), 1198 (s), 1179 (s), 1104 (s), 1020 (s), 970 (m), 942 (w), 912 (w), 837 (w), 734 (s), 699 (m), 683 (w). HRMS (ESI): *m/z* calcd for $C_{19}H_{20}NO_3S$ $[M + H]^+$: 342.1158; found: 342.1165.

***Tert*-butyl (4-(4-cyanophenyl)-4-(dimethyl(oxo)-λ^6-sulfaneylidene)-3-oxobutan-2-yl)carbamate (6)**. Obtained from racemic **41** (105 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel; ethyl acetate/methanol = 95:5 to 92:8): 127 mg, 87%. Yellow solid; m.p.: 130-133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 5.28 (d, J = 7.3 Hz, 1H), 4.29 (q, J = 7.3 Hz, 1H), 3.53 (s, 3H), 3.42 (s, 3H), 1.35 (s, 9H), 1.00 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.5 (e), 154.8 (e), 135.9 (e), 134.6 (o, 2C), 132.0 (o, 2C), 118.6 (e), 110.9 (e), 83.1 (e), 78.9 (e), 49.5 (o), 42.9 (o), 42.8 (o), 28.2 (o, 3C), 19.3 (o); IR (neat): $\tilde{\nu}$ = 3245 (m, br), 2934 (m), 2934 (w), 2227 (m), 1685 (s), 1603 (w), 1536 (s), 1452 (w), 1391 (m), 1365 (m), 1337 (w), 1311 (w), 1296 (m), 1280 (m), 1253 (m), 1213 (m), 1199 (s), 1165 (s), 1107 (m), 1058 (m), 1011 (s), 963 (m), 943 (m), 880 (w), 852 (w), 792 (w), 744 (m), 681 (m). HRMS (ESI): *m/z* calcd for $C_{18}H_{25}N_2O_4S$ $[M + H]^+$: 365.1530; found: 365.1532.

***Tert*-butyl 4-(2-(4-cyanophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetyl)piperidine-1-carboxylate (7)**. Obtained from **42** (121 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure (after purification by flash chromatography (ethyl acetate/methanol = 95:5 to 92:8): 138 mg, 85%. Off-white solid; m.p.: 154–156 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 4.01 (br s, 2H), 3.49 (s, 6H), 2.57-2.36 (m, 3H), 1.60 (qd, J = 12.8, 4.4 Hz, 2H), 1.53-1.42 (m, 2H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 189.9, 154.5, 136.8, 134.3 (2C), 131.9 (2C), 118.6, 110.7, 84.1, 79.2, 43.4 (2C), 43.1 (2C, not visible but inferred from HSQC), 42.8, 28.4 (2C), 28.3 (3C); IR (neat): $\tilde{\nu}$ = 3667 (w), 3008 (w), 2976 (w), 2919 (w), 2855 (w), 2228 (m), 1673 (s), 1601 (w), 1571 (w), 1540 (s), 1499 (w), 1477 (w), 1466 (w), 1431 (m), 1388 (m), 1364 (w), 1349 (w), 1304 (w), 1273 (w), 1242 (w), 1192 (s), 1159 (s), 1125 (m), 1068 (w), 1031 (s), 989 (w), 965 (m), 945 (w), 928 (w), 865 (w), 845 (w), 812 (w), 756 (w), 727 (s), 680 (w). HRMS (ESI): *m/z* calcd for $C_{21}H_{29}N_2O_4S$ $[M + H]^+$: 405.1843; found: 405.1849.

4-(1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-2-oxo-3,3-diphenylpropyl)benzonitrile (8). Obtained from **43** (115 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel; petroleum ether/ethyl acetate = 1:4): 138 mg, 89%. Pale-orange solid; m.p.: 99–102 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, J = 7.6 Hz, 2H), 7.30-7.16 (m, 12H), 5.01 (s, 1H), 3.49 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 185.9, 140.5 (2C), 136.7, 134.7 (2C), 131.7 (2C), 128.6 (4C), 128.2 (4C), 126.4 (2C), 118.6, 110.8, 85.5, 57.7, 43.0 (2C). IR (neat): $\tilde{\nu}$ = 3674 (w), 3083 (w), 3060 (w), 3029 (w), 3008 (w), 2913 (w), 2221 (m), 1755 (w), 1718 (w), 1673 (w), 1600 (m), 1539 (s), 1495 (m), 1448 (w), 1397 (w), 1371 (m), 1302 (m), 1272 (w), 1198 (s), 1180 (m), 1110 (w),

1077 (w), 10323 (w), 1014 (m), 970 (m), 957 (w), 935 (m), 877 (w), 836 (m), 782 (w), 734 (s), 704 (s), 681 (m). HRMS (ESI): *m/z* calcd for $C_{24}H_{22}NO_2S$ $[M + H]^+$: 388.1366; found: 388.1363.

4-(2-(3,5-Bis(trifluoromethyl)phenyl)-1-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-oxoethyl)benzonitrile (9). Obtained from **32** (132 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel; petroleum ether/ethyl acetate = 6:4 to 3:7): 142 mg, 82%. Yellow solid; m.p.: 91–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (s, 3H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 3.67 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.1, 141.4, 136.4, 134.3 (2C), 131.8 (2C), 131.0 (q, *J* = 34.0 Hz, 2C), 128.9* (q, *J* = 2.6 Hz), 123.1 (sept, *J* = 3.7 Hz, 2C), 121.7 (q, *J* = 273.2 Hz, 2C), 118.5, 110.6, 86.8, 42.8 (2C) (the signal marked by an asterisk is an unresolved quartet; the coupling constant was determined from the two central resonances). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): *δ* -63.2. IR (neat): $\tilde{\nu}$ = 3675 (w), 3075 (w), 3004 (w), 2989 (w), 2918 (w), 2223 (m), 1624 (w), 1602 (w), 1538 (s), 1505 (m), 1444 (w), 1407 (w), 1389 (w), 1349 (m), 1275 (s), 1240 (m), 1211 (m), 1196 (m), 1169 (s), 1112 (s), 1027 (s), 991 (w), 968 (w), 944 (w), 922 (w), 891 (s), 844 (m), 835 (m), 754 (m), 729 (m), 698 (m), 678 (s). HRMS (ESI): *m/z* calcd for $C_{19}H_{14}F_6NO_2S$ $[M + H]^+$: 434.0644; found: 434.0644.

4-(1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-2-(4-methoxyphenyl)-2-oxoethyl)benzonitrile (10). Obtained from **44** (91 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel; ethyl acetate/methanol = 95:5 to 90:10): 105 mg, 80%. Yellow solid; m.p.: 149–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.40 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 3.71 (s, 3H), 3.60 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): *δ* 183.1, 160.8, 138.0, 133.9 (2C), 131.8, 131.3 (2C), 130.4 (2C), 119.0, 112.8 (2C), 109.2, 84.5,

55.0, 43.3 (2C). IR (neat): $\tilde{\nu}$ = 2991 (w), 2914 (w), 2839 (w), 2228 (s), 1601 (m), 1579 (m), 1505 (s), 1494 (s), 1463 (w), 1374 (s), 1303 (m), 1250 (s), 1187 (s), 1171 (s), 1119 (w), 1016 (s), 984 (w), 967 (w), 954 (m), 942 (m), 861 (w), 844 (s), 818 (m), 781 (w), 770 (w), 757 (s), 728 (m), 689 (w), 675 (w). HRMS (ESI): *m/z* calcd for $C_{18}H_{18}NO_3S$ $[M + H]^+$: 328.1002; found: 328.1007.

4-(1-(Dimethyl(oxo)-λ⁶-sulfaneylidene)-2-oxo-2-(thiophen-2-yl)ethyl)benzonitrile (11). Obtained from **45** (81 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel, ethyl acetate to ethyl acetate/methanol = 95:5): 95 mg, 82%. Off-white solid; m.p.: 201–203 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62-7.57 (m, 2H), 7.44-7.40 (m ,2H), 7.32 (dd, J = 5.0, 1.1 Hz, 1H), 6.81 (dd, J = 5.0, 3.8 Hz, 1H), 6.66 (dd, J = 3.8, 1.0 Hz, 1H), 3.65 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 174.4, 144.8, 136.7, 135.5 (2C), 132.0 (2C), 129.6, 129.3, 127.1, 118.8, 111.3, 83.9, 43.6 (2C). IR (neat): $\tilde{\nu}$ = 3112 (w), 3069 (w), 3023 (w), 2999 (m), 2914 (w), 2220 (m), 1601 (w), 1518 (m), 1504 (s), 1492 (s), 1415 (m), 1405 (m), 1380 (s), 1347 (w), 1306 (w), 1289 (w), 1251 (m), 1230 (w), 1191 (s), 1180 (s), 1108 (w), 1092 (m), 1071 (w), 1044 (w), 1020 (s), 980 (m), 962 (m), 947 (s), 868 (w), 846 (m), 831 (w), 763 (m), 741 (m), 718 (s), 674 (m), 664 (m). HRMS (ESI): *m/z* calcd for $C_{15}H_{14}NO_2S_2$ $[M + H]^+$: 304.0460; found: 304.0495.

4-(1-(Dimethyl(oxo)-λ⁶-sulfaneylidene)-2-(5-methylisoxazol-3-yl)-2-oxoethyl)benzonitrile (12). Obtained from **46** (80 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel, ethyl acetate/methanol = 95:5 to 92:8): 100 mg, 83%. Beige solid; m.p.: 162–165 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (dt, J = 8.5, 1.8 Hz, 2H), 7.32 (dt, J = 8.5, 1.8 Hz, 2H), 5.90 (s, 1H), 3.66 (s, 6H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 172.2, 169.0, 162.3, 135.6, 134.4 (2C), 131.4 (2C), 118.7, 110.6, 101.1, 88.1, 42.5 (2C), 11.9. IR (neat): $\tilde{\nu}$ = 3122 (w), 2995

(w), 2914 (w), 2227 (m), 1601 (m), 1526 (s), 1444 (m), 1406 (m), 1348 (m), 1308 (m), 1274 (w), 1260 (m), 1992 (s), 1108 (w), 1017 (s), 986 (w), 961 (m), 943 (s), 920 (w), 900 (m), 846 (m), 792 (w), 765 (m), 738 (w), 727 (w), 681 (m), 657 (w). HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_2NaO_3S$ [M + Na]$^+$: 325.0617; found: 325.0622.

1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-1-phenylpropan-2-one (13). Obtained from **34** (134 mg, 1.0 mmol, 1 equiv) and bromobenzene (160 μL, 2.5 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography on a short pad of silica gel (ethyl acetate/methanol = 90:10 to 87:13): 147 mg, 70%. Amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.25 (m, 5H), 3.49 (s, 6H), 1.90 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.4, 134.3 (2C), 132.5, 128.4 (2C), 127.7, 85.8, 42.9 (2C), 26.5. IR (neat): $\tilde{\nu}$ = 3393 (w), 3013 (m), 2921 (m), 1532 (s), 1489 (m), 1410 (w), 1366 (s), 1308 (w), 1234 (s), 1166 (s), 1023 (s), 1001 (s), 967 (m), 939 (w), 914 (w), 850 (w), 804 (w), 760 (m), 738 (w), 702 (s), 661 (w), 654 (w). HRMS (ESI): *m/z* calcd for $C_{11}H_{15}O_2S$ [M + H]$^+$: 211.0787; found: 211.0790.

1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-1-(p-tolyl)propan-2-one (14). Obtained from **34** (54 mg, 0.4 mmol, 1 equiv) and 4-bromotoluene (123 μL, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography on a short pad of silica gel (ethyl acetate/methanol = 90:10 to 86:14): 62 mg, 69%. Amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (apparent broad s, 4H), 3.46 (s, 6H), 2.35 (s, 3H), 1.88 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.5, 137.6, 134.2 (2C), 129.4, 129.3 (2C), 85.4, 42.8 (2C), 26.5, 21.1; IR (neat): $\tilde{\nu}$ = 3350 (m), 3018 (m), 2920 (m), 2232 (w), 1536 (s), 1509 (m), 1406 (m), 1366 (s), 1306 (w), 1234 (s), 1165 (s), 1107 (w), 1024 (s), 970 (m), 940 (w), 923 (w), 814 (m), 794 (w), 722 (s), 695 (m). HRMS (ESI): *m/z* calcd for $C_{12}H_{17}O_2S$ [M + H]$^+$: 225.0944; found: 225.0947.

1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-1-(4-methoxyphenyl)propan-2-one (15). This compound was obtained from **34** (54 mg, 0.4 mmol, 1 equiv) and 4-bromo-anisole (125 μL, 1.0 mmol, 2.5 equiv) following the representative procedure. The compound underwent degradation under the reaction conditions but the maximal yield reached 51% after 2 hours of reaction as judged by ^{1}H NMR with internal standard (1,3,5-trimethoxybenzene). Attempted purification by flash chromatography on a short pad of silica gel (ethyl acetate/methanol = 4:1 to 1:1) gave 26% of the compound contaminated by some remaining starting material **34** (5%) and DMSO (1%). Only the resonances corresponding to **15** are described herein. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (dt, J = 8.7, 2.1 Hz 2H), 6.88 (dt, J = 8.7, 2.1 Hz, 2H), 3.81 (s, 3H), 3.46 (s, 6H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.8, 159.3, 135.7 (2C), 124.5, 113.4 (2C), 85.0, 55.2, 42.8 (2C), 26.5.

1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-1-(4-nitrophenyl)propan-2-one (16). Obtained from **34** (54 mg, 0.4 mmol, 1 equiv) and 1-bromo-4-nitrobenzene (202 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel, ethyl acetate/methanol = 95:5 to 90:10): 92 mg, 90%. Yellow solid; m.p.: 135-140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dt, J = 8.9, 2.1 Hz, 2H), 7.36 (dt, J = 8.9, 2.1 Hz, 2H), 3.56 (s, 6H), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.0, 146.0, 139.8, 133.5 (2C), 123.1 (2C), 84.6 (e), 43.5 (2C), 26.5. IR (neat): $\tilde{\nu}$ = 3066 (w), 3022 (w), 3000 (w), 2916 (m), 2436 (w), 1586 (m), 1526 (s), 1508 (s), 1437 (w), 1405 (w), 1363 (m), 1346 (m), 1324 (s), 1307 (m), 1245 (m), 1194 (s), 1108 (s). HRMS (ESI): *m/z* calcd for $C_{11}H_{14}NO_4S$ $[M + H]^+$: 256.0638; found: 256.0644.

4-(1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-2-oxopropyl)benzonitrile (17). Obtained from **34** (54 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel, ethyl acetate/methanol = 95:5 to 85:15): 70 mg, 74%. Yellow solid; m.p.: 106-109 °C. ^{1}H NMR (500

MHz, $CDCl_3$): δ 7.55 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 3.51 (s, 6H), 1.92 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.8, 137.6, 133.8 (2C), 131.7 (2C), 118.8, 110.0, 84.7, 43.3 (2C), 26.4. IR (neat): $\tilde{\nu}$ = 3411 (w), 3054 (w), 3016 (m), 2995 (m), 2910 (m), 2227 (s), 1601 (m), 1521 (s), 1403 (w), 1376 (s), 1348 (w), 1310 (m), 1267 (w), 1242 (m), 1200 (s), 1114 (w), 1033 (s), 1011 (m), 985 (w), 968 (s), 949 (s), 917 (w), 865 (w), 850 (m), 840 (m), 777 (m), 732 (s), 685 (s). HRMS (ESI): *m/z* calcd for $C_{12}H_{14}NO_2S$ $[M + H]^+$: 236.0740; found: 236.0742.

1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-1-(4-(trifluoromethyl)phenyl)propan-2-one (**18**). Obtained from **34** (54 mg, 0.4 mmol, 1 equiv) and 4-bromobenzotrifluoride (140 µL, 1.0 mmol, 2.5 equiv) following the representative procedure) and after purification by flash chromatography (silica gel, ethyl acetate/methanol = 9:1): 96 mg, 86. Off-white amorphous solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 3.48 (s, 6H), 1.89 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.0, 136.3, 134.0 (2C), 128.9 (q, J = 32.0 Hz), 125.0 (q, J = 3.5 Hz, 2C) 124.1 (q, J = 272.0 Hz), 84.5, 43.1 (2C), 26.4 (o). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ -62.4. IR (neat): $\tilde{\nu}$ = 3025 (w), 2925 (w), 1609 (w), 1538 (s), 1403 (w), 1376 (m), 1322 (s), 1241 (m), 1177 (s), 1110 (s), 1067 (s), 1019 (m), 1005 (m), 983 (w), 972 (w), 946 (w), 835 (s), 777 (w), 735 (m), 701 (m), 664 (w). HRMS (ESI): *m/z* calcd for $C_{12}H_{14}F_3O_2S$ $[M + H]^+$: 279.0661; found: 279.0667.

1-(4-Chlorophenyl)-1-(dimethyl(oxo)-λ^6-sulfaneylidene)propan-2-one (19). Obtained from **34** (54 mg, 0.4 mmol, 1 equiv) and 1-bromo-4-chlorobenzene (192 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel, ethyl acetate/methanol = 95:5 to 85:15): 68 mg, 69%. Yellow solid; m.p.: 111–114 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 (dt, J = 8.5, 2.5 Hz, 2H), 7.16 (dt, J = 8.6, 2.1 Hz, 2H), 3.46 (s, 6H), 1.86 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.1, 135.4 (2C), 133.6, 130.8, 128.5 (2C),

84.2, 42.9 (2C), 26.4. IR (neat): $\tilde{\nu}$ = 3050 (w), 3030 (w), 3014 (m), 2998 (w), 2929 (m), 1587 (w), 1552 (s), 1488 (m), 1421 (w), 1395 (w), 1361 (s), 1343 (m), 1322 (w), 1259 (w), 1235 (s), 1177 (w), 1156 (s), 1101 (w), 1086 (m), 1057 (w), 1033 (s), 1012 (s), 989 (m), 979 (s), 924 (m), 911 (m), 842 (m), 818 (m), 752 (m), 730 (w), 718 (m), 689 (m). HRMS (ESI): *m/z* calcd for $C_{11}H_{14}ClO_2S$ $[M + H]^+$: 245.0398; found: 245.0402.

1-(3,5-Difluorophenyl)-1-(dimethyl(oxo)-λ⁶-sulfaneylidene)propan-2-one (20). Obtained from **34** (54 mg, 0.4 mmol, 1 equiv) and 1-bromo-3,5-difluorobenzene (110 µL, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel, ethyl acetate/methanol = 95:5 to 90:10): 68 mg, 69%. Yellow solid; m.p.: 134–136 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82–6.70 (m, 3H), 3.51 (s, 6H), 1.93 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.1, 163.4 (d, J = 13.6 Hz, 2C), 161.5 (d, J = 13.6 Hz), 135.6 (t, J = 10.0 Hz), 116.7 (dd, J = 19.0, 5.8 Hz, 2C), 103.0 (t, J = 25.4 Hz), 43.2 (2C), 26.5 (o); $^{19}F\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ -110.6. IR (neat): $\tilde{\nu}$ = 3675 (w), 3063 (w), 3014 (w), 2943 (w), 2916 (m), 2848 (w), 1534 (s), 1490 (w), 1439 (w), 1375 (s), 1312 (w), 1294 (w), 1272 (w), 1225 (m), 1182 (s), 1112 (w), 1073 (w), 1007 (m), 994 (m), 965 (m), 939 (m), 916 (w), 888 (w), 848 (w), 795 (w), 760 (w), 742 (m), 701 (s). HRMS (ESI): *m/z* calcd for $C_{11}H_{13}F_2O_2S$ $[M + H]^+$: 247.0608; found: 247.0599.

1-(Dimethyl(oxo)-λ⁶-sulfaneylidene)-3,3-diphenyl-1-(thiophen-3-yl)propan-2-one (21). Obtained from **43** (115 mg, 0.4 mmol, 1 equiv) and 3-bromothiophene (94 µL, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel, hexane/ethyl acetate = 1:1 to 1:4): 92 mg, 63%. Off-white solid; m.p.: 118–120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.16 (m, 11H), 7.03 (dd, J = 2.9, 1.0 Hz, 1H), 6.83 (dd, J = 4.8, 0.9 Hz, 1H), 5.03 (s, 1H), 3.40 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 187.0, 141.3 (2C), 132.5, 131.0, 129.3, 129.0 (4C), 128.3 (4C), 126.4 (2C), 125.2, 80.6, 57.9, 42.5 (2C). IR (neat): $\tilde{\nu}$

= 3081 (w), 3060 (w), 3026 (w), 2929 (w), 1753 (w), 1716 (w), 1656 (w), 1560 (s), 1492 (m), 1447 (w), 1392 (w), 1344 (m), 1315 (w), 1304 (w), 1248 (w), 1210 (w), 1168 (s) 1155 (s), 1076 (w), 1028 (s), 953 (w), 927 (w), 904 (w), 876 (w), 850 (m), 807 (m), 783 (w), 752 (w), 736 (m), 714 (s), 699 (s), 683 (s). HRMS (ESI): *m/z* calcd for $C_{21}H_{21}O_2S_2$ $[M + H]^+$: 369.0977; found: 369.0978.

1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-1-(2,6-dimethylpyridin-4-yl)propan-2-one (22). Obtained from **34** (54 mg, 0.4 mmol, 1 equiv) and 4-bromo-2,6-dimethylpyridine (186 mg, 1 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel, ethyl acetate/methanol = 85:15 to 80:20): 92 mg, 96%. Yellow solid; m.p.: 138–141 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 (s, 2H), 3.44 (s, 6H), 2.41 (s, 6H), 1.88 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.9, 157.2 (2C), 141.2, 124.2 (2C), 84.1, 43.2 (2C), 26.3, 24.2 (2C); IR (neat): $\tilde{\nu}$ = 3037 (w), 2977 (w), 2922 (w), 2904 (w), 1597 (m), 1567 (s), 1549 (s), 1397 (m), 1384 (m), 1356 (m), 1291 (s), 1221 (w), 1170 (s), 1063 (m), 1031 (s), 998 (m), 948 (w), 911 (w), 893 (w), 870 (w), 787 (w), 756 (w), 741 (m), 688 (m). HRMS (ESI): *m/z* calcd for $C_{12}H_{18}NO_2S$ $[M + H]^+$: 240.1053; found: 240.1057.

1-([1,1'-Biphenyl]-4-yl)-3-cyclohexyl-1-(dimethyl(oxo)-λ^6-sulfaneylidene)propan-2-one (23). Obtained from **1** (87 mg, 0.4 mmol, 1 equiv) and (1,1'-biphenyl)-4-yl trifluoromethanesulfonate[57] (302 mg, 1.0 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography (silica gel, ethyl acetate/methanol = 95:5 to 92/8): 79 mg, 54%. White solid; m.p.: 126–128 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 7.3 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 3.49 (s, 6H), 2.08 (d, J = 7.1 Hz, 2H), 1.87-1.76 (m, 1H), 1.76-1.70 (m, 5H), 1.29-1.18 (m, 2H), 1.12-1.00 (m, 1H), 0.86-0.76 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 188.5, 140.4, 140.2, 135.0 (2C), 131.0,

128.7 (2C), 127.3, 127.0 (2C), 126.9 (2C), 86.2, 45.4, 43.1 (2C), 35.2, 33.1 (2C), 26.3, 26.2 (2C). IR (neat): $\tilde{\nu}$ = 3025 (w), 2918 (s), 2846 (m), 1550 (s), 1485 (m), 1446 (w), 1374 (m), 1321 (w), 1276 (w), 1254 (w), 1228 (m), 1177 (s), 1164 (s), 1112 (m), 1076 (w), 1066 (w), 1008 (m), 1019 (m), 969 (w), 937 (w), 889 (w), 836 (w), 796 (w), 765 (m), 730 (s), 693 (s). HRMS (ESI): *m/z* calcd for $C_{23}H_{29}O_2S$ $[M + H]^+$: 369.1883; found: 369.1887.

7-(1-(Dimethyl(oxo)-λ⁶-sulfaneylidene)-2-oxo-3,3-diphenylpropyl)-2H-chromen-2-one (24). Obtained from **43** (115 mg, 0.4 mmol, 1 equiv) and 2-oxo-2H-chromen-7-yl trifluoromethanesulfonate[7] (294 mg, 1.0 mmol, 2.5 equiv) following the representative procedure but using 2 mL of acetonitrile and after purification by flash chromatography (silica gel, petroleum ether/ethyl acetate = 1:1 to ethyl acetate only) and trituration with diethyl ether: 86 mg, 50%. Coral-colored solid; m.p.: 134–138 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 9.5 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.29-7.23 (m, 4H), 7.23-7.17 (m, 6H), 7.14 (d, J = 0.8 Hz, 1H), 7.04 (dd, J = 7.9, 1.5 Hz, 1H), 6.41 (d, J = 9.5 Hz, 1H), 5.07 (s, 1H), 3.53 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.1, 160.5, 153.6, 142.9, 140.7 (2C), 135.7, 130.6, 128.8 (4C), 128.3 (4C), 127.2, 126.5 (2C), 122.1, 118.0, 116.6, 85.5, 57.7, 43.1 (2C). IR (neat): $\tilde{\nu}$ = 3660 (w), 3060 (w), 3025 (w), 3008 (m), 2924 (w), 1721 (s), 1610 (m), 1540 (s), 1493 (m), 1449 (w), 1402 (m), 1360 (m), 1308 (m), 1290 (w), 1278 (w), 1247 (m), 1227 (w), 1193 (s), 1152 (m), 1134 (m), 1103 (m), 1077 (w), 1024 (s), 1013 (m), 982 (m), 941 (m), 924 (m), 909 (w), 897 (w), 878 (w), 816 (w), 784 (w), 770 (w), 750 (m), 727 (m), 719 (s), 695 (s). HRMS (ESI) *m/z* calcd for $C_{26}H_{22}NaO_4S$ $[M + Na]^+$: 453.1131; found: 453.1136.

4-(1-(Dimethyl(oxo)-λ⁶-sulfaneylidene)-2-oxoethyl)benzonitrile (25). Obtained from **47** (48 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography on a short pad of silica

gel (ethyl acetate/methanol = 92:8 to 85:15; the silica was pre-treated with an ethyl acetate/methanol/triethylamine (92:8:1) mixture, and then washed with ethyl acetate/methanol (92:8) before loading the crude mixture): 74 mg, 83%. Beige amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.92 (s, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 3.58 (s, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 178.0, 137.2, 132.0 (2C), 128.5 (2C), 119.1, 108.5, 87.5, 42.6 (2C). IR (neat): $\tilde{\nu}$ = 3661 (w), 3028 (w), 2989 (w), 2919 (w), 2903 (w), 2219 (m), 1577 (s), 1503 (m), 1415 (w), 1391 (m), 1313 (s), 1303 (s), 1275 (w), 1189 (s), 1175 (s), 1113 (w), 1076 (w), 1066 (w), 1056 (w), 1025 (s), 984 (m), 959 (m), 946 (m), 919 (w), 835 (m), 819 (m), 770 (w), 739 (m), 724 (w), 703 (m), 656 (w). HRMS (ESI): *m/z* calcd for $C_{11}H_{12}NO_2S$ $[M + H]^+$: 222.0583; found: 222.0585.

2-(1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-2-oxoethyl)benzonitrile (26). Obtained from **47** (54 mg, 0.4 mmol, 1 equiv) and 2-bromobenzonitrile (182 mg, 1 mmol, 2.5 equiv) following the representative procedure and after purification by flash chromatography on a short pad of silica gel (ethyl acetate/methanol = 90:10 to 84:16; the silica was pre-treated with an ethyl acetate/methanol/triethylamine (90:10:1) mixture, and then washed with ethyl acetate/methanol (90:10) before loading the crude mixture): 76 mg, 85%. Beige amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.63 (dd, J = 7.8, 1.1 Hz, 1H), 7.52 (td, J = 7.8, 1.5 Hz, 1H), 7.38-7.31 (m, 2H), 3.61 (s, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 177.5, 134.9, 134.1, 132.8, 132.6, 127.5, 119.5, 116.1, 84.9, 42.2 (2C). IR (neat): $\tilde{\nu}$ = 3026 (w), 2995 (w, 2915 (w), 2854 (w), 2220 (m), 1154 (s), 1483 (m), 1450 (w), 1400 (m), 1358 (m), 1330 (w), 1314 (w), 1281 (w), 1261 (w), 1204 (s), 1163 (m), 1103 (w), 1004 (s), 994 (w), 949 (m), 939 (m), 877 (w), 788 (w), 763 (m), 952 (m), 742 (s), 701 (w), 686 (s). HRMS (ESI): *m/z* calcd for $C_{11}H_{12}NO_2S$ $[M + H]^+$: 222.0583; found: 222.0583.

1-(Dimethyl(oxo)-λ^6-sulfaneylidene)-1-(4-((2-(dimethylamino)ethoxy)(phenyl)methyl)phenyl)-3,3-diphenylpropan-2-one (27). Under nitrogen, a J-Young Schlenck tube was charged with XPhos (21 mg, 0.044 mmol, 0.11 equiv), Pd_2dba_3 (18 mg, 0.02 mmol, 0.05 equiv) and Cs_2CO_3 (143.4 mg, 0.44 mmol, 1.1 equiv). Acetonitrile (0.4 mL) was then added and the mixture was stirred at room temperature for 10 minutes. Then, bromazine (147 mg, 0.44 mmol, 1.1 equiv) was added in solution in acetonitrile (0.4 mL) followed by sulfoxonium ylide **43** (115 mg, 0.4 mmol, 1 equiv). The tube was then sealed, placed in a preheated oil bath set at 80 °C and stirred for 13 hours. The crude was then filtered over celite at room temperature using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles, purification by flash chromatography (silica gel, CH_2Cl_2/MeOH: 95:5 to 85:15) afforded compound **27** (170 mg, 79%). Amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.31 (m, 4H), 7.30-7.25 (m, 3H), 7.27-7.19 (m, 4H), 7.18-7.13 (m, 6H), 7.08 (d, J = 8.2 Hz, 2H), 5.38 (s, 1H), 4.98 (s, 1H), 3.62 (t, J = 5.7 Hz, 2H), 3.45 (s, 6H), 2.69 (t, J = 5.8 Hz, 2H), 2.34 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.2, 141.8, 141.6, 141.0 (2C), 134.7 (2C), 130.6, 128.8 (4C), 128.2 (2C), 127.9 (4C), 127.4, 126.9 (2C), 126.8 (2C), 126.0 (2C), 86.6, 83.5, 66.8, 58.5, 57.4, 45.5 (2C), 42.5 (2C). IR (neat): $\tilde{\nu}$ = 3416 (w), 3023 (w), 2971 (w), 2971 (w), 2923 (w), 2820 (w), 2771 (w), 1599 (w), 1546 (s), 1493 (m), 1451 (m), 1406 (w), 1362 (w), 1302 (w), 1266 (w), 1186 (s), 1165 (s), 1098 (m), 1073 (m), 1057 (m), 1021 (s), 971 (m), 935 (w), 853 (w), 811 (w), 784 (w), 737 (m), 697 (s). HRMS (ESI): *m/z* calcd for $C_{34}H_{38}NO_3S$ $[M + H]^+$: 540.2567; found: 540.2570.

***Tert*-butyl (5-(dimethyl(oxo)-λ^6-sulfaneylidene)-4-oxo-5-phenylpentyl)carbamate (29)**. Under nitrogen, a J-Young Schlenck tube was charged with XPhos (189 mg, 0.396 mmol, 0.11 equiv), Pd_2dba_3 (165 mg, 0.18 mmol, 0.05 equiv) and Cs_2CO_3 (1.29 g, 3.96 mmol, 1.1 equiv). Acetonitrile

(3.6 mL) was then added and the mixture was stirred at room temperature for 10 minutes. Then, bromobenzene (0.58 mL, 5.4 mmol, 1.5 equiv) was added followed by sulfoxonium ylide **28** (1.00 g, 3.6 mmol, 1 equiv). The inner wall of the Schlenck tube was rinsed with acetonitrile (3.6 mL) and the tube was then sealed, placed in a preheated oil bath set at 80 °C and stirred for 15 hours. The crude was then filtered over celite at room temperature using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles, purification by flash chromatography (silica gel, ethyl acetate/methanol: 95:5 to 9:1) afforded compound **29** (1.00 g, 79%). Off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.30 (m, 3H), 7.28-7.22 (m, 2H), 4.80 (br s, 1H), 3.49 (s, 6H), 3.14-2.96 (m, 2H), 2.19 (t, J = 6.6 Hz, 2H), 1.71 (q, J = 6.6 Hz, 2H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 188.2, 155.9, 134.6 (2C), 131.8, 128.6 (2C), 128.0, 82.2, 78.7, 43.0 (2C), 40.4, 35.5, 28.4 (3C), 25.3; IR (neat): $\tilde{\nu}$ = 3373 (m), 3019 (w), 2999 (w), 2969 (w), 2949 (w), 2930 (w), 2867 (w), 1684 (s), 1557 (s), 1520 (s), 1489 (w), 1447 (w), 1439 (w), 1409 (w), 1365 (m), 1346 (m), 1321 (w), 1290 (w), 1267 m), 1246 (s), 1189 (s), 1151 (s), 1088 (w), 1063 (w), 1030 (s), 988 (s), 938 (w), 915 (w0, 863 (w), 791 (w), 781 (w), 771 (w), 758 (w), 728 (w), 700 (m), 677 (w). HRMS (ESI): *m/z* calcd for $C_{18}H_{28}NO_4S$ $[M + H]^+$: 354.1734; found: 354.1740.

1-(3,5-Bis(trifluoromethyl)phenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylethan-1-one (33). Obtained from **32** (132 mg, 0.4 mmol, 1 equiv) and bromobenzene (107 µL, 1 mmol, 2.5 equiv) following the representative procedure and after difficult purification by flash chromatography (silica gel petroleum ether/ethyl acetate = 1:1 to 3:7) that led to a moderate yield despite a conversion of 73% determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard: 76 mg, 47%. White solid; m.p.: 145–147 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (s, 2H), 7.69 (s, 1H), 7.31-7.23 (m, 3H), 7.19-7.13 (m, 2H), 3.64 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz,

$CDCl_3$): δ 178.4, 141.9, 134.7 (2C), 130.8, 130.7 (q, J = 33.2 Hz, 2C), 128.9* (q, J = 3.3 Hz, 2C), 128.7 (2C), 128.2, 123.0 (q, J = 271.1 Hz, 2C), 122.6 (sept., J = 3.7 Hz), 88.3, 42.6 (2C) (the signal marked by an asterisk is an unresolved quartet; the coupling constant was determined from the two central resonances). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ -63.1. IR (neat): $\tilde{\nu}$ = 3083 (w), 3040 (w), 3023 (w), 2990 (w), 2914 (w), 1621 (w), 1523 (s), 1463 (w), 1436 (w), 1411 (m), 1348 (s), 1304 (w), 1283 (s), 1274 (s), 1232 (s), 1197 (s), 1187 (s), 1169 (s), 1159 (m), 1120 (s), 1109 (s), 1069 (w), 1012 (s), 984 (m), 961 (m), 935 (s), 905 (s), 876 (s), 843 (m), 773 (w), 753 (s), 699 (s), 681 (s), 672 (m). HRMS (ESI): *m/z* calcd for $C_{18}H_{15}F_6O_2S$ $[M + H]^+$: 409.0691; found: 409.0690.

Iridium-catalyzed cyclization. *Tert*-butyl 3-oxo-2-phenylpiperidine-1-carboxylate (**30**). Under nitrogen, a J-Young Schlenck tube was charged with **29** (71 mg, 0.2 mmol, 1 equiv) and $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%). The tube was evacuated and refilled three times with nitrogen. 1,2-Dichloroethane (1.0 mL) was then added and the mixture was stirred at 80 °C overnight. After cooling down to room temperature, the reaction mixture was transferred to a round bottomed flask using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles under vacuum, purification by flash chromatography (silica gel, petroleum ether/ethyl acetate: 90:10 to 85:15) afforded compound **30** (40 mg, 73%. Colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.35 (t, J = 7.4 Hz, 2H), 7.31-7.26 (m, 1H), 7.21 (d, J = 7.6 Hz, 2H), 5.64 (br s, 1H), 4.08 (br s, 1H), 3.39-3.24 (m, 1H), 2.53-2.37 (m, 2H), 2.01-1.83 (m, 2H), 1.43 (s, 9H), in agreement with previously reported data.[57]

Synthesis of complex 37. This complex was prepared in three steps. First, following the procedure described by Gómez-Ruiz and co-workers,[58] $PdCl_2$ (2.00 g, 11.3 mmol, 1 equiv) was dissolved in 37% HCl (12 mL) in a round-bottomed flask opened to air. The mixture was stirred until it cooled to room temperature and was then diluted with ethanol (226 mL) and filtered. The residue was

washed with ethanol (2 × 10 mL). Then, 1,5-cyclooctadiene (3.3 mL, 27.1 mmol, 2.4 equiv) was added while stirring, which triggered the immediate formation of a yellow precipitate. The reaction was allowed to stir for another 20 minutes. The solid was then filtered, washed with Et_2O (2 × 20 mL) and dried under high vacuum to afford dichloro(1,5-cyclooctadiene)palladium (3.07 g, 95%, yellow solid) which was used in the next step without further purification. Second, following the procedure described by Skrydstrup and co-workers,[59] dichloro(1,5-cyclooctadiene)palladium (2.00 g, 7 mmol, 1 equiv) was suspended in Et_2O (35 mL) in a flame-dried round bottom flask under nitrogen. The reaction was cooled to 0 °C and (trimethylsilyl)methylmagnesium chloride (1 M in Et_2O, 21 mL, 21.0 mmol, 3 equiv) was added dropwise over 10 minutes via syringe. The reaction was stirred at 0 °C for another 20 min. The reaction was quenched with acetone (1 mL). All volatiles were removed under high vacuum at 0 °C. The flask was then open to air. The residue was triturated with pentane (70 mL) at 0 °C. After filtration on celite, the filtrate was recovered into an ice-cooled round-bottomed flask and all volatiles were removed under vacuum at 0 °C. The flask containing the desired complex bis((trimethylsilyl)methyl)(1,5-cyclooctadiene)palladium (1.77 g, white solid, 65%) was transferred into an argon-filled glovebox for storage at -30 °C. The compound can be handled briefly at room temperature and is air stable, but decomposes at quickly at room temperature and turns black. The compound can be stored indefinitely at 0 °C or below. ^{1}H NMR (400 MHz, C_6D_6): δ 5.15 (s, 4H), 2.03-1.83 (m, 8H), 0.77 (s, 4H), 0.34 (s, 18H), in agreement with the previously reported data.[60] Finally, using a modification of the procedure reported by Iwasawa and co-workers,[48] a J-Young Schlenck tube was charged with $Pd(cod)(CH_2SiMe_3)_2$ (195 mg, 0.5 mmol, 1 equiv) and XPhos (238 mg, 0.5 mmol, 1 equiv) in an argon-filled glovebox. The tube was sealed and taken out of the glovebox. Under N_2, distilled cyclohexane (100 mL) and *p*-$CF_3C_6H_4Br$ (0.14 mL, 1 mmol, 2 equiv) were added. The tube was

sealed and the mixture was stirred at room temperature for 16 hours. Pentane (10 mL) was then added to the reaction which was then stirred slowly (*ca* 100 rpm) at -30 °C for 1 hour. The precipitate thus formed was filtered, washed with pentane (2 × 10 mL), and dried under high vacuum to afford **37** (126 mg, 31%). White solid. Crystals suitable for X-ray were obtained by slow evaporation over two weeks of a solution of complex **37** (10 mg) in CH_2Cl_2/hexane (1:2, 3 mL). The ^1H NMR (500 MHz, $CDCl_3$) is complicated by a slow equilibration between conformers.[61] $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ -61.90 (s), -61.95 (br s), -62.8 (s); $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 57.6 (br), 28.7, 26.7; HRMS (ESI, MeCN): *m/z* calcd for $C_{40}H_{53}F_3PPd$ $[M - Br]^+$: 727.2872; found: 727.2878.

Synthesis of bromazine. A flame-dried round bottom flask was charged with 2-(dimethylamino)ethan-1-ol (1.6 mL, 16 mmol, 2 equiv) in dry *p*-xylene (32 mL). 1-Bromo-4-(bromo(phenyl)methyl)benzene (2.61 g, 8 mmol, 1 equiv) was then added in solution in *p*-xylene (8 mL) and the mixture was heated to reflux for 24 hours. The reaction mixture was then cooled to 0 °C and a saturated aqueous solution of Na_2CO_3 (50 mL) was carefully added. The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. After filtration and evaporation of the solvent *in vacuo*, the crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 9:1) to afford bromazine (2.02 g, 76%, yellow oil). ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J = 8.3 Hz, 2H), 7.32-7.29 (m, 4 H), 7.27-7.20 (m, 3H), 5.31 (s, 1H), 3.55 (t, J = 6.0 Hz, 2H), 2.60 (t, J = 6.0 Hz, 2H), 2.27 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 141.7, 141.4, 131.4 (2C), 128.7 (2C), 128.5 (2C), 127.6, 127.0 (2C), 121.2, 83.3, 67.6, 58.9, 46.0 (2C). IR (neat): $\tilde{\nu}$ = 3026 (w), 2940 (w), 2861 (w), 2817 (w), 2768 (w), 2449 (w), 1590 (w), 1485 (m), 1453 (m), 1397 (m), 1337 (w), 1295 (w), 1184 (w), 1103 (s), 1070 (s), 1035 (s), 1010 (s), 957 (w), 930 (w), 889 (w), 794 (s), 748 (m),

714 (m), 714 (w), 700 (s), 673 (w). HRMS (ESI): *m/z* calcd for $C_{17}H_{21}BrNO$ $[M + H]^+$: 334.0801; found: 334.0804.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

Copies of NMR spectra of new compounds, data of kinetic experiments, ORTEP drawing of complex **37** (PDF)

Crystallographic data for complex **37** (CIF)

Accession Codes

CCDC 1970048 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif, or by emailimg data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

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