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Communication

C–H Functionalization

Palladium-Catalyzed C–S Bond Formation of Stable Enamines with Arene/Alkanethiols: Highly Regioselective Synthesis of β-Amino Sulfides

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Abstract: A direct and regiocontrolled thiolation method to access β-amino sulfides through the palladium-catalyzed C(sp^2)–H functionalization of stable enamines was described. The reaction was realized under mild conditions by adding an external phosphine ligand to prevent poisoning of the palladium catalyst by the sulfuric reagents. A possible mechanism was proposed according to the obtained results. The DFT calculation results were consistent with the experiment data, which gave the *E* isomers of the β-amino sulfides. The reaction was also performed on a gram scale and shows potential application in organic synthesis.

Introduction

The synthesis of organosulfur compounds through simple C–S bond-forming reactions is of crucial importance in organic synthesis and chemical biology.[1] In particular, the β-amino sulfide scaffold, containing a cysteine-type skeleton, is featured widely in natural products and drugs and also plays a pivotal role in biological chemistry [Figure 1 (a), precursor of native chemical ligation (NCL)].[2] Therefore, many researchers have directed their efforts towards the development of new methods for the construction of β-amino sulfide compounds.[3]

During the course of the total synthesis of ECT-743, synthetic chemists have found that it is essential to introduce a C–S bond to construct the β-amino sulfide moiety.[4] Following the pioneering work of Yu and co-workers, who employed Cu to mediate the direct thioetherification of arene C–H bonds with arenethiols,[5] significant achievements have been uncovered by employing different sulfur sources and catalytic systems.[6] A nickel catalytic system was developed for the thiolation of C(sp^2)–H[7] and C(sp^3)–H[8] bonds by several groups independently. Deng demonstrated the possibilities of constructing this moiety through a silver-mediated reaction of enamides by using aryl disulfides.[3c] However, the use of arene/alkanethiols as sulfur sources resulted in low yields or no desired product. Recently, Wang's group disclosed a facile and atom-economical method to construct β-acetamido sulfides through the metal-free direct difunctionalization of alkenes with thiols and nitriles.[9] During the course of the preparation and submission of the present manuscript, Wan's group reported a catalytic method for the thiolation of enaminones and related enamines by using a KIO_3/air system.[10] We envisage that palladium-catalyzed C–S bond formation of enamines may yield the desirable β-amino sulfide fragment. To prevent poisoning of the catalyst by the sulfur reagent, we thought that a suitable ligand that could bind to the transition metal might circumvent this problem.[11] With our continued interest in the functionalization of C(sp^2)–H bonds,[12] we herein report a direct "catalytic dehydrogenative cross-coupling" reaction between simple thiols and enamines to construct β-amino sulfides by using a catalytic amount of Pd (Scheme 1). This reaction works with a wide variety of enamines and arene/alkanethiols.

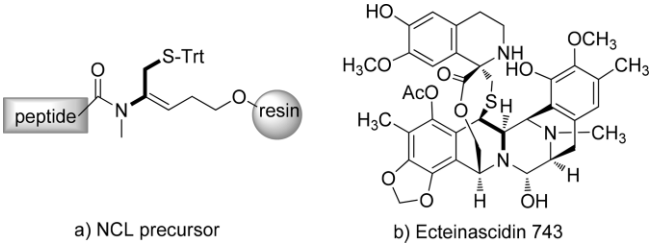

Figure 1. Representative useful β-amino sulfide derivatives; Trt = triphenylmethyl (trityl).

Results and Discussion

Our initial exploration began by treating (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**1a**) with benzenethiol (**2a**) by using

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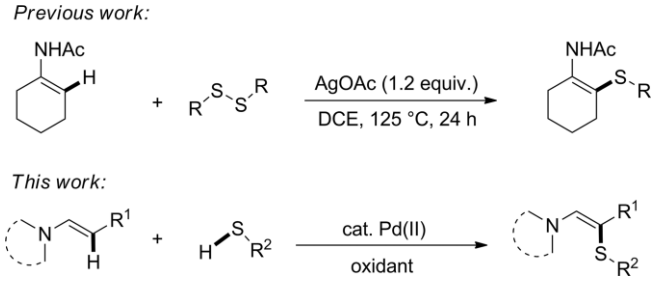
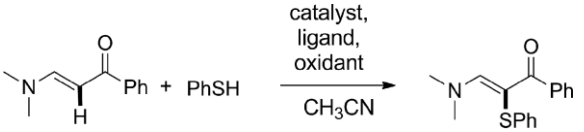


Scheme 1. Synthesis of β-amino sulfide derivatives; DCE = 1,2-dichloroethane.

a catalytic amount of $Pd(OAc)_2$ in CH_3CN at 75 °C under a nitrogen atmosphere. We were delighted to find that desired C–S coupling product **3aa** was obtained, albeit in low yield, by using metal oxidants (Table 1, entries 2 and 3), whereas the reaction was completely suppressed without the use of an oxidant (Table 1, entry 1). The geometrical configuration of coupling product **3** was supported by NOESY analysis (**3aa**) and was further confirmed by single-crystal X-ray diffraction analysis (Table 2/Figure 2, **3ba**).[13] The low yield was probably due to poisoning of the palladium catalyst by the thiol. With the preliminary positive result in hand, different ligands were tested by using this catalytic system to improve the reaction efficiency. It was found that phosphine ligands (Table 1, entries 5–7) enhanced the reactivity more than nitrogen ligands (Table 1, entry 4), especially if dppe was used, which gave the desired product in 42 % yield. Gratifyingly, the yield was improved to 91 % upon performing the reaction under an oxygen atmosphere (Table 1, entry 8). It is noteworthy that the oxidant combination of $Cu(OAc)_2$/air as well as $PhI(OAc)_2/O_2$ also gave the desired product in yields of 73 and 74 %, respectively (Table 1, entries 9 and 10), whereas silver acetate exerted a negative effect on the reaction (Table 1, entry 11). Non-metallic oxidants such as *tert*-butyl hydroperoxide (TBHP) and benzoquinone were investigated and gave lower yields than those obtained with metal oxidants (Table 1, entries 13 and 14). Other transition metals, such as rhodium and ruthenium, were also examined for the direct thiolation of the $C(sp^2)$–H bond, but a significant decrease in yield was observed (Table 1, entries 15 and 16).

Using the optimized reaction conditions, benzenethiol was examined in coupling reactions with a variety of enamines to

Table 1. Optimization of the reaction conditions for C–S bond construction.[a]



1a **2a** **3aa**

Entry	Catalyst	Ligand	Oxidant	Yield [%][b,c]
1	$Pd(OAc)_2$	–	–	–
2	$Pd(OAc)_2$	–	$Mn(OAc)_3$	12
3	$Pd(OAc)_2$	–	$Cu(OAc)_2$	26
4	$Pd(OAc)_2$	2,2′-bipyridine	$Cu(OAc)_2$	2
5	$Pd(OAc)_2$	dppb	$Cu(OAc)_2$	33
6	$Pd(OAc)_2$	$P(Cy)_3$	$Cu(OAc)_2$	34
7	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	42
8	$Pd(OAc)_2$	dppe	$Cu(OAc)_2/O_2$	91
9	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$/air	73
10	$Pd(OAc)_2$	dppe	$PIDA/O_2$	74
11	$Pd(OAc)_2$	dppe	$AgOAc/O_2$	26
13	$Pd(OAc)_2$	dppe	TBHP	18
14	$Pd(OAc)_2$	dppe	benzoquinone	32
15	$[Rh^{III}Cp^*Cl_2]_2$[d]	–	$Cu(OAc)_2/O_2$	12
16	Rubpy[d]	–	hγ	5

[a] Unless otherwise noted, reactions were performed with **1a** (0.10 mmol), **2a** (0.12 mmol), Pd catalyst (7.5 mol-%), ligand (15.0 mol-%), and oxidant (0.10 mmol) in CH_3CN (0.1 M, 1 mL) at 75 °C for 24–36 h under a nitrogen atmosphere; dppb = 1,4-bis(diphenylphosphanyl)butane, $P(Cy)_3$ = tricyclohexylphosphine, dppe = ethylenebis(diphenylphosphine), PIDA = $PhI(OAc)_2$, Cp* = η^5-pentamethylcyclopentadienyl, bpy = 2,2′-bipyridyl. [b] Yield was determined by GC analysis against an internal standard. [c] The remaining materials were **1a** and PhSSPh. [d] By using a catalyst loading of 2 mol-%.

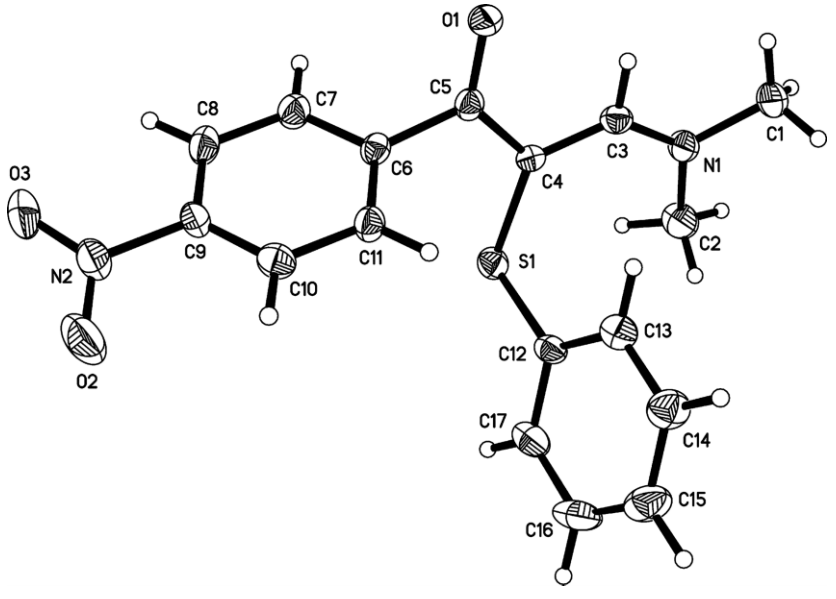
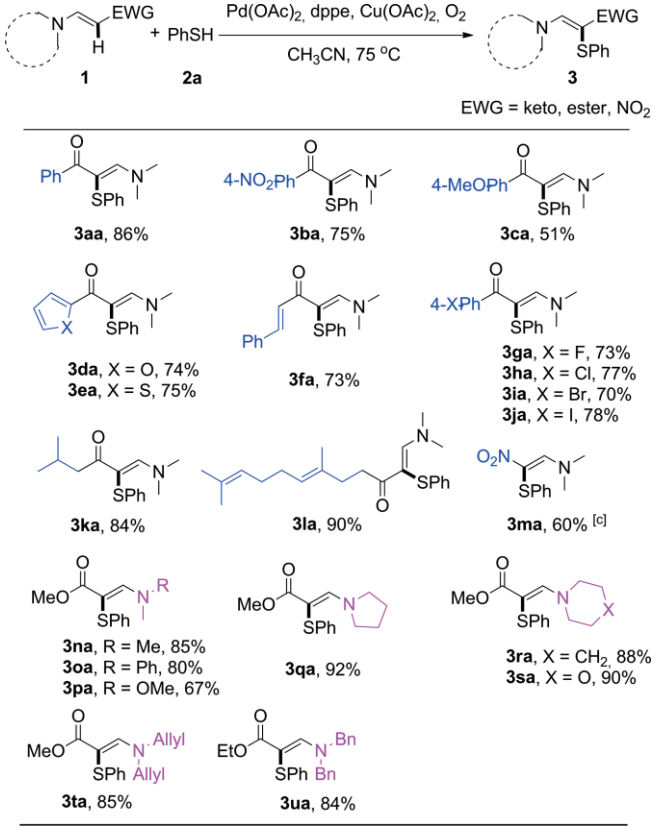


Figure 2. X-ray structure of **3ba**.

produce β-amino sulfide derivatives **3** (Table 2). In general, the reaction tolerated a broad range of substituents to afford the *trans*-β-sulfuryl-enamine regioisomers in good to excellent yields. Initially, enaminones with various substituents were tested under the standard reaction conditions. To examine the electronic effects of the substituents at the keto site of the enaminones, substrates with aryl groups bearing electron-donating and electron-withdrawing groups were subjected to the optimized reaction conditions. Whereas a substrate with an electron-deficient aryl group provided the desired product in good yield (see product **3ba**), a decreased yield was observed with a substrate bearing an electron-rich aryl group (see product **3ca**). Substituents such as heterocycles and vinyl groups remained intact during the reaction (see products **3da**, **3ea**, and **3fa**). Excellent regioselectivity occurred at the β site of the enamines rather than the other reactive C(sp^2)–H bonds in the heterocycles and chalcones. Halogen substituents (i.e., F, Cl, Br, and I) at the *para* position of the phenyl group were also well tolerated (see products **3ga**–**3ja**). Notably, the bromo and iodo functionalities could be further employed in many useful coupling reactions.[14] Alkyl-substituted substrates with a simple isopropyl group (see product **3ka**) or multiple functionalities (see product **3la**) provided single regioisomers in excellent yields of 84 and 90 %, respectively. Besides enaminones, other functionalized enamines were also studied to extend the potential application of this methodology. In view of the reactivity of the nitro group as a synthetic precursor of amine and other aza groups,[15] the thiolation reaction of (*E*)-*N*,*N*-dimethyl-2-nitroethenamine was performed. Delightfully, **3ma** was obtained in a promising yield with a higher catalyst loading (20 mol-%). Next, we turned our attention to examine the influence of the *N*-substituents on the 3-aminoalkenolates in our reaction. Generally, both acyclic and cyclic amino groups were well tolerated under the established reaction conditions. By changing the *N*-substituent to an alkyl or aryl group, the desired thiolation product was obtained in excellent yield (85 and 80 % for **3na** and **3oa**, respectively). On the other hand, an electron-donating substituent such as a methoxy group had a slightly negative influence on the transformation and gave **3pa** in 67 % yield. It should be noted that if the substrate was substituted with allyl/benzyl groups including other active C(sp^2)–H/C(sp^3)–H bonds, these reactions proceeded smoothly under the palladium catalyst system to afford the β-thiolation products with absolute regioselectivity (see products **3ta** and **3ua**). These active functional groups allow the construction of complex molecules containing a sulfur moiety after subsequent derivatization.

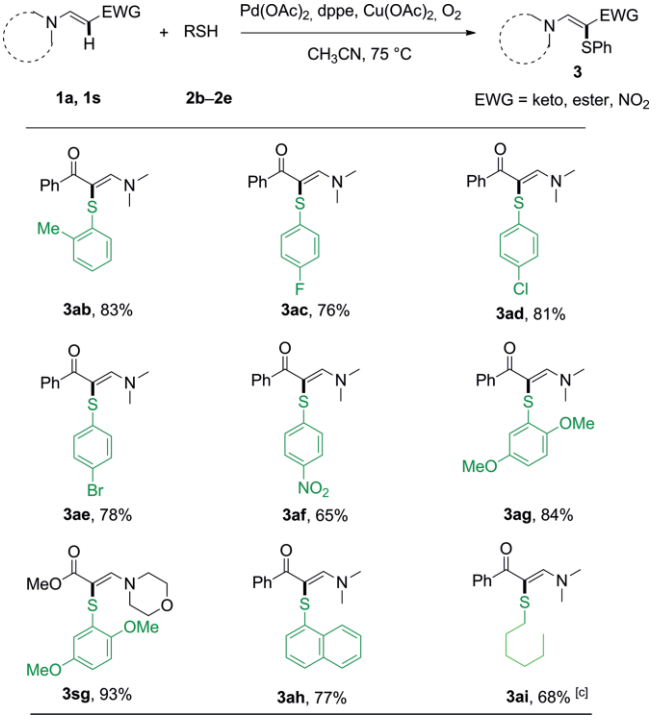
The generality of the reaction was also examined with a variety of thiols bearing aromatic and aliphatic substituents (Table 3). The reaction worked well for *ortho*- and *para*-halogen-substituted benzenethiols (see products **3ab**–**3ae**) under the standard conditions, and the desired products were delivered

Table 2. Substrate scope of the enamines.[a,b]



[a] Unless otherwise noted, the reactions were performed with **1** (0.20 mmol), **2a** (0.24 mmol), $Pd(OAc)_2$ (7.5 mol-%), dppe (15.0 mol-%), and $Cu(OAc)_2$ (0.20 mmol) in CH_3CN (0.1 M, 2 mL) at 75 °C for 24–36 h under an oxygen atmosphere. [b] Yield of isolated product. [c] Using 20 mol-% $Pd(OAc)_2$ and 40 mol-% dppe.

Table 3. Substrate scope of thiols.[a,b]



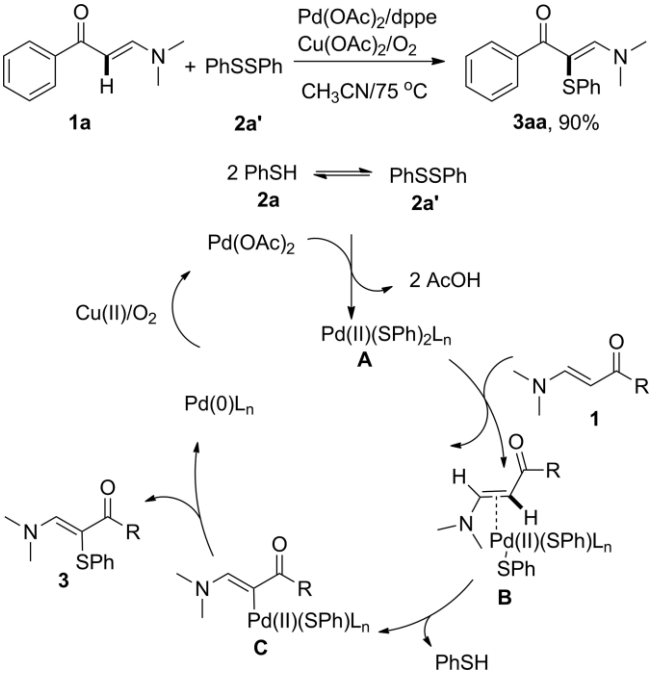
[a] Unless otherwise noted, the reactions were performed with **1** (0.20 mmol), **2** (0.24 mmol), $Pd(OAc)_2$ (7.5 mol-%), dppe (15.0 mol-%), and $Cu(OAc)_2$ (0.20 mmol) in CH_3CN (0.1 M, 2 mL) at 75 °C for 36 h under an oxygen atmosphere. [b] Yield of isolated product. [c] By using $PhI(OAc)_2$ (0.20 mmol) instead of $Cu(OAc)_2$.

in good to excellent yields (76–83 %). Notably, halogen substituents (i.e., F, Cl, and Br) on the aryl group are important functionalities that allow these substrates to be further functionalized or derivatized. Examination of the electronic influence of the aryl group revealed that electron-donating groups gave excellent results (see products **3ag**–**sg**), whereas an electron-withdrawing substituent had a deleterious electronic effect on the reaction and resulted in a decreased yield of 65 % (see product **3af**). Naphthalene-1-thiol was well suited to this reaction protocol, and it delivered the corresponding product, (*Z*)-3-(dimethylamino)-2-(naphthalen-1-ylthio)-1-phenylprop-2-en-1-one (**3ah**), in 77 % yield. Finally, an alkanethiol was also examined, and the desired β-thiolation product was obtained in 68 % yield (see product **3ai**) by using $PhI(OAc)_2$ instead of $Cu(OAc)_2$ as the oxidant.

To check the feasibility of the thiolation of enamine derivatives in a preparative demand, the reaction was performed on a gram scale (Scheme 2). To our delight, the reaction proceeded smoothly and generated the corresponding product in 75 % yield under the standard catalytic conditions. β-Amino sulfide derivatives are versatile synthetic intermediates that are widely utilized for the synthesis of pharmaceuticals and natural products. For example, **3aa** could be easily transformed into pyrazole **5aa**, which is a key intermediate for the synthesis of FAAH (fatty acid amide hydrolase) inhibitors.[16] Besides, the amine moiety of β-amino sulfides is capable of undergoing facile hydrolysis, which leads to enolates, and this further allows other useful functionalization to generate organosulfur molecules.[3c]

On the basis of the results in hand, a plausible Heck-type mechanism is proposed, as depicted in Scheme 3.[14c] Initially, $Pd(OAc)_2$ reacts with 1,1′-disulfanediyldibenzene (**2a′**, probably generated from the oxidation of PhSH) to give palladium–sulfur complex **A**.[17] This hypothesis is supported by a control experiment in which **2a′** was used instead of benzenethiol (**2a**). Palladium complex **A** then coordinates with the C=C bond of enamine **1**, which leads to intermediate **B**, and this species is subsequently deprotonated to afford **C**. Reduction and elimination processes then take place to give β-amino sulfide **3** and Pd^0. The catalytic cycle can be realized through a Wacker oxidation process in the presence of $Cu(OAc)_2$ under an oxygen atmosphere.

To better understand the reaction pathway that gives only the *E* thiolation isomer, a theory calculation experiment was performed (Figure 3). According to DFT calculations [B3LYP/6-31G(d)/LanL2DZ level of theory],[18] the palladium prefers to attach the β site of the enamine from the same side of the C–H bond, which leads to retention of configuration in the *E* isomer of product **3**. The calculation is consistent with the experimental result (see the Supporting Information for details of the calculation).



Scheme 3. A proposed mechanism.

Conclusion

In summary, we developed a method for the regioselective synthesis of β-amino sulfides through palladium-catalyzed C(sp^2)–

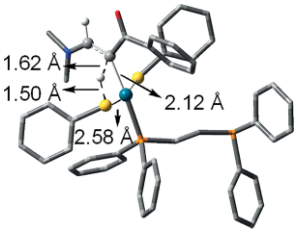
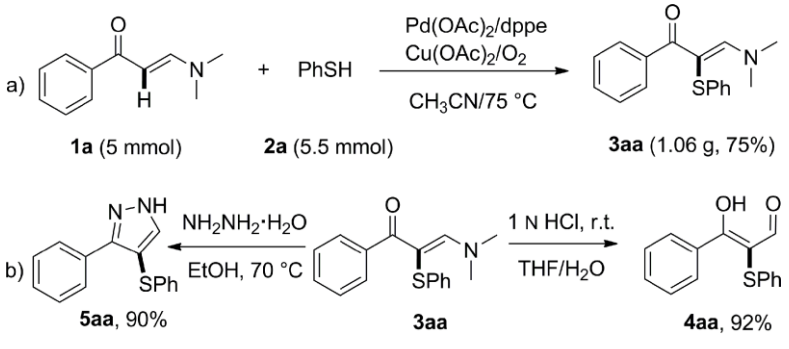


Figure 3. Geometry of transition state from **B** to **C**.



Scheme 2. Gram-scale synthesis of β-amino sulfides and its applications.

H functionalization of enamines by using simple thiols. The reaction was realized by adding an external phosphine ligand to prevent poisoning of the palladium catalyst by the sulfuric reagents. The results reveal the possible coexistence of transition metals and reactive thiols in the area of C–H functionalization. Furthermore, the formed cysteine-type products possess the potential to be used in the area of native chemical ligation in biological chemistry. Research in this direction and the application of this method for the synthesis of ECT-743 are in progress in our group, and the results will be reported in due course.

Experimental Section

Synthesis of 3aa: An oven-dried Schlenk tube was charged with **1a** (35.1 mg, 0.20 mmol), **2a** (24.6 μL, 0.24 mmol), $Pd(OAc)_2$ (3.4 mg, 7.5 mol-%), dppe (12.0 mg, 15.0 mol-%), and $Cu(OAc)_2$ (0.20 mmol, 36.3 mg) in CH_3CN (2 mL) under an oxygen atmosphere. The mixture was heated at 75 °C for 36 h. After cooling, the mixture was directly concentrated and purified by flash chromatography (10 to 20 % ethyl acetate in hexane) to afford **3aa** (48.7 mg, 86 %).

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and analytical data.

Acknowledgments

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Keywords: Oxygen · Phosphane ligands · Thiolation · Dehydrogenation · C–H functionalization

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[13] CCDC 1452382 (for **3ba**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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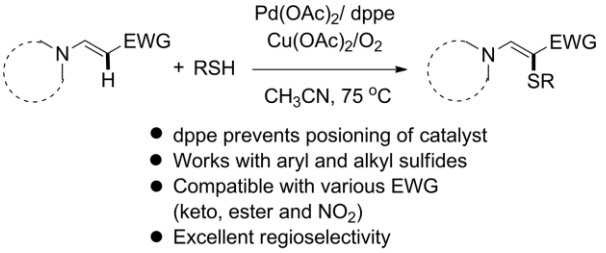

From poisoning to activation: Thiols are normally considered to poison the transition-metal catalysts that are used in coupling chemistry. We herein develop a new palladium-catalyzed system that allows the direct thiolation of enamine derivatives with simple thiols through a "catalytic dehydrogenative cross-coupling" process under mild oxidative conditions; dppe = ethylenebis(diphenylphosphine).

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