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# Palladium catalyzed aroylation of NH-sulfoximines with aryl halides using chloroform as the CO precursor

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ABSTRACT

A palladium-catalyzed aroylation of NH-sulfoximines for the efficient synthesis of *N*-aroyl sulfoximines from aryl halides and chloroform has been developed. The mild reaction conditions (temperature, catalyst loading) and the use of a CO surrogate render this transformation a useful method for the synthesis of *N*-aroyl sulfoximines from available feedstock.



Transition-metal catalyzed carbonylation reaction using carbon monoxide as C═O source has evolved as one of the most powerful protocol to introduce C1 building block into an organic molecule.[1] While the intrinsic odorless toxic and high pressure make it difficult to using normal flask in the application of CO gas. Aiming at this issue, some "CO-free" carbonylation methods have been devised to avoid CO gas directly by using such as $Mo(CO)_6$, formic acid, acid chloride or aryl formate.[2] Recently, the chloroform ($CHCl_3$) serves as a highly practical CO precursor for transition-metal-mediated carbonylation reactions attracted chemists attention.[3] In 2015, Hull reported Pd-catalyzed aminocarbonylation of aryl halides with amines by using chloroform as CO source.[3a] The metal-catalyzed carbonylative Suzuki and Sonogashira coupling reaction using $CHCl_3$ as the CO source were also described in 2016 by the Jain, Lei and Han groups.[3c–e] This "CO-free" carbonylation shows some superior performance such as readily available and strong practical compared to direct use of CO gas, although remarkable advances have been achieved using CO gas as carbonyl surrogates. Undoubtedly, exploration of "CO-free" strategies to construct the carbonyl scaffold through a low cost and highly efficient process will be highly valuable.

Sulfoximines are mono-aza analogues of sulfones with an additional NH group which appear as a valuable structural unit in biological and medicinal molecules or as exciting species for drug discovery programs.[4] Some typical examples are exemplified by Fig. 1[5] the compound AZD6738 from AstraZeneca is a novel and potent inhibitor of ATR kinase activity[5a]; the heterocyclic sulfoximine Go 4962 is known as a partial benzodiazepine receptor agonist.[5a] However, the more general use of the sulfoximine group in medicinal chemistry follows the development of BAY 1000394, a pan-CDK inhibitor for cancer in patients with advanced solid tumors.[5b] In comparison to sulfones, the inherent nucleophilicity of N—H group allows sulfoximines for more valuable building blocks in organic synthesis.[6] In the past decade, Bolm and others have developed many NH group functionalizations methods such as *N*-arylations,[7] *N*-alkynylation,[8] *N*-silylation,[9] *N*-trifluoromethylation,[10] *N*-thioetherification,[11] *N*-acylation[12] and so on.[13] In the case of direct *N*-aroylation of sulfoximines, Bolm reported some elegant work relative to transition-metal catalyzed oxidative *N*-acylation of sulfoximine using aldehyde, and methyl arenes as coupling partner.[12e–h] Very recently, Sekar disclosed a three-component strategy for the synthesis of *N*-aroyl sulfoximines skeleton, direct using CO gas as a carbonyl source.[14] Stimulated by those pioneering works and continue to our ongoing project on the synthesis of functionalized sulfides, we herein demonstrate a simple and efficient aroylation of NH-sulfoximines using $CHCl_3$ as in situ CO source.

At the beginning of the reaction, the model substrate S-methyl-S-phenylsulfoximine (**1a** 1.0 equiv) was treated with iodobenzene (**2a** 1.2 equiv.), and $CHCl_3$ (10.0 equiv). To our delight, the desired aroylation product **3aa** was obtained in 79% yield using $Pd(OAc)_2$ (2 mol%) as catalyst, $PPh_3$ (20 mol%) as ligand and KOH (6.0 equiv)

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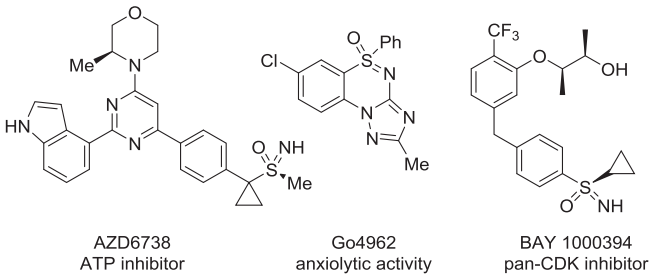


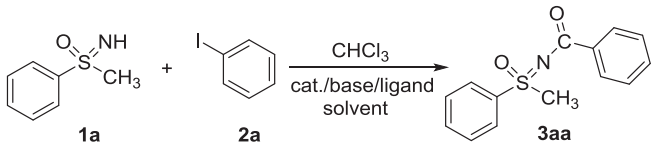

**Fig. 1.** Examples of biologically relevant sulfoximines.

as base in toluene after 12 h at 80 °C (Table 1, entry 1). The reported relative reaction mechanism suggested that the Pd-catalyst serves two purposes: to catalyze the hydrolysis of $CHCl_3$ and to catalyze the subsequent formation of aroyl intermediate, and it is obvious that the CO group is from chloroform. Screening of other catalyst revealed that no aroylation was observed when using $FeCl_2$, $Cu(OAc)_2$, $Ru_3(CO)_{12}$, AgOAc as catalyst (entries 2–5). Other palladium catalysts such as $PdCl_2$ and $Pd(dba)_2$ were also examined, and both were found to be active and yielded **3aa** in 36 and 58% yields, respectively (entries 6 and 7). Since $Pd(OAc)_2$ was found to have the highest activity, it was used for further optimizations. Next, the effect on selected ligands toward the process was examined. It turned out that the reaction failed with 1,10-phenanthroline and BINAP as the ligand (entries 8 and 9), In contrast, other ligands such as DBU, DMAP, and 2,6-lutidine led to the formation of the desired product **3aa** (entries 10–12), DBU was found to be the best ligand giving **3aa** in 85% yield, albeit with lower efficiency lowering or raising the amount of DBU to 10 or 40 mol%. Following the above investigation, the screening of base was conducted. A low yield was observed with NaOH and LiOH (entries 13 and 14), while $CsOH{\cdot}H_2O$ resulted in an 88% yield. However, taking into account the higher cost as well as hygroscopic nature of $CsOH{\cdot}H_2O$, we used KOH as base. After a brief solvent screening, we found out that toluene was the best solvent under our optimized reaction parameters (entries 15–18). Therefore, optimal reaction conditions involved heating 1 equiv of **1a**, 1.2 equiv of **2a**, 2 mol% of $Pd(OAc)_2$, 20 mol% of DBU as ligand, 6 equiv of KOH and 10 equiv of $CHCl_3$ at 80 °C for 12 h in the toluene solvent. It is noteworthy that no desired product **3aa** was obtained in the absence of palladium or base (entries 19 and 20).

With the optimized reaction conditions, scope of this transformation was investigated. The reactivity of S-methyl-S-phenylsulfoximine **1a** toward different substituted aryl iodides was seen. As shown in Table 2, the electron-withdrawing as well as electron-donating functional groups in aromatic ring of aryl iodides were well tolerated. Aryl iodides bearing alkyl or alkoxyl group at the para position, such as $-CH_3$,$-OCH_3$, coupled smoothly with **1a** to give the corresponding products in 89% (**3ab**) and 82% (**3ac**) yields, respectively (entries 2–3). Halogen substituents on the benzene ring, including 4-F and 4-Cl, were compatible for this kind of coupling reaction (entries 4–5). The electron-withdrawing functional group, such as 4-$CF_3$ and 4-CN were well tolerated to give the desired product in 90% and 82% yield (entries 6–7). In addition, a slight steric effect was observed since the substrates bearing a *meta*-substituent such as $-CH_3$,$-OCH_3$, $-SCH_3$, -F, Br, -$NO_2$ and $-CF_3$ led to relatively lower yields compared to *para*-substituted variant (entries 8–14). Heterocyclic compounds such as thiophenes are also readily functionalized (entries 15–16). Unfortunately, the *ortho*-substituted aryl iodides failed to afford the desired products. These results obviously suggested that the steric hindrance of aryl iodides has significant effect on this carbonylative coupling reaction. The reaction was also applied for gram-scale synthesis starting from 1 g of S-methyl-S-phenylsulfoximine **1a** and 1579 mg of iodobenzene to yield **3aa** in a 70% yield (1169 mg).

Subsequently, the reaction scope with respect to NH-sulfoximine substrates is presented in Table 3. They proved to efficiently

**Table 1**
Optimization of the reaction conditions.[a]




| Entry | Cat. | Ligand/base | Solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $PPh_3$/KOH | Toluene | 79 |
| 2 | $FeCl_2$ | $PPh_3$/KOH | Toluene | 0 |
| 3 | $Cu(OAc)_2$ | $PPh_3$/KOH | Toluene | 0 |
| 4 | $Ru_3(CO)_{12}$ | $PPh_3$/KOH | Toluene | 0 |
| 5 | AgOAc | $PPh_3$/KOH | Toluene | 0 |
| 6 | $PdCl_2$ and | $PPh_3$/KOH | Toluene | 36 |
| 7 | $Pd(dba)_2$ | $PPh_3$/KOH | Toluene | 58 |
| 8 | $Pd(OAc)_2$ | 1,10-Phenanthroline/KOH | Toluene | 0 |
| 9 | $Pd(OAc)_2$ | BINAP/KOH | Toluene | 0 |
| 10 | $Pd(OAc)_2$ | DBU/KOH | Toluene | 85 |
| 11 | $Pd(OAc)_2$ | DMAP/KOH | Toluene | 80 |
| 12 | $Pd(OAc)_2$ | 2,6-Lutidine/KOH | Toluene | 82 |
| 13 | $Pd(OAc)_2$ | DBU/NaOH | Toluene | 75 |
| 14 | $Pd(OAc)_2$ | DBU/LiOH | Toluene | 70 |
| 15 | $Pd(OAc)_2$ | DBU/$CsOH{\cdot}H_2O$ | Toluene | 88 |
| 16 | $Pd(OAc)_2$ | DBU/KOH | Dioxane | 20 |
| 17 | $Pd(OAc)_2$ | DBU/KOH | DMF | 0 |
| 18 | $Pd(OAc)_2$ | DBU/KOH | DCE | 50 |
| 19 | $Pd(OAc)_2$ | – | Toluene | 0 |
| 20 | – | DBU/KOH | Toluene | 0 |

[a] Reaction conditions: S-methyl-S-phenylsulfoximine (0.5 mmol), iodobenzene (0.6 mmol), chloroform (5 mmol, 10 equiv.), Ligand (20 mol%) and base (3 mmol, 6 equiv.) and solvent (2 mL) heated at 80 °C for 12 h.
[b] Isolated yield.