Palladium Catalysis

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α-Arylation of Ketimines with Aryl Sulfides at a Low Palladium Catalyst Loading

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Abstract: *Instead of using aryl halides, aryl sulfides, typically poisonous to transition-metal catalysts, were found to serve as aryl electrophiles in the catalytic α-arylation of ketimines, a class of carbonyl derivatives. Low catalyst loadings (down to 0.5 mol %) of a palladium–NHC complex are sufficient for efficient arylation. α-Arylated ketimine products are useful for the synthesis of various azaarenes, including 2,3-diarylpyrroles, an indole, and pyrrolediones.*

Transition-metal-catalyzed α-arylation of carbonyl compounds is an important synthetic method in organic synthesis and has found numerous applications in pharmaceutical, agrochemical, and material industries.[1] Aryl halides and phenol-derived pseudohalides have been the most commonly employed arylating agents since the independent discovery of the catalytic α-arylation reactions by the groups of Miura, Buchwald, and Hartwig.[2,3] In light of the importance of α-arylation, many researchers have focused on modification of the reaction in pursuit of high efficiency, high selectivity, and a wider scope. For instance, Itami et al. recently reported nickel-catalyzed α-arylation of ketones with less reactive, yet cheaper and readily available, phenol derivatives, such as aryl pivalates and carbamates.[4] However, harsh conditions and a high catalyst loading (10 mol %) have diminished the synthetic usefulness of this method.

Compared to aryl halides and phenol derivatives, aryl sulfides have been underdeveloped as aryl electrophiles in catalytic transformations because they are poisonous to transition-metal catalysts and they have unpleasant smells.[5] Even worse, much more poisonous thiolate anions are inevitably formed as byproducts. Known catalytic C–S bond-cleavage reactions,[6] including ours,[7] required large amounts of catalysts (over 2 mol %, but generally 5–20 mol %)[8] and/or stoichiometric amounts of transition-metal salts (typically thiophilic copper salts). By considering that C–S bonds exist widely in organic feedstock and synthetic intermediates, the development of efficient transformations of C–S bonds with a minimal amount of a catalyst has been an important challenge both in academia and in industry.

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As a part of our contributions to the investigation of catalytic C–S bond transformations,[7] we recently reported palladium-catalyzed arylation of amines of soft nucleophilicity with aryl sulfides as aryl electrophiles.[7c,f] This success encouraged us to extend these catalytic C–S bond transformations to the α-arylation of carbonyl compounds. Thus, the reaction of acetophenone with thioanisole (**1a**) was set out as a model reaction. We screened various reaction conditions, with an emphasis on the use of palladium N-heterocyclic carbene (NHC) catalysts[9] (Figure 1) according to our previous success.[7] However, in all attempts the formation of the desired benzyl phenyl ketone was not observed.

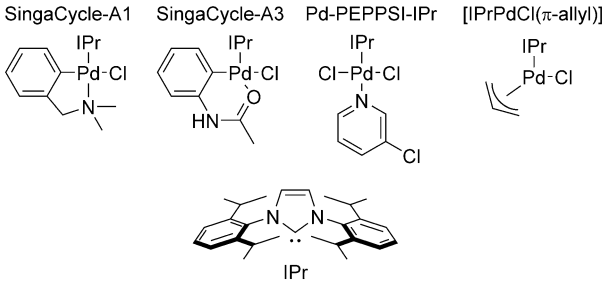
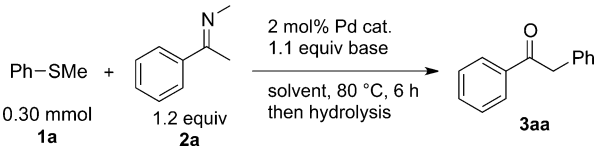


Figure 1. Palladium precatalysts employed in this study. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

Azaallylic anions formed by deprotonation of imines are known to be more reactive than enolates in S_N2 α-alkylation reactions.[10] However, only one report of α-arylation of imines with aryl halides was described by Barluenga and coworkers, who aimed to synthesize indoles through a palladium-catalyzed cascade annulation of ketimines with *o*-dihalobenzenes.[11] We thus decided to exploit the synthetic potential of imines in an α-arylation reaction with aryl sulfides.

With this idea in mind, acetophenone *N*-methylimine (**2a**) was subjected to α-arylation with **1a** with the aid of SingaCycle-A1[9a] as the catalyst (see Figure 1 for structure) and $KN(SiMe_3)_2$ as the base (Table 1, entry 1). Gratifyingly, the reaction indeed afforded the α-arylated product **3aa** in 32 % yield after hydrolysis. This initial positive outcome encouraged us to optimize reaction conditions. Changing the base to $LiN(SiMe_3)_2$ improved the yield of **3aa** to 46 % (entry 3). Another lithium amide, $LiN(iPr)_2$, could also be employed, albeit with slightly lower efficiency (entry 4). Subsequent screening of solvents revealed that hexane is the best solvent (entries 5–7). Other palladium–NHC precatalysts, including SingaCycle-A3,[9b] Pd-PEPPSI-IPr,[9c–e] and [IPrPdCl(π-

Table 1: Optimization of reaction conditions.



Entry	Pd catalyst	Base	Solvent	Yield [%][a]
1	SingaCycle-A1	$KN(SiMe_3)_2$	toluene	32
2	SingaCycle-A1	$NaN(SiMe_3)_2$	toluene	32
3	SingaCycle-A1	$LiN(SiMe_3)_2$	toluene	46
4	SingaCycle-A1	$LiN(iPr)_2$	toluene	41
5	SingaCycle-A1	$LiN(SiMe_3)_2$	dioxane	8
6	SingaCycle-A1	$LiN(SiMe_3)_2$	Et_2O	48
7	SingaCycle-A1	$LiN(SiMe_3)_2$	hexane	65
8	SingaCycle-A3	$LiN(SiMe_3)_2$	hexane	41
9	Pd-PEPPSI-IPr	$LiN(SiMe_3)_2$	hexane	46
10	[IPrPdCl(π-allyl)]	$LiN(SiMe_3)_2$	hexane	45
11[b]	SingaCycle-A1	$LiN(SiMe_3)_2$	hexane	81
12[b,c]	SingaCycle-A1	$LiN(SiMe_3)_2$	hexane	89[d]
13[b,e]	SingaCycle-A1	$LiN(SiMe_3)_2$	hexane	49

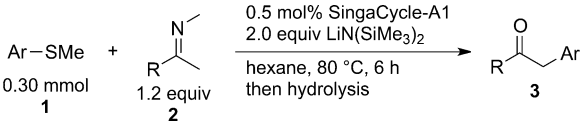
[a] Determined by NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b] 2.0 equiv of $LiN(SiMe_3)_2$. [c] 0.5 mol% of SingaCycle-A1. [d] Yield of isolated product. [e] 0.1 mol% of SingaCycle-A1.

allyl)][9f,g] promoted the arylation reaction, though the reaction was less efficient in each case (entries 8–10). The yield of **3aa** was dramatically improved to 81% by increasing the amount of $LiN(SiMe_3)_2$ to two equivalents (entry 11) to compensate for deprotonation of the initially formed α-arylated ketimine product of higher acidity. Surprisingly, the catalyst loading could be decreased to 0.5 mol% without losing the efficiency (entry 12), an exceptionally low homogeneous catalyst loading for C–S bond cleavage. A further decrease of the catalyst loading to 0.1 mol% resulted in a marked decrease in yield to 49% (entry 13).

With the optimized conditions in hand, we examined the scope of various aryl sulfides (Table 2, entries 1–12). Sterically hindered *o*-tolyl sulfide **1b** afforded the desired product **3ba** in 76% yield, albeit in the presence of 1 mol% of SingaCycle-A1 (still a low catalyst loading). Either electron-donating or -withdrawing groups at the *para* position of aryl sulfides had only little influence on the reaction efficiency to afford the corresponding products **3da–la** in moderate to good yields (entries 3–11). Interestingly, the C–S bond in *p*-chlorophenyl methyl sulfide (**1i**) reacted predominantly over the C–Cl bond to produce **3ia** in 58% yield in 1 h, along with the monoarylated product at the C–Cl bond in 6% yield (entry 8). The reaction showed reasonable compatibility with functional groups, including dimethylamino (**3fa**), fluoro (**3h**), and trimethylsilyl (**3la**). With another equivalent of $LiN(SiMe_3)_2$, phenol (**3ga**) and carboxylic acid (**3ka**) could be obtained through deprotonative protection (entries 6, 10). Selective α-arylation of **2a** took place in the reaction with *p*-acetylphenyl methyl sulfide (**1j**), leaving the acetyl moiety of **1j** intact.

Subsequently, we investigated the scope of various ketimines[12] (Table 2, entries 13–24). In most cases, the reactions proceeded smoothly. Steric hindrance of *o*-tolyl imine **2b** decreased the efficiency to afford **3ab** in 67% yield

Table 2: Scope of α-arylation reactions.



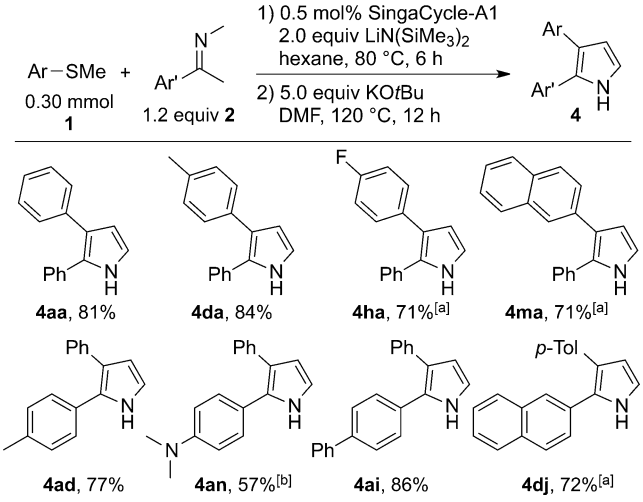
Entry	Ar	R	3	Yield [%]
1	2-MeC_6H_4 (**1b**)	Ph (**2a**)	**3ba**	76[a]
2	3-MeC_6H_4 (**1c**)	Ph (**2a**)	**3ca**	98
3	4-MeC_6H_4 (**1d**)	Ph (**2a**)	**3da**	96
4	4-$MeOC_6H_4$ (**1e**)	Ph (**2a**)	**3ea**	80
5	4-$Me_2NC_6H_4$ (**1f**)	Ph (**2a**)	**3fa**	62
6	4-HOC_6H_4 (**1g**)	Ph (**2a**)	**3ga**	51[a,b,c]
7	4-FC_6H_4 (**1h**)	Ph (**2a**)	**3ha**	93[a]
8	4-ClC_6H_4 (**1i**)	Ph (**2a**)	**3ia**	58[d]
9	4-$CH_3COC_6H_4$ (**1j**)	Ph (**2a**)	**3ja**	68[a,b]
10	4-$HOCOC_6H_4$ (**1k**)	Ph (**2a**)	**3ka**	38[a,b]
11	4-$Me_3SiC_6H_4$ (**1l**)	Ph (**2a**)	**3la**	75
12	2-Naphthyl (**1m**)	Ph (**2a**)	**3ma**	75[a]
13	Ph (**1a**)	2-MeC_6H_4 (**2b**)	**3ab**	67[a]
14	Ph (**1a**)	3-MeC_6H_4 (**2c**)	**3ac**	83
15	Ph (**1a**)	4-MeC_6H_4 (**2d**)	**3ad**	89
16	Ph (**1a**)	4-$MeOC_6H_4$ (**2e**)	**3ae**	50
17	Ph (**1a**)	4-$THPOC_6H_4$ (**2f**)	**3af**	73[a,e]
18	Ph (**1a**)	4-FC_6H_4 (**2g**)	**3ag**	76[a,f]
19	Ph (**1a**)	4-$CF_3C_6H_4$ (**2h**)	**3ah**	20[a]
20	Ph (**1a**)	4-PhC_6H_4 (**2i**)	**3ai**	86
21	Ph (**1a**)	2-Naphthyl (**2j**)	**3aj**	78
22	Ph (**1a**)	2-Ferrocenyl (**2k**)	**3ak**	44[a]
23	Ph (**1a**)	C_8H_{17} (**2l**)	**3al** + **3al′**	66[g,h]
24	Ph (**1a**)	*c*-C_6H_{11} (**2m**)	**3am**	52[g]

[a] 1 mol% of SingaCycle-A1. [b] 3.0 equiv of $LiN(SiMe_3)_2$. [c] At 100 °C. [d] Reaction time: 1 h. [e] THP was deprotected upon acid work-up. [f] Reaction time: 3 h. [g] Reaction time: 24 h. [h] 83:17 mixture of 1-phenyl-2-decanone (**3al**) and 3-phenyl-2-decanone (**3al′**).

with 1 mol% of SingaCycle-A1. The tetrahydropyranyl (THP) protection in ketimine **2f** survived to afford phenolic product **3af** in 73% yield after acidic deprotection. The electron-withdrawing *p*-fluoro group in **2g** required 1 mol% of the catalyst. *p*-Trifluoromethylphenyl imine **2h** reacted sluggishly, probably because of the insufficient nucleophilicity of the corresponding azaallylic anion. Aliphatic ketimines could participate in the arylation, although requiring a longer, yet still reasonable, reaction time (entries 23, 24). Although the regioselectivity in the reaction of 2-decanone *N*-methylimine (**2l**) was moderate (83:17 in favor of the arylation at the 1 position), cyclohexyl methyl ketone *N*-methylimine (**2m**) underwent the arylation exclusively at the methyl group.

To trace the fate of the methylsulfanyl group, we performed the reaction of **1a** with **2a** and quenched the reaction with benzyl bromide. Benzyl methyl sulfide was formed quantitatively, which indicates the formation of lithium methanethiolate. A plausible catalytic cycle is shown in Scheme S1 in the Supporting Information.

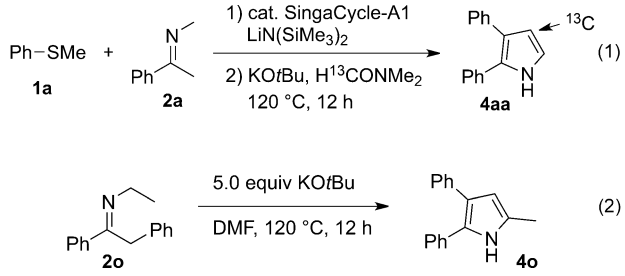
The initially produced α-arylated ketimines held significant synthetic potential. Employing these compounds, a new method for the synthesis of N-unsubstituted 2,3-diarylpyrroles was discovered.[13] Treatment of crude α-arylated ketimines with KO*t*Bu in *N*,*N*-dimethylformamide (DMF) at 120 °C for 12 h afforded a variety of 2,3-diarylpyrroles **4** in



Scheme 1. Synthesis of N-unsubstituted 2,3-diarylpyrroles. [a] 1.0 mol% of SingaCycle-A1. [b] **1n**/**2a** = 1.2/1.

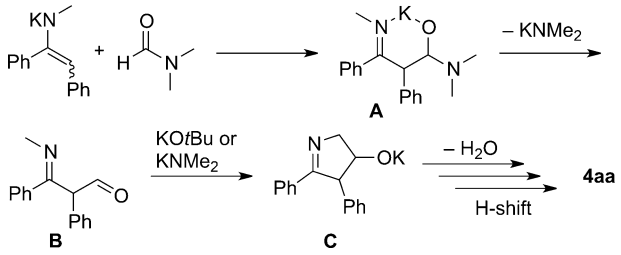
moderate to good yields (Scheme 1). It is worth noting that N,4,5-unsubstituted 2,3-diarylpyrroles are difficult to synthesize and are useful precursors for boron-dipyrromethenes (BODIPYs), an important class of highly fluorescent dyes.[14]

The formation of compounds **4** should involve the reaction of ketimine products with the solvent DMF. To clarify the reaction mechanism, a series of control experiments and isotope-labelling experiments were performed. For instance, mono-^{13}C-labelled DMF, H^{13}CONMe$_2$, transferred its ^{13}C atom to the 4 position of the product [Eq. (1)]. Additionally, reaction with *N*,*N*-diethylformamide also afforded the same pyrrole as that obtained with DMF (see the Supporting Information), which suggests that the two methyl groups of DMF were not incorporated. Lastly, an *N*-ethyl ketimine **2o** reacted with DMF to afford 2,3-diphenyl-5-methylpyrrole (**4o**) [Eq. (2)]. This reaction revealed that the pyrrolic carbon at the 5 position comes from the *N*-alkyl group on **2**.



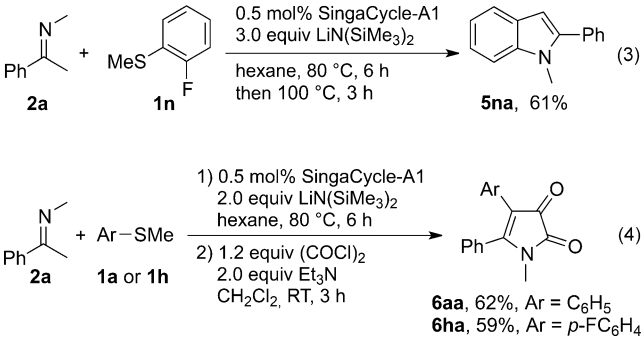
Based on these experiments, we propose a plausible mechanism as shown in Scheme 2. First, the potassium azaallylic nucleophile would react with DMF to form intermediate **A**, which would then release dimethylamine to yield intermediate **B**. Base-mediated intramolecular cyclization would afford intermediate **C**. Finally, pyrrole **4aa** was formed through aromatization and a 1,5-hydrogen shift.

Two additional examples showcase the synthetic potential of the α-arylation. The reaction of **2a** with *o*-fluorophenyl



Scheme 2. Proposed mechanism for the formation of 2,3-diarylpyrroles.

methyl sulfide (**1n**) followed by elevating the reaction temperature to 100 °C prior to aqueous workup afforded indole **5na** in 61% yield through an intramolecular S_NAr cyclization reaction [Eq. (3)]. In the other example, crude α-arylated ketimines react with oxalyl chloride in the presence of amine to afford pyrrolediones **6aa** and **6ha** in 62% and 59% yields, respectively [Eq. (4)].



In summary, we have presented a new efficient palladium-catalyzed α-arylation reaction of ketimines with catalytically poisonous aryl sulfides, typically with a catalyst loading of less than 1 mol%. The synthetic utility of ketimine products was explored to uncover several new routes for the preparation of azacycles, including N-unsubstituted 2,3-diarylpyrroles, an indole, and pyrrolediones. Further investigations to take full advantage of organosulfur compounds in catalytic transformations are ongoing in our laboratory.

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Keywords: α-arylation · aryl sulfides · C–S bond cleavage · homogeneous catalysis · palladium

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