

Acylsilanes in Iridium-Catalyzed Directed Amidation Reactions and Formation of Heterocycles via Siloxycarbenes

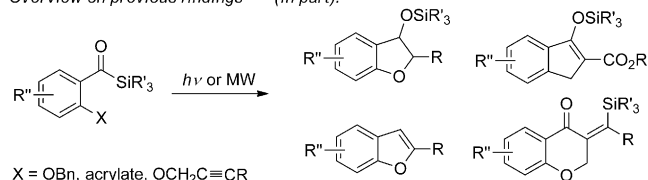
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Abstract: Exposing *ortho*-amido aroylsilanes to visible light or heat leads to cyclization reactions that provide *N*-heterocyclic compounds via siloxycarbenes as key intermediates. The previously unreported starting materials have been prepared by directed amidations of aromatic acylsilanes in the presence of an iridium catalyst followed by *N*-alkylation.

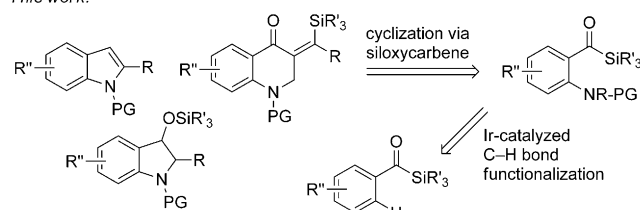
Acylsilanes undergo thermally or photochemically induced 1,2-silicon-to-oxygen migrations (known as Brook rearrangements) to form siloxycarbenes.^[1] Although the generation of such intermediates is preparatively simple and their application in C–C bond-forming processes appears synthetically attractive, reports focusing on the use of siloxycarbenes in synthetic chemistry are rare.^[2–5] In 2009, Shen and Dong described the insertion of siloxycarbenes into benzylic C–H bonds to thermally generate the reacting carbenes under microwave irradiation and form furan derivatives.^[2] We reported light-induced intra- and intermolecular additions of siloxycarbenes to C–C triple bonds to afford ketonic vinylsilanes after structural reorientations.^[3] More recently, access to indanone derivatives was developed by using sequential Rh^{III}-catalyzed oxidative Heck-type olefinations of aromatic acylsilanes and intramolecular reactions of photochemically generated siloxycarbenes.^[4] The underlying cyclization process was induced under very mild reaction conditions and resulted in excellent yields and selectivities of the products as well as absolute atom economy.

While the aforementioned transformations^[2–5] proved effective for the preparation of carbo- and oxygen-based heterocycles (Scheme 1, top), analogous reactions leading to nitrogen-containing products were unreported. A retrosynthetic analysis (Scheme 1, bottom) revealed that approaching such *N*-heterocycles by similar routes required aroylsilanes with *N*-tethered side chains in the *ortho*-position. To our surprise, compounds of this type were unprecedented.^[6] Preparing them by applying classical concepts such as Umpolung^[7] appeared to have significant synthetic limitations, and consequently, a new approach had to be developed. Guided by our previous study,^[4] transition-metal-catalyzed processes utilizing acylsilanes as weakly coordinating substrates were considered most attractive. The realization of this strategy is reported herein.

Overview on previous findings^[2–4] (in part):



This work:



Scheme 1. Summary of previous work and retrosynthetic analysis of the current challenges. Bn = benzyl, MW = microwaves, PG = protecting group.

Ortho-directed amidation reactions of aroylsilanes were investigated first. Inspired by the intermolecular C–H functionalizations of aromatic ketones by Sahoo^[8] and co-workers as well as related reactions reported by others,^[9] 4-methylphenyl trimethylsilyl ketone (**1a**) and tosyl azide (**2a**) were selected as representative substrates. Initially, a combination of [Ru(*p*-cymene)Cl₂]₂, AgBF₄, and Cu(OAc)₂ was applied as the catalytic system at 60 °C. To our delight, the system proved active and provided the desired product **3a** in 37% yield (Table 1, entry 1). Substituting Cu(OAc)₂ by AgOAc increased the yield of **3a** to 57% (Table 1, entry 2). In the absence of a salt additive, **3a** was formed in only 8% yield (Table 1, entry 3). Both results support suggestions by Ackermann and co-workers as well as others^[10] that the acetate

Table 1: Optimization of the *ortho*-amidation of aroylsilanes.^[a]

Entry	Catalyst ^[b] (mol %)	Additive (mol %)	Yield [%]
1	[Ru(<i>p</i> -cymene)Cl ₂] ₂ (2.5)	Cu(OAc) ₂ (50)	37
2	[Ru(<i>p</i> -cymene)Cl ₂] ₂ (2.5)	AgOAc (50)	57
3	[Ru(<i>p</i> -cymene)Cl ₂] ₂ (2.5)	–	8
4	[Ir(Cp*)Cl ₂] ₂ (2.5)	AgOAc (5)	98 ^[c]
5	[Ir(Cp*)Cl ₂] ₂ (1)	AgOAc (5)	96 ^[c,d]
6	[Ir(Cp*)Cl ₂] ₂ (0.5)	AgOAc (5)	95 ^[e]

[a] Stirring of **1a** (0.30 mmol), **2a** (0.33 mmol, 1.1 equiv), catalyst, and additive in DCE (0.5 mL) at 60 °C. [b] Ratio of catalyst and AgBF₄ = 1:4. [c] 1 h reaction time. [d] The same yield was observed on a 4 mmol scale. [e] Use of 0.2 mL of solvent.

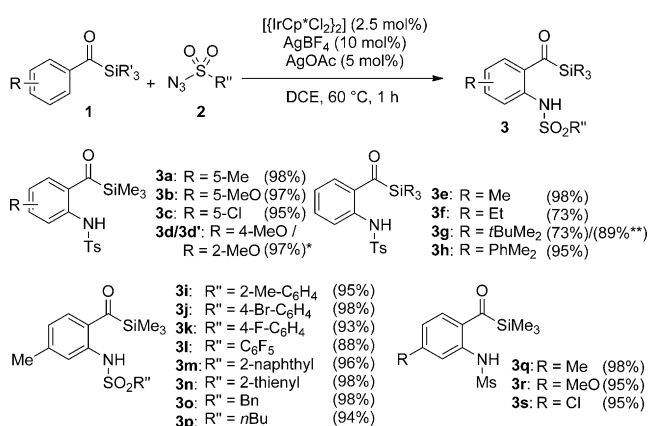
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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201508501>.

plays a key role as a basic anion in such directed C–H functionalizations. Varying other reaction parameters (temperature, reaction time, solvent) did not further improve the yield of **3a**, and so the catalyst was changed.

In light of seminal reports by Chang and co-workers as well as others,^[11] $[\text{Ir}(\text{Cp}^*)\text{Cl}_2]_2$ ($\text{Cp}^* = \text{C}_5\text{Me}_5$) was selected as the catalyst. To our delight, the result was superb. With a catalyst derived from 2.5 mol % of the iridium complex, 10 mol % AgBF_4 , and 5 mol % AgOAc , **3a** was obtained in 98 % yield after only 1 h (Table 1, entry 4). Lowering the catalyst amount to 1.0 mol % (with respect to the dimeric iridium complex) had almost no effect, and the product was obtained in 96 % yield (Table 1, entry 5). When the catalyst loading was decreased further to 0.5 mol % $[\text{Ir}(\text{Cp}^*)\text{Cl}_2]_2$, the reaction time had to be extended to 12 h to obtain **3a** in 95 % yield (Table 1, entry 6).

Next, the substrate scope was investigated (Scheme 2). Arylsilanes with various substituents on the aromatic core



Scheme 2. Iridium-catalyzed *ortho*-amidation of aroylsilanes (*: obtained as a ca. 4:1 regioisomeric mixture; **: reaction time of 2 h). DCE = 1,2-dichloroethane, Ts = *p*-toluenesulfonyl.

reacted well in the iridium(III)-catalyzed amidation reaction with **2a** to afford the corresponding tosyl amides in excellent yields (95 %–98 % for **3a–d**). Applying substrates with bulkier silyl groups than trimethylsilyl (TMS) resulted in slightly lower yields (73 % for both **3f** and **3g**, Scheme 2). However, the results could be improved by extending the reaction time to 2 h, with **3g** being obtained in 89 % yield.^[12] Next, the sulfonyl azide component **2** was varied. A wide range of substrates with substituted phenyl rings, a thienyl, a benzyl, and a butyl group reacted well (Scheme 2), and in all cases the corresponding products **3i–p** were obtained in high yields (88 %–98 %), with electronic effects playing only a minor role. Finally, the use of methanesulfonyl azide led to excellent yields of the corresponding amides **3q–s**.

To study intramolecular ring-forming processes proceeding via photochemically or thermally generated siloxycarbene, the initially obtained products **3** had to be connected with a reactive tether. Methanesulfonyl amides **3q–s** were chosen as the preferred substrates to minimize steric interactions and inhibit photo-Fries rearrangements.^[13] *N*-Tosyl-

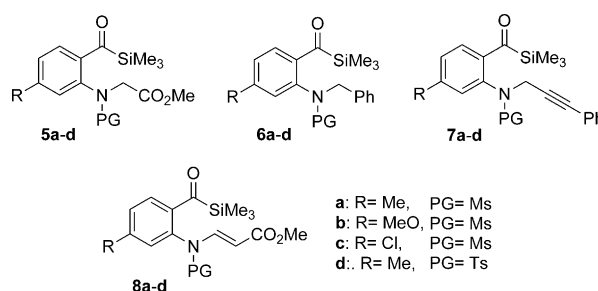
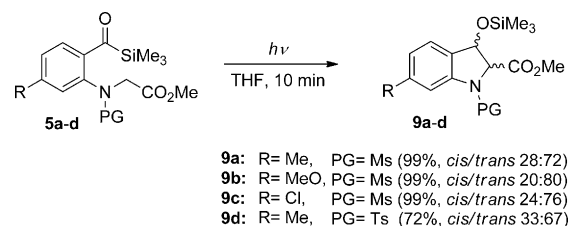


Figure 1. Products obtained by NH modifications of **3**; for details see the Supporting Information.

protected compound **3a** was used for comparison. Three methods were used to derivatize the NH group (Figure 1, for details see the Supporting Information). First, *N*-aryl glycinates **5a–d** were prepared. Their syntheses involved deprotonation of the substrates with NaH in THF at 0 °C followed by treatment with α -bromomethyl acetate. After stirring the reaction mixture at ambient temperature for 3 days, products **5a–d** were obtained in yields of 92 %–95 %. Second, an analogous process with benzyl bromide and (3-bromoprop-1-yn-1-yl)benzene as the electrophiles was developed for the syntheses of *N*-benzylated and *N*-propagylated derivatives **6** and **7**. In these cases, K_2CO_3 served as the base in acetone, and NaI was added to promote an upstream Finkelstein reaction. As a result, **6a–d** and **7a–d** were obtained in very good yields after 3 days (92 %–95 %). Third, Michael-type additions of **3q–s** and **3a** to methyl propiolate in the presence of a 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyst gave acrylic products **8a–d** in yields ranging from 90 % to 97 %.

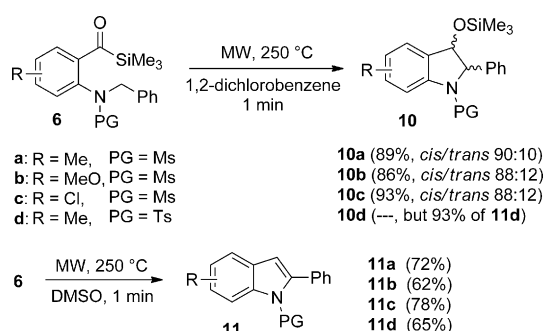
The light-induced reactivity was investigated by irradiating a solution of glycinate **5a** in THF with an actinic blue LED (20 W). To our delight, the substrate underwent a smooth transformation within 10 min to afford the highly substituted indoline-2-carboxylate **9a** with a *cis/trans* selectivity of 28:72 in 99 % yield (Scheme 3). The procedure was also applicable



Scheme 3. Light-induced cyclizations of the glycinates **5**. Ms = methanesulfonyl.

to substrates with substituents at the arene, and resulted in yields of 99 % for both **9b** and **9c**. The stereoselectivities were also good (*cis/trans* of 20:80 for **9b** and 24:76 for **9c**; Scheme 3). Although the reaction could be performed in other solvents (benzene, acetone, MeCN, or pentane), the use of THF led to the highest stereoselectivities.^[13] The *N*-tosyl-protected **5d** afforded the corresponding product **9d** in only 72 % yield, presumably because of a competitive photo-Fries rearrangement.^[14] Furthermore, the stereoselectivity proved moderate (*cis/trans* of 33:67, Scheme 3).

Next, the ability of the photochemically generated siloxycarbenes derived from **6a–d** to insert into the methylene group of the *N*-benzyl groups was investigated. When those aroylsilanes were irradiated under the photochemical conditions applied to glycinate **5**, no reaction occurred and the starting materials were fully recovered. Inspired by the report by Shen and Dong on benzofuran syntheses via thermally generated siloxycarbenes,^[2] the application of microwave irradiation was considered. Setting this idea into practice, a solution of **6a** in 1,2-dichlorobenzene was heated to 250 °C under microwave conditions for 10 min. As a result, 2-phenylindoline (**10a**) was formed, but the yield was low, and **10a** was accompanied by several unidentified decomposition products. Realizing that the reaction time was an important factor, the microwave irradiation period was shortened to only 1 min, and under those conditions **10a** was obtained in 89 % yield with a *cis/trans* selectivity of 90:10 (Scheme 4). Compounds **6b** and **6c** also reacted well to afford

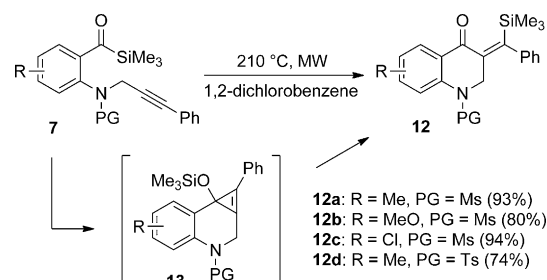


Scheme 4. Thermally induced cyclizations of *N*-benzylated aroylsilanes **6**.

10b and **10c** in yields of 86 % and 93 %, respectively. In both reactions the stereoselectivities were high (*cis/trans* 88:12 for **10b** and **10c**).^[13] To our surprise, *N*-tosyl-protected **6d** reacted differently, and none of the expected 2-phenylindoline derivative was observed. Instead, indole **11d** was obtained in 93 % yield (Scheme 4). As indoles are of high synthetic relevance, a direct conversion of **6a–c** into the corresponding indole derivatives was desirable. This goal was achieved by switching the solvent from 1,2-dichlorobenzene to DMSO. Thus, heating solutions of **6a**, **6b**, or **6c** in DMSO to 250 °C under microwave irradiation for 1 min resulted in the formation of the targeted indoles **11a–c** in good yields (Scheme 4). As shown by the reaction leading to **11a**, an extension of the reaction time to 7 min decreased the yield significantly and various decomposition products were formed. With **6d** as substrate, indole **11d** was formed again, although in lower yield than before (93 % in 1,2-dichlorobenzene versus 65 % in DMSO). Mechanistically, the indole formations most likely proceed by insertions of thermally induced siloxycarbenes into the tethered benzylic methylene groups of the substrates followed by desiloxylation processes of the resulting intermediates to yield indoles **11**.

Intramolecular additions of in situ generated siloxycarbenes to unsaturated tethers were studied with aroylsilanes **7** and **8** as substrates. On the basis of our previous studies,^[3] we

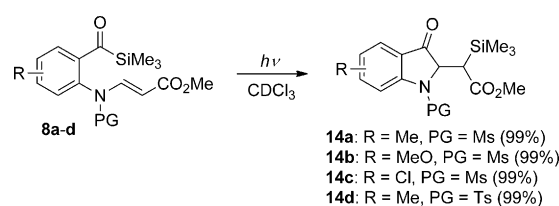
applied the aforementioned photochemical conditions to **7a**, which has a propargyl group at the aroylsilane nitrogen atom. This reaction resulted in dihydroquinolinone **12a**. However, the procedure was synthetically of low value, as a light-induced *Z*-to-*E* isomerization occurred, which was accompanied by product degradation. A better result was achieved when the siloxycarbene was thermally generated. Thus, heating a solution of **7a** in 1,2-dichlorobenzene to 210 °C under microwave irradiation afforded **12a** in 93 % yield (Scheme 5). The *Z* configuration at the double bond was



Scheme 5. Microwave-induced cyclizations of aroylsilanes **7**.

assigned by NMR spectroscopy. Applying the same procedure to aroylsilanes **7b–d** gave **12b–d** in high yields. Both *N*-methanesulfonyl and *N*-tosyl groups were tolerated but, from the product yields, the former appeared to be more suitable. Presumably, the reactions proceeded by additions of the in situ generated siloxycarbenes to the tethered triple bonds, thereby leading to cyclopropanes **13**, which ring opened through retro-Brook rearrangements to give the observed products.

Finally, reactions of acrylates **8a–d** were investigated. Subjecting them (in CDCl₃) to the aforementioned photochemical conditions using the actinic blue LED afforded 3-oxoindoline derivatives **14** in essentially quantitative yields after 10 min (Scheme 6). It is noteworthy that in this case



Scheme 6. Light-induced cyclizations of acyclic aroylsilanes **8**.

N-methanesulfonyl- and *N*-tosyl-protected substrates reacted equally well, and the products were formed in an atom-efficient manner with excellent purity. Mechanistic analogies to the transformation of substrates **7** are assumed for the formation of products **14**.

In summary, we have developed a highly efficient iridium-catalyzed *ortho*-amidation reaction of aroylsilanes with sulfonyl azides. The reaction proceeds with low catalyst loadings in short reaction times and has a broad tolerance to substituents on all reaction partners. After subsequent

N-functionalizations, the products undergo photochemically or thermally induced cyclization reactions to give N-heterocyclic compounds, including dihydroquinolinone and indoles, in up to quantitative yields. Mechanistically, the transformations involve in situ generated siloxycarbenes that react intramolecularly with excellent selectivities.

Experimental Section

Iridium-catalyzed amidation process: $[\{\text{IrCp}^*\text{Cl}_2\}_2]$ (6.0 mg, 0.0075 mmol, 2.5 mol %), AgBF_4 (5.8 mg, 0.03 mmol, 10 mol %), AgOAc (2.5 mg, 0.015 mmol, 5 mol %), and DCE (0.5 mL) were added to an argon-flushed vial. Then, aroylsilane **1** (0.3 mmol) was added, followed by sulfonyl azide **2** (0.33 mmol, 1.1 equiv). The reaction mixture was stirred at 60 °C for 1 h open to the air. After cooling the mixture to room temperature, silica was added, and the solvent was removed in vacuo. The product was isolated by column chromatography (silica gel 35–70 mesh, 4:1, hexane/EtOAc) and analyzed by NMR and IR spectroscopy as well as ESI-LCMS. For additional experimental details, see the Supporting Information.

Photochemically or thermally induced cyclization processes: The N-functionalized aroylsilanes were irradiated with an actinic blue LED spotlight (20 W) or heated in a microwave apparatus (CEM Discover) above 200 °C. In the case of the photochemical induction, emission of heat from the LED was not observed. The microwave experiments were performed in the dark. The products were either directly subjected to NMR spectroscopy or purified by column chromatography. For additional experimental details, see the Supporting Information.

Acknowledgements

We cordially thank Dr. Daniel L. Priebbenow (Monash University) and Dr. Shunxi Dong (RWTH Aachen University) for helpful discussions.

Keywords: acylsilanes · carbenes · C–H functionalization · heterocyclic chemistry · iridium catalysis

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 15493–15496
Angew. Chem. **2015**, *127*, 15713–15716

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Received: September 10, 2015

Published online: November 5, 2015