

Letter pubs.acs.org/OrgLett

Addition of N-Heterocyclic Carbene Catalyst to Aryl Esters Induces Remote C–Si Bond Activation and Benzylic Carbon Functionalization

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Supporting Information

ABSTRACT: Through the incorporation of a silicon atom to an aryl carboxylic ester substrate, the resulting C-Si bond can be activated via the addition of a carbene catalyst on a remote site. This strategy allows for efficient functionalization of the benzylic sp³-carbons of aryl carboxylic esters.



The utilization of silicon atom in organic synthesis has L enjoyed enormous success.¹ For instance, carbon-silicon bond is weaker than carbon-carbon bond, and the silicon atom has strong affinity with fluoride.² These properties have allowed chemists to modulate the reactivities of other atoms by incorporating silicon to the molecules. N-Heterocyclic carbenes (abbreviated as NHCs or carbenes)³ have been proven to be a powerful class of organic catalysts that can often enable unique activation and reaction modes. However, it is still a challenge to bring the benefits of carbene catalysis for the functionalization of aromatic sp²-carbons and the attached sp³-carbons, such as benzylic carbons.⁴ For example, our long-term efforts to activate the sp² and sp³-carbons of the simple aryl aldehydes (such as 2methylbenzaldehyde A) remain unsuccessful until date (Figure 1a). To overcome this problem, we found that by incorporating an electronegative heteroatom (such as N) to the aromatic scaffold and using indole-derived aryl aldehydes (B) as the substrates, the nearby sp³-carbon of methyl unit can be functionalized under oxidative NHC catalytic conditions.⁵ Recently, the Glorius and Rovis groups found that the introduction of an electronegative Br atom to an aryl aldehyde (C) can lead to NHC-mediated functionalization of its benzylic carbon.^{6a,b} It is noted that when the 2-(bromomethyl)benzaldehyde was used, the reaction typically gave moderate yields. Side reactions resulting from the electronegative property of Br atom (as a leaving group) led to unproductive consumption of both the carbene catalyst and aldehyde substrate.^{6a} Conventional approaches in using strong bases for deprotonation of benzylic CH⁷ have very limited controls over chemo- and stereoselectivities. Reported photoinitiation approaches⁸ do not provide handles for chiral inductions.

We reasoned that when electropositive atoms (such as silicon) are properly incorporated to the aryl aldehyde/ester

(a) Progress in NHC-catalyzed aryl aldehyde benzylic carbon activation



Figure 1. NHC-catalyzed activation and reaction modes of aryl aldehydes and esters.

substrates, different reactivity patterns shall become possible (Figure 1b). Here we report that by using 2-[(trimethylsilyl)-

Received: November 15, 2017 Published: December 29, 2017

methyl]benzoate with a Si atom attached to the benzylic carbon as the substrate, the addition of a carbene catalyst to the ester can activate the remote C–Si bond (intermediate I). An F⁻ anion attacks the Si atom of I and leads to a breakage of the C–Si bond^{2e,f} that is already weakened by the azolium moiety from the NHC catalyst. This step generates intermediate *o*-quinodimethane (*o*-QDM) II.¹⁰ This intermediate (II) then undergoes formal [4 + 2] reaction with reactive ketone to form a δ -lactone product.¹¹

Our catalytic reactions based on C–Si bond modulation are relatively clean, and products are obtained with good to excellent yields. Notably, the use of Si atom to facilitate NHC-mediated activation is mostly unexplored. To the best of our knowledge, the most relevant study in this direction is Scheidt's elegant use of acylsilanes as aldehyde equivalents to generate Breslow intermediates.¹²

Key results of condition optimization, by using 2-[(trimethylsilyl)-methyl]benzoate (1a) and trifluoromethyl ketone (2a) as the model substrates, are summarized in Table 1. The reactions were performed in THF as the solvent at room





^{*a*}Reaction conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), base (0.1 mmol), 4 Å MS (100 mg), THF (2.0 mL), rt, 36 h. ^{*b*}Yield are isolated yield after purification by column chromatography; isolated yield based on **2a**. ^{*c*}nr = no reaction. DIEA = *N*,*N*-diisopropylethylamine. DMAP = 4-dimethylaminopyridine. DABCO = 1,4-diazabicyclo[2.2.2]octane.

temperature with Cs_2CO_3 as the base and CsF as an F^- source to break the Si-C bond. No product (3a) was observed in the absence of NHCs, indicating that the formation of azolium ester intermediate I (Figure 1b) is necessary to activate the remote C-Si bond for further reactions. The ester substrate (1a) remained unreacted without the presence of NHC. Triazoliumbased NHC precatalysts were then examined. Catalysts with an *N*-phenyl substituent (C1¹³ and C4¹⁴) were ineffective (entries 2 and 5) likely due to the *ortho*-substitution effect;^{15c} in both reactions the substrates were recovered. Similar observations using the sterically small *N*-phenyl substituent NHCs were reported in several studies.¹⁵ Replacing the N-phenyl substituent of the NHC catalysts with a mesityl unit led to the formation of 3a with good yield (entries 3 and 6). The superior effectiveness of N-mesityl substituted triazolium NHC catalysts (over the corresponding *N*-phenyl analogs) in carboxylic ester activation reactions has been observed in several of our previous studies.^{9d-g} We next found that N-C₆F₅ substituted catalysts performed even better yields (entries 3 and 7). When catalyst $C6^{16}$ was used, product 3a was formed in 88% yield (entry 7). The switch of $C_{s_2}CO_2$ to K_2CO_2 as the base led to a small, while consistent, improvement of the reaction yield (entry 8). The use of organic bases (such as DMAP, DABCO, and DIEA) could also lead to efficient reactions (entries 9-11). The presence of CsF is critical (for the generation of key intermediate II as illustrated in Figure 1b), and no product could be obtained under various conditions when CsF was not added (entry 12). Our efforts for enantioselective reactions using chiral NHC catalysts did not give satisfied results at this point (see SI). It appears under this type of reaction mode (e.g., with intermediate II involved in the key step, Figure 1b), the current chiral NHC catalysts were ineffective for enantioselective inductions, as observed in several related reactions.^{6a,t}

We next used the optimal condition (Table 1, entry 8) to examine the scope of the reactions between 2-[(trimethylsily])methyl]benzoate (1) and trifluoromethyl ketones (2) (Scheme 1). Installation of different substituents to the phenyl ring of the trifluoroketones were all tolerated, giving the desired lactone compounds in 70–94% yields (3a-e). Replacing the phenyl unit of 2 to heteroaryl substituent did not affect the reaction outcomes (3f). When the aryl group of trifluoroketone was replaced with alkyl substituent, the lactone product (3g) was

Scheme 1. Examples of Esters and Trifluoromethyl Ketones^a



^{*a*}Reaction conditions: 1 (0.12 mmol), 2 (0.10 mmol), C6 (0.02 mmol), K_2CO_3 (0.1 mmol), 4 Å MS (100 mg), THF (2.0 mL), rt, 36 h. Yields (after SiO₂ column chromatography purification) based on the ketones 2.

also obtained with good yield (75%). Different substituents and substitution patterns on the aryl carboxylic ester substrates (1) were also tolerated (3h-o). It should be noted that in most of the examples the reaction gave lactone products with over 80% yields. In contrast, with previous approaches using 2-(bromomethyl)-benzaldehyde substrates, most of the reactions give low to moderate yields.

 α -Ketoesters were also effective electrophiles for reactions with 2-[(trimethylsilyl)-methyl]benzoate 1a (Scheme 2). In

Scheme 2. Ketoesters and Isatins as Electrophilic Substrates To React with the Aryl Ester $1a^a$



^{*a*}Reaction conditions: **1a** (0.12 mmol), **4** or **6** (0.10 mmol), NHC (0.02 mmol), base (0.1 mmol), 4 Å MS (100 mg), THF (2.0 mL), rt, 36 h. Yields (after SiO₂ column chromatography purification) based on the electrophiles **4** or **6**.

these reactions, the optimal condition used for trifluoromethyl ketone substrates (Table 1, entry 8) gave **5a** with 68% yield. The switch of the NHC catalyst from **C6** to **C3**¹³ led to a consistently higher yield (e.g., 75% yield of **5a**). We finally found that by using **C3** as the NHC precatalyst and DABCO as the base, the reaction could give product **5a** in excellent yield (91%). Under this slightly modified condition, various ketoester substrates were tolerated, and most of the reactions gave excellent yields (**5a**-**5h**). We also studied isatins as ketone substrates. Cs₂CO₃ was found as an optimal base, and these isatin substrates examined here led to spirocyclic lactone products with excellent yields (**7a**-**7h**, 80-94% yields).

The products of our catalytic reactions contain a lactone moiety that is widely found in natural products and other bioactive molecules. Our laboratories are interested in the antiviral and antibacterial activities of these compounds for potential agricultural use.¹⁷ We then evaluated the in *vitro* bioactivities of our products against *X. oryzae* by the turbidimeter test (Table 2). The commercially available and

Table 2. Preliminary Evaluations on the Antibacterial Activities of Our ${\rm Products}^a$

	X. oryzoe pv. oryzae inhibition rate [%]	
product	$200 \ \mu g/mL$	100 μ g/mL
3c	52 ± 1.16	41 ± 1.71
5h	88 ± 0.41	48 ± 1.50
7e	89 ± 0.52	53 ± 1.24
positive control	70 ± 0.85	54 ± 1.11
negative control	0	0

^{*a*}Data is the average of three replicates. Commercial bacteriocide bismerthiazol was used as the positive control, and DMSO was used as the negative control.

commonly applied bacteriocide bismerthiazol was used as the positive control, and dimethyl sulfoxide (DMSO) was used as the negative control. A number of our compounds showed promising antibacterial activities. For example, at concentrations of 200 and 100 μ g/mL, compounds **3c**, **5h**, and **7e** showed inhibitory rates comparable to the commercial bacteriocide bismerthiazol against *X. oryzae.*¹⁸

In summary, we have developed a carbene-catalyzed approach for the functionalization of benzylic carbons of aryl carboxylic esters. The approach relies on the incorporation of a C–Si bond that can be further activated through the addition of a carbene catalyst to the ester moiety of the substrate. Several types of activated ketones could react effectively as electrophiles. Products of our catalytic reactions showed promising antibacterial activities against *X.oryzae*. We believe this study shall inspire new exploration on carbene-catalyzed activations that go beyond carbon–carbon bonds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03544.

Experimental procedures, characterization data, and calculation details (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge financial support by the National Natural Science Foundation of China (No. 21472028), National Key Technologies R&D Program (No. 2014BAD23B01), "Thousand Talent Plan", The 10 Talent Plan (Shicengci) of Guizhou Province, Guizhou Province Returned Oversea Student Science and Technology Activity Program, Guizhou University (China) and Singapore National Research Foundation (NRF-NRFI2016-06), the Ministry of Education of Singapore (MOE2013-T2-2-003; MOE2016-T2-1-032; RG108/16), A*STAR Individual Research Grant (A1783c0008), and Nanyang Technological University

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