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Samarium(III)-Catalyzed C(sp^3)–H Bond Activation: Synthesis of Indolizines *via* C–C and C–N Coupling between 2-Alkylazaarenes and Propargylic Alcohols

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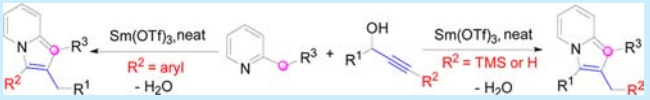
Supporting Information

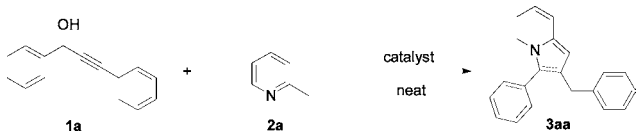
ABSTRACT: A new rare earth metal and samarium-catalyzed C(sp^3)–H bond activation is reported in which 2-alkylazaarenes and propargylic alcohols were converted to indolizines. This process operates under mild conditions and solvent-free conditions. A broad scope of coupling partners has been established, and a likely mechanism has also been suggested.



Transition metal catalyzed activation of C–H bonds has become a powerful strategy for organic synthesis in an energy-efficient and step-economic fashion.[1,2] Among the many elegant examples of transition metal catalyzed C–H activation, chelation-assisted protocols have recently attracted increasing attention, because this is an advantageous process in that no prefunctionalization of C–H bonds is necessary.[3] In recent decades, impressive achievements have been made in enhancing the efficiency of direct C–H bond activation of heteroaromatics using various transition metal catalysts such as Pd,[4] Ru,[5] Rh,[6] Cu,[7] Ir,[8] and others.[9] It has been realized that transition metal catalysts stand out in the area of C–C coupling that proceed *via* a C–H activation pathway owing to their high functional group tolerance and a wide range of synthetic utility. However, relatively little work has focused on the unreactive C(sp^3)–H bonds, because the C(sp^3)–H bonds are less acidic and lack proximal empty low-energy or filled high-energy orbitals that readily interact with orbitals of the metal. For these reasons, the efficient and atom-economic activation of C(sp^3)–H bonds have emerged as an attractive and challenging goal. On the other hand, the use of rare earth metal catalyzed reactions has emerged as a versatile tool for developing syntheses due to their numerous advantages, namely, their relatively high efficiency, water compatibility, mild reaction conditions, and eco-friendly catalytic reactions.[10] To the best of our knowledge, there have been no reports in the literature concerning the rare earth metal catalyzed activation of C(sp^3)–H bonds. As a result of our efforts in the development of transition-metal-catalyzed C–H functionalization,[11] herein, we describe a new samarium-catalyzed C(sp^3)–H bond activation of 2-alkylazaarenes with propargylic alcohols for the formation of indolizines[12,13] under mild conditions with minimal waste production.

To identify suitable conditions for the reaction, a series of catalysts were screened as shown in Table 1. Initially, the desired product **3aa** was obtained in 20% yield in the presence of 10 mol % $Sc(OTf)_3$ in a solvent-free and sealed tube at 120 °C for 24 h (Table 1, entry 1). With other catalysts, including

Table 1. Optimization of the Formation of Substituted Indolizine[a]



entry	catalyst	time (h)	yield (%)[b]
1	$Sc(OTf)_3$	24	20
2	$In(OTf)_3$	24	0
3	$Zn(OTf)_2$	24	0
4	$Er(OTf)_3$	24	0
5	$Ce(OTf)_3$	24	0
6	$Cu(OTf)_2$	24	0
7	$Y(OTf)_3$	24	0
8	$Pr(OTf)_3$	24	0
9	$AuBr_3$	24	0
10	$[RhCp^*Cl_2]_2$	24	0
11	AgOTf	24	0
12	$Pd(MeCN)_2Cl_2$	24	0
13	$Bi(OTf)_3$	24	15
14	$Sm(OTf)_3$	6	90
15[c]	$Sm(OTf)_3$	6	45
16[d]	$Sm(OTf)_3$	6	91

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (1.5 mmol), catalyst (10 mol % to **1a**), solvent-free, 120 °C, sealed tube. [b]Isolated yield of pure product based on **1a**. [c]The reaction was carried out using 5 mol % catalyst. [d]The reaction was carried out using 15 mol % catalyst.

$In(OTf)_3$, $Zn(OTf)_2$, $Er(OTf)_3$, $Ce(OTf)_3$, $Cu(OTf)_2$, $Y(OTf)_3$, $Pr(OTf)_3$, $AuBr_3$, $[RhCp^*Cl_2]_2$, AgOTf, and $Pd(MeCN)_2Cl_2$, the desired product **3aa** was not obtained at all (Table 1, entries 2–12). However, when $Bi(OTf)_3$ and

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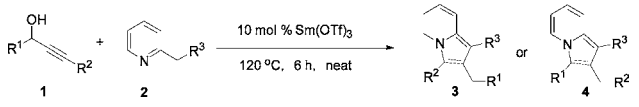
$Sm(OTf)_3$ were used as the catalysts, the desired product **3aa** was obtained in 15% and 90% yields, respectively (Table 1, entries 13 and 14). Notably, the $Sm(OTf)_3$-catalyzed reaction provided a higher yield and required a shorter reaction time. A very slow reaction rate and low yield were also observed when the catalytic amount of $Sm(OTf)_3$ decreased from 10 to 5 mol % (Table 1, entry 15 vs 14), but no obvious improvement in the yield could be obtained as the amount of $Sm(OTf)_3$ was increased to 15 mol % (Table 1, entry 16 vs 14). Hence, **1a** (0.3 mmol), **2a** (1.5 mmol), $Sm(OTf)_3$ (10 mol %), solvent-free, and in a sealed tube at 120 °C for 6 h were chosen as the optimized conditions.

With these optimal reaction conditions in hand, we started to investigate the scope and limitation of this reaction, and the results are summarized in Table 2. To our delight, various

Table 2. Synthesis of Substituted Indolizines from Propargyl Alcohols and 2-Alkylazaarenes[a]



entry	propargyl alcohol	2-alkylazaarene	product	yield (%)[b]
1	**1a**: $R^1 = R^2$ = Ph	**2a**: R^3 = H	**3aa**	90
2	**1a**: $R^1 = R^2$ = Ph	**2b**: $R^3 = CH_3$	**3ab**	85
3	**1a**: $R^1 = R^2$ = Ph	**2c**: R^3 = COOEt	**3ac**	95
4	**1a**: $R^1 = R^2$ = Ph	**2d**: R^3 = Ph	**3ad**	92
5	**1a**: $R^1 = R^2$ = Ph	**2e**: R^3 = CN	**3ae**	93
6	**1b**: $R^1 = 4\text{-}FC_6H_4$; R^2 = Ph	**2a**: R^3 = H	**3ba**	79
7	**1e**: $R^1 = 2\text{-}ClC_6H_4$; R^2 = Ph	**2a**: R^3 = H	**3ea**	80
8	**1b**: $R^1 = 4\text{-}FC_6H_4$; R^2 = Ph	**2b**: $R^3 = CH_3$	**3bb**	81
9	**1e**: $R^1 = 2\text{-}ClC_6H_4$; R^2 = Ph	**2b**: $R^3 = CH_3$	**3eb**	82
10	**1e**: $R^1 = 2\text{-}ClC_6H_4$; R^2 = Ph	**2c**: R^3 = COOEt	**3ec**	92
11	**1e**: $R^1 = 2\text{-}ClC_6H_4$; R^2 = Ph	**2d**: R^3 = Ph	**3ed**	86
12	**1e**: $R^1 = 2\text{-}ClC_6H_4$; R^2 = Ph	**2e**: R^3 = CN	**3ee**	89
13	**1c**: $R^1 = 4\text{-}MeC_6H_4$; R^2 = Ph	**2a**: R^3 = H	**3ca**	91
14	**1c**: $R^1 = 4\text{-}MeC_6H_4$; R^2 = Ph	**2c**: R^3 = COOEt	**3cc**	96
15	**1c**: $R^1 = 4\text{-}MeC_6H_4$; R^2 = Ph	**2e**: R^3 = CN	**3ce**	95
16	**1d**: R^1 = 2-Thienyl; R^2 = Ph	**2b**: $R^3 = CH_3$	**3db**	83
17	**1f**: R^1 = Ph; R^2 = H	**2c**: R^3 = COOEt	**4 fc**	80
18	**1g**: R^1 = Ph; R^2 = TMS	**2c**: R^3 = COOEt	**4gc**	81

[a]Reaction conditions: **1** (0.3 mmol), **2** (1.5 mmol), $Sm(OTf)_3$ (10 mol % to **1**), solvent-free, at 120 °C, sealed tube, 6 h. [b]Isolated yield of pure product based on **1**.

pyridines with C-2 functional groups such as CH_2CN, CH_2COOEt, CH_2Ph, and CH_2CH_3 were compatible with the reaction conditions, resulting in the formation of the desired products in high yields. The reactions of 2-alkylazaarenes having an electron-withdrawing group at R^3, such as CN, COOEt, and Ph groups, furnished the corresponding products **3ac**–**3ae** in 92–95% yields (Table 2, entries 3–5). The 2-alkylazaarenes bearing an electron-donating group at R^3, such as the CH_3 group, also gave the desired product **3ab** in high yield (Table 2, entry 2). Obviously, electron-poor pyridines with C-2 functional groups provided the desired products in higher yields than electron-rich pyridines with C-2 functional groups (Table 2, entries 3–5 vs entry 2). The C6 substituted pyridine such as 2,6-lutidine has also been examined in the reaction. However, the desired product was not obtained at all. This reaction has features of high yields with water as the only byproduct, suggesting good prospects toward commercialization.

Additionally, all the secondary propargylic alcohols **1** bearing not only terminal alkyne groups but also internal alkyne groups participated well in the C–H functionalization/cyclization, producing the products in good yields and showing good functional group tolerance. The propargyl alcohols **1c** possessing an electron-donating group on the aryl ring (R^1 = $4\text{-}MeC_6H_4$) afforded the desired products **3ca**–**3ce** in 91%–96% yields (Table 2, entries 13–15). Substrates **1b** and **1e** possessing an electron-withdrawing group ($R^1 = 4\text{-}FC_6H_4$ and $2\text{-}ClC_6H_4$) on the benzene ring also reacted smoothly and afforded the desired products in high yields (Table 2, entries 6–12). We also have observed some variation in yields as a function of electronic effects: that is, aromatic propargyl alcohols with an electron-donating group at the benzene ring gave the corresponding products in higher yields than propargyl alcohols which possessed an electron-withdrawing group on the benzene ring (Table 2, entries 13–15 vs entries 6–12). The electron-donating group presumably facilitated the process that converted propargyl alcohols into propargylic cations. The crystallization of compound **3ee** from ethanol gave a single crystal suitable for X-ray analysis. Figure 1 illustrates the

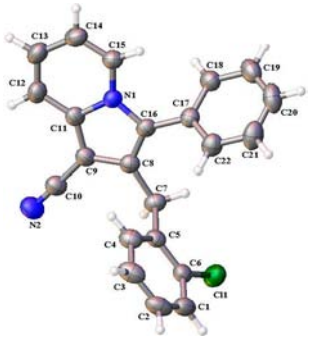


Figure 1. X-ray crystal structure of indolizine **3ee**.

molecular structure of the substituted indolizine **3ee**. In addition, a propargyl alcohol bearing a heterocyclic substituent such as **1d** (R^1 = 2-thienyl) gave the desired product **3db** in 83% yield (Table 2, entry 16). Interestingly, an unactivated terminal propargyl alcohol such as 1-phenyl-prop-2-yn-1-ol **1f** (R^2 = H) was efficient, coupling with pyridin-2-yl-acetic acid ethyl ester **2c** to form the substituted indolizine **4fc** in 80% yield (Table 2, entry 17). The reaction of propargylic alcohol **1g** (R^2 = TMS) with **2c** also led to the coupled product **4gc** in 81% yield (Table 2, entry 18). However, when the propargylic aliphatic ether (e.g., benzyl propargyl ether) and the propargylic alcohols with alkyl groups (R^1 or R^2 = alkyl) were used, the reaction failed to afford the desired products.

Fortunately, the reaction of 2-methyl-quinoline **4a** with propargyl alcohol **1a** under the standard conditions produced the desired product 2-benzyl-1,3-diphenyl-pyrrolo[1,2-*a*]-quinoline **4aa** in 78% yield (Scheme 1). The structure of **4aa** was confirmed by extensive spectroscopic analysis (see Suporting Information pp S27, S33). The pyrrolo[1,2-*a*]-quinoline derivatives have significant antibacterial and antifungal effects. Of particular note is that pyrrolo[1,2-*a*]quinoline derivatives are important synthetic targets for developing new pharmaceuticals.[14] Herein, we have provided a rapid method for the synthesis of the pyrrolo[1,2-*a*]quinoline derivatives.

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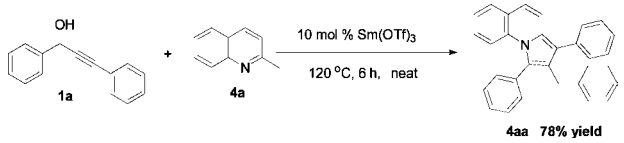
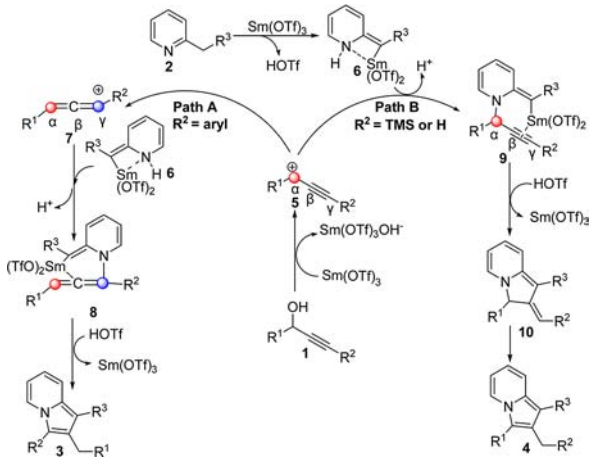
Scheme 1. Synthesis of 2-Benzyl-1,3-diphenyl-pyrrolo[1,2-*a*]quinoline 4aa from 2-Methyl-quinoline and Propargyl Alcohol



On the basis of these data, we propose the process detailed in Scheme 2 as the most likely mechanism for this transformation.

Scheme 2. Possible Reaction Mechanism



For the samarium-catalyzed C(sp^3)−H bond functionalizations of 2-alkylazaarenes with propargylic alcohols, cyclometalation of **2** affords a chelating Sm(III) intermediate **6**. Subsequently, the propargylic cation **5** or the allenyl cation **7** is attacked by the nitrogen atom of the chelated Sm(III) intermediate **6**. The secondary propargylic alcohols (R^3 = aryl) follow path A. In path A, the ionization of propargylic alcohols **1** would lead to propargylic cation **5**. The propargyl cations would isomerize to the allenyl cation **7**, and the subsequent nucleophilic attack of the intermediate **6** gives a six-membered metallacyclic species **8**, which easily cyclizes, leading to the indolizines **3**. When the secondary propargylic alcohols (R^3 = TMS or H) are used, instability of the allenyl cation intermediate **7** (R^3 = H) and the steric effect of the trimethylsilane group at the γ-position of the intermediate **7** (R^3 = TMS) makes path A less favorable. Accordingly, the reaction would proceed through path B, which is more favorable. In path B, the reaction of the propargylic cation **5** and the chelated Sm(III) intermediate **6** gives a six-membered metallacyclic complex **9**. A subsequent cyclization occurs to generate the intermediate **10**, which then undergoes isomerization to the indolizines **4**. Another likely mechanism might be ionization of the propargyl alcohol to give **5**, which is then attacked by a neutral pyridine to give a pyridinium ion. However, we have found that pyridine does not react with propargyl alcohol, presumably due to the weaker nucleophilic ability of neutral pyridine relative to that of intermediate **6**. Therefore, it is more reasonable that the propargylic cation **5** or the allenyl cation **7** is attacked by the nitrogen atom of the chelated Sm(III) intermediate **6**.

In conclusion, we have successfully developed flexible and rapid samarium-catalyzed C(sp^3)−H bond activation for the synthesis of indolizines from readily available 2-alkylazaarenes and propargylic alcohols. The reaction proceeds under solvent-free conditions and displays wide functional group compatibility. The ability to incorporate halogen substituents, as well as cyano and ester groups, into the product makes this process potentially valuable for further synthetic transformations.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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