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Gold-Catalyzed Direct Alkynylation of Azulenes

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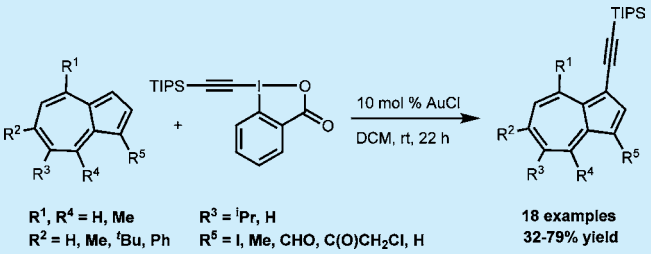
Supporting Information

ABSTRACT: A novel catalytic method for the direct C−H alkynylation of azulenes is developed. The gold catalyzed functionalization of this special carbacycle is achieved with hypervalent iodonium reagent TIPS-EBX under mild reaction conditions. With the aid of the developed procedure, several TIPS alkynylated azulene derivatives were synthesized bearing important functional groups for further functionalization.

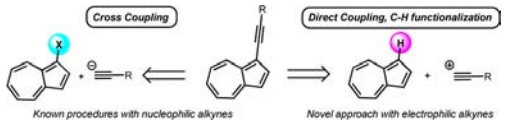


Azulene derivatives have fascinated scientists through the ages with their particular color in Nature.[1] In general, the naturally occurring derivatives can be obtained from plant sources.[2] The azulene ring system can be constructed in the laboratory through Ziegler−Hafner synthesis,[3] Danheiser ring expansion,[4] Nozoe azulene synthesis,[5] or starting from fulvenes.[6] The physical and chemical properties of azulenes are unique due to the condensed 7 + 5 membered carbacycles. The special ring system contributes to the dipolar nature of the molecule with a high, 1.08 D dipole moment[7] and increased reactivity. Its five-membered ring carries partial negative charge; thus, it can be substituted in C-1 and C-3 positions in electrophilic substitution reactions.[8]

Considering the transition metal catalyzed transformations, there are several examples for the cross-coupling reactions of azulenes, e.g. Suzuki−Miyaura, Stille, and Negishi cross-couplings.[9] Lewis and co-workers have recently found that shelf-stable azulenesulfonium salts bear enhanced stability and activity in Suzuki−Miyaura cross-coupling reactions.[10] The applicability of this latter reaction has been demonstrated using various coupling partners. Contrarily, there are only sporadic examples for the functionalization of azulenes with metal catalyzed C−H activation reaction.[11]

Substituted azulenes have diverse applications in medicinal chemistry,[12] in photosensitizers,[13] multistate switches,[14] as metal−organic frameworks for hydrogen storage,[15] chromophores,[16] and electroactive oligomers.[17] Among the substituted azulenes applied in the fields mentioned above, a significant number of the azulene derivatives are equipped with alkynyl functional groups. The introduction of the alkynyl moiety onto the carbacyclic scaffold can be achieved on azulenyl halides, mostly on the labile iodo derivatives, by Sonogashira coupling reactions (Scheme 1).[18] Considering the importance of the ethynylazulenes, development of new methods for the mild direct alkynylation of versatile azulenes via C−H functionalization is highly desirable.

Scheme 1. Introduction of Alkyne Function to Azulene Scaffold



In our work, we aimed to develop a novel procedure for the alkynylation of this interesting carbacycle through the direct modification of its C−H bonds with λ^3 iodine reagents[19] utilizing transition metal catalysts. The reaction of the azulene skeleton and electrophilic hypervalent iodine reagents is unknown. The C−H functionalization with λ^3 iodine reagents for different substrates often requires increased reaction temperatures,[20] which is not suitable for the azulene scaffold due to its tendency to undergo rearrangement.[21] However, the triisopropylsilylethynyl-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **2**) is an efficient reagent for the alkynylation of heteroaromatic molecules even under mild conditions.[22]

Our investigations for the alkynylation of the azulene ring started with the study of the reaction of guaiazulene as an easily available substrate. Utilization of TIPS-EBX as an alkynylating agent did not afford the product without a proper catalyst. Considering the fact that gold catalysis is a valuable tool in both the activation of TIPS-EBX and other C−H functionalization reactions,[23] we intended to explore the possibilities offered by this noble metal for the direct ethynylation of the azulene scaffold. Examination of possible catalysts revealed that AuCl and $AuCl(CH_3)_2$ provided the desired product (Table 1, entries 1−7) at a 5 mol % loading. After finding the most suitable catalyst (entry 7), we found that the presence of 10 mol % AuCl provides better conversion (entry 8). When 1.5 or 3 equiv of iodonium

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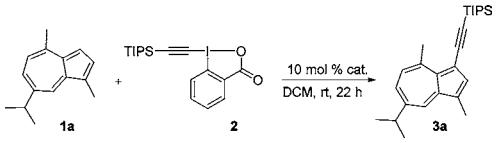
Table 1. Optimization of the Alkynylation Reaction[a]



entry	catalyst	2 (equiv)	conversion (%)[b]
1	–	1.1	0
2	$AgBF_4$	1.1	0[c]
3	$Cu(OTf)_2$	1.1	<5[c]
4	$Pd(OAc)_2$	1.1	17[c]
5	$Ph_3PAuOTs$	1.1	0[c]
6	$AuClS(CH_3)_2$	1.1	36[c]
7	AuCl	1.1	48[c]
8	AuCl	1.1	67
9	AuCl	1.5	60
10	AuCl	3.0	79
11	AuCl	1.1	19[d]
12	AuCl	1.5	100[d]
13	AuCl	3.0	97[d]
14	AuCl	1.5	100[e]

[a]Reaction conditions: **1a** (0.2 mmol), catalyst (0.02 mmol), and **2** in DCM (0.5 mL). [b]Conversions were obtained by GC-FID measurements: % = [*I*(product)/(*I*(product) + *I*(starting material))] × 100. [c]5 mol % of catalyst was used. [d]**2** was added portionwise (5 portions in 8 min) to the mixture of **1** (0.2 mmol) and AuCl (0.02 mmol) in DCM (0.5 mL). [e]AuCl (0.02 mmol) was added to the mixture of **1a** (0.2 mmol) and **2** in DCM (0.5 mL).

reagent **2** were added to the reaction mixture the reactions took place with 60% and 79% conversions respectively (entries 9, 10).

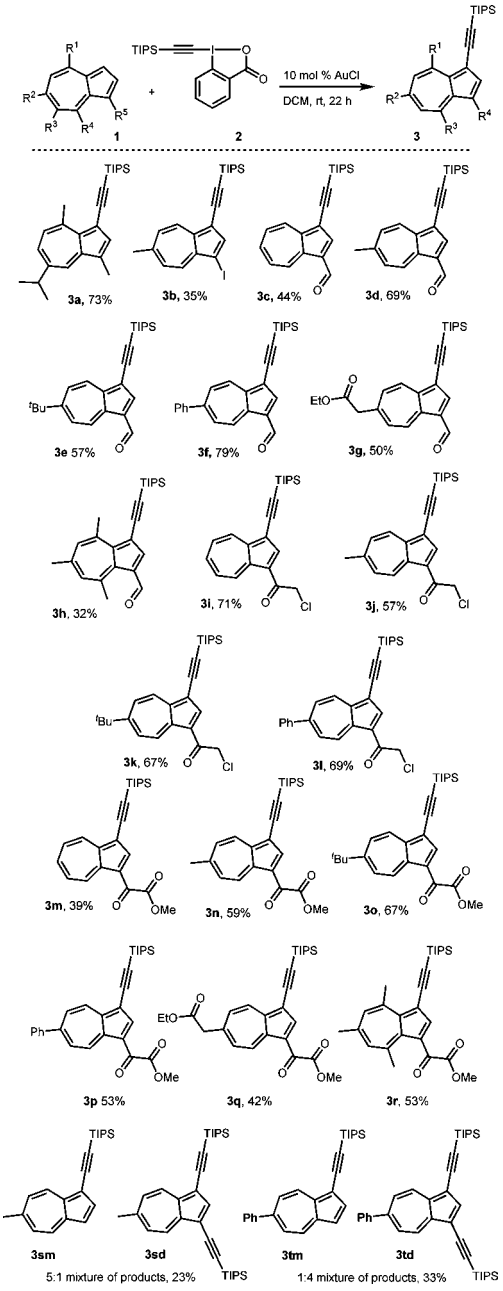
The robustness of the reaction could be greatly improved by modifying the order of addition of the reactants and catalysts. When a different amount (1.1−3 equiv) of TIPS−EBX (**2**) was added portionwise to the mixture of azulene (**1a**) and 10 mol % AuCl in DCM (entries 11−13), full conversion of the transformation was observed with 1.5 equiv of the iodonium reagent (entry 12). We found similar efficiency (100% conversion) when AuCl was added to the mixture of azulene **1a** and TIPS-EBX (**2**) (entry 14). The latter implementation of the reaction was used for the study of the substrate scope.

After finding the optimal stoichiometry and conditions for the reaction, we examined the alkynylation of guaiazulene (**1a**) as well as 6-methyl- and 1-iodo-6-methylazulene (**1s** and **1b**) with **2** in the presence of the AuCl catalyst (Scheme 2). For that purpose, these azulene derivatives were synthesized by a novel method published by Leino et al.,[24] which is based on the Ziegler−Hafner synthesis of azulenes.

The natural azulene derivative **1a** was alkynylated under the optimized conditions, and the TIPS ethynylated guaiazulene (**3a**) was isolated in 73% yield. In the case of unstable 1-iodo-6-methylazulene, **3b** was isolated in 35% yield, which might be transformed into valuable compounds through the iodo function by cross-coupling.

To expand the scope of the transformation, azulenes with synthetically useful functionalities were synthesized. In this regard, several formylated,[25] 2-chloroacylated,[26] and ketoester[8g] derivatives of azulene have been prepared using literature procedures. The prepared azulene derivatives bearing the transformable functional groups aforementioned in position 1 were subjected to the gold catalyzed alkynylation utilizing the previously applied conditions (Scheme 2). First, 1-formyl

Scheme 2. Alkynylation of Various Azulene Derivatives[a]



[a]Reaction conditions: Azulene **1** (0.5 mmol) in dichloromethane (1 mL), TIPS-EBX (**2**, 0.75 mmol) followed by AuCl (0.05 mmol, 10 mol %). The reaction mixtures were stirred at 25 °C for 22 h.

azulenes were successfully alkynylated with TIPS-EBX in position 3. The azulene ring bearing no functional group on the seven-membered ring (**3c**) was alkynylated in 44% yield. The presence of electron-donating groups such as methyl or *tert*-butyl in position 6 proved to be beneficial for the transformation, and the expected products (**3d** and **3e**) were isolated in higher, 69% and 57% yields. 1-Formyl-6-phenylazulene served as an excellent substrate, and the appropriate TIPS-ethynyl product **3f** was isolated in 79% yield. An ester function connected by a methylene linker to the azulene ring was also compatible with the conditions of the transformation, and the ethynylated product (**3g**) was isolated in 50% yield. This derivative (**3g**) offers multiple transformations in three positions due to its

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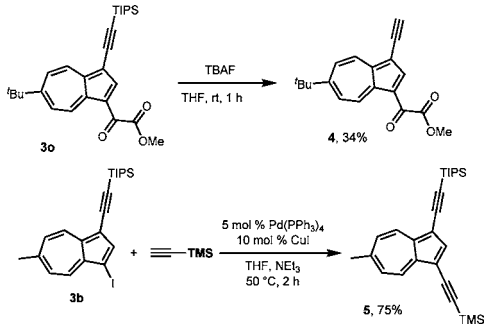
versatile functional groups attached to the azulene frame. In the presence of three methyl groups on the seven membered ring of the azulene frame the alkyne derivative **3h** was obtained only in 32% yield.

In the case of the series of 1-choroacylated azulenes, we subjected the substrates (R^1 = H, Me, *t*-Bu, Ph) to the transformation under the same catalytic conditions and the appropriate products (**3i**−**3l**) were obtained in good yields (57−71%). Similarly to the aldehyde series, the scope of the direct gold catalyzed alkynylation of azulenes containing a ketoester-function in position 1 was examined. The appropriate 3-TIPS-ethynyl products (**3m**−**3r**) were obtained in 39−67% yield, providing a direct route to produce these complex products.

The direct alkynylation of azulene derivatives, unsubstituted on the smaller ring, were also successfully achieved in the gold catalyzed transformation. However, in the case of 6-methyl- and 6-phenylazulene the mono- and disubstituted azulene derivatives were formed, and the mixture of appropriate mono- and dialkynylated products (**3sm, 3sd** and **3tm, 3td**) was obtained.

We have attempted the removal of the TIPS protecting group from the installed ethynyl moiety of compound **3o** with tetrabutylammonium fluoride (TBAF) in THF at room temperature (Scheme 3), and the desired azulene derivative (**4**) bearing terminal alkyne function was obtained in 34% yield.

Scheme 3. Postmodifications on the TIPS Alkynylated Azulene Scaffold



As an additional reaction we transformed the ethynylated iodoazulene product **3b** in Sonogashira coupling with TMS-acetylene under standard coupling conditions. The dialkynylated azulene product (**5**) was successfully obtained in 75% yield.

Summarizing our work, we have developed a novel, mild procedure for the direct alkynylation of azulenes utilizing TIPS-EBX in a gold catalyzed transformation. The applicability of the optimized reaction conditions was demonstrated on several synthetic examples. The efficient introduction of the TIPS acetylene moiety ensures further functionalizations via desilylation to extend the conjugation through the molecule. This synthetic opportunity enables the fine-tuning of the electronic properties of these carbacyclic molecules. The developed method is suitable for the alkynylation of azulenes equipped with aldehyde, chloroacetyl, or ketoester motifs, which are also excellent functional groups for further chemical transformations. The multifunctionality and versatile transformability of the prepared azulene derivatives through their installed functional groups make the procedure a valuable synthetic tool not only for organic chemistry but also for materials science, and could facilitate their application in electronic devices. We have demonstrated the possibility of C−H functionalization of the azulene scaffold, with a particularly interesting ethynylation reaction, opening the pathway for other similar transformations using hypervalent iodine reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00259.

Experimental procedures, spectroscopic data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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