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Lewis Acid Catalyzed Regioselective Hydroheteroarylation of Pentafulvenes

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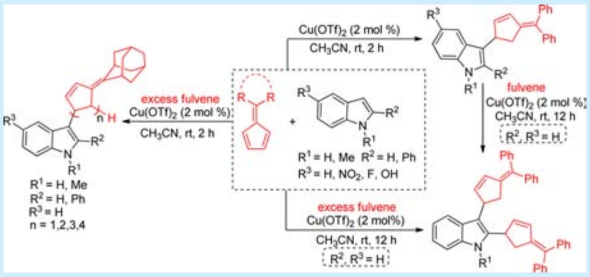
S *Supporting Information*

ABSTRACT: A diverse approach toward the catalytic regioselective nucleophilic addition of nitrogen heterocycles to Lewis acid activated pentafulvenes has been established. The developed protocol introduces pentafulvenes as nonsymmetrical alkenes for the hydroheteroarylation reaction, providing alkylidenecyclopentenylation at the C-3 position of indoles and the C-2 position of pyrrole.



Hydroarylation reactions for the functionalization of unactivated alkenes have emerged as an exciting area of research over the last two decades.[1] A wide range of transition-metal complexes, including Au, Pd, Rh, Pt, Ru, Cu, Ir, Ni, and Sc, have been effectively utilized in the formal addition of a C(arene)−H or C(heteroarene)−H bond onto olefins.[2] Recent advances have shown that even mild Lewis acidic conditions ($Bi(OTf)_3$, $AlCl_3$, $FeCl_3$, $[PF(C_6F_5)_3][B(C_6F_5)_4]$) can lead to the hydro(hetero)arylation of various alkenes.[3] Furthermore, the substrate scope could be extended beyond alkenes: hydro(hetero)arylations of alkynes, allenes, vinyl ethers, and alkynoles have been well documented in the literature.[4] In this context, we introduce pentafulvenes, an interesting class of cross-conjugated trienes, as nonsymmetrical alkenes for the regioselective Lewis acid catalyzed hydroheteroarylation reaction.

Pentafulvenes give rise to a vast array of reaction pathways depending on substitution patterns and reaction conditions.[5] The cycloaddition profile of fulvenes is now well established,[6] while new, often transition-metal-mediated transformations are emerging.[7] Reactions of nucleophiles with these nonbenzenoid dipolar hydrocarbons have been mainly exploited in metallocene chemistry; i.e., the exocyclic carbon of fulvenes is partially positively charged and readily reacts with numerous nucleophiles leading to a cyclopentadienyl precursor for metal complexation.[8] In contrast, nucleophilic attack on the endocyclic ring system of fulvenes is rare. The homopolymerization of fulvenes under acid catalysis reported by Neuenschwander could be considered as such an example (Figure 1a).[9] Low-temperature NMR studies by Olah showed that reaction of super acids with fulvenes lead to fulvenium ions, which should make the endocyclic ring a good target for nucleophilic addition (Figure 1b).[10] We herein disclose our preliminary results on the Lewis acid catalyzed regioselective nucleophilic addition of indoles and pyrrole to the endocyclic ring of pentafulvenes (Figure 1).

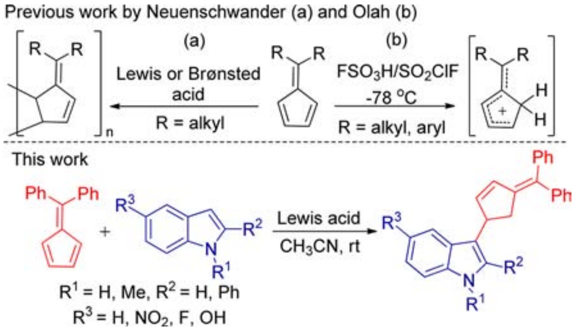


Figure 1. Activation of pentafulvenes by Lewis and Brønsted acids.

In line with our previous results on the reactivity of pentafulvene-derived diazanorbornenes which afforded cyclopentene-fused nitrogen or sulfur heterocyclic ring systems under Lewis acid catalysis,[11] we conducted a reaction between diphenylfulvene **1a** and *N*-methylindole **2b** by employing 2 mol % of $Sc(OTf)_3$ as the catalyst in acetonitrile at room temperature. To our delight, the indole substitution occurs exclusively at the C-2 carbon of the endocyclic ring system of fulvene furnishing the product **3ab** in 91% yield (Scheme 1). The structure of the product was characterized by various spectroscopic methods and unequivocally confirmed by single-

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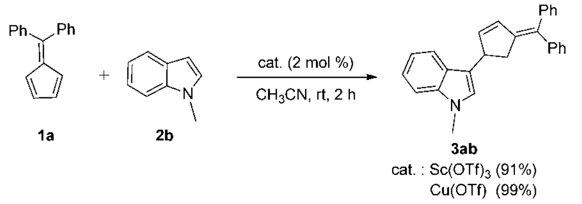
Scheme 1. Lewis Acid Catalyzed Regioselective Hydroarylation of Fulvene with *N*-Methylindole

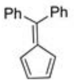
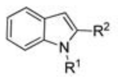
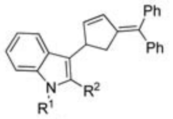
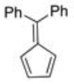
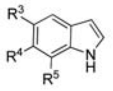
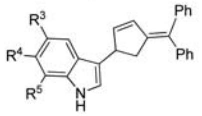
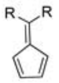
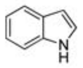
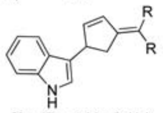


crystal X-ray analysis of the compound **3ac** (see the Supporting Information).

Encouraged by this unusual regioselective 1,2 addition of indole to fulvene, we screened various reaction parameters to optimize the reaction conditions. From the detailed optimization study (see Table S-1, SI), 2 mol % of Cu(OTf)$_2$ in 2 mL of acetonitrile at room temperature for 2 h were found to be the best catalytic conditions for the reaction, affording a 99% yield for product **3ab**. It was found that in the absence of Lewis acid the starting materials **1a** and **2b** were fully recovered.

With the optimized reaction conditions in hand, we investigated the viability of the reaction with different substituted indoles (Table 1). Indole and *N*-methylindole showed remarkable reactivity toward fulvene, affording products in excellent yields. The hydroxyl group at the C-5 position of indole **2h** decreased the efficiency of the reaction (entry 8), whereas 5-aminoindole **2i** (entry 9) did not furnish the desired product.

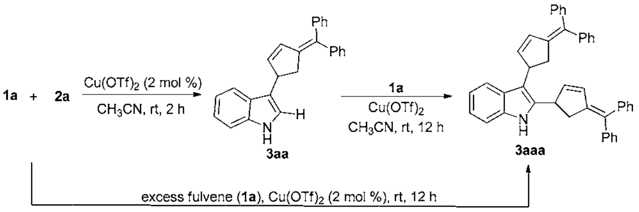
Table 1. Scope of Hydroarylation Reaction Using Substituted indoles[a]

entry	fulvene	indole	product	yield (%)
				
1	**1a**	**2a** (R^1 = H, R^2 = H)	**3aa**	98
2	**1a**	**2b** (R^1 = Me, R^2 = H)	**3ab**	99
3	**1a**	**2c** (R^1 = H, R^2 = Ph)	**3ac**	99
4	**1a**	**2d** (R^1 = Me, R^2 = Ph)	**3ad**	99
5	**1a**	**2e** (R^1 = H, R^2 = Me)	**3ae**	96
				
6	**1a**	**2f** (R^3 = NO$_2$, R^4 = H, R^5 = H)	**3af**	75
7	**1a**	**2g** (R^3 = F, R^4 = H, R^5 = H))	**3ag**	100
8	**1a**	**2h** (R^3 = OH, R^4 = H, R^5 = H)	**3ah**	42
9	**1a**	**2i** (R^3 = NH$_2$, R^4 = H, R^5 = H))	**3ai**	0
10	**1a**	**2j** (R^3 = H, R^4 = H, R^5 = CH$_3$)	**3aj**	67
11	**1a**	**2k** (R^3 = H, R^4 = CH$_3$, R^5 = H)	**3ak**	62
12	 **1b** (R = 4-Me-C$_6$H$_4$)	 **2a**	 **3ba** (R = 4-Me-C$_6$H$_4$)	78

[a] Reaction conditions: fulvene (1.0 equiv), indole (1.0 equiv), Cu(OTf)$_2$ (2 mol %), CH$_3$CN (2 mL), rt, 2 h.

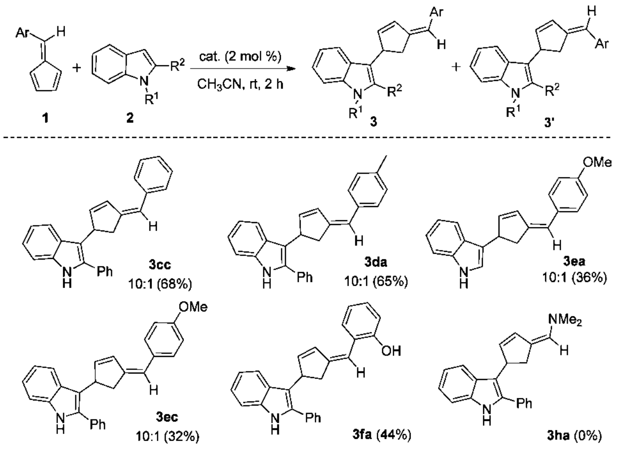
We were pleased to observe the formation of a new product **3aaa** along with **3aa** by doubling the equivalents of fulvene **1a**. The compound **3aaa** was isolated in 35% yield and was identified as a product formed by double alkylidenecyclopentenylation of indole at its C-2 and C-3 position. The formation of **3aaa** was further checked by conducting a reaction between 3-alkylidenecyclopentenylated indole **3aa** and 1.0 equiv of fulvene **1a** (Scheme 2), which revealed the nucleophilicity of the C-2 position of indole for hydroarylation in succession.

Scheme 2. Lewis Acid Catalyzed Double Alkylidenecyclopentenylation of Indole



To study the scope and uniqueness of the reaction, we extended the developed strategy to unsymmetrical fulvenes. With a monosubstitution at the exocyclic double bond, unsymmetrical fulvenes are expected to be more prone toward nucleophilic addition at the more exposed C-6 position. But the reaction is selective toward the endoselective addition affording the C-2 hydroarylated product **3** with a minor amount of the other regioisomer **3′** (with indole substituted on the same side as the 6-aryl substitutent) in minor amounts in all cases except **3fa** (Scheme 3). In addition, the reaction of fulvene with an electron-donating group at the exocyclic position, *N*,*N*-dimethylaminofulvene, did not afford the expected product **3ha** (Scheme 3).

Scheme 3. Substrate Scope for Hydroarylation in Unsymmetrical Fulvene



Subsequently, we sought to extend the developed protocol to fulvenes with alkyl substituents at its exocyclic (C-6) position. Interestingly, the reaction between adamantanone-derived fulvene **1g** and 2-phenylindole **2c** afforded two products under standard conditions, the expected product **3gc** and the new product **4gc**, containing two fulvene fragments (Scheme 4).

The unprecedented formation of product **4gc** prompted us to optimize the selectivity of the reaction by varying the fulvene/indole ratio and the reaction temperature (Table 2). It could be shown that the best yield of **3gc** was obtained with a small excess of indole at 0 °C and a shorter reaction time (entry 9). On the other hand, the optimum yield of **4gc** was isolated

Scheme 4. Preliminary Result of Hydroarylation Reaction Using Alkyl-Substituted Fulvene

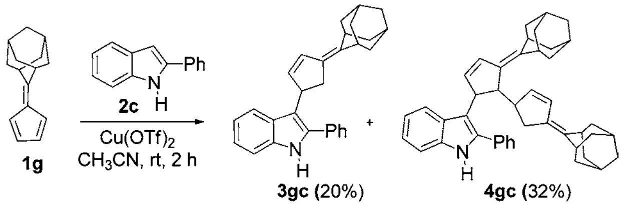
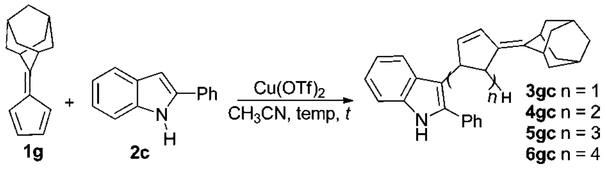


Table 2. Termination of Lewis Acid Catalyzed Polymerization of Fulvene with Indole



entry	1g (equiv)	2c (equiv)	temp (°C)	time (h)	isolated yield (%) 3gc	4gc	5gc	6gc
1	1.0	1.0	25	2	20	32		
2	1.5	1.0	25	2	24	37	12	trace
3	2.0	1.0	25	2	28	36	14	8
4	1.0	1.0	0	0.75	39	17	trace	
5	1.5	1.0	0	0.75	22	46	trace	
6	2.0	1.0	0	0.75	20	58	trace	
7[b]	1.0	1.3	0	0.75	54	15		
8[b]	1.0	2.0	0	0.75	50	8		
9[b]	1.0	1.3	0	0.25	62	12		

[a] Reaction conditions: $Cu(OTf)_2$ (2 mol %), CH_3CN (2 mL). [b] Formation of an additional new product **7gcc** (see the SI).

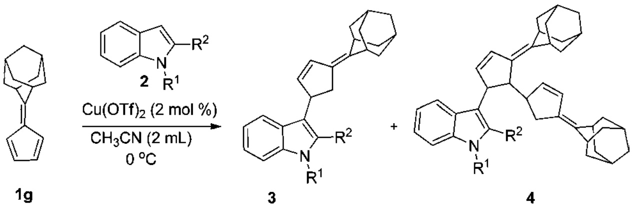
with a 2-fold excess of fulvene at 0 °C (entry 6). Furthermore, an increase of fulvene/indole ratio at room temperature allowed the isolation of higher analogues of **4gc** containing three or four fulvene moieties, **5gc** and **6gc**, respectively (entry 3). 2-D NMR experiments (^{1}H−^{1}H COSY, ^{1}H−^{13}C HSQC, ^{1}H−^{13}C HMBC) were used to confirm the structures of compounds **3gc**, **4gc**, **5gc**, and **6gc**.

The previously reported self-polymerization of fulvene in acidic condition endorses the polymerization of the dipolar structures of alkyl-substituted fulvenes and its competence with substitution reactions.[9,10] In our case, the self-polymerization is stopped by indole at different stages depending on the amount of fulvene. This is in contrast to the results obtained in Scheme 2 with diarylfulvene, where two fulvenes were introduced consecutively. This was further shown by the attempted reaction of isolated product **3gc** with fulvene **1g** in the presence of Lewis acid, from which only polymerized fulvene and intact **3gc** were recovered.

With the optimized conditions in hand, the generality of the reaction was shown with differently substituted indoles (Table 3).

A plausible mechanism for the trapping of Lewis acid generated intermediate **A**, postulated in accordance with previous NMR studies,[10] by indole leading to the hydroheteroarylation of pentafulvene is illustrated in Scheme 5. Electron-deficient fulvenes (aromatic substituents at the exocyclic double bond) selectively underwent 1,2-hydroheteroarylation with indole under Lewis acidic conditions, whereas electron-rich fulvene has sufficient time to furnish its cationic dimeric species **B** (and higher oligomeric species), which leads to **4** along with minor amounts of higher oligomers in addition to the expected 1,2-hydroheteroarylation product **3**.

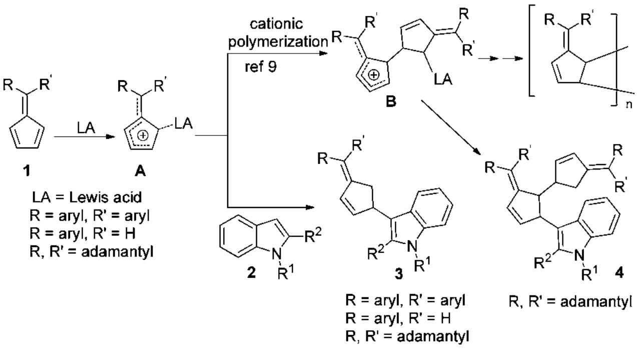
Table 3. Lewis Acid Catalyzed 1,2-Addition of Indoles to 6-Adamantyl-Substituted Fulvene



entry	indole	yield (%) 3	4
1	**2a** (R^1 = H, R^2 = H)	**3ga** (59)[a]	**4ga** (15)[a]
		3ga (17)[b]	**4ga** (57)[b]
2	**2d** (R^1 = Me, R^2 = Ph)	**3gd** (57)[a]	**4gd** (14)[a]
		3gd (23)[b]	**4gd** (50)[b]

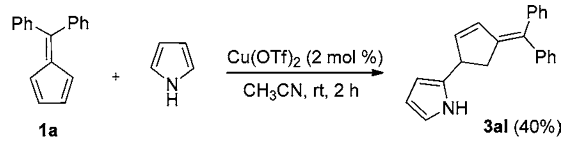
[a] Reaction conditions: fulvene (1.0 equiv), indole (1.3 equiv), $Cu(OTf)_2$ (2 mol %), 15 min. [b] Reaction conditions: fulvene (2.0 equiv), indole (1.0 equiv), 45 min.

Scheme 5. Proposed Mechanistic Pathway for the Trapping of Lewis Acid Generated Fulvenium Ion by Indole



Finally, in a preliminary experiment, the scope of the reaction was also extended to pyrrole for the selective synthesis of alkylidenecyclopentenyl-2,3-dihydro-1*H*-pyrrole **3al** (Scheme 6).

Scheme 6. Lewis Acid Catalyzed Hydroarylation of Fulvene with Pyrrole



In conclusion, we have developed an exceptional strategy toward the regioselective endocyclic ring functionalization of pentafulvenes with indoles and pyrrole. This operationally simple reaction protocol does not require dry solvents or inert atmosphere and easily occurs at ambient temperature. The method has provided a wide range of C-3 alkylidenecyclopentenylated indoles and is the first example for the Lewis acid catalyzed endoselective 1,2-addition of a nucleophile to fulvene. Experiments based on other nucleophiles/(hetero)arenes are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00047.

Experimental procedures and ^{1}H and ^{13}C NMR spectra of all new compounds and 2D NMR spectra for **3gc**, **4gc**, **5gc**, and **6gc** (PDF)

X-ray data for **3ac** (CCDC 1034751) (CIF)

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Notes

The authors declare no competing financial interest.

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