Carbocyclization

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Direct Intramolecular Arylation of Aldehydes Promoted by Reaction with IPy_2BF_4/HBF_4: Synthesis of Benzocyclic Ketones**

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Dedicated to Professor K. Peter C. Vollhardt on the occasion of his 60th birthday

The Friedel–Crafts acylation of arenes is a prevailing reaction for accessing aryl ketones.[1] However, conditions for carrying out the desired arene acylation directly from an aryl-substituted aldehyde have not yet been described. Herein, an intramolecular version of such a process is presented. Thus arenecarboxaldehydes are converted into benzocyclic ketones[2,3] in a straightforward one-pot process.

The iodoarylation of alkenes and alkynes is an efficient tool for the modular assembly of heterocycles with rapid generation of diversity.[4] During the course of these iodoarylation studies, we discovered by chance that the advanced intermediate **1** underwent not only the expected arylation of the alkyne functionality, but also conversion into the benzocyclic ketone **2** [Eq. (1), Py = pyridine]. In this conceptually attractive transformation, an aryl aldehyde acts formally as a proper acylating agent in a novel intramolecular reaction sequence triggered by iodonium ions. We decided to further

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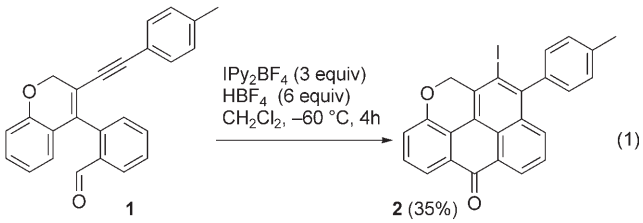
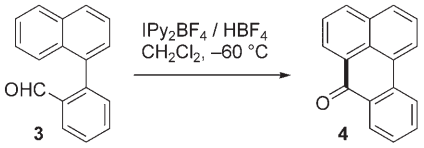
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



(1)

explore the generality of this formal C–H functionalization to produce ketones. We chose 2-(1-naphthyl)benzenecarboxaldehyde (**3**) as a suitable starting material to test the feasibility of this challenging reaction with simpler compounds [Eq. (2)].



(2)

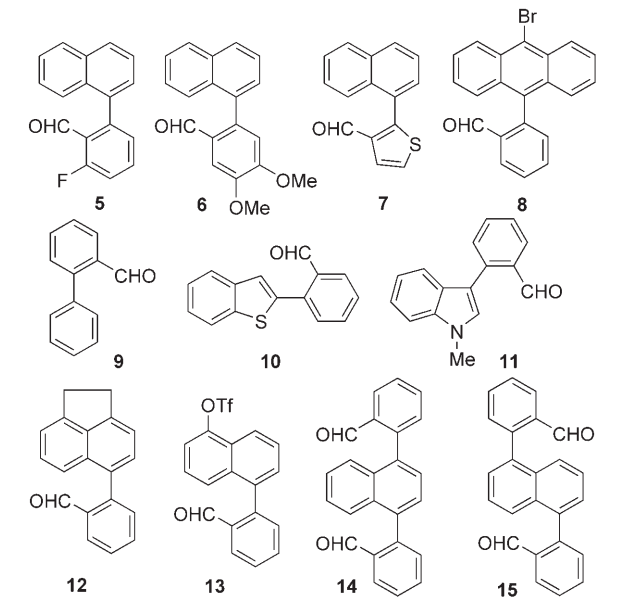
An initial optimization procedure revealed that the desired process was most efficient when a 2:1 molar ratio of HBF_4 to the iodinating reagent and a 2:1 ratio of the latter with respect to **3** were used (Table 1). When the ratio of IPy_2BF_4 was increased, the yield of **4** was not improved. However, the use of more electrophilic conditions gave better results (Table 1, entry 6). For entries 1–5, **3** was added to a cooled solution that contained the iodinating reagent and the acid. However, in the case of entry 6, a different experimental protocol was adopted. First, the iodinating agent and the acid were mixed at −80 °C, and the pyridinium salts generated in the neutralization were removed to a great extent by filtration at low temperature under an inert atmosphere. After **3** had been added to this solution,[5] the temperature was allowed to rise to −60 °C and was kept constant while the mixture was stirred for the time stated.

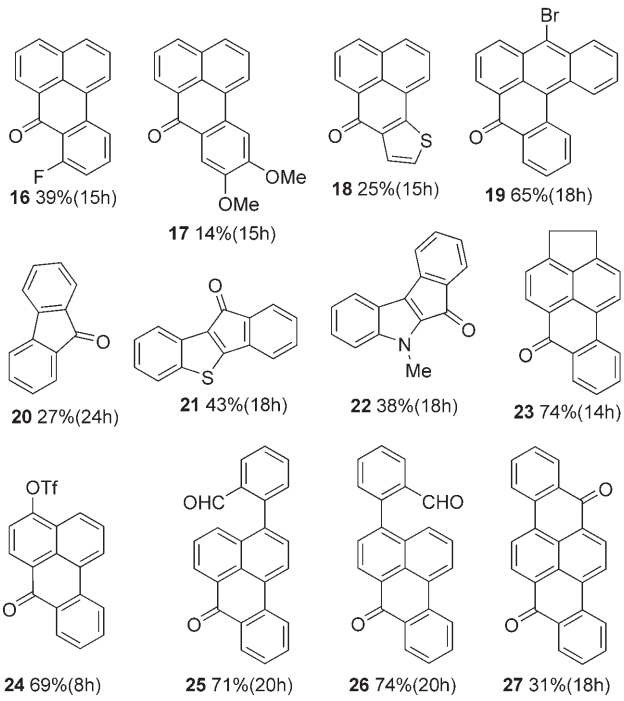
Table 1: Optimization of conditions for the direct conversion of **3** into **4** [Eq. (2)].

Entry	IPy_2BF_4 [equiv]	HBF_4 [equiv]	*t* [h]	Conversion[a] [%]	Yield[b] [%]
1	1	1	24	5	–
2	1	2	24	20	17
3	2	4	18	50	46
4	–	4	24	–	–
5	3	6	18	75	48[c]
6[d]	2	4	15	94	61[e]

[a] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture with respect to **3**. [b] Of isolated **4** with respect to **3**. [c] An iodinated derivative of **3** was formed in 19% yield. [d] The reaction was conducted by following the modified experimental protocol discussed in the text; see also the Experimental Section. [e] Iodinated derivatives of **3** (28%) and **4** (4%) were also formed.

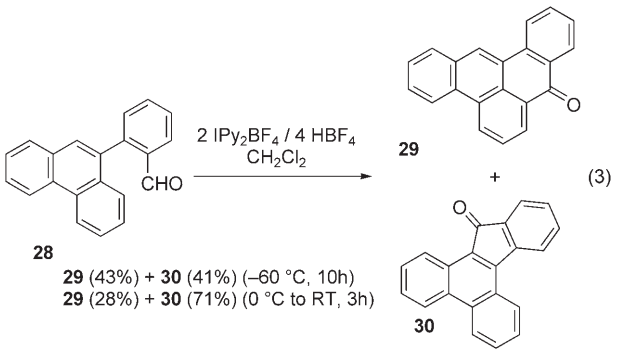
We explored the scope and the selectivity of the process by preparing and screening the reactivity of the set of aromatic aldehydes **5**–**15** (Tf = trifluoromethanesulfonyl).[6] The arylation reactions were conducted under the modified experimental conditions described for entry 6 of Table 1, unless otherwise specified. The structures of the aromatic polycyclic ketones obtained as well as the yields and the reaction times are depicted in Scheme 1.





Scheme 1. Polycyclic aromatic ketones obtained in the formal Friedel–Crafts acylation of arenes **5**–**15** with aldehydes, yields, and reaction times.

The formation of a single isomer was observed consistently for the cyclization of compounds **5**–**15**. However, the reaction of 2-(9-phenanthrenyl)benzenecarboxaldehyde (**28**) gave mixtures of **29** and **30** [Eq. (3)]. When the reaction was

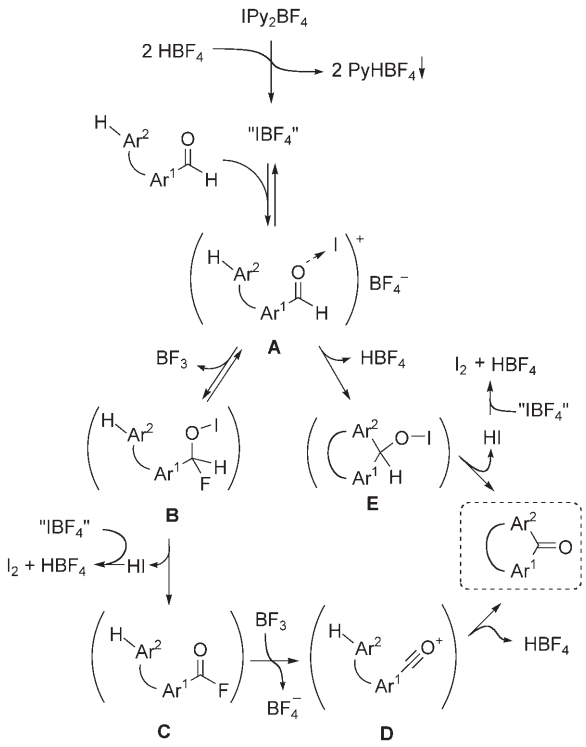


carried out under the standard conditions, the two compounds were isolated in nearly a 1:1 ratio. Interestingly, a larger amount of **30** was obtained when the reaction was carried out at 0°C.

For the other systems tested, six-membered rings were formed exclusively when the formation of both six- and five-membered carbocycles from a given precursor was feasible. One exception to this trend was found for the indole derivative **11**, which probably reflects the preference for the attack of electrophilic intermediate species at C2 to that at C4. Five-membered rings were formed in the reactions of **9** and **10**, though the products were only obtained in low to moderate yields. In the case of six-membered rings, the yields could reach 74%; however, they were lower when side reactions were observed, as in the case of product **17** (iodinated **6** was recovered in 81% yield), or for clean reactions with low conversion, as in the case of **16** (45% conversion; most of the recovered material was unaltered **5**). In an interesting process, the cyclization of **15** gave **26** smoothly in 74% yield; this product can also be seen as an attractive substrate for further cyclization. Consequently, **26** was transformed subsequently into the aromatic diketone structure **27**. Overall, **27** is derived from **15** through a formal double C–H functionalization process.

A mechanistic proposal to account for the formation of the ketones from the aldehydes is outlined in Scheme 2. Two alternative pathways are compatible with the observed effect of additional substituents on the aromatic rings and with the possible occurrence of competing aromatic iodination when electronically activated aromatic rings are present; this side reaction has been observed for some substrates.

First, the acid protonates the pyridine molecules, which are initially associated with the iodonium species. The pyridinium salt formed precipitates at low temperature and is removed by filtration to give rise to a more reactive mixture.[5] The interaction of the resulting solution with the starting aldehyde would give species **A**. Such a complex could then further react to yield the ketone product in two different ways. As depicted on the left-hand side of Scheme 2, it could undergo formal addition of IF to form intermediate **B**. Further oxidation[7] would give **C** and liberate HI into the solution, thus accounting for the use of two equivalents of IPy_2BF_4. One equivalent is decomposed by reaction with HI to form I_2. In situ activation of the resulting acyl fluoride by the BF_3 present in the reaction medium would lead to an acyl cation, which could undergo cyclization to form the benzocyclic ketone product according to the characteristics of an electrophilic process, as discussed above.



Scheme 2. Proposed mechanistic pathways that account for the observed aldehyde-to-ketone conversion.

Alternatively, as outlined in the right-hand part of Scheme 2, a direct addition of the arene to the activated carbonyl group can not be ruled out at present. Subsequent loss of HI would give the ketone and would also account for the need for a second equivalent of the iodinating reagent. Both mechanistic pathways are plausible and compatible with the formation of the observed products and the available information on the process.

In short, a new reaction promoted by the presence of iodonium ions has been reported. The reaction makes it possible to use aldehydes as acylating agents for arenes in a straightforward synthesis of ketones.

Experimental Section

Typical procedure: IPy_2BF_4 (0.74 g, 2 mmol, 2 equiv) was dissolved in dry CH_2Cl_2 (10 mL) and the resulting solution was stirred for 5 min at room temperature. It was then cooled to −80°C, and HBF_4 (542 μL, 54% solution in diethyl ether, 4 mmol, 4 equiv) was added. After 10 min the mixture was filtered under nitrogen. The aldehyde was added to the filtrate at −60°C, and the resulting mixture was stirred until the starting material had disappeared or until no further evolution of the reaction was observed. The reaction mixture was then poured onto crushed ice (100 g) and vigorously stirred until the temperature of the mixture had risen to room temperature. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (50 mL), dried over sodium sulfate, and concentrated under reduced pressure. The ketone product was purified by column chromatography (silica gel, hexane/EtOAc).

Experimental procedures for the preparation of the starting aldehydes, as well as characterization data for ketones **2**, **4**, **16**–**27**, **29**, and **30**, are provided in the Supporting Information.

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