Access to Fluorenones Using Benzocyclopentynone Surrogate as Partner for the [2 + 2 + 2] Cycloaddition Reaction

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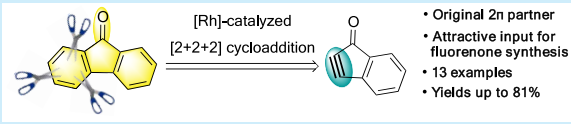
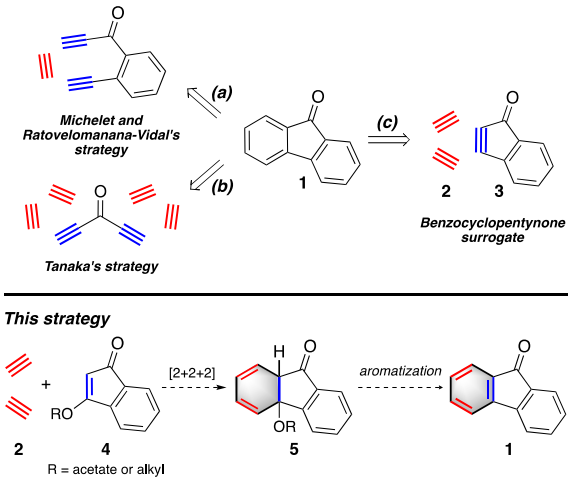
ABSTRACT: A convenient and versatile procedure for the straightforward synthesis of substituted fluorenones as valuable scaffolds is described under rhodium catalysis. The present [2 + 2 + 2] cycloaddition reaction of diynes with 3-acetoxy or-3-alkoxyindenones as surrogates of the highly reactive benzocyclopentynone 2π partner allows the preparation of various fluorenone-type derivatives in good yields and provides an additional and tunable process for the generation of more challenging molecules with application in pharmaceutical, polymer, and material sciences.



9*H*-Fluoren-9-ones **1** are a significant class of organic scaffolds that combine a planar aromatic backbone and an exposed oxygen atom. Such compounds have been intensively described as important key synthetic intermediates in total synthesis[1] or potent biologically active compounds[2] with important medical applications.[3] Fluorenone derivatives also represent important precursors to synthesize a variety of organic electronic materials.[4−6]

In light of these aspects, many groups have contributed to the development of synthetic methods to prepare these privileged structures. They mainly include Friedel−Crafts acylation,[7] radical cyclization,[8] cascade reactions based on C−H activation process,[9] oxidative dehydrogenative couplings by dual C−H functionalization,[10] and transition-metal-catalyzed cyclization.[11] Fluorenones could also be obtained through cycloaddition reactions,[12] which does represent a powerful atom-economy route toward functionalized polycyclic compounds. Surprisingly, even if [2 + 2 + 2] cycloaddition reactions are the most established strategies to access arene derivatives, only two elegant examples have been reported in the literature for the construction of fluorenones[13] and sophisticated fluorenones-[9]helicenes[14] (Scheme 1, (a) and (b)). Conceptually, a very intuitive strategy (Scheme 1, (c)) to prepare fluorenone moiety **1** would involve a metal-catalyzed [2 + 2 + 2] cycloaddition reaction of two alkyne moieties **2** (2π + 2π partner) and a five-membered ring containing a triple bond such as the hypothetic benzocyclopentynone **3** (2π partner). Here, we anticipate that 3-acetoxy- or 3-alkoxy-1*H*-inden-1-one **4**, by reacting through its double bond, could be an alkyne surrogate for benzocyclopentynone **3**. Indeed, the groups of Takeuchi,[15] Tanaka,[16] and Aubert and Vollhardt[17] have shown that enol ethers and enol acetates can be considered as alkyne equivalents in metal-catalyzed [2 + 2 + 2] cycloaddition reactions to afford the corresponding substituted aromatic compound after rearomatization through

Scheme 1. Strategies for the Preparation of Fluorenone Scaffold via [2 + 2 + 2] Cycloaddition Reactions



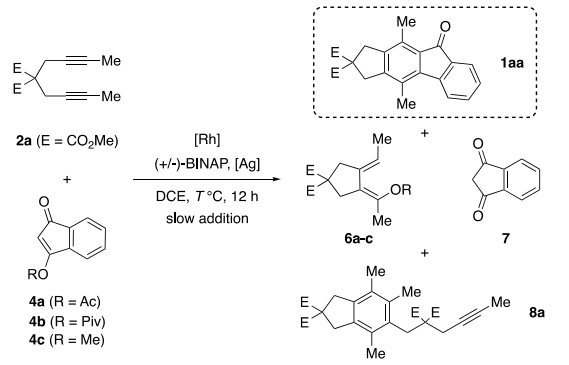
elimination of an alcohol or acetic acid molecule. Therefore, from a mechanistic point of view, this implies that the double bond of indenone **4** would first react as a regular 2π partner leading to cycloadduct **5**. Then, because aromatization is the driving force of the β-elimination step, formation of the desired fluorenone **1** should occur. Herein, we report a new and

straightforward route to the synthesis of fluorenone scaffolds **1** via rhodium-catalyzed [2 + 2 + 2] cycloaddition reaction involving a hypothetic benzocyclopentynone **3** as original 2π partner, providing a nice and attractive input for the existent synthetic toolbox.

To probe the feasibility of our strategy, the model reaction of diyne **2a** bearing a *gem*-bis(methyl ester) tether and readily available 3-acetoxy-1*H*-inden-1-one **4a** (ratio **2a**/**4a** = 1:1) was first examined under classical rhodium catalysis in anhydrous 1,2-dichloroethane (DCE) at 80 °C. Because indenone **4a** turned out to be poorly reactive as 2π partner toward diyne **2a**, the latter was slowly introduced to the reaction mixture in order to avoid undesirable formation of cyclodimer **8a** (see the SI for more detailed studies).[18a] In the presence of [Rh(cod)$_2$]BF$_4$ and racemic BINAP[19] ligand, the reaction proceeded smoothly with a complete conversion of diyne **2a** to afford the desired fluorenone adduct **1aa** in 32% yield along with **6a** (40%) and the indene-1,3-dione **7** (27%) (Table 1, entry 1). By increasing the catalyst loading to 20 mol % the yields of **6a** and **7** could be further decreased resulting in a more convenient purification (Table 1, entry 2). We next screened various neutral rhodium complexes in association with a silver salt[20] and racemic BINAP as ligand (Table 1, entries 3−5). Pleasingly, the reaction catalyzed by the combination [Rh(C$_6$H$_{10}$)Cl]$_2$/AgBF$_4$/(±)-BINAP formed the corresponding fluorenone adduct **1aa** in 79% yield (Table 1, entry 5). Unfortunately, when the catalytic system loading was reduced in half, reaction efficiency and selectivity were altered (Table 1, entry 6). Interestingly, no lack of reactivity could be noted in the absence of the silver salt as the starting diyne **2a** was fully consumed although leading to the undesired cyclodimer **8a** as major compound (Table 1, entry 7), thus illustrating a less common feature for AgBF$_4$ in this reaction process, probably through activation of partner **4** and possible decomposition to furnish dione **7**. Finally, reactions in the presence of AgSbF$_6$ or AgOTf occurred with deleterious side reactions (Table 1, entries 8 and 9). Further screening of solvent and ligand revealed that DCE and racemic BINAP were the most effective for this reaction (see SI for more detailed studies).[18b] The selectivity of the reaction under our best conditions (Table 1, entry 5) was significantly influenced by the reaction temperature since fluorenone **1aa** could be isolated in only moderate yields of 29 and 28% at 50 °C and room temperature respectively (Table 1, entries 10 and 11). Finally, strict removal of water traces did not show an improvement on the reaction outcome, and the desired product and byproducts ratios remained unchanged (Table 1, entry 12). Because the formation of five-membered ring 1,3-diene **6** byproducts would be the result of a rhodium-catalyzed carboxylative cyclization of diyne **2a** in the presence of the released competitive carboxylic acid in the medium, as already reported by Tanaka and co-workers[21] (see mechanistic discussion for more details, Scheme 3), the latter could be suppressed by changing the nature of the indenone derivative **4**. Unfortunately, the use of indenone **4b** as precursor of less acidic pivalic acid in the medium after the sequence [2 + 2 + 2] cycloaddition/β-elimination did not show any improvement (Table 1, entry 13). As expected, generation of methanol instead of acetic acid did not allow the 1,3-diene formation but the corresponding indenone **4c** appeared less reactive in the desired cycloaddition process affording cycloadduct **1aa** in a moderate 44% yield with a large amount of cyclodimer **8a** (Table 1, entry 14). Finally, the reaction proceeded smoothly using indenone **4a** in the presence of a hydride source in the medium, resulting in an efficient quenching of the competitive carboxylic acid released during the course of the reaction (2 equiv for a complete suppression of the carboxylative cyclization, Table 1, entries 15 and 16). Because of a cleaner purification step, we chose to continue with CaH$_2$ as a beneficial additive.

Under the previous optimized conditions (Table 1, entry 16), we next explored the scope and limitations of the reaction. We first examined the efficiency of this process with a range of diynes as summarized in Table 2. Diynes bearing different tethers were tested providing the desired fluorenone adducts in good to excellent yields up to 81% (Table 2, entries 1−3). Gratifyingly, in the special case of diyne **2c** displaying a *gem*-biscyano tether, the reaction was highly selective and the corresponding cycloadduct **1ca** could be isolated as the sole product (Table 2, entry 3). Dimethyl-substituted 3-acetoxyindenone **4d** also afforded a good 51% yield when chosen as substrate for the reaction with diyne **2a** (Table 2, entry 4). Using nonsubstituted diynes at the alkyne termini caused no

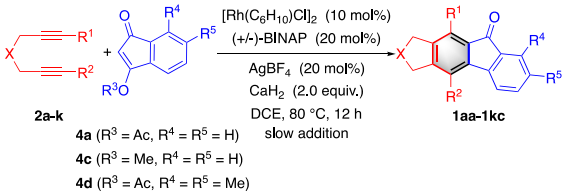
Table 1. Optimization of the Reaction Conditions



entry	[Rh][a,b] (mol %)	4	[Ag][c]	T (°C)	yield of 1aa/6/7/8a[d] (%)
1	[Rh(cod)$_2$] BF$_4$ (10)	4a	none	80	32/40/27/0
2	[Rh(cod)$_2$] BF$_4$ (20)	4a	none	80	39/12/10/0
3	[Rh(C$_2$H$_4$)$_2$Cl]$_2$ (10)	4a	AgBF$_4$	80	46/31/13/0
4	[Rh(cod)Cl]$_2$ (10)	4a	AgBF$_4$	80	14/45/27/0
5	[Rh(C$_6$H$_{10}$)Cl]$_2$ (10)	4a	AgBF$_4$	80	79/20/0/0
6	[Rh(C$_6$H$_{10}$)Cl]$_2$ (5)	4a	AgBF$_4$	80	49/31/22/0[e]
7	[Rh(C$_6$H$_{10}$)Cl]$_2$ (10)	4a	none	80	26/0/27/54
8	[Rh(C$_6$H$_{10}$)Cl]$_2$ (10)	4a	AgSbF$_6$	80	9/−/−/−[f]
9	[Rh(C$_6$H$_{10}$)Cl]$_2$ (10)	4a	AgOTf	80	−[f]
10	[Rh(C$_6$H$_{10}$)Cl]$_2$ (10)	4a	AgBF$_4$	50	29/34/20/0
11	[Rh(C$_6$H$_{10}$)Cl]$_2$ (10)	4a	AgBF$_4$	rt	28/37/15/0
12[g]	[Rh(C$_6$H$_{10}$)Cl]$_2$ (10)	4a	AgBF$_4$	80	79/21/5/0[f]
13	[Rh(C$_6$H$_{10}$)Cl]$_2$ (10)	4b	AgBF$_4$	80	61/26/18/0
14	[Rh(C$_6$H$_{10}$)Cl]$_2$ (10)	4c	AgBF$_4$	80	44/0/26/30[h]
15[i]	[Rh(C$_6$H$_{10}$)Cl]$_2$ (10)	4a	AgBF$_4$	80	73/13/7/0
16[j]	[Rh(C$_6$H$_{10}$)Cl]$_2$ (10)	4a	AgBF$_4$	80	76/0/10/0

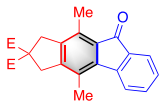
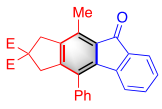
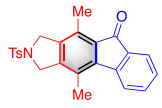
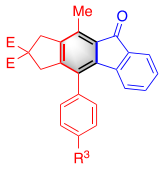
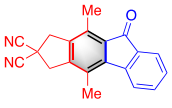
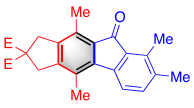
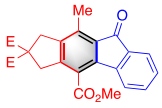
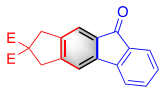
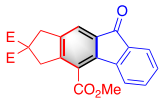
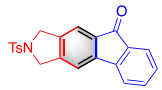
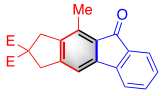
[a]See ref 19 for specification on rhodium source. [b][Rh]/(±)-BINAP = 1:1 when using a cationic rhodium source and [Rh]/(±)-BINAP = 1:2 when using a neutral dimeric rhodium source. [c][Rh]/[Ag] = 1:2 when [Ag] was used. [d]Unless noted otherwise, full conversion of diyne **2a** was observed. [e]Conversion of diyne **2a** was 90%. [f]Degradation was observed. [g]2.0 equiv of crushed 4 Å molecular sieves was used. [h]Conversion of diyne **2a** was 75%. [i]1.0 equiv of CaH$_2$ was used. [j]2.0 equiv of CaH$_2$ was used.

Table 2. Rhodium-Catalyzed Synthesis of Substituted Fluorenones: Substrate Scope



2a-k → **1aa-1kc**

4a (R^3 = Ac, R^4 = R^5 = H)
4c (R^3 = Me, R^4 = R^5 = H)
4d (R^3 = Ac, R^4 = R^5 = Me)

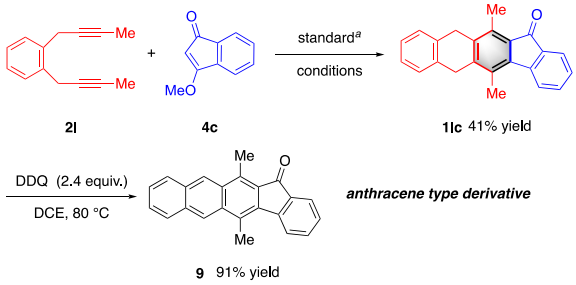
entry	product **1**, yield (%)	entry	product **1**, yield (%)
1	 **1aa** (E = CO_2Me) 76%	7	 **1fa** (E = CO_2Et) 41%,[c] (1 : 1) ratio[d]
2	 **1ba** 54%	8	 **1ga** (E = CO_2Me, R^3 = MeO) 65%,[c] (1 : 1) ratio[d] **1ha** (E = CO_2Me, R^3 = NO_2) 54%,[c] (1 : 1) ratio[d]
3	 **1ca** 81%[a,b]		
4	 **1ad** (E = CO_2Me) 51%	9	 **1ia** (E = CO_2Me) 73%
5	 **1da** (E = CO_2Me) 67%	10	 **1ja** (E = CO_2Me) 56%,[c] (90 : 10) ratio[d]
6	 **1ea** 62%	11[e]	 **1kc** (E = CO_2Me) 36%,[f] (1 : 1) ratio[d]

[a]Fluorenone **1c** was observed and isolated as the sole compound. [b]Reaction was scaled up from 0.127 to 0.5 mmol with a 71% yield and to 1 mmol with a 66% yield. [c]The corresponding yield refers to a mixture of both regioisomers that could be isolated as pure compounds from a complex mixture. [d]The regioisomeric ratio was determined by ^{1}H NMR analysis of the crude mixture. [e]Reaction was carried out with 3-methoxyindenone **4c**. [f]Only 36% yield of the above regioisomer could be isolated as pure compound from a complex mixture containing both regioisomers.

problem in this cycloaddition process (Table 2, entries 5 and 6). Diynes **2f–h** with different terminal groups such as phenyl and *para*-substituted phenyl (electron-donating and -withdrawing) were also tolerated, and satisfactory yields of fluorenones **1f–h** were produced although the reactions proved to be poorly regioselective (Table 2, entries 7 and 8). In contrast, the present cycloadditions exhibited an excellent regioselectivity when employing diynes **2i–j** possessing at least one methylester group at the alkyne terminus (Table 2, entries 9 and 10). This clear trend would be explained by a strong directing effect of the ester group mainly through additional chelation of the rhodium center (see intermediate **B**, Scheme 3). The reaction of unsymmetrical diyne **2k** with indenone **4a** was also examined under standard conditions (Table 2, entry 11). According to the previous results, fluorenone **1ka** should be obtained as major compound. However, no desired product could be observed and the reaction provided a complex mixture containing mainly the corresponding 1,3-diene with acetate incorporation and hydrolyzed indenone **7**. Because, competing carboxylative cyclization of diyne **2k** appeared problematic in the presence of a carboxylic acid source,[21] we envisioned an alternative approach in which indenone **4a** was switched to indenone **4c** bearing a methoxy group. As expected, the carboxylative competitive pathway was suppressed and the desired fluorenone **1kc** could be isolated in a modest 36% yield and no regioselectivity.

The concept was also broadened to the synthesis of an anthracene type derivative **9** illustrating the potential application of this methodology for the generation of new π-conjugated systems with optical and electronic properties (Scheme 2). Cycloaddition of diyne **2l** displaying a carbon

Scheme 2. Reaction of Diyne 2l with Indenone 4c and Synthetic Transformation



2l + **4c** → **1lc** 41% yield

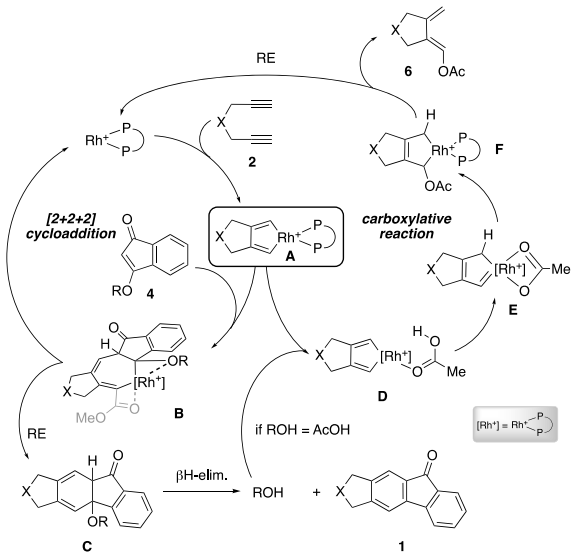
9 91% yield

[a]Reactions were carried out under standard conditions as described in Table 2.

tether with indenone **4c** proceeded smoothly to afford the corresponding fused polycyclic fluorenone **1lc** with a satisfactory yield. Gratifyingly, the obtained cycloadduct could be easily oxidized to produce the targeted anthracene derivative **9**.

A plausible reaction mechanism is depicted in Scheme 3. Fluorenone **1** would be obtained through the well-established rhodium-catalyzed [2 + 2 + 2] cycloaddition mechanism. Oxidative coupling of the two alkyne moieties of diyne **2** would afford the common rhodacyclopentadiene intermediate **A**. Subsequent insertion of indenone **4** would conduct to rhodacycle **B** stabilized by internal coordination of the enol ether group, the latter favored when indenone **4** is featuring a more coordinating acetate group.[16] In the special case of diynes **2i** and **2j** bearing an ester group on the alkyne terminus,[16] such additional coordination to the rhodium center would lead to an excellent regioselectivity. With unsymmetrical diynes, no discrimination would occur because of the existing competition between steric hindrance and beneficial coordination of the acetate group over ketone group (diynes **2f–h** and indenone **4a**) or the equivalent coordination mode displayed by the methoxy and ketone groups (diyne **2k** and

Scheme 3. Mechanistic Proposal



indenone **4c**). Final reductive elimination and following rearomatization would furnish the corresponding fluorenone **1**. Carboxylative cyclizations of 1,6- and 1,7-diynes using carboxylic acids have been previously accomplished under rhodium catalysis[21] and these reactions would involve the addition of a O−H bond on a metallacyclopentadiene intermediate. Under our reaction conditions, the released carboxylic acid would react with the shared rhodacyclopentadiene intermediate **A** to form a novel intermediate **E** bearing a carboxylate ligand after protonation of the metallacycle. Further evolution of this intermediate through acylation (formation of the C−O bond) would generate a rhodacyclopentene intermediate **F**. Final reductive elimination forming the corresponding 1,3-diene as byproduct would end up the catalytic cycle.

In summary, we have designed a complementary methodology providing yet controlled access to substituted fluorenones in good yields as valuable scaffolds for the development of novel pharmaceuticals, dyes, polymers and ligands. The originality of this process, centered on a rhodium-catalyzed [2 + 2 + 2] cycloaddition, is based on the use of 3-alkoxy- or 3-acetoxyindenones as surrogates of the highly reactive benzocyclopentynone 2π partner. Importantly, this easily tunable and convergent methodology could enable the straightforward synthesis of more complex polycyclic fluorenone-type targets with defined properties from readily available starting materials. Further investigations to explore the full potential of this method and to reach more challenging higher value products are underway in our laboratory.

■ ASSOCIATED CONTENT

Accession Codes

CCDC 1977637−1977638 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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