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Fused Benzo[*b*]fluorenols: Palladium-Catalyzed Intramolecular Dehydroaromatization and Carbonyl Reduction

Quansheng Zhao,[a] Qiong Hu,[a] Lei Wen,[a] Min Wu,[a] and Yimin Hu[a,*]

[a] Laboratory of Functional Molecular Solids, Ministry of Education; Anhui Key Laboratory of Molecular-Based Materials; School of Chemistry and Materials Science, Anhui Normal University, Wuhu, Anhui 241000, People's Republic of China
Fax: (+86)-553-388-3517; e-mail: yiminhu@mail.ahnu.edu.cn

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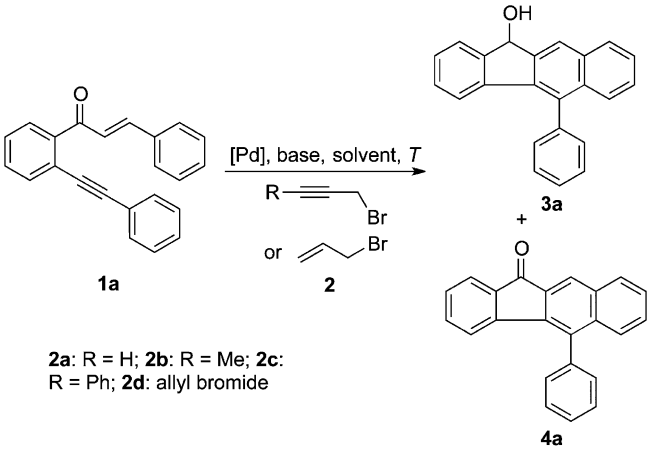
Abstract: Benzo[*b*]fluorenols were prepared by a new palladium-catalyzed one-pot reaction of en-one-ynes with 3-bromoprop-1-yne through intramolecular dehydroaromatization and carbonyl reduction.

Keywords: benzo[*b*]fluorenols; dehydroaromatization; domino reactions; hydrogen-transfer reduction; palladium

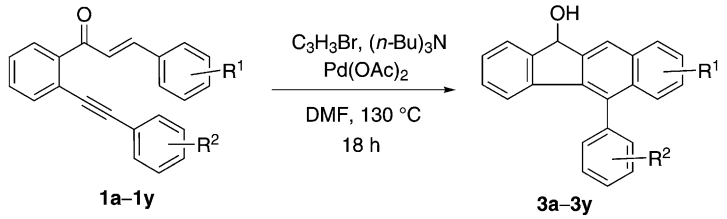
Fused benzo[*b*]fluorenols are important classes of chiral alcohols that possess a broad range of biological and pharmaceutical activities.[1] Molecules containing fluorenol have been the subject of considerable interest as potent antitumor, antimicrobial, and antiviral agents.[2] Recently, dehydrogenation strategies for the preparation of aromatic scaffolds have produced significant synthetic challenges.[3] Stahl reported on an unconventional *ortho*-dimethylaminopyridine ligand-mediated conversion of substituted cyclohexanones into the corresponding phenols.[4] Grützmacher reported on the domino rhodium-/palladium-catalyzed dehydrogenation reactions of alcohols to acids.[5] Maier demonstrated the convenient synthesis of 7-aryltetralones using a novel arylation–dehydroaromatization sequence.[6] Beckhaus described the dehydroaromatization of quinoxalines through three-fold dehydrogenative C–C coupling.[7] Carbonyl reduction has become increasingly involved in biological systems in which the reduction of a ketone leads to secondary alcohol.[8] In the current study, novel domino methods[9] and hydrogen transfer reactions were developed to synthesize fused benzo[*b*]fluorenol compounds through intramolecular dehydroaromatization and carbonyl reduction, which led directly to a secondary alcohol through transformation of the linear en-one-yne. As this study focuses on the development of palladium-catalyzed processes and direct C–H functionalization,[10] we performed the palladium-catalyzed reactions of **1a** to **1y** (Table 1) with 3-bromoprop-1-yne, providing a direct, efficient, and economical methodology for the construction of fused benzo[*b*]fluorenol compounds through intramolecular dehydroaromatization and carbonyl reduction.[11]

A survey of the reaction conditions using (*E*)-3-phenyl-1-(2-(phenylethynyl)phenyl)prop-2-en-1-one (**1a**), 3-bromoprop-1-yne or allyl bromide (**2a** to **2d**), as a test experiment was performed (Scheme 1). The efficiency of the domino reaction can be enhanced considerably by increasing the reaction temperature to 130 °C. The additive bases play an important role in the overall efficiency of this domino reaction, thus simple variation of the base from potassium carbonate to tributylamine under otherwise identical conditions, as well as furnishing the unexpected benzo[*b*]-fluorenol **3a** in 84% yield, also produced a small quantity of benzo[*b*]fluorenone (**4a**). Among the catalysts investigated, the palladium(II) acetate/(3-bromoprop-1-yne) catalytic system was found to be the most

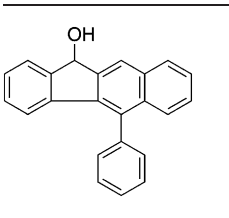


Scheme 1. Strategy for the synthesis of benzo[*b*]fluorenol.

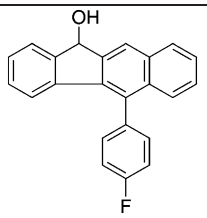
Table 1. Palladium-catalyzed dehydroaromatization and carbonyl reduction for the formation of fused PAHs.[a,b]



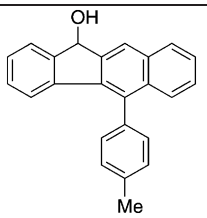
1a–1y **3a–3y**



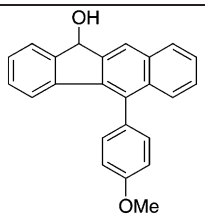
3a (84%)



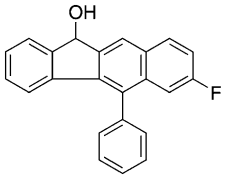
3b (75%)



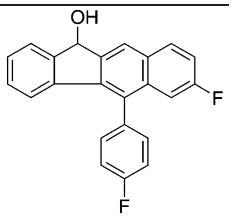
3c (86%)



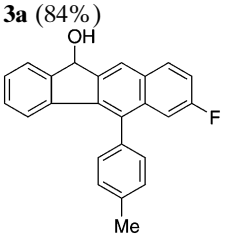
3d (88%)



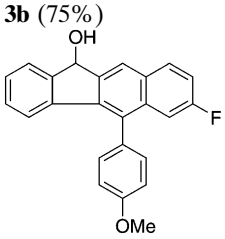
3e (73%)



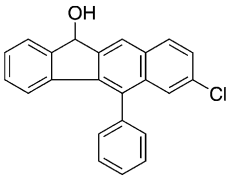
3f (65%)



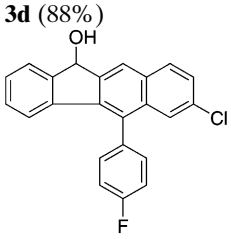
3g (77%)



3h (80%)



3i (80%)



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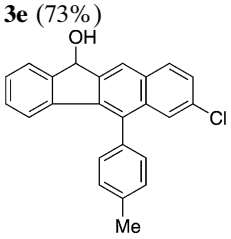
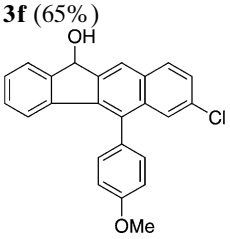
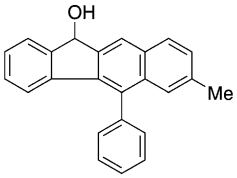


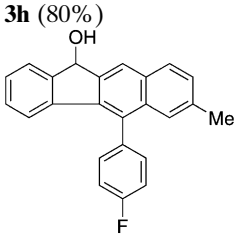
3k (83%)



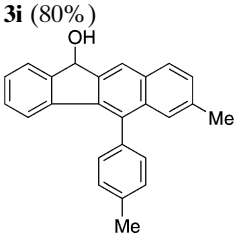
3l (85%)



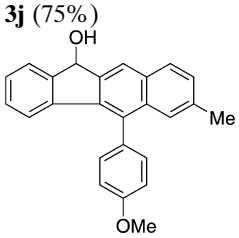
3m (85%)



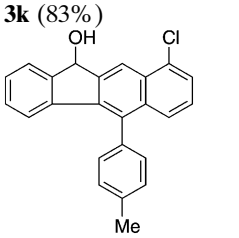
3n (76%)



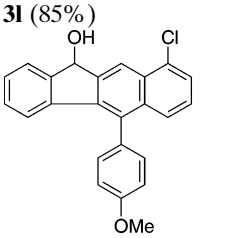
3o (85%)



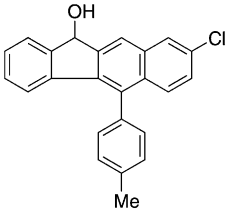
3p (89%)



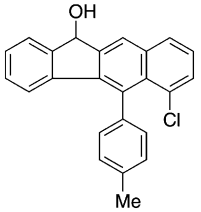
3q (75%)



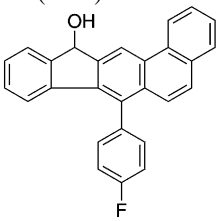
3r (68%)



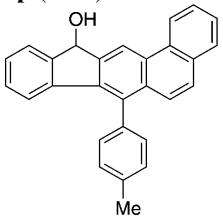
3s[1] (45%)



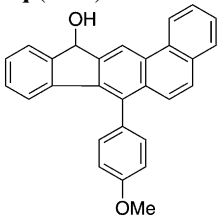
3s[2] (38%)



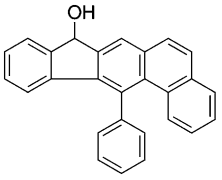
3t (60%)



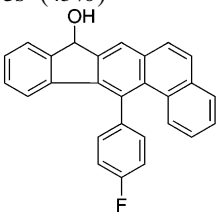
3u (66%)



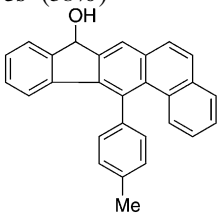
3v (70%)



3w (62%)



3x (59%)



3y (65%)

[a] *General conditions:* **1a–1y** (1.0 equiv.), C_3H_3Br (1.2 equiv.), $Pd(OAc)_2$ (2 mol%), $(n\text{-}Bu)_3N$ (2 equiv.), DMF 10 mL, 130 °C.
[b] Yield given for isolated product.

effective in cross-coupling screens. DMF proved to be a better solvent than toluene. Benzo[*b*]fluorenol compound **3a** was only isolated in yields of 66% and 35%, respectively, when 1-bromobut-2-yne or allyl bromide was employed as a reactant, indicating the effects of 3-bromoprop-1-yne or allyl bromide on the outcome of the reactions and on the formation of the final products. Thus, the following standard reaction conditions were used to carry out the following studies: 1 equiv. of **1a** was reacted with 1.2 equiv. of 3-bromo-

prop-1-yne in the presence of 2 mol% palladium(II) catalyst and 2 equiv. of $(n\text{-Bu})_3N$ as an additive in DMF at 130 °C.

Illustrative examples of the scope are shown in Table 1. Interestingly, various intramolecular en-yn-ones are compatible with this palladium-catalyzed dehydroaromatization and carbonyl reduction. A range of 5-phenyl-11*H*-benzo[*b*]fluoren-11-ol compounds were readily isolated in good to excellent yields, with the exception of **3t** or **3x**, when 3-phenyl-1-[2-(phenylethynyl)phenyl]prop-2-en-1-one was employed with a variety of substituted groups. The substituted groups could be *para*-, *ortho*-, or *meta*- substituted groups on the benzene ring (i.e., chloro, fluoro, methyl, methoxy and benzo). Using 3-bromoprop-1-yne with en-yn-one substrates (**a**, **c**, **d**, **h**, **i**, **k**–**m**, **o**, and **p**), the reaction gave 5-phenyl-11*H*-benzo[*b*]fluoren-11-ols **3a**, **3c**, **3d**, **3h**, **3i**, **3k**, **3l**, **3m**, **3o**, and **3p**, respectively, in yields beyond 80%. The yields of compounds **3d** and **3p** were the highest at 88% and 89%. Simultaneously, when 3-bromoprop-1-yne was used in the reaction with **b**, **e**–**g**, **j**, **n**, **q**, **r**, **u**–**w**, the desired phenanthridines were obtained in good yields ranging from 62% to 77% (**3b**, **3e**–**3g**, **3j**, **3n**, **3q**, **3r**, **3u**–**3w**, and **3y**). Interestingly, the comparison of the products **3s**[1] and **3s**[2] indicates that the electronic properties of the substrates also influenced the regioselectivity of the C–H bond functionalization because the en-yno-nes reacted with the same 3-bromoprop-1-yne but produced different C–H bond functionalization products. Results indicate that **3s**[1] and **3s**[2] gave good yields at 43% and 38%, respectively.

All the resulting tetracyclic and pentacyclic compounds were confirmed by one- (^1H, ^{13}C) and two-dimensional (COSY) NMR spectral analyses, and elemental or HR-MS analyses, respectively. The structure of **3o** was confirmed independently through an X-ray crystal structure analysis (Figure 1).[12] Further details can be found in the Supporting Information (see also the Experimental Section).

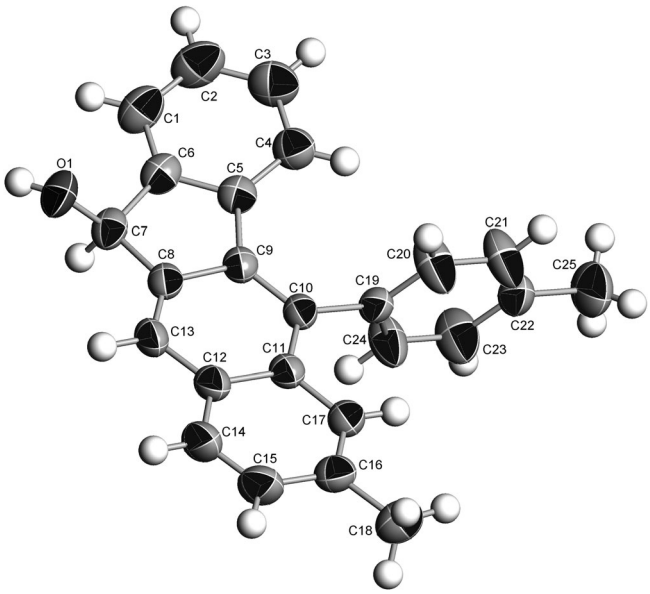


Figure 1. The molecular structure of compound **3o**. Thermal ellipsoids are drawn at the 25% probability level.

In conclusion, a one-pot synthesis of fused benzo[*b*]fluorenols through aryl-substituted en-one-yne systems *via* domino reactions was reported. To the best of our knowledge, there have been no reports thus far on such a domino process, a topic which could be of general interest. The dihydronaphthalene is then oxidized into the fully aromatic system and the hydrogen transferred to the keto group to give the benzo[*b*]fluorenols. The hydrogen transfer pattern of the products is not readily available when other methods are used. The generality of this process makes the reaction highly valuable in view of the synthetic and medicinal importance of these kinds of PAHs. The mechanism is not clear so far. Further mechanistic and synthetic studies are in progress.

Experimental Section

Typical procedure

Substrate **1a** (1.0 mmol), 3-bromoprop-1-yne (1.2 mmol), and $Pd(OAc)_2$ (2 mol%) were added to a degassed solution of $(n\text{-Bu})_3N$ (2 mmol) in DMF (10 mL). and the mixture was stirred at room temperature for half an hour, and then heated at 130 °C for 18 h. The reaction mixture was cooled, and then quenched with water and extracted with EtOAc (3×5 mL). The combined organic layers were washed with hydrochloric acid (5%), sodium carbonate (5%), and saturated sodium chloride solution. After separation, the organic layer was dried over $MgSO_4$ and then concentrated. The residue was loaded onto a silica gel column and purified by flash chromatography (eluent: petroleum ether/ethyl acetate = 10:1) to give the corresponding product **3a**; yield: 84%.

Acknowledgements

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[12] CCDC 862040 (**3o**), CCDC 862041 (**3s**[1]), and CCDC 862042 (**3v**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; Fax: (+44)-1223-336-033; or deposit@ccdc.cam.ac.uk.

