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8-Iodonaphthalene-1-carbaldehyde: A Versatile Building Block for Diversity-Oriented Synthesis

Lidia Herrera,[†] Pablo Barrio,*[,†] Ignacio Ibáñez,[‡] Raquel Román,[†] Natalia Mateu,[§] and Santos Fustero*[,†,‡]

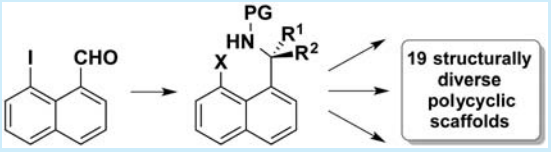
[†]Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain

[‡]Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, E-46012 Valencia, Spain

[§]Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom

Supporting Information

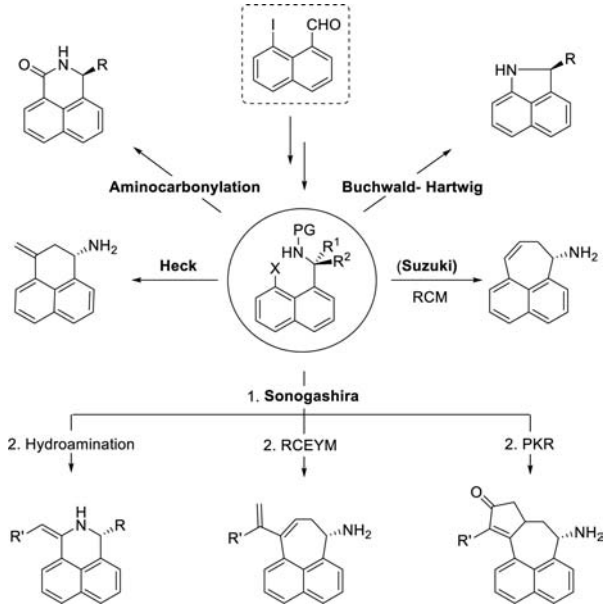
ABSTRACT: The scarcely studied 8-halonaphthalene-1-carbaldehyde structure has been converted into the corresponding Ellman's imine and subjected to several transformations, thus achieving an assorted library of polycyclic carbo- and heterocycles. The potential of this scaffold for Diversity-Oriented Synthesis has been shown. Most of these skeletons are unprecedented and, therefore, cover unexplored regions of the chemical space.



The search for new molecular architectures with unprecedented biological activities may expand the number of therapeutic targets and, thus, broaden the available treatments for a given disease or provide an alternative for maladies which still have no cure. In this context, diversity-oriented synthesis (DOS) has been shown as the most efficient way to cover the maximum portion of the chemical space.[1,2] This strategy consists of the use of a common building block decorated with carefully designed functional groups at specific positions which, subjected to a number of given transformations, afford substrates bearing a new set of functionalities amenable for further diversification of the molecular architecture.

For the past few years, our group has been engaged in a research line dealing with the use of 2-halobenzaldehyde derivatives in the context of DOS.[3] Hence, the asymmetric synthesis of a variety of benzo-fused carbo- and heterocyclic scaffolds has been accomplished from a common precursor in no more than five steps. Interesting skeletons such as isoindolines, isoindolinones, isoquinolines, indanones, or 1-hydroxy- and 1-amino dihydronaphthalene derivatives have been efficiently achieved by the careful choice of the neighboring group introduced in the proximity of the aldehyde (or imine).[3] Herein, we want to report a parallel study carried out on the scarcely studied 8-iodo-1-naphthalenecarbaldehyde skeleton **1** (Scheme 1).[4,5] Thus, we envisaged that the presence of both the halogen atom and the imine, formed upon the condensation with Ellman's sulfinimide, would allow the selective introduction of different functionalities amenable for further diversification by means of well-established palladium catalyzed cross-coupling reactions (Scheme 1). First, the resulting amine could participate in intramolecular aminocarbonylation or Buchwald–Hartwig amination reactions. In addition, the presence of an allyl substituent at the α-position of the amine would give rise to a suitable substrate for a subsequent intramolecular Heck reaction. Finally, intermolecular cross-coupling Sonogashira and Suzuki reactions would generate potential intermediates for their further transformation into more complex structures. In this way, carbo- and heterocycles of several sizes (5-, 6-, and 7-membered) were targeted. Moreover, not only tricycles but also tetracycles were envisioned. As a result, functionalities of a highly diverse nature, such as primary and secondary amines, lactames, enamines, or enones will decorate the final products.

Scheme 1. DOS Strategy on 8-Iodo-1-naphthalenecarbaldehyde



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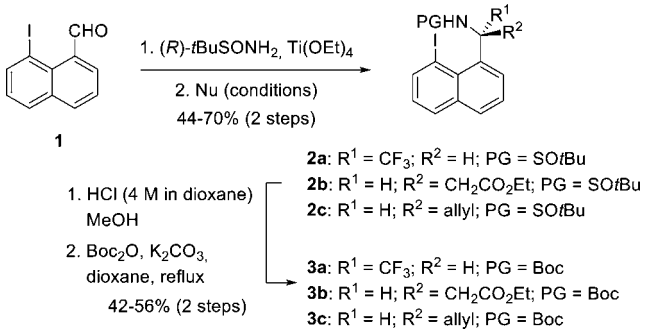
Initially, three representative nucleophiles namely, the Ruppert-Prakash reagent, allylzinc bromide, and the Reformatsky reagent derived from ethyl bromoacetate, were reacted with the corresponding *tert*-butanesulfinyl imine, which was then converted into the corresponding *N*-Boc protected derivatives **2a−c** (Scheme 2). The opposite facial selectivity for the

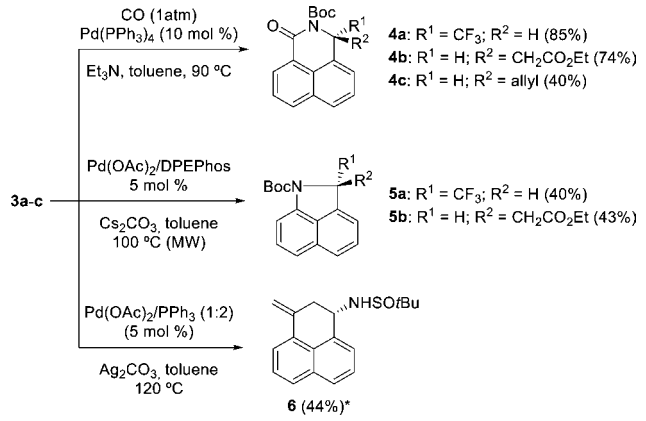
Scheme 2. Synthesis of the Starting Materials



trifluoromethylation with respect to the allylation and Reformatsky reaction processes was to be expected, given our own experience in the field and the well-established open and chairlike TSs described for such transformations, respectively.[3,6]

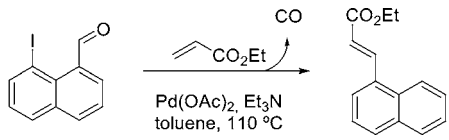
The thus obtained carbamates **3a−c** were in turn subjected to an intramolecular aminocarbonylation[3b,7] reaction leading to 2-azaphenalone derivatives **4a−c**, bearing a polycyclic backbone which also remains understudied, in moderate to good yields (Scheme 3).[8] On the other hand, Buchwald−Hartwig

Scheme 3. Intramolecular Buchwald−Hartwig Amination and Heck Reaction



amination[9] conditions afforded 1,2-dihydrobenzo[*cd*]indole derivatives **5a,b** in modest yields. In our previous studies using 2-bromobenzaldehyde, the intramolecular amination product could not be obtained due to the high strain of the benzofused azetidine that would be formed; however, in this case, the formation of a five-membered ring results in moderate yields. Again, this interesting polycyclic heterocycle has scarcely been studied. Recently, this scaffold has been found in compounds showing several interesting biological activities.[10] Noteworthy, under these conditions the homoallylamine derivative **3c** underwent intramolecular Heck reaction giving rise to a new skeleton **6′** (PG = Boc). Thus, this process was optimized independently affording 3-methylene-1-aminophenalene derivative **6** in moderate yield.[11] In this case, sulfonamide **2c** gave rise to better results than the corresponding carbamate **3c** (see Supporting Information (SI)) .

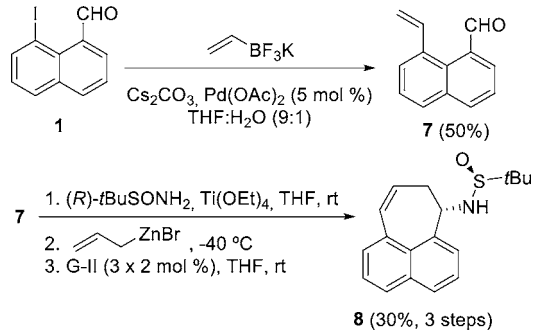
In the transformations described thus far, the 8-iodo functionality is reacted intramolecularly with functional groups present on the other side of the molecule (i.e., carbamate or allyl groups). However, it can also be used as a handle for the introduction of suitable functional groups by means of well-established palladium catalyzed cross-coupling chemistry.[12] First, we attempted to perform a Heck reaction with acrylate, aiming to carry out a nucleophilic addition/intramolecular *aza*-Michael reaction sequence.[3e,g] However, the ideal space orientation of the neighboring aldehyde resulted in an unexpected decarbonylation process yielding ethyl 3-(1-naphthalene) acrylate (eq 1). Related transformations have



(1)

recently been reported by Larock.[13] Therefore, a Suzuki coupling with potassium vinyltrifluoroborate was carried out affording vinyl aldehyde **7**,[14] which was in turn subjected to the one-pot condensation/asymmetric allylation/ring-closing metathesis (RCM)[15] sequence developed by us,[3f] using second generation Grubbs' catalyst (G-II), affording **8** in an overall moderate yield in a three-step one-pot procedure (Scheme 4).

Scheme 4. One-Pot Condensation/Asymmetric Allylation/RCM



This tricyclic motif may be found in a number of natural products,[16] and some derivatives have also been shown to inhibit several genes such as MRE11, RAD 50, or NBS1 involved in DNA damage signaling, among other functions.[17] Based on our own experience,[3c,d,18] we envisaged that the introduction of alkyne residues by means of Sonogashira cross-coupling would give rise to very versatile and highly functionalized natural products such as intermediates. Hence, a variety of terminal alkynes **9** were reacted with **2a−c** affording alkynyl derivatives **10** in good yields (Scheme 5).

Similar to the reactions depicted in Scheme 3, we envisioned that the alkynyl residue may react with the carbamate on the other side of the molecule while, in the case of **2c**, several intramolecular transformations may be carried out in which both unsaturated functionalities (alkyne and alkene) react with each other (*vide infra*). First the gold catalyzed intramolecular hydroamination reaction was investigated.[19] Again, a brief optimization led to the identification of S-PhosAuNTf$_2$ as the optimum catalyst in DCM at room temperature.[3d,14] The scope of the reaction was then studied under the aforementioned

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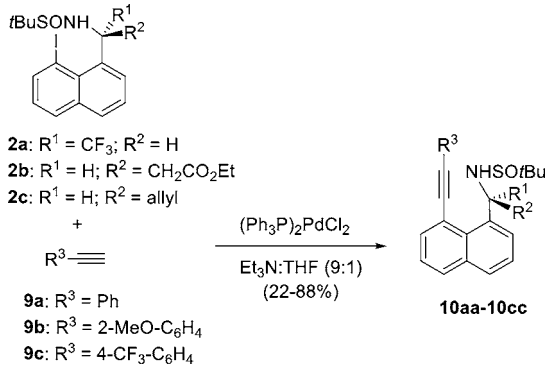
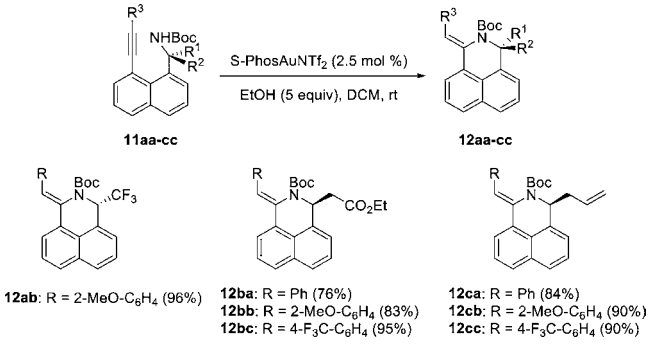
Scheme 5. Introduction of Alkynyl Residues by Means of Sonogashira Couplings



reaction conditions, obtaining in all cases exclusive *Z* selectivity in agreement with the well-established *anti* attack of the nucleophile to the π-alkynyl gold complex (Scheme 6).[19]

Scheme 6. Gold-Catalyzed Intramolecular Hydroamination

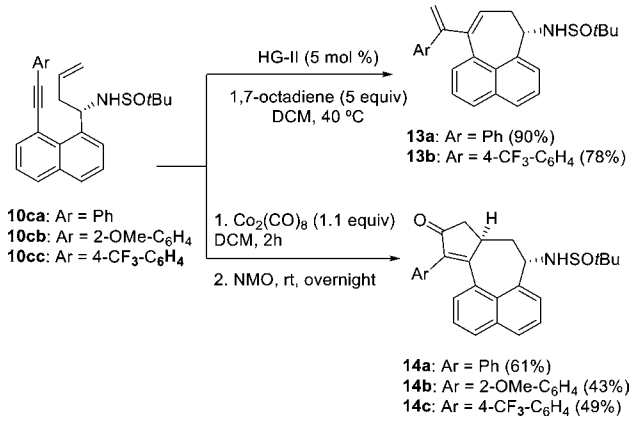


Electron-donating and -withdrawing groups are tolerated at the terminal alkyne position without any significant effect on chemical yields or regioselectivity. Likewise, substitution at both 2- and 4-positions is well tolerated. Similar to other reactions in which the nitrogen group participates (see Scheme 3), protecting group exchange from *tert*-butanesulfinyl to Boc was required for the success of this transformation. Thus, a small library of compounds bearing the rare 2,3-dihydro-1*H*-benzo[*de*]isoquinoline (2-azaphenalene) skeleton have been synthesized.[20]

The presence of two unsaturated functionalities namely, alkyne and alkene, was then exploited in two transformations: ring-closing enyne metathesis (RCEYM) and intramolecular Pauson–Khand reaction (PKR).[3c] First, the use of 1,7-octadiene as an ethylene surrogate[21] resulted in good yields of dienes **13** upon reaction with Hoveyda–Grubbs' second generation catalyst (HG-II; see Scheme 3) in refluxing DCM (Scheme 7).[13] Finally, the intramolecular PKR was also accomplished by using stoichiometric amounts of $Co_2(CO)_8$ and NMO as a promoter in refluxing toluene.[14] The reaction showed tolerance toward electron-deficient and -rich aromatic residues at the terminal alkyne, allowing the synthesis of a small library of tetracyclic amino enones (Scheme 7). To the best of our knowledge, this tetracyclic cyclopentenone core is unprecedented.

Using the outlined strategy, a library of 19 polycyclic carbo- and heterocyclic compounds containing a common naphthalene framework has been prepared. In order to assess and visualize the diversity achieved from this DOS-approach in the

Scheme 7. RCEYM



"molecular shape space", normalized ratios of principal moments of inertia (PMI) descriptors, based on the lowest-energy conformations, were calculated and plotted in a two-dimensional triangular graph spanned by three shape types: "rod-like", "disk-like", and "spherical" (see SI).[22] In addition, two reference molecular collections[23] based on (a) 40 top-selling drugs and (b) 60 randomly selected natural products were subjected to the same computational method so as to provide a comparative PMI analysis (Figure 1). To our delight,

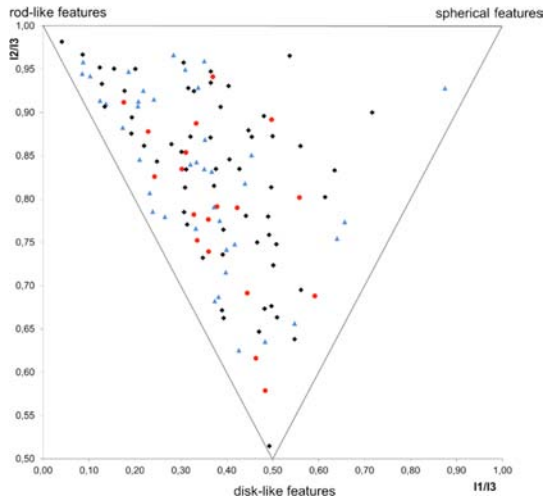


Figure 1. PMI plot showcasing the molecular shape diversity of the DOS library (red dots) vs 40 top-selling drugs (blue triangles) and 60 diverse natural products (black rhombus).

despite the presence of the common flat naphthalene backbone, our collection displayed a good distribution covering a broad region within the three shape extremes (Figure 1, red dots). As expected, most of the molecules were situated on the disk-rod side of the plot. However, a good deal of compounds deviated from this trend and covered some of the region toward the spherically shaped molecules covering an overall significant portion of the chemical space overlapping with a considerable range of the natural product set (Figure 1, black rhombus) and the marketed drug set (Figure 1, blue triangles).

In summary, we have demonstrated the versatility of the scarcely studied 8-iodo-1-naphthalenecarbaldehyde in the context of DOS. The asymmetric synthesis of several families of polycyclic carbo- and heterocyclic scaffolds, most of them unprecedented in the literature, has been achieved in 4–6 steps.

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With the aid of PMI calculations, the distribution of the obtained molecules has been plotted, demonstrating a broad coverage of the chemical space. The potential biological activity of some of these derivatives is currently under study, and the results derived thereof will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02372.

Experimental procedures and NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: pablo.barrio@uv.es.
*E-mail: santos.fustero@uv.es.

Notes

The authors declare no competing financial interest.

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