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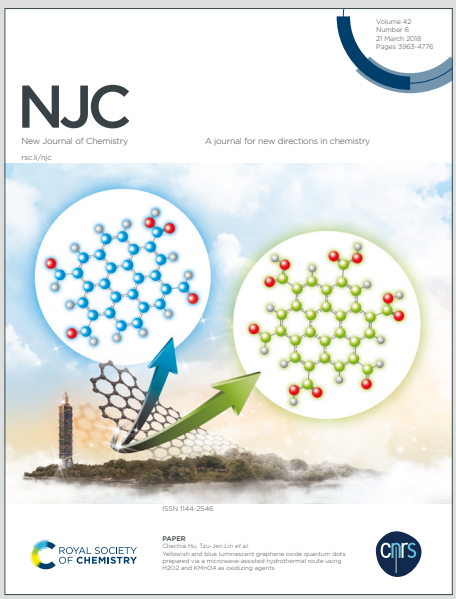

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COMMUNICATION

A diversity-Oriented Synthesis of Polyheterocycles *via* Cyclocondensation of Azomethine Imine

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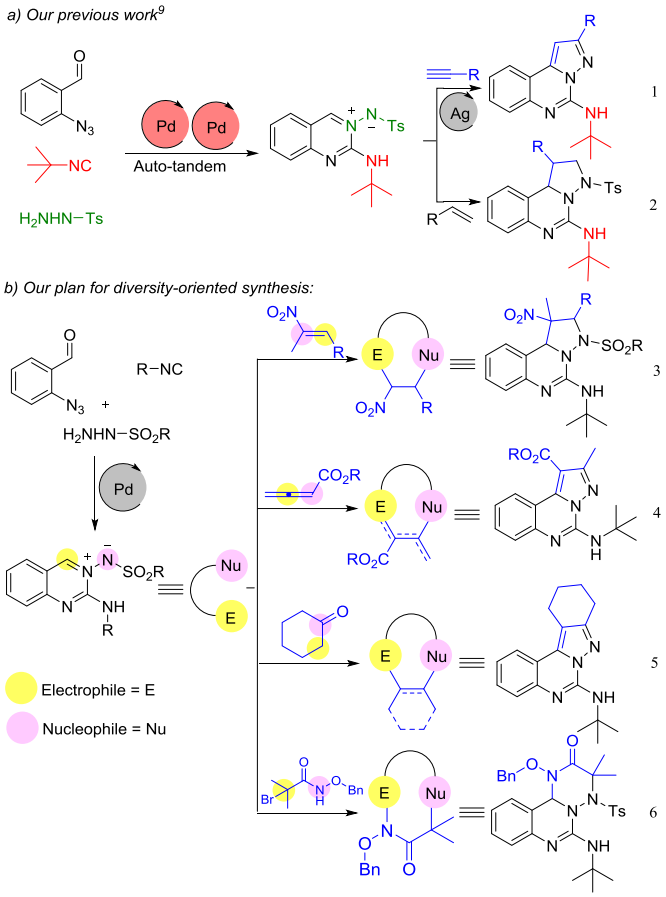
Pd-catalyzed sequential reaction to skeletally diverse molecule is described. The Reaction involved azomethine imine formation and cyclocondensation reaction as individual steps. The methodology exhibited excellent regio- and stereocontrol. The skeletal diversity was ensured by changing the electrophilic counterpart of azomethine imine. Due to its broader diversity and complexity, the DOS methodology is likely to benefit drug discovery and development in the future.

The human genome, a treasure trove of hidden information, comprised of 25,000 genes that encode hundreds of thousands of proteins. Modulation of these protein function using small organic molecules represents the basis for chemical biology and medicinal chemistry.[1] However, exploration of astronomically huge biologically accessible chemical space (10^{60} molecules) is like "searching a needle in haystack.[2] Natural product space, enriched with bioactive structure, is considered as a good starting point for targeting proteins of human diseases.[3] However, natural products are evolved as a defense mechanism against invaders in the absence of advanced immune response in plants and marine organisms; thus they tend to target highly connected and more essential target proteins compared to genes implicated for human diseases.[4] In contrast, protein targets of marketed drugs exhibited a connectivity distribution closer to that of human disease genes. Thus, design and assembly of compound collections based on small molecules, instead of natural products, play a decisive role in driving drug discovery research. In this context, diversity and complexity of small organic molecules are critical to ensure high performance in the drug discovery. [5]



Scheme 1. Transition metal catalyzed cascade reactions for the synthesis of sophisticated polyheterocycles.

Diversity-oriented synthesis (DOS), an efficient and simultaneous generation of chemical space with a high degree of skeletal diversity, emerged as a popular method in organic synthesis for generating a diverse compound collection from readily accessible and common intermediates.[6] Nevertheless, a huge library can be assembled by altering either functional group or skeletal framework[7] of at least one of the precursor. Owing to its high skeletal diversity, DOS-based on compound collections contribute meaningfully in the area of drug

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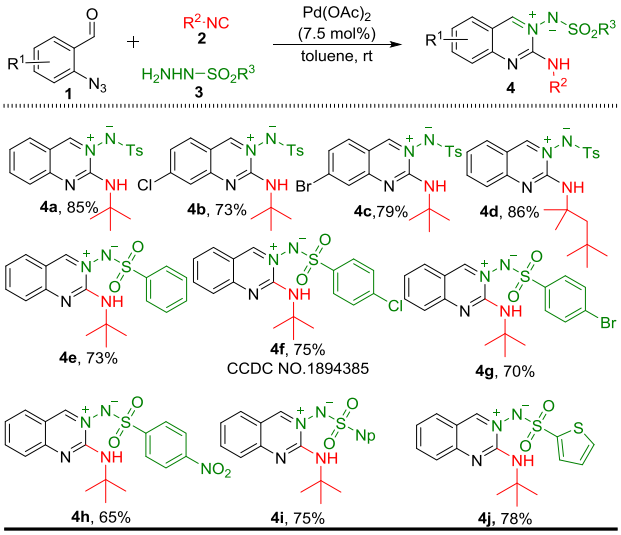
discovery. To this end, a significant volume of research based on diversity-oriented synthesis was published during the last decade.[8]

Recently, we reported a robust preparation of diverse azomethine imine through a three-component reaction promoted by auto-tandem Pd(II) catalysis (Scheme 1a).[9] In continuation of our efforts to develop new EGFR inhibitors by cyclocondensation of azomethine imines,[9] we envisaged that owing to its ambiphilic nature, azomethine imines could react with reagents having orthogonal functionality to generate skeletally diverse compound collections (Scheme 1b). Azomethine imines were popular in 1,3 dipolar cycloaddition reaction.[10] In this context, we report the diversity-oriented synthesis of two classes of quinazoline-based polyheterocycles from common intermediates, azomethine imine.

We embarked our journey by preparing a spectrum of diverse azomethine imine **4** from readily available 2-azido benzaldehyde **1**, isocyanide **2**, and aryl sulfonyl hydrazide **3** using our reported protocol (scheme 2). Irrespective of substitution pattern on aryl ring, the corresponding azomethine imines **4** were obtained in 65-86% yield. A good diversity of substitutions on the aryl ring (R^3) of sulfonyl hydrazides **3** is tolerated under the standard reaction condition. However, diversity on isocyanide **2** was restricted to *tert*-butyl an *iso*-octyl group. Overall, all title compound were obtained as stable solids at ambient temperature by flash chromatography. Single crystal X-ray analysis confirmed the structure of the compound 2-(*tert*-butylamino)quinazolin-3-ium-3-yl)((4-chlorophenyl)sulfonyl) amide **4f** in Fig 1.

With an assortment of azomethine imine **4** at hand, we attempted cyclocondensation with various orthogonally functionalized precursors. We were keen to develop a one-pot. multicomponent route for generating pharmaceutically active polyheterocyclic skeletons. We commenced the cyclo-condensation studies of azomethine imine **4** with nitroolefins **5**



Scheme 2. Preparation of functional azomethine imine through one-pot three-component reaction. Reaction condition: 2-azidobenzaldehyde **1** (0.51 mmol), isocyanide **2** (1.2 equiv, 0.612 mmol), sulfonyl hydrazide **3** (1.1 equiv, 0.561 mmol), palladium acetate (7.5 mol %) in toluene, 4 A MS and stirred at room temperature.

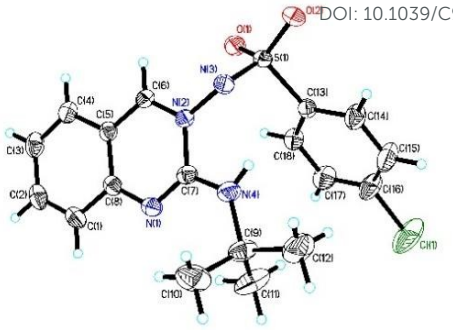
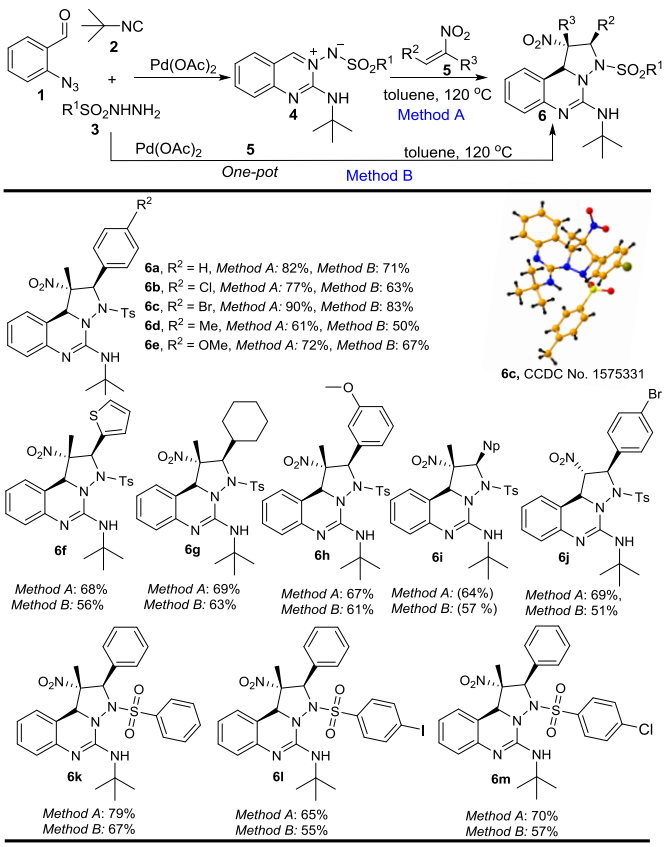


Figure 1. The X-ray crystal structure of compound **4f** showing with ORTEP diagram using 50% ellipsoidal plot.

for the synthesis of 1-nitro-2-aryl -1,2,3,10 b-tetrahydropyrazolo[1,5-*c*]quinazolin **6** (Table 1). The reaction was carried out in toluene at reflux (method A). The reaction exhibited excellent substrate scope and diversity, and various substitutions on azomethine imine **4** and **5** were well tolerated under standard conditions. Various substitutions on the aryl ring of nitroolefins and sulfonyl hydrazides can be incorporated. The chemical integrity of functional groups such as Cl and Br, remained unperturbed in the standard conditions,

Table 1: Substrate scope of 4-CR with nitroolefins.

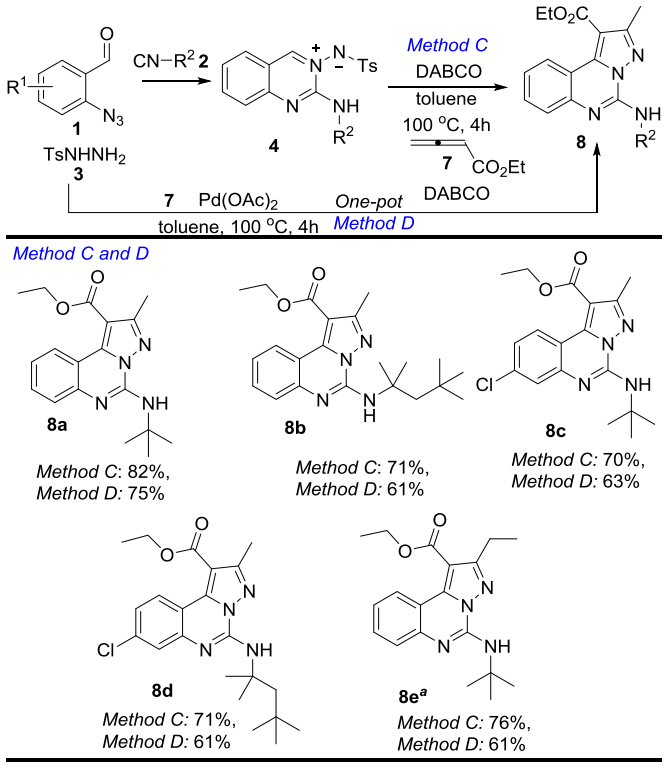


Reaction condition: Method A: azomethine imine **4** (0.14 mmol), nitroolefins **5** (0.65 equiv, 0.091 mmol) in toluene and reflux for 2h. Method B: 2-azidobenzaldehyde **1** (0.51 mmol), isocyanide **2** (1.2 equiv, 0.612 mmol), sulfonyl hydrazide **3** (1.1 equiv, 0.561 mmol), palladium acetate (7.5 mol %) in toluene, 4 A MS followed by nitroolefins **5** (0.65 equiv, 0.091 mmol) at 120 °C for 2h.

providing a chemical handle for further functionalization. We succeeded in the development of a one-step four-component protocol by developing method B.

The cyclocondensation of azomethine imine **4** was then elegantly extended to allenes for the synthesis of 2-methylpyrazolo[1,5-*c*]quinazoline **8** (Table 2). The feasibility of cyclocondensation reaction was explored in various solvents (refer to ESI). The reactions carried out in toluene at 100 °C temperature furnished best yields of 2-methyl pyrazolo[1,5-*c*]quinazoline **8** (Method C). The reaction exhibited a broader substrate scope and applicability. Various substitutions on azomethine imine **4** and allenoates **7** were well tolerated under standard conditions. Since toluene was a common solvent for the reaction of azomethine imine and allenoates, and preparation of azomethine imine itself, a one-pot 4-CR protocol for the synthesis of **8** from four different precursors was successfully established (method D).

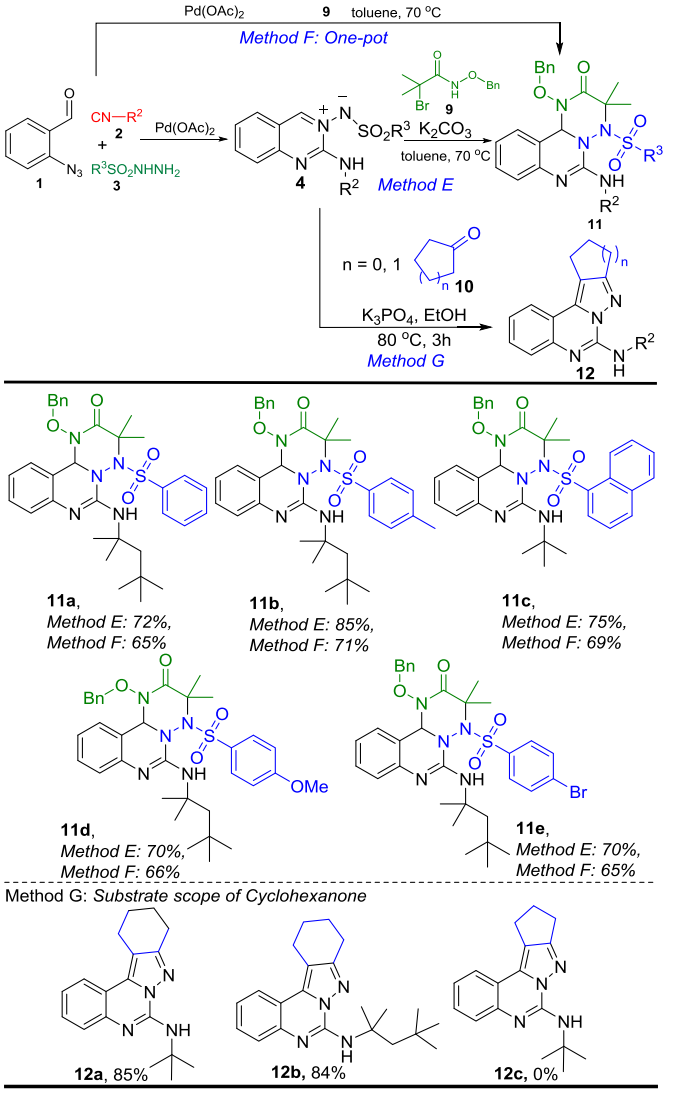
Table 2: Substrate scope of 4-CR with allenoates



Reaction condition: **Method C**: azomethine imine **4** (1 equiv, 0.51 mmol), allenoates **7** (2 equiv, 0.612 mmol) in toluene, DABCO at 100 °C for 4h. **Method D**: 2-azidobenzaldehyde **1** (0.51 mmol), isocyanide **2** (1.2 equiv, 0.612 mmol), sulfonyl hydrazide **3** (1.1 equiv, 0.561 mmol), palladium acetate (7.5 mol %) in toluene, 4 A MS followed by allenoates **7** (1.2 equiv, 0.612 mmol) and DABCO at 100 °C for 4 h. [a] Ethyl 2,3-pentadienoate is used as allenoates.

With the successfully venturing into the functional diversity employing allenoates and nitroolefins, we turned our attention on expanding the scaffold diversity by reacting azomethine imine **4** with α-halo hydroxamates **9** and cyclic ketones **10**. The reaction furnished rather an interesting scaffold, 1,3,4,11b-tetrahydro-2H-[1,2,4]triazino[2,3-*c*]quinazolin-2-one **11**. The reaction with α-halo hydroxamates displayed broader substrate scope and diversity (Table 3). Toluene again proved to be a common platform for the development of a one-pot tandem protocol from four different precursors. In contrast, reaction with cyclohexanone presented limited substrate scope and reaction failed with pentanone to give the desired product **12c**.

Table 3: Substrate scope of 4-CR α-halo hydroxamates **9** and cyclicketones **10** with azomethine imine **4**.



Reaction condition: Method E: azomethine imine **4** (0.14 mmol), α-halo hydroxamates **9** (1.2 equiv, 0.168 mmol) K_2CO_3 (2.0 equiv) in toluene as solvent (1.0 mL) stirred at 70 °C. Method F: 2-azidobenzaldehyde **1** (0.51 mmol), isocyanide **2** (1.2 equiv, 0.612 mmol), sulfonyl hydrazide **3** (1.1 equiv, 0.561 mmol), palladium acetate (7.5 mol %) in toluene, 4 A MS followed by α-halo hydroxamates (1.2 equiv) K_2CO_3 (2.0 equiv) in toluene as solvent (1.0 mL) stirred at 70 °C for 3-4 h. Method G: Azomethine imine **4** (0.51 mmol) reacted with cyclohexanone (1.02 mmol) in EtOH 1.0 ml with K_3PO_4 (1 equiv) at 80 °C 3 h.

Conclusions

In conclusion, we successfully demonstrated that cyclocondensation of azomethine imine and electrophilic reactant could be effectively utilized for generating skeletal diversity. As azomethine imine can be generated *via* three-

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component reaction, the protocol was further transformed to the sequential one-pot four-component methodology. The optimal 4-CR protocol ensured a high degree of step/atom economy. The reaction demonstrates excellent regio- and stereoselectivity, good functional group tolerance, and good conversion. A compound collection based on diverse and intricate molecular architecture plays a crucial role in drug discovery and development in the future.

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Conflicts of interest

"There are no conflicts to declare."

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