Conference paper

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New opportunities in the stereoselective dearomatization of indoles

DOI 10.1515/pac-2016-0101

Abstract: The regio- and stereoselective dearomatization of indoles is realized for the first time by combining readily available indolyl precursors and electron-rich allenes, namely allenamides and aryloxyallenes. Inter- as well as intramolecular condensations were realized under gold and Brønsted acid catalysis providing a range of densely functionalized indoline and indolenine cores in high yields and excellent stereochemical outcome. Chemodivergent reaction profiles (Micheal-type addition vs. [2 + 2]-cycloaddition) were realized by a tailored design of both reaction conditions and functionalization of the reaction partners.

Keywords: asymmetric catalysis; Brønsted acid; dearomatization; ESOC-19; gold; indole.

Introduction

The general statement: *Indole is among the most abundant heteroaromatic rings in nature* is probably not entirely correct. Undoubtedly, indole is abundant in naturally occurring species [1], however, in most of these cases, the bicyclic fused system is not present as an aromatic entity. In fact, in many alkaloid derivatives the indolyl core is represented by its tautomeric form (i.e. indolenine), reduced analogs (i.e. indoline), oxidized derivatives (i.e. oxindole) or even isomeric forms (i.e. isoindole) [2–4]. These fragments are frequently embedded into elaborated polycyclic fused molecular architectures featuring numerous stereogenic centers in stereochemically-defined manner. Herein, the C(3)-position of the indolyl scaffold frequently localizes an all-carbon stereogenic center that represents a not trivial synthetic exercise to be pursued.

Based on that, it is not surprising to record the growing interest by the synthetic chemistry community towards the realization of valuable catalytic and enantioselective protocols to obtain such heterocyclic motifs by means of metal- and metal-free catalysis. In this context, readily available and cheap indoles represent a desirable and convenient platform to be subjected to dearomative procedures.

Among many catalytic site-controlled stereodefined dearomatizations of indoles [5–9], a most diffuse approach involves the condensation of electron-rich arenes with electrophilic partners properly adapted in a side-chain of the heteroarenes (intramolecular route). Alternatively, intermolecular methodologies have been documented. Commonly, these chemical events enable cascade reactions to be realized with the concomitant formation of multiple C–C/C–X bonds and polycyclic fused scaffolds (Fig. 1). Functional group tolerance and robustness are demanding requirements for catalytic entities to be successfully employed in these reactions.

Article note: A collection of invited papers based on presentations at the 19th European Symposium on Organic Chemistry (ESOC-19), Lisbon, Portugal, 12–16 July 2015.

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Fig. 1: Examples of natural products featuring dearomatized indolyl-scaffolds and stereochemically defined stereogenic center at the C(3)-position.

Homogeneous gold(I) [Au (I)]-catalysis [10–24] played a prominent role in the field [25] and our group has already reported on the stereoselective dearomatization of indoles via gold-catalyzed condensation to propargylic alcohols, delivering an unprecedented class of densely functionalized tetracyclic-fused furoindolines and pyranyl-indolines [26, 27].

Results and discussion

With the aim to further extend the applicability of the methodology to a direct intermolecular variant, we identified in the allenamides **2** [28, 29] a valuable, ready available electron-rich class of allenes for the titled transformation. Allenamides are known to undergo electrophilic activation upon treatment with Brønsted acids or soft metal species, delivering the electrophilic Michael-acceptor type intermediate **A** (Fig. 2).

At the outset of the project, the working idea dealt with the regioselective trapping of 2,3-disubstituted indoles with allenamides, in order to provide indolenine cores featuring quaternary stereogenic centers at the C(3)-position and containing synthetically flexible side-chains. However, regioselectivity emerged as a major challenge being several reaction channels potentially competitive under mild reaction conditions [i.e. α vs. γ position of the allenamide and N(1) vs. C(3) position of the indole, Fig. 2] [30]. This issue was efficiently addressed and solved by screening a range of gold counterions with the idea that, the creation of a tailored network of hydrogen bond-interactions between the N(1)-H indole position and the gold anion, would result in the “shielding” of the N(1)-H site and the concomitant nucleophilic activation of the desired C(3)-position.

The model reaction involved the condensation of the 2,3-(Me)₂-indole **1a** and allenamide **2a** in the presence of [Au(I)] catalysts. Interestingly, an extensive survey of reaction parameters elected AgTFA (TFA = trifluoroacetate) as the optimal halide scavenger for the titled transformation providing the indolenine core **3a** in high yield (95 %) and synthetically acceptable regioselectivity (98:2, Scheme 1) [31]. It should be mentioned that, while strongly coordinating counterions (i.e. OAc, *p*NB, OTs) caused a marked drop in reaction rate, poorly coordinating ones allowed moderate to high combined isolated yields to be obtained with the *N*-alkylated indole derivate **3a'** as the predominant compound.

The scope of the reaction proved to be remarkably wide in terms of reaction partners. As a matter of fact, beside the request for substituents at the positions 2 and 3 of the indolyl core, a wide range of functionalizations was tolerated under best conditions (dichloromethane, rt, 16 h).

Fig. 2: Electrophilic activation modes of allenamides. Regioselectivity: a major challenge in the dearomatization of C(2,3)-disubstituted indoles with allenamides.

Scheme 1: Effect of the counterion on the gold catalyzed C(3)-allylic dearomatization of indoles. nr, no reaction.

Commonly, the resulting dearomatized indolenines **3** were isolated in highly regioselective manner and good to excellent yield (Scheme 2a) and best reaction parameters were also efficiently extended to an intramolecular example (Scheme 2b) [32]. Here, the regioselective C(3)-attack to the alpha position of the allenamide unit was recorded exclusively, providing the corresponding spiro-compound in 82% yield and 4.6:1 diastereoisomeric ratio.

Mechanistically, the reaction is thought to initiate via the electrophilic activation of the allenyl-framework by the gold center (**A**) followed by the regioselective condensation of the 2,3-disubstituted indole **1** (**B** → **C**) [33]. The subsequent protodeauration of the gold-alkenyl adduct **C** would result into the final product **3** along with the restoring of the gold species in its active form (Scheme 3). In this line, the unique role of the counterion [34, 35] was addressed by means of a spectroscopic investigation via mono- and bi-dimensional NMR analysis. Interestingly, the presence of trifluoroacetate generated a network hydrogen-bond contacts between the gold anion and the indole species N(1)H (**B** in Scheme 3). This event could probably orient the incoming nucleophile toward a site-selective C(3)-alkylation [36].

We then turned our attention towards the development of an enantioselective variant of this allylating dearomative process. Disappointingly, beside many attempts dealing with the use of chiral gold complexes (i.e. chiral ligand and/or chiral counterions) [37–43], the desired indolenine core was isolated always in synthetically unacceptable stereochemical outcomes. The well-known isolobal principle that interconnects

Scheme 2: Scope of the [Au(I)]-assisted intermolecular dearomatization of indoles with allenamides.

Scheme 3: Hypothetical reaction mechanism of the condensation of indoles with allenamides. The hydrogen-bonding interaction between the gold catalyst and the indole was proved via a spectroscopic investigation. A pictorial representation of the adduct **B** is depicted.

[Au(I)]-species and the proton, in terms of electronic properties and consequently “acidity” [44], led us considering the electrophilic activation of the allenamide with chiral Brønsted acids (**4**) as a valuable metal-free chemical activation. This approach would result into the formation of an iminium ion species coupled with chiral anions. The instauration of contact ion points between these entities across the enantiodiscriminating step of the process could provide a fruitful stereochemical environment to control the enantioselection of the reaction. This would also represent the first catalytic enantioselective manipulation of allenamides under metal-free conditions.

Interestingly, after an extensive survey of reaction conditions, we identified in the C_8 -TCyP acid **4a** (10 mol %) the catalyst of choice, enabling the chemo-, regio- and stereoselective dearomatization of 2,3(Me)₂-indole **1a** in 98 % yield and 92 % ee. The reaction can be extended to a wide range of indoles featuring cyclic as well as acyclic substituents at the pyrrole ring and both EWGs and EDGs on the benzene unit. In all cases high enantiomeric excesses were obtained (Scheme 4a) [45]. Additionally, by combining this reactivity with the well-known Brønsted acid-assisted enantioselective reduction of C=N double bonds with metal-free reductant (i.e. Hantzsch esters, **5** and catalyst **4b**) [46, 47], the simultaneous dearomatization of the indolyl-scaffold and the reduction of the *in situ* formed C=N bond were perused in moderate yield (51 %) and high stereochemical control (Scheme 4b). Based on that, the methodology can be considered as a valuable synthetic tool to obtain both indoline and indolenine scaffolds in high enantiomerically enriched form.

Furthermore, the catalytic cycle depicted in the Scheme 3 led us to explore a possible alternative reaction channel by preventing the protodeauration event (**C** → **3**) in favor of an intramolecular C–C bond-forming step involving the electrophilic keto-imine moiety and the alkenyl-gold framework (**C** → **9**). In order to drive the reaction course towards the new channel we envisioned the possibility to increase the electrophilicity of the indolenine group by introducing an EWG at the N(1)-position of the starting indole.

Delightly, upon a severe reconsideration of the reaction conditions (i.e. use of oxazolidinone-based allenamide **2b** and N(Boc)- as well as N(Cbz)-indoles **7**), the predominant/exclusive formation of the formal [2+2]-adduct namely 2,3-cyclobutyl-fused indolines **9** was successful [48–50].

In particular, the complex [JohnPhosAu(CH₃CN)SbF₆] (5 mol %) furnished the cycloadducts **9** regiochemically and diastereomerically in excellent yields (Scheme 5) [51]. Additionally, the configuration of the C=C double bond was obtained in a stereochemically defined fashion and this output was rationalized by means

Scheme 4: Brønsted acid catalyzed enantioselective dearomatization of indoles. A collection of results is reported. Below: the cascade dearomatization/reduction sequence for the synthesis of indolines **6**.

of computational tools. Here, DFT calculations provided insights into a step-wise mechanism that deals with the initial C–C bond-forming event as the rate-determining step of the entire process.

Having in hand a set of reliable reaction conditions, the scope of the process was then investigated. Interestingly, the chemistry turned out to be highly robust with tolerance towards functional groups featuring divergent electronic as well as steric properties. In addition, aryloxyallenes **8** [52] were also successfully employed enabling the installation of a synthetically useful enol ethers in the final cyclobutyl adduct.

It is worthy to note that this type of dearomative alkylation of indoles [i.e. forming C(2,3)-fused cyclobutyl scaffold] is still poorly explored in literature [53, 54], therefore, we turned out attention on the development of the enantioselective variant of the latter cycloaddition reaction. In principle, being the gold catalysis intimately involved in the formation of the first stereogenic center (**1** → **B**, Scheme 3), the introduction of suitable chiral ligands on the gold center could govern the overall stereochemical profile of the process. Delightfully, the combination of (*R*)-DTBM-segphos($AuCl$)₂ and $AgNTf_2$ (2.5 mol %) enabled the isolation of the desired cycloadduct **9** in high yield, single diastereoisomer and synthetically useful enantiomeric ratio (Scheme 6) [55].

The substrate scope was very general with particular concern to indole peripheral decoration. On the contrary, main limitations lied on the C(2,3)-disubstitution of the pyrrolyl unit and the presence of an electron-withdrawing groups at the nitrogen center. Classic Friedel-Crafts addition/elimination mechanism or a marked drop in reaction turnover, were observed in the latter case, respectively.

Scheme 5: Gold-assisted formal [2 + 2]-cycloaddition between allenamide **2b** or aryloxyallenes **8** and *N*-protected indoles **7**. A collection of results is reported. Ar = *p*-NO₂-C₆H₄ or β-naphthyl.

Scheme 6: Enantioselective gold-catalyzed formal [2 + 2]-cycloaddition of allenamides or aryloxyallenes with *N*-protected indoles **7**.

Interestingly, the C(2,3)-cyclobutyl-indolenine scaffold **9** showed at the same time robustness and flexibility. In particular, the [2+2]-core tolerated acidic conditions (i.e. removal of the nitrogen protecting group) and reductive regimes (i.e. hydrogenation of the exocyclic C=C double bond). Additionally, by subjecting the [2+2]-cycloadduct to oxidative conditions ($\text{RuCl}_3/\text{NaIO}_4$) the formation of a γ -lactone was obtained in good yields. To be mentioned that all these transformation occurred without any appreciable racemization.

Conclusions

In conclusion, a set of new catalytic approaches for the dearomatization of indolyl cores was documented. Au(I) catalysis contributed in disclosing a range of regio- and stereoselective condensations of C(2,3)-disubstituted indoles with allenamides and aryloxyallenes by means of electrophilic activation of the π -system. Inter- as well as intramolecular variants have been studied leading to both indoline and indolenine cores. Last but not the least, spectroscopic [nuclear magnetic resonance (NMR)] and computational analysis contributed to shed some light on the: 1) rational of the role of TFA-counterion in the allylating dearomative reaction; 2) reaction machinery of the formal [2+2]-cycloaddition process. Additionally, an example of isolobal analogy between [Au(I)] and the $[\text{H}^+]$ that reflects on their catalytic capability was also provided by disclosing the first Brønsted acid assisted enantioselective dearomative condensation of allenamides with differently substituted indoles.

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