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Construction of enantioenriched polysubstituted hexahydropyridazines *via* a sequential multicatalytic process merging palladium catalysis and aminocatalysis†

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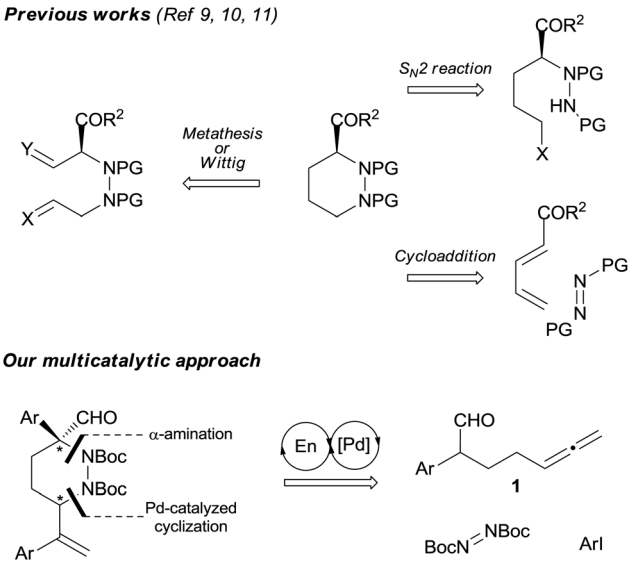
An efficient multicatalytic strategy for the construction of nitrogen-containing heterocycles has been reported. The powerful combination of organic and metal catalysis in a single vessel allowed the formation of enantioenriched polysubstituted cyclic 6-membered hydrazines bearing a quaternary stereocenter in good yields and selectivities.

Asymmetric catalysis remains a challenge to synthetic chemists as the demand for enantiomerically enriched drug-like molecules continues to increase.[1] Inspired by the cooperative catalysis in enzymatic processes, the combination of different catalysts to reach an inaccessible synthetic efficiency and stereoselectivity by a single catalyst has attracted increasing attention over the past few years.[2] The development of multicatalytic processes that merge the complementary activation offered by a metal and an organocatalyst has allowed the construction of enantioenriched complex structures from simple starting materials.[3] In the meantime, nitrogen-containing heterocycles are ubiquitous building blocks in natural products[4] and pharmaceuticals.[5] Among the wide variety of structures, cyclic hydrazines represent an interesting class of compounds owing to their presence in a myriad of molecules of biological interest.[6] Numerous efficient syntheses of hydrazine-containing heterocycles have been reported in the literature[7] and the main strategies to construct enantioenriched structures include sequential multi-step sequences or one-pot processes (Scheme 1). Electrophilic amination[8] was generally chosen for the stereoselective formation of the nitrogen-containing stereocenter and the cyclization step involved ring-closure metathesis,[9] the Wittig reaction[10] or S_N2 reaction.[11] Catalytic asymmetric [4 + 2] cycloaddition with diazene compounds has also been reported as a straightforward method to such motifs.[12] Despite these elegant achievements, enantioselective examples remain scarce and there is still a need for original catalytic methods aiming at synthesizing chiral polyfunctionalized structures. In connection with our ongoing program devoted to the preparation of nitrogen-containing heterocycles,[13] we describe herein a multicatalytic approach for the synthesis of enantioenriched cyclic 6-membered hydrazines. The reaction sequence involves a stereoselective organocatalytic C–N bond formation followed by an unprecedented palladium-catalyzed cyclization reaction of 4,5-allenylic hydrazine with aryl halides[14] to afford hexahydropyridazines bearing a quaternary stereocenter (Scheme 1). Inspired by our previous work providing enantioenriched α-hydrazino aldehydes,[15] we reasoned that the aminocatalyzed α-amination of aldehydes **1** could afford the key intermediates that would undergo cyclization under palladium catalysis. We also assumed that the intramolecular formation of the second C–N bond could be



Scheme 1 Main strategies towards hexahydropyridazines.

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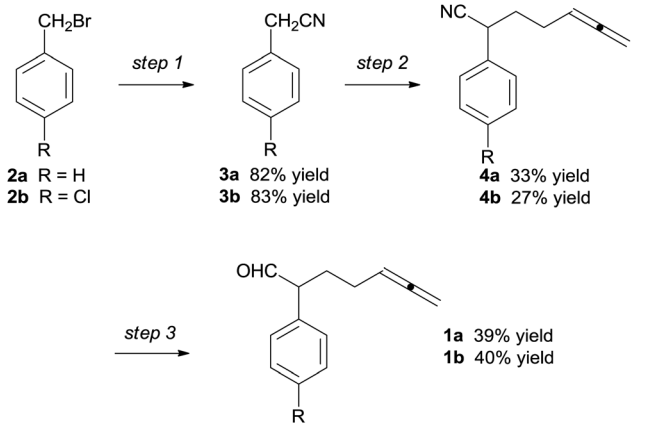
facilitated by a *gem*-disubstituent effect induced by the stereocenter formed in the first step.[16]

The starting aldehydes **1** were readily prepared according to the synthetic strategy depicted in Scheme 2. Benzyl bromide derivatives **2** were converted into the corresponding benzyl cyanides **3** by treatment with trimethylsilyl cyanide under basic conditions.[17] After deprotonation of **3** with sodium hydride in *N*,*N*-dimethylformamide, the addition of 5-iodopenta-1,2-diene[18] enabled the preparation of **4a** and **4b** in 33% and 27% yields respectively. The nitrile moiety was finally reduced by using diisobutylaluminium hydride in dichloromethane to provide the aldehydes **1**.

With the substrate **1a** in hand, the transformation was first investigated as a two-step protocol. Preliminary studies[19] revealed that a combination of 9-amino(9-deoxy)*epi*-quinine **5** used under the previously reported conditions for the enantioselective α-amination (aldehyde (1.5 equiv.), di-*tert*-butylazodicarboxylate (D*t*BAD, 1 equiv.), catalyst **5** (5 mol%), TFA (15 mol%) in $CHCl_3$ ([D*t*BAD] = 0.5 M)) and a Pd catalyst used under the conditions described by Ma[20] (hydrazine **6a** (1 equiv.), PhI (1.2 equiv.), Cs_2CO_3 (1.1 equiv.), and $[Pd(PPh_3)_4]$ (5 mol%) in MeCN ([**6a**] = 0.08 M)) was efficient for a sequential process (Scheme 3, eqn (1)). The challenge was then to



Scheme 2 Synthesis of **1**: (step 1) TMSCN, K_2CO_3, MeCN, 60 °C, 16 h; (step 2) (i) NaH, DMF, 0 °C, 1 h; (ii) 5-iodopenta-1,2-diene, 0 °C, 0.5 h, r.t., 0.5 h; (step 3) DIBAL, CH_2Cl_2, –78 °C, 3 h.

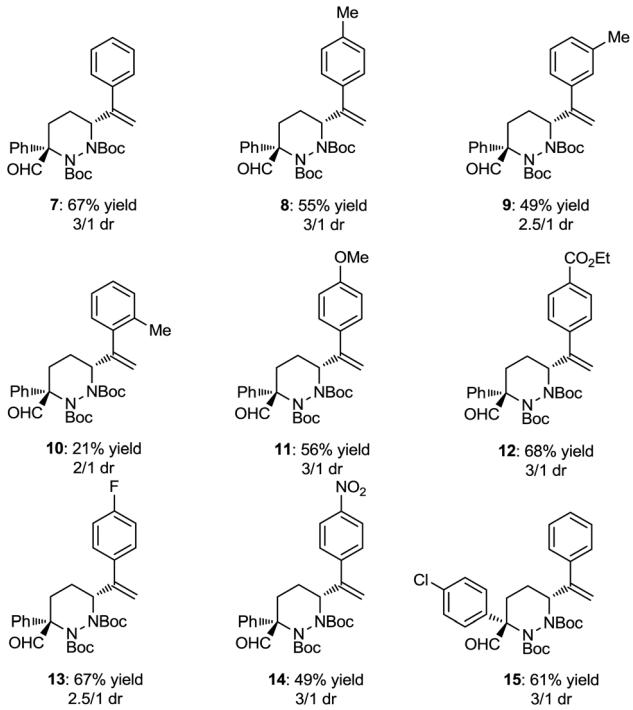
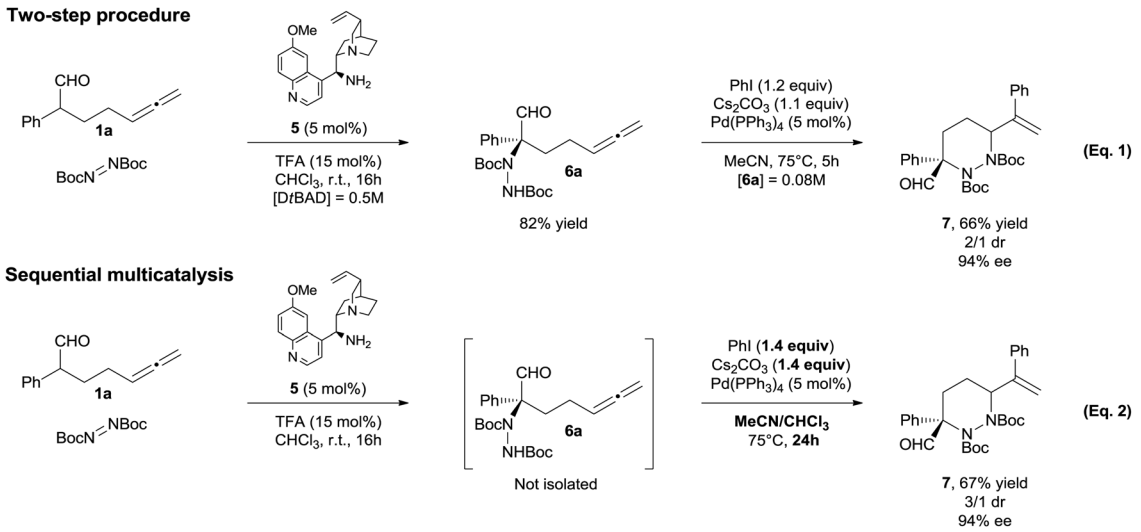


Fig. 1 Scope of the one-pot sequence (major diastereomers are drawn; yields of the isolated mixture of diastereomers; dr have been determined by ^{1}H NMR analysis of the crude product, see the ESI† for details).



Scheme 3 Optimization of the sequential multicatalysis.

optimize these conditions toward a one-pot procedure. In order to circumvent the compatibility problems (acidic medium of the first step and basic medium of the second one, solvent systems), a sequential multicatalysis, which describes reactions that rely on the addition of another catalyst or/and reagents to initiate a subsequent catalytic cycle, was envisaged. We also accounted for the difference in concentration in the two reaction media to homogenize the solvent system. Hence, the reaction of 2-phenylhepta-5,6-dienal **1a** with D*t*BAD in the presence of aminocatalyst **5** (5 mol%) and TFA (15 mol%) in $CHCl_3$ was carried out under stirring overnight at room temperature and the mixture was diluted with MeCN. $[Pd(PPh_3)_4]$ (5 mol%) and a slightly increased amount of iodobenzene and Cs_2CO_3 (1.4 instead of 1.2 equiv.) were then added and the reaction mixture was stirred at 75 °C for 24 h to ensure completion of the cyclization (Scheme 3, eqn (2)). The expected product **7** was obtained in 67% yield as a 3/1 mixture of diastereomers and a high level of enantioselectivity (94% ee).

With the optimized conditions in hand, the scope of the sequence was surveyed using various iodoarenes (Fig. 1). We first examined whether the position of a methyl group on the aromatic ring could influence the efficiency and stereoselectivity of the reaction. Starting from 4-, 3-, or 2-iodotoluene, the formation of the corresponding cyclic hydrazines was accompanied by a continuous decrease in reactivity and diastereoselectivity in the following order: *para* (**8**, 55% yield, 3/1 dr), *meta* (**9**, 49% yield, 2.5/1 dr), *ortho* (**10**, 21% yield, 2/1 dr) showing that the second step of the sequence was influenced by the steric hindrance of the iodoarene coupling partner. We then focused our attention on the influence of the electronic nature of the substituent of the aromatic ring on the outcome of the reaction. Employing an electron-rich aryl group like *para*-iodoanisole for the multicatalytic process afforded **11** in 56% yield and 3/1 dr. Identical results as for **7** (67% yield, 3/1 dr) were obtained when aromatics with electron-withdrawing substituents such as an ester (compound **12**) or a fluorine atom (compound **13**) were used in the transformation. A slight decrease in the reaction rate was observed when the sequence was performed with 1-iodo-4-nitrobenzene and the corresponding hexahydropyridazine **14** was synthesized in 49% yield and 3/1 dr. Finally, aldehyde **1b** was employed in the sequence with iodobenzene as the coupling partner and compound **15** was isolated in 61% yield and 3/1 dr. It is worth noting that due to the high enantioselectivity reached during the first step, compounds **7–14** were obtained in 94% ee and compound **15** with 93% ee.

The absolute configuration of the stereocenter formed during the electrophilic amination step, obviously *S*, if we referred to our previous work, has been confirmed by X-ray analysis of a single crystal of a minor diastereomer of compound **13**. Therefore, absolute and relative configurations of all other products have been assigned by analogy to be (1*S*,4*R*) for major diastereomers and (1*S*,4*S*) for the minor ones (Fig. 2).

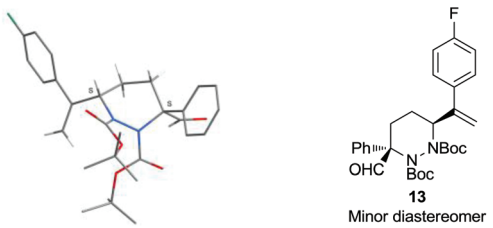
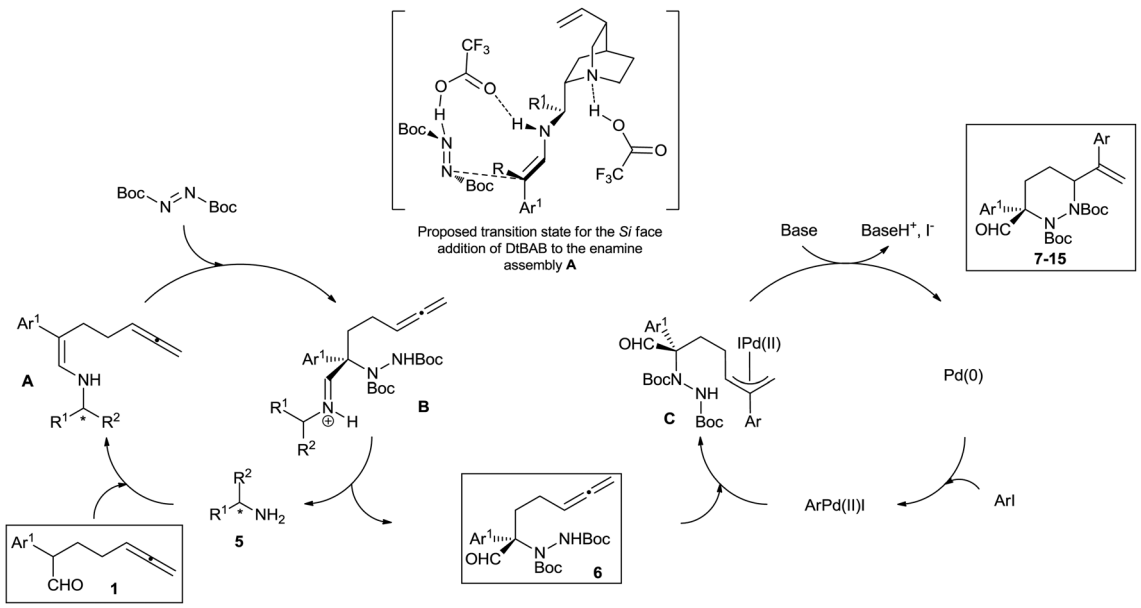


Fig. 2 X-Ray structure for compound **13** (minor diastereomer).



Scheme 4 Proposed mechanism for the sequential multicatalysis.

Based on the above results related to the sequential multicatalysis, a plausible double catalytic cycle is proposed in Scheme 4. The first catalytic cycle which corresponds to the known organocatalytic α-amination would start by the formation of the enamine **A** which would react with D*t*BAD to afford the iminium intermediate **B**. A subsequent hydrolysis would regenerate the primary amine catalyst **5** and would liberate the α-hydrazino aldehyde **7**. Based on a mechanistic study published by Melchiorre in 2013,[21] a postulated transition state explaining the *Si* face selectivity of the addition was proposed. The second catalytic cycle would start by the oxidative addition of aryl iodide to palladium(0) followed by the insertion of this complex to the allene moiety of the newly synthesized compound **7**. An intramolecular reaction to form cyclic 6-membered heterocycles between hydrazine and π-allyl species of intermediate **C** in the presence of a base would give rise to hexahydropyridazines **7–15**. The low diastereoselectivities could originate from the existence of different conformations for **C** which are in equilibrium. This would lead to both diastereomers of the cyclization product.

To conclude, we have developed an efficient one-pot multicatalytic synthesis of nitrogen-containing heterocycles from 2-arylhepta-5,6-dienal. The overall protocol involves an organocatalytic α-amination reaction and a Pd-catalyzed cyclization. The methodology provides rapid and mild access toward useful and interesting cyclic 6-membered hydrazines. The application of the multicatalytic process to more challenging substrates is currently in progress in our laboratory.

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