Asymmetric Allylation / Pauson-Khand Reaction: a Simple Entry to Polycyclic Amines. Application to the Synthesis of Aminosteroid Analogs

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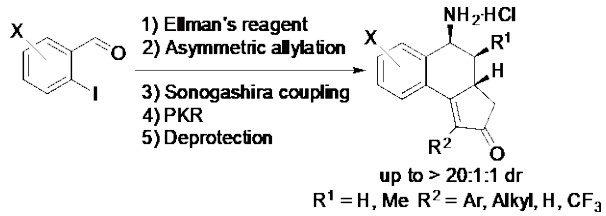
Supporting Information Placeholder

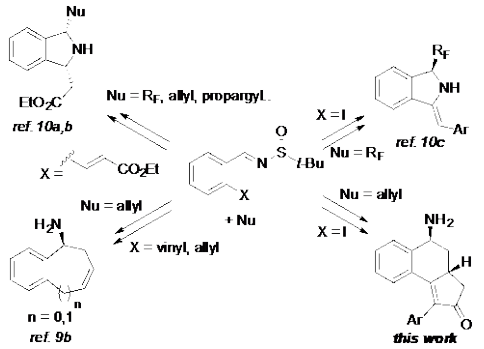


ABSTRACT: The asymmetric allylation of *ortho*-iodoarylsulfinylimines has been achieved in high diastereoselectivities. The thus obtained *ortho*-iodoarylhomoallylic sulfinamides participate in a subsequent Sonogashira coupling followed by a diastereoselective intramolecular Pauson-Khand reaction. In this way, tricyclic amines showing a unique benzo-fused indenyl backbone were obtained. The methodology has been applied to the synthesis of amino steroid analogs.

Chiral homoallylic amines are versatile building bock in organic synthesis. The presence of a pendant double bond enables further synthetic transformations for the assembly of more complex backbones. [1] Undoubtedly, the asymmetric allylation of imines[2,3] is the most widely used methodology for their synthesis and, among the existing methods, the addition of allyl-metal reagents to Ellman's *tert*-butylsulfinimines[4] shows some salient features: high degree of stereocontrol and chemical yields, reliability, and functional group compatibility, among others. On the other hand, the Pauson-Khand reaction (PKR) is arguably the method of choice for the construction of the cyclopentenone ring from acyclic precursors.[5,6] Astonishingly, despite the impressive development undergone by these two powerful transformations they have never been combined for the construction of complex polyclyclic amines.[7] To the best of our knowledge, there is only one example of PKR on a homoallylic amine bearing a pendant triple bond in its carbon backbone reported in the literature, in a racemic form.[8]

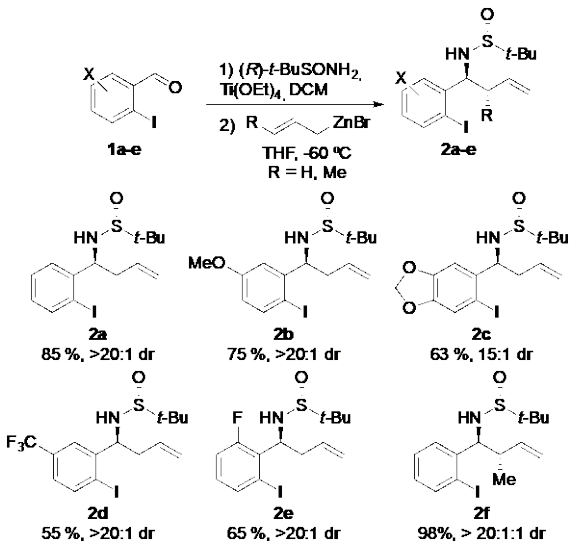
On the other hand, our group has been interested in the use of 2-halobenzaldehyde derived Ellman's sulfinimines for the asymmetric synthesis of a variety of benzo-fused carbo-[9] and heterocycles[10] in the context of diversity oriented synthesis (DOS).[11] Hence, we have found that the introduction of a suitable functional group at the *ortho*-position of substrates of this kind enables a series of reaction sequences iniciated by a nucleophilic addition (A_N) of a suitable nucleophile to the imine, namely: A_N / intramolecular *aza*-Michael reaction,[10a,b] A_N / RCM[9b] and A_N / intramolecular hydroamination (Scheme 1).[10c] Continuing with our interest in expanding the structural diversity from these readily available starting materials, we disclose here our results in the allylation / PKR sequence giving rise to polycyclic amines in very high diastereoselectivities (Scheme 1). Building on the principles of diversity oriented synthesis we selected *ortho*-iodobenzyliden *tert*-butanesulfinamides, previously described by our research group, as starting materials for our study.

Scheme 1. Synthetic versatility of 2-substituted aromatic Ellman's sulfinimines



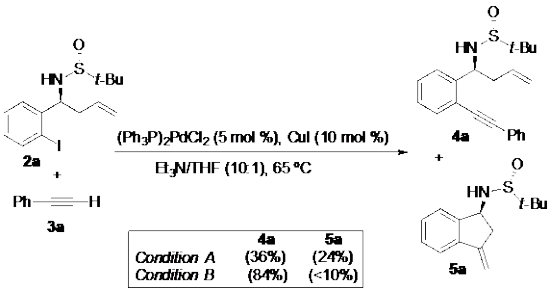
First of all, we tested the allylzinc addition to a model substrate, in order to rule out any possible interaction between the organometallic reagent and the labile C-I bond[12] and check the diastereoselectivity, which is known to be sensitive to steric hinderance.[13] Based on our recent findings,[10b] the allylation reaction was performed on the crude imine giving rise to product **2a** in good yield and excellent diastereoselectivity. In view of these results we decided to prepare a small library of analogs for the subsequent Sonogashira coupling (Scheme 2). Electron-donating (**2b,c**), electron-withdrawing (**2d**) and halogen atoms (**2e**) are suitable substituents on the aromatic ring giving rise to the desired products in moderate to good yields and excellent diastereoselectivities in all cases. In addition, we evaluated the crotylation reaction aimed to the creation of an additional stereocenter in the final product. To our delight, compound **2f** was obtained in excellent yield and, more importantly, complete diastereoselectivity.

Scheme 2. Asymmetric allylation of 2-iodosulfinilimines 1



Next, the Sonogashira cross-coupling of substrate **2a** and phenylacetylene **3a** was investigated (Scheme 3). The main difference with the *ortho*-iodohomoallylic amines we recently described[10c] is the presence of a pendant double bond, which may interfere, in the cross-coupling processes. Indeed, when substrate **2a** was subjected to cross-coupling with phenyl acetylene **3a** the desired product was obtained in moderate yield along with an appreciable amount of **5a** arising from an intramolecular Heck reaction (Scheme 3, condition A). In order to avoid the formation of this undesired byproduct, the reaction was carried out with a larger excess of the alkyne (5 equiv) and under more concentrated reaction conditions (0.5 M) to facilitate the intermolecular process over the intramolecular one (Scheme 3, condition B). Under these reaction conditions the formation of the intramolecular Heck reaction byproduct was almost completely suppressed and the desired product **4a** was obtained in good chemical yield.

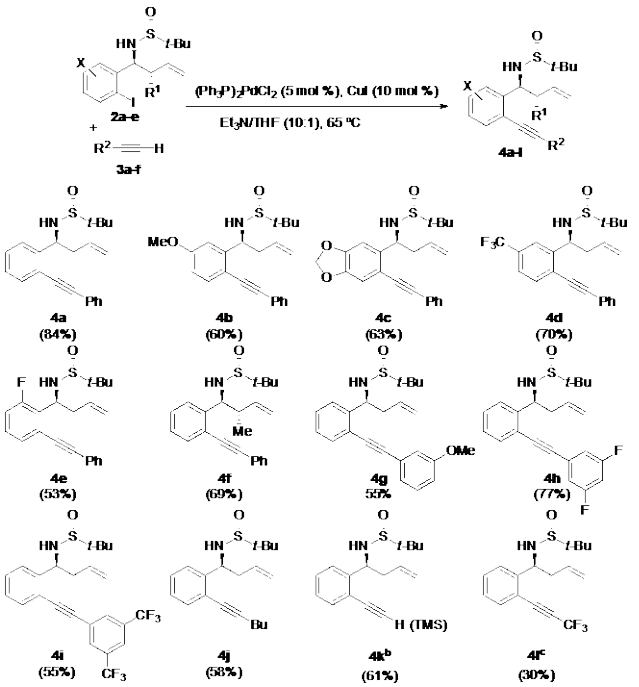
Scheme 3. Optimization of the reaction conditions for the Sonogashira cross-coupling [a]



[a] Condition A: 3 equiv of alkyne, 0.1M; Condition B: 5 equiv of alkyne, 0.5M

With this optimized conditions in hand, the *ortho*-iodophenylhomoallylic amines **2a-f** (Scheme 3) were coupled with a variety of terminal alkynes affording *ortho*-alkynylhomoallylic amines suitable the intramolecular PKR (Scheme 4). First, substrates **2a-f** bearing both electron-donating and electron withdrawing groups were coupled with phenyl acetylene affording products **4a-f** and, secondly, substrate **2a** was coupled with alkynes **3b-f** (see SI for their structures) giving rise to products **4g-l**.

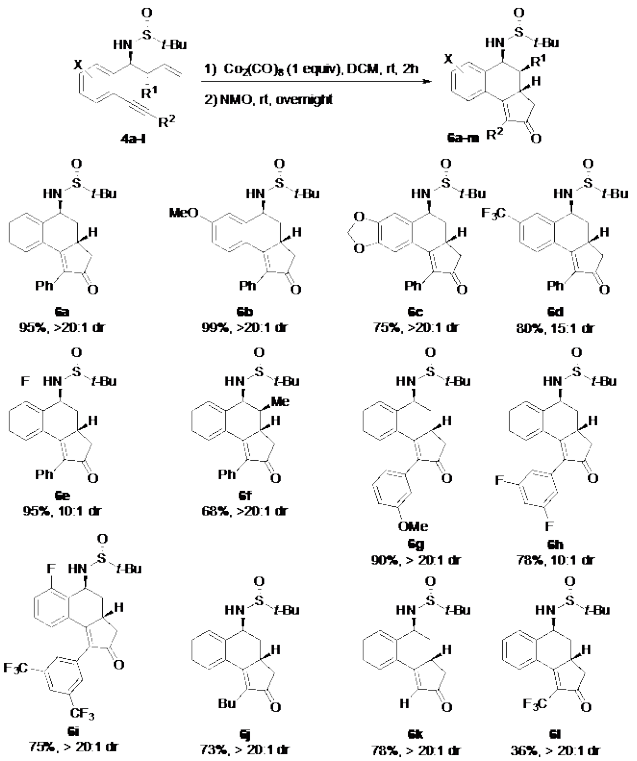
Scheme 4. Scope of the Sonogashira cross-coupling of substrates 2a-f with terminal alkynes [a]



[a] A small amount of the intramolecular Heck product (5-10%) was obtained in most cases. [b] Obtained from the corresponding TMS derivative **4k'** in the indicated yield (see, SI for details). [c] Obtained from **4k** in the indicated yield.

Once an assorted library substrates had been obtained, we evaluated the intramolecular PKR (Scheme 5). Again, good to excellent yields and diastereoselectivitites were obtained regardless the substitution pattern in the aromatic tether (**6a-e**) and the nature of the substituent at the triple bond: activated (**6g**) and deactivated (**6h,i**) aromatic rings, alkyl chains (**6j**), terminal (**6k**) and, noteworthy, CF_3 (**6l**) for the first time in an intramolecular PKR.[14] The last two examples were not obtained by direct Sonogashira coupling. Instead, the terminal alkyne was prepared from the corresponding TMS derivative[15] by base-mediated desilylation; while the CF_3 derivative was obtained from the latter by copper catalyzed electrophilic trifluorination using Togni's reagent (see SI, for details).

Scheme 5. Scope of the intramolecular PKR



The relative configuration of the new stereocenter created upon the PKR was determined by 2D-NMR experiments (NOE on **6b**, see SI) and confirmed by X-ray diffraction analysis on derivative **6f**, exhibiting three consecutive stereocenters (Figure 1, left).

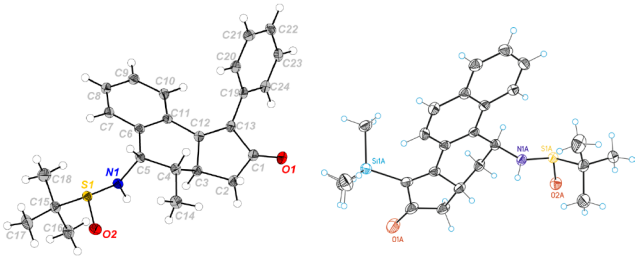
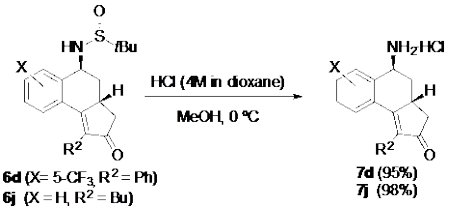


Figure 1. ORTEP diagrams for **6f** (left) and **9a** (right).

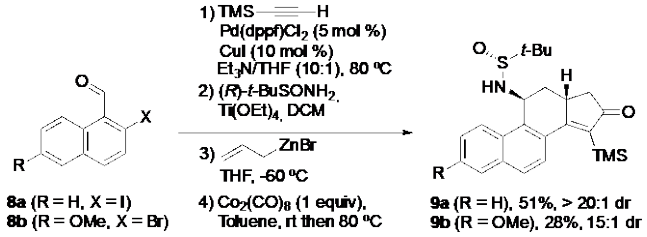
Removal of the chiral auxiliary under standard conditions (HCl in dioxane 10 equiv, MeOH, rt) resulted in partial racemization of the benzylic stereocenter (for details, see SI). However, by lowering the amount of acid to 1 equivalent and the reaction temperature to 0 ºC, the chiral auxiliary was successfully removed from two representative substrates rendering the free amines as the corresponding hydrochlorides (Scheme 6).

Scheme 6. Removal of the chiral auxiliary



Finally, as a further application of our methodology, we envisioned the synthesis of the steroidal skeleton (scheme 7). Aminosteroids are an important subclass of steroids and some of them display interesting biological properties mostly used in the field of anesthesia.[16,17] To this end, substrates **8a,b** were synthesized according to literature procedures[18] and subjected to the methodology reported herein (Scheme 7). Products **9a,b** were obtained in good overall yields (4 steps) and diastereoselectivities and represent, to the best of our knowledge, the first *de novo* syntheses of the sterane backbone of aminosteroids.

Scheme 7. Application to the synthesis of amino steroid derivatives



Interestingly, the reaction sequence needed to be adapted to the new skeleton. In this case, the Sonogashira coupling on the homoallylic amine did not afford the desired product. To overcome this difficulty the alkyne was introduced prior to condensation with the chiral auxiliary. A second difference was the complete diastereoselectivity obtained even in the presence of the trimethylsilylethynyl moiety (for the benzaldehyde derivative **4k'** a 10:1 diastereoselectivity was observed).[13] Finally, as opposed to the corresponding benzaldehyde derivative, the PKR proceeded uneventfully on the TMS protected derivative (see reference 15) accomplishing the formation of the tetracyclic framework. The stereochemistry of **9a** was confirmed by X-ray diffraction analysis (Figure 1, right).

In conclusion, the 2-iodobenzaldehyde derived Ellman's imines allylation/PKR reaction sequence has been established as a useful tool for the asymmetric synthesis of polycyclic amines containing the fusion of two ubiquituos domains both in natural products and drugs, namely: the tetrahydonaphthalene and the cyclopentenone rings. The new methodology has succesfully been applied to the first *de novo* synthesis of aminosteroid derivatives.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and NMR spectra for all new compounds, as well as crystallographic data for compounds **6f** and **9a** including their CIF files are available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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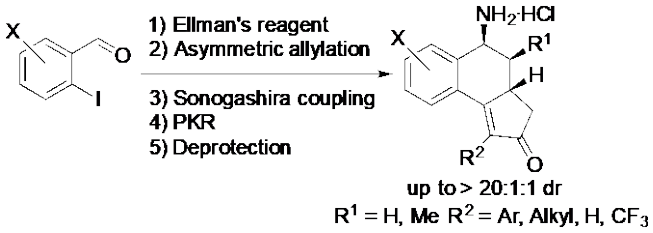

up to > 20:1:1 dr

R^1 = H, Me R^2 = Ar, Alkyl, H, CF_3