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Asymmetric Allylation/Ring Closing Metathesis: One-Pot Synthesis of Benzo-fused Cyclic Homoallylic Amines. Application to the Formal Synthesis of Sertraline Derivatives

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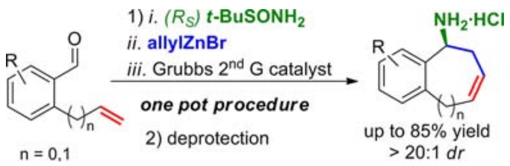
ABSTRACT



A one-pot asymmetric allylation/ring closing metathesis (RCM) sequence for the synthesis of cyclic homoallylic amines has been developed. A library of six- and seven-membered benzo-fused products has been synthesized in good yields and complete diastereoselectivity. The new methodology has been applied to the formal syntheses of the antidepressant Sertraline and the epimeric Norsertraline. The methodology is amenable for the synthesis of analogs.

Arguably, the asymmetric allylation of imines is the most important method for the synthesis of homoallylic amines which are versatile building blocks in organic synthesis.[1] Among existing methods, the diastereoselective addition of allylzinc bromide to Ellman's *tert*-butylsulfinimines presents a number of advantages: a high degree of diastereocontrol and chemical yields, reliability, and functional group compatibility, among others.[2] On the other hand, ring closing metathesis (RCM) is one of the most reliable methods for the construction of medium-sized rings.[3] The combination of these two powerful strategies enables the rapid construction of cyclic homoallylic amines. Our group[4] as well as others[5] have used this reaction sequence for the synthesis of cyclic amino acid derivatives, pyrroloazepines, or pharmaceutical compounds, respectively. However, it has never been applied to the synthesis of benzo-fused systems.

Several years ago, in the context of diversity oriented synthesis (DOS), we launched a research program to study the use of *ortho*-substituted aromatic *tert*-butylsulfinyl imines for the asymmetric synthesis of a variety of benzo-fused carbo- and heterocycles such as fluorinated isoindolines[6a,b] and isoquinolines[6b] or indanones,[6c] respectively (Scheme 1).

Among benzo-fused systems, the tetrahydronaphthalene core belongs to the so-called privileged structures,

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(1) For reviews on asymmetric allylation, see: (a) Yus, M.; González-Gómez, J. C; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. (b) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815. (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(2) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(3) (a) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (b) Blanchard, N.; Eustache, J. Synthesis of Natural Products Containing Medium-size Carbocycles by Ring-closing Alkene Metathesis. In *Metathesis in Natural Product Synthesis*; Cossy, J., Arseniyadis, S., Meyer, C., Eds.; Wiley-VCH: Weinheim, 2010; pp 1–43.

(4) (a) Fustero, S.; Sánchez-Roselló, M.; Rodrigo, V.; del Pozo, C.; Sanz-Cervera, J. F.; Simón, A. *Org. Lett.* **2006**, *8*, 4129. (b) Fustero, S.; Sanz-Cervera, J. F.; Aceña, J. L.; Sánchez-Roselló, M. *Synlett* **2009**, 525.

(5) Grainger, R. S.; Welsh, E. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5377.

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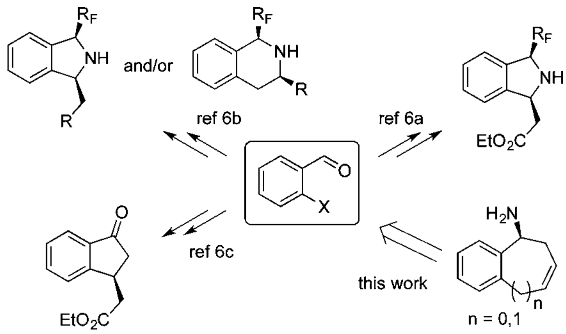
Scheme 1. DOS Strategy on 2-Halobenzaldehyde



i.e. structures more commonly found in natural products or drugs (Figure 1).

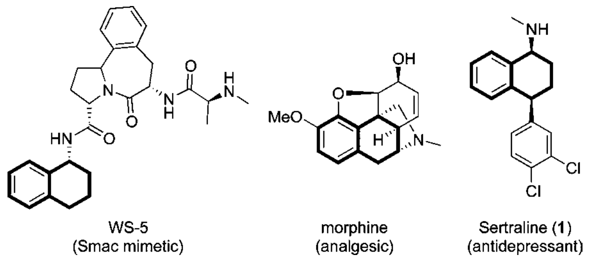
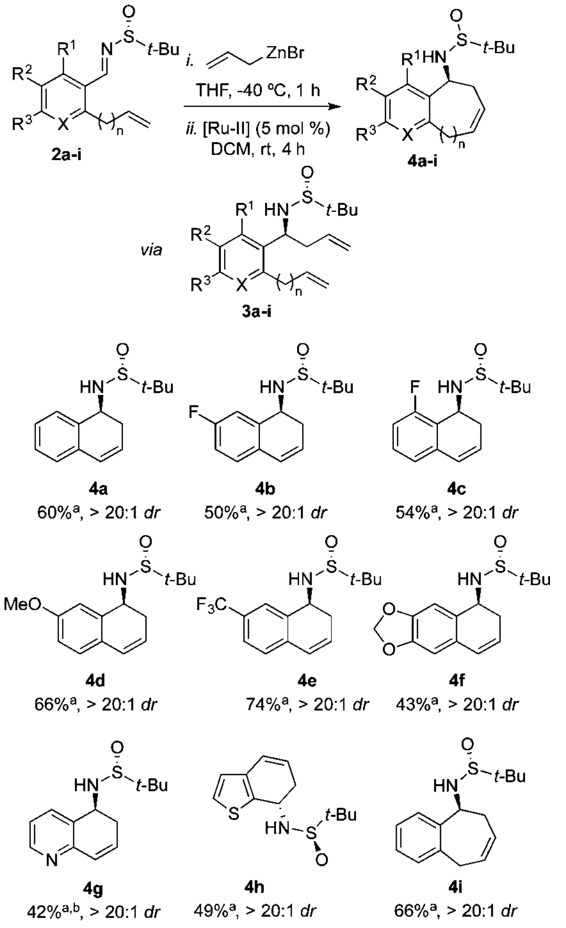


Figure 1. Tetrahydronaphthalene containing natural products and pharmaceuticals.

An example of such tetrahydronaphthalene derivatives is Sertraline (Figure 1, **1**), a selective serotonine reuptake inhibitor (SSRI) antidepressant.[7] Sertraline has attracted a great deal of interest, and several asymmetric syntheses have been reported in the literature.[8] However, only a few analogs have been described; specifically, no derivative on the tetrahydronaphthalene ring has been reported. On the other hand, the development of one-pot processes is of pivotal importance in modern organic synthesis, as they entail a minimum number of manipulations, including chromatographic purifications, resulting in the optimization of the amount of solvents, energy, and working time. The design of such one-pot processes requires the careful evaluation of functional groups, solvents, and reactant compatibility. Very recently, we have reported a relay catalysis approach to cyclic homoallylic alcohols.[9] Our interest in benzo-fused systems prompted us to design an analogous strategy for the synthesis of the parent amines.

Scheme 2. Scope of the Stepwise Allylation/RCM Sequence



[a] Overall yield for the two steps; experiments were typically carried out in a 0.30 mmol scale (for details on the yields for each step see Supporting Information). [b] For the RCM step, formation of the corresponding iminium salt by pretreatment with PTSA in refluxing DCM was required.

Readily available sulfinimes **2a**–**i** were submitted to the stepwise protocol[10] giving rise to the desired products in good overall yields, in most of the cases, and complete diastereoselectivity (Scheme 2).[11] Electron-donating (**2d**,**f**), electron-withdrawing (**2e**), and fluorine substituents (**2b**,**c**)

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(6) (a) Fustero, S.; Moscardó, J.; Sánchez-Roselló, M.; Rodríguez, E.; Barrio, P. *Org. Lett.* **2010**, *12*, 5494. (b) Fustero, S.; Ibañez, I.; Barrio, P.; Maestro, M. A.; Catalán, S. *Org. Lett.* **2013**, *15*, 832. (c) Fustero, S.; Rodríguez, E.; Herrera, L.; Asensio, A.; Maestro, M. A.; Barrio, P. *Org. Lett.* **2011**, *13*, 6564.

(7) (a) Welch, W. M.; Kraska, A. R.; Sarges, R.; Koe, B. K. *J. Med. Chem.* **1984**, *27*, 1508. (b) Williams, M.; Quallich, G. *Chem. Ind. (London)* **1990**, *10*, 315. (c) Quallich, G. J.; Woodall, T. M. *Tetrahedron* **1992**, *48*, 10239. (d) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373. (e) Johnson, B. M.; Chang, P.-T. L. *Anal. Profiles Drug Subst.* **1996**, *24*, 443.

(8) For some selected examples, see: (a) Lee, S. H.; Kim, I., S.; Li, Q. R.; Dong, G. R.; Jeong, L. S.; Jung, Y. H. *J. Org. Chem.* **2011**, *76*, 10011. (b) Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 879. (c) Han, Z.; Wang, Z.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5345. (d) Alexakis, A.; Hajjaji, S. E.; Polet, D.; Rathgeb, X. *Org. Lett.* **2007**, *9*, 3393. (e) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028. (f) Nair, V.; Rajan, R.; Rath, N. P. *Org. Lett.* **2002**, *4*, 1575. (g) Lautens, M.; Rovis, T. *Tetrahedron* **1999**, *55*, 8967. (h) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373.

(9) Fustero, S.; Rodriguez, E.; Lázaro, R.; Herrera, L.; Catalán, S.; Barrio, P. *Adv. Synth. Catal.* **2013**, *355*, 1058.

(10) For optimization of the experimental conditions, see Supporting Information.

(11) *S* absolute configuration was assumed for all products in agreement with Ellman's proposed transition state; see: Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883.

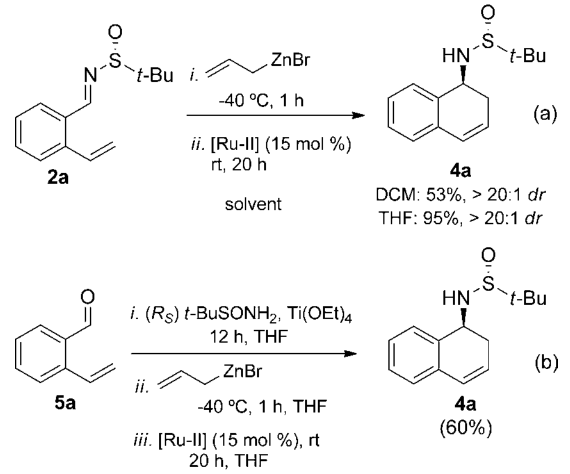
are tolerated on the aromatic ring. Moreover, heteroaromatic imines are also compatible with the reaction conditions (**2g**,**h**). Finally, the introduction of an allyl chain in the *ortho* position allows for the synthesis of seven-membered benzo-fused products (**2i**).

In order to increase the efficiency of the methodology, we studied the one-pot procedure. For this goal, several compatibility issues have to be addressed, namely: (1) functional groups present in the starting materials **2** and the intermediates **3** are compatible with all the reactants; (2) both steps (allylation and RCM) have been described in common solvents such as THF and DCM;[12] (3) both steps are clean and conversion takes place in an efficient manner, avoiding the formation of byproducts, which could interfere in the next reaction step. Our major concern was the compatibility between organozinc species and ruthenium metathesis catalysts, which has never been described to the best of our knowledge. Hence, the one-pot procedure was tested in both DCM and THF as solvents using **2a** as the model substrate (Scheme 3, equation a).

To our delight, the one-pot procedure in THF gives rise to product **4a** in an excellent 95% yield and equally high diastereoselectivity. Despite the apparent complete compatibility between the allylzinc species and the ruthenium catalyst, a higher catalyst loading is required and the reaction is much slower (20 vs 4 h). In addition, the catalyst must be loaded in three 5 mol % portions, as deactivation is observed.[13] Thus, some kind of interaction between the two organometallic species is actually taking place.

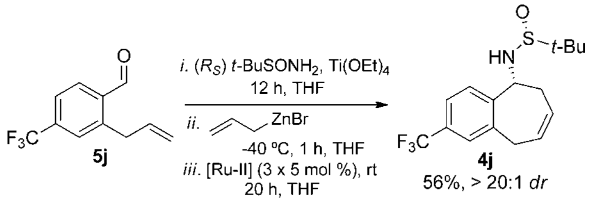
In a further development stage, we tested the one-pot procedure starting from aldehyde **5a** as the compatibility of titanium alkoxyde with both organozinc reagents[14] and ruthenium based metathesis catalysts[15] as well as the use of THF as solvent for the condensation step have been reported.[16] Our initial experimental conditions lead to a promising 45% yield for the three steps. In view of the excellent yield obtained for the allylation/RCM sequence (see Scheme 3, equation a) the drop in chemical yield may be caused by the interaction between the excess $Ti(OEt)_4$ and the allylzinc bromide. Therefore, an optimization of the number of equivalents of $Ti(OEt)_4$ was carried out[17] showing that the use of 2 equiv led to an improved 60% yield comparable with the 63% obtained in the stepwise procedure but only requiring one isolation step and one chromatographic purification resulting in time, solvent, and personnel optimization (Scheme 3, equation b).

Scheme 3. One-Pot Procedures



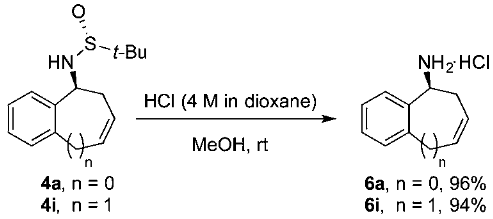
To show the applicability of this one-pot procedure, it was used in the synthesis of the new seven-membered analogue **4j** in a global 56% yield, in three steps (Scheme 4).

Scheme 4. Application of the One-Pot Strategy for the Synthesis of the Seven-Membered Analog **4j**



Deprotection under standard conditions was carried out on representative products **4a** and **4i** giving rise to the corresponding chlorohydrates **6a** and **6i** in excellent yields (Scheme 5).

Scheme 5. Deprotection of Some Representative Substrates



Finally, the methodology was challenged in the formal synthesis of the antidepressant Sertraline and the epimeric Norsertraline (Scheme 6). During the scale-up, we found out that an improved yield of **4a** (85%) could be obtained by using crude **2a** in the allylation/RCM one-pot procedure. After some fruitless efforts aimed at the introduction of the 3,4-dichlorophenyl moiety by means of an

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(12) For examples of allylations in DCM and THF, see: (a) van der Sluis, M.; Broxterman, Q. B. *Org. Lett.* **2001**, *3*, 3943. (b) Sun, X. W.; Xu, M. H.; Lin, G. Q. *Org. Lett.* **2006**, *8*, 4979. For examples of RCM in DCM and THF, see: (c) Leduc, A. B.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 7945. (d) Grainger, R. S.; Welsh, E. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5377.

(13) At a larger reaction scale (10 mmol) 3 × 2 mol % portions may be used without affecting the final yield.

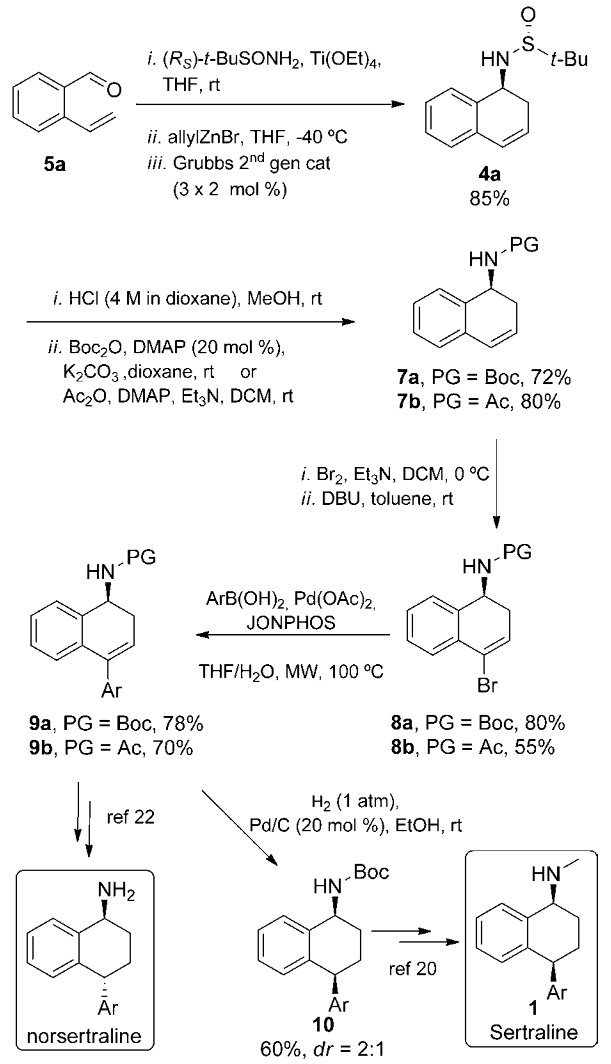
(14) Forrat, V. J.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2009**, *20*, 65.

(15) Fustero, S.; Monteagudo, S.; Sánchez-Roselló, M.; Flores, S.; Barrio, P.; del Pozo, C. *Chem.—Eur. J.* **2010**, *16*, 9835.

(16) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

(17) For details, see Supporting Information.

Scheme 6. Formal Total Syntheses of Sertraline and Norsertraline



intermolecular Heck reaction (see Supporting Information), a more conservative double bond preactivation strategy was adopted. Hence, a dibromination/debromination sequence lead to cross-coupling counterpart bromoolefin **8a**,**b**. The success of this step required protecting group exchange from *tert*-butylsulfinyl to either Boc or Ac; otherwise partial deprotection of the amine was observed.[18] A thorough optimization allowed us to identify high yielding Suzuki coupling conditions under microwave irradiation for the introduction of the 3,4-dichlorophenyl moiety.[19] Heterogenous hydrogenation of the double bond on Boc protected derivative **9a** gives rise to **10**, an intermediate in Chandrasekar's total synthesis of sertraline,[20] in poor 2:1 diastereoselectivity.[21] On the other hand, homogeneous hydrogenation of the acetylated derivative **9b**, an intermediate in Bäckvall's total synthesis of norsertraline,[22] using Crabtree's catay sts has been reported to proceed in excellent diastereoselectivity.[23]

In conclusion, a one-pot procedure for the asymmetric synthesis of cyclic benzo-fused homoallylic amines by diastereoselective allylation of Elllman's sulfinylimines followed by RCM has been developed. The methodology shows broad scope and is amenable for the three-step one-pot protocol starting from the corresponding aldehyde. While other syntheses of sertraline are very limited with respect to the introduction of functionalities in the aromatic ring of the tetrahydronaphthalene ring, our methodology is suitable for the preparation of analogs bearing substitution at the aromatic ring of the tetrahydronaphthalene core.

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Supporting Information Available. Detailed experimental procedures, optimization tables, and complete characterization data including ^{1}H, ^{13}C, and ^{19}F NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Overoxidation of the chiral auxiliary by bromine seems to be responsible for this undesired side reaction.

(19) See Supporting Information for details.

(20) Chandrasekhar, S.; Reddy, M. V. *Tetrahedron* **2000**, *56*, 1111.

(21) Compound **10** is obtained in five steps from **5a** in 23% global yield (2:1 *dr*), while in Chandraserkar's synthesis the global yield is 22% (9:1 *dr*) for seven steps starting from phenylglycine limiting its applicability for the synthesis of analogs.

(22) Thalén, L. K.; Zhao, D.; Sortais, J.-B.; Paetzold, J.; Hoben, C.; Bäckvall, J. E. *Chem.—Eur. J.* **2009**, *15*, 3403.

(23) Compound **9b** is obtained in four steps from **5a** in 26% global yield, while in Bäckvall's synthesis the global yield is 31% for four steps starting from racemic 1,2,3,4-tetrahydro-1-naphthylamine which is in turn acetylated under chemoenzymatic dynamic kinetic resolution (DKR) conditions. Once again, the applicability of this strategy for the synthesis of derivatives is limited.

The authors declare no competing financial interest.