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Stereodivergent Synthesis of 1,3-*syn*- and -*anti*-Tetrahydropyrimidinones

Michael Morgen, Sebastian Bretzke, Pengfei Li, and Dirk Menche*

University of Heidelberg, Department of Organic Chemistry, INF 270, D-69120 Heidelberg, Germany

dirk.menche@oci.uni-heidelberg.de

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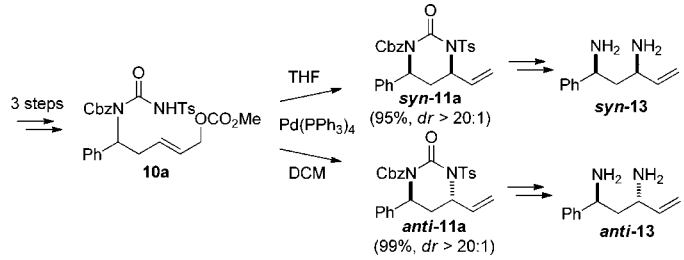
ABSTRACT



An efficient protocol for the stereoselective synthesis of 1,3-*syn* and -*anti*-tetrahydropyrimidinones (*syn*- and *anti*-11a) is reported. The modular procedure is based on a stereodivergent cyclization of readily available urea-type substrates (10a) by intramolecular allylic substitution. The cyclization proceeds with excellent yield (up to 99%) and selectivity (up to dr > 20:1), purely based on substrate control. The product pyrimidines can be readily transformed into the corresponding free *syn*- and *anti*-amines.

The chiral 1,3-diamine motif constitutes an important structural element in various bioactive natural products and medicinal compounds.[1] Prominent examples include the marine alkaloids batzelladines (**1**, Figure 1)[2] or HIV-1 protease inhibitors, such as A-74704 (**2**).[3] It is also present in the chiral core of ligands and synthetic reagents.[4] Because of its prevalence, there are a number of strategies for the construction of such systems.[5,6] However, they are primarily based on reduction protocols of suitable precursors, including diimines,[6b] pyrazolidines,[6c,d] pyrimidines,[6e] azides,[6f] or

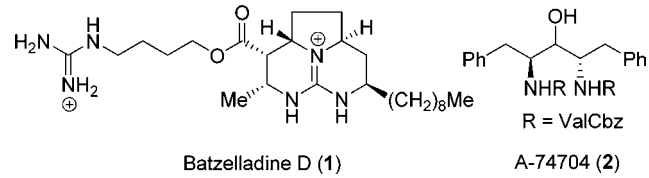


Figure 1. Chiral 1,3-diamine motif: a key element in the natural product batzelladine D (**1**) and the HIV-protease inhibitor A-74704 (**2**).

(1) For examples of bioactive 1,3-amines of natural or synthetic origin, see: (a) Jahn, T.; König, G. M.; Wright, A. D. *Tetrahedron Lett.* **1997**, *38*, 3883. (b) When, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950. (c) Kammermeier, T.; Wiegrebe, W. *Arch. Pharm.* **1995**, *328*, 409. (d) Vickery, K.; Bonin, A. M.; Fenton, R. R.; O'Mara, S.; Russell, P. J.; Webster, L. K.; Hambley, T. W. *J. Med. Chem.* **1993**, *36*, 3663.

(2) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512.

(3) Erickson, J.; Neidhart, D. J.; VanDrie, J.; Kempf, D. J.; Wang, X. C.; Norbeck, D. W.; Plattner, J. J.; Rittenhouse, J. W.; Turon, M.; Wideburg, N.; Kohlbrenner, W. E.; Simmer, R.; Helfrich, R.; Paul, D. A.; Knigge, M. *Science* **1990**, *249*, 527.

(4) For examples, see: (a) Ozaki, S.; Mimura, H.; Yasuhara, N.; Masui, M.; Yamagata, Y.; Tomita, K. *J. Chem. Soc., Perkin Trans. 2* **1990**, 353. (b) Pini, D.; Mastantuono, A.; Uccello-Baretta, G.; Iuliano, A.; Salvatori, P. *Tetrahedron Lett.* **1993**, *49*, 9613.

(5) For a recent review on chiral amine synthesis, see: Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753.

(6) (a) Merla, B.; Risch, N. *Synthesis* **2002**, 1365. (b) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1983**, *48*, 2255. (c) Alexakis, A.; Lensen, N.; Tranchier, J.-L.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 4563. (d) Denmark, S. E.; Kim, J.-H. *Synthesis* **1992**, 229. (e) Barluenga, J.; Tomas, M.; Kouznetsov, V.; Pardon, J.; Rubio, E. *Synlett* **1991**, 821. (f) Enders, D.; Jegelka, U.; Dücker, B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 423. (g) Merla, B.; Arend, M.; Risch, N. *Synlett* **1997**, 177. (h) Trost, B. M.; Malhotra, S.; Olson, D. E.; Maruniak, A.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 4190.

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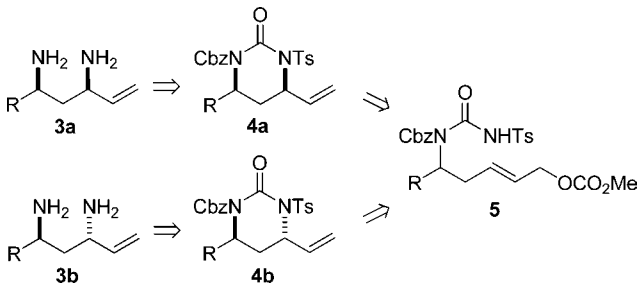
quaternary immonium salts, generated in situ by aminoalkylation of enamines.[6g] Recently, also a sequential process has been reported involving an asymmetric allylic amination and subsequent formation and opening of an aziridine intermediate.[6g] Inspired by the natural products in combination with certain limitations of existing methods, in particular with respect to modularity and convergence, herein we report a more direct and flexible procedure for 1,3-*diamine* synthesis, based on a stereodivergent intramolecular allylic substitution reaction.[7]

Our conceptually novel approach relies on an intramolecular allylic substitution reaction[8,9] of acyclic urea derivatives of type **5**, as shown in Scheme 1. Depending on suitable

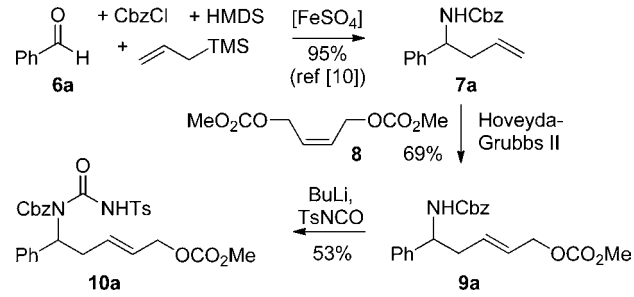
Scheme 1. Concept for a Stereodivergent Cyclization to *syn*- and *anti*-Tetrahydropyrimidinones and the Respective Free Diamines



reaction conditions, it was envisioned that they might enable access to both 1,3-*syn*- and -*anti*-tetrahydropyrimidinones (**4a** and **4b**) in a diastereodivergent fashion. Subsequently, these heterocycles may then be cleaved to the corresponding *syn*- or *anti*-amines **3a**/**3b**. Notably, this synthetic concept is highly flexible and convergent and thus offers the potential to be readily adopted to natural products and pharmaceuticals.

As shown in Scheme 2, the required urea substrates were obtained in a straightforward sequence in three steps from commercial material. As depicted for phenyl analogue **10a**, the synthesis was based on a known four-component reaction developed by Tian,[10] which involves condensation of aldehyde **6a** with benzyl chloroformate (CbzCl), hexamethyld-

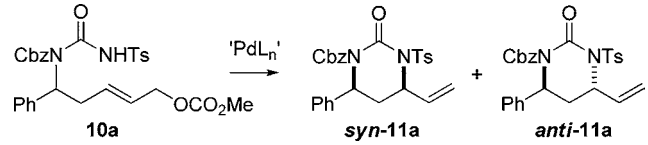
Scheme 2. Three-Step Preparation of Urea Substrate **3**



isilazide (HMDS), and allyltrimethylsilane in the presence of catalytic amounts of iron(II) sulfate to access homoallylic amines of type **7a** in high yields. Subsequent homologation with allylcarbonate **8** by cross metathesis proceeded smoothly in the presence of Hoveyda−Grubbs catalyst II. Finally, attachment of tosylisocyanat proceeded with preparatively useful yields by use of strong bases.[11−13]

To test our notion for a stereoselective intramolecular allylic substitution, **10a** was submitted to various reaction conditions. As shown in Table 1 (entry 1), initial attempts

Table 1. Diastereodivergent Cyclization of Urea Derivative **10a** to *syn*- and *anti*-Tetrahydropyrimidinones **11a**



entry	"PdL_n"	conditions	*syn*/*anti*-**11a**[a]	conversion [%][b]
1	$Pd_2(dba)_3$·$CHCl_3$/ $(^iPrO)_3P$	THF, rt, 10 min	1:1	>95%
2	$Pd_2(dba)_3$·$CHCl_3$/ $EtC(CH_2O)_3P$	ACN, rt, 10 min	1:12	>95%
3	$Pd(PPh_3)_4$	THF, rt, 10 min	20:1	>95%
4	$Pd(PPh_3)_4$	toluene, rt, 10 min	4:1	>95%
5	$Pd(PPh_3)_4$	Et_2O, rt, 10 min	2:1	>95%
6	$Pd(PPh_3)_4$	DCM, rt, 10 min	1:20	>95%
7	$Pd(PPh_3)_4$	ACN, rt, 10 min	1:10	>95%

[a] Ratio was determined by ^1H NMR of the crude products. [b] Conversion determined by NMR spectroscopy.

were based on Pd/phosphite catalyst (entry 1) which resulted in smooth cyclization to the desired product tetrahydropyrimidinones **11a**, albeit with no stereoselectivity. However,

(7) For previous work from our group on direct stereoselective amine synthesis, see :(a) Menche, D.; Hassfeld, J.; Li, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* **2006**, *8*, 741. (b) Menche, D.; Arikan, F.; Li, J.; Rudolph, S. *Org. Lett.* **2007**, *9*, 267.

(8) For reviews on allylic substitution reactions, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(9) For examples of syntheses of nitrogen-containing heterocycles by intramolecular allylic substitutions, see: (a) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Oh, C.-Y.; Ham, W.-H. *J. Org. Chem.* **1999**, *64*, 9450. (b) Butler, D. C.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887. (c) Amador, M.; Ariza, X.; Garcia, J.; Sevilla, S. *Org. Lett.* **2002**, *4*, 4511. (d) Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Dübon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239. (e) Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc.* **2006**, *128*, 6745. (f) Broustal, G.; Ariza, X.; Campagne, J.-M.; Garcia, J.; Georges, Y.; Marinetti, A.; Robiette, R. *Eur. J. Org. Chem.* **2007**, 4293. (g) Gnamm, C.; Krauter, C.; Brödner, K.; Helmchen, G. *Chem.—Eur. J.* **2009**, *15*, 2050. (h) For a related process, see; Muñiz, K.; Streuff, J.; Chávez, P.; Hövelmann, C. H. *Chem. Asian J.* **2008**, *3*, 1248.

(10) Song, Q.-Y.; Yang, B.-L.; Tian, S.-K. *J. Org. Chem.* **2007**, *72*, 5407.

(11) Weaker bases (NEt_3, LHMDS, DBU, proton sponge) and less electron-deficient isocyanates resulted in lower degrees of conversion.

(12) For recent related amination reactions with urea substrates, see ref 9h and: Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707.

(13) For an amination reaction using a tosyl amide, see: Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978.

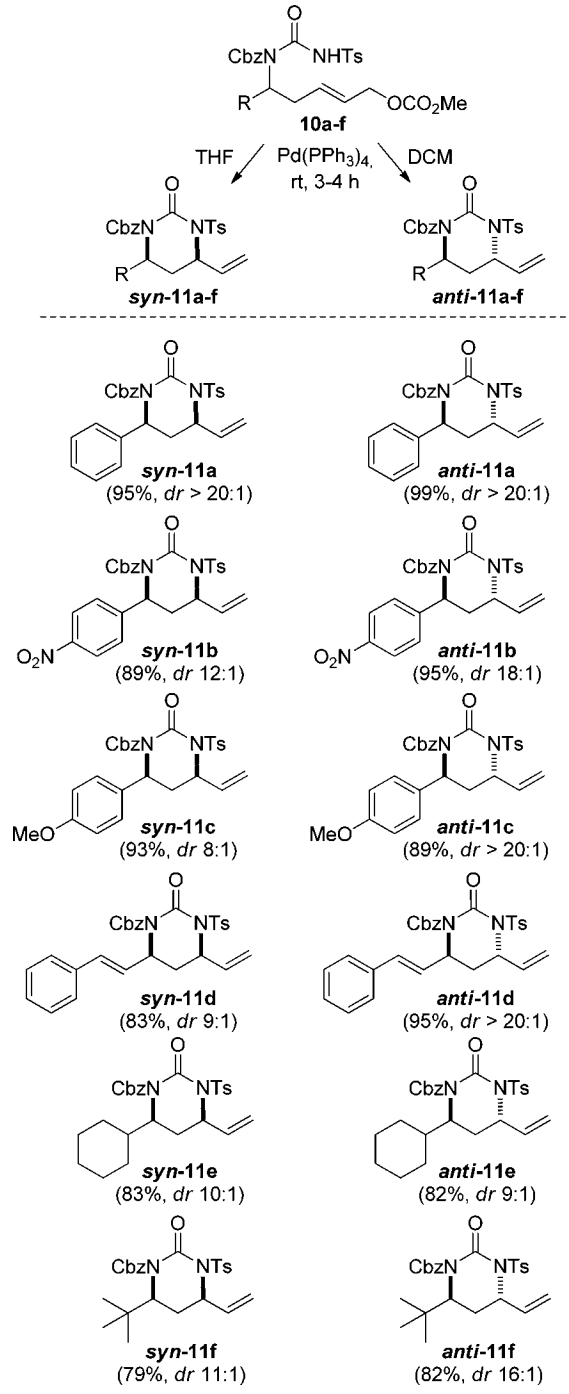
a more elaborate phosphite ligand in combination with $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ resulted in a distinct preference of either the *syn*- or *anti*-diastereomer (entries 2 and 3), again with very high degrees of conversion. Due to the ready commercial availability of the latter catalyst, further optimizations were carried out with $Pd(PPh_3)_4$. As shown in entries 3−7, the solvent had a critical influence on the stereochemical outcome of the reaction. Best results to access the *syn*-isomer were obtained in THF (entry 3), while the *anti*-diastereomer was effectively generated in DCM (entry 6).[14,15]

To assess the generality of this procedure for stereoselective synthesis of *syn*- and *anti*-tetrahydropyrimidinones, various substrates with different electronic and steric properties were evaluated.[16] As shown in Scheme 3, cyclization proceeded in all cases with good yields and selectivities, without the necessity of further adopting the procedure to specific substrates. This demonstrates the general usefulness of our protocol for the modular and stereoselective synthesis of 1,3-*syn*- and -*anti*-tetrahydropyrimidinones. It should be noted that, in contrast to previous work,[9] our procedure enables a much more concise and direct entry into heterocycles. Also, both the *syn*- and *anti*-diastereomer can be obtained with excellent yields and asymmetric induction, purely based on substrate control in a divergent manner from the same substrate.

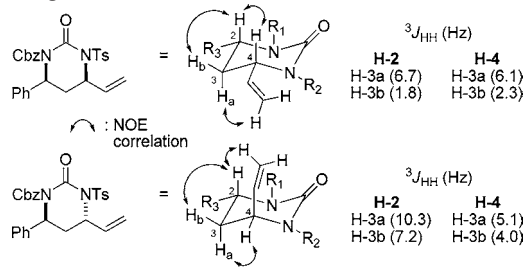
Finally, the applicability of this procedure also for preparation of the respective free amines was demonstrated. As depicted in Scheme 4 for substrates *syn*- and *anti*-**11a**, the tetrahydropyrimidinones may be readily converted to the respective *syn*- and *anti*-amines **14**. Notably, selective deprotection of the two amine moieties is possible. This involves first deprotecting the "left" nitrogen by removal of the Cbz group with TMSI giving **12** in high yields for both the *syn*- and *anti*-diastereomer.[17] Subsequent treatment with magnesium/MeOH then removes the tosyl substituent liberating the remaining amide moiety, giving *syn*- and *anti*-**13** in essentially quantitative yields. Finally, cleavage of the urea can be effected under acidic conditions to give the free diamines **14**.[18] These conversions likewise proceeded with good yields,[19] which demonstrates the ready adaptability of our procedure for stereoselective amine synthesis.

In summary, we have devised a novel method for the stereoselective synthesis of 1,3-*syn*- and -*anti*-tetrahydropyrimidinones and their conversion to the corresponding

Scheme 3. Diastereodivergent Tetrahydropyrimidinone Synthesis



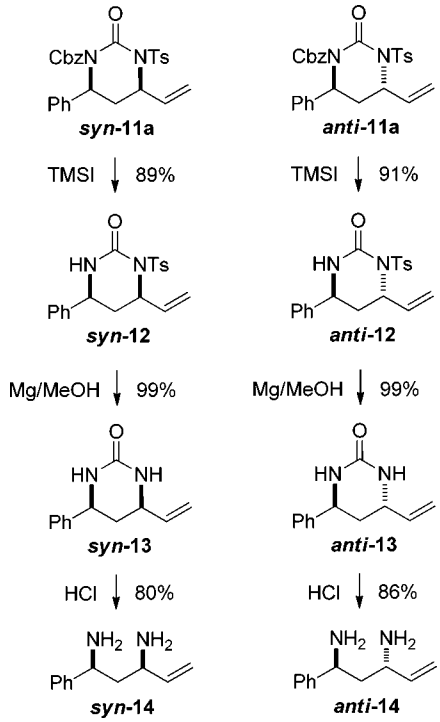
(14) In all cases, stereochemical assignment was based on NMR methods, e.g.:



(15) Potentially, this pronounced solvent effect may be rationalized by a reversal of the enantiofacial bias of the allylic substitution reaction. Presumably, in THF a conventional attack of the nucleophile on the side opposite to the π-allyl complex is expected, leading to an inversion at the configuration of the respective carbon center. In contrast to THF, the nucleophilic amide should be much less solvated in DCM. Possibly, the nucleophile may then directly attack the π-allyl intermediate on the same side as the cationic π-allyl complex, based on attractive charge−charge interactions. This would then lead to retention of the configuration . For a recent mechanistic study with "hard" and "soft" nucleophiles in allylic substitution reactions, see: Shintani, R.; Tsuji, T.; Park, S.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7508.

(16) All required urea substrates (**10a**−**f**) were readily prepared by four-component coupling, in analogy to Scheme 2, by using either the method of Tian (ref 10) or: Phukan, P. *J. Org. Chem.* **2004**, *69*, 4005. For full details: see Supporting Information.

Scheme 4. Selective Stepwise Cleavage of Tetrahydropyrimidinones to 1,3-*syn*- and -*anti*-Amines



free amines. The procedure is based on an intramolecular allylic substitution reaction of readily available urea-type substrates (**5**). Depending on reaction conditions, either the *syn*- or *anti*-diastereomer can be obtained with good to excellent yields and asymmetric induction, purely based on substrate control. These results may find useful applications in natural product synthesis or medicinal chemistry and stimulate further studies for direct asymmetric amine synthesis.

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Supporting Information Available: Experimental details, spectral data, and copies of 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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(17) Bolós, J.; Pérez-Beroy, Á.; Gubert, S.; Anglada, L. *Tetrahedron* **1992**, *48*, 9567.

(18) (a) Kumar, V.; Ramesh, N. G. *Tetrahedron* **2006**, *62*, 1877. (b) Dunn, P. J.; Häner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017.

(19) In contrast, efforts to remove the urea under similar conditions at the stage of **11** or **12** resulted in only low degrees of conversion.