Multicomponent Reactions

DOI: 10.1002/anie.201107831

A Catalytic Multicomponent Approach for the Stereoselective Synthesis of *cis*-4,5-Disubstituted Pyrrolidinones and Tetrahydro-3*H*-pyrrolo[3,2-*c*]quinolines**

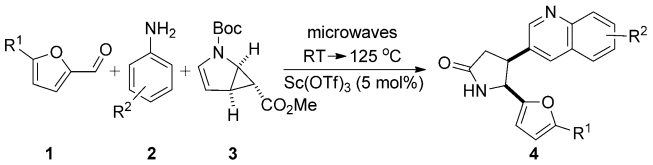
*Sudipta Roy and Oliver Reiser**

Dedicated to Professor Lutz F. Tietze on the occasion of his 70th birthday

Pyrrolidinones are privileged structures in pharmaceutical development.[1] In particular, *cis*-4,5-disubstituted pyrrolidinones containing aromatic and heteroaromatic groups were identified as lead structures for inhibition of type II 17β-hydroxysteroid dehydrogenase, which is implicated in the treatment of osteoporosis.[1a] Likewise, *cis*-4,5-diarylated pyrrolidinones have been reported to inhibit transcription factor HOXA13,[1c] a regulator of mammalian development[2] and of certain cancer types.[3]

While many synthetic approaches are available for the synthesis of substituted pyrrolidinones,[4–10] only a few methods exist towards the *cis*-4,5-substitution pattern.[1a,6a,b,7,10] Moreover, multicomponent reactions, which are especially powerful methods for creating molecular complexity and diversity,[11] for the synthesis of pyrrolidinones are scarce in general.[9a,d]

Donor–acceptor-substituted cyclopropanes have proven to be of great utility in synthetic organic chemistry.[12] The cyclopropanation of furans and pyrroles with ethyl diazoacetate provides a facile entry to this class of compounds in diastereomerically and enantiomerically pure form.[13] Based on the monocyclopropanated *N*-Boc-protected pyrrole **3** (Boc = *tert*-butoxycarbonyl), we report herein an efficient Lewis acid catalyzed multicomponent assembly with readily available furancarbaldehydes **1** and aromatic amines **2** to afford synthetically challenging *cis*-4,5-disubstituted pyrrolidinones **4** in high yield with excellent stereoselectivity (Scheme 1).



Scheme 1. Stereoselective synthesis of *cis*-4,5-disubstituted pyrrolidinones.

Among a number of Lewis acids that were screened,[14] we found that $Sc(OTf)_3$ (5 mol%) under microwave (MW) irradiation is best suited for this process, which combines a Povarov reaction,[15] donor–acceptor-induced cyclopropane ring opening, a 1,4-furan ring migration, and quinoline formation. For the majority of transformations investigated (±)-**3** was employed; nevertheless, employing enantiopure (+)-**3** (Table 1, entry 1) gives rise to **4a** with no erosion of stereochemistry. Both electron-withdrawing and -donating substituents on aniline **2** are tolerated well, allowing the generation of a variety of quinoline moieties in 4-position of the pyrrolidinone (Table 1, entries 2–7, 9–11). Out of the two regioisomers possible when 3-substituted anilines are employed (entries 5 and 7), only the sterically less-hindered quinoline placing that group in 7- rather than 5-position is formed. When the sterically more crowded 5-position cannot be avoided, the product yield significantly decreases as demonstrated when 3,5-dimethyl aniline is used as substrate (entry 6). Replacement of anilines with 1-napthylamine resulted in the corresponding benzo[h]quinoline moiety instead of a quinoline (entry 8). Also, phenyl substitution in the 5-position of furans is tolerated well (entries 9–11). The structural assignment of pyrrolidinones **4** (Table 1, entries 1 and 10) was confirmed unambiguously by single-crystal X-ray analysis of **4a** and **4j** (see the Supporting Information).

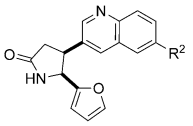
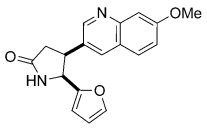
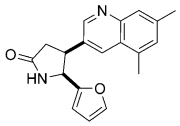
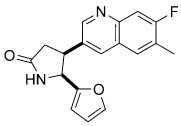
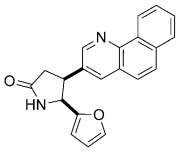
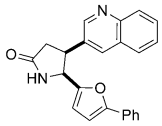
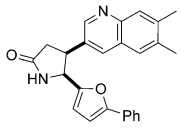
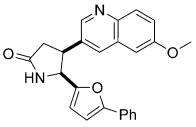
A plausible mechanism for the synthesis of **4** (Scheme 2) involves an initial Povarov reaction[15] of aldimine **5** onto enamide **3** at its convex face to give rise to **6**. Interestingly, the bicyclic structure of **3** must also control the stereochemistry of the carbon center the furan group is located, which is found on the *endo* face of the bicyclo[4.3.0] ring system, being opposite as found in Povarov reactions with simple 2,3-dihydrofuran or 2,3-dihydro-1*H*-pyrroles.[15a] As a consequence of this stereochemical outcome, the disfavored *cis*-configured aldimine **5** rather than the *trans* isomer would have to undergo if the reaction would proceed by a concerted cycloaddition, making a stepwise sequence (Mannich reaction followed by aromatic electrophilic substitution) more likely as recently suggested by elegant mechanistic studies with enecarbamates as dienophiles in the Povarov reaction.[15f,g] Subsequent formation of iminium ion **7** by $Sc(OTf)_3$-mediated cyclopropane ring opening followed by furan migration

[*] M. Sc. S. Roy, Prof. Dr. O. Reiser
Institut für Organische Chemie, Universität Regensburg
Universitätsstrasse 31, 93053 Regensburg (Germany)
E-mail: oliver.reiser@chemie.uni-regensburg.de

[**] This work was supported by the DAAD. We thank Dr. M. Zabel and S. Stempfhuber, Department of Crystallography, Universität Regensburg, for carrying out the X-ray crystal structure analysis and H. Konkel for carrying out HPLC measurements

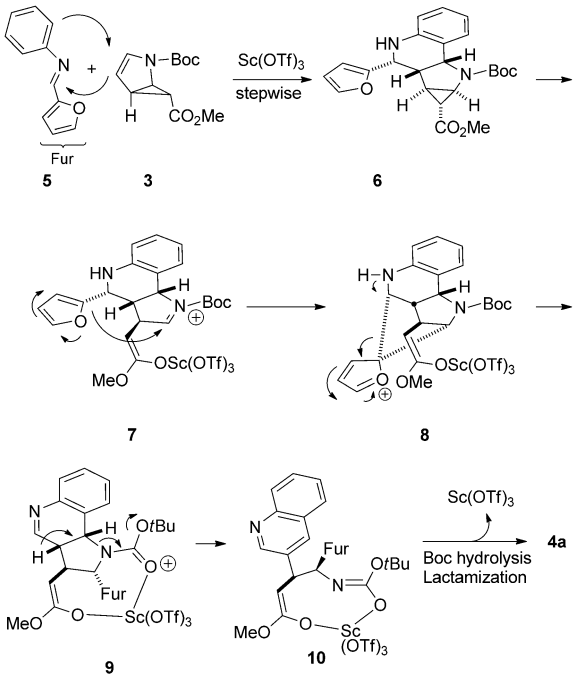
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201107831.

Table 1: Sc(OTf)$_3$-catalyzed multicomponent reactions of **1**–**3**.[a]

Entry	R^1 in **1**	R^2	Product **4**		*t* [h]	Yield [%][b]
1[c]	H	H		**4a**	6.0	82
2	H	4-F		**4b**	5.0	76
3	H	4-OMe		**4c**	5.5	75
4	H	4-NO_2		**4d**	4.0	83
5	H	3-OMe		**4e**	5.5	65
6	H	3,5-Me_2		**4f**	6.0	38
7	H	3-F, 4-Me		**4g**	4.5	84
8	H	1-naphthyl		**4h**	5.5	77
9	Ph	H		**4i**	5.5	71
10	Ph	3,4-Me_2		**4j**	5.5	69
11	Ph	4-OMe		**4k**	5.5	74

[a] **1** (0.40 mmol), **2** (0.40 mmol), **3** (0.33 mmol), Sc(OTf)$_3$ (5 mol%), 1.5 h room temperature, 3–4.5 h 125 °C. [b] Yield of isolated product. [c] (+)-**3** was employed, **4a** was obtained in enantiomerically pure form.

via a spiroannulated intermediate[16] **8** leads to **9**, which undergoes rearomatization that requires an unusual C–N bond cleavage to give rise to **10** that finally collapses to the pyrrolidinone **4a** upon *N*-Boc hydrolysis and lactamization. Indeed, the Povarov products **6** (as shown for **6a**, Scheme 3) could be obtained by carrying out the reaction at ambient temperature rather than at reflux conditions. Notable, both *endo* and *exo* epimers with respect to the stereochemistry of the furan substituent, which is readily separated on silica, were isolated. Subjecting *endo*- and *exo*-**6a** individually to those conditions, *endo*-**6a** cleanly rearranged to the previously obtained pyrrolidinone **4a**, while *exo*-**6a** yielded the ring-opened polycyclic imine **11**, indicating that the specific conformational arrangement of the *endo*-**6a** is optimal for the rearrangement to proceed. In the case of *exo*-**6a**, the bridge

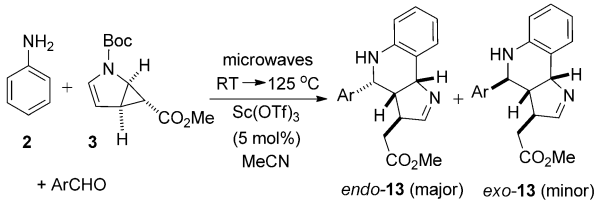


Scheme 2. Mechanism for the synthesis of substituted pyrrolidinones **4**.

H-atoms on the neighboring ring junction presumably block the furan migration to the iminium center.

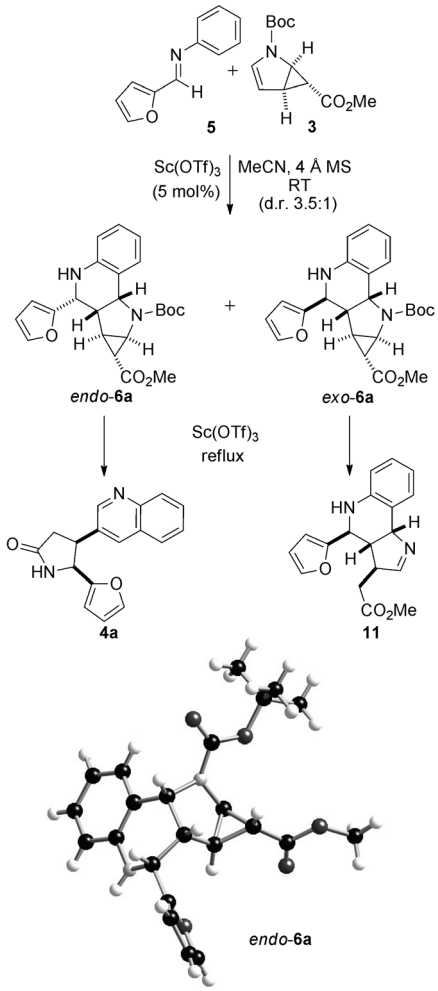
If other aromatic aldehydes but furans were employed, stable polycyclic imines **13** were obtained as a diastereomeric mixture in very good overall yields (Table 2), suggesting that the furan moiety is unique for the observed migration. The structure of **13a** (Table 2, entry 1) was unequivocally established by single-crystal X-ray analysis (see the Supporting Information).

Table 2: Synthesis of tricyclic imines **13**.



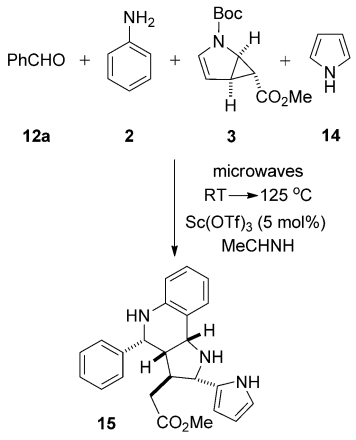
Entry	Ar	**13**[a,b]	*t* [h]	Yield [%][c]	d.r.[d]
1	Ph	**13a**	3.5	64	2:1
2	4-ClC_6H_4	**13b**	3.0	69	2.5:1
3	4-MeC_6H_4	**13c**	3.0	61	2:1
4	4-$MeOC_6H_4$	**13d**	3.0	60	2:1
5	4-$NO_2C_6H_4$	**13e**	2.5	65	2:1
6	1-naphthyl	**13f**	2.0	70	2.6:1
7	2-thionyl	**13g**	1.0	53	1.5:1

[a] Major diastereomer, separated by column chromatography. [b] Stereochemistry determined by analogy to Table 2, entry 1. [c] Yield of isolated major diastereomer. [d] Determined by ^{1}H NMR spectroscopy.



Scheme 3. Top: Povarov reaction between **5** and **3** and subsequent rearrangement. M.S. = molecular sieves. Bottom: Crystal structure of *endo*-**6a**; C back, H white, N light gray, O dark gray.

This result opens up the opportunity for a four-component reaction by introducing suitable external nucleophiles that could add to the imine functionality in **13**. Indeed, $Sc(OTf)_3$ catalyzed multicomponent reactions between benzaldehyde (**12a**), aniline **2**, enamide **3**, and pyrrole (**14**) resulted in the formation of addition product of imine **13a** and pyrrole (**14**) in quantitative yield as a mixture of four diastereomers (45:25:20:10), from which the major diastereomer **15** could be isolated in pure form in 42% yield (Scheme 4).



Scheme 4. Four-component reaction to give **15**.

In conclusion, we have developed an operationally simple, catalytic three-component assembly based on readily available furancarbaldehydes, anilines, and the monocyclopropanated adduct of *N*-Boc-pyrrole **3**. A range of functionalized *cis*-pyrrolidinones **4** was obtained this way in a stereoselective manner with high yield, which are relevant structural constituents in pharmacologically important molecules.

Received: November 7, 2011
Published online: March 27, 2012

Keywords: donor–acceptor systems · microwave chemistry · multicomponent reactions · pyrrolidinones · quinolines

[1] a) J. Wood, C. M. Bagi, C. Akuche, A. Bacchiocchi, J. Baryza, M. L. Blue, C. Brennan, A. M. Campbell, S. Choi, J. H. Cook, P. Conrad, B. R. Dixon, P. P. Ehrlich, T. Gane, D. Gunn, T. Joe, J. S. Johnson, J. Jordan, R. Kramss, P. Liu, J. Levy, D. B. Lowe, I. McAlexander, R. Natero, A. M. Redman, W. J. Scott, C. Town, M. Wang, Y. Wang, Z. Zhang, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4965; b) K. Tang, J. T. Zhang, *Neurol. Res.* **2002**, *24*, 473; c) P. Y. Ng, Y. Tang, W. M. Knosp, H. S. Stadler, J. T. Shaw, *Angew. Chem.* **2007**, *119*, 5448; *Angew. Chem. Int. Ed.* **2007**, *46*, 5352; d) A. Spaltenstein, M. R. Almond, W. J. Bock, D. G. Cleary, E. S. Furfine, R. J. Hazen, W. M. Kazmierski, F. G. Salituro, R. D. Tung, L. L. Wright, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159; e) P. A. Reddy, B. C. H. Hsiang, T. N. Latifi, M. W. Hill, K. E. Woodward, A. M. Rothman, J. A. Ferrendelli, D. F. Covey, *J. Med. Chem.* **1996**, *39*, 1898.

[2] R. Morgan, *Trends Genet.* **2006**, *22*, 67.

[3] a) I. G. Maroulakou, D. D. Spyropoulos, *Anticancer Res.* **2003**, *23*, 2101; b) D. G. Grier, A. Thompson, A. Kwasniewska, G. J. McGonigle, H. L. Halliday, T. R. Lappin, *J. Pathol.* **2005**, *205*, 154.

[4] Palladium-catalyzed cyclizations: a) D. Craig, C. J. T. Hyland, S. E. Ward, *Chem. Commun.* **2005**, 3439; b) D. Madec, G. Prestat, E. Martini, P. Fristrup, G. Poli, P. O. Norrby, *Org. Lett.* **2005**, *7*, 995; c) G. Poli, G. Giambastiani, M. Malacria, S. Thorimbert, *Tetrahedron Lett.* **2001**, *42*, 6287; d) S. Lee, J. F. Hartwig, *J. Org. Chem.* **2001**, *66*, 3402; e) K. H. Shaughnessy, B. C. Hammann, J. F. Hartwig, *J. Org. Chem.* **1998**, *63*, 6546.

[5] Rhodium-catalyzed C–H insertion: a) M. K. W. Choi, W. Y. Yu, C. M. Che, *Org. Lett.* **2005**, *7*, 1081 and references therein; b) C. H. Yoon, D. L. Flanigan, B. D. Chong, K. W. Jung, *J. Org. Chem.* **2002**, *67*, 6582, and references therein.

[6] Addition of homoenolates to imines: a) R. B. Lettan II, C. C. Woodward, K. A. Scheidt, *Angew. Chem.* **2008**, *120*, 2326; *Angew. Chem. Int. Ed.* **2008**, *47*, 2294; b) R. B. Lettan II, C. V. Galliford, C. C. Woodward, K. A. Scheidt, *J. Am. Chem. Soc.* **2009**, *131*, 8805; c) M. Abbas, C. Neuhaus, B. Krebs, B. Westermann, *Synlett* **2005**, 473; d) S. Okamoto, X. Teng, S. Fujii, Y. Takayama, F. Sato, *J. Am. Chem. Soc.* **2001**, *123*, 3462; e) E. DiMauro, A. J. Fry, *Tetrahedron Lett.* **1999**, *40*, 7945.

[7] NHC-catalyzed addition of enals to imines: M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131, and references therein.

[8] Ring expansion of β-lactams: J. H. Park, J. R. Ha, S. J. Oh, J. A. Kim, D. S. Shin, T. J. Won, Y. F. Lam, C. Ahn, *Tetrahedron Lett.* **2005**, *46*, 1755, and references therein.

[9] Cycloadditions: a) J. Wei, J. T. Shaw, *Org. Lett.* **2007**, *9*, 4077; b) Q. Wang, S. Nara, A. Padwa, *Org. Lett.* **2005**, *7*, 839; c) P. P.

Sun, M. Y. Chang, M. Y. Chiang, N. C. Chang, *Org. Lett.* **2003**, *5*, 1761; d) B. Beck, A. Picard, E. Herdtweck, A. Dömling, *Org. Lett.* **2004**, *6*, 39.

[10] a) S. H. Xiang, H. Q. Yuan, P. Q. Huang, *Tetrahedron: Asymmetry* **2009**, *20*, 2021; b) M. Pohmakotr, N. Yotapan, P. Tuchinda, C. Kuhakarn, V. Reutrakul, *J. Org. Chem.* **2007**, *72*, 5016; c) N. K. Yee, *Tetrahedron Lett.* **1997**, *38*, 5091.

[11] Selected examples: a) S. Santra, P. R. Andreana, *Angew. Chem.* **2011**, *123*, 9590; *Angew. Chem. Int. Ed.* **2011**, *50*, 9418; b) L.-M. Frederic, C. Thierry, R. Jean, *J. Am. Chem. Soc.* **2005**, *127*, 17176; c) S. L. Schreiber, *Science* **2000**, *287*, 1964; d) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259; e) B. M. Trost, *Science* **1991**, *254*, 1471; f) P. A. Wender, S. T. Handy, D. L. Wright, *Chem. Ind.* **1997**, 765; g) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**; h) *Domino Reactions in Organic Synthesis* (Eds.: L. F. Tietze, G. Brasche, K. Gericke), Wiley-VCH, Weinheim, **2006**; i) U. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168; j) L. Banfi, R. Riva, *Org. React.* **2005**, *65*, 1; k) M. Passerini, *Gazz. Chim. Ital.* **1921**, *51*, 181; l) A. Dömling, *Chem. Rev.* **2006**, *106*, 17; m) I. Ugi, R. Meyr, U. Fetzer, C. Steinbruckner, *Angew. Chem.* **1959**, *71*, 386; n) N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445; o) N. A. Petasis, I. Akritopoulou, *Tetrahedron Lett.* **1993**, *34*, 583.

[12] Selected Reviews: a) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051; b) H. U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151.

[13] a) E. Wenkert, M. Guo, R. Rodolfo, B. Porter, K. Ramachandran, J.-H. Sheu, *J. Org. Chem.* **1990**, *55*, 6203; b) S. R. Tanny, J. Grossman, F. W. Fowler, *J. Am. Chem. Soc.* **1972**, *94*, 6495; c) C. Böhm, O. Reiser, *Org. Lett.* **2001**, *3*, 1315; d) R. Beumer, C. Bubert, C. Cabrele, O. Vielhauer, M. Pietzsch, O. Reiser, *J. Org. Chem.* **2000**, *65*, 8960; e) M. Schinnerl, C. Böhm, M. Seitz, O. Reiser, *Tetrahedron: Asymmetry* **2003**, *14*, 765; f) C. Böhm, M. Schinnerl, C. Bubert, M. Zabel, T. Labahn, E. Parisini, O. Reiser, *Eur. J. Org. Chem.* **2000**, 2955; g) N. Koglin, C. Zorn, R. Beumer, C. Cabrele, C. Bubert, N. Sewald, O. Reiser, A. G. Beck-Sickinger, *Angew. Chem.* **2003**, *115*, 212; *Angew. Chem. Int. Ed. Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 202; h) A. Gheorghe, M. Schulte, O. Reiser, *J. Org. Chem.* **2006**, *71*, 2173; i) K. Harrer, O. Reiser, *Chem. Commun.* **2012**, *48*, 3457.

[14] See the Supporting Information.

[15] a) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986; b) L. S. Povarov, *Russ. Chem. Rev. Engl. Transl.* **1967**, *36*, 656; c) L. S. Povarov, V. I. Grigos, B. M. Makhailov, *Iz*V. *Akad. Nauk. SSSR* **1963**, 2039; d) L. S. Povarov, B. M. Makhailov, *Iz*V. *Akad. Nauk. SSSR* **1963**, 955; e) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598; f) G. Dagousset, F. Drouet, G. Masson, J. Zhu, *Org. Lett.* **2009**, *11*, 5546; g) G. Dagousset, J. Zhu, G. Masson, *J. Am. Chem. Soc.* **2011**, *133*, 14804.

[16] a) A. V. Butin, F. A. Tsiunchik, V. T. Abaev, V. E. Zavodnik, *Synlett* **2008**, 1145; b) V. T. Abaev, F. A. Tsiunchik, A. V. Gutnov, A. V. Butin, *J. Heterocyclic Chem.* **2008**, *45*, 475.

