Rearrangement Reactions

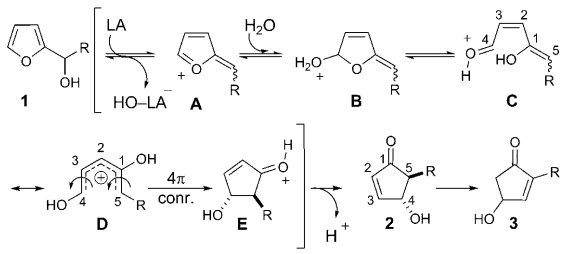
DOI: 10.1002/ange.201005131

Versatile Method for the Synthesis of 4-Aminocyclopentenones: Dysprosium(III) Triflate Catalyzed Aza-Piancatelli Rearrangement**

*Gesine K. Veits, Donald R. Wenz, and Javier Read de Alaniz**

In memory of Marianna Rovis

Well-represented in natural products and biologically active molecules, the cyclopentenone scaffold has long been an inspiration for the development of new methodologies.[1] In 1976, Piancatelli and co-workers reported a new method for the synthesis of 4-hydroxycyclopentenone derivatives by an acid-catalyzed rearrangement of suitable 2-furylcarbinols (Scheme 1).[2] The overall transformation is believed to proceed through a cascade sequence that terminates with a 4π electrocyclic ring closure of a pentadienyl cation (**D**), analogous to the Nazarov cyclization.[3]



Scheme 1. Proposed mechanism of the Piancatelli reaction. LA = Lewis acid, conr. = conrotatory

Investigations by Piancatelli and co-workers focused exclusively on accessing 4-hydroxycyclopentenones, presumably because reaction development was largely driven by application of this methodology to the synthesis of prostaglandins.[4] The synthetic utility of the Piancatelli rearrangement has been limited because the reaction often requires stoichiometric amounts of acid, dilute reaction conditions (<0.005 M), and excess water. Furthermore, there has been only one subsequent investigation that probes this interesting cascade rearrangement to access compounds besides substituted 4-hydroxycyclopentenones. This seminal study by Denisov and et al. also required stoichiometric amounts of acid (BF_3·OEt_2 or *p*-TsOH) and was limited to 2-furylcarbinols that were activated with a cobalt/alkyne complex.[5]

The Piancatelli rearrangement caught our attention because both the cascade rearrangement and access to *trans*-4,5-disubstituted cyclopentenones appear ideally suited for various applications in synthesis. We reasoned that an efficient catalytic aza-Piancatelli rearrangement would be a powerful synthetic reaction for the preparation of *trans*-substituted 4-amino-5-alkylcyclopentenones, a functional scaffold that is rich in potential for the synthesis of biological and medicinal compounds. Few processes are available for the synthesis of 4-aminocyclopentenones,[6] and all of the previously reported methods require multiple steps and typically lack substitution at the 5-position. Herein, we report a mild catalytic single-step procedure for the conversion of readily available 2-furylcarbinols into their corresponding *trans*-substituted 4-amino-5-alkylcyclopentenones.

Our investigation began by identifying a catalyst capable of activating 2-furylcarbinols in the presence of potentially problematic Lewis basic amines. We were encouraged by a report by Li and Batey that rare-earth Lewis acids mediate the rearrangement of furfural-derived iminium cations in the presence of excess Lewis basic amines.[7] Therefore, we hypothesized that such acids would allow us to extend the range of possible nucleophiles beyond electron-deficient *para*-substituted anilines.[8]

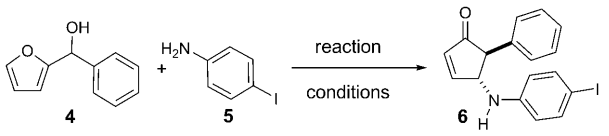
Initial studies were conducted by examining the addition of commercially available *para*-iodoaniline **5** to furylcarbinol **4** in the presence of 5 mol % of either scandium or dysprosium trifluoromethanesulfonate (Table 1). We were pleased to find that both Lewis acids catalyzed the desired transformation, affording 4-aminocyclopentenone **6** in excellent yield as a single diastereomer (Table 1, entries 1 and 2). The rearrangement was found to be most effective at 80 °C (Table 1, entry 3). Although 5 mol % of triflic acid can serve as an active catalyst for this rearrangement (Table 1, entry 4), control experiments demonstrated that a trace quantity of triflic acid was not solely responsible for the catalysis when a metal triflate was employed (Table 1, entries 5 and 6).[9] We chose to develop the reaction with $Dy(OTf)_3$ because of its lower cost compared to $Sc(OTf)_3$ and because it is experimentally easier to handle than triflic acid.[10] Lewis acid reactions mediated by $Dy(OTf)_3$ have not attracted tremendous interest from the synthetic community, despite the fact that it exhibits similar reactivity and shares the advantageous properties of other lanthanide salts: low toxicity and cost, ease of handling, and stability toward moisture.[11]

[*] G. K. Veits, D. R. Wenz, Prof. J. Read de Alaniz
Department of Chemistry and Biochemistry
University of California-Santa Barbara
Santa Barbara, CA 93106-9510 (USA)
Fax: (+1) 805-893-4120
E-mail: javier@chem.ucsb.edu
Homepage: Homepage: http://www.chem.ucsb.edu/~read

[**] This research was supported by the UCSB. We thank Professors Lipshutz, Pettus, Zakarian, and Zhang for helpful discussions and access to chemicals and equipment. We also thank Dr. Guang Wu (UCSB) for X-ray analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201005131.

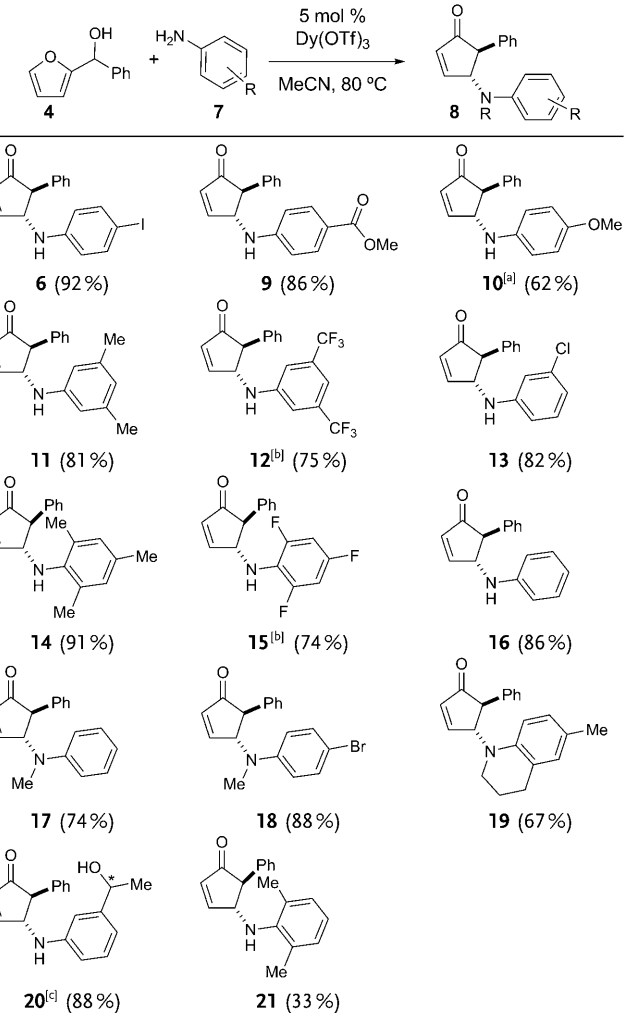
Table 1: Optimization of the rearrangement conditions.



4 5 6

Entry[a]	Catalyst (mol%)	*T* [°C]	*t* [h]	Yield [%]
1	$Sc(OTf)_3$ (5)	40	3	83
2	$Dy(OTf)_3$ (5)	40	2	79
3	$Dy(OTf)_3$ (5)	80	0.5	92
4	HOTf (5)	80	0.5	62
5[b]	HOTf (5) K_2CO_3 (100)	80	4	0
6	$Dy(OTf)_3$ (5) K_2CO_3 (100)	80	1	93

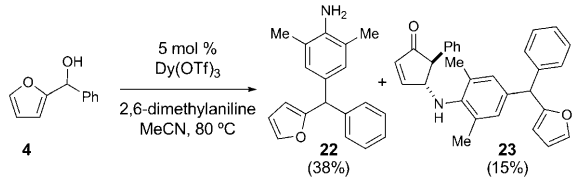
[a] Reaction conducted in MeCN. [b] The starting material was recovered from the reaction.



Scheme 2. Scope of the rearrangement with substituted anilines. [a] 20 mol% $Dy(OTf)_3$. [b] 3 equiv of the corresponding aniline. [c] Formed as a 1:1 ratio of diastereomers at the stereocenter marked with an *. Yields reported are those of the isolated products.

Under the optimized reaction conditions (5 mol% $Dy(OTf)_3$, MeCN, 80 °C), we investigated the scope of this transformation. Scheme 2 summarizes results obtained with *ortho*-, *meta*-, and *para*-substituted aniline derivatives. The reaction of anilines substituted at the *para*- or *meta*-positions generated the best results. Sterically hindered 2,4,6-trimethylaniline also successfully participated in the reaction (**14**). Secondary acyclic and cyclic anilines produced the desired product in 74%, 88%, and 67% yield, respectively (**17**, **18**, and **19**).

Several additional observations merit note. Typically, it is difficult to prevent product isomerization (Scheme 1, **2**→**3**) in the Piancatelli rearrangement; however, presumably because of the mild nature of the $Dy(OTf)_3$ catalyst, product isomerization was not observed in the aza-Piancatelli rearrangement. One significant side-reaction did occur when 2,6-dimethylaniline was employed. In this case, **21** was formed in only 33% yield (Scheme 2), with the rest of the remaining starting material consumed by Friedel–Crafts alkylation to give **22** and **23** (Scheme 3).[12]



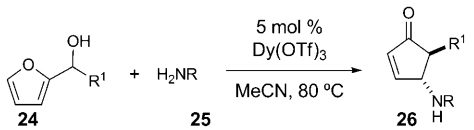
Scheme 3. Products resulting from Friedel–Crafts alkylation.

Subsequently, we performed a series of experiments to explore the initial scope of the furylcarbinol component **24** using **25** in this rearrangement to give **26**. As shown in Table 2, the rearrangement is compatible with 2-aryl furylcarbinols possessing electron-donating or electron-withdrawing groups on the aromatic ring (Table 2, entries 1–6). It is noteworthy that 2-alkyl-substituted furylcarbinols can be accommodated without a significant loss in reactivity (Table 2, entries 7–12). Increasing the steric bulk of the alkyl group on the 2-substituted furylcarbinol from methyl to isopropyl groups appreciably decreased the formation of the competing Friedel–Crafts alkylation with *meta*-chloroaniline (Table 2, entries 8 and 11).

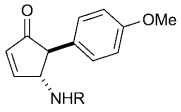
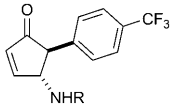
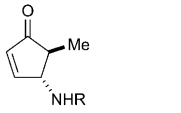
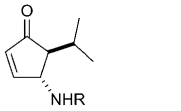
We believe that the high *trans* diastereoselectivity is a result of a 4π conrotatory electrocyclization.[13] It seems likely that the initial step in the cascade rearrangement involves loss of the alcohol and the formation of a stabilized carbocation. At this point, the stabilized carbocation can react with the aniline through two predominant pathways: Friedel–Crafts alkylation at the benzylic position or addition at the 5-position of the furylcarbinol, the latter triggering the product-forming cascade reaction.

To highlight the synthetic utility of this methodology, we began to explore the application of the cascade rearrangement for the efficient synthesis of biological and medicinal molecules. A recent structure–activity relationship (SAR) study by Merck found 1,2-*trans*-2,3-*trans*-cyclopentane-based scaffolds of type **39** to be comparable to the current clinical

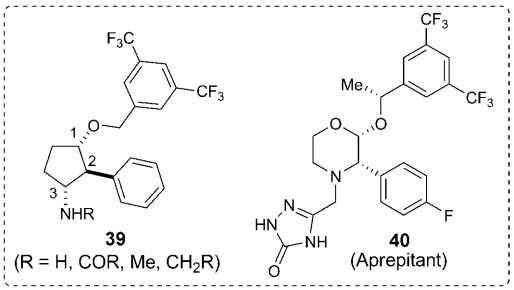
Table 2: Scope of the rearrangement with various 2-furylcarbinols.



24 25 26

Entry	Product	R	Yield [%]
1[a]		*p*-IC_6H_4 (**27**)	68
2[a]		*m*-ClC_6H_4 (**28**)	82
3[a]		2,4,6-$Me_3C_6H_2$ (**29**)	89
4		*p*-IC_6H_4 (**30**)	83
5		*m*-ClC_6H_4 (**31**)	87
6[b]		2,4,6-$Me_3C_6H_2$ (**32**)	78
7		*p*-IC_6H_4 (**33**)	68
8[c]		*m*-ClC_6H_4 (**34**)	10
9		2,4,6-$Me_3C_6H_2$ (**35**)	74
10		*p*-IC_6H_4 (**36**)	73
11		*m*-ClC_6H_4 (**37**)	52
12		2,4,6-$Me_3C_6H_2$ (**38**)	89

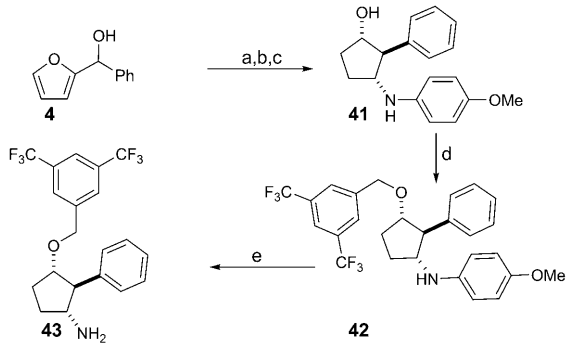
[a] Reaction conducted at RT. [b] 10 mol% $Dy(OTf)_3$. [c] Products arising from Friedel–Crafts alkylation were mainly observed. Yields reported are those of the isolated products.



Scheme 4. Representative cyclopentane-based hNK1 antagonist.

compound **40** in assays of hNK1 inhibition (Scheme 4).[14] Aprepitant (**40**) is an hNK1 antagonist and FDA approved for use as an antiemetic for chemotherapy-induced nausea and vomiting.

The synthesis of a cyclopentane scaffold containing an oxygen functionality at the C1 position, the required aryl group at the C2 position, and a functionalizable amine group at the C3 position began with the rearrangement of **4** with *para*-anisidine on a gram scale (Scheme 5). Luche reduction of cyclopentenone **10** gave the 1,2-*trans*-2,3-*trans*-cyclopentene-based scaffold in two steps from commercially available reagents. Subsequent alkene reduction and hydroxyl alkylation with 3,5-bis(trifluoromethyl)benzyl bromide and sodium hydride gave the racemic ether **42**. Oxidative dearylation of the *para*-methoxyphenyl group with periodic acid (H_5IO_6) provided the primary amine.[15] The hNK1 binding affinity for racemic cyclopentane **43** was moderate ($IC_{50} = 5.7$ nM); however, enhanced affinity ($IC_{50} < 0.1$ nM) and aqueous solubility were achieved by simple derivatization of **43**.[14]



Scheme 5. Direct synthesis of the cyclopentane scaffold: a) 5 mol% $Dy(OTf)_3$, *para*-anisidine, MeCN, 80 °C, 60% (1 gram scale) b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 98% (2:1 *trans/cis*); c) 10 mol% Pd/C, H_2, MeOH, 500 psi, 76% (2:1 *trans/cis*; **41** = 49%); d) NaH, 3,5-bis(trifluoromethyl)benzyl bromide, THF, 75%; e) H_5IO_6, H_2SO_4, MeCN/H_2O (1:1), RT, 58%. THF = tetrahydrofuran.

In conclusion, we have developed an efficient aza-Piancatelli rearrangement that constructs a carbon–carbon bond plus a carbon–nitrogen bond and two stereocenters in a single operation. This strategy offers a practical solution for the synthesis of 4-aminocyclopentenones, a versatile building block for the synthesis of structurally diverse biologically active molecules. Reactions are performed in reagent grade acetonitrile, open to air, with commercially available $Dy(OTf)_3$. Further investigation of this rearrangement and its application toward complex synthetic targets will be forthcoming.

Received: August 16, 2010
Published online: November 4, 2010

Keywords: cyclization · domino reactions · dysprosium · lanthanides · rearrangement

[1] For recent reviews of the Nazarov and Pauson–Khand reactions, see: a) M. A. Tius, *Eur. J. Org. Chem.* **2005**, 2193; b) H. Pellissier, *Tetrahedron* **2005**, *61*, 6479; c) A. J. Frontier, C. Collison, *Tetrahedron* **2005**, *61*, 7577; d) T. N. Grant, C. J. Rieder, F. G. West, *Chem. Commun.* **2009**, 5676; e) J. Blanco-Urgoiti, L. Anorbe, L. Perez-Serrano, G. Dominguez, J. Perez-Castells, *Chem. Soc. Rev.* **2004**, *33*, 32; f) S. E. Gibson, N. Mainolfi, *Angew. Chem.* **2005**, *117*, 3082; *Angew. Chem. Int. Ed.* **2005**, *44*, 3022.

[2] G. Piancatelli, A. Scettri, S. Barbadoro, *Tetrahedron Lett.* **1976**, *17*, 3555.

[3] A. N. Faza, C. S. Lopez, R. Alvarez, I. R. de Lera, *Chem. Eur. J.* **2004**, *10*, 4324.

[4] G. Piancatelli, M. Dauria, F. Donofrio, *Synthesis* **1994**, 867.

[5] V. R. Denisov, S. E. Shustitskaya, M. G Karpov, *Zh. Org. Khim.* **1993**, *29*, 249.

[6] For select examples, see: a) F. A. Davis, Y. Z. Wu, *Org. Lett.* **2004**, *6*, 1269; b) J. Dauvergne, A. M. Happe, V. Jadhav, D. Justice, M. C. Matos, P. J. McCormack, M. R. Pitts, S. M. Roberts, S. K. Singh, T. J. Snape, J. Whittall, *Tetrahedron* **2004**, *60*, 2559; c) J. Dauvergne, A. M. Happe, S. M. Roberts, *Tetrahedron* **2004**, *60*, 2551; d) M. Zaja, S. Blechert, *Tetrahedron* **2004**, *60*, 9629.

[7] S. W. Li, R. A. Batey, *Chem. Commun.* **2007**, 3759.

[8] The rearrangement reported by Denisov et al. was limited to three *para*-substituted anilines; see Ref. [5].
[9] D. C. Rosenfeld, S. Shekhar, A. Takemiya, M. Utsunomiya, J. F. Hartwig, *Org. Lett.* **2006**, *8*, 4179.
[10] Price from Strem Chemicals: $Dy(OTf)_3$ = \$36.00/5 g, $Sc(OTf)_3$ = \$172.00/5 g.
[11] For select examples of dysprosium(III)-catalyzed reactions, see: a) S. Kobayashi, I. Hachiya, *J. Org. Chem.* **1994**, *59*, 3590; b) R. A. Batey, D. A. Powell, A. Acton, A. J. Lough, *Tetrahedron Lett.* **2001**, *42*, 7935; c) W. Li, Y. Ye, J. Zhang, R. Fan, *Tetrahedron Lett.* **2009**, *50*, 5536.
[12] For select related examples of Friedel–Crafts acylation and alkylation of aniline derivatives, see: a) M. Beller, O. R. Thiel, H. Trauthwein, *Synlett* **1999**, 243; b) S. Kobayashi, I. Komoto, J.-I. Matsuo, *Adv. Synth. Catal.* **2001**, *343*, 71; c) L. L. Anderson, J. Arnold, R. G. Bergman, *J. Am. Chem. Soc.* **2005**, *127*, 14542.
[13] Alternative mechanisms cannot be ruled out at this time.
[14] a) P. E. Finke, L. C. Meurer, D. A. Levorse, S. G. Mills, M. MacCoss, S. Sadowski, M. A. Cascieri, K.-L. Tsao, G. G. Chicchi, J. M. Metzger, D. E. MacIntyre, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4497; b) L. C. Meurer, P. E. Finke, K. A. Owens, N. N. Tsou, R. G. Ball, S. G. Mills, M. MacCoss, S. Sadowski, M. A. Cascieri, K.-L. Tsao, G. G. Chicchi, L. A. Egger, S. Luell, J. M. Metzger, D. E. MacIntyre, N. M. J. Rupniak, A. R. Williams, R. J. Hargreaves, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4504.
[15] J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, P. L. Alsters, F. L. van Delft, F. P. J. T. Rutjes, *Tetrahedron Lett.* **2006**, *47*, 8109.

