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Domino Reactions

Direct and Highly Diastereoselective Synthesis of Azaspirocycles by a Dysprosium(III) Triflate Catalyzed Aza-Piancatelli Rearrangement**

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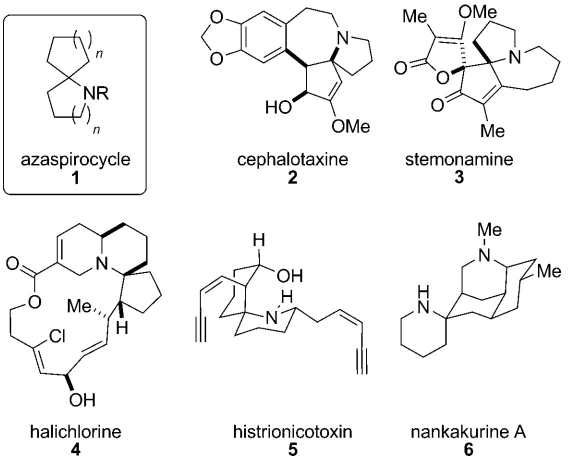


Figure 1. Alkaloids that contain 1-azaspirocycle motifs.

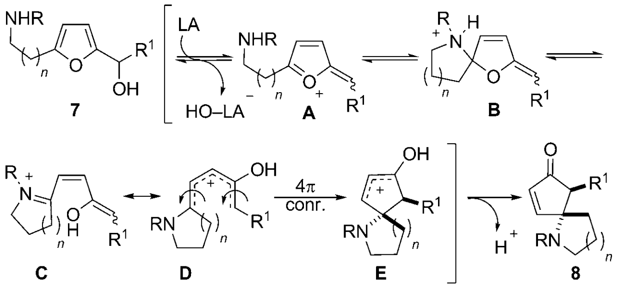
The azaspirocycle structural motif of type **1** (Figure 1) is embedded in numerous remarkable natural products, such as cephalotaxine (**2**),[1] stemonamine (**3**),[2] halichlorine (**4**),[3] histrionicotoxin (**5**),[4] nankakurine A (**6**),[5] and others.[6] A number of elegant approaches to construct azaspirocycles have been developed.[6,7] The methods differ in the strategy used to address the two main synthetic challenges: construction of the tertiary carbon center bearing the nitrogen atom, and the formation of the spirocyclic ring system. Generally, the synthetic routes rely on a two-step process where the tertiary carbon center and the spirocycle are formed in separate, discrete synthetic steps. The most practical, but also the most difficult and rare approach to construct this challenging azaspirocyclic framework is to combine the construction of the tertiary stereocenter and the formation of the spirocyclic ring system within a single operation.[6,8]

Recently, our group developed a new cascade strategy for the efficient synthesis of *trans*-4,5-disubstituted cyclopentenones based on the aza-Piancatelli rearrangement.[9] The overall transformation is highly diastereoselective and believed to proceed through a cascade sequence that terminates with a 4π-electrocyclic ring closure to give a pentadienyl cation; a step that is analogous to the Nazarov cyclization.[10] Given the synthetic importance of the azaspirocycle structural motif and the stereospecificity of the 4π electrocyclizations, we hypothesized that 2-furylcarbinols bearing an aminoalkyl side chain at the 5-position of the furan ring would be effective for the general synthesis of functionalized azaspirocycles.

Piancatelli et al. demonstrated that 2-furylcarbinols with substituents at the 5-position undergo an intermolecular rearrangement to give the corresponding cyclopentenone containing a tertiary alcohol; often a decrease in both yield and reaction rate was observed.[11] More recently, Wu et al. described the reactivity of 2-furylcarbinols containing a hydroalkyl side chain at the 5-position of the furan ring. In their case the rearrangement led exclusively to the more stable oxa-bicyclic cyclopentenone and they believe the reaction does not proceed through an intramolecular Piancatelli rearrangement.[12]

We envisioned a mechanistic scenario that would proceed in an intramolecular fashion, analogous to the proposed aza-Piancatelli rearrangement (Scheme 1). By employing the proposed cascade rearrangement, we sought to overcome the challenges associated with the generation of an azaspirocyclic framework by relying on the electrocyclization to construct the sterically congested azaspirocycle (**D**–**E**). Herein, we report an efficient and highly diastereoselective synthesis of functionalized azaspirocycles, based on the first example of an intramolecular aza-Piancatelli rearrangement.

Furylcarbinol **9** was selected as a model substrate to probe the feasibility of the new intramolecular rearrangement and dysprosium(III) triflate ($Dy(OTf)_3$) was chosen as the catalyst



Scheme 1. The proposed mechanism of the intramolecular aza-Piancatelli rearrangement. conr. = conrotatory, LA = Lewis acid.

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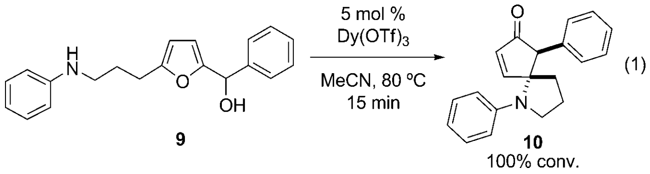
because of our our long-term interest in this intriguing Lewis acid.[9,13] We were delighted to discover that **9** undergoes quantitative rearrangement to the azaspirocycle **10** in 15 minutes upon exposure to 5 mol% of Dy(OTf)$_3$ in acetonitrile heated to reflux [Eq. (1)].



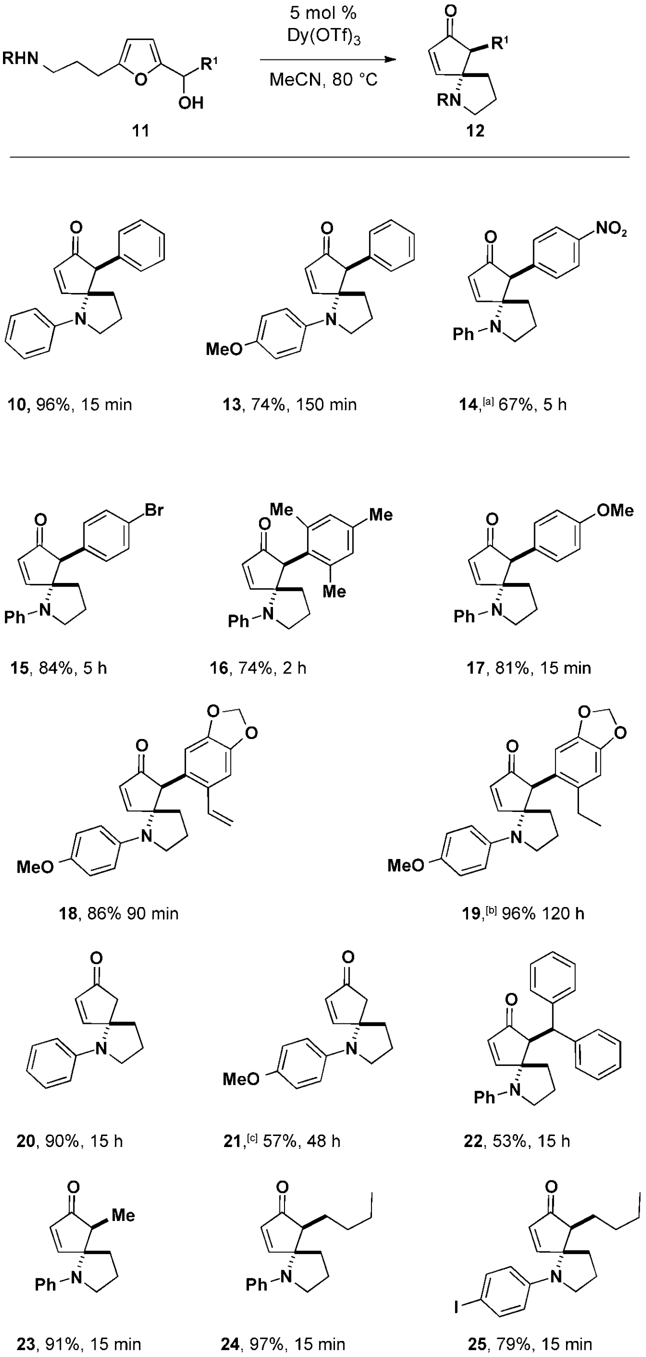
(1)

Investigation of the scope of the intramolecular aza-Piancatelli rearrangement revealed that this method provides access to a range of substituted azaspirocycles in excellent yield and as a single diastereomer (Scheme 2). Single-crystal X-ray analysis of products **10**, **19**, and **39** confirmed that the rearrangement had taken place with the expected *trans* selectivity, consistent with a 4π electrocyclization.[14]

As illustrated in Scheme 2 the rearrangement is compatible with 2-aryl furylcarbinols possessing common functional groups on the aromatic ring; these groups range from electron-withdrawing nitro (**14**)[15] and bromo groups (**15**) to electron-rich methyl ether (**17**) and methylenedioxy groups (**18**–**19**). Sterically bulky aryl substituents also successfully gave the rearranged products (**16**, **18**, and **19**) in good yield. Furylcarbinols substituted at the 2-position with an alkyl group participated in the rearrangement to afford the desired product in excellent yield (**23**–**25**), but in the sterically demanding case of **22** a modest 53% yield was observed.

Importantly, substrates possessing the removable *para*-methoxyphenyl (PMP) group on the nitrogen atom were also tolerated, although we did notice a decrease in both yield and reaction rate when compared to the analogous substrates with a phenyl group on the nitrogen atom (**10** vs. **13** and **20** vs. **21**).[9,16] In contrast to our previous intermolecular aza-Piancatelli rearrangement, simple unsubstituted furylcarbinols **20** and **21** underwent the reaction smoothly. This rearrangement presumably benefits from the unimolecular nature of the reaction.

The 6-azaspiro[4.5]decane framework has received significant attention in recent years because of its interesting biological activities and challenging architecture.[3,6] Consequently, we turned our attention to this important structural motif and found it can also be constructed by the intramolecular aza-Piancatelli rearrangement in good yield as a single diastereomer (Table 1).



10, 96%, 15 min

13, 74%, 150 min

14,[a] 67%, 5 h

15, 84%, 5 h

16, 74%, 2 h

17, 81%, 15 min

18, 86% 90 min

19,[b] 96% 120 h

20, 90%, 15 h

21,[c] 57%, 48 h

22, 53%, 15 h

23, 91%, 15 min

24, 97%, 15 min

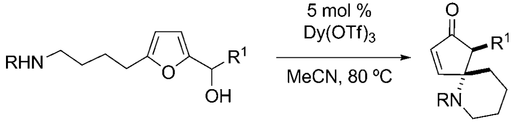
25, 79%, 15 min

Scheme 2. The scope of the intramolecular aza-Piancatelli rearrangement. [a] Isolated as a 5:1 mixture of products, see the Supporting Information for details. [b] Reaction conducted at RT. [c] 10 mol% of catalyst was used.

A more pronounced effect on the rate of the rearrangement was observed while investigating the formation of 6-azaspirocycles. Perhaps the most striking example is shown in entry 3 (Table 1). In this case, the rearrangement product **30**, which has no substituent adjacent to the alcohol and possesses an electron-rich *para*-methoxy aniline tether in the furylcarbinol starting material, was obtained in only 37% yield, and 20 mol% of Dy(OTf)$_3$ catalyst was necessary to achieve moderate conversion. Within the series, longer reaction times were required as the N-aryl group became more electron rich (entries 1–8). In addition, substrates that lack substitution are more difficult to activate.

We have observed that the efficiency of the intramolecular cascade rearrangement benefits from a polarized substrate bearing an electron-donating group adjacent to the alcohol and an electron-withdrawing group on the nitrogen nucleophile. This result could occur because the more electron-rich anilines are competing with the hydroxy group on the 2-furylcarbinol for Lewis acid coordination. The high

Table 1: Scope of the 6-azaspirocycle.



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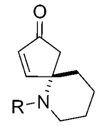
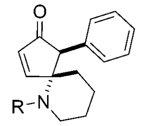
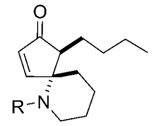
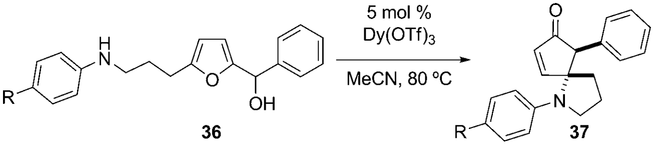
Entry	Product		R	t [h]	Yield [%][a]
1		**28**	p-IC$_6$H$_4$	8	90
2		**29**	Ph	48	70
3[b]		**30**	p-OMeC$_6$H$_4$	72	37
4		**31**	p-IC$_6$H$_4$	5 min	69
5		**32**	Ph	1	75
6		**33**	p-OMeC$_6$H$_4$	75	74
7		**34**	p-IC$_6$H$_4$	2	65
8		**35**	Ph	15	54

[a] Yield of the isolated product. [b] 20 mol% of catalyst was used.

trans diastereoselectivity and the increased aptitude of the polarized substrates to undergo the rearrangement are consistent with a 4π conrotatory electrocyclization. These results are similar to the Nazarov reaction, a process well known to proceed through a 4π conrotatory electrocyclization and benefit from polarization of the substrates.[10]

Intrigued by the rate acceleration observed during the formation of the 6-azaspirocycles, we prepared a series of 2-furylcarbinols bearing an aminoalkyl side chain containing different *para*-substituted anilines. Our preliminary experiments were designed to probe the net electronic effect of the aniline substituent on the intramolecular aza-Piancatelli rearrangement. Consistent with our previous observation in the formation of the 6-azaspirocycles, the electronic nature of the aniline group affected reaction rate (Table 2). In general, more electron-rich anilines were slower to rearrange relative to more electron-poor anilines (Table 2; entries 1–7). However, it is interesting to note that the reaction time increased slightly with the *para*-chloro (**40**), *para*-bromo (**41**), and *para*-trifluoromethyl (**42**) anilines, suggesting a possible change in mechanism or change in the rate-determining event (Table 2; entries 5–7).[17]

Table 2: Electronic effect of the aniline on rate of the rearrangement.



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Entry	R	Product	t [min]	Yield [%][a]
1	OMe	**13**	150	74
2	Me	**38**	30	79
3	H	**10**	15	96
4	I	**39**	5	84
5	Cl	**40**	10	96
6	Br	**41**	10	78
7	CF$_3$	**42**	15	82

[a] Yield of the isolated product.

In conclusion, we have developed a general and practical intramolecular aza-Piancatelli rearrangement that constructs a fully substituted carbon center bearing a nitrogen atom and a spirocyclic ring system in a single operation. The rearrangement is catalyzed by commercially available dysprosium (III) triflate under operationally simple reaction conditions. The azaspirocycles are formed exclusively as the *trans* diastereomer, which is consistent with a 4π electrocyclization. Further investigation of this rearrangement and its application toward complex azaspirocyclic natural products will be forthcoming.

Experimental Section

General procedure for the intramolecular aza-Piancatelli rearrangement: To a stirred solution of 5-substituted furylcarbinol (**11**; 0.16 mmol) in MeCN (< 6 mL) was added Dy(OTf)$_3$ (5 mol%) at 23°C. The reaction flask was immediately fitted with a reflux condenser and placed in an oil bath preheated to 80°C. Upon completion (as evident by TLC), the reaction mixture was cooled to RT then quenched with saturated aqueous NaHCO$_3$ and extracted with ethyl acetate. The combined organic layers were dried over MgSO$_4$, filtered and then concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate 9:1) to afford the desired azaspirocycle (**12**).

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Keywords: aza-Piancatelli · azaspirocycles · domino reactions · lanthanides · rearrangement

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[14] See the Supporting Information. CCDC 815278 (**10**),815279 (**19**), and 815280 (**39**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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