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Sulfoxide-Controlled Stereoselective Aza-Piancatelli Reaction

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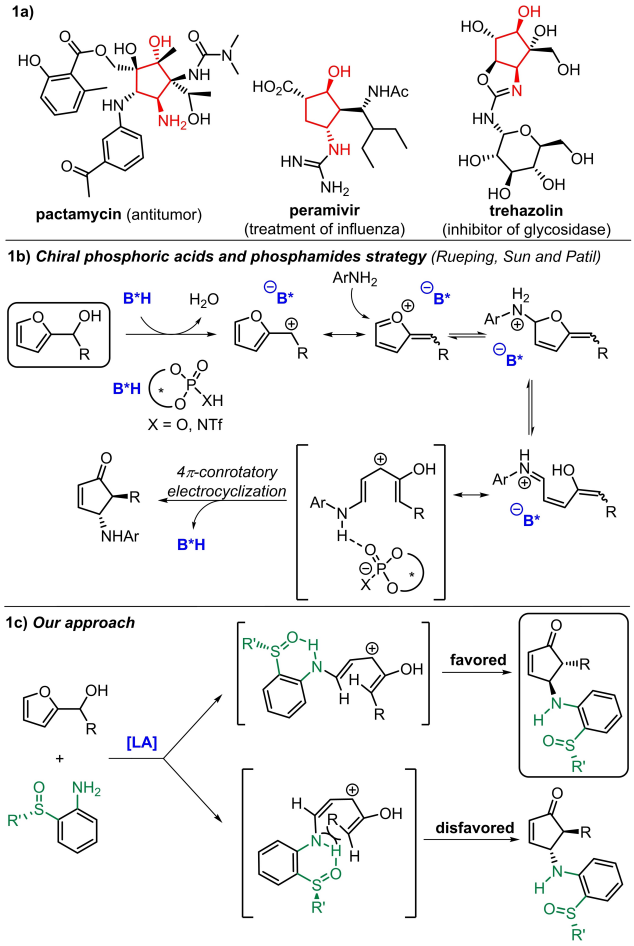
Abstract: The development of a stereoselective aza-Piancatelli reaction to access 4-aminocyclopentenones is reported. This transformation relies on the use of chiral *o*-sulfinyl anilines as chiral inductors to afford the targeted products in good to excellent yields. Remarkably, the high value-added cyclopentenones could be obtained in drs up to >95:5, depending upon the furan substitution pattern.

Keywords: aza-Piancatelli cyclization; calcium; chiral sulfoxide; hexafluoroisopropanol; 4-aminocyclopentenones

The Nazarov cyclization represents an extremely versatile and powerful synthetic tool for a straightforward, atom- and step-economical construction of complex molecular scaffolds.[1] Among the Nazarov-type electrocyclizations, the aza-Piancatelli reaction has a unique place due to the simplicity with which it is possible to introduce nitrogen functionalities.[2] In particular, this transformation enables a rapid access to 4-aminocyclopentenones from 2-furylcarbinols and nitrogen-containing derivatives such as anilines. Those compounds are of high interest for synthetic chemists as direct precursors of aminocyclopentitols, which are key motifs in manifold natural and bioactive molecules, including pactamycin, peramivir and trehazolin (Scheme 1a). Despite its significant potential, achieving stereocontrol during this electrocyclization remains highly challenging. To date, only few enantioselective versions of this reaction have been reported, using mainly chiral phosphoric acids and phosphoramides (Scheme 1b).[3] These methods exploit H-bonding to induce the enantioselectivity during the 4π-conrotatory electrocyclization. However, they have a limited flexibility regarding the furan substitution pattern.

In this context, devising new strategies towards a more general access to these molecules still represents a compelling challenge to be tackled. As part of our continuing interest in the development of the aza-Piancatelli reaction,[4] we hypothesized that an efficient, general and highly stereocontrolled reaction could be achieved by combining a classical Lewis acid catalysis featuring calcium(II) salts to trigger the transformation and the use of a chiral inductor prompt to generate H-bonding with the amine moiety.[5] Such H-bonding should allow to lock the configuration of the aniline in order to control the torquoselectivity of the electrocyclization (Scheme 1c). In addition, this strategy would provide access to new sulfoxide-containing scaffolds. This aspect seems particularly appealing as not only the introduction of the sulfoxide motif in bio-active molecules has become increasingly popular in drug discovery as illustrated by sulindac and omeprazole, but also chiral sulfur is a valuable motif in biology. The reason behind is that sulfoxides impart an enhanced water-solubility and fast metabolism when compared to their sulfide counterparts,



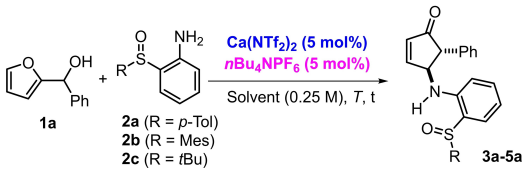
Scheme 1. Biologically relevant aminocyclopentitols and stereocontrolled induction for the aza-Piancatelli reaction.

while providing a possibility of confining a chiral character.[6]

Despite a rather common use of chiral auxiliaries in intramolecular Nazarov cyclizations,[1] as reported by the group of Flynn using Evans' chiral auxiliary,[7–8] it remains surprisingly scarce regarding intermolecular reactions and is usually limited to chiral allenyl ethers, as exemplified by the Tius group.[9] In order to fill this gap, we embarked on the development of a stereoselective aza-Piancatelli reaction by exploiting the potential of chiral *o*-sulfinyl anilines as chiral auxiliaries. The sulfoxide moiety has established itself as a powerful chiral inductor with numerous applications,[10] such as stereoselective reductions of β-ketosulfoxides, conjugate additions to α,β-unsaturated sulfoxides, additions of sulfinyl carbanions to imines, cycloadditions and even atroposelective Ullmann type N-arylation.[11] More recently, *o*-sulfinyl anilines, which are easily accessible in one step, have emerged as remarkable chiral bi-coordinating directing groups for asymmetric C(sp^3)–H activation.[12] Herein, we demonstrate that we can extend the range of applications of chiral *o*-sulfinyl anilines to stereoselective electrocyclizations, using the aza-Piancatelli reaction as a springboard.

To validate this concept, our investigations started by focusing on 2-furylcarbinol **1a** and various racemic *o*-sulfinyl anilines **2a**–**2c** as model substrates to evaluate the efficiency of such process and the influence of *o*-sulfinyl anilines on the diastereoselectivity of the reaction (Table 1). First, we performed the reaction using our standard catalytic system for the aza-Piancatelli reaction ($Ca(NTf_2)_2$/nBu_4NPF_6 (5 mol%))[4a,13] in common solvents with *o*-(*p*-tolylsulfinyl)aniline **2a** as a nucleophile (entries 1–4). While, in each case, the full conversion was rapidly reached at 80 °C, the diastereomeric ratio (dr) remained low (at best 1.5:1 in toluene, entry 3), arguably due to the weak H-bonding at high temperature. Thus, we turned our attention to hexafluoroisopropanol (HFIP),[14] which has proven to be highly efficient in the aza-Piancatelli reaction, allowing the cyclization to proceed at lower temperature.[4b] In that case, the reaction could be conducted at 20 °C, but the diastereoselectivity

Table 1. Reaction optimization for the formation of 4-aminocyclopentenones **3a**–**5a**.[a]



Entry	2	Solvent	T [°C]	t [h]	Conversion 3 [%] (dr)
1	**2a**	$MeNO_2$	80	1	**3a**, 100 (1.3:1)[b]
2	**2a**	1,2-DCE	80	0.15	**3a**, 100 (1.4:1)[b]
3	**2a**	Toluene	80	0.15	**3a**, 100 (1.5:1)[b]
4	**2a**	HFIP	20	3	**3a**, 100 (1.1:1)[b]
5	**2a**	1,2-DCE/HFIP (4:1)	20	3	**3a**, 100 (1.5:1)[b]
6	**2a**	Toluene/HFIP (4:1)	20	0.6	**3a**, 100 (2.2:1)[b]
7	**2a**	Toluene/HFIP (8:1)	20	3.5	**3a**, 100 (1.9:1)[b]
8	**2a**	Toluene/HFIP (4:1)	0	32	**3a**, 100 (2.8:1)[b]
9	**2b**	Toluene/HFIP (4:1)	20	16	**4a**, 100 (1.1:1)[b]
10[c]	**2c**	Toluene/HFIP (4:1)	20	2	**5a**, 99 (3.9:1)[d]
11[c]	**2c**	Toluene/HFIP (2:1)	0	54	**5a**, 97 (3:1)[d]
12[e]	**2c**	Toluene/HFIP (4:1)	0	54	**5a**, 98 (3.1:1)[d]

[a] Reactions conditions: 2-furylcarbinol **1a** (1 equiv.) and aniline **2a**–**2c** (1.3 equiv.) in the indicated solvent (0.25 M) in the presence of $Ca(NTf_2)_2$ (5 mol%) and nBu_4NPF_6 (5 mol%) at the indicated temperature until full conversion was reached.

[b] dr determined by ^1H NMR on the crude reaction mixture.

[c] 2-furylcarbinol **1a** (1.3 equiv.) and aniline **2c** (1 equiv.).

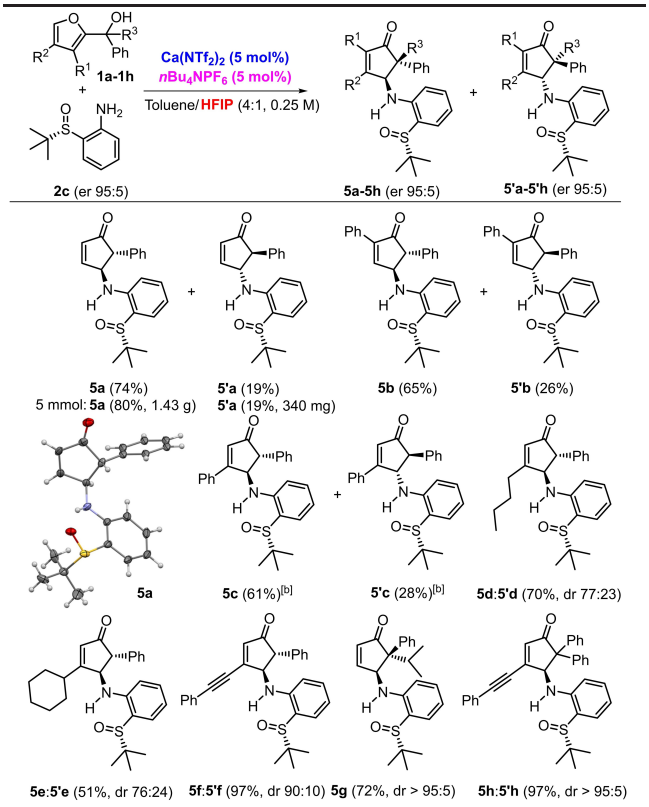
[d] Isolated yields.

[e] 2-furylcarbinol **1a** (1.3 equiv.) and aniline **2c** (1 equiv.) in the presence of $Ca(NTf_2)_2$ (10 mol%) and nBu_4NPF_6 (10 mol%).

remained disappointing (dr 1.1:1, entry 4). The reason behind is likely the H-bonding formation between the HFIP solvent and the sulfoxide.[15] Consequently, as the amine moiety is not involved in the weak bonding, a loss of selectivity during the electrocyclization step is observed.[16] Based on these results, we hypothesized that the use of a solvent mixture, and, thus, a decreased amount of HFIP, should allow maintaining the high reactivity at 20 °C while preventing the undesirable participation of HFIP in H-bonding with the *o*-sulfinyl aniline (entries 5–8). Gratifyingly, this approach increased the dr from 1.5:1 to 2.2:1 by employing a mixture toluene/HFIP 4:1 (entry 6), and even to 2.8:1 when performing the reaction at lower temperature (0 °C, entry 8). Subsequently, other *o*-sulfinyl anilines were screened (entries 9–12). In the case of a mesityl substituent, a significant decrease of the dr was observed (entry 9). On the other hand, *o*-(*tert*-butylsulfinyl)aniline **2c** led to the corresponding 4-aminocyclopentenone **5a** in 99% yield with a dr of 3.9:1 (entry 10). The reaction required an excess of 2-furylcarbinol (1.3 equiv.) to ensure the complete conversion of **2c** as both **2c** and **5a** have the same Rf on TLC. Of note, at 0 °C, no further improvement in stereoselectivity was witnessed and the reaction required either a larger amount of HFIP (entry 11) or of the catalyst (entry 12) to reach the full conversion.

With these reaction conditions in hand, we then focused on the stereocontrolled version of this transformation using (*S*)-*o*-(*tert*-butylsulfinyl)aniline **2c** (er 95:5) (Table 2). The reaction with 2-furylcarbinol **1a** furnished the desired compounds **5a** and **5'a** in 74% and 19% yields (dr 3.9:1), respectively. To our delight, the diastereomeric products **5a** and **5'a** could be separated by flash column chromatography and the chiral information of the *o*-chiral sulfinyl aniline was retained. The configuration of the major product **5a** was determined by X-ray crystallography. Remarkably, the reaction could be carried out on a large scale (5 mmol) to provide **5a** in a further improved yield (80%). Then, we explored the scope of the reaction, mainly the influence of the substitution at the positions either C-3 or C-4 of the furan. In the case of a phenyl substitution at C-3 and C-4, the diastereomeric ratios were moderate (2.5:1 and 2:1), but the overall yields were excellent (combined yields of 91% and 89%). In particular, the major compounds **5b** and **5c** were obtained in high yields (65% and 61%) and were separated from the minor compounds **5'b** and **5'c** by flash column chromatography. In the case of substrate **1c**, a decreased amount of HFIP was used (toluene/HFIP 16:1 mixture) due to the instability of **1c** in the standard solvent mixture. The reaction was compatible with the presence of alkyl substituents at the position C-4, delivering the products **5d** and **5e** in good yields and diastereomeric ratios. Of note, the dr was greatly improved in the presence of an alkyne moiety at C-4

Table 2. Scope of 2-furylcarbinols **1a–1h** with aniline **2c**.[a]



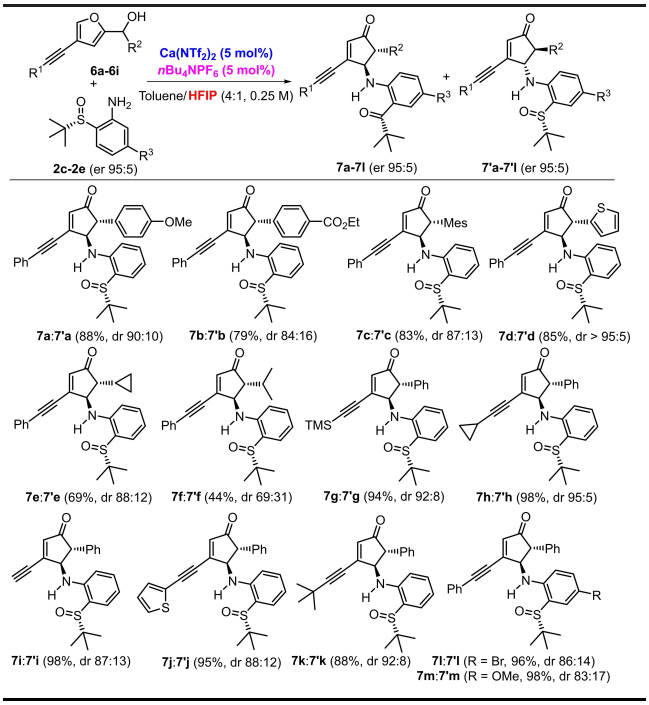
[a] Reactions conditions: 2-furylcarbinol **1a–1h** (1–2.3 equiv.) and aniline **2c** (1–1.5 equiv.) in toluene/HFIP (4:1, 0.25 M) in the presence of $Ca(NTf_2)_2$ (5 mol%) and nBu_4NPF_6 (5 mol%) at 20 °C for 0.75–36 h.

[b] In toluene/HFIP (16:1, 0.25 M). ORTEP drawing of compound **5a** (thermal ellipsoids at 50% probability level), CCDC 1906328.

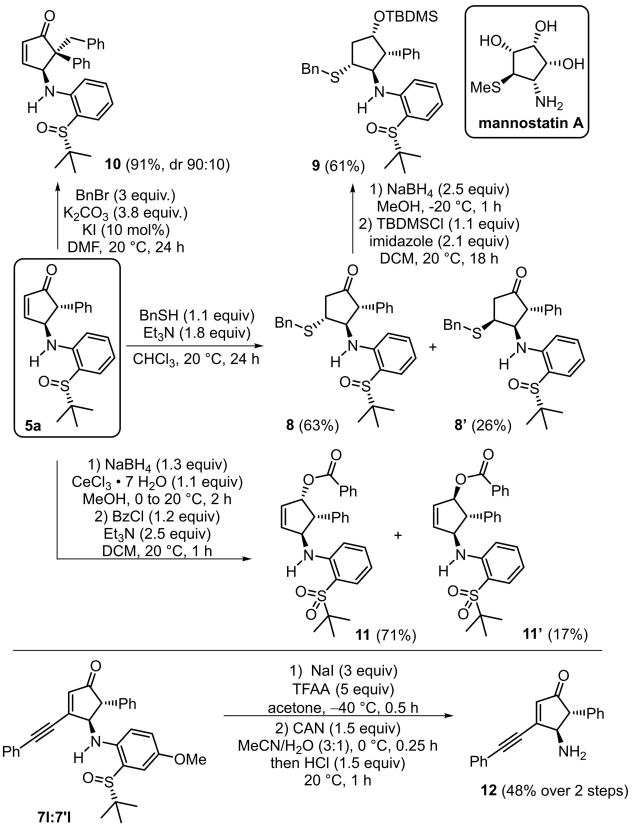
(**1f** and **1h**), providing products **5f** and **5h** in high yields (97% in both cases). Moreover, the reaction of the tertiary 2-furylcarbinol **1g**, incorporating two different substituents, could also be achieved with an excellent selectivity and the expected product was afforded in 72% yield.

Encouraged by the excellent stereoselectivities observed for the substrates **1f** and **1h** bearing an alkyne moiety at C-4 position, the reactivity of alkyne-substituted 2-furylcarbinols was examined (Table 3). The reaction occurred smoothly for a large variety of substrates bearing both electron-rich and electron-poor aryls, (**6a–6b**), sterically hindered aryls (**6c**), heteroaryl (**6d**), cyclopropyl (**6e**) and alkyl (**6f**) groups at the carbinol moiety. Apart from **6f**, the corresponding 4-aminocyclopentenones were generated in high yields and good to excellent drs (up to > 95:5). Additionally, the reaction was compatible with various functional groups at the alkyne moiety, such as alkyl, trimethylsilyl and thienyl groups, and even with a terminal alkyne (**6g–6k**). It is also noteworthy that electron-

Table 3. Scope of 2-furylcarbinols bearing an alkyne moiety **6a–6k** with anilines **2c–2e**.[a]



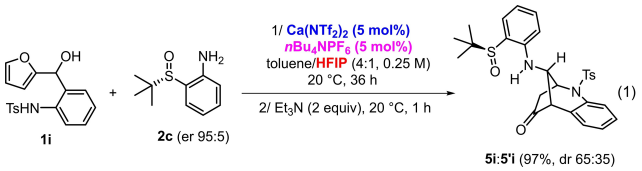
[a] Reactions conditions: 2-furylcarbinol **1** (1–1.3 equiv.) and aniline **2c** (1–1.5 equiv.) in toluene/HFIP (4:1, 0.25 M) in the presence of $Ca(NTf_2)_2$ (5 mol%) and nBu_4NPF_6 (5 mol%) at 20–40 °C for 2–36 h. Mes = 1,3,5-trimethylbenzene.



Scheme 2. Post-modifications.

donating and -withdrawing groups (**2d** and **2e**) could be also introduced on the *o*-sulfinyl aniline to yield the desired products (**7l**/**7'l** and **7m**/**7'm**) with excellent yields and good overall drs.

Among other applications possible, we succeeded in accessing a densely functionalized tetrahydrobenzo [*b*]azepine **5i** following an aza-Piancatelli/Michael addition (Equation 1).[4e] While the selectivity remains moderate, the yield is nearly quantitative (97%).



To further highlight the synthetic utility of the newly accessed complex molecules presenting three stereocenters, post-modifications of **5a** were undertaken (Scheme 2). In the presence of phenylmethanethiol under basic conditions, the Michael addition occurred smoothly to deliver **8** and **8'** in 89% yield with a dr of 2.4:1. Rewardingly, both diastereomers were easily separated in 63% and 26% yields, respectively. Subsequent reduction of **8** in the presence of $NaBH_4$ followed by in situ protection gave the ether-silyl congener **9** in 61% yield, offering a pathway to analogs of mannostatin A, a glycosidase inhibitor.[17] Compound **10** featuring an all-carbon quaternary stereocenter was also successfully prepared in 91% yield with an excellent control of the diastereoselectivity. Finally, when treating **5a** with $NaBH_4$ and cerium (III) chloride heptahydrate, followed by addition of benzoyl chloride, ester **11** was generated in 71% yield and, unexpectedly, oxidation of the sulfoxide moiety took place to provide the corresponding sulfone. Then, to illustrate the removable character of our *o*-sulfinyl aniline auxiliary, the mixture of **7l**:**7l'** was first reduced to the corresponding thioether and then, treated with cerium ammonium nitrate (CAN). A subsequent acidic treatment led to the expected highly substituted amine-derived cyclopentenone in 48% yield over three steps.

In order to rationalize the stereoselectivity of this electrocyclization, the origin of the torquoselectivity has been investigated by means of DFT computations at the M06-2X/6-311 + G(d,p) level of theory (see the Supporting Information for details). A proton has been used as model catalyst. Since a mixture of solvents has been used, we will first discuss the gas phase Gibbs free energies. Four conrotatory 4π-electrocyclization transition states that would lead to the diastereomeric compounds **5a** and **5'a** are shown in Figure 1. Their $\Delta\Delta G^{\ddagger}_{298}$ (kcal/mol) are indicated in parentheses. **TS1**

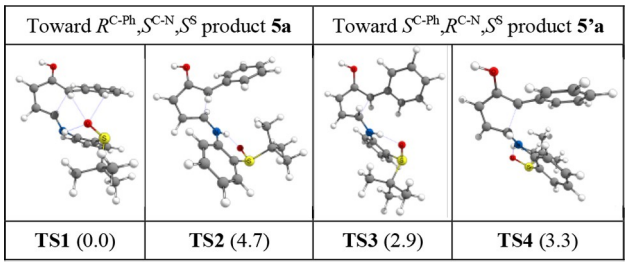


Figure 1. Computed **TS1**-**TS4** for compounds **5a** and **5'a** ($\Delta\Delta G^{+}_{298}$, kcal/mol).

and **TS2** display the same helicity of the pentadienyl carbocationic fragment. Both would produce the experimentally observed stereoselectivity in **5a**. However, the orientation of the chiral auxiliary is less favorable in **TS2** because of the steric clash between the Ph and *t*Bu groups. In **TS3** and **TS4**, the helix has the opposite configuration compared to the previous two transition states. This time, as they point in opposite directions, the Ph/*t*Bu clash becomes much less important. Having the *t*Bu outward remains the best option, but **TS3** lies higher in energy than **TS1**. In addition to these steric considerations, the preference for **TS1** in the gas phase can be explained by analyzing the non-covalent interactions. While each transition state exhibits a N–H…O–S hydrogen bond, only **TS1** can establish additional hydrogen bonds between the sulfoxide oxygen and protons of the π-extended pentadienyl-phenyl carbocation. The maximum electron density in these two C–H…O–S areas is $\rho_{max} = 0.010$ e.Å^{-3}, which is quite appreciable (about a third of the N–H…O–S hydrogen bond ($\rho_{max} = 0.033$ e.Å^{-3}), but twice). Taking HFIP as solvent (SMD method), the difference between **TS1** and **TS3** drops to 0.2 kcal/mol, which is in line with the absence of selectivity reported in Table 1, entry 3. With toluene as solvent, the $\Delta\Delta G^{+}_{298}$ between **TS1** and **TS3** is computed to be 1.4 kcal/mol. There is indeed a slight preference for **5a** under toluene-only conditions (Table 1, entry 4). Thus, the torquoselectivity appears to be governed by both the steric hindrance brought about by the bulky *t*-Bu group and non-covalent interactions that will be strongly affected by the reaction medium.[18]

In conclusion, we reported herein the first examples of stereoselective aza-Piancatelli reaction using enantiopure *o*-sulfinyl anilines as nucleophiles, which allows the synthesis of highly substituted cyclopentenones bearing two C-stereocenters with up to 98% yield and 95:5 dr. The synthetic value of this approach was further illustrated by post-derivatizations of the newly accessed scaffolds, thus, paving the way towards versatile molecules of interest for potential pharmaceutical applications.

Experimental Section

General procedure for the aza-Piancatelli cyclization: 2-Furylcarbinol **1a** (38 mg, 0.20 mmol, 1.3 equiv.) and aniline **2c** (30 mg, 0.15 mmol, 1 equiv.) were charged (in air) in a 10 mL screw-cap vial equipped with a stir bar. A mixture toluene/HFIP 4:1 (0.60 mL, 0.25 M) then $Ca(NTf_2)_2$ (4.6 mg, 0.0076 mmol, 5 mol%) and nBu$_4$NPF$_6$ (2.9 mg, 0.0076 mmol, 5 mol%) were added, and the tube was sealed. The reaction mixture was stirred at 20 °C for 0.75 h. Then, the reaction mixture was quenched with saturated NH_4Cl aqueous solution and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography using Pentane/EtOAc 7:3 then 6:4 as eluent to give **5a** (39.8 mg, 74%) and **5'a** (10.2 mg, 19%).

5a: CCDC 1906328 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/Community/Requestastructure.

Acknowledgements

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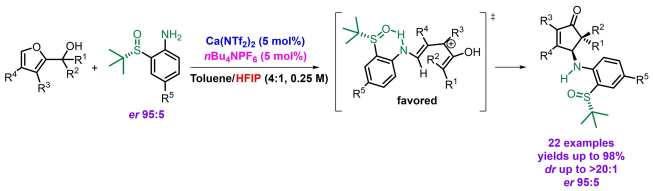
Sulfoxide-Controlled Stereoselective Aza-Piancatelli Reaction



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