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Rapid Access to Densely Functionalized Cyclopentenyl Sulfoximines through a Sc-Catalyzed Aza-Piancatelli Reaction

Emilie Werner,^[a] Milena Wiegand,^[a,b] Joseph Moran,^{*,[a,c,d]} and David Lebœuf^{*,[a]}

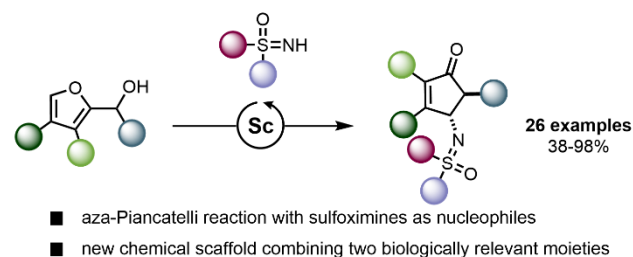
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Supporting Information Placeholder



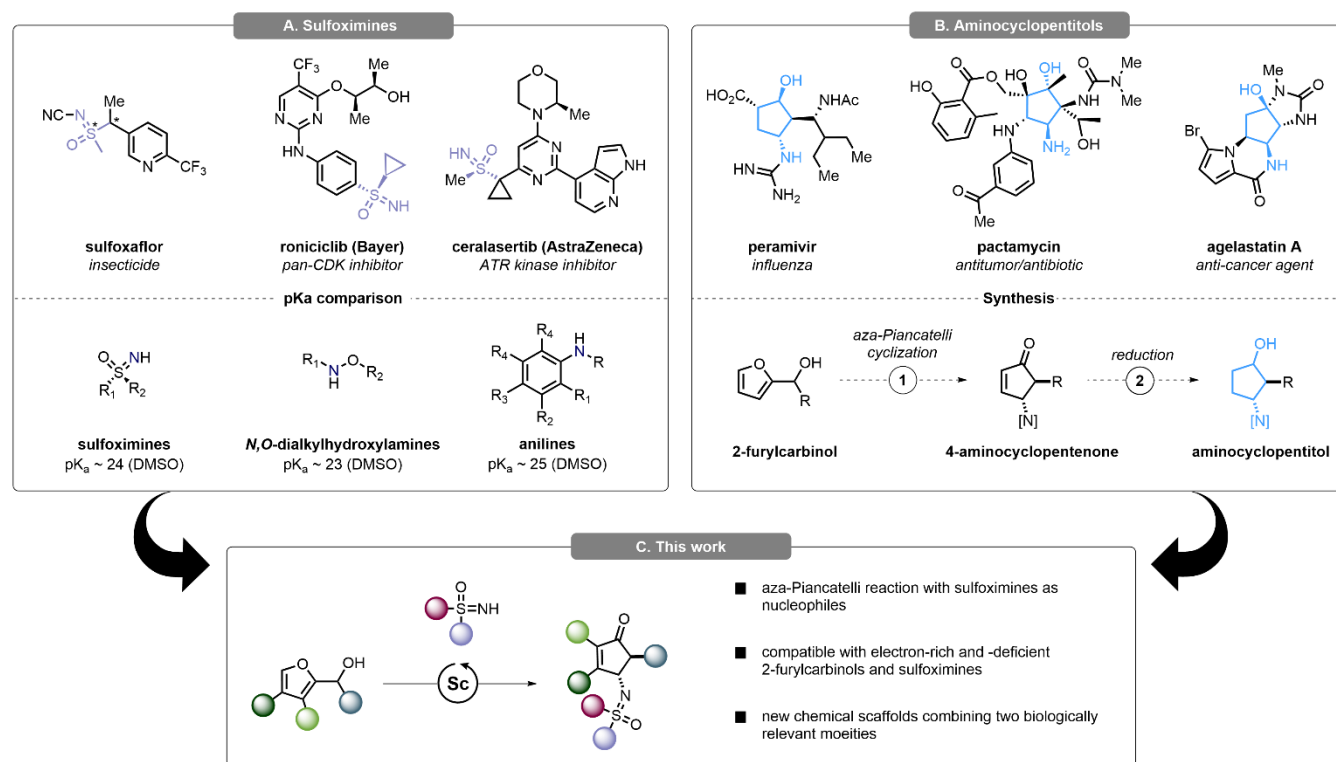
ABSTRACT: Sulfoximines are a class of compounds of growing interest for crop science and medicinal chemistry, but methods to directly incorporate them into complex molecular scaffolds are lacking. Here we report a scandium-catalyzed variant of the aza-Piancatelli cyclization that can directly incorporate sulfoximines as nucleophiles, rather than the classical aniline substrates. Starting from 2-furylcarbinols and sulfoximines, the reaction provides direct access to 4-sulfoximinocyclopentenones, a new scaffold bearing cyclopentenone and sulfoximine motifs, both of interest for bioactive compounds. The reaction partners tolerate a wide range of electronically diverse substituents, and the products are easily derivatized in divergent ways. The work represents the first inclusion of sulfoximines in 4π -electrocyclizations.

Sulfur-containing frameworks are often encountered in drug design due to their structural diversity and their ability to easily modulate physicochemical properties.^[1] Sulfoxides, sulfonamides and sulfones are common in commercially available drugs, whereas related isosteres such as sulfoximines, sulfonimidamides and sulfonimide esters, which have more handles for structural diversification, have traditionally been left behind.^[2] This has started to change, as sulfoximines have now gained significant interest in medicinal chemistry due to their simple synthesis, typically a single step from sulfides, their easy derivatization and pKa fine-tuning with the potential for chirality at sulfur,^[3] their metabolic stability, and their improved solubility in protic solvents compared to the widely used isosteric sulfones.^[1] Sulfoximines were first reported in 1949,^[4] but were largely disregarded until the approval of the first commercially available sulfoximine-containing pesticide, sulfoxaflor (Isoclast active), in 2013.^[5] Bayer's roniciclib, a pan-CDK inhibitor,^[6] was the first sulfoximine compound to enter clinical trials,^[7] with others now clinical

candidates. Ceralasertib (AstraZeneca), a sulfoximine containing ATR kinase inhibitor,^[8] recently passed phase II studies (Scheme 1A).^[9] In this context, expanding the range of complex frameworks incorporating sulfoximines has become a priority for several synthetic groups.

Separately, the aza-Piancatelli reaction, a Nazarov-type electrocyclization, has emerged as a powerful tool to assemble high value-added 4-aminocyclopentenones from feedstock furans in a single step with complete diastereocontrol.^[10,11] Simple derivatizations of these compounds enable the rapid construction of biologically relevant aminocyclopentitols.^[12-15] Densely functionalized cyclopentylamines are core motifs in a variety of natural and synthetic products such as peramivir,^[12] pactamycin,^[13] and agelastatin A^[14] as well as key building blocks in synthesis (Scheme 1B).^[15] Despite their growing importance, the preparation of cyclopentylamines remains highly challenging, often requiring lengthy syntheses. The aza-Piancatelli reaction therefore represents an attractive platform to access underexplored cyclopentylamine scaffolds for drug discovery.^[16]

Our group has recently demonstrated how domino or



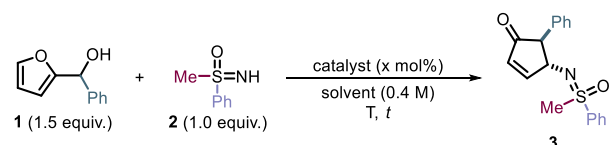
Scheme 1. Importance of sulfoximine groups and aminocyclopentitol moieties in bioactive molecules.

sequential reactions involving the aza-Piancatelli reaction can deliver cyclopenta[*b*]pyrroles,^[17] cyclopenta[*b*]piperazinones^[18] and bridged tetrahydrobenzo[*b*]azepines.^[19,20] Despite these successes, the aza-Piancatelli reaction remains restricted to aniline and *N,O*-hydroxylamine^[21] nucleophiles, limiting its utility for medicinal chemistry since the aniline residue is classified as a structural alert moiety in the assessment of drug toxicity.^[22] Sulfoximines have pK_a values comparable to anilines and *N,O*-hydroxylamines, hinting at potentially similar reactivity. We therefore wondered whether sulfoximines could be incorporated into the aza-Piancatelli reaction to deliver 4-sulfoximinocyclopentenones, which are thus far unreported and might constitute a new potentially biologically relevant scaffold. Here we disclose a scandium-catalyzed aza-Piancatelli cyclization that furnishes 4-sulfoximino-cyclopentenones from readily available 2-furylcarbinols and sulfoximines in a stereoselective fashion (Scheme 1C), while introducing several functional groups of interest. The work represents the first inclusion of sulfoximines in 4Π-electrocyclizations.

We began our optimization studies with 2-furylcarbinol **1** (1.5 equiv.) and sulfoximine **2** (1 equiv.) as model substrates, using Sc(OTf)₃ as a Lewis acid catalyst (5 mol%) in MeNO₂ (0.4 M) (Table 1). Anticipating possible side-reactions such as cationic oligomerizations or decomposition of the 2-furylcarbinol under our conditions, we conducted the reaction in the presence of a slight excess of **1** (1.5 equiv.). After 1 h at 50 °C, only trace conversion to cyclopentenone **3** was observed (entry 1). However, increasing the temperature to 80 °C afforded the target product **3** in 96% yield with a 1:1 diastereomeric ratio (dr) (entry 2). In this case, the diastereomeric products **3a** and **3b** were separated by

flash column chromatography. Lowering the catalyst loading (1 mol%) resulted in a decrease in yield (72%, entry 3)

Table 1. Optimization of the reaction conditions for the formation of 4-sulfoximinocyclopentenone **3.**



Entry	Catalyst	Cat. loading	Solvent	T (°C)	t (h)	Yield ^[a] (%)
1	Sc(OTf) ₃	5 mol%	MeNO ₂	50	1	traces
2	Sc(OTf) ₃	5 mol%	MeNO ₂	80	1	96 ^[b]
3	Sc(OTf) ₃	1 mol%	MeNO ₂	80	2	72
4	-	-	MeNO ₂	80	2	traces
5	Sc(OTf) ₃	5 mol%	HFIP	50	1	-
6	Sc(OTf) ₃	1 mol%	HFIP	22	17	-
7	Sc(OTf) ₃	5 mol%	1,2-DCE	80	1	91
8	Sc(OTf) ₃	5 mol%	MeCN	80	1	88
9	Sc(OTf) ₃	5 mol%	toluene	80	1	60
10	Bi(OTf) ₃	5 mol%	MeNO ₂	80	1	67
11	Cu(OTf) ₂	5 mol%	MeNO ₂	80	1	33
12	Yb(OTf) ₃	5 mol%	MeNO ₂	80	1	88
13	Ca(NTf ₂) ₂	5 mol%	MeNO ₂	80	1	39
14	Ca(NTf ₂) ₂ / <i>n</i> Bu ₄ NPF ₆	5 mol%	MeNO ₂	80	1	41

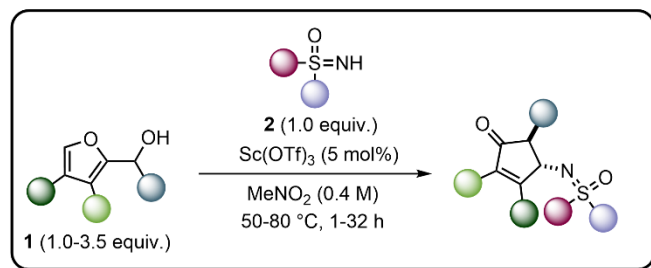
15	Dy(OTf) ₃	5 mol%	MeNO ₂	80	1	75
16	HOTf	5 mol%	MeNO ₂	80	1	96 ^[b]

[a] NMR yield using mesitylene as an external standard. [b] Isolated yield.

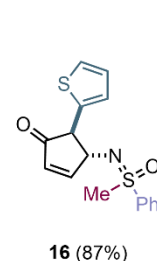
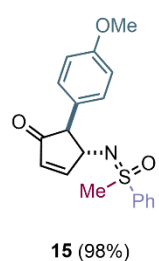
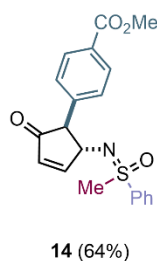
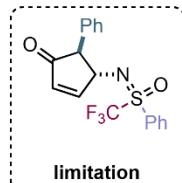
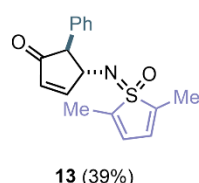
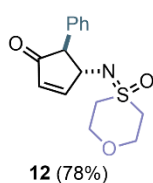
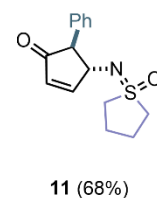
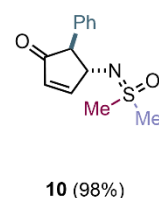
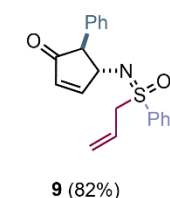
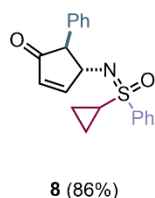
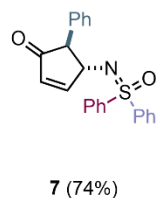
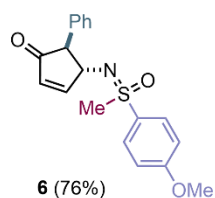
and in the absence of catalyst, no reaction occurred (entry 4). We then decided to examine other solvents. The use of hexafluoroisopropanol (HFIP) led to a complete degradation of **1** at 50 °C (entry 5), yet no conversion was detected at room temperature (entry 6). Other solvents such as 1,2-dichloroethane, acetonitrile and toluene were found to be compatible with the reaction, affording the product **3** in 91, 88 and 60% yield, respectively (entries 7-9). We then tested a series of common Lewis and Brønsted acids (entries 10-16). Among them, only triflic acid gave results comparable to Sc(OTf)₃ (entry 16). Being safer and more user-friendly, Sc(OTf)₃ was chosen as a catalyst for the rest of the study.

Of note, the reaction was also attempted with enantiopure **2**. Unfortunately, no asymmetric induction was observed.

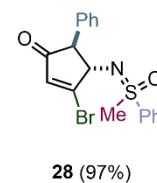
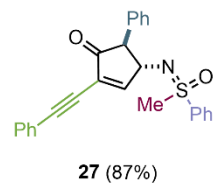
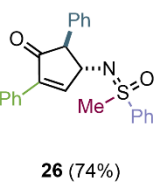
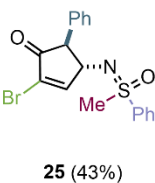
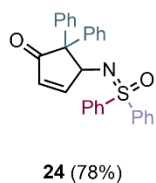
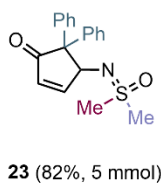
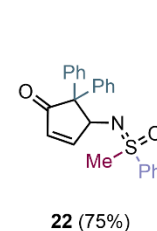
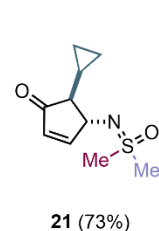
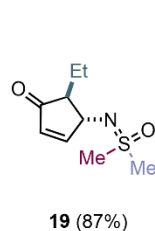
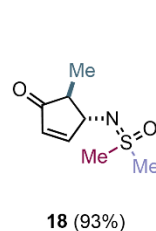
With the optimized reaction conditions in hand (Table 1, entry 2), we then investigated the scope of the scandium-catalyzed aza-Piancatelli cyclization using a variety of 2-furylcarbinols and sulfoximines. We first aimed at evaluating the aza-Piancatelli reaction with a wide range of sulfoximines (Scheme 2). Aryl groups bearing electron-withdrawing substituents on the sulfoximine were well-tolerated (**4** and **5**), although strongly deactivating groups led to a lower yield (**5**, 57%). On the other hand, we observed the decomposition of the 2-furylcarbinol under the reaction conditions when a less reactive sulfoximine bearing trifluoromethyl group was used. Electron-donating *S*-aryl sulfoximines were also compatible with the reaction conditions, as exemplified by compound **6**. The methyl group on



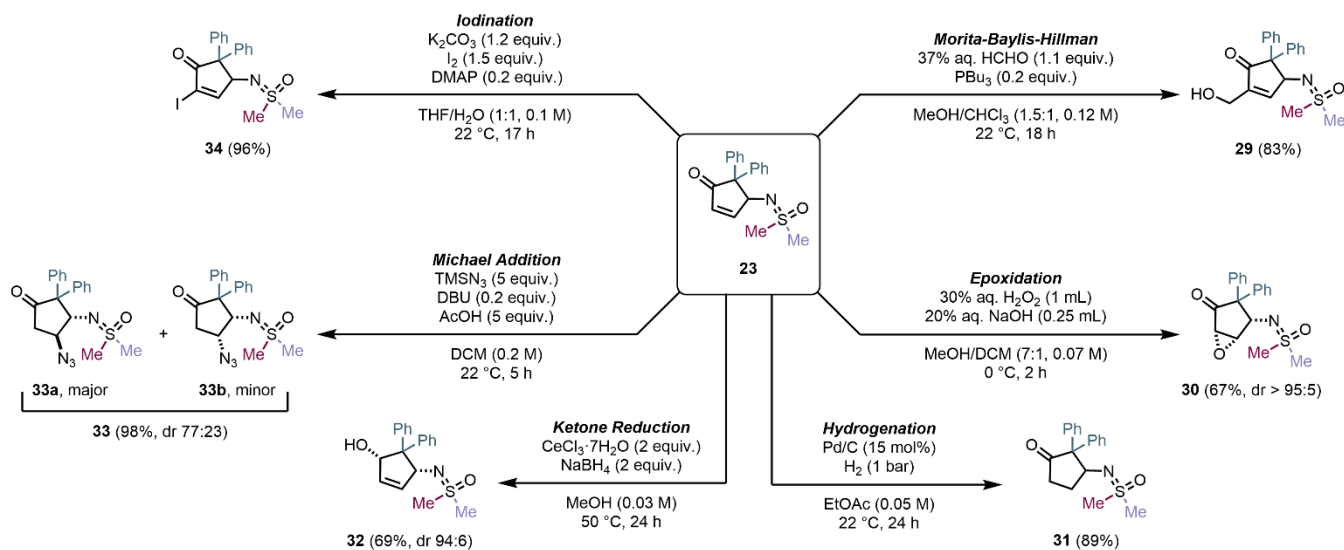
Scope of sulfoximines



Scope of 2-furylcarbinol



Scheme 2. Scope of 4-sulfoximinocyclopentenones. [a] Reaction performed in acetonitrile instead of nitromethane.



Scheme 3. Post-functionalization of 4-sulfoximinocyclopentenone 23.

the sulfoximine could be replaced with phenyl, allyl, and alkyl substituents to provide the corresponding products in high yields (up to 98%, **7-10**). Increasing the steric bulk around sulfur had no significant impact on the reaction (**7**). Importantly, several key *S*-heterocyclic moieties, including thiolane (**11**),^[23] thioxane (**12**),^[24] and thiophene (**13**)^[25] were smoothly incorporated into the target products, albeit in a lower yield in the latter case (39%), which was the result of its degradation under the reaction conditions.

We then explored the scope of 2-furylcarbinols, installing several common building blocks for drug discovery. Substrates bearing a moderately deactivating substituent were tolerated and only led to a slight decrease in yield (**14**, 64%). As expected, electron-rich (hetero)aryl groups proved favorable to the reaction (**15** and **16**), since they better stabilize the carbocation intermediate. Vinyl (**17**), alkyl (**18-21**) and diaryl (**21-23**) substituents were all well tolerated, regardless of the steric bulk. Interestingly, cyclopentenone **19** bearing an ethyl substituent shares a similar substructure with jogyamycin, a natural bioactive product against the protozoa responsible for malaria.^[26] In addition, this method allows the introduction of popular cyclopropyl groups (**21**), which offer a reactivity and conformational stability, resulting from bent bonds and high ring constraints. Compared to those of an ethyl group, their C-H bonds are shorter and stronger, making them metabolically more stable.^[27] Lower yields in conjugated systems (**17**, 40%) and allylic compounds (**20**, 38%) might result from side reactions, such as carbenium-migration, hydride shifts, Wagner-Meerwein-type rearrangement, or oligomerizations. The reaction was also applied to more functionalized 2-furylcarbinols incorporating readily modifiable functions at the C3 and C4 positions, such as halides, aryls, and alkynes (**25-28**, 43-97% yields), which could serve to implement several derivatizations to further decorate the cyclopentenone ring. We also looked at the scalability of the process, successfully preparing product **23** in 82% yield (1.33 g) on a 5 mmol scale.

Lastly, we studied the compatibility of the sulfoximine functionality towards classical post-functionalization of cy-

clopentenones. An undeniable advantage of the aza-Piancatelli reaction is the large range of derivatizations with respect to the outgoing product. Here, we focused on transformations enabling the introduction of key functionalities that are present in biologically active molecules (Scheme 3). For instance, a Morita-Baylis-Hillman reaction afforded compound **29** with a methylene alcohol moiety in 83% yield. Epoxidation of **23** furnished product **30** with a syn relationship between the epoxide and the sulfoximine, indicating that the sulfoximine likely serves as a directing group for the reaction. It is worth noting that anilines are often poorly compatible with oxidative reaction conditions, which is not the case here with sulfoximines. Pd-catalyzed hydrogenation of the alkene under atmospheric pressure gave cyclopentanone **31** in 89% yield. The ketone was also orthogonally reduced to give cyclopentenol **32** in 69% yield (dr 94:6), a compound that can be further functionalized at the alkene to give substituted aminocyclopentitols. Furthermore, an azide functionality was introduced through a Michael addition to generate azido compound **33** in high yield (98%) with good control of the diastereoselectivity (dr 77:23). Finally, iodination was successfully achieved at position 5 of the cyclopentenone to give product **34** in nearly quantitative yield, which could serve as an anchor for cross-coupling reactions. Here, one can see that the sulfoximine remains intact for all these transformations.

In conclusion, we have developed scandium-catalyzed conditions that allow sulfoximine nucleophiles to be incorporated into an aza-Piancatelli cyclization, giving direct access to 4-sulfoximinocyclopentenones for the first time in good yields. The reaction scope includes aromatic and aliphatic sulfoximines and 2-furylcarbinols bearing electron-withdrawing or -donating groups. The examples showcased include readily modifiable functions such as halide, alkene, and alkyne groups, but also common synthons for medicinal chemistry such as cyclopropyl groups or heterocycles. Importantly, the sulfoximine group in the aminocyclopentenone product proved to be compatible with various classical derivatizations. These new compounds hold promise for applications in medicinal chemistry, as they bear both the cyclopentenone motif, a common precursor in bioactive

molecules, and the sulfoximine functionality, an emerging group in drug discovery.

ASSOCIATED CONTENT

Supporting Information

The data that support the findings of this study are available in the Supporting Information of this article. This includes suppliers, references for the preparation of substrates, general and detailed reaction procedures, as well as full characterization of the products by HRMS, ¹H NMR, ¹³C NMR, ¹H-¹³C HSQC and additional ¹H-¹H NOESY NMR when needed (PDF).

The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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