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Strain-Release Driven Cycloadditions for Rapid Construction of Functionalized Pyridines and Amino Alcohols

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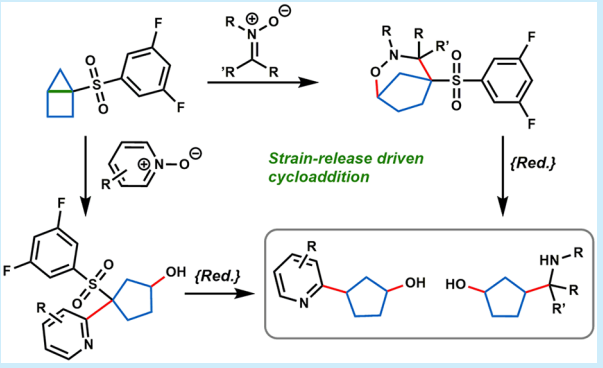
Supporting Information

ABSTRACT: This paper describes the development of a new variant of stereoselective strain-release driven reactions (formal homo [3 + 2] dipolar cycloadditions) which utilize housane (**1**) to construct functionalized amino alcohols and pyridine-substituted cyclopentanes in two to three steps from simple and easily available building blocks (nitrones and pyridine *N*-oxides respectively).



Relief of ring strain[1−3] is a powerful tactic to enable efficient access to complex molecular scaffolds which would otherwise be difficult to synthesize.[4−7] Recently, the bench-stable strain-release reagent "housane" (**1**), which is now commercially available, was introduced for the synthesis of a wide range of 1,3-disubstituted cyclopentanes via an S_N2'-type reaction.[8] Bicyclic sulfone **1** can be prepared in 99.5% enantiopurity, and the reaction proceeds with complete stereochemical control at the new C−Nu bond (Figure 1A).

In connection with a medicinal chemistry synthesis program, we considered the prospect of reacting 1,3-dipoles with **1** in order to form 1,3-difunctionalized cyclopentane moieties by intramolecular trapping of the presumed sulfone-stabilized anionic intermediate (Figure 1B). For exploratory studies of this formal homo [3 + 2] dipolar cycloaddition we chose nitrones, which have previously been shown to react with strained cyclic molecules.[9−12]

Initially, nitrone **2** was combined with **1** in DMSO at 85 or 100 °C. After 3 days, the consumption of **1** was complete, and the oxazabicyclo[3.2.1]octane (*exo*-**3**) was isolated as the major component of a 5:1 mixture of diastereomers (Scheme 1 and Table 1, entry 3). Neither addition of Lewis acids (entries 5−11) nor bases (entries 12 and 13) improved the outcome (e.g., Lewis base−housane adducts were usually observed in the crude product). A concise survey of high-boiling polar solvents identified sulfolane as the most suitable candidate, delivering *endo*- and *exo*-**3** in 64% total yield.

To explore the scope and limitations of this reaction, **1** was reacted with a number of readily available nitrones in sulfolane (Scheme 2, compounds **3**−**13**). It was found that the dihydroisoquinoline-nitrones were generally the most reactive, while simpler cyclic nitrones gave products in modest yields

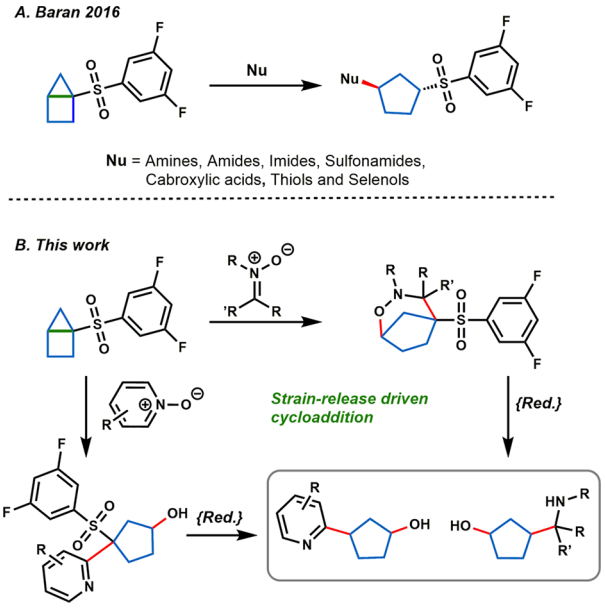


Figure 1. (A) Baran's cyclopentylation reaction. (B) Strain-release driven cycloadditions.

and the aniline-type cycloadduct **13** was not formed at all. A particularly pleasing result was the installation of the new quaternary stereocenter in compound **4**.

In all of the oxazabicyclo[3.2.1]octane products, the *exo* diastereomer was observed as the major component. This

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Scheme 1. Cycloaddition of Nitrone 2 with Housane 1

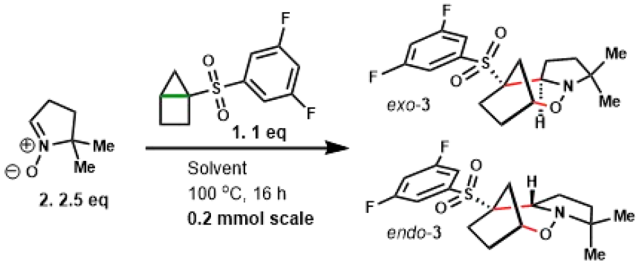


Table 1. Evaluation of Conditions for the Cycloaddition

entry	solvent	additive (10%)	result
1	DMSO[a]		mixture **1**/**3** 2:1[b]
2	DMSO[c]		mixture **1**/**3** 1:3[b]
3	DMSO[d]		43% exo[e]
4	DMSO		44% exo[e,f]
5	DMSO	$BF_3{\cdot}OEt_2$	mixture **1**/**3** 2:1[a,b]
6	DMSO	$Cu(OTf)_2$	mixture **1**/**3** 3:1[a,b]
7	DMSO	$NiCl_2(PPh_3)_2$	18% exo[b,e]
8	DMSO	$ZnCl_2$	mixture **1**/**3** 2:1[a,b]
9	DMSO	$AgSbF_6$	mixture **1**/**3** 1:2[a,b]
10	DMSO	$(AuNTf_2(PPh_3))_2$−toluene	mixture **1**/**3** 1.5:1[a,b]
11	DMSO	$PtCl_2$	mixture **1**/**3** 1:1[a,b]
12	DMSO	DMAP	20% exo[a,e]
13	DMSO	PPh_3	mixture **1**:**3** 1.3:1[a,b]
14	MeCN[g]		mixture **1**/**3** 1:1.4[b]
15	dioxane[g]		mixture **1**/**3** 2:1[b]
16	NMP[g]		40% exo[e]
17	sulfolane		64% exo[e,f]

[a]85 °C. [b]Based on crude ^{1}H NMR. [c]30 h. [d]72 h. [e]Full conversion. Isolated yield. [f]120 °C. [g]120 h.

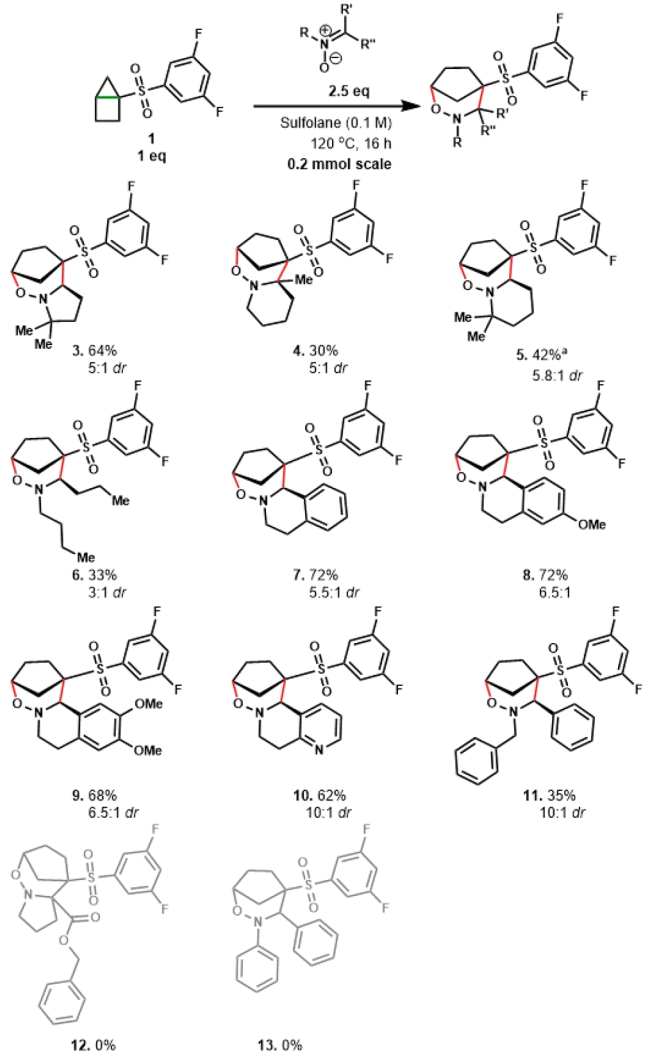
assignment is based on the isolation and ROESY-NMR analysis of both diastereomers in each case. For the minor *endo*-diastereomers, a through-space correlation was observed between the methine proton α to the nitrogen and one of the protons of the bridging methylene group. This correlation was absent for the major diastereomers.

For our medicinal chemistry project, cycloadditions using pyridine *N*-oxides[13] such as **14** were also of interest, and these were submitted to the same initial conditions (DMSO as solvent, which proved superior to sulfolane) as the nitrones (Scheme 3).

Not unexpectedly, the reaction did not halt at the cycloadduct stage and presumed intermediate **15** rearomatized to form *cis*-**16** in 50% yield. The results with other pyridine *N*-oxides are shown in Scheme 4 (compounds **16**–**24**). It became apparent that this reaction was sensitive to electronic influence: alkyl substituents on the pyridine ring are well tolerated in all positions and even sterically encumbered species such as **20** were readily formed, while electron-withdrawing substituents directly on the pyridine ring gave a complex mixture of products from which only trace amounts of the desired product could be isolated. Surprisingly, compound **21** was formed in only low yield (<10%) and was difficult to purify.

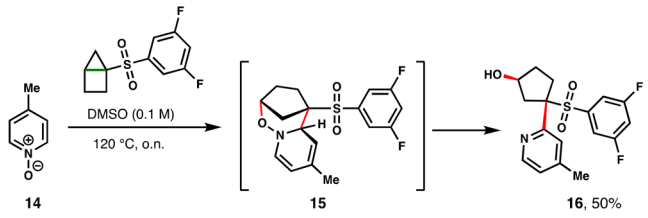
To showcase the usefulness of this methodology, oxazabicyclo[3.2.1]octanes **3** and **7** were desulfonylated, reduced to the corresponding amino alcohols, and then subsequently isolated as bis-acetates **26** and **28** (Scheme 5).

Scheme 2. Substrate Scope for the Cycloaddition, with Nitrones, Relative Stereochemistry



[a]For DMSO.

Scheme 3. Cycloaddition−Elimination with Pyridine *N*-Oxide 14



Compounds **16** and **19** could also be desulfonylated easily, providing pyridine alcohols **29** and **30**, respectively, as *trans*-cyclopentanes (presumably via thermodynamic control at the benzylic center).

In conclusion, we have developed a new variant of stereoselective strain-release driven reactions (formal homo [3 + 2] dipolar cycloadditions) which utilize housane (**1**) to construct functionalized amino alcohols and pyridine-substituted cyclopentanes in two to three steps from simple and easily available building blocks (nitrones and pyridine *N*-oxides respectively). These pyridine and amino alcohols can be used,

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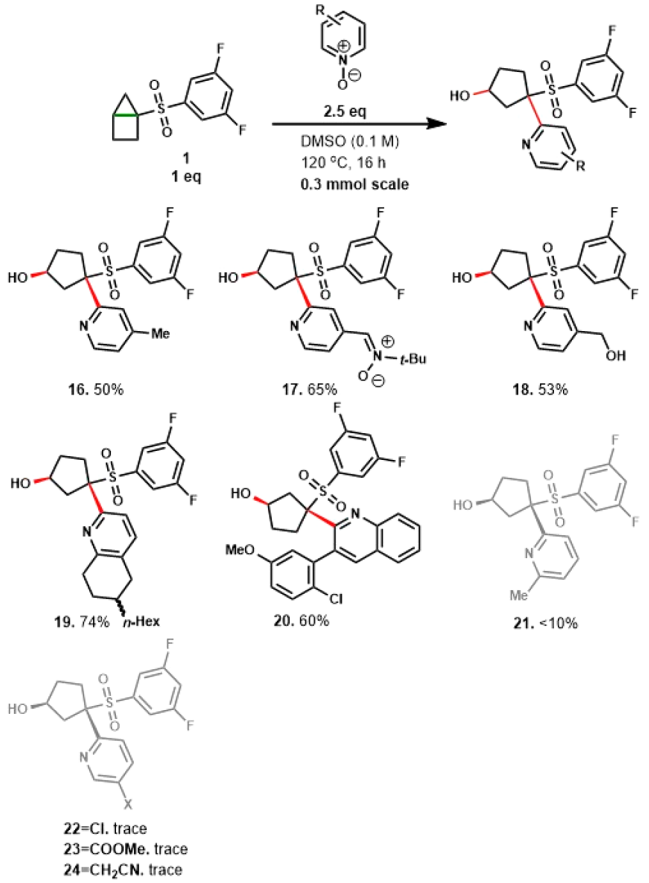
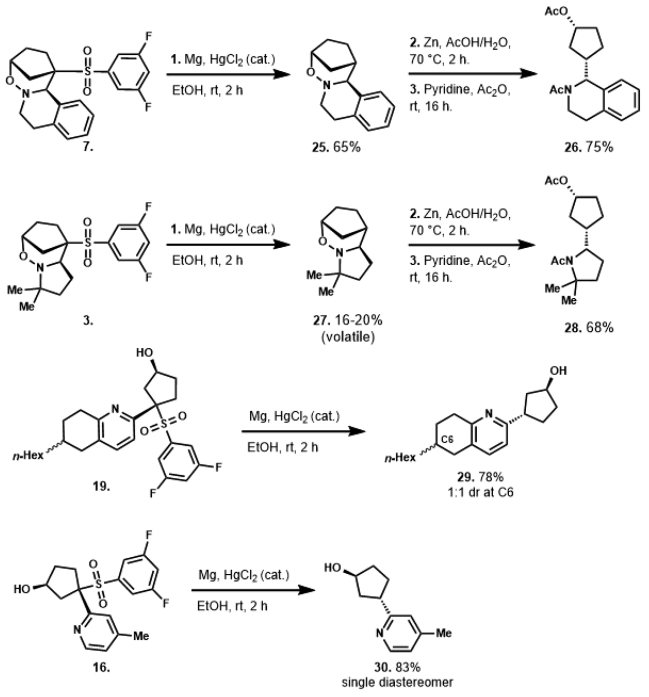
Scheme 4. Substrate Scope for the Cycloaddition and Cycloaddition Elimination, with Pyridine *N*-Oxides, Relative Stereochemistry



Scheme 5. Representative Reduction of Compounds (3, 7 and 16, 19) To Form *cis*-1,4-Amino Alcohols and Pyridine Alcohols, Respectively[a]



[a]Relative stereochemistry is shown.

after further chemoselective manipulations, in medicinal chemistry programs, as exemplified by the use of the oxidized version of **29** (the ketone), in search for a PDE4 ligand.[14]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01652.

Experimental details and spectroscopic data (PDF)

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§S.C. and A.R. contributed equally.

Notes

The authors declare no competing financial interest.

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