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# Aza-Prins Cyclization on Ketones to Access Piperidines with Tetrasubstituted Carbon Stereocenters

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**Abstract:** The aza-Prins cyclization in presence of a variety of aliphatic, aromatic, and heterocyclic ketones is disclosed. The developed method allows an access to diverse C-2 functionalized piperidines, bearing a tetrasubstituted or spiranic carbon stereocenter, in a range of 30 to 87% yields. When diastereomers were formed, the *trans* isomer was identified as the major product.

**Keywords:** Aza-Prins; Ketones; 2-Spiropiperidines; tetrasubstituted stereocenter; Titanium

The modern Prins cyclization involves simple starting materials such as a homoallylic alcohol or amine and an aldehyde, to provide tetrahydropyrans or piperidines in only one step with the concomitant carbon-carbon and carbon-heteroatom bond formation. While the Prins cyclization is very well documented,<sup>[1]</sup> its nitrogen-based version is significantly less developed,<sup>[2]</sup> although the piperidine ring is more widespread than tetrahydropyrans in natural products and drugs.<sup>[3]</sup> Despite the great potential of aza-Prins cyclization for the synthesis of natural and/or bioactive compounds, particular attention has been paid solely to the diversification of the homoallylic amines. In particular, aza-silyl Prins reactions<sup>[4]</sup> have been developed to obtain 3,4-dehydropiperidines with loss of the silicon group, alkynyl aza-Prins annulations<sup>[5]</sup> have provided similar compounds with a nucleophile in position C-4, and finally cascade aza-Prins reactions<sup>[6]</sup> have been reported for the formation of fused bi- and tricyclic systems. Concerning the carbonyl partner, apart from aldehydes, only two examples have been published to date: one with a very narrow range of ketones<sup>[7]</sup> and the other limited to 1,2-dicarbonyl substrates,<sup>[8]</sup> both leading to the synthesis of piperidines containing a tetrasubstituted carbon stereocenter in position 2.

To the best of our knowledge, an effective aza-Prins cyclization with non-activated ketones has not been reported so far. In continuation with our interest

in Prins processes,<sup>[9]</sup> we disclose here the first aza-Prins cyclization with aliphatic, aromatic, and heterocyclic ketones. Noteworthy, the present method competes well with other accesses to 2-spiranic piperidines.<sup>[10]</sup>

We have already reported the effectiveness of a synergistic combination of Lewis and Brønsted acids in the aza-Prins cyclization between secondary alkyl homoallylic amines and aldehydes.<sup>[11]</sup> Therefore, we first investigated the reactivity between *N*-benzyl homoallylamine **1** and cyclohexanone (**2a**) in the presence of 1 equiv. of TiCl<sub>4</sub> and 0.1 equiv. of *p*-TsOH·H<sub>2</sub>O in DCM at 60 °C in a sealed Schlenk tube for 24 h (Table 1, entry 1). Unfortunately, a disappointing lack of reactivity has been observed. We next investigated the effect of the Brønsted and Lewis acids alone (Table 1, entries 2 and 3 respectively), and only 9% conversion of the desired 2-spiropiperidine **3a** could be observed in the presence of 1 equiv. of TiCl<sub>4</sub> by <sup>1</sup>H-NMR analysis of the crude reaction mixture. Encouraged by this result, we decided to explore the effect of different additives such as molecular sieves, water and also PPh<sub>3</sub> (Table 1, entries 4-6) without further improvements. Gratifyingly, the use of 1 and then of 2 equiv. of triethylamine (TEA) (Table 1, entries 7 and 8) led to respectively 25% and 52% conversion into the desired product. This last result prompted us to examine diamines, in particular *N,N,N',N'*-tetramethylethylenediamine (TMEDA), *N,N,N',N'*-tetraethylethylenediamine (TEEDA), 1,4-diazabicyclo[2,2,2]octane (DABCO), and 1,2-dipiperidinyethane. As depicted in entries 9-12 in Table 1, TEEDA was found to be superior, leading to 2-spiropiperidine **3a** in 61% conversion, and was retained as the additive of choice for the rest of this study. In order to further improve the reactivity, the reaction was next performed in 1,2-DCE at 80 °C and indeed the analysis of the crude mixture showed 75% conversion (Table 1, entry 13). Increasing again the temperature to 100 °C proved detrimental to the reaction as by-products arising from the self-condensation/enolization of ketone **2a** became too

abundant. Finally, the stepwise addition of an excess of ketone during the reaction, i.e. 1.5 equiv. at the start followed by 0.5 equiv. after 8 hours, allowed us to obtain **3a** in 90% conversion (Table 1, entry 14).

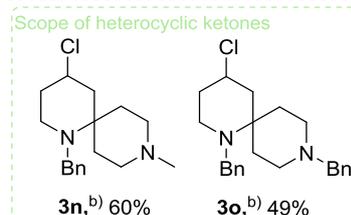
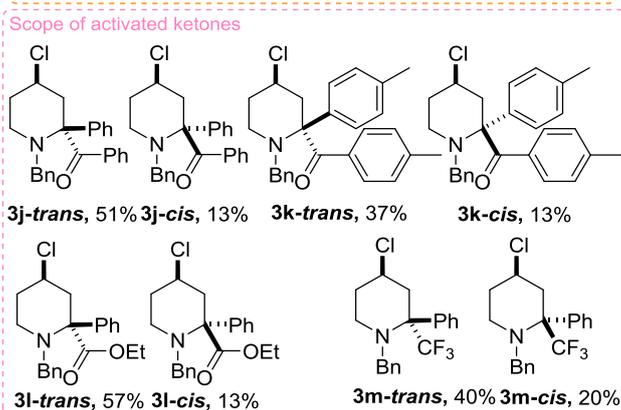
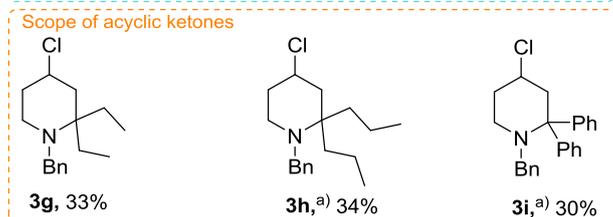
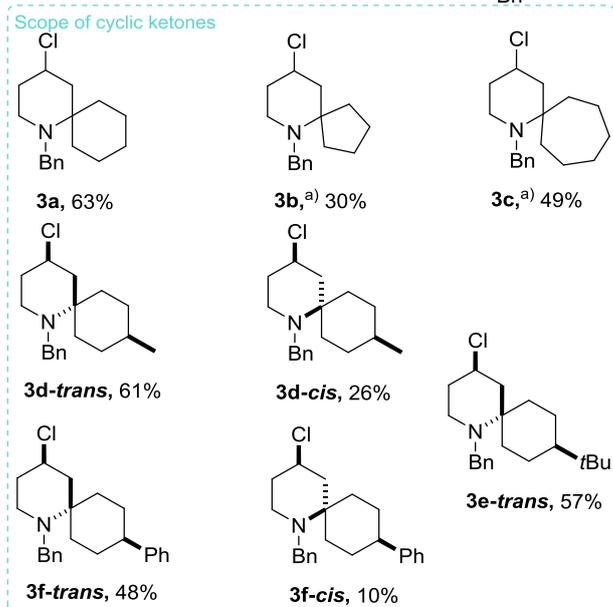
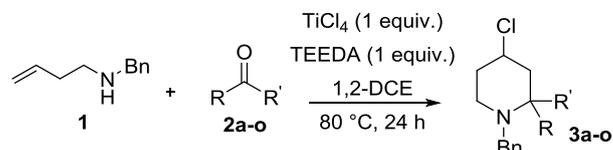
**Table 1.** Optimization of the reaction conditions between *N*-benzyl homoallylamine **1** and cyclohexanone (**2a**).

Entry <sup>a)</sup>	Additive (equiv.)	Solvent	T (°C)	Conv. (%) <sup>b)</sup>
1	<i>p</i> -TsOH·H <sub>2</sub> O (0.1)	DCM	60	0
2 <sup>c)</sup>	<i>p</i> -TsOH·H <sub>2</sub> O (1)	DCM	60	0
3	none	DCM	60	9
4	MS (3Å)	DCM	60	0
5	H <sub>2</sub> O (1)	DCM	60	0
6	PPh <sub>3</sub> (1)	DCM	60	0
7	TEA (1)	DCM	60	25
8	TEA (2)	DCM	60	52
9	TMEDA (1)	DCM	60	58
10	TEEDA (1)	DCM	60	61
11	DABCO (1)	DCM	60	43
12	1,2-dipiperidinyl ethane (1)	DCM	60	55
13	TEEDA (1)	1,2-DCE	80	75
14 <sup>d)</sup>	TEEDA (1)	1,2-DCE	80	90

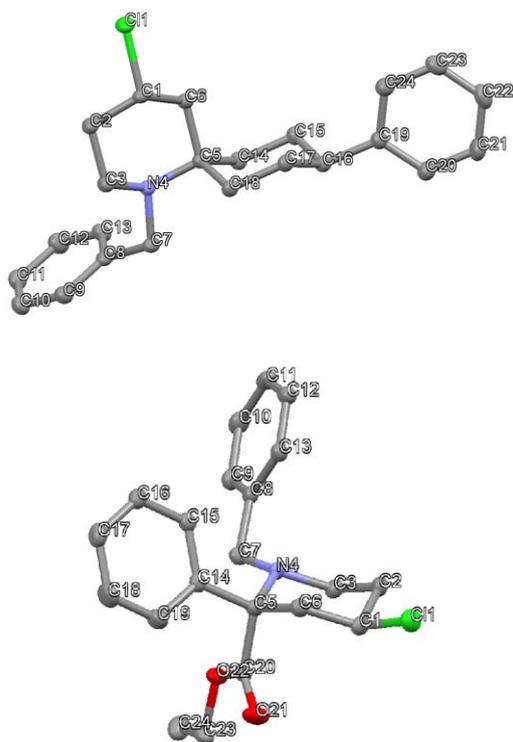
<sup>a)</sup> Unless otherwise noted, reactions were performed with homoallylamine **1** (1 mmol, 1 equiv.), **2a** (1 mmol, 1 equiv.), and TiCl<sub>4</sub> (1 mmol, 1 equiv.) in a sealed Schlenk tube for 24 h. <sup>b)</sup> Conversions were calculated by <sup>1</sup>H-NMR analysis of the crude reaction mixtures. <sup>c)</sup> Reaction was performed without TiCl<sub>4</sub>. <sup>d)</sup> Reaction was performed with 1.5 + 0.5 equiv. of **2a**.

Under the above optimized conditions, compound **3a** was isolated in 63% yield and the scope of the reaction was first evaluated on various other cyclic ketones (Scheme 1). Cyclopentanone (**2b**) and cycloheptanone (**2c**) gave satisfactory results albeit both reaction needed to be carried out at 100 °C, and products **3b** and **3c** were isolated in 30% and 49% yields, respectively. Next, a series of cyclohexanone derivatives substituted at the C-4 position **2d-f** were screened, and regardless the presence of an alkyl or aryl group in this position, these substrates readily participated in the reaction leading to **3d**, **3e**, and **3f** in 87%, 57%, and 58% yields, respectively. It has to be stressed that cyclanic isomerism has been observed for this series of 2-spiropiperidines and that the formation of the most stable *trans* isomer is favoured, if not exclusive, as in

the case of **3e** possessing the bulky *t*-Bu group. When present, the two isomers are separable by column chromatography on silica gel and the relative stereochemistry of **3f-trans** has been unambiguously confirmed by single crystal X-ray analysis, as shown in Figure 1.<sup>[12]</sup>



**Scheme 1.** Scope of the aza-Prins cyclization. Reaction conditions: **1** (1 mmol), **2** (1.5 + 0.5 equiv.), TiCl<sub>4</sub> (1 equiv.), TEEDA (1 equiv.) in 1,2-DCE at 80 °C in a sealed Schlenk tube for 24 h. Yields were determined after purification by column chromatography on silica gel (General procedure A). <sup>a)</sup> Reactions performed with **2** (1.5 + 1.5 equiv.) at 100 °C (General procedure B). <sup>b)</sup> Reactions performed without TEEDA (General procedure C).



**Figure 1.** ORTEP representations of **3f-trans** (top) and **3l-trans** (bottom) at 50% thermal ellipsoids. Hydrogen atoms are omitted for clarity.

The aza-Prins cyclization was then applied to more challenging acyclic substrates. In the presence of 3-pentanone (**2g**), 4-heptanone (**2h**), and benzophenone (**2i**), we were pleased to observe the formation of compounds **3g-i**. Given the difficulty of constructing tetrasubstituted carbon stereocenters from acyclic systems due to their inherent conformational mobility,<sup>[13]</sup> the yields obtained here, ranging from 30% to 34%, are still acceptable.

Encouraged by those results, we next examined the reaction between *N*-benzyl homoallylamine **1** and various activated (di)ketones. We were satisfied to conclude that this panel efficiently underwent aza-Prins cyclization with a very marked diastereoselectivity in favour of the *trans* isomer. As depicted in Scheme 1, benzil (**2j**) and its analog 4,4'-dimethylbenzil (**2k**) gave separable mixtures of diastereomers **3j** and **3k** with overall yields of 64% and 50%, respectively. The use of keto-ester **2l** allowed to recover **3l-trans** and **3l-cis** in 70% yield, whereas trifluoromethylated ketone **2m** gave

piperidines **3m-trans** and **3m-cis** in 60% overall yield. Moreover, single crystal X-ray analysis of **3l-trans** allowed to establish the relative stereochemistry of the two stereogenic centers that were formed during the reaction (Figure 1).<sup>[12]</sup>

Finally, we looked at the reactivity of *N*-heterocyclic ketones. Piperidones in particular were considered because their reaction could provide an access to spiro-fused dipiperidines, a class of compounds with strong biological activities.<sup>[14]</sup> Therefore, the aza-Prins cyclization between **1** and 1-methyl-4-piperidone (**2n**) was attempted under the optimized conditions but led to a loss of the reactivity. It was assumed that, if TEEDA is required to carry out the reaction, the combination of this additive and a nitrogen-containing substrate could deactivate the titanium active species. Indeed, without adding TEEDA to the reaction medium, the reactivity was recovered and product **3n** was isolated in 60% yield (Scheme 1). This trend could be extended to 1-benzyl-4-piperidone (**2o**), leading to the corresponding dipiperidine **3o** in 49% yield.

In summary, we have developed a titanium-TEEDA promoted aza-Prins cyclization of aliphatic, aromatic, and heterocyclic ketones. Our methodology provides an access to piperidines bearing tetrasubstituted or even spiranic carbon centers at the C-2 position, which are common naturally occurring scaffolds. The reaction proceeds diastereoselectively in favour of the *trans* isomer, both when non-symmetric substrates are used and when cyclanic isomerism is present. Further applications and substrate variations are in progress in our laboratory.

## Experimental Section

### General procedure A

To a solution of *N*-benzyl homoallylamine **1** (163 mL, 1 mmol) and the ketone (1.5 mmol) in dry 1,2-DCE (10 mL) was added TEEDA (213 mL, 1 mmol). The mixture was stirred for 10 min and a solution of TiCl<sub>4</sub> (1 mL, 1.0 M in DCM, 1 mmol) was added dropwise. The solution was stirred at 80 °C for 8 hours. After cooling to room temperature, the ketone (0.5 mmol) was again added to the mixture and the solution was further stirred at 80 °C overnight. After cooling to room temperature, the reaction was quenched with sat. NaHCO<sub>3</sub> (15 mL) and filtered on a Buchner funnel (1 layer of filter paper). The product was extracted with DCM (2 x 20 mL), the combined organic phases were washed with water (1 x 20 mL), dried over anhydrous MgSO<sub>4</sub>, and evaporated to dryness. The residue was purified by column chromatography on silica gel.

### General procedure B

To a solution of *N*-benzyl homoallylamine **1** (163 mL, 1 mmol) and the ketone (1.5 mmol) in dry 1,2-DCE (10 mL) was added TEEDA (213 mL, 1 mmol). The mixture was stirred for 10 min and a solution of TiCl<sub>4</sub> (1 mL, 1.0 M in DCM, 1 mmol) was added dropwise. The solution was stirred at 100 °C for 8 hours. After cooling to room temperature, the ketone (1.5 mmol) was again added to the mixture and the solution was further stirred at 100 °C overnight. After cooling to room temperature, the reaction was quenched with sat. NaHCO<sub>3</sub> (15 mL) and filtered on a Buchner funnel (1 layer of filter paper). The product was extracted with DCM (2 x 20 mL), the combined organic

phases were washed with water (1 x 20 mL), dried over anhydrous MgSO<sub>4</sub>, and evaporated to dryness. The residue was purified by column chromatography on silica gel.

### General procedure C

A solution of *N*-benzyl homoallylamine **1** (163 mL, 1 mmol) and the ketone (1.5 mmol) in dry 1,2-DCE (10 mL) was stirred for 10 min before adding a solution of TiCl<sub>4</sub> (1 mL, 1.0 M in DCM, 1 mmol) dropwise. The solution was stirred at 80 °C for 8 hours. After cooling to room temperature, the ketone (0.5 mmol) was again added to the mixture and the solution was further stirred at 80 °C overnight. After cooling to room temperature, the reaction was quenched with sat. NaHCO<sub>3</sub> (15 mL) and filtered on a Buchner funnel (1 layer of filter paper). The product was extracted with DCM (2 x 20 mL), the combined organic phases were washed with water (1 x 20 mL), dried over anhydrous MgSO<sub>4</sub>, and evaporated to dryness. The residue was purified by column chromatography on silica gel.

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