Template Catalysis

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4-*exo* Cyclizations by Template Catalysis**

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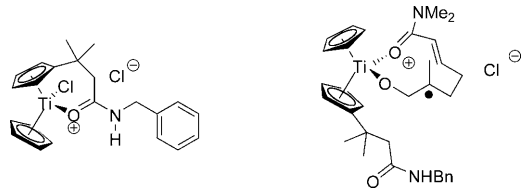
The cyclobutane ring is an important structural motif in many natural products. A number of synthetic approaches to four-membered rings have been described, but none of them is general.[1] This is also the case for radical cyclizations, even though they are in principle amongst the most powerful reactions for the construction of carbocyclic rings. Difficulties encountered in the preparation of cyclobutanes are caused by their inherent strain and by the low rate constant of the cyclization of the archetypal pentenyl radical.[2]

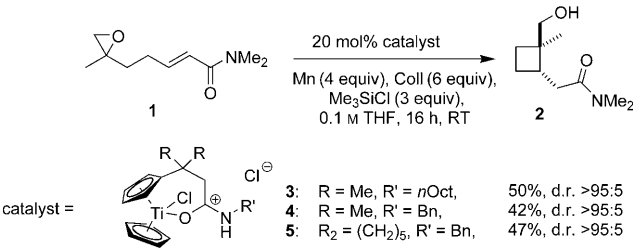
Therefore, the few efficient examples of 4-*exo* cyclizations in classical free radical chemistry, and in metal-mediated and metal-catalyzed radical reactions using SmI_2[3] and titanocene(III) reagents[4] have to rely on special structural features. In these cases, the presence of *gem*-dialkyl or *gem*-dialkoxyl substitution[5] adjacent to the radical center[6] or the incorporation of the cyclization into transannular tandem sequences[7] was necessary for obtaining useful yields of the desired products. A general access to cyclobutanes by the 4-*exo* cyclization is still elusive.

Herein, we address this issue by using cationic functionalized titanocenes[8] as template catalysts for such reactions. In these complexes the pendant amide ligand as well as the chloride ligand can be replaced by polar groups. For a suitably substituted radical this results in an energetically favorable two-point binding to the template in which the radical center and radical acceptor are forced into close spatial proximity. As a consequence, the 4-*exo* cyclization becomes a transannular transformation, which is thermodynamically and kinetically more favorable. With careful adjustment of the steric interactions this template effect can lead to highly ordered intermediates and transition states, and hence to a stereoselective cyclization (Scheme 1).

We have realized the two-point binding with unsaturated epoxides as radical precursors. Reductive electron transfer to the epoxide generates a radical which is covalently attached to titanium through a Ti–O bond. The pivotal second binding can be enforced by a donor group displacing the amide ligand. To this end, we chose **1** as the substrate, because α,β-unsaturated carbonyl groups usually constitute better ligands than the corresponding saturated carbonyl groups. The reaction of a tertiary radical renders the process thermodynamically unfavorable. Our results of the first 4-*exo* cyclization without *gem* disubstitution are summarized in Scheme 2 and Table 1 (Coll = collidine = 2,4,6-trimethylpyridine).



Scheme 1. Cationic titanocene complexes and templated radical binding. Bn = benzyl.



Scheme 2. Influence of template substitution on the 4-*exo* cyclization.

Table 1: Optimization of the 4-*exo* cyclization with **5**.

Entry	**5** [mol%]	*t* [h]	**2**/yield [%]	d.r.[a]
1	20	40	64	>95:5
2	10	60	55	>95:5
3	40	40	62	>95:5
4[b]	20	72	41	>95:5
5[c]	20	24	64	>95:5

[a] Determined by ^{1}H NMR spectroscopy. [b] Reaction temperature of 0 °C. [c] Reaction temperature of 68 °C.

From these investigations three points became clear, and they lend conclusive support to our postulated template mechanism. First, neither $[Cp_2TiCl_2]$ (Cp = cyclopentadienyl) nor any of the usually employed alkyl-substituted titanocenes gave any **2**, even though for substrates possessing *gem*-dialkyl substitution these complexes can give excellent yields of cyclobutanes.[6k] Instead, extensive decomposition of **1** was observed. Therefore, the opening of a second coordination site on titanium for templated radical binding is essential for the synthesis of **2**. The influence of the structure of the template on the reaction is small but noticeable. The *n*-alkyl chain in **3** proved to be superior to other groups. A bulkier substituent such as the cyclohexylidene in the nonhygro-

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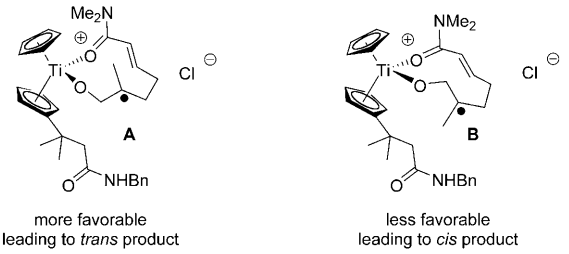
scopic, air-stable complex **5**, was sufficient to compensate for this effect.

Second, the protic conditions[9] usually employed for mediating turn-over are not suitable for the preparation of **2**. These unsuitable conditions must be the result of the cationic complexes, as the presence of amides and hydroxy groups is generally not detrimental to $[Cp_2TiCl_2]$ or alkyl-substituted titanocenes as catalysts.[9] The combination of Me_3SiCl and collidine as introduced by Oltra and Cuerva[10] is suitable to this end. In titanocene-catalyzed epoxide openings, this reagent combination is superior to Me_3SiCl,[11] which was introduced by Fürstner et al. in his seminal catalytic reactions.[12] It appears that only the silylated product can be displaced by the substrate from the template, because **2** is an excellent ligand for the titanocenes.

Third, the cyclization is completely diastereoselective at temperatures ranging from 0 to 70 °C (refluxing THF). This is remarkable in two respects. First, 4-*exo* cyclizations of substrates similar to **1**, without templated radical binding, have been predicted to proceed without diastereoselectivity.[6k] For substrates identical to **1** but containing a *gem*-dimethyl substitution, the cyclizations proceed with low selectivity. Second, in contrast to typical radical cyclizations the diastereoselectivity of our reaction is not temperature dependent.

The selectivity of our reactions can be explained by a two-point binding of the radical intermediate (Scheme 3). The templated cyclic radical will be more stable as conformer **A**, leading to the *trans* product. Therefore, the transannular cyclization should be diastereoselective over a wide temperature range as indeed observed.

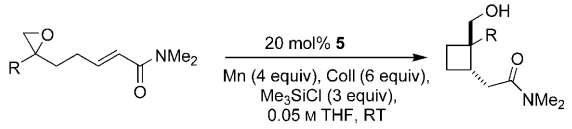


Scheme 3. Mechanistic rationale for the diastereoselectivity of the templated 4-*exo* cyclization.

To investigate the general applicability of our concept and to understand the relative importance of the steric interactions for the diastereoselectivity of the cyclization, we investigated substrates having different epoxide and amide substitution (Table 2 and Scheme 4). The presence of *n*-alkyl substituents at the epoxide (Table 2, entries 1–4) led to a slightly decreased diastereoselectivity with the yield of the products remaining almost unaffected. Introduction of the bulkier cyclohexyl group results in a low-yielding and unselective reaction (Table 2, entry 5).

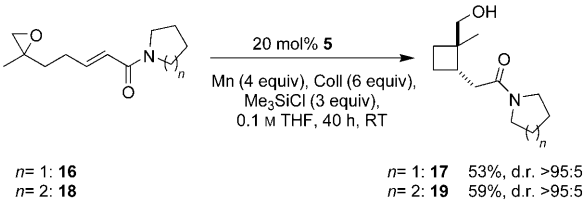
Amide substitution does not appear to be critical (Scheme 4) as both **17** and **19** are obtained in slightly lower yields than **2** and with complete diastereoselectivity. The relative configuration of *trans*-**15** was proven by X-ray

Table 2: Influence of epoxide substitution on the 4-*exo* cyclization.



Entry	Substrate/R	*t* [h]	Product [%]	d.r.[a]
1	**6**/Et	40	**7**/63	90:10
2	**8**/*n*Pr	60	**9**/70	87:13
3	**10**/*n*Bu	40	**11**/63	90:10
4	**12**/*n*Oct	72	**13**/60	88:12
5	**14**/Cy	40	**15**/46	68:32

[a] Determined by ^{1}H NMR spectroscopy. Cy = cyclohexyl.



n= 1: **16**
n= 2: **18**

n= 1: **17** 53%, d.r. >95:5
n= 2: **19** 59%, d.r. >95:5

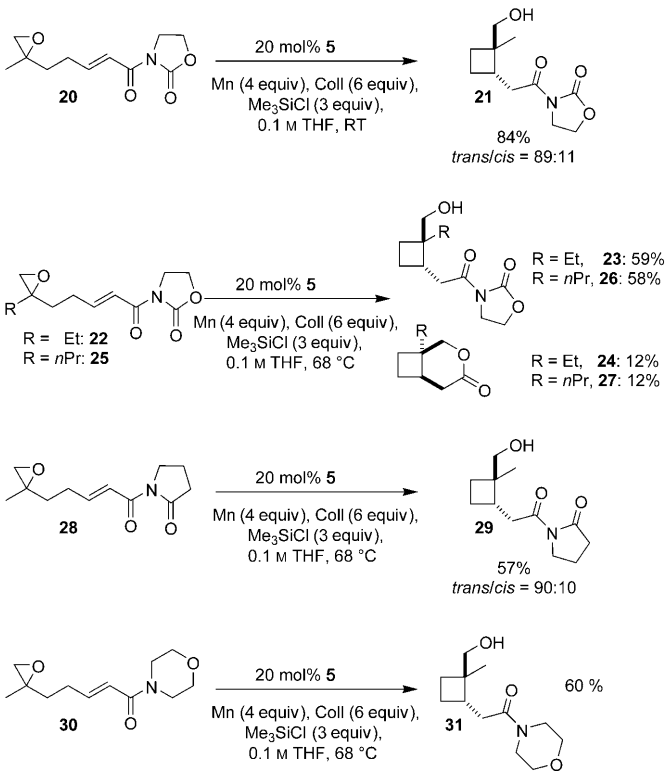
Scheme 4. Dependence of the templated 4-*exo* cyclization on amide substitution.

crystallography (see the Supporting Information for details).[13] This structure supports our hypothesis of product inhibition, because both the alcohol and the amide group are ideally positioned to render the cyclobutanes excellent bidentate ligands.

Finally, we turned our attention to alternative functional groups for enforcing the two-point binding of the radical intermediates (Scheme 5). Particularly interesting in this respect are oxazolidinones and morpholine-derived amide, because both can be additionally manipulated, for example, through alkylation, or transformed into acids, alcohols, ketones, or aldehydes[14] in a straightforward manner. Thus, a large number of functionalized cyclobutanes can in principle be accessed from the corresponding cyclization products.

Cyclobutane **21** can be obtained in 84% yield as an 89:11 mixture of separable diastereoisomers. Therefore, the use of oxazolidinones for binding to the cationic catalyst is not only possible but even results in higher yields of the corresponding products relative to those obtained when the amides are used; this is additionally corroborated by the results of **22** and **25**. Notably, for the latter two cases it was necessary to heat the reaction mixture to reflux to ensure a high conversion into the desired products **23** and **26**. In these cases, the minor *cis* isomers were obtained as the lactones **24** and **27**. Finally, both the pyrrolidinone derivative **28** and the morpholine-derived amide **30** gave the desired cyclobutanes **29** and **31**, respectively. As expected, **31** was formed with complete diastereoselectivity.

In conclusion, we have devised a novel concept for the realization of one of the most difficult radical cyclizations based on the use of our cationic titanocene complexes. Through binding of both the radical and radical acceptor to



Scheme 5. Additional examples of the template-catalyzed 4-*exo* cyclization.

the template catalyst in a two-point mode the 4-*exo* cyclization is rendered thermodynamically and kinetically favorable. Our method allows an easy access to many functionalized cyclobutanes in good yields and high diastereoselectivities. The products can be additionally functionalized in a straightforward manner. Moreover, our approach should be of broad significance for other radical reactions, because it can in principle be applied to any kinetically or thermodynamically difficult transformation.

Experimental Section

A typical procedure: In an oven-dried schlenk-flask, under Ar, **5** (48 mg, 100 μmol, 0.200 equiv) and manganese (110 mg, 2.00 mmol, 4.00 equiv) were suspended in THF (5 mL). After the reaction mixture turned lime-green, **20** (113 mg, 0.500 mmol, 1.00 equiv), collidine (0.39 mL, 3.00 mmol, 6.00 equiv), and Me_3SiCl (0.19 mL, 1.50 mmol, 3.00 equiv) were added, and the reaction mixture was stirred at RT for 24 h. After addition of methyl *tert*-butyl ether (MTBE; 5 mL), phosphate-buffer (5 mL), and KF (290 mg, 5.00 mmol, 10.0 equiv) stirring was continued for 2 h at RT. The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL), MTBE (3 × 10 mL), and CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and all volatiles were removed in vacuo. The resulting crude reaction mixture was purified by flash column chromatography (SiO_2, EtOAc) to give **21** (96 mg, 84 %, d.r. (*trans/cis*) 89:11) as separable diastereoisomers.

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