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Catalytic Enantioselective Radical Cyclization via Regiodivergent Epoxide Opening

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Abstract: A catalytic enantio- and diastereoselective radical cyclization using a regiodivergent epoxide opening (REO) for radical generation is described. It is demonstrated for the first time that the diastereoselectivity of cyclizations of acyclic radicals can be controlled catalytically. Building blocks for important applications in stereoselective synthesis are readily accessed.

Because of their high versatility, selectivity, and compatibility with densely functionalized substrates, radical cyclizations are frequently employed in the synthesis of complex molecules.[1] Unfortunately, enantioselective cyclizations allowing highly selective access to important structures are still rare.[2]

The reported cyclizations are based on Lewis acid chelation of the substrates, such as β-dicarbonyl compounds[2a,b] or hydroxamate esters,[2c] to obtain cyclic radicals under chain conditions. Our concept employs enantioselective radical generation via titanocene-catalyzed regiodivergent epoxide opening (REO) and catalyst-controlled diastereoselectivity of the 5-exo cyclization of an acyclic radical (Scheme 1).[3,4]

The pivotal radicals are generated under catalytic conditions[5b−e] that are based on the stoichiometric reaction of RajanBabu and Nugent.[5a] As the catalyst we investigated Kagan's complex (**4**).[6] Although **4** can exert high reagent control in enantio- or regioselective epoxide openings,[3,7] it was not clear if this would also be the case for the sterically and electronically biased silylated

Scheme 1. Concept of Enantioselective Radical Cyclization after Regiodivergent Epoxide Opening (REO)

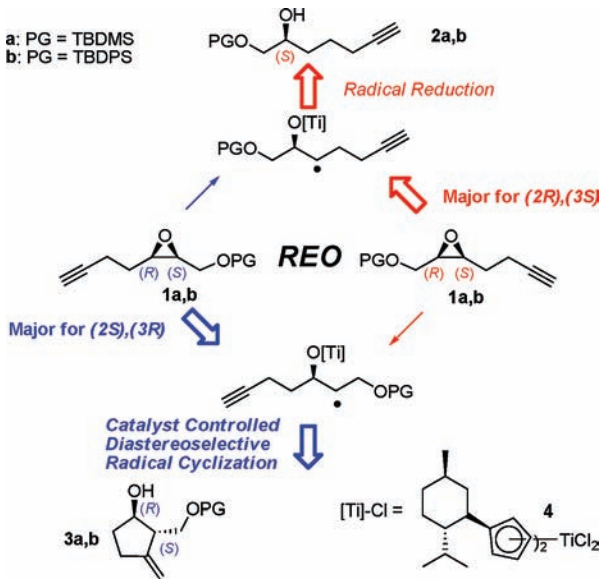


Table 1. REO Cyclization of **1** Catalyzed by 10 mol % Cp_2TiCl_2 or **4** in the Presence of Mn, 1,4-C_6H_8, and 2,4,6-Collidinde*HCl

entry	cat., substrate, er[a]	**2**, yield, **er**	**3**, yield, trans:cis, **er (trans)**
1	Cp_2TiCl_2, **1a**, 50:50	**2a**, 31%, **50:50**	**3a**, 9%, 66:34, **50:50**
2	**4**, **1a**, 50:50	**2a**, 36%, **12.5:87.5**	**3a**, 30%, 91:9, **94:6**
3	**4**, **1a**, 93:7	**2a**, 15%, **ND**	**3a**, 68%, 91:9, **>99:<1**
4	*ent*-**4**, **1a**, 93:7	**2a**, 56%, **>99:<1**	**3a**, 2%, ND, **ND**
5	Cp_2TiCl_2, **1b**, 50:50	**2b**, 40%, **50:50**	**3b**, 11%, 68:32, **50:50**
6	*ent*-**4**, **1b**, 50:50	**2b**, 42%, **84:16**	**3b**, 34%, 91:9, **3:97**
7	**4**, **1b**, 93:7	**2b**, 14%, **ND**	**3b**, 68%, 91:9, **>99:<1**

[a] (2*S*,3*R*):(2*R*,3*S*).

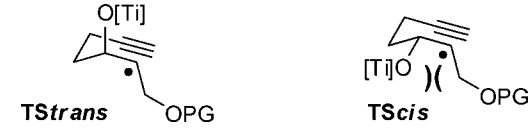
Sharpless epoxides **1**. Moreover, no precedent for the ability of **4** or any other titanocene to induce high 1,2-induction in radical cyclizations was available.

Alkynes were chosen as radical acceptors in our model substrates **1** because the exocyclic olefin present in the products **3** can be exploited for further stereoselective transformations with a large degree of flexibility. The reactions of **1** with Cp_2TiCl_2 and **4** are summarized in Table 1.

Cp_2TiCl_2 (entries 1 and 5) is not an attractive catalyst, as the yields of the products are bad, **1** is opened to the undesired **2** preferentially (3−4:1), and the induction of diastereoselectivity by the C_5H_5 ligands is too low (∼2:1). REOs with **4** are highly enantioselective with the TBDPS group (97:3 in **3b**; 94:6 in **3a**). Enantiomerically enriched substrates (entries 3 and 7) lead to **3a** and **3b** in even higher selectivity. Complex **4** induces a 91:9 diastereoselectivity of the cyclization (Scheme 2). The alkyne renders both transition states methylenecyclopentane-like rather than cyclohexane-like as in the Beckwith−Houk model.[8] In **TS*trans***, steric interactions between the alkyne, CH_2OPG, and O[Ti] groups are minimized. In **TS*cis***, there is an unfavorable interaction between the CH_2OPG and O[Ti] groups. This is especially relevant for the menthyl-substituted ligands of **4**. The pseudoaxial orientation of the CH_2OPG group is supported by the higher diastereoselectivities with substituted alkynes (Table 2). Similar trans selectivities in substrate-controlled radical cyclizations to give methylenecyclopentanes have been reported.[8c]

The flexibility of our approach is highlighted by the transformation of **3b** into either **5a** or **5c** (Scheme 3). **5a** can be obtained from **3b** by hydrogenation with Crabtree's catalyst.[9] **5c** can be synthesized using the same methodology from **3b** after inversion of the protection pattern in a two-step sequence.

Scheme 2. Origin of the Diastereoselectivity of the Cyclization



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Scheme 3. Stereoselective Directed Hydrogenations with **3b**

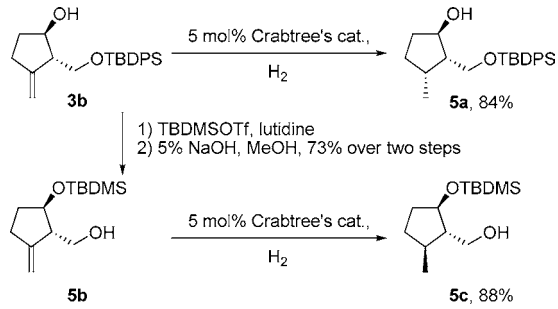
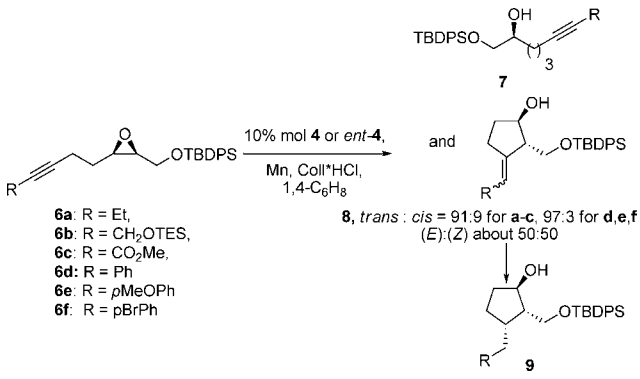


Table 2. REO Cyclization of **6a**−**f** Catalyzed by **4**

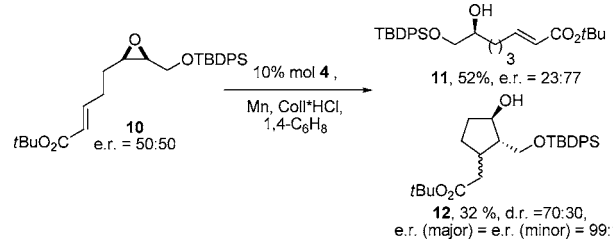


entry	substrate, er[a]	**7**, yield, **er**	**8**, yield, **er (trans)**[d]
1	**6a**, 50:50[b]	**7a**, 38%, **88.5:11.5**	**8a**, 38%, **97:3**
2	**6a**, 93:7[b]	**7a**, 14%, **ND**	**8a**, 67%, **>99:<1**
3	**6b**, 50:50[b]	**7b**, 36%, **85:15**	**8b**, 25%, **97.5:2.5**
4	**6b**, 93:7[b]	**7b**, 22%, **ND**	**8b**, 58%, **99:1**
5	**6c**, 50:50[b]	**7c**, 47%, **85.5:14.5**	**8c**, 33%, **97.5:2.5**
6	**6c**, 93:7[b]	**7c**, 31%, **ND**	**8c**, 51%, **98:2**
7	**6d**, 50:50[b]	**7d**, 46%, **88:12**	**8d**, 36%, **97.5:2.5**
8	**6d**, 91:9[b]	**7d**, 24%, **ND**	**8d**, 56%, **>99:<1**
9	**6e**, 50:50[c]	**7e**, 44%, **18:82**	**8e**, 37%, **4:96**
10	**6e**, 93:7[b]	**7e**, 11%, **ND**	**8e**, 68%, **>99:<1**
11	**6f**, 50:50[c]	**7f**, 46%, **26:74**	**8f**, 40%, **1.5:98.5**
12	**6f**, 84:16[b]	**7f**, 24%, **ND**	**8f**, 55%, **99:1**

[a] (2*S*,3*R*):(2*R*,3*S*). [b] cat = **4**. [c] cat = *ent*-**4**. [d] Determined by chiral HPLC of **9** and ^{19}F NMR analysis of the Mosher esters of **9**.

The high enantioselectivities of the reactions of all of the racemic substrates (>97:3 except for 96:4 with **6e**; Table 2) underlines the efficiency of the REO of silylated Sharpless epoxides. The use of enantiomerically enriched substrates resulted in almost enantiomerically pure products (entries 2, 4, 8, 10, and 12). The catalyst-induced diastereoselectivity of the cyclizations was good (91:9, **8a**−**c**) to excellent (97:3, **8d**−**f**). From **8a**−**f**, compounds **9a**−**f** were prepared as single isomers by hydrogenation. Both the cis and trans isomers are useful for the synthesis of products with interesting biological or olfactory properties, such as deoxyprostaglandins[10] or dihydrojasmonates, respectively.[11] Finally, it was established that alkenes are inferior to alkynes as radical acceptors (Scheme 4). While the enantioselectivity is excellent, the diastereoselectivity of the cyclization is too low because of the opposing inductions of the O[Ti] group and the CH_2OPG radical substituent in cyclohexane-like transition structures according to the Beckwith−Houk rules.[8]

Scheme 4. REO Cyclizations with Acrylate Acceptors



In summary, we have devised enantioselective catalytic radical cyclizations for the stereodivergent synthesis of cyclopentanols.

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Supporting Information Available: Experimental details and compound characterization, including NOE studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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