Radical Catalysis Hot Paper

International Edition: DOI: 10.1002/anie.201509548
German Edition: DOI: 10.1002/ange.201509548

Amide-Substituted Titanocenes in Hydrogen-Atom Transfer Catalysis

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Abstract: *Two new catalytic systems for hydrogen-atom transfer (HAT) catalysis involving the N–H bonds of titanocene(III) complexes with pendant amide ligands are reported. In a monometallic system, a bifunctional catalyst for radical generation and reduction through HAT catalysis depending on the coordination of the amide ligand is employed. The pendant amide ligand is used to activate Crabtree's catalyst to yield an efficient bimetallic system for radical generation and HAT catalysis.*

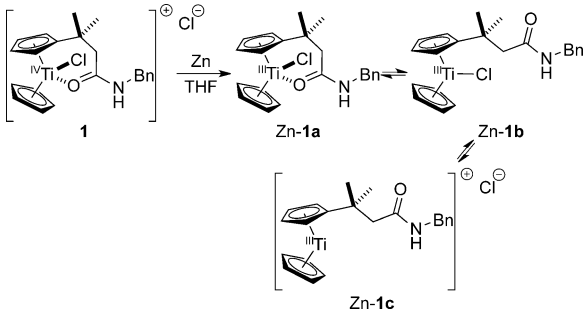
The reduction of C-centered radicals is an essential chemical reaction that is usually accomplished by hydrogen-atom transfer (HAT) from compounds containing weak M–H bonds.[1] In chain reactions, HAT has usually been carried out with Bu_3SnH,[1] $(Me_3Si)_3SiH$,[2] or NHC-Boranes as stoichiometric H-atom donors.[3]

With respect to sustainability, the use of HAT catalysts is clearly more attractive. To date, the generation of such catalysts has relied on the in situ generation of metal complexes containing M–H bonds generated from H_2 or silanes.[4,5] An attractive alternative for HAT catalysis that does not require the use of H_2 is lowering of the bond dissociation energy (BDE) of molecules with strong O–H bonds, such as H_2O or CH_3OH, by coordination to low-valent metal reagents, such as titanocene(III) complexes.[6] However, the titanocene reagent is often used in stoichiometric amounts.

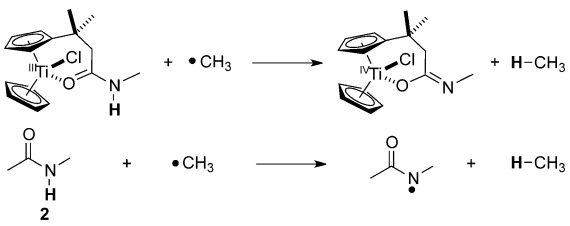
The activation of amide N–H bonds by complexation to low-valent metals is a particularly interesting alternative to HAT catalysis in this respect.[7] This is because amides can be readily prepared in a modular fashion from carboxylic acids and amines, which are both available in large numbers and with large structural diversity. Amide coordination to the metals, especially early transition metals, is usually strong and, if necessary, can be favored by covalent attachment to the ligand scaffold. Employing the amide in large excess or as a co-solvent can thus be avoided. A particularly intriguing aspect of our approach is that the simple amide-derived catalysts serve as leads for the design of peptide-containing HAT catalysts.

Herein, we report the activation of N–H bonds for HAT when using titanocene(III) catalysts with pendant amide ligands.[8] These can be conveniently generated from the corresponding cationic titanocene(IV) complexes by reduction with Zn powder.

As shown in Scheme 1, Zn-**1** contains three species in THF.[9] The neutral Zn-**1a** displays the desired coordination of the pendant amide and could serve as a HAT reagent or catalyst. This notion is supported by DFT calculations with the TURBOMOLE 7.0 program package.[10] The geometries were fully optimized at the TPSS[10]-D3[10]/def2-TZVP[10] level of theory. Final reaction free energy values were obtained through single-point calculations on the PW6B95[10]-D3/def2-QZVP(-g/-f)[10] level in the gas phase, with the COSMO-RS[10] model applied to include solvation (Scheme 2, see the Supporting Information for details). The HAT from



Scheme 1. Mixture of complexes of Zn-reduced **1** (hereafter Zn-**1**) in THF.



	ΔE (gas)	ΔH (gas)	ΔG (gas)	ΔG (THF)
with titanocene	−40.9	−39.5	−38.2	−34.5
no titanocene	0.3	0.4	1.1	4.3

Scheme 2. Computational analysis (PW6B95-D3-COSMO-RS/def2-QZVP(-g/-f)//TPSS-D3/def2-TZVP in THF at 298.15 K) of methyl radical reduction by a model of Zn-**1a** (kcal mol^{-1}).[10]

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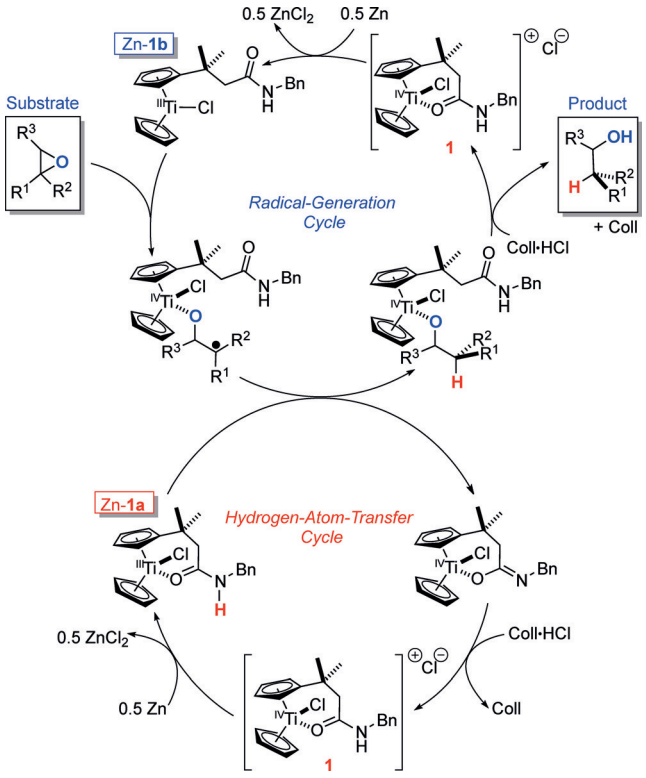
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201509548.

a model of Zn-**1a** to the methyl radical is more favorable than that from **2** by about 39 kcal mol^{-1}. The reason for this remarkable decrease in the BDE of the N–H bond is the oxidation of Ti^{III} to Ti^{IV} that occurs in combination with HAT.[11] These results highlight the fact that the weakening of X–H bonds through coordination to low-valent metals is not confined to H_2O or simple alcohols.

An important aspect for the development of HAT catalysis is that Zn-**1** exists as an equilibrating mixture of mainly Zn-**1a**, some Zn-**1b**, and a minor amount of cationic Zn-**1c**. The neutral Zn-**1b** has a vacant coordination site for substrate binding. Therefore, solutions of Zn-**1** should be suited for bifunctional catalysis incorporating electron transfer (ET) reactions for radical generation (Zn-**1b**) and HAT (Zn-**1a**). The two functions can be merged in the coupled cycles shown in Scheme 3.

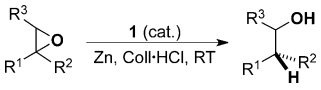


Scheme 3. Coupling of catalytic cycles for the reduction of epoxides by Zn-**1**.

According to our postulated mechanism, only a catalytic amount of **1**, one equivalent of Zn, and two equivalents of collidine·HCl, but no external H-atom donor such as 1,4-cyclohexadiene or Bu_3SnH, are required for epoxide reduction. This is indeed the case for a variety of epoxides (Table 1).

The reaction conditions are generally applicable to monosubstituted, *cis*-1,2 disubstituted, 1,1-disubstituted, and trisubstituted epoxides. A number of functional groups, incuding the sensitive tosylate (entry 9), are tolerated. The low diastereoselectivity detected in the opening of **13** (entry 6) is

Table 1: Examples of HAT Catalysis with Zn-**1**.



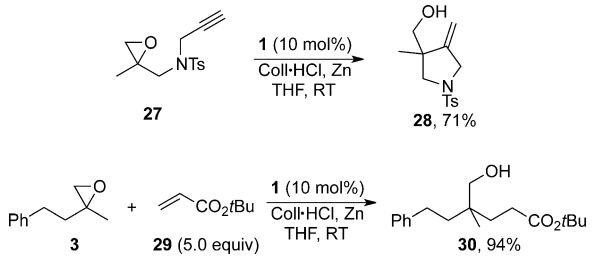
Entry	Substrate	Product	Yield [%]
1	**3**	**4**	84[a]
2	**5**	**6**, d.r. = 88:12	80
3	**7**	**8**	69
4	**9**	**10**	78
5	**11**	**12**	79[b,c]
6	**13**	**14**, *cis*/*trans* = 55:45	85[b]
7	**15**	**16**	84[d,e]
8	**17**	**18**	52[b,f]
9	**19**, R = H; **21**, R = Bn; **23**, R = Ts; **25**, R = Piv	**20**, R = H; **22**, R = Bn; **24**, R = Ts; **26**, R = Piv	**20**, 81 **22**, 78 **24**, 91 **26**, 88

Conditions unless otherwise noted: **1** (10 mol%), Zn (2.0 equiv), Coll·HCl (2.5 equiv),epoxide (0.2 M in THF), RT. [a] Zn-**1** (2.2 equiv), no Coll·HCl: 90% of **4**. [b] **1** (15 mol%). [c] **11** added over 10 h, 96:4 mixture of **12** and elimination product obtained. [d] **1** (20 mol%). [e] 83:17 mixture of 1- and 2-dodecanol. [f] Obtained as single diastereomer.

in line with an intermolecular HAT and rules out the involvement of titanocene(III) hydrides. In the case of the rigid bicyclic **17** (entry 8), very high diastereoselectivity is observed. The opening of **11** highlights the fact that the HAT does not interfere with the fragmentation of a cyclobutylcarbinyl radical. The undesired formal radical disproportionation can be largely suppressed by slow addition of **11**. For **7** (entry 3), conversion was complete. The somewhat reduced yield is due to the water solubility of **8**.

An important aspect of HAT reactions is their relative rate compared to C–C-bond forming reactions. If the HAT is too efficient, C–C bond formation is prevented by interception of the radicals by the HAT reagent. This is not a problem under our conditions, as summarized in Scheme 4. These conditions are compatible with cyclizations and intermolecular additions to acrylates.[12] In both cases investigated, none of the products arising from radical reduction prior to C–C bond formation could be isolated.

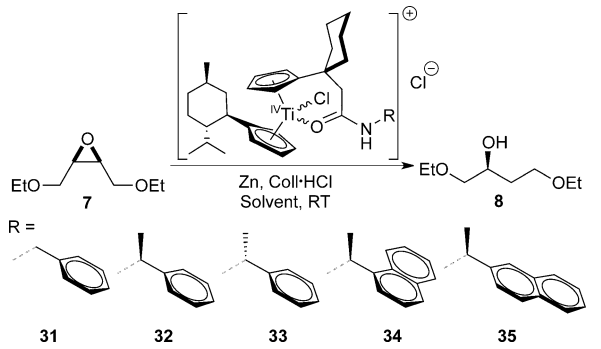
Zn-**1** can be readily modified for enantioselective catalysis by using our modular titanocene synthesis.[8] Our findings



Scheme 4. Competition experiments between HAT catalysis and C–C bond formation.

with catalysts containing a menthyl-substituted cyclopentadienyl ligand together with amides containing benzyl and naphthyl amines are summarized in Table 2.

Table 2: Enantioselective catalysis of epoxide opening with amide-substituted titanocene.

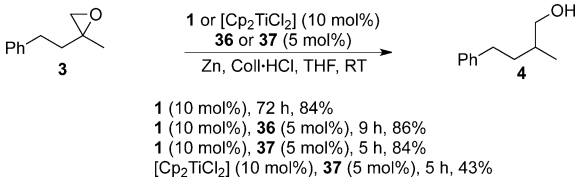


Entry	Catalyst	Solvent	Yield [%]	e.r.
1	**31**	THF	67	86:14
2	**32**	THF	69	87:13
3	**33**	THF	64	81:19
4	**34**	THF	64	80:20
5	**35**	THF	65	87:13
6	**32**	Tol	68	91:9[a]

Conditions unless otherwise noted: catalyst (15 mol%), Zn (2.0 equiv), Coll·HCl (2.5 equiv), epoxide (0.2 M in solvent). [a] catalyst **32** (20 mol%), Zn (8.0 equiv).

The enantioselectivity of ring opening is noticeable (e.r. 86:14, entry 1), even with **31** containing the achiral benzylamine. Use of both enantiomers of methylbenzyl amine in catalysts **32** and **33** results in matching and mismatching of selectivity. 2-Naphthyl amine is better suited than the bulkier 1-naphthyl amine. Changing the solvent from THF to toluene resulted in an increase in enantioselectivity (91:9 vs. 87:13). The titanocenes used so far in enantioselective redox chemistry are C_2-symmetrical (Kagan's complex for epoxide opening[13] and Brintzinger's complex for ketyl radical additions to nitriles).[14] Our results show that this is not an essential condition.

To obtain a more active and selective catalytic system, we explored cooperative catalysis with **1**. The idea was to exploit the weak N–H bond for the possible donation of H atoms to transition-metal complexes to yield the corresponding hydrides.[4,15] To this end, Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] (**36**)[16] or Crabtree's catalyst [$Ir(cod)PyPCy_3]PF_6$ (**37**)[17] were employed together with Zn-**1**. Both catalysts resulted in a remarkable acceleration in the formation of **4** (Scheme 5).

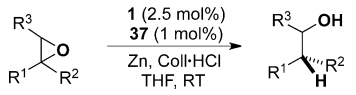


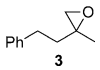
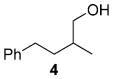
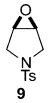
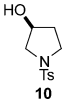
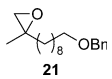
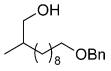
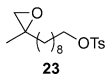
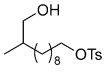
Scheme 5. Cooperative catalysis in epoxide opening with **1**, Wilkinson's catalyst (**36**), and Crabtree's catalyst (**37**) in the absence of H_2.

37 was even more efficient than **36**. When **1** was replaced with [Cp_2TiCl_2] in the presence of **37**, a distinctly inferior reaction resulted. The yield of **4** dropped from 84% to 43% despite complete conversion. A number of byproducts, most noticeably the aldehyde generated from the cationic rearrangement of **3** (about 30%), were formed.

The experiments demonstrate two points. First, the amide group is essential for the selectivity and activity of the bimetallic catalytic system. Second, no H_2 is required for radical reduction. Catalyst loading can be further reduced to 2.5 mol% **1** and 1 mol% **37** without a significant loss of yield (Table 3).

Table 3: Cooperative catalysis with **1** (2.5 mol%) and **37** (1 mol%).

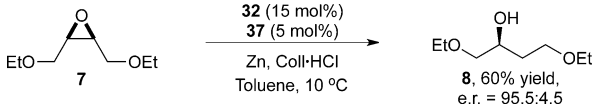


Entry	Substrate	Product	Yield [%]
1	 3	 4	81
2	 9	 10	63
3	 21	 22	82
4	 23	 24	90

Conditions: Zn (2.0 equiv), Coll·HCl (2.5 equiv), epoxide (0.4 M in THF).

An important practical advantage of the bimetallic catalysis resulting from the enhanced reactivity with **37** is illustrated in Scheme 6. The temperature can be lowered and already at 10°C, the enantioselectivity of ring opening is greater than 95:5 (95.5:4.5).

In summary, we have developed two novel reactions for HAT catalysis. The first system employs a bifunctional amide-



Scheme 6. Enantioselective ring opening of **7** by bimetallic catalysis.

substituted titanocene(III) catalyst for epoxide opening and radical reduction depending on the coordination mode of the amide. When coordinated to Ti^{III}, the N–H bond of the amide is activated for HAT. Our method not only leads the way for the use of peptides in HAT catalysts, but also suggests a mechanism by which alkyl radicals can potentially be reduced in biological systems. In the bimetallic system, the role of the amide is to activate Crabtree's catalyst for HAT without H_2 as the terminal reductant. These conditions are especially well suited for enantioselective catalysis.

Experimental Section

2,4,6-collidine hydrochloride (197 mg, 1.25 mmol, 2.5 equiv) under Ar was gently heated under vacuum until complete sublimation. Then Zn (65 mg, 1.0 mmol, 2.0 equiv), **1** (22 mg, 0.05 mmol, 0.1 equiv), freshly distilled THF (2.5 mL) were added and the mixture was stirred for 10 min it turned green. Then **3** (81 mg, 0.5 mmol, 1.0 equiv) was added and the reaction was stirred at room temperature for 72 h. The mixture was diluted with CH_2Cl_2, washed with 2 N HCl and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by chromatography (SiO_2, cyclohexane/ethyl acetate 80:20) gave 69 mg (0.42 mmol, 84 %) of **4**.

Acknowledgements

We thank the DFG (SFB 813, "Chemistry at Spin Centers"), the Alexander von Humboldt-Stiftung (fellowship to Y.-Q. Z.), the Jürgen Manchot Stiftung (fellowship to S. K.) and the Regional Government of Andalucía (projects P12-FQM-790) for support.

Keywords: enantioselectivity · homogeneous catalysis · hydrogen-atom transfer · radicals · titanium

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 1523–1526
Angew. Chem. **2016**, *128*, 1546–1550

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Received: October 12, 2015
Published online: December 4, 2015

