Dramatic rate acceleration in titanocene catalyzed epoxide openings: cofactors and Lewis acid cocatalysis

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High synthetic efficiency concerning yield and catalytic turn-over in intermolecular C–C bond forming reactions of radicals derived from epoxides can be achieved by means of hydrogen bonding with cofactors or by Lewis acid cocatalysis.

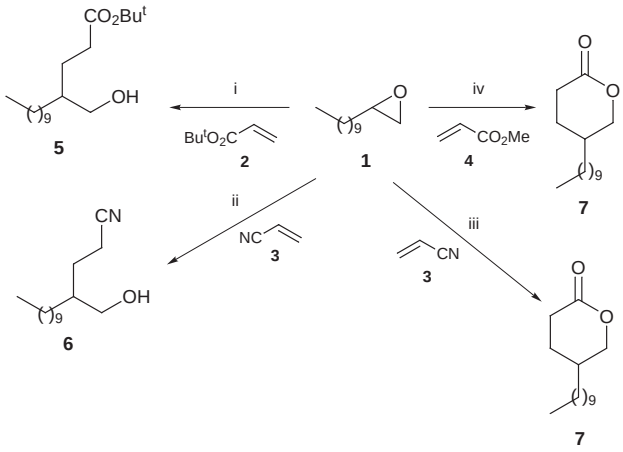
Catalytic reactions emerging from stoichiometric transformations have become increasingly important over the last three years.[1,2] We have developed protonation of carbon–titanium and oxygen–titanium bonds as an alternative to silylation for achieving catalytic turnover.[3] This has allowed highly diastereoselective pinacol couplings and chemo- and regioselective reductive openings of epoxides. Here we describe an efficient method for the addition of radicals derived from epoxides to α,β-unsaturated carbonyl compounds yielding synthetically important δ-lactones, hydroxy esters and hydroxy nitriles in high yield, with low catalyst loading in short times.

Under the standard conditions for the reductive opening of epoxides with hydrogen atom donors[3a] dodec-1-ene oxide gives only 21 and 40% yield of the addition products to methyl acrylate (**7**) and acrylonitrile (**6**), respectively, after 72 h in the presence of 5 mol% Cp_2TiCl_2 (Scheme 1). Moreover, the products are contaminated with polymeric material derived from the radical acceptor. We reasoned that low yields and turnovers are due to product inhibition. Compound **6** and MeOH formed after lactonization seemed to be able to efficiently complex at least one of the titanocene species in the catalytic cycle. Similar problems were noticed in reactions of higher substituted epoxides as well as in addition reactions to *tert*-butyl acrylate. Since this type of product inhibition could be a general problem in the *de novo* design of catalytic electron transfer reactions with densely functionalized molecules, a widely applicable solution is of interest for this rapidly expanding field.

Two conceptually different and novel approaches towards binding of the reaction products and thus catalyst activation seemed to be at hand. Since alcohols are formed during the course of the reaction, complexation of the products by hydrogen bond formation with a suitable acceptor, *e.g.* a sterically demanding amine, should be possible.[4] On the other hand a Lewis acid stronger than Cp_2TiCl_2[5] should be complexed by the reaction products and thus allow for catalyst activation and thus higher turnover.[6] Table 1 summarizes the results of our initial optimization studies. Other Lewis acids not included, *e.g.* $AlCl_3$, gave vastly inferior results.

Gratifyingly, using Zn as stoichiometric reductant[7] led to a distinct acceleration of the reaction. It seems that $ZnCl_2$ formed during the course of the reduction of Cp_2TiCl_2 acts as a Lewis acid strong enough to bind MeOH and restore catalyst activity. This effect is even more pronounced when 1 equiv of $ZnCl_2$ is added to the reaction mixture. The same effect could be observed in addition reactions to *tert*-butyl acrylate. Interestingly in the reaction of **1** with **3**, lactone **7** is isolated as the sole product of the reaction in high yield after aqueous work-up when Zn is used as stoichiometric reductant. A detailed kinetic analysis reveals formation of 85% of **6** after 3 h. Subsequently, $ZnCl_2$-initiated cyclization occurs. Thus, it seems that $ZnCl_2$ first allows for efficient formation of **6** and then activates the nitrile strongly towards intramolecular attack by the hydroxy group. The resulting imino ester is hydrolyzed during work-up. Compared to other methods of lactone formation from hydroxy nitriles[8,9] our reaction conditions are clearly milder and a wider variety of functional groups is tolerated. Also the product is formed in a one step procedure without the necessity of isolating and purifing any intermediates.[10] However, with Mn as reductant and $ZnCl_2$ as an additional Lewis acid only **6** is formed after 8 h. Thus, $MnCl_2$ seems to coordinate the nitrile group without allowing activation towards cyclization. Accordingly, the beneficial role of $ZnCl_2$ involves prevention of product inhibition by complexation of the hydroxy group. The utility of our approach was further demonstrated by the fact that catalyst loading in these reactions can be reduced to 1 mol% without significant decrease in yields when reaction times are prolonged.

Table 2 summarizes some of the examples conducted under the optimized reaction conditions. While sterically more



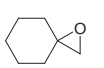
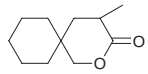
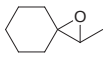
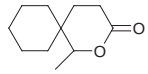
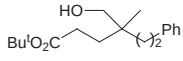
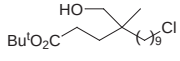
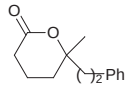
Scheme 1 *Reagents and conditions*: i, $ZnCl_2$, Zn, collidine·HCl; ii, $ZnCl_2$, Mn, collidine·HCl; iii, $ZnCl_2$, Zn, collidine·HCl, or collidine, collidine·HCl; iv, $ZnCl_2$, Zn, collidine·HCl, or collidine, collidine·HCl

Table 1 Optimization of the addition of 1-dodecene oxide to α,β-unsaturated carbonyl compounds

Acceptor	Reductant	Additive	*t*/h	Product	Yield (%)[a]
2	Mn	—	66	**5**	68
2	Zn	$ZnCl_2$	16	**5**	81
2	Zn[b]	—	44	**5**	73
3	Zn	—	16	**7**	83
3	Zn[b]	—	43	**7**	73
3	Zn	$ZnCl_2$	12	**7**	88
3	Mn	$ZnCl_2$	14	**6**	80
4	Mn	—	65	**7**	21
4	Zn	$ZnCl_2$	16	**7**	72

[a] As 94:6 mixture of 5-substituted pyran-2-one **7** and 6-substituted pyranone or 94:6 mixture of 4-hydroxymethyltetradecanenitrile or ester **6** or **5** and 5-hydroxypentadecanenitrile or ester. [b] 1 mol% of catalyst employed.

Table 2 Addition reactions of other epoxides to α,β-unsaturated carbonyl compounds with Lewis acid cocatalysis

Substrate	Reductant/ additive	*t*/h	Product	Yield (%)
	$Zn/ZnCl_2$	24		86
	$Zn/ZnCl_2$	16		78
	Zn	64		93[a]
	$Zn/ZnCl_2$	12		91
	Zn	10		65[b]

[a] Reaction performed in the presence of 4-phenyl-2-butanone (95% recovery). [b] Compound **3** as acceptor, 12 h reflux to complete the reaction.

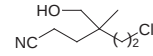
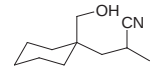
demanding hydroxy nitriles can be readily obtained in the presence of $ZnCl_2$, refluxing of the reaction mixture yields the lactones in good yields. The reaction conditions tolerate a number of functional groups, *e.g.* ketones and halides, sensitive to stronger SET reagents, *e.g.* SmI_2.[11]

Lewis acid cocatalysis thus offers an attractive means for catalyst activation and alteration of selectivity in titanocene-catalyzed addition reactions of radicals derived from epoxides to α,β-unsaturated carbonyl compounds. Compared to the stoichiometric parent system[12] the amount of Cp_2TiCl_2 to be utilized is reduced by a factor of 200 and only 1.2 equiv. of radical acceptor have to be used compared to the 10 equiv. usually employed under stoichiometric conditions. No significant reduction in isolated yields is observed. Also deoxygenation, constituting a major side reaction under stoichiometric conditions especially for monosubstituted epoxides, was never observed.[12] Our catalytic conditions are therefore clearly superior to the stoichiometric conditions.

Hydrogen bonding also constitutes a convenient way to achieve catalyst activation and to obtain the desired products under mild conditions. However, care has to be taken in choosing the appropriate hydrogen bond acceptor. If the acceptor represents a powerful ligand, *e.g.* DMPU, catalyst deactivation was observed. If a base is chosen as acceptor instead, it should not constitute a sterically accessible ligand and its hydrochloride must not have a higher pK_a[13] than collidine hydrochloride. Otherwise proton transfer precludes catalytic turnover.[3]

Accordingly we decided to test collidine and ran the reaction under buffered protic conditions. Table 3 summarizes the results of our investigations. Clearly collidine has a beneficial role on both catalytic activity and yields of the products.

Table 3 Collidine as cofactor in addition reactions

Substrate	*t*/h	Product	Yield (%)
1	36	**6**	75
	36		73
	36		73

Addition to **3** proceeded smoothly to give the desired product **6** in good yields and in reasonable reaction times. It seems that collidine is indeed able to bind hydroxy groups of the reaction products *via* hydrogen bonding. Thus, collidine acts as a cofactor to restore catalytic activity *via* hydrogen bonding.

Notes and References

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