Multicomponent Catalysis for Reductive Bond Formations

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Abstract: New concepts are outlined for reductive C–C- and C–H-bond formations catalyzed by early transition metals in low oxidation states based on the use of chlorosilanes, silicon hydrides, or related oxophilic additives as mediators of the catalytic cycles. Amongst other examples, these new protocols account for the first instances of intramolecular carbonyl coupling reactions catalyzed by titanium, Nozaki–Hiyama–Kishi reactions catalyzed by chromium, pinacol couplings catalyzed by titanium, vanadium, or samarium, and reactions of enals or epoxyalkenes catalyzed by "Cp_2Ti". A similar approach also permits catalysis of Barton–McCombie reductions by Bu_3SnH.

Keywords: chlorosilanes • heterogeneous catalysis • homogeneous catalysis • redox chemistry • silanes

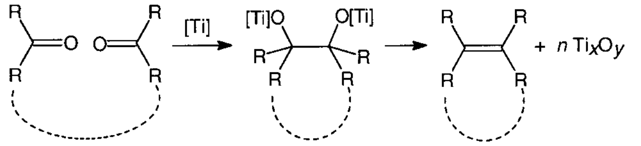
Introduction

Catalysis in general and asymmetric catalysis in particular are at the forefront of chemical research.[1] Their impact on industrial production can hardly be overestimated and is likely to increase further.[2] However, the high degree of sophistication reached in many respects may hide the simple notion that there still remain fairly large domains in preparative organic chemistry in which no catalytic alternatives to well-established stoichiometric transformations yet exist. The following account intends to put into perspective some pioneering studies which address this problem and try to develop new concepts for metal-catalyzed reductive bond formations.

Discussion

Catalytic processes mediated by chlorosilanes

Titanium: The high reducing ability and the pronounced oxophilicity of early transition metals in low oxidation states act jointly as a formidable driving force in many transformations. However, such processes are usually hampered by the fact that the metal oxides or alkoxides formed as the inorganic by-products usually resist attempted re-reductions to the active species and thus render catalysis a difficult task. An example is the famous McMurry coupling of carbonyl compounds to alkenes (Scheme 1).[3] The very high stability of the accumulating titanium oxides constitutes the thermodynamic sink which drives the conversion but extorts the use of stoichiometric or excess amounts of the low-valent titanium reagent [Ti]. Only recently has it been possible to elaborate a procedure that for the first time enables us to perform intramolecular carbonyl coupling reactions catalyzed by titanium species.[4]



Scheme 1. The McMurry coupling of carbonyl compounds to alkenes.

This development was triggered by some earlier insights into the essentials of this transformation: it has been shown that a large number of low-valent titanium species, [Ti], differing in their formal oxidation states, ligand spheres, and solubilities promote carbonyl coupling processes with comparable ease. Because this fact refutes previous assumptions that metallic titanium was essential, the strong and aggressive reducing agents required for its preparation can be avoided. As a consequence it was possible to develop a particularly convenient—but still stoichiometric—"instant method" for performing carbonyl coupling reactions based on the formation of [Ti] from $TiCl_3$ and Zn *in the presence of the substrate*.[5] Since the latter feature meets a fundamental requirement for catalysis, this set-up paved the way for a truly catalytic process. However, Zn dust cannot re-reduce the titanium oxides or oxychlorides initially formed into any active low-valent [Ti] species. Therefore an indirect way to complete a catalytic cycle was devised which relies on a ligand exchange between the titanium oxides or oxychlorides and a chlorosilane (Scheme 2). In fact, a multicomponent redox system consisting of $TiCl_3$ cat., Zn, and a chlorosilane accounts for

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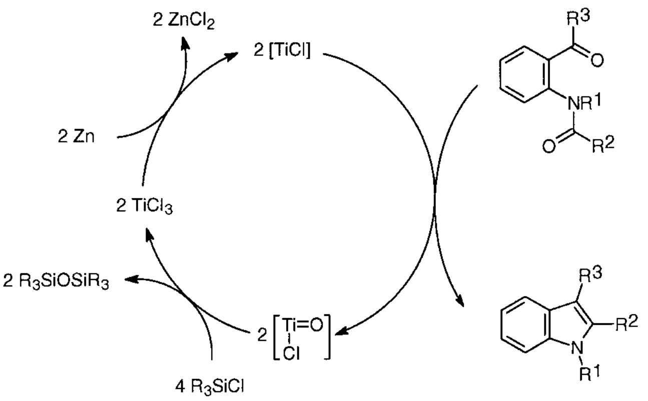
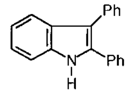
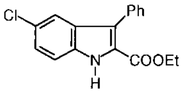
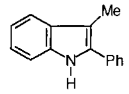
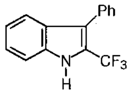
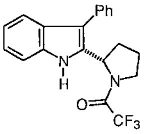


Scheme 2. Catalytic cycle for McMurry-type couplings.

the first titanium-catalyzed carbonyl coupling reactions. The efficiency of this method can be tuned to some extent by choosing the proper R_3SiCl additive. The examples compiled in Table 1 show that this new catalytic procedure compares favorably with the existing stoichiometric precedent in terms of yields and reaction rates. These studies have been carried out using oxo-amide derivatives as the substrates, which exhibit a pronounced tendency to cyclize to indole derivatives on treatment with [Ti].[4–6]

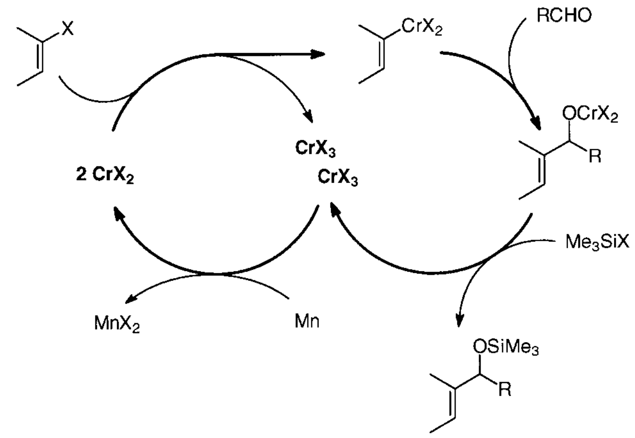
Table 1. Titanium-induced indole syntheses: comparison of the catalytic and stoichiometric procedures.

Product	Catalytic procedure $TiCl_3$ cat., Zn, TMSCl, 0.5h	"Instant method" $TiCl_3$ (2-4 equiv), Zn, 1-4h
	80%	98%
	79%	87%
	82% [a]	76%
	88%	82%
	67%	90%

[a] Using $ClMe_2Si(CH_2)_3CN$ as additive instead of TMSCl.

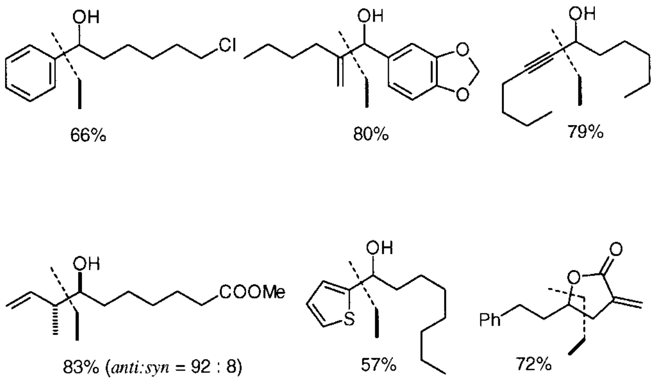
It was clear at the outset that the basic principle of this catalytic scenario may apply to other transformations as well. An obvious extension concerns the pinacol coupling since any McMurry reaction probably passes through the 1,2-diolate stage (cf. Scheme 1).[3] In fact, two different titanium-catalyzed procedures have been reported which rely on chlorosilane additives for the liberation of the product and the simultaneous regeneration of the $TiCl_x$ salt. One involves $[Cp_2TiCl_2]$ cat., Zn, chlorosilane, $MgBr_2$,[7] whereas the other method is based on $[TiCl_3(THF)_3]$ cat., Zn, TMSCl, *t*BuOH.[8] The use of Cp_2TiCl_2 in this context deserves particular emphasis, because titanium sources of this type open up new vistas for stereocontrol if *ansa*-titanocene derivatives are used to transfer chiral information from the ligand to the diol.[9]

Chromium: Similar chlorosilane-mediated catalytic processes can be envisaged with many other early transition metals. The development of the first Nozaki–Hiyama–Kishi reactions catalyzed by chromium species[10] illustrates how to avoid use of an excess of a physiologically suspect and rather expensive salt without compromising the efficiency, practicality, and scope of the reaction. The tentative catalytic cycle is depicted in Scheme 3. In this case, the silylation of the metal alkoxide initially formed represents the key step of the overall process which releases the chromium salt from the organic product. The other crucial parameter is the use of the stoichiometric reducing agent for the regeneration of the active Cr^{II} species. Commercial Mn turned out to be particularly well suited, as it is very cheap, its salts are essentially nontoxic and rather weak Lewis acids, and the electrochemical data suggest that it will form an efficient redox couple with Cr^{III}. Moreover, the very low propensity of commercial Mn to insert on its own into organic halides guarantees that the system does not deviate from the desired chemo- and diastereoselective chromium path. Thus, a mixture of catalytic amounts of CrX_n ($n = 2, 3$), TMSCl, and Mn account for the first Nozaki reactions catalyzed by chromium.[10]



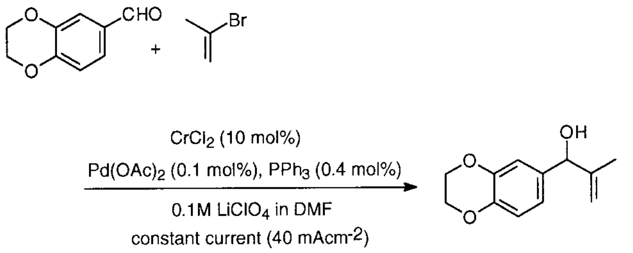
Scheme 3. Proposed catalytic cycle for the first Nozaki–Hiyama–Kishi reaction catalyzed by chromium species.

This method applies to aryl, alkenyl, allyl and alkynyl halides as well as to alkenyl triflates and exhibits the same selectivity profile as its stoichiometric precedent (Scheme 4). Moreover, it does not matter if the catalytic cycle is started at the Cr^{II} or Cr^{III} stage, as implied by Scheme 3. Therefore it is possible to substitute cheap and stable $CrCl_3$ for the expensive and air-sensitive $CrCl_2$ previously used for Nozaki reactions. In some cases other chromium templates such as $[Cp_2Cr]$ or $[CpCrCl_2]$ can be employed, improving the total turnover number of this transformation even further.[10]



Scheme 4. The scope of Nozaki reactions catalyzed by chromium resembles that of the stoichiometric version.

Electrochemically driven Nozaki–Hiyama–Kishi reactions constitute an attractive modification of this basic concept (Scheme 5).[11] Although the current density turned out to be a critical parameter and must be carefully controlled, the authors show that in this case the $LiClO_4$ used as supporting electrolyte also acts as the oxophilic mediator instead of TMSCl. They also used a palladium cocatalyst in order to form more highly nucleophilic "chromium ate" complexes as the actual intermediates. Encouraged by this precedent, further studies using electrons as the ultimate reducing agent are likely to appear in the near future.



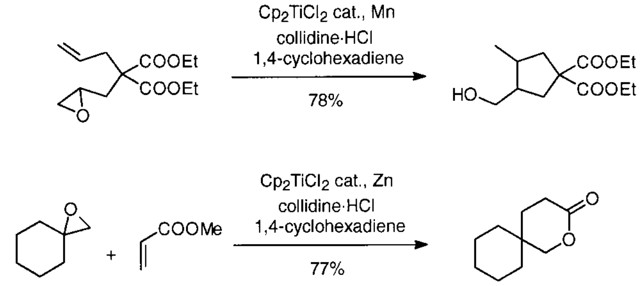
Scheme 5. An electrochemically driven Nozaki–Hiyama–Kishi reaction.

Other transition metals: The rather general validity of the chlorosilane-based catalysis concept is further substantiated by some recent examples of pinacol coupling processes catalyzed either by low-valent vanadium ([CpV(CO)$_4$] cat., Zn, chlorosilane)[12] or low-valent samarium (SmI_2 cat., Mg, chlorosilane).[13] Likewise, a report from Corey's group on samarium-iodide-catalyzed additions of carbonyl compounds to acrylates deserves mention; these follow essentially the same rationale (SmI_2 cat., Zn(Hg), TMSOTf, LiI).[14] In view of the extensive use of SmI_2 in stoichiometric transformations, the possible impact of catalytic alternatives is easy to imagine.

Catalytic processes based on other mediators

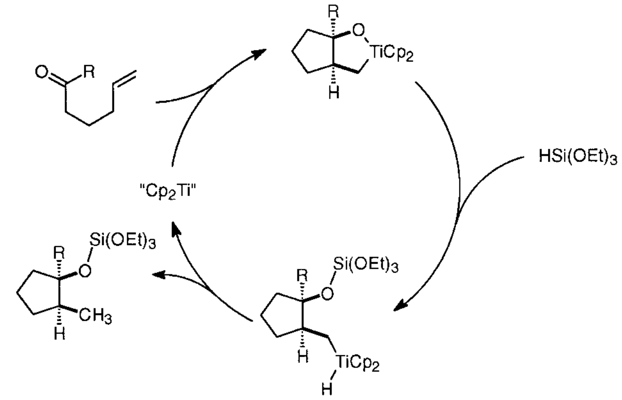
Although chlorosilanes are an obvious choice as mediators for catalysis on account of their high affinity to oxygen, low price and lack of toxicity, several other additives can also be envisaged. The recent publication on the electrochemical version of the Nozaki reaction mentioned above simply employs the Li cations of the supporting electrolyte for this very purpose,[11] whereas another titanium-catalyzed pinacol coupling reaction ($TiCl_4$ cat., Li(Hg), $AlCl_3$) is based on the oxophilicity of Al^{III}.[15]

An even more interesting development concerns the use of protons. Thus, Gansäuer et al. were able to achieve catalysis of epoxide ring-opening reactions by Cp_2TiCl_2 simply by using pyridinium hydrochlorides as scavengers for the product and Zn or, preferably, Mn as the stoichiometric reducing agent.[16] The pK_a of the pyridinium salt is properly adjusted, and the protic medium does not interfere with the radical intermediates prior to product formation. This method applies to inter- and intramolecular C–C-coupling reactions (Scheme 6) as well as to simple reductions, and turned out to be compatible with various sensitive functional groups in the oxirane substrates.



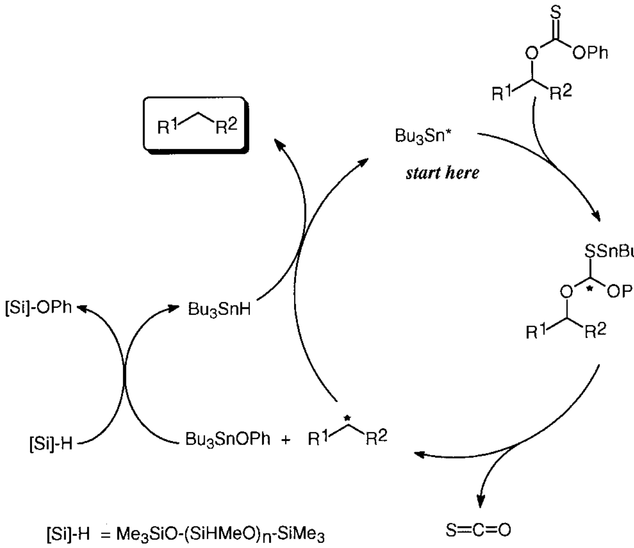
Scheme 6. Inter- and intramolecular C–C-coupling reactions by the method of Gansäuer et al.

Another approach to multicomponent redox catalysis employs silanes (R_3SiH) as the additives. This allows the stoichiometric reducing agent and the oxophilic reaction partner to be merged into a single component. Two independent reports from Buchwald[17] and Crowe[18] on the cyclization of unsaturated carbonyl compounds based on the turnover of a "Cp_2Ti" template rely on this principle (Scheme 7).[19]



Scheme 7. The cyclization of unsaturated carbonyl compounds based on the turnover of a Cp_2Ti template with a silane as the additive.

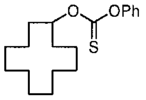
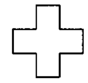
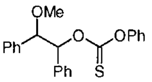
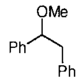
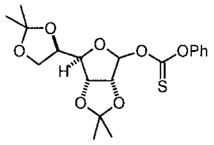
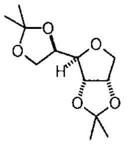
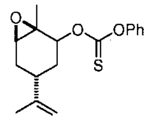
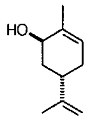
A similar idea allows the well-known Barton–McCombie deoxygenation of alcohols to proceed for the first time with catalytic rather than stoichiometric or excess amounts of tributylstannane (Scheme 8).[20] As shown in the proposed



Scheme 8. The Barton–McCombie deoxygenation of alcohols with catalytic rather than stoichiometric or excess amounts of tributylstannane.

catalytic cycle, this exceptionally versatile but highly toxic reagent is regenerated from the otherwise accumulating dead-end product $Bu_3Sn(OPh)$ by means of polymethylhydrosiloxane (PMHS). Once again it is the affinity to oxygen in combination with the reducing ability of this inexpensive, nontoxic and easily handled silicon hydride which qualifies it as an ancillary component for catalysis. The authors show that the addition of *n*BuOH facilitates the regeneration of the tin hydride, improves the key step of the catalytic process and makes the reaction as efficient as the stoichiometric version (Table 2).

Table 2. Barton–McCombie deoxygenation of phenyl thionocarbonate esters: comparison of the yields (%) of the catalytic and stoichiometric reactions.[20]

Substrate	Product	Catalytic	Stoichiometric
		66	68
		70	65
		63	72
		68	61

These and related examples rival—and may well replace—their stoichiometric counterparts. Although none of them is atom economical [21] in the pure sense, they do at least permit economy in the key component. If the latter is expensive, difficult to handle, and/or of physiological concern, such multicomponent catalyst systems upgrade established transformations to a significant extent, quite apart from the heuristic lessons in and the stimulus for catalysis research which they provide.

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[19] There are closely related reports from the same authors in which isocyanates or CO insert into titanaoxacycles in order to release the catalytically active Cp_2Ti species; see: a) F. A. Hicks, S. C. Berk, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 2713–2718; b) W. E. Crowe, A. T. Vu, *J. Am. Chem. Soc.* **1996**, *118*, 1557–1558 and references therein.

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