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Low-valent transition metal induced C–C bond formations: Stoichiometric reactions evolving into catalytic processes

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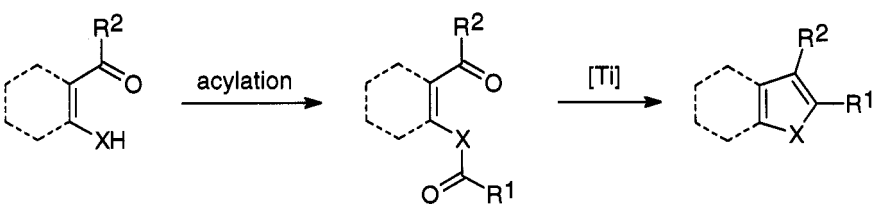
Abstract: A new concept for C-C-bond formations catalyzed by early transition metals in low oxidation state is outlined. It allows to perform intramolecular reductive carbonyl coupling reactions catalytic in titanium, accounts for the first chromium-catalyzed Nozaki-Hiyama-Kishi reactions, and has been successfully applied to titanium-, samarium- or vanadium-catalyzed pinacolization reactions.

The high reducing ability and the pronounced oxophilicity of early transition metals in low oxidation states constitutes the driving force of many well established C-C-bond formations. However, these reactions usually suffer from the inconvenience that the metal oxides or -alkoxides formed as the inorganic by-products can hardly be recycled into the active species and therefore render catalysis a difficult task.

Carbonyl Coupling Reactions. A prototype example of such a process is the low-valent titanium [Ti] induced coupling of carbonyl compounds to alkenes. Generally referred to as „McMurry reaction", this transformation has witnessed a considerable scope and has found many applications to advanced organic synthesis [1,2]. Intramolecular McMurry couplings benefit from the template effect of [Ti] and provide access to cycloalkenes of almost any ring size. The titanium oxides or -oxyhalides formed in the reaction serve as the thermodynamic sink which drives the conversion; however, their stability is responsible for the fact that this transformation has been notoriously (over)stoichiometric in [Ti] so far.

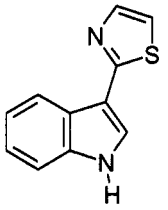
McMurry reactions had been essentially confined to aldehydes and ketones as the substrates for a rather long period of time [1]. Only recently it was found that various other functional groups, which were considered as hardly reactive or even as inert, readily undergo intramolecular *cross-coupling* reactions. This allows to convert well accessible oxo-amide, oxo-ester, oxo-carbonate, oxo-urethane and oxo-urea derivatives into aromatic heterocycles as shown in Scheme 1 [3,4].



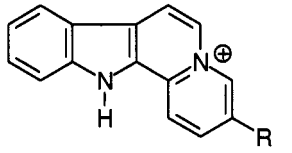
Scheme 1. Low-Valent Titanium Induced Heterocycle Synthesis:
X = O, NH, NR^3; R^1 = H, Alkyl, Aryl, OR, NR_2; R^2 = Alkyl, Aryl, (H); R^3 = Alkyl, Tosyl.

This transformation turned out to be very flexible with regard to the substituents R^1 and R^2, is compatible with many functional groups and pre-existing chiral centers, and also provides access to sterically hindered products. Moreover, a remarkable chemo- and regioselectivity has been observed in reactions of

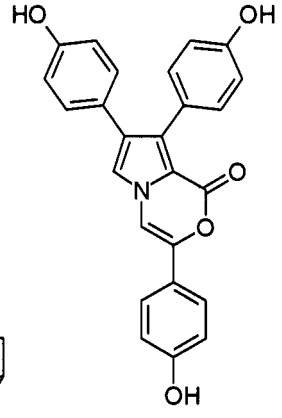
polyfunctional substrates, with the formation of the 5-membered ring being highly favored over other conceivable coupling events. Various syntheses of indole and pyrrole alkaloids (*e. g.* **1-6**) as well as of pharmaceutically relevant targets clearly feature the advantages of this new reductive approach to heterocycles [3,4].

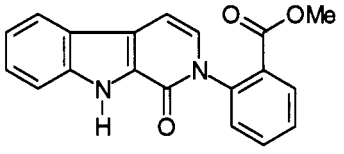


Camalexin (**1**)

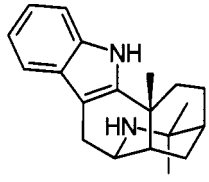


Indolopyridocolin (**2**) (R = H)
Flavopereirine (**3**) (R = Et)





Secofascaplysin (**4**)



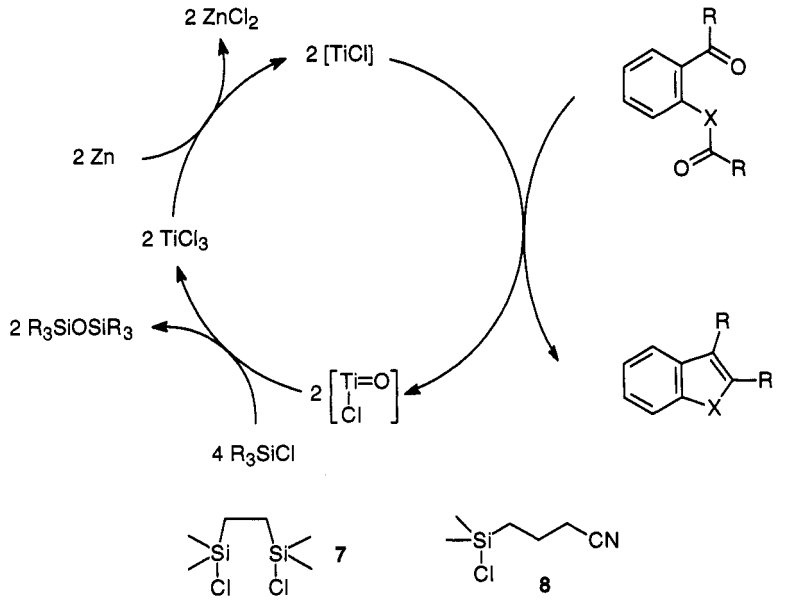
(+)-Aristoteline (**5**)

Lukianol A (**6**)

Conventionally, McMurry-type reactions are carried out in two consecutive steps [1]: first, the active species is prepared by the reduction of $TiCl_x$ (x = 3, 4) in an ethereal solvent, followed by the addition of the carbonyl compound to the slurry of [Ti] thus obtained. Metallic titanium of varying particle sizes and textures has been believed to be the active species [1]. Therefore, strong reducing agents such as K, Na, Li, Mg, C_8K, $LiAlH_4$ were usually employed for its preparation, which are incompatible with the reducible substrates and hence impose this stepwise procedure. Although the need for Ti(0) has never been proved beyond doubt and had already been queried some time ago [5], this opinion still seems to persist up to date. However, a recent screening of different titanium samples including $TiCl_3$/3 C_8K, $TiCl_3$/2 C_8K, $TiCl_4$/4 $K(BEt_3H)$, $Ti(toluene)_2$, $Cp_2Ti(PMe_3)_2$ and $[HTiCl{\cdot}(THF)_n]$ [3], as well as some in-depth studies on the actual nature of the classical McMurry reagents derived from $TiCl_3/LiAlH_4$ or $TiCl_3$/Mg [6] clearly disproved this view. These investigations provided compelling evidence that *various low-valent titanium species differing in their formal oxidation states, ligand spheres and solubilities promote reductive carbonyl coupling reactions with comparable ease* [2].

As no stringent need for Ti(0) exists, it is possible to re-evaluate the current practice of using the strong and hazardous reducing agents mentioned above. In fact, a very convenient and short-cut procedure for performing carbonyl coupling reactions has been developed which is based on the addition of $TiCl_x$ to the substrate *prior* to reduction [3]. This method, which is in clear contrast to current practice, ensures a pre-organization of both reaction partners by the coordination of the Lewis-acidic salt to the carbonyl groups. Subsequent treatment of the complexes thus formed with a mild reducing agent such as Zn (or Mn, Sn or Fe powder) affords the active low-valent [Ti] in a *site selective* manner within the coordination sphere of the substrate.

This new „instant procedure" [3] is particularly convenient to carry out and can be applied to conventional McMurry olefin formations as well as to reductive heterocycle syntheses. It simply consists in mixing and heating of all ingredients in an inert solvent, avoids all potentially hazardous reducing agents, and can easily be scaled up [7]. Carbonyl coupling reactions under „instant conditions" exhibit essentially the same performance, scope and selectivity as those using pre-formed [Ti]. Limits are only set in the case of very acid sensitive starting materials which may suffer from exposure to the Lewis-acidic $TiCl_x$.

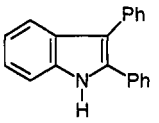
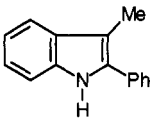
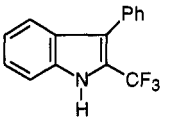
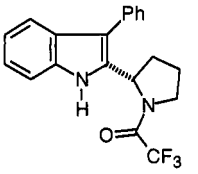
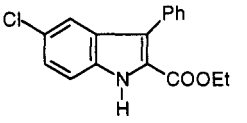


Scheme 2.

It is important to note that the „instant method" allows for the first time to prepare the active low valent titanium species in the presence of the substrate. Therefore it may evolve into a *catalytic procedure* if the titanium oxides or oxyhalides initially formed can be recycled into [Ti]. However, as Ti_xO_y resists to any attempted direct reduction with Zn-dust, an indirect method had to be devised for this purpose which relies on the use of chlorosilanes as oxophilic additives (Scheme 2) [8]. They may react with the titanium oxychlorides formed in situ and re-convert them into $TiCl_x$. If the latter then effects the next „instant" coupling event, a catalytic cycle will emerge in which a siloxane accumulates as the final oxygen trap. In fact, a multicomponent redox system consisting of catalytic amounts of $TiCl_3$, Zn dust and R_3SiCl in DME or MeCN accounts for the *first intramolecular carbonyl coupling reactions catalytic in titanium* [8]. The formation of siloxanes during the course of the reaction has been unambiguously confirmed by GC/MS and ^{29}Si NMR studies, thus providing good evidence for the proposed catalytic cycle.

The efficiency of this scenario can be tuned by varying the additive. When TMSCl is used, 5-10 mol% of $TiCl_3$ are necessary to reach complete conversions. However, if TMSCl is replaced by a bis(chlorosilane) such as **7**, a better turn-over number can be achieved since the siloxane formation is then intramolecular and hence entropically biased. Cyanopropyl(dimethyl)chlorosilane (**8**) also turned out to be well suited; it is highly recommended for the preparation of indoles with alkyl substituents at C-3, which show an intrinsically lower propensity towards cyclization. Since nitriles are known to be reasonably good ligands to titanium in all oxidation states, this additive combines the necessary oxophilicity with a sufficient affinity to titanium and thus facilitate the crucial oxygen transfer step [8].

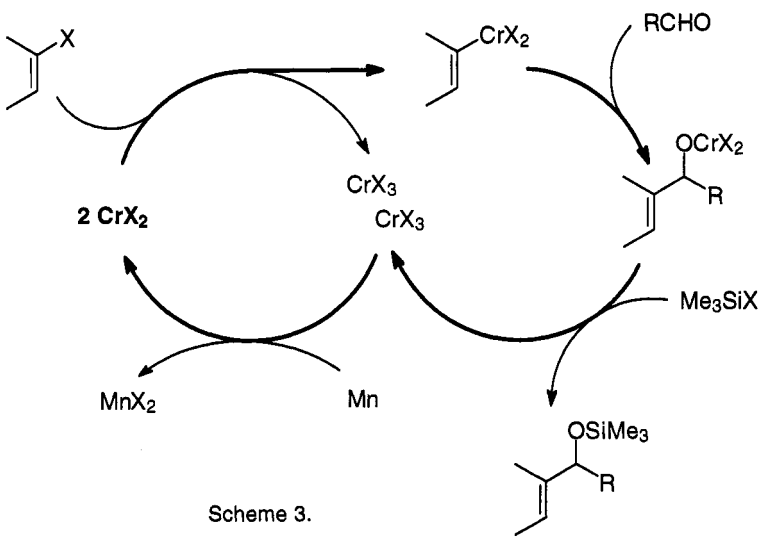
TABLE 1. Comparison of Various Titanium-Based Indole Syntheses.

Method[a]					
A	90%	75%			93%
B	98%	76%	82%	90%	87%
C	80%	82%[b]	88%	67%	79%

[a] Method **A**: Ti-graphite (formed from $TiCl_3$ and 2 C_8K); Method **B**: $TiCl_3$, Zn („Instant"); Method **C**: $TiCl_3$ cat., Zn, TMSCl; [b] Using chlorosilane **8** instead of TMSCl.

Table 1 compiles some representative examples of titanium-based reductive indole syntheses using different procedures. As can be deduced from this comparison, the reactions proceed with great ease and in good to excellent yields independent of whether preformed [Ti], the particularly convenient „instant method", or this new catalytic procedure are employed.

Nozaki-Hiyama-Kishi Reactions Catalytic in Chromium. The addition of organochromium reagents to aldehydes, originally described by Nozaki and Hiyama et al. [9], has evolved into a very powerful method for C-C-bond formation. This reaction is highly chemo- and diastereoselective and displays an exceptional compatibility with various functional groups in both reaction partners. It is carried out in a one-pot „Barbier-type" manner, with the actual nucleophiles being formed in situ by oxidative insertion of $CrCl_2$ into a wide range of (functionalized) allyl-, propargyl-, alkenyl-, alkynyl-, or aryl halides, alkenyl triflates, allyl phosphates etc. Kishi's finding that nickel salts exhibit a catalytic effect on the formation of the C-Cr bond has greatly improved the reliability of this process [10], which has found many applications to the total synthesis of natural products of utmost complexity.



Scheme 3.

Since Cr(2+) is a one-electron donor, 2 mol of this reducing agent per mol of halide (triflate) are necessary for the formation of the organochromium nucleophile; in practice, a huge excess is usually required. The need for large amounts of toxic chromium (and nickel) salts does not only impede the development of an enantioselective version of the reaction, but clearly makes this very selective transformation less attractive for applications to pharmaceutical chemistry and large scale syntheses.

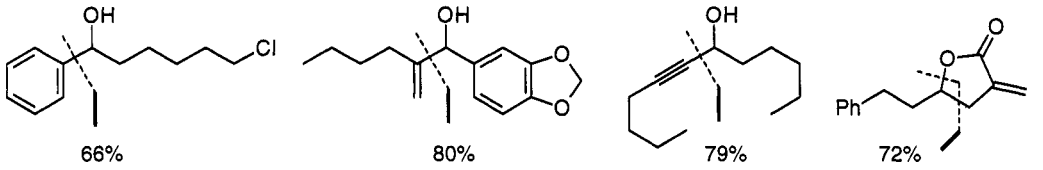
The high stability of the O-Cr(3+) bond formed on addition of the nucleophile to an aldehyde drives the conversion but impedes catalysis. We reasoned that the use of chlorosilanes as additives may again lend itself to the development of a catalytic process as shown in Scheme 3 [11,12]: The silylation of the alkoxide initially formed will release the Cr(3+) salt; if the latter can be efficiently recycled into the active Cr(2+) species, a catalytic process will ensue.

The choice of the stoichiometric reducing agent turned out to be decisive: It must efficiently reduce Cr(3+), but has to be inert towards the reducible substrates. Moreover, it should not insert on its own into halides, the salts which accumulate have to be significantly less toxic than those of chromium and must exhibit only weak Lewis acidity in order to prevent undesirable side reactions of the carbonyl compounds. Commercial manganese powder matches these requirements best: This metal is very cheap, oxidative additions of unactivated Mn into organic halides are essentially unknown, its salts are non-toxic, the Lewis acidity of Mn(2+) is significantly lower than that of Zn(2+), and the electrochemical data hold the promise that it will promote the reduction Cr(3+)→Cr(2+) without incident.

Our investigations have shown that a redox system consisting of commercial Mn powder, TMSCl and *catalytic* amounts of chromium chloride accounts for Nozaki-Hiyama-Kishi reactions which rival their stoichiometric precedent in all preparative aspects [11,12]. Because the reaction owes its performance to

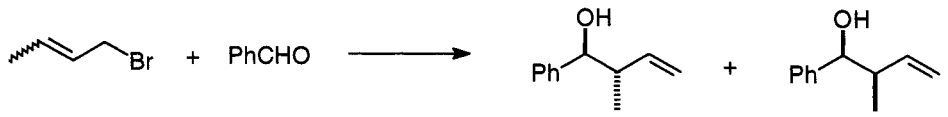
an efficient redox process Cr(3+)→Cr(2+) mediated by Mn(0), it does not matter whether $CrCl_2$ or $CrCl_3$ is used to initiate the reaction. In fact, both salts were found to afford similar results [12]; for practical reasons, however, $CrCl_3$ is generally preferred because this salt is cheap, air-stable, and easy to handle.

According to this procedure, Nozaki-Hiyama-Kishi reactions catalytic in chromium can be performed with aryl-, alkenyl-, alkynyl- and allyl halides as well as alkenyl triflates [11,12]. The total turn-over number turned out to depend on the particular type of substrate: allyl halides react properly in the presence of 5-7 mol% of $CrCl_x$ (x = 2, 3), whereas up to 15 mol% of this salt must be used in reactions with aryl iodides. In analogy to the stoichiometric process, a variety of functional groups were found to be compatible with the reaction conditions. Futhermore, the catalytic and the stoichiometric reactions display the same chemoselectivity for additions to aldehydes in the presence of ketones [12]. The selected examples depicted below show the scope of this new catalytic procedure.



A particularly important feature of Nozaki-Hiyama-Kishi reactions is the highly diastereoselective addition of crotyl bromide to aldehydes. In all cases the formation of the *anti*-configurated homoallyl alcohol is favored, independent of the configuration of the starting crotyl bromide. The new catalytic procedure fully matches this well established *stereoconvergent* behavior of the stoichiometric precedent [12]. In marked contrast, crotyl manganese reagents formed upon insertion of highly activated Mn-graphite into crotyl bromide were shown to react in a stereodivergent manner which translates the configuration of the starting material into the stereochemistry of the homoallyl alcohol [13]. Therefore this set of data confirms the notion that the multicomponent redox system consisting of $CrCl_x$ cat/Mn/TMSCl truly accounts for chromium catalyzed and not for manganese-induced reactions of organic halides (triflates) with aldehydes (Table 2).

TABLE 2. Comparison of Chromium- and Manganese-Based Reactions of Crotyl Bromide.



9 **10** *anti*-**11** *syn*-**11**

Substrate	Conditions	Yield (%)	*anti* : *syn*
(*E*)-**9**	$CrCl_2$ (400 mol%)	100	90 : 10
(*E*)-**9**	$CrCl_2$ (7 mol%), Mn, TMSCl	79	94 : 6
(*E*)-**9**	$CrCl_3$ (7 mol%), Mn, TMSCl	85	91 : 9
(*Z*)-**9**	$CrCl_2$ (7 mol%), Mn, TMSCl	64	90 : 10
(*Z*)-**9**	$CrCl_3$ (7 mol%), Mn, TMSCl	74	90 : 10
(*E*)-**9**	Mn-graphite	72	64 : 36
(*Z*)-**9**	Mn-graphite	65	41 : 59

Some attempts were made to further improve the total turn-over number of these reactions [12]. Both Cp_2Cr and „$CpCrCl_2$" (either in form of $[CpCrCl_2]_2$ or $CpCrCl_2$·THF) exhibit a somewhat higher performance than $CrCl_x$ (x = 2, 3), with as little as 1 mol% being sufficient in many cases. However, these more electron rich chromium templates promote the concomitant pinacol coupling of aromatic aldehydes and can therefore only be employed in reactions with aliphatic substrates. Although these results indicate some flexibility as to the ligand sphere of the chromium and suggest that it might be possible to endow the catalyst with a chiral periphery, out attempts to develop an enantioselective version of this catalytic protocol have not yet been successful.

Further Extensions of the Basic Concept. The applications reported above clearly prove that notoriously stoichiometric C-C-bond formations induced by early transition metals in low oxidation states can be rendered catalytic by means of chlorosilane additives. It is not surprising to find that this basic concept is valid in other cases as well. In this context we would like to refer to some reports in the recent literature which rely on the very same principle. Among them, pinacol coupling reactions catalytic in either low-valent samarium (SmI_2 cat., Mg, chlorosilane) [14], or low-valent vanadium ($CpV(CO)_4$ cat., Zn, chlorosilane) [15], or low-valent titanium (Cp_2TiCl_2 cat., Zn, chlorosilane, $MgBr_2$ [16]; or $TiCl_3(THF)_3$, Zn, TMSCl, t-BuOH) [17] play a prominent role. A publication from Corey's group on samarium iodide catalyzed reactions of carbonyl compounds with acrylates also follows a similar rationale (SmI_2 cat., Zn(Hg), TMSOTf, LiI) [18]. These examples provide additional evidence for the rather general applicability of this basic concept and encourage further explorations along these lines.

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