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Evolution of the stereoselective pinacol coupling reaction

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Contents

Keywords: Pinacol coupling; Reductive dimerization; Diastereoselective; Enantioselective.
Abbreviations: AIBN, 2,2-Azobisisobutyronitrile; BOC, *tert*-Butoxycarbonyl; Cbz, Benzyloxycarbonyl; COD, Cyclooctadiene; Cp, Cyclopentadienyl; DDB, 1,4-Bis(dimethylamino)-2,3-dimethoxybutane; DCM, Dichloromethane; DEPU, Diethyldiisopropylurea; DIPEA, Diisopropylethylamine; EBTHI, Ethylene-bis-tetrahydroindenyl; HMPA, Hexamethylphosphoric triamide; LAH, Lithium aluminium hydride; MOM, Methoxymethyl; PTSA, *para*-Toluenesulfonic acid; SET, Single electron transfer; TBAF, Tetrabutylammonium fluoride; TBAI, Tetrabutylammonium iodide; TBATFB, Tetrabutylammonium tetrafluoroborate; TBDMS, *tert*-Butyldimethylsilyl; TBDPS, *tert*-Butyldiphenylsilyl; TEA, Triethylamine; TESCl, Triethyl silylchloride; TfO, Trifluoromethylsulfonyl; THP, Tetrahydropyranyl; TIPS, Triisopropylsilyl; TMEDA, Tetramethylethylene diamine; TMSCl, Trimethylsilyl chloride.
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1. Introduction

Carbon–carbon bond-forming reactions are pivotal to organic synthesis. Chemists in many cases have succeeded in achieving good control over a number of such reactions and pinacol coupling can be placed in this category. Ever since the pioneering work by Fittig in 1859,[1] this reaction has remained as a challenging target for organic chemists, due to the need for dual control, diastereoselectivity and enantioselectivity in a single step. A slow and sustained evolution took place over about 150 years through a number of stages, an exponential growth being noticed in the last 10 years. The popularity of this reaction stems from its intrinsic ability to furnish 1,2-diols, which are a very important class of compounds. These can serve as the structural motif in total synthesis, and as chiral auxiliaries or chiral ligands. These diols can be even converted into a number of compounds such as aminoalcohols, epoxides, ketones etc. (Fig. 1).

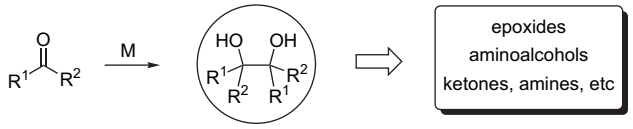


Figure 1. Pinacol coupling: a versatile reaction.

A variety of methods have been used to perform this reaction. Of these, the most reliable is the use of low-valent metals or metal complexes in stoichiometric or catalytic amount. Although the reaction path followed in pinacol coupling is described in the literature, the origin of the enantioselectivity is still not clear.[2] In the present report, we will describe different protocols adopted to pursue pinacol coupling in both a diastereoselective fashion and enantioselective fashion. A glimpse of the various compounds prepared using pinacol coupling as the key step will also be provided.

The most general method of presenting the mechanism of the pinacol coupling reaction is shown in Figure 2. The first step of this reaction is the generation of a ketyl radical, generally achieved through the homolytic cleavage of the carbonyl bond in the presence of a metal. A simultaneous electron transfer from the metal atom furnishes the metal bound ketyl radical, which can have several fates depending upon its stability. When the dimerization of two such radicals takes place through a pseudo-bridged metal atom, the *dl* selectivity in the product predominates, owing to steric reasons. On the other hand, when two such species couple through a non-bridged intermediate, the formation of the *meso* product is favoured. In the case of intramolecular

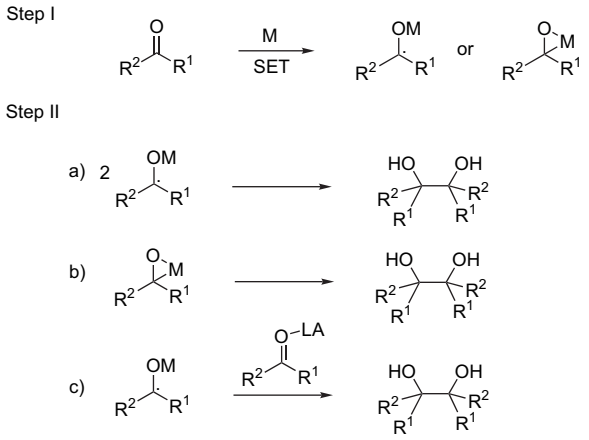


Figure 2. Mechanism of pinacol coupling.

pinacol coupling, the cis product is formed in a higher ratio through a metal-bridged intermediate. However, in the case of transition metals, the metal insertion into the carbonyl group generates an oxirane. Thus the carbonyl character is umpoled to initiate the attack by another molecule. The last possibility is the dimerization of a ketyl radical with an activated carbonyl group.

2. Reagents for pinacol coupling

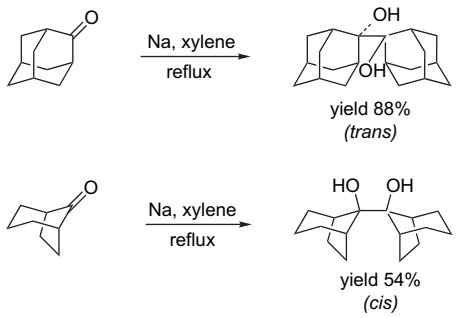
Earlier efforts on pinacol coupling utilized alkali or alkaline earth metals as the reagents, which provided poor diastereoselection. Later, several transition metals, lanthanides or p-block elements were used successfully to induce higher selectivity. More recently, high levels of diastereoselection and even enantioselection have been achieved using specifically designed metal complexes. The use of the reagents has therefore been subdivided into two classes. The stoichiometric use of metals or metal complexes for achieving stereoselectivity, is discussed in Section 2.1, whilst Section 2.2 deals with the catalytic protocols.

2.1. Stoichiometric protocols

2.1.1. Diastereoselective protocols.

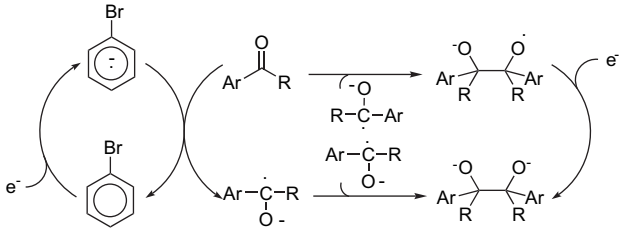
2.1.1.1. Alkali and alkaline earth metals. The use of sodium in the pinacol coupling reaction is an age-old process, frequently resulting in an unsatisfactory yield and selectivity or, sometimes, drastic conditions. In a few cases, a high selectivity was reported for hindered ketones (Scheme 1).[3,4]

Among other alkali metals, lithium in combination with a stoichiometric amount of TMSCl or liquid NH_3 provided



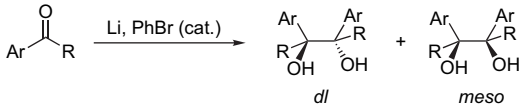
Scheme 1. Pinacol coupling of hindered ketones.

pinacols with low yield and selectivity.[5,6] Recently, Guo et al. reported a novel solvent-free system where a high diastereoselectivity was achieved using lithium and a catalytic amount of bromobenzene as the electron carrier (Scheme 2).[7] The selectivity in the case of aromatic aldehydes was very high (Table 1). Good diastereoselectivity was also achieved using amalgamated lithium.[8]



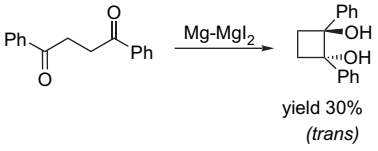
Scheme 2. Bromobenzene as electron carrier.

Table 1. Lithium mediated pinacol coupling



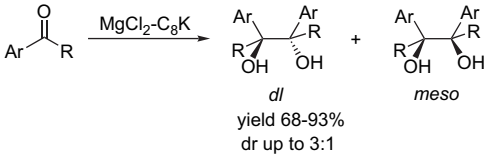
Entry	Substrate	Yield (%)	*dl*:*meso*
1	PhCHO	84	99:1
2	2-ClC_6H_4CHO	81	*dl* only
3	2,4-$Cl_2C_6H_3CHO$	90	*dl* only
4	PhCOMe	87	74:26
5	PhCH=CHCOMe	75	*dl* only

Magnesium is the only alkaline earth metal, which found early application in the pinacol coupling reaction in an amalgamated form. The selectivity, however, remained low in most cases. Even a combination of Mg/TMSCl was equally inefficient.[9] A equimolar mixture of Mg/MgI_2 proved little better in few cases (Scheme 3).[10]



Scheme 3. Preparation of a cyclobutanediol.

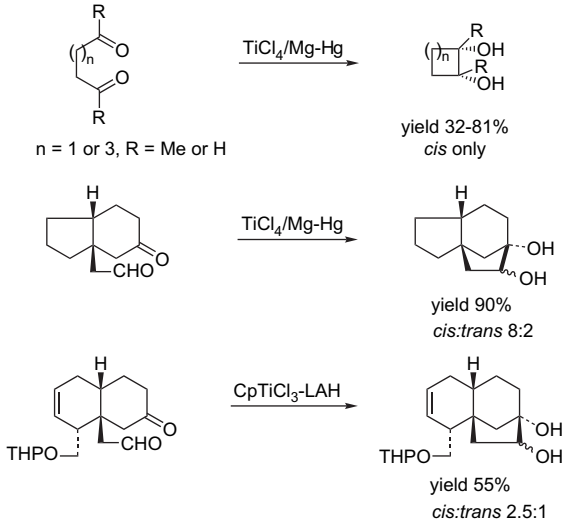
Magnesium as a fine dispersion on graphite can couple aldehydes or ketones with moderate selectivity.[11] A variety of aldehydes were coupled in high yields. The intramolecular cyclization also proceeded smoothly (Scheme 4).



Scheme 4. Magnesium-mediated pinacol coupling.

2.1.1.2. Transition metals. Titanium is the most popular reagent for pinacol coupling. The development of titanium chemistry proliferated in the early 1980s following three independent discoveries by Tyrlik et al.,[12] Mukaiyama et al.,[13] and McMurry and Fleming[14] that described low-valent titanium species for the reductive coupling of ketones/aldehydes. All these investigations unveiled the synthetic utility of low-valent titanium and opened new vistas in organometallic chemistry.

A number of reducing agents have been employed for the generation of low-valent titanium species, which are thought to be efficient reagents for the pinacol coupling reaction. Initially, Ti(II)-based coupling agents were used and these met with moderate success in terms of selectivity.[15] One of the most efficient precursor was developed by Corey et al. using $TiCl_4$ and magnesium amalgam.[16] This was further modified to $CpTiCl_3$–LAH for the cross-coupling of ketones with aldehydes (Scheme 5).

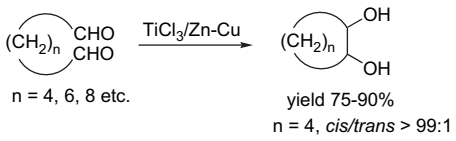


Scheme 5. Titanium(II)-mediated pinacol coupling.

A Ti(II)–porphyrin complex was also found to promote the pinacol coupling of aromatic ketones in moderate selectivity.[17]

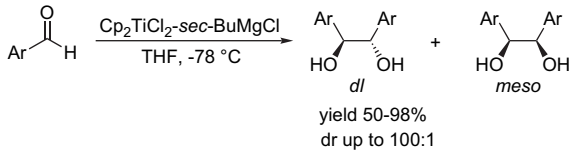
The combination of $TiCl_3$/Zn–Cu, introduced by McMurry and Rico, was used successfully for the intramolecular coupling of various aldehydes.[18] The cis isomer dominated in the smaller rings, whereas the trans isomer became prominent with rings containing 10 or more carbon atoms (Scheme 6).

Until the early 1980s there were hardly any reports of pinacol coupling using well-defined Ti^{3+} species.[19] Inanaga in



Scheme 6. Cyclization of dialdehydes using pinacol coupling.

1987 reported a cyclopentyl-bound Ti^{3+} reagent, generated by the reduction of Cp_2TiCl_2 with *sec*-BuMgCl, for the coupling of aromatic aldehydes.[20] Aldehydes containing an electron-donating group were coupled in excellent selectivity (Scheme 7).



Scheme 7. Titanium(III)-mediated pinacol coupling.

Aliphatic aldehydes showed poor selectivity. The stereochemical outcome was attributed to a dimeric structure (**1**), as shown in Figure 3.

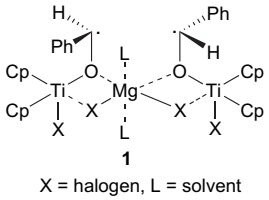
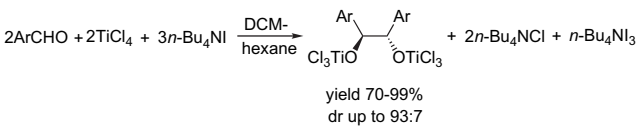


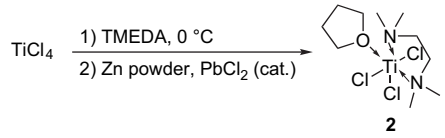
Figure 3. Trinuclear Ti(III)-complex responsible for high selectivity.

The high *dl* selectivity originated from repulsion of the aromatic groups. This assumption was reinforced by the experimental finding that the *dl* selectivity decreases with an electron-withdrawing substituent in the aromatic ring. Porta et al. showed that anhydrous $TiCl_3$ solutions in dichloromethane can provide pinacols with high selectivities.[21] Various other combinations, e.g., $Ti(O^iPr)_4$/EtMgBr,[22] $TiCl_4$/Zn,[23] Cp_2TiCl_2/SmI_2,[20] Cp_2TiCl_2/Zn,[20] or $Cp_2TiCl_2/^iPrMgI$,[20] were also used for pinacol coupling with a high degree of success. In most cases, a stoichiometric reductant was used to produce the low-valent titanium with a concomitant generation of a metal halide. This caused the undesired paths to operate simultaneously, resulting in a poor selectivity. To avoid such a possibility, Oshima et al. used tetrabutylammonium iodide as a stoichiometric reductant (Scheme 8).[24] Tetrabutylammonium triiodide, which was generated as the side product, did not interfere in the reaction. The newly generated Ti(III) was found to be very efficient for both aliphatic as well as aromatic aldehydes. The mechanism proposed was proved by further experimental studies.



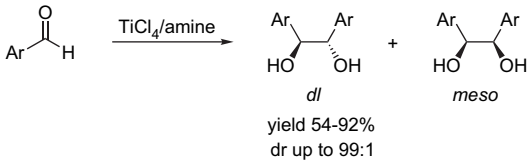
Scheme 8. Use of TBAI for the generation of titanium(III).

Addition of TMEDA and zinc to $TiCl_4$ in the presence of a catalytic amount of $PbCl_2$ provided [$TiCl_3$(TMEDA)(THF)] (**2**) in quantitative yield (Scheme 9). On employing the complex (**2**) with aromatic aldehydes, a high yield and excellent selectivity were observed in the pinacols.[25]



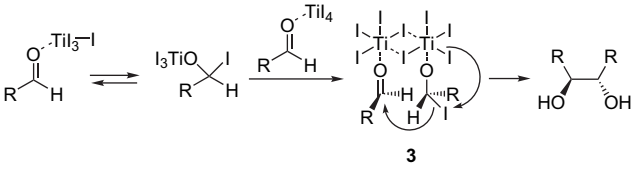
Scheme 9. Preparation of [$TiCl_3$(TMEDA)(THF)].

Addition of non-chelating amines, e.g., TEA,[26] or DIPEA,[27] to $TiCl_4$ proved to be equally effective in generating a Ti^{3+} species (Scheme 10).



Scheme 10. Use of amines for generation of titanium(III).

Pinacol coupling has also been achieved with Ti^{4+} species avoiding the use of any stoichiometric reductant. Titanium tetraiodide in propionitrile under an argon atmosphere provided hydrobenzoins in excellent yields and selectivities.[28] Aliphatic aldehydes were found to be inert in this reagent. To circumvent this problem, β-halogenated or α,β-unsaturated aliphatic aldehydes were employed.[29] The mechanism was believed to involve an iodination in the first step. The iodinated intermediate on reacting with another activated molecule formed (**3**) and, finally, the pinacol (Scheme 11).



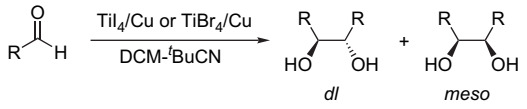
Scheme 11. Titanium(IV)-mediated pinacol coupling.

Other low-valent halogen derivatives were also employed for pinacol coupling reactions. Indeed, a low-valent titanium iodide generated by mixing TiI_4 and copper was found to provide better results than titanium dibromide or dichloride.[30] The superiority of the iodide derivative was explained by its monomeric nature, due to its larger size. Thus the inhibition of cluster formation resulted in a higher solubility and, in turn, a better selectivity.[31] The use of pivalonitrile as a co-solvent increased the solubility through coordination of the nitrogen lone pair (Table 2).

A number of other reagents, e.g., $TiCl_3$–K/I_2,[32] $TiCl_3$–Li/napthalene,[33] or $TiCl_2$–Zn,[34] to generate low-valent titanium were also employed for the pinacol coupling reaction.

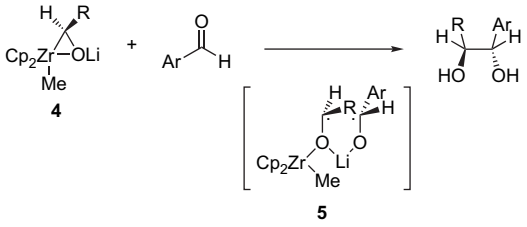
Pinacol coupling was also achieved through dimerization of anionic zirconaoxiranes (**4**) with aromatic aldehydes or

Table 2. Low-valent titanium halides for pinacol coupling



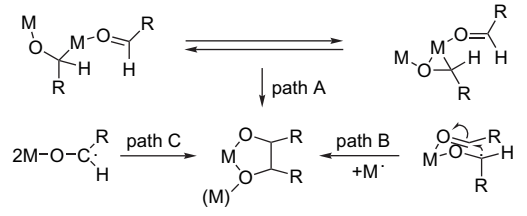
Entry	R	TiI_4/Cu		$TiBr_4$/Cu	
		Yield (%)	*dl*:*meso*	Yield (%)	*dl*:*meso*
1	Ph	94	>99:1	95	96:4
2	4-ClC_6H_4	93	>99:1	97	99:1
3	4-$MeOC_6H_4$	76	98:2	74	94:6
4	PhCH=CH	76	99:1	80	91:9
5	C_6H_{11}	98	85:15	75	75:25
6	Me_3C	92	85:15	—	—

ketones.[35] The cross-coupled products were produced in high yield with the selectivity up to 19:1 for *dl*:*meso* in the case of *p*-tolualdehyde. The higher selectivity was explained by a lithium-bound intermediate **5** (Scheme 12).



Scheme 12. Zirconium-mediated pinacol coupling.

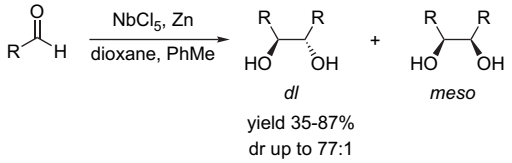
Among other early transition metals, vanadium has found widespread application in the stereoselective pinacol coupling reactions. In 1989 Pedersen et al. prepared a low-valent vanadium complex using $VCl_3(THF)_3$ and Zn. This complex showed a coupling ability towards aryl aldehydes with good yield and selectivity.[36] Aldehydes containing a chelating group in aromatic ring were found to be more suitable as a substrate. The reaction is believed to proceed via either path **A** or path **B** and not through path **C**, furnishing a cross-coupled product with two aldehydes of different reactivities in moderate yield, but poor selectivity (Scheme 13).



Scheme 13. Vanadium-mediated pinacol coupling.

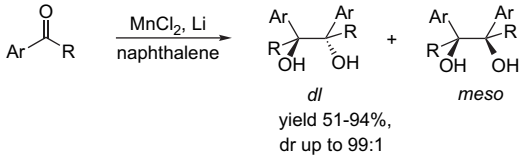
Aldehydes containing a sulfide or sulfone group were also coupled by employing this reagent. The effect of the size of the sulfur substituent was found to be optimum at a certain limit.[37]

Niobium proved to be effective for the coupling of aliphatic aldehydes in high selectivity. Even the intramolecular coupling proceeded with a high cis:trans ratio.[38] The in situ generation of Nb(III) by reducing $NbCl_5$ with Zn has been shown to be an excellent methodology for the pinacol coupling reaction (Scheme 14).[39] This reaction is believed to proceed through a niobiooxirane intermediate. Oshima et al. used Bu_4NI to reduce $NbCl_5$, which also provides a very high selectivity in the coupling of aromatic aldehydes.[24]



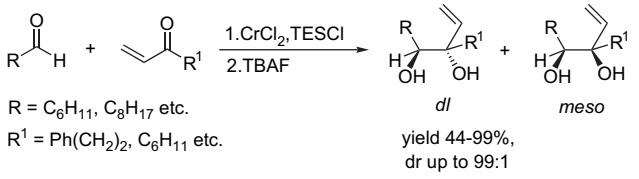
Scheme 14. Niobium-mediated pinacol coupling.

Reduction of manganese halides with lithium in the presence of an electron carrier generates active manganese species, which has been found to be an excellent promoter for the pinacol coupling reaction of a variety of aromatic aldehydes.[40] The ratio of manganese to aldehyde was found to be extremely important for a good yield. This protocol was equally effective for aromatic ketones, where a high selectivity was observed (Scheme 15).



Scheme 15. Manganese-mediated pinacol coupling.

A chromium-mediated cross-coupling between an α,β-unsaturated ketone and an aldehyde was reported by Takai et al. using an excess of $CrCl_2$ and TESCl.[41] The role of the silylating reagent was to trap the γ-siloxy-substituted allylic radical. This radical immediately reacts with Cr(II) to form γ-siloxy-substituted chromium complex, which couples with the aldehyde. A cyclopropane derivative was recovered in the absence of the silylating agent. The yield and selectivities were quite good (Scheme 16).



Scheme 16. Chromium-mediated pinacol coupling.

Zinc in the presence of trimethylsilyl chloride promoted the pinacol coupling of aromatic aldehydes.[42] Although the yields were moderate, the selectivities were very poor.

Inoue et al. used $FeCl_3$ and ^{n}BuLi to couple aromatic aldehydes and ketones. The yield and selectivity remained moderate.[43] The iron cluster **6** (Fig. 4) was also found to act as an efficient electron-transfer carrier in combination with ^{n}BuLi. The yield and the selectivity varied with the molar ratios of ^{n}BuLi employed.

2.1.1.3. p-Block elements. Very few p-block elements have been used in stoichiometric amounts to perform a stereoselective pinacol coupling reaction.

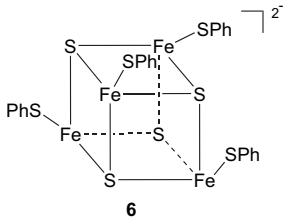


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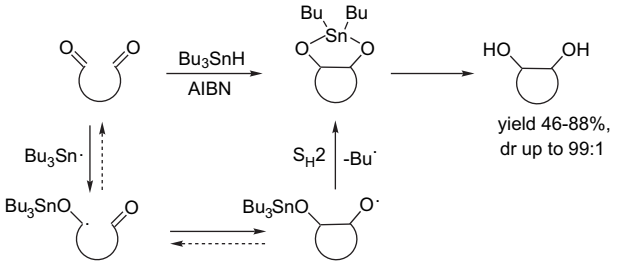
Figure 4. Iron complex used for pinacol coupling.

Schreibmann reported the pinacol coupling of acetophenone using aluminium amalgam in dichloromethane with a very high *dl* selectivity.[44]

Hexamethyldisilane in combination with a catalytic amount of CsF or TBAF afforded pinacols in moderate to good yield, but poor selectivity.[45]

Tributyltin hydride was found to promote intramolecular pinacol coupling in the presence of AIBN.[46] This reagent, with the ability to form five- or six-membered rings, showed an excellent selectivity for the cis isomer in very good yield. A thorough study of the reaction mechanism was conducted using isotope-labelling experiments. The key step was found to be an unprecedented addition of a tin ketyl radical to carbonyl. A subsequent intramolecular homolytic substitution (S_H2) provided the pinacol (Scheme 17).

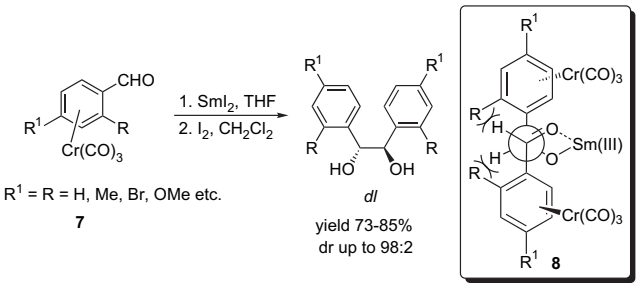


Scheme 17. Tin-mediated pinacol coupling.

2.1.1.4. Lanthanides. Among the lanthanides, samarium has been used most widely for both intra- and intermolecular pinacol coupling reactions. Hirao et al. showed however, that it is possible to promote pinacol coupling by using almost every lanthanide in the presence of TMSCl under sonication.[47] The selectivities varied, depending upon the lanthanide employed.

Kagan et al. introduced SmI_2 in 1983 for the pinacol coupling of aromatic or aliphatic aldehydes, which proceeded with very poor selectivity.[48] Although the addition of TMSCl accelerated the reaction considerably, there was no improvement in the diastereoselectivity of the product.[49] Yanada and Negoro later performed this reaction in protic solvents like MeOH without any improvement in the selectivity.[50] The story remained the same with other reagents, e.g., Sm/TMSCl/NaI[51] or Sm/Et_2AlI.[52]

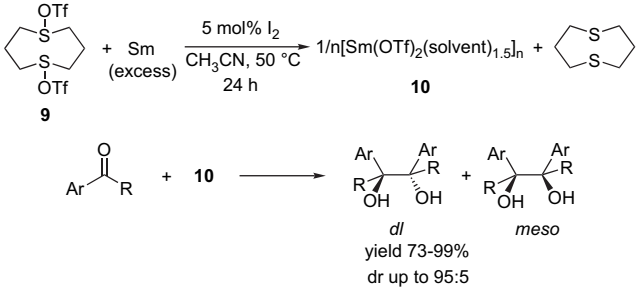
Uemura et al. reported *dl* selective pinacol coupling using a chromium-bound benzaldehyde complex (**7**).[53] A very high yield and selectivity were observed with various aldehydes (Scheme 18).



Scheme 18. Diastereoselective pinacol coupling using chromium-bound aldehydes.

Surprisingly, the addition of HMPA reversed the selectivity. The rationale for this high selectivity was explained through a Newman model (**8**), where both the oxygen atoms of the carbonyls were bound to the same samarium. This conformation was disrupted through coordination of a heteroatom or by an *o*-substituent, as a result of which, a reversal in the selectivity was observed in the case of the *o*-bromo derivative.

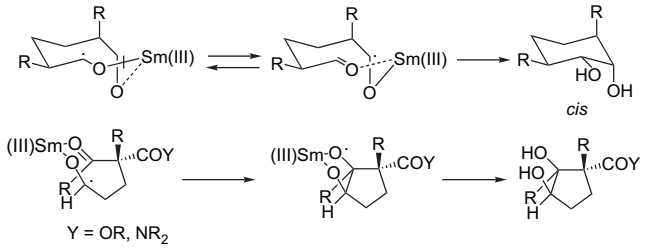
Besides samarium halides, divalent samarium triflate was found to be an excellent precursor. The in situ generation was achieved by reducing $Sm(OTf)_3$ with EtMgBr[54] or *sec*-BuLi.[55] The selectivity was very low in both cases. An excellent diastereoselectivity with aromatic ketones was reported by Tani et al. with a divalent samarium complex (**10**) prepared in situ from the hypervalent sulfur compound (**9**) (Scheme 19).[56]



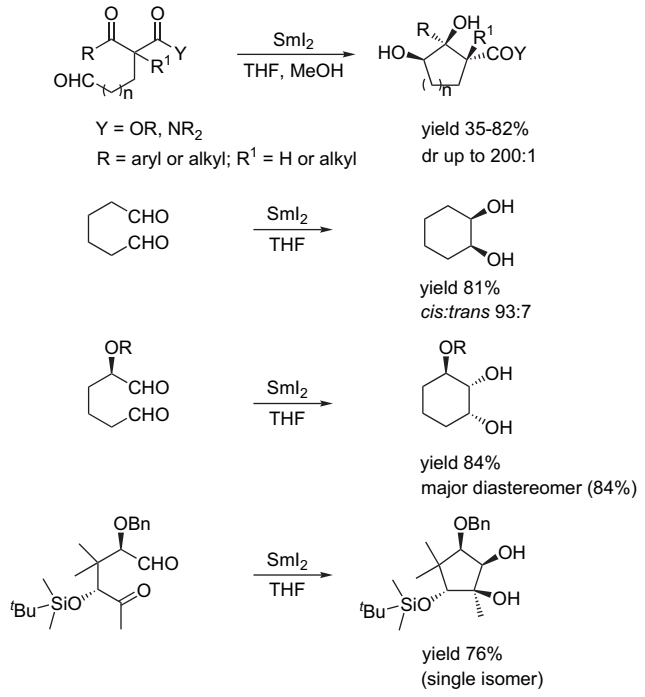
Scheme 19. Samarium triflate-mediated diastereoselective pinacol coupling.

The chemistry of samarium-mediated intramolecular pinacol coupling is rather rich and well established. The first example in this category was reported by Kagan et al. in the year 1983 during the synthesis of 1,2-diphenyl-1,2-cyclohexanediol.[57] Later, a number of publications appeared reporting that a definite stereocontrol was achieved with the help of a neighbouring coordinating group. Hanessian et al. prepared a number of cyclic diols from the corresponding dialdehydes or ketones with a high cis selectivity.[58] The stereochemical outcome was attributed to the inherent geometric preference for the coordination of the ketyl radical with the distal aldehyde carbonyl and the samarium(III) ion (Scheme 20). The most interesting feature of this coupling reaction is that the presence of an alkoxy,[58] ester,[59] amide[59] or siloxy[60] group in the neighbouring carbon on either or one of the carbonyl groups forces an *anti* orientation of the hydroxyl group with respect to the substituent (Scheme 21).

It is logical to assume that the dipolar repulsion (β-substituent effect) plays a key role in this reaction. To minimize the



Scheme 20. Origin of selectivity in samarium-mediated intramolecular pinacol coupling.

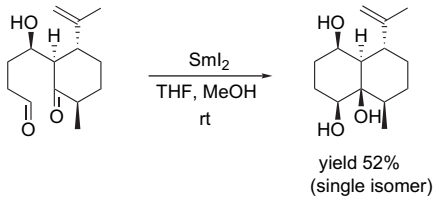


Scheme 21. Influence of neighbouring group in pinacol coupling.

electronic as well as steric repulsion with the α-substituent, a trans orientation of the hydroxyl group is favoured.

A free OH group was also found to effect the selectivity through coordination (Scheme 22).[61]

Fujiwara et al. proposed a detailed mechanism for the umpoled behaviour of the diaryl ketones during the synthesis of pinacols with a poor selectivity using ytterbium.[62] In the presence of trimethylsilyl bromide[63] or phenylthiotrimethylsilane,[64] metallic ytterbium was found to promote pinacol coupling efficiently. The former reagent was applied for



Scheme 22. Influence of hydroxyl group in pinacol coupling.

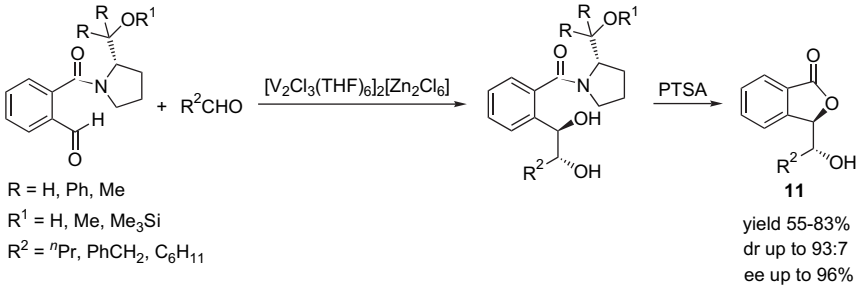
cyclic aliphatic ketones whereas the latter was effective for aromatic systems. The ratio of *dl*:*meso* went up to 4:1 in the case of the *p*-chloro derivative. The yields were all moderate.

2.1.2. Enantioselective protocols. There are very few examples of enantioselective pinacol coupling using stoichiometric protocols. Enantioselectivity in most cases has been achieved by either using a chiral auxiliary or by transferring the axial chirality to the central atom. The use of a stoichiometric amount of chiral complexes proved to be the most effective.

2.1.2.1. Alkali and alkaline earth metals. The enantioselectivity in a lithium-induced pinacol coupling of camphor originated from a selective coupling between two similar enantiomers. Pradhan et al. reported that, when optically active or racemic camphor was subjected to pinacol coupling under the same conditions, only a single pinacol or racemate was produced, respectively.[6] The stereochemistry of the single product formed was established to be *endo*:*endo*. The conclusion drawn was that the reaction took place only between a (+) and (+) or a (−) and (−) enantiomer. The single isomer was produced in moderate yield, but high selectivity.

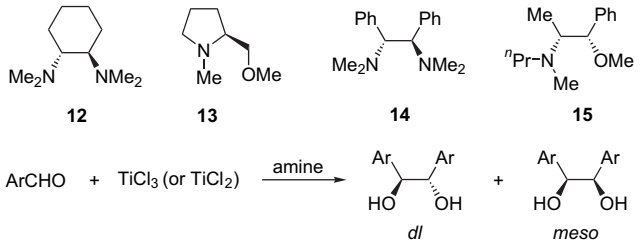
2.1.2.2. Transition metals. Using $[V_2Cl_3(THF)_6]_2$-$[Zn_2Cl_6]$ for the cross-coupling between an aliphatic and an aromatic aldehyde containing a chiral auxiliary, high enantioselectivity in the final product (**11**) was obtained (Scheme 23).[65]

Titanium is the most successful among all the metals in producing optically active pinacols from prochiral aldehydes. A preformed chiral titanium complex or titanium in combination with a chiral ligand is used as the most reliable tool to perform enantioselective pinacol coupling reactions. Matsubara et al. achieved a moderate enantioselectivity using a chiral amine with a low-valent titanium species.[66] Among the variety of chiral amines examined (**12**–**15**), *N*,*N*,*N*,*N*-tetramethylcyclohexylamine (**12**) proved to be the most effective in combination with $TiCl_3$, inducing 40% ee in hydrobenzoin. An insight into the reaction mechanism using various



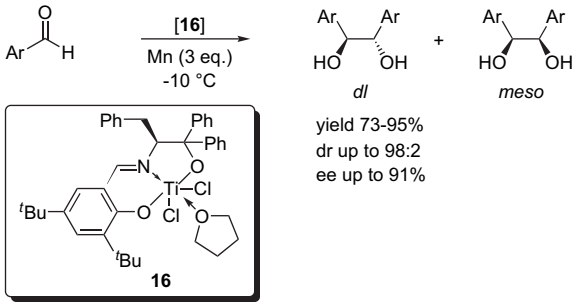
Scheme 23. Vanadium-mediated enantioselective pinacol coupling.

instrumental measurements revealed the presence of two types of particles in the solution. Cluster particles with the general formula $[(TiCl_3)_n(amine)_m]$ were inert and responsible for the drop of ee, whereas the monomeric particles $[TiCl_3(amine)_{1-2}(THF)_{1-2}]$ were responsible for the coupling. The addition of a co-solvent to break up the cluster resulted in an increased ee of 58%. In another report, Enders and Ullrich achieved 65% ee with a high *dl*:*meso* ratio using $TiCl_2$/amine **13** for the coupling of benzaldehyde.[67] No better selectivity was observed with other aldehydes (Scheme 24).



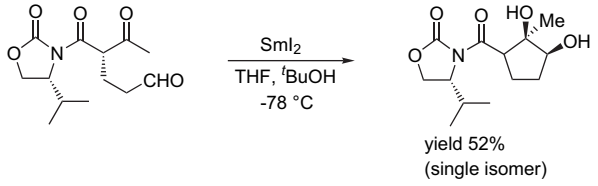
Scheme 24. Enantioselective pinacol coupling using optically active amines.

An enantioselectivity of up to 91% was reported by Riant et al. using a titanium hemi-SALEN complex **16** (Scheme 25).[68] A decrease in ee was observed with electron-withdrawing substituents at the *para* position.



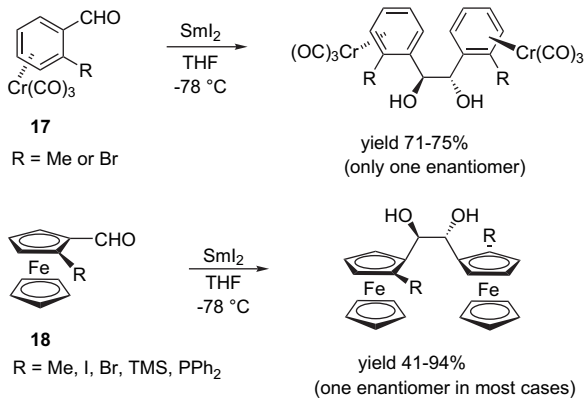
Scheme 25. Enantioselective pinacol coupling using a stoichiometric titanium complex.

2.1.2.3. Lanthanides. With a knowledge of the preferential cis selectivity of samarium-mediated intramolecular pinacol coupling reactions, a number of optically pure aldehydes were treated with SmI_2 to form the enantiomerically pure diols. One of the first examples was provided by Molander and Kenny through an intramolecular cross-coupling reaction (Scheme 26).[69]



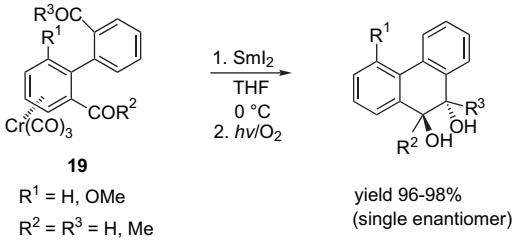
Scheme 26. Samarium-mediated enantioselective pinacol coupling.

Kagan et al. performed an intermolecular enantioselective pinacol coupling reaction between camphor and benzophenone using $SmBr_2$. As predicted, an optically pure diol was formed.[70] Uemura and Taniguchi showed that optically active chromium-bound *ortho*-substituted benzaldehydes (**17**) can be coupled in an enantioselective fashion using SmI_2.[71] The same methodology was further extended to optically active 2-substituted ferrocenecarboxaldehydes (**18**) (Scheme 27).



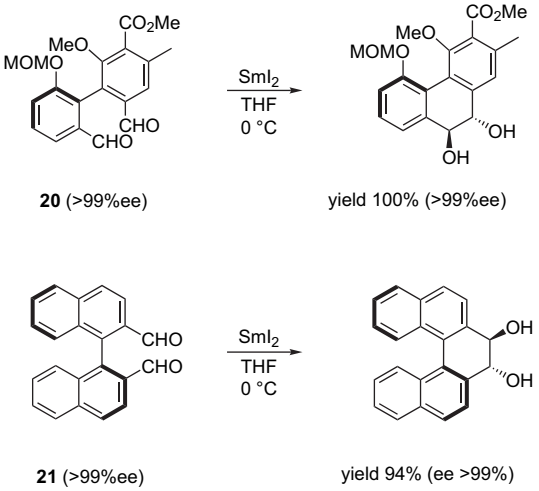
Scheme 27. Enantioselective pinacol coupling using optically active aldehydes.

Applying a similar methodology, chiral 1,2-diols were prepared from chiral mono $Cr(CO)_3$-complexed biphenyl derivatives **19** (Scheme 28).[72]



Scheme 28. Enantioselective pinacol coupling using chiral biaryls.

Suzuki et al. developed a new method for transferring the axial chirality of biphenyl derivatives to the central chirality through a pinacol coupling reaction.[73] After examining a variety of coupling agents, SmI_2 proved to be the most effective. The trans diols were obtained in a diastereomerically pure form starting from the aldehydes **20** and **21** (Scheme 29).



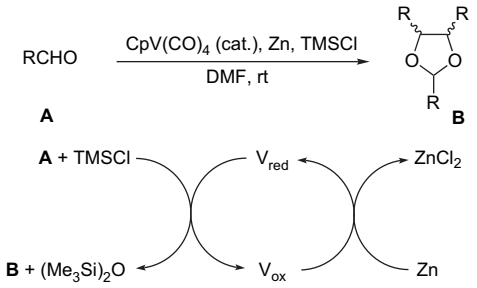
Scheme 29. Transfer of axial chirality.

2.2. Catalytic protocols

2.2.1. Diastereoselective protocols.

2.2.1.1. Transition metals. Although the introduction of catalytic protocols in the pinacol coupling reaction is not very old, it has developed exponentially in the last 10 years. Transition metals remained the most favoured reagents in this context.

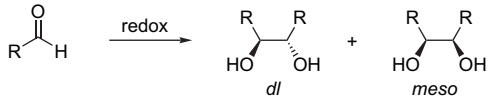
Hirao et al. in 1996 described the first catalytic cycle for a vanadium-mediated pinacol coupling reaction using Zn and TMSCl (Scheme 30).[74]



Scheme 30. First catalytic protocol for vanadium-mediated pinacol coupling.

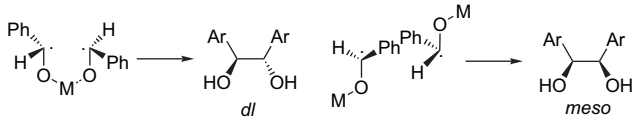
Soon after this report, various other methods were developed, based on similar reagents, e.g., $Cp_2VCl_2/Me_3SiCl/Zn$,[75] $VOCl_3/Me_3SiCl/Al$[76] etc. In most cases, a good selectivity was achieved (Table 3).

Table 3. Vanadium-mediated catalytic pinacol coupling



Entry	R	Redox	Yield (%)	*dl*:*meso*	Ref.
1	Ph	$VOCl_3$/Al/TMSCl	68	>95:5	76
2	4-ClC_6H_4	$VOCl_3$/Al/TMSCl	89	>95:5	76
3	4-MeC_6H_4	$VOCl_3$/Al/TMSCl	62	>95:5	76
4	C_6H_{11}	Cp_2VCl_2/Zn/TMSCl	66	90:10	75
5	Ph(Me)CH	Cp_2VCl_2/Zn/TMSCl	66	94:6	75
6	Me_2CH	Cp_2VCl_2/Zn/TMSCl	89	91:9	75

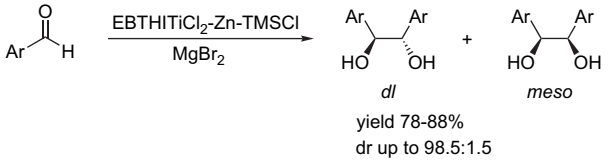
The higher *dl* selectivity was attributed to a metal-bridged intermediate. On the other hand, an acyclic intermediate was proposed for the *meso* product (Scheme 31).



Scheme 31. Origin of diastereoselectivity.

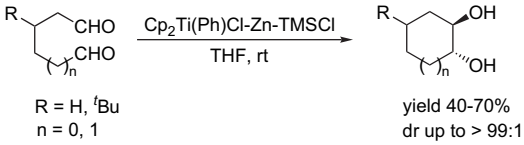
In addition to TMSCl, acetic anhydride was also found to regenerate the catalyst.[77] The pinacols were obtained in more than 80% yield with a variety of substituents at the *ortho*- or *para*-positions of the aromatic ring. The diastereoselectivity went up to 94:6 for *dl*:*meso* in the case of 2,6-$Me_2C_6H_3CHO$.

The immense potential of titanium to promote a high diastereoselection in the pinacol coupling reaction was realized through its stoichiometric protocols. A catalytic version is, however, highly desirable for expensive complexes. The first breakthrough came after the report by Fürstner and Hupperts on recycling titanium using TMSCl.[78] The well-documented Cp_2TiCl_2 prompted Gansäuer to pursue pinacol coupling with this reagent. As expected, a very good yield and diastereoselectivity were obtained with several aromatic aldehydes.[79] The preferential *syn* selectivity was attributed to a similar dimeric structure (**1**), as proposed by Inanaga and Handa.[20] The need to add 1 equiv of $MgBr_2$ was argued to contribute to a tighter trimeric species for better steric tuning. The slow addition of the mixture of TMSCl and aldehyde was the key to a higher selectivity and provided evidence for the silylation to be the rate-determining one. Hirao et al. applied the same protocol for the pinacol coupling of aliphatic aldehydes and ketones.[80] A high diastereoselectivity (96:4) for *dl*:*meso* was reported for cyclohexane carboxaldehyde, but it remained low for other acyclic aldehydes and ketones. A slightly higher selectivity for the aromatic aldehydes was achieved using *rac*-ethylenebis-(η^5-tetrahydroindenyl)titanium dichloride ($EBTHITiCl_2$) as a catalyst (Scheme 32).[81]



Scheme 32. Titanium-mediated catalytic pinacol coupling.

In most cases, the success of an organometallic complex depends upon the monomeric nature of the reagent in the solution state and, probably, this is the reason for the different behaviour of the newly generated titanium complexes from different sources. One of the easiest ways of prohibiting dimerization would be to increase the steric bulk of the ligand. With this logic in mind, Itoh et al. prepared the bulky $Cp_2TiPhCl$ for the coupling reaction.[82] Although the selectivity was lower with aliphatic or aromatic aldehydes, the intramolecular pinacol coupling of dialdehydes containing five to six carbon atoms proceeded with an excellent selectivity (Scheme 33).



Scheme 33. Catalytic pinacol coupling for cyclization of dialdehydes.

The high trans selectivity observed was contrary to the report of McMurry and Rico using $TiCl_3$/Zn–Cu.[18] This was explained by the restriction of the bulky titanium radical to coordinate with another aldehyde moiety, unlike McMurry's protocol, as a result of which, the repulsion of the two bulky titanium radicals favoured a trans orientation of the hydroxyl groups (Fig. 5).

Nelson et al. showed that instead of using complex ligands, it was possible to achieve high diastereoselection through a

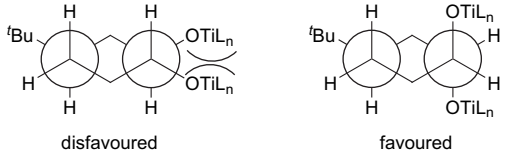
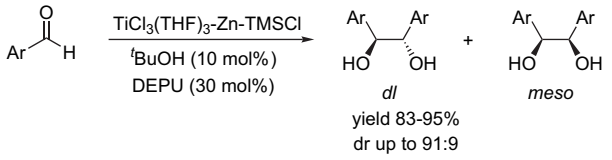


Figure 5. Origin of selectivity in cyclic diols.

proper tuning of the catalyst architecture.[83] $TiCl_3(THF)_3$–Zn–TMSCl redox in the presence of 10 mol % ^{t}BuOH and 30 mol % DEPU furnished a high *dl* selectivity for various aromatic aldehydes. In the optimized conditions, the 1,5-dialdehyde was also coupled with high selectivity (cis:trans=89:11) (Scheme 34).



Scheme 34. Diastereoselective pinacol coupling through ligand modification.

The catalytic cycle of titanium so far described was based on the stoichiometric use of TMSCl. Gansäuer and Bauer with 2,4,6-collidine hydrochloride salt also achieved a catalytic turnover through protonation of the metal–oxygen bond (Fig. 6).[84] This new protocol was found to be very effective for a variety of substituted aldehydes, furnishing an excellent selectivity (>95% for *dl*) and a high yield.

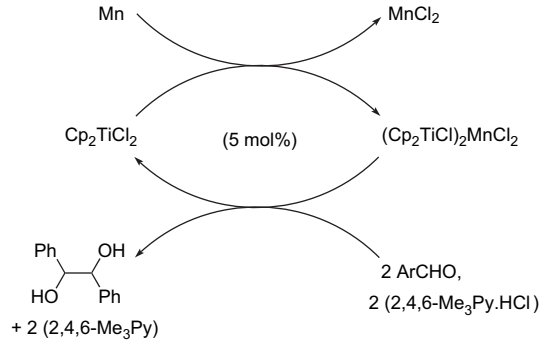
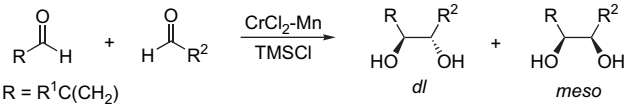


Figure 6. Development of a new catalytic cycle.

Hirao et al. established another catalytic cycle using acetyl chloride to cleave the metal–oxygen bond.[77] $TiCl_4$ in the presence of aluminium as a reductant and acetyl chloride as the catalyst regenerator provided a successful cycle for catalytic pinacol coupling of aromatic aldehydes. The yields were in the range 78–94% and the diastereomeric ratio for *dl*:*meso* was up to 91:9 for *p*-$CF_3C_6H_4CHO$.

Following the catalytic path established by Fürstner and Shi for the Nozaki–Hiyama–Kishi reaction,[85] a number of publications have appeared for the catalytic pinacol coupling of aldehydes or ketones using chromium.[86] A good yield and high selectivity have been achieved after optimizing the solvent polarity, steric properties of the silylating agent and the coreductant. Intramolecular pinacol coupling was also achieved in high cis selectivity. 2-Substituted acroleins were coupled with aldehydes in high selectivity using

Table 4. Catalytic, diastereoselective pinacol coupling using chromium salts



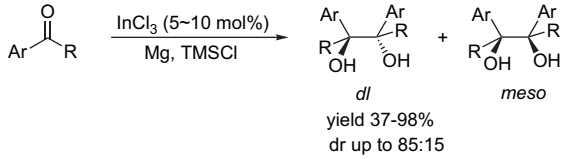
Entry	R^1	R^2	Yield (%)	*dl*:*meso*
1	^{t}Bu	^{t}Bu	61	>98:2
2	^{t}Bu	$Ph(CH_2)_2$	73	86:14
3	Me	^{t}Bu	54	28:72
4	H	^{t}Bu	52	22:78

$CrCl_2$/Mn/TMSCl (Table 4).[87] With decrease in the steric demand, a fall in the selectivity was noticed. The change of product conformation from *dl* to *meso* with changes in sterics was believed to be a consequence of the preferred conformation for the six-membered transition state for the cross-coupling reaction. It should be noted here that the reaction in this case does not proceed through a classical dimerization of two ketyl radicals. Instead, a chromium–allyl species attacks another aldehyde.[88]

Tu et al. proposed a similar catalytic method using nickel(II) chloride in combination with magnesium and TMSCl.[89] The catalytic cycle was believed to follow a similar path to that described for titanium. Although a variety of aromatic aldehydes were coupled in good yield, the diastereoselectivity remained low. Aromatic ketones and aliphatic aldehydes were also coupled with this protocol.

A cationic thiolate-bridged diruthenium complex [Cp*RuCl-($\mu_2S^iPr)_2$RuCp*][OTf] (Cp*=η^5–C_5Me_5) was used for the catalytic pinacol coupling reaction.[90] Unlike acetophenone, aromatic aldehydes were coupled in quantitative yield. The selectivity was low in all the cases.

2.2.1.2. p-Block elements. Among the p-block elements, only indium has been found to catalyze pinacol coupling reaction. $InCl_3$ in combination with Mg and TMSCl can couple aromatic aldehydes and ketones[91] (Scheme 35). An electron-withdrawing group in the aromatic ring was found to decrease both the yield and selectivity, whereas an electron-donating substituent seemed to have a favourable effect.

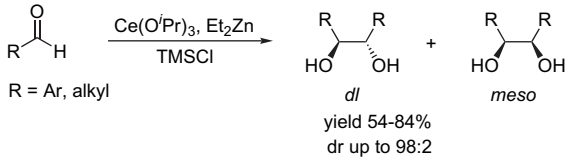


Scheme 35. Catalytic, diastereoselective pinacol coupling using indium.

2.2.1.3. Lanthanides. For the catalytic pinacol coupling reaction, cerium and samarium are the only successful candidates from the lanthanide group.

Groth and Jeske reported the first catalytic use of cerium in a method analogous to that described by Fürstner.[92] Diethylzinc was used in excess to generate the low-valent cerium, which was regenerated by TMSCl. The protocol proved to be effective even at a 3 mol % loading. Various aromatic

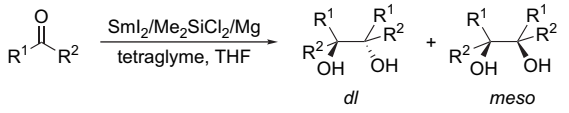
aldehydes were coupled in very high yield and excellent selectivity (Scheme 36). To overcome the need for demanding steric features for a higher selectivity, the reducing agents or the ligand framework were modified.[93] Long-chain aldehydes were also coupled for the first time with high selectivity using this modified procedure. The authors showed that, with an increase in the ligand sterics, the selectivity as well as the yield increased sharply.



Scheme 36. Catalytic, diastereoselective pinacol coupling using cerium.

Recently, Greeves et al. [94] have improved the selectivity through a slight modification of the original catalytic cycle proposed for samarium. Tetraglyme as an additive and Me_2SiCl_2 as the catalyst regenerator afforded a selectivity as high as 95:5 for the *dl*/*meso* for pivalaldehyde (Table 5).

Table 5. Catalytic, diastereoselective pinacol coupling using samarium



Entry	R^1	R^2	Yield (%)	*dl*:*meso*
1	Ph	H	83	20:80
2	Ph	Me	62	19:81
3	C_6H_{11}	H	63	81:19
4	Me_3C	H	76	95:5
5	C_6H_{11}	Me	74	94:6

For intramolecular pinacol coupling also protocol met with good success. The reversal of selectivity was attributed to the ease of reduction of aromatic aldehydes as compared to their aliphatic counterparts due to their low-energy LUMO electrons, as a result of which the concentration of these radicals becomes sufficiently high to allow dimerization between two such species resulting in *meso* products. On the other hand, the aliphatic ketyl radicals being less in population, prefer to attach to another aldehyde through a pseudo-bridged transition state (Fig. 7).

Namy and Hélion established a catalytic cycle using a new approach.[95] The reduction of trivalent samarium as well as cleavage of the Sm–O bond was achieved using mischmetall (a cheap alloy of light lanthanoids for industrial applications) (Fig. 8).

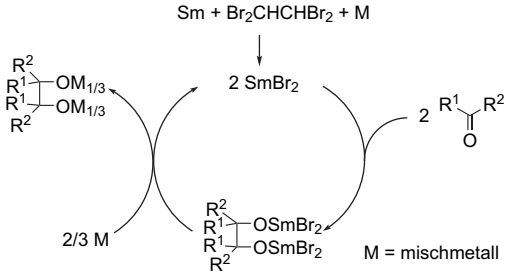
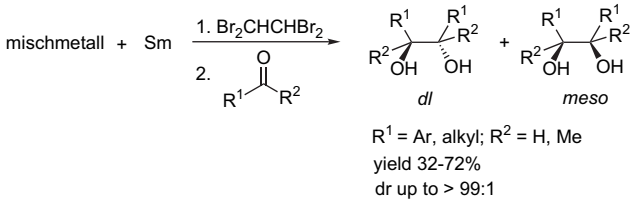


Figure 8. Development of catalytic cycle using mischmetall.

The *dl* selectivity went up to 100% in a highly demanding aldehyde.[96] The addition sequence and the addition time were found to be determining factors towards high selectivity. Following this protocol, under optimized conditions, a number of aldehydes and ketones were coupled with a high degree of success (Scheme 37).



Scheme 37. Catalytic, diastereoselective pinacol coupling using samarium.

2.2.2. Enantioselective protocols. Achieving enantioselectivity through the use of a chiral catalyst is considered to be the most modern way of synthesizing chiral compounds. For catalytic enantioselective pinacol coupling, titanium remains the most popular metal.

A variety of ligands (**22**–**28**) have been explored (Fig. 9). Cozzi and Umani-Ronchi were the first to notice a low chiral induction in the pinacols while using Ti–Schiff base complexes.[97] After examining various Schiff bases, they found that **22** induced 10% ee with high diastereoselectivity (*dl*:*meso*=90:10). Taking advantage of a high diastereoselectivity with *rac*-Brintzinger's catalyst (ethylenebis(tetrahydroindenyl)titanium dichloride), Nicholas and Dunlap tried to apply its chiral version to the catalytic pinacol coupling reaction.[98] They reported a moderate ee (60%) for the resulting pinacol in unoptimized conditions. To check the enantioselectivity of the pinacols using a similar ligand framework, the *ansa*-bis(indenyl) (Ti-**24**) and *ansa*-bis(tetrahydroindenyl)

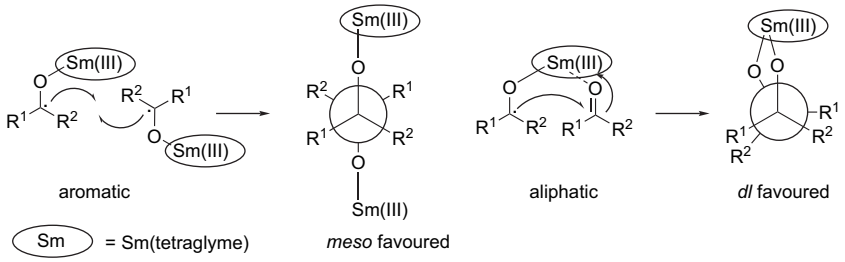


Figure 7. Rationale for reversal of selectivity.

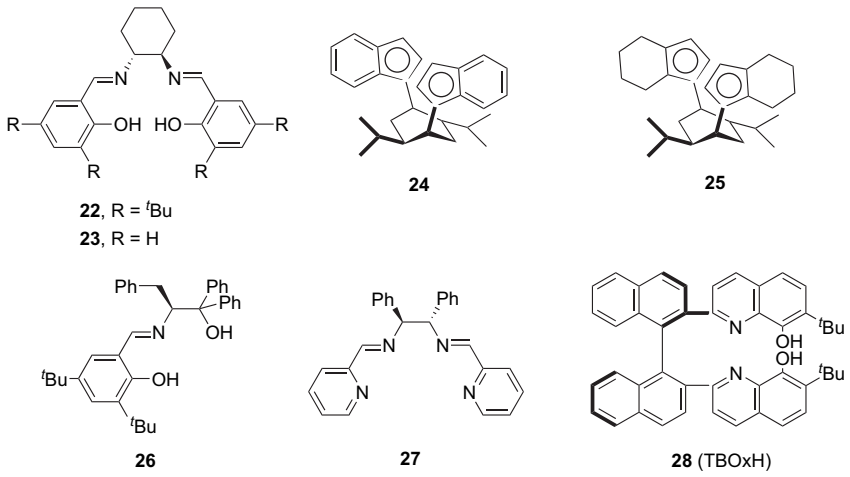


Figure 9. Chiral ligands used in catalytic, enantioselective pinacol coupling.

(Ti-**25**) metal complexes were employed.[99] A racemic product was, however, obtained using the bis(indenyl)complex (Ti-**24**), whereas a low ee resulted with the other complex (Ti-**25**). More recently, Riant et al. came up with a complex (**16**) using the hemi-SALEN ligand (**26**), which induced a moderate ee (64%) through a catalytic path.[68] This lower ee, as compared to its stoichiometric version, was rationalized through the inhibition of the proper catalytic path at a lower temperature. Later, our group reported a Ti-SALEN complex (Ti-**23**) as the first successful catalyst for this reaction.[100] Recently, You et al. reported an in situ generation of a Ti–Schiff base complex (Ti-**27**), which also showed a good enantioselectivity in most cases.[101]

The most effective catalyst for enantioselective pinacol coupling has been designed by Yamamoto et al. using a Cr complex of a tethered bis(8-quinolinolato) moiety (Cr-**28**).[102] The chromium complex was prepared in three steps in very high yield starting from the optically active 2,2-diiodo-1,1-binaphthyl. An X-ray crystallographic study of the racemic catalyst revealed a cis-β configuration of TBO*x*CrCl. This catalyst proved to be quite insensitive to steric as well as electronic changes in the aromatic ring. The enantioselectivity remained >95% in all cases. Indeed, the author also reported the first enantioselective coupling of aliphatic aldehydes.

A summary of various successful catalysts for pinacol coupling is provided in Table 6.

2.3. Other methods

2.3.1. Photochemical irradiation. The formation of benzopinacols upon irradiation was observed in 1900 by Ciamician[103] and, since then the photo-irradiation through sunlight has become a reliable method to prepare these compounds. The major drawback of this procedure, however, is the poor selectivity.[104] Recently, Li et al. reported the coupling of various aromatic aldehydes and ketones in excellent yields and, in some cases, very high selectivity.[105] The general mechanism involved in this reaction is excitation of the aldehyde group followed by extraction of hydrogen from the solvent to form the α-hydroxybenzyl radical. Finally, dimerization of this radical furnishes the product (Fig. 10).

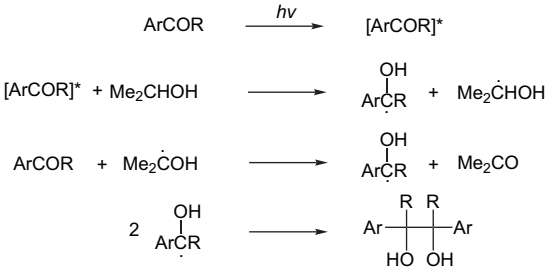
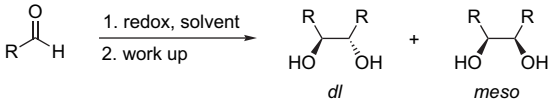


Figure 10. Mechanism of photo-induced pinacol coupling.

Table 6. Enantioselective pinacol coupling using various protocols

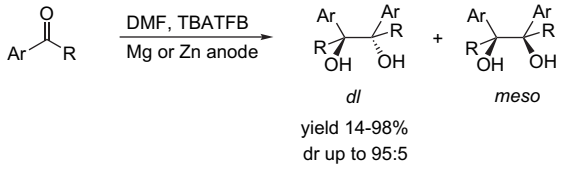


R	Redox	Cat. loading (mol %)	Temp (°C)	Yield (%)	*dl*:*meso*	ee (%)	Ref.
Ph	(Ti-**24**)–Zn–TMSCl	10	−10	94	98:2	95	100
4-MeC_6H_4	(Ti-**24**)–Zn–TMSCl	10	−10	84	91:9	96	100
2-MeC_6H_4	(Ti-**24**)–Zn–TMSCl	20	−10	75	96:4	82	100
2-Naphthyl	(Ti-**24**)–Zn–TMSCl	10	−10	82	94:6	91	100
Ph	(Cr-**28**)–Mn–TESCl	3	rt	94	98:2	97	102
3-MeOC_6H_4	(Cr-**28**)–Mn–TESCl	3	rt	92	98:2	97	102
4-$CF_3C_6H_4$	(Cr-**29**)–Mn–TESCl	3	rt	89	92:8	95	102
1-Naphthyl	(Cr-**28**)–Mn–TESCl	3	rt	92	96:4	98	102
–$(CH_2)_6$–	(Cr-**28**)–Mn–TMSCl	3	rt	44	93:7	84	102

Seebach and Daum showed that irradiation of a solution of acetophenone in the presence of a chiral amine at low temperature produced pinacol in 58% yield with 6% optical purity.[106]

2.3.2. Sonication. Ultrasonic irradiation has been used for quite some time as a tool to achieve pinacol coupling in a non-aqueous medium. Alkali metals such as Na or Li[107] or a combination of Sm/NH_4Cl[108] provided pinacols of various aromatic aldehydes and ketones in moderate to high yields, but with poor selectivity. Recently, Ranu et al. achieved high selectivity using Li in THF under sonication.[109] Aromatic aldehydes and ketones were coupled in moderate to high yields with the selectivity ranging from 75:25 to 98:2 for *dl*/*meso*.

2.3.3. Electrolysis. Electrochemical reductions have been used for a long time to prepare pinacols using a metal cathode (generally Hg) in an aqueous acidic or basic medium. Indeed, it is observed that the proportion of the *dl* isomer increases in aqueous alkaline solution over acidic conditions.[110] Using a Zn or Mg anode and a stainless steel cathode in the presence of TBATFB as a supporting electrolyte in DMF, a variety of aldehydes and ketones were coupled (Scheme 38).[111]



Scheme 38. Pinacol coupling using electrochemical methods.

Duñach et al. achieved a catalytic cycle of samarium in the presence of 5–10% of $SmCl_3$, based on the use of sacrificial anodes of Mg or Al.[112] A variety of aromatic aldehydes and ketones were coupled successfully in high yield, but with poor selectivity.

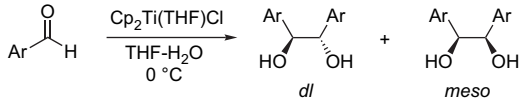
Seebach and Oei showed that it is possible to achieve some enantioselectivity using an achiral supporting electrolyte in a chiral medium.[113] The hydrodimerization of acetophenone in a solution containing (+)-DDB in combination with MeOH and LiBr, proceeded in 95% yield with a slight excess of one enantiomer. A maximum of 20% asymmetric induction was achieved in the electrochemical dimerization of acetophenone and its derivatives using chiral salts, e.g., (1*R*,2*S*)-$HOCHPhCHMeN^+Me_3I^-$.[114]

2.3.4. Reactions in aqueous media.

2.3.4.1. Alkali and alkaline earth metals. Magnesium is the only alkaline earth metal that can produce pinacol in a dilute aqueous solution of ammonium chloride, albeit with poor selectivity.[115]

2.3.4.2. Transition metals. Among the transition metals, titanium has remained the most successful in terms of selectivity. The reducing ability of titanium is very much dependant upon the pH of the medium and increases sharply with an increase in the pH value. In fact, aldehydes or ketones undergo coupling easily in a basic medium,[116] although with a low selectivity. A reagent-controlled highly selective pinacol coupling was reported by Schwartz and Barden using Cp_2TiCl in a mixed solvent of THF/H_2O for the α,β-unsaturated aldehydes (Table 7).[117] The selectivity was very high with $[(EBTHI)_2TiCl]$ for aromatic aldehydes.

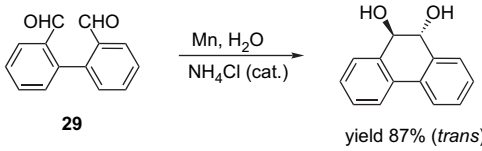
Table 7. Pinacol coupling in aqueous media



Entry	Ar	THF:H_2O	Yield (%)	*dl*:*meso*
1	Ph	20:80	82	95:5
2	4-FC_6H_4	80:20	85	94:6
3	4-$MeOC_6H_4$	80:20	88	94:6
4	Furfuraldehyde	80:20	75	95:5
5	Cinnamaldehyde	80:20	83	98:2

A variety of combinations such as Zn–Cu[118] or $Zn–ZnCl_2$[119] under ultrasonic irradiation were found to be effective. Zinc in the absence of any organic solvents, also afforded diols with a low selectivity.[120]

Aromatic aldehydes were found to react with manganese in an aqueous solution in the presence of a catalytic amount of acetic acid or in aqueous ammonium chloride. The yields were good but the selectivity was poor. [121] Surprisingly the intramolecular coupling of **29** afforded only the trans diastereomer in 87% yield (Scheme 39).

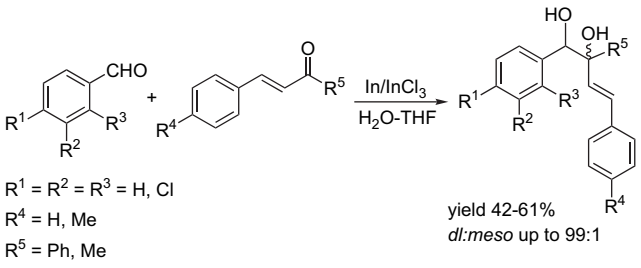


Scheme 39. Manganese-mediated pinacol coupling in aqueous media.

In situ generation of cadmium from $CdCl_2 \cdot H_2O$ in a DMF/H_2O medium by reduction with samarium metal enabled coupling of aromatic aldehydes in good yield with a *dl*:*meso* ratio of 89:11 for *o*-bromobenzaldehyde.[122]

2.3.4.3. p-Block elements. Among the p-block elements, aluminium has been widely used to promote pinacol coupling in an aqueous medium. In aqueous alkaline solution, aluminium powder was found to produce *vic* diols in moderate yield and selectivity under sonication.[123] An increase in the *meso* selectivity was noticed in the presence of metal fluorides.[124] Aluminium in an amalgamated form can also promote pinacol coupling of cycloalkanones in the mixed solvent THF/H_2O.[125]

Indium under prolonged sonication was found to promote pinacol coupling of substituted aromatic aldehydes in good yields, but with moderate selectivity.[126] Nair et al. showed that the cross-coupling between an aromatic aldehyde and a chalcone can be readily performed in aqueous THF in the presence of $In/InCl_3$.[127] The product yields were moderate and the *dl* selectivity was high (Scheme 40).



Scheme 40. Indium-mediated pinacol coupling in aqueous media.

2.3.4.4. Lanthanides. Samarium is the only lanthanide, which has been used for pinacol coupling in an aqueous medium. In aqueous acidic solution, samarium was found to couple aromatic aldehydes and diaryl ketones in high yield.[128] A binary combination of $SmCl_3$ with Sm or Mg was equally effective.[129] The selectivity was poor in all cases.

3. Synthetic applications of pinacol coupling

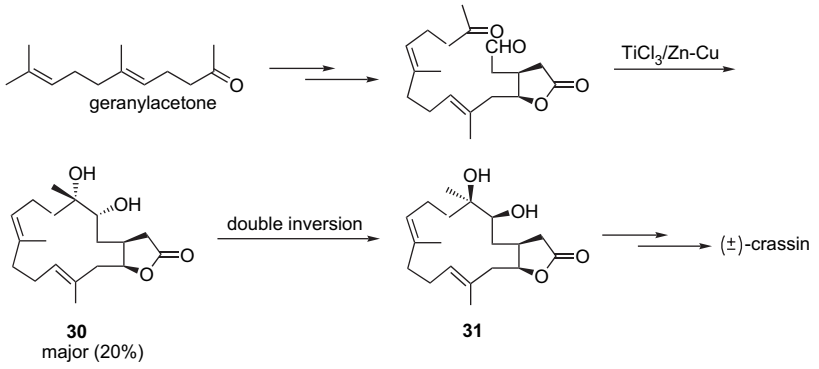
3.1. Terpenes

Pinacol coupling has been used successfully in many syntheses of di-, tri- or sesquiterpenes. McMurry and Dushin prepared racemic crassin, a diterpenoid, using $TiCl_3$/Zn–Cu to construct the 14-membered ring.[130] The keto–aldehyde coupling proceeded with 48% yield (including four isomers). As the yield of the desired isomer (**31**) was very low, the major isomer (**30**) was epimerized at the C_3, C_4 centre through double inversion (Scheme 41).

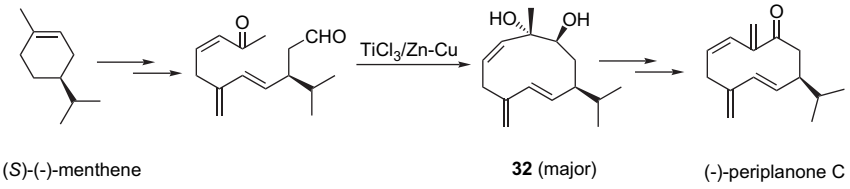
In another example, McMurry and Siemers reported the synthesis of (−)-periplanone C, a 10-membered sesquiterpene, which is an insect pheromone.[131] The 10-membered ring was constructed in a similar manner. Unlike the previous example and contrary to mechanistic calculations, the trans diol (**32**) was formed as the major product. Further transformations led to the final product (Scheme 42).

Corey and Kania prepared *rac* palominol and dolabellatrienone, a dolabellane class of marine diterpenoids, using pinacol coupling as the key step for the ring formation.[132] The coupling with low-valent titanium gave a mixture of two diastereomers (**33**) in a ratio of 2.1:1 as a separable mixture (53% yield) (Scheme 43).

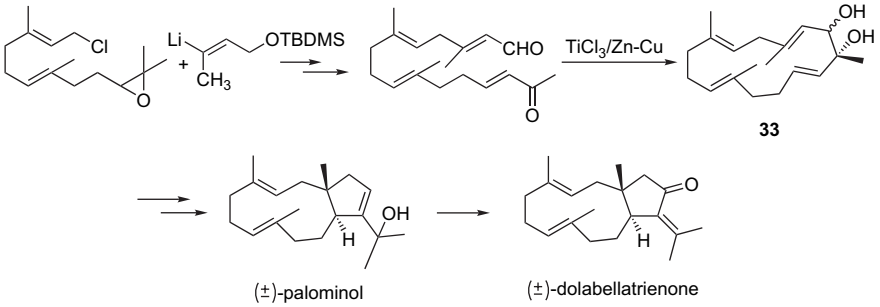
Li and Yue constructed the 14-membered ring of the macrocyclic diterpene, (+)-3,4-epoxycembrene-A, using $TiCl_4$/Zn.[133] The final product was obtained as a mixture of four



Scheme 41. Synthesis of (±)-crassin.

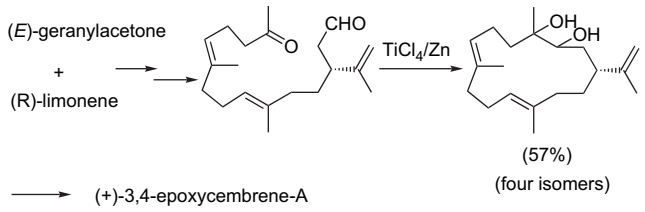


Scheme 42. Synthesis of (−)-periplanone C.



Scheme 43. Synthesis of (±)-dolabellatrienone.

stereoisomers (23:21:15:6), which were separated as epoxides through HPLC (Scheme 44).



Scheme 44. Synthesis of (+)-3,4-epoxycembrene-A.

During the synthesis of (+)-4,5-deoxyneodolabelline, a bicyclic diterpene, Williams and Heidebrecht showed that the low-valent titanium produced by $TiCl_3$/Zn–Cu, although less selective, is more efficient than the low-valent vanadium complex (Scheme 45).[134] The final product was separated after oxidation to obtain the desired isomer.

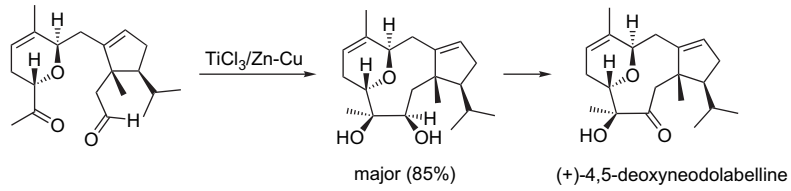
SmI_2 has proved to be equally effective for the preparation of various terpenes. Marcos et al. synthesized (+)-totarol, a tricyclic diterpene known to have pronounced biological activity, from zamoranic acid (**34**) using SmI_2 to form the C-ring. The major isomer (**35**) was shown to contain two α-OH groups (80%) (Scheme 46).[135]

Following a similar approach, another tetracyclic diterpene, 15-hibaen-14-one, was synthesized by the same group (Scheme 47).[136]

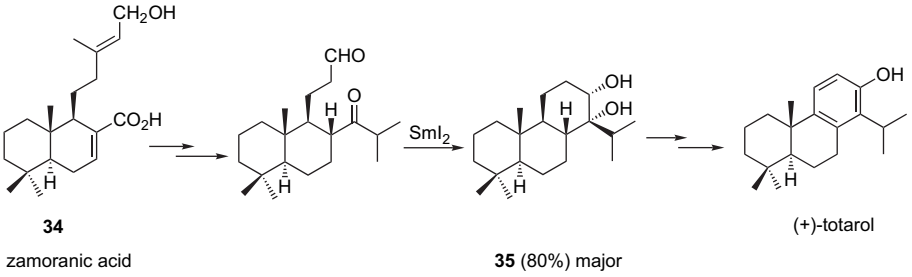
3.2. Sugars

The reaction of methyl trifluoropyruvate (**36**) and 2,3-di-*O*-isopropylidene-D-glyceraldehyde (**37**) in the presence of $TiCl_3$/Zn proceeded smoothly in moderate yield with a higher ratio of the trans isomer (**38**). This coupled product was further manipulated through a series of reactions to prepare D-ribose (Scheme 48).[137]

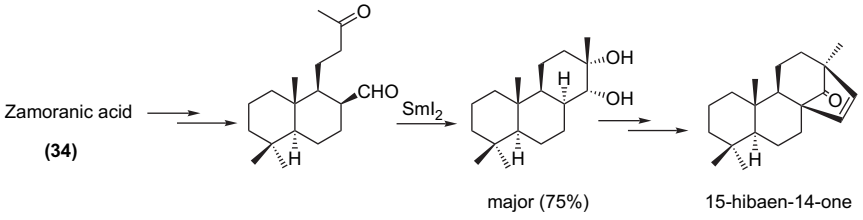
Schwartz and Barden have also prepared a mannitol derivative from 2,3-di-*O*-isopropylidene-D-glyceraldehyde (**37**) using acyclopentadienylzirconium complex (**39**) (Scheme 49). Although the yield was moderate, the selectivity was high (mannitol:iditol=88:12).[138]



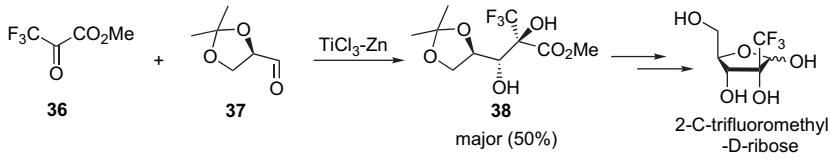
Scheme 45. Synthesis of (+)-4,5-deoxyneodolabelline.



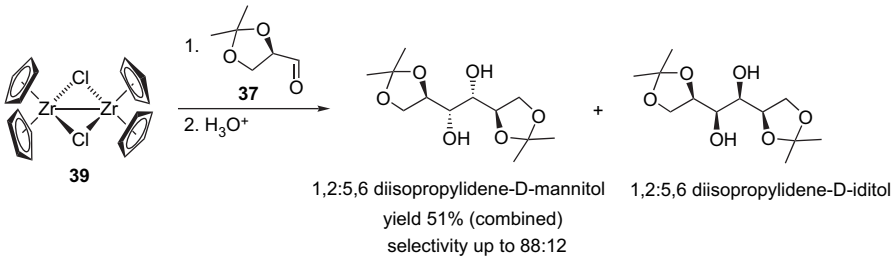
Scheme 46. Synthesis of (+)-totarol.



Scheme 47. Synthesis of 15-hibaen-14-one.



Scheme 48. Synthesis of D-ribose.



Scheme 49. Synthesis of protected sugars.

3.3. Inositols

Polyphosphoinositides play a significant role in the cellular signal transduction system. Among other derivatives, many *myo* and *chiro* inositols have been prepared from cheap chiral sources such as glucose isomers[139] or natural products, e.g., tartaric acid (Table 8).[140] SmI_2 has been used extensively for the intramolecular pinacol coupling, a key step for the preparation of these molecules. In all cases, a very high *syn* selectivity was observed.

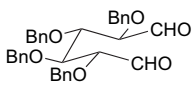
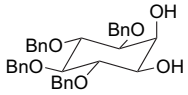
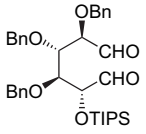
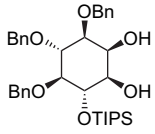
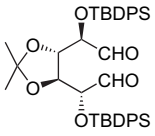
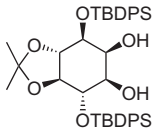
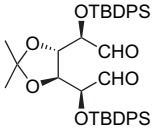
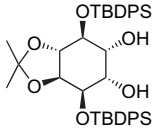
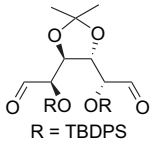
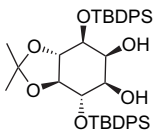
3.4. Taxol

Taxol, isolated from *Taxus brevifolia*, is a clinically very useful anticancer agent. There are many reports with different approaches for the synthesis of this molecule (Fig. 11). In many cases, intramolecular pinacol coupling has been used as the most reliable tool to synthesize this molecule or similar molecular structures (taxanes or taxadienes or hydroxytaxols) with the desired stereochemistry. Nicolaou et al. have used pinacol coupling as a key step to link the A- and C-ring by forming the C_9–C_{10} bond using $TiCl_3$/Zn–Cu with a predominant *syn* stereochemistry (**40**).[141] In a different approach, Swindell and Fan constructed the B-ring (**41**) by forming C_1–C_2 bond through pinacol coupling using $TiCl_4$/Zn, which was found to be more effective than SmI_2 in terms of selectivity.[142] In a few cases, SmI_2 has also proved to be a useful reagent for the construction of the C-ring with *syn* selectivity in a related molecular framework (**42**).[143] The keto-aldehyde coupling proceeded in 43% yield with the formation of the C_3–C_4 bond. Recently, Mukaiyama et al. have even constructed the A-ring of hydroxytaxol (**43**) using a $TiCl_2$/LAH combination with *syn* selectivity (64%).[144] Shirahama et al. constructed a similar molecular framework using SmI_2 to prepare the B-ring.[145] Although the yield was moderate, the selectivity was high.

3.5. Protease inhibitors

C_2-symmetric HIV protease inhibitor **44** was prepared using pinacol coupling as the key step. $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ or $NbCl_3$ proved to be equally effective, favouring a high

Table 8. Synthesis of inositols using pinacol coupling

Starting	Intermediate	Reagent	Product	Yield (%)/selectivity (Ref.)
L-Iditol		SmI_2, ^{t}BuOH–THF, −78 °C		56, *myo*, cis (139a)
D-Xylose		SmI_2, THF, −78 °C		70, *myo*, cis:trans>20:1 (139c)
D-Mannitol		SmI_2, ^{t}BuOH–THF, −50 °C		86, *myo*, cis:trans>92:8 (139b)
D-Sorbitol		SmI_2, ^{t}BuOH–THF, −70 °C		78, *chiro*, cis:trans 94:6 (139d)
2,3-*O*-Iso-propylidene-D-tartarate		SmI_2, ^{t}BuOH–THF, −78 °C		87, *myo*, cis (140)

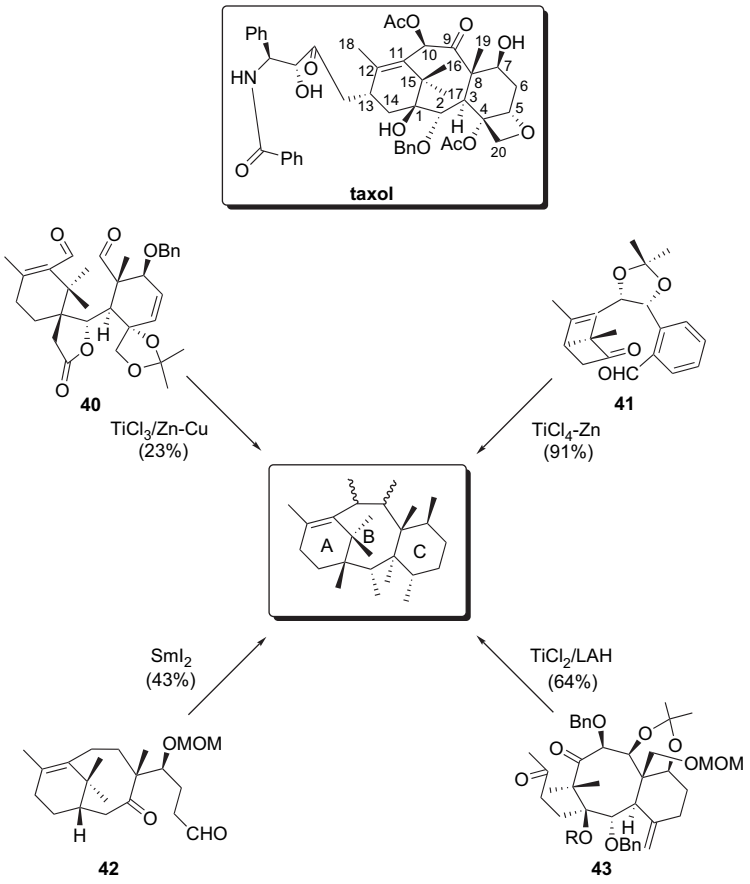
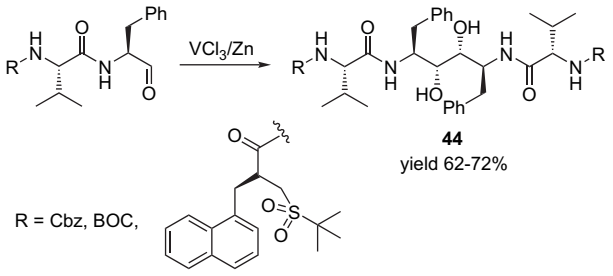


Figure 11. Construction of taxol and related frameworks using pinacol coupling.



Scheme 50. Synthesis of C_2-symmetric HIV protease inhibitors.

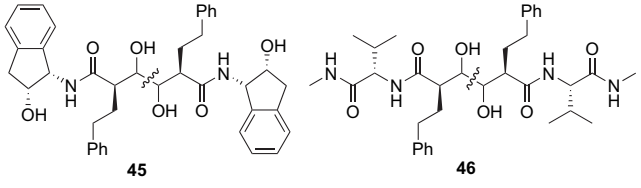


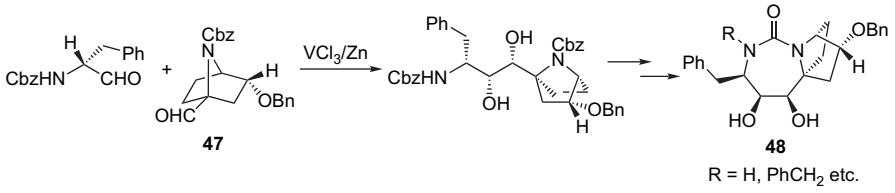
Figure 12. HIV protease inhibitors synthesized using pinacol coupling.

selectivity in the coupled product.[146] The yields were, however, high in the former case and this reagent was applicable, even on a multigram scale (Scheme 50).

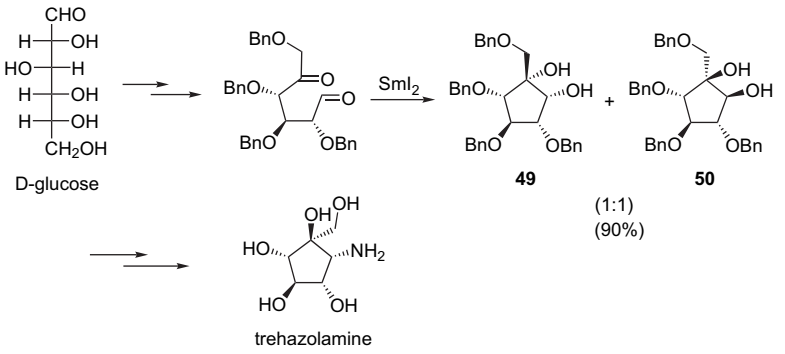
Samuelsson et al. prepared similar C_2-symmetric protease inhibitors (**45** and **46**) using vanadium to induce pinacol coupling as the key step (Fig. 12).[147] The selectivity in this case was not high.

Han et al. prepared a new class of HIV protease inhibitor, a tricyclic urease (**48**), through coupling of D-phenylalaninal and a hindered aldehyde (**47**) using VCl_3/Zn.[148] The selectivity of the cis isomer was found to be 85%. Further transformation of the diol led to the final product (Scheme 51).

Chiara et al. prepared the aglycon of the potent trehalase inhibitor, trehazolamine, from D-glucose using SmI_2-mediated pinacol coupling.[149] Although the relative stereochemistry of the newly generated stereocenters was cis, the two diastereomers (**49** and **50**) were produced in equal amounts



Scheme 51. Synthesis of tricyclic HIV protease inhibitors.



Scheme 52. Synthesis of trehazolamine.

(Scheme 52). They were separated either through crystallization or derivatization.

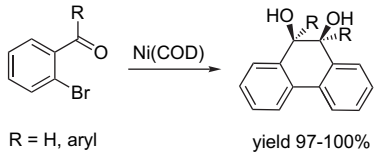
3.6. Antibiotics

Pedersen et al. synthesized the broad-spectrum antibiotics, fortimicins AM and AK, via successive inter- and intramolecular pinacol coupling.[150] Starting from an *N*-protected serine derivative (**51**), the first pinacol coupling using VCl_3/Zn determined the cis stereochemistry of the two hydroxyl groups in an intermolecular path (**52**). In another step, the intramolecular version with the same reagent provided the cyclic unit (**53**) with the desired orientation of the hydroxyl groups (Scheme 53).

3.7. Other compounds

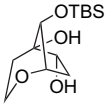
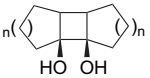
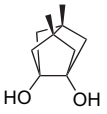
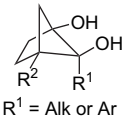
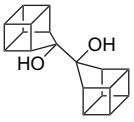
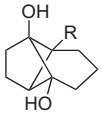
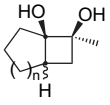
Besides the above complex molecules, pinacol coupling has been widely used for preparing various classes of compounds. Pedersen et al. prepared chiral [*N*-(alkoxycarbonyl)-amino]-1,2-diols[151] and γ-butyrolactones[152] using low-valent vanadium. They showed that hydroxymethylation of an aldehyde can also be effected via this reagent.[153] In all cases, a high yield and selectivity were observed. Banfi et al. prepared lactenediynes in high selectivity using low-valent vanadium.[154] 2-Bromobenzaldehyde was transformed into pinacols in one pot using an Ni(0)-mediated cascade reaction.[155] The pinacol coupling proceeded in excellent yield, resulting in only the cis isomer (Scheme 54).

Low-valent titanium has been used to prepare macrocyclic stilbenediol derivatives from bis-carbaldehydes.[156] High yields were realized, albeit with moderate selectivity. A variety of other molecular frameworks have been synthesized via the pinacol coupling reaction (Table 9).



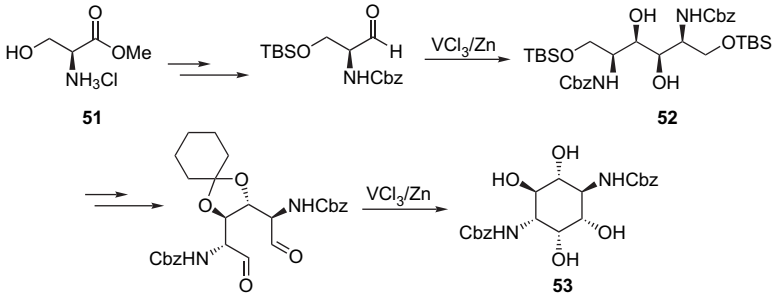
Scheme 54. Nickel-mediated cascade coupling.

Table 9. Miscellaneous frameworks prepared using pinacol coupling

Molecule	Reagent	Ref.	Molecule	Reagent	Ref.
	$TiCl_3$/Zn–Cu	157	 n = 1~4	SmI_2	159
	SmI_2	159	 R^1 = Alk or Ar R^2 = H	SmI_2	160
	$TiCl_4$/Zn	158	 R = H, Me	SmI_2	160
 R^1 = R^2 = Alk or Ar	SmI_2	159	 n = 1 - 3	SmI_2	159

4. Concluding remarks

It is evident from the above account that pinacol coupling, one of the earliest known carbon–carbon bond-forming



Scheme 53. Synthesis of fortimicins AM and AK.

reactions, has evolved as a versatile tool in synthetic organic chemistry. The initial bottleneck for the reaction was to obtain a preparatively useful yield. This was followed by efforts to improve the diastereoselectivity and more recently, the enantioselectivity. In these pursuits, a large number of metals from the periodic table have been examined. The reaction has now been frequently used during the synthesis of a variety of natural/unnatural products. The most recent success in this area has been the establishment of enantioselective protocols. Almost all kinds of aldehydes can now be coupled with high diastereoselectivity and enantioselectivity. The challenge, however, remains for the stereoselective coupling of ketones and imines. Equally interesting and useful will be the heterocoupling of carbonyl compounds and imines. This daunting task will require a deeper insight into the reaction mechanisms and fine tuning of metal complexes. The age-old reaction thus remains a fertile ground for exciting research in the future.

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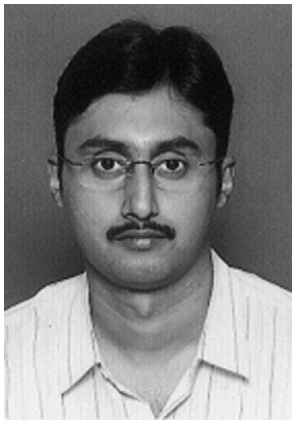
Biographical sketch



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