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Modern applications of low-valent early transition metals in synthesis and catalysis

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Abstract

Low-valent early transition metals are often intrinsically highly reactive as a result of their strong propensity toward oxidation to more stable high-valent states. Harnessing these highly reducing complexes for productive reactivity is potentially powerful for C-C bond construction, organic reductions, small-molecule activation and many other reactions that offer orthogonal chemoselectivity and/or regioselectivity patterns to processes promoted by late transition metals. Recent years have seen many exciting new applications of low-valent metals through building new catalytic and/or multicomponent reaction manifolds out of classical reactivity patterns. In this Review, we survey new methods that employ early transition metals and invoke low-valent precursors or intermediates in order to identify common themes and strategies in synthesis and catalysis.

Early transition metals are excellent candidates for the design and implementation of new catalytic reactions: they are earth abundant, often highly reactive and frequently exhibit different structures and orthogonal reactivity compared with late transition metals[1,2]. However, owing to their electropositive, oxophilic[3] nature, the organometallic chemistry of early transition metals has historically been dominated by complexes in high-valent states (FIG. 1). By contrast, there are considerably fewer examples of the application of low-valent early transition metals: such complexes are often highly reducing and require strong stabilizing ligands, such as strong π-acceptors or bulky cyclopentadienyls.

Nonetheless, there is great interest in harnessing the highly reactive nature of low-valent early transition metals for practical synthesis and catalysis. There are myriad elegant examples of stoichiometric N_2 activation[4–17], reductive coupling[18–22] and radical reactions[23–25] mediated by low-valent early transition metals. The majority of this reactivity is dependent on the fact that highly reduced early metals can activate otherwise unreactive

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molecules, wherein metal oxidation and the formation of strong metal-ligand bonds provide a large thermodynamic driving force.

Although many seminal contributions to the field were carried out decades ago, there has been a renaissance in the field over the past 15 years enabled by new ligand designs, reagents and approaches. Early transition metals are well positioned to have considerable impact in a wide array of fields, from small-molecule activation and energy storage to photoredox catalysis and other new organic methods. This Review covers new applications of low-valent early transition metals[26] (classified here as groups 3, 4 and 5, excluding V because it does not predominantly exist in its highest oxidation state) in synthesis and catalysis. In particular, this Review highlights how the unique properties of low-valent metals can access new mechanisms and enable challenging chemical transformations inaccessible by their late transition metal counterparts.

Generation of low-valent complexes

The most common routes for generating low-valent early transition metal complexes involve the reduction of metal halides with strong alkali metals[27–32]; reduction with other (often weaker) reducing metals, such as Mg (REFS[33,34]), Mn (REF.[35]), Al (REFS[36,37]) or Zn (REF.[38]) (providing more functional group tolerance); or p-H abstraction[39–43] from a metal alkyl (Fig. 2a). Many of these reductions can be performed in situ to directly generate reactive low-valent intermediates or in the presence of π-accepting ligands to generate isolable or transiently stable ‘masked’ species that can liberate a reactive low-valent metal fragment upon loss of the re-accepting ligand. For example, the Negishi reagent, $Cp_2Zr(\eta^2$-butene) (**1**), is synthesized by the treatment of Cp_2ZrCl_2 with ^{n}BuLi or ^{n}BuMgBr, wherein the $Cp_2Zr^{n}Bu_2$ intermediate undergoes β-H abstraction to liberate one equivalent of butane along with the product[44–46]. $Cp_2Ti(TMS_2C_2)$ (**2**) (TMS_2C_2 = bistrimethylsilylacetylene) and related Ti and Zr analogues can be synthesized by reduction of the corresponding high-valent chlorides with Mg in the presence of the π-accepting alkyne TMS_2C_2 (REF[47]), while substituted hafnocene analogues have been synthesized using Li as a reductant[48,49].

Stable low-valent coordination complexes of the early transition metals that lack strongly stabilizing ligands are uncommon. However, examples continue to emerge that challenge the limits of stability (FIG. 2b). For example, a suite of divalent group 3 amides has recently been reported[50–53], including the first crystallographically characterized Sc^{11} compound[52], extending the chemistry of low-valent Sc and Y beyond metallocene derivatives[54,55]. The Sc^{II} amide complex **3** exhibits remarkably different reactivity from other reduced group 3 and lanthanide complexes, for the first time revealing end-on, reversible binding of N_2 to form the bridged bimetallic **4** (REF[53]). Bulky aromatic heterocycles derived from phosphaalkynes, which are much poorer donors than Cp-based ligands, can also stabilize Sc^{II} complexes[56]. An improved synthesis and full electronic characterization of py_4TiCl_2 (**5**)[57], a rare example of a Ti^{II} coordination complex, have recently been reported, building upon earlier studies by several groups[58,59]. The chemistry of low-valent early transition metal isocyanide[60–62] and arene complexes[63,64] has also continued to expand, including the recent synthesis of the formally Ta^0 complex **6** (REF[60]).

The high reactivity of strong alkali metal reductants places an inherent restriction on the solvent and reagent compatibility of reactions that employ them as reductants. Considerable progress has been made in designing new reactions and reductants that overcome this challenge. One creative workaround that was recently introduced is to reduce compounds by passing them through columns of KC_8, limiting (or at least fine tuning) the contact time of the reagent and solvent with the strong reductant[65]. Another strategy is to use inner-sphere reductants that are less prone to over-reduction. In this context, Tsurugi and Mashima have promoted the use of organosilicon reductants, such as 3,6-bis(trimethylsilyl)-1,4-cyclohexadiene[66–68] (**7**) and 1,4-bis(trimethylsilyl)-1,4-dihydropyrazine[69–71] derivatives (for example, **8**), to reduce group 4 and group 5 metal halides (Fig. 2c) for homogeneous catalytic applications. In the case of **8**, the steric bulk of the tetramethylpyrazine by-product prevents its coordination to the reduced metal catalyst, which is critical for productive chemistry. These organosilicon reductants derive their reduction potential (ranging from +0.83 V to −0.40 V versus Cp_2Fe) from the aromatization of the 1,4-diene core. These reductants have been used by the broader community for wide-ranging applications, from the in situ reduction of Ti precursors in chemical vapour deposition[72] to the in situ generation of Ti^{III} for reductive umpolung reactions[73]. Similarly, commercially available tris(trimethylsilyl)silane has been used to generate Nb^{III} cyclotrimerization catalysts in situ[74]. A major advantage of these silicon-based reductants is that the by-products are simple to remove: Me_3SiCl is less likely than alkali metal halides to coordinate to electrophilic metals, and the aromatic by-products can be removed in vacuo. Metal salt by-products are often difficult and/or tedious to remove and may interfere with productive chemistry of the reduced complex; thus, these procedures offer an important advancement for applications of reduced early metal chemistry.

Alternative reduction methods of early transition metals include single-electron transfers from weak reductants such as citrate[75] or benzylamine[76]. Hydrogenolysis of metal alkyls has also been used to synthesize low-valent Nb (REF[77]) and Zr (REF[78]) arene complexes. Redox non-innocent ligands can also engender redox reactivity with early transition metals without formally changing the metal oxidation state[67,68,79–82].

Reductive coupling reactions

Reductive coupling of unsaturated organics by d^2 early transition metals has been exploited for a vast array of synthetically useful C-C bond forming reactions. Typically, these reactions involve activation of an alkene or an alkyne to form either a metallacyclopropane or metallacyclopropene, respectively. These species can be considered as 1,2-dianion equivalents and can be intercepted sequentially by two different electrophiles. Often, the resulting metallacycles can be further functionalized, forming the basis for a diverse set of coupling reactions, such as the Negishi[21,22,45], Fagan-Nugent[19,83–85], Kulinkovich[43,86–88], Pauson-Khand[89–94] and several other stoichiometric coupling reactions of alkynes, alkenes, alkyl halides and carbonyl compounds[18,20]. Although most d^2 early metals exhibit this type of reactivity, low-valent Ti and Zr complexes — in particular, Cp_2M^n (M = Ti, Zr) and (O’’Pr)$_2$T^{II} fragments — have seen the most development in this field, and as such the use of such reagents in the total synthesis of natural products has flourished[23,95–97].

Ti(O^{i}Pr)$_4$/RM-mediated reductive coupling reactions.

The discovery of the main group metal alkyl reduction of early metals[45] inspired many reductive coupling reactions using titanium. In 1989, Kulinkovich reported the Ti(O’Pr)$_4$-catalysed cyclopropanation of esters with Grignard reagents to form cyclopropanols[86] (FIG. 3a). Shortly after, the Kulinkovich reaction was translated to amides (de Meijere modification), which results in the formation of cyclopropylamines by a similar mechanism[98]. Since these initial reports, several improvements have been made to this chemistry. Intermolecular alkene couplings can be achieved by using cyclohexyl or cyclopentylmagnesium chloride to activate Ti(O^{i}Pr)$_4$, as the resulting Ti-cyclopentene (or cyclohexene) adduct **9** can be displaced by monosubstituted or tethered alkenes to make a new alkene adduct **10** (REFS[99], [100]) (FIG. 3a, bottom). This discovery has helped dramatically expand the scope of Kulinkovich reactions, as alkene starting materials are more widely available than Grignard reagents. The Kulinkovich cyclopropanation has an intrinsic diastereoselectivity for the cis-1,2-dialkylated cyclopropanol when using Grignard reagents larger than ethyl, and the use of chiral TADDOL (a,a,a’,a’-tetraaryl-2,2-disubstituted-1,3-dioxolane-4,5-dimethanol) ligands has allowed for good enantioselectivity[88,101,102]. This diastereoselectivity can be reversed when cyclopropanating homoallylic alcohols as a result of coordinating directing group effects[99] or remote stereocentre influences[103].

A recent modification of the Kulinkovich-de Meijere reaction allows for the synthesis of carbocyclic amino ketones mediated by Ti(O^{i}Pr)$_4$/RMgBr (REF[104]) (FIG. 3b, top). By using allyl-substituted lactams such as **11**, the cyclopropanation step of the de Meijere mechanism can be arrested, as the bridgehead nitrogen atom of the alkene-inserted intermediate **12** cannot π-bond with the neighbouring carbon (Bredt’s rule)[105]. This ultimately leads to cyclic aminoketone **13** upon protic workup. Increasing the ring size of the lactam relieves ring strain in the intermediate **12**; thus, larger ring systems are no longer affected by Bredt’s rule and typical de Meijere cyclopropylamine generation proceeds. Similarly, interrupted Kulinkovich-de Meijere reactions yield hydroxyl-substituted lactams (**16**) with homoallylic imide (**14**) substrates[106–108], which do not undergo cyclopropanation owing to resonance stabilization of the metallacyclic intermediate **15** (FIG. 3b, bottom).

Micalizio has shown that regioselectivity and stereoselectivity in the reductive coupling of various unsaturated compounds can be induced through the use of alkoxide directing groups (FIG. 3c) — a strategy similar to that employed by Sharpless for asymmetric alkene epoxidation[109]. This is an advancement from the limited selectivity obtained through Fagan-Nugent chemistry: substrate-directed metallacycle-mediated cross-couplings, although requiring prefunctionalization with potentially undesirable functional groups, allow for the regiospecific assembly of target molecules. By contrast, undirected cross-couplings of the same type typically give statistical mixtures in unbiased systems[110,111].

Regioselective and stereoselective coupling of alkenes with imines is possible when using Ti(O^{i}Pr)$_4$/^{n}BuLi as opposed to Ti(O^{i}Pr)$_4$/RMgBr (REFS[112,113]). Using BuLi as the metal alkyl reductant rather than a Grignard reagent grants dramatically enhanced stability to the titanacyclopropane intermediate as a result of the interaction of LIO^{i}Pr with the metal centre, forming a tentative ‘ate’ complex[113]. Homoallylic alcohols cross-couple with aromatic imines to give 1,5-aminoalcohols using $Ti(O^iPr)_4$/RMgBr (REF[109]), but the employment of $Ti(O^iPr)_4/^n$ BuLi allows for both aromatic and aliphatic imines to be used successfully in the reaction[114]. Imines (**17**) couple with allylic alcohols (**18**) to form stereodefined homoallylic amines (**19**)[115] (FIG. 3c, top). Alkene stereoselectivity is achieved in these reactions through coordination of the deprotonated alcohol to the preformed Ti-imine complex, which undergoes syn-carbometallation (**20**) and syn-elimination through boat-like transition states (**21** and **22**) (FIG. 3c, top right). Primary homoallylic amines are accessible through similar coupling reactions with aldehydes in the presence of LiHMDS (lithium hexamethyldisilazide), which forms the TMS-imine complex in situ. These primary homoallylic amines have been applied as starting materials for the synthesis of complex bicycles[116] and pyridines[117].

Substrate-directed selective alkene-alkyne-alkyne formal [2+2+2] reactions are also possible. For example, alkoxide-directed annulations can give hydroindane derivatives (**26** and **27**) and angularly substituted decalins[118–122] (FIG. 3c, bottom). The reactions proceed through alkoxide-directed insertion of an alkyne into the titanacyclopropene **23** to make the bicyclic metallacyclopentadiene **24**. The chemoselectivity of this insertion is driven by the electronic bias of the a-$SiMe_3$ group: the Ti-C(TMS) bond is more difficult to insert into than the Ti-C(Ph) bond of **23**. Next, [4+2] cycloaddition of the pendent alkene forms a bridged bicyclic metallacyclopentene **25**, which can undergo allylic isomerization and be quenched through protonation with allylic transposition (**26**) or oxidation (**27**). The choice of alcohol for the quench affects the selectivity for either cis-hydroindanes or trans-hydroindanes, although the origin of this effect remains unclear[119].

Other early-transition-metal-mediated reductive coupling reactions.

Metallacycle **28**, formed by reducing Cp^*TiCl_3 ($Cp^* = C_5Me_5^-$) in the presence of dimethylbutadiene, can react with two equivalents of isocyanide to give an asymmetric metal-bound bis(imine) **29** (REF[123]) (FIG. 4a). Furthermore, upon heating **29** at 55°C in pyridine, cyclopentenimine **30** is extruded, and Cp*TiCl(py) (N′Bu) is formed. The result is a unique formal [4+1] coupling reaction alongside cleavage of an isocyanide triple bond, such that the C atom is inserted into both C-H bonds at the 2 position to give an exo-methylene. By contrast, the reaction with the hafnium analogue of **28** results in **31**, which was initially misidentified as a cyclic amidine complex[124] but instead is the result of imine C-C coupling from the Hf analogue of **29**. The Cp^*_2Zr analogue can selectively insert one equivalent of isocyanide (or CO) into the metal-butadiene bond, allowing for sequential reactions to be carried out[125].

$Cp^R_2M(TMS_2C_2)$ (M = Ti, Zr; R = H, alkyl) can act as a masked source of $Cp^R_2M^{II}$, easily liberating TMS_2C_2 upon treatment with a variety of reagents[47]. Recently, Rosenthal has discovered that $Cp^*_2{}^{II}$ fragments can couple nitriles to form metalla-2,5-diazacyclopentadienes, which can undergo further reaction and exchange one nitrile partner for another unsaturated substrate (for example, a different nitrile, CO_2 or H_2)[126–128]. Nitrile-nitrile couplings are quite uncommon, although they have been observed with Ti^{III} complexes much earlier[129]. Taking advantage of this reaction manifold, Tilley has recently used $Cp_2Ti(TMS_2C_2)$ for the coupling of tethered dinitriles, such as **32**, to diazametallacyclopentadienes, such as **33** (REF[100]). Once coupled, **33** can be reacted further with electron-deficient alkynes, H_3O+ or ECl_2 (E = SO, POPh, S, Se, Te) to generate pyrazines (**34**), diones (**35**) or diazoles (**36**) (FIG. 4b). Although this work focused primarily on installing these moieties in polycyclic aromatic hydrocarbons, [2+2+2] pyrazine synthesis at an early transition metal had not been previously observed, providing new insight on routes to incorporate nitriles more effectively into reductive coupling reactions mediated by early transition metals. In a similar vein, stoichiometric $Cp_2Zr(TMS_2C_2)$ has been used as a general platform for C-C coupling and can be used to couple tethered diynes to make polycyclic aromatic hydrocarbons[130–133]. Cp_2M^{II} fragments can also be used to construct metallacyclocumulenes and other highly strained metallacycles[47,49,134–142]. Here, the steric bulk of the Cp* ligands imbue stability, which enables easy isolation of the metal complexes that feature exotic bonding motifs. Structural characterization of the products of reductive metallacyclization of 1,3-butadiynes reveals that the rich chemistry is strongly dependent on the terminal diyne substituents. Similarly, Beckhaus has coupled unsaturated organics with group 4 metal pentafulvene complexes[143–148], presenting an interesting approach to the synthesis of exotic appended Cp-type ligands. Likewise, fulvenes can be homocoupled to give ansa-metallocene complexes from group 4 metal chlorides and ^{n}BuLi (REFS[149,150]).

There are fewer examples of group 5 metals facilitating reductive coupling reactions. Alkyne-stabilized masked Ta^{III} hydrides can stoichiometrically insert isonitriles and alkynes into the Ta-H bond, followed by C-C reductive coupling of the bound alkyne to give butadienyl and azadiene fragments[151]. Dimethyltantalum corrole complexes can react with CO to give coupled diacetyl complexes[152]. This process is presumed to occur via insertion of two CO molecules into the two Ta-Me bonds, followed by reductive elimination of the two acyl ligands to give diacetyl, which then binds to the resulting low-valent tantalum as the ene-diolate form to formally oxidize Ta^{III} to Ta^{V}.

Catalytic alkyne cyclotrimerization is also common with low-valent group 4–5 transition metals[34,110,153]. There are two limiting mechanisms for cyclotrimerization: triple insertion followed by reductive elimination through a metallacycloheptatriene (**37**) or [4+2] cycloaddition of the 3rd unsaturated partner to make a metallanorbornadiene (**38**) (FIG. 4c, left). Recent mechanistic work on a ditantalum system indicates that the [4+2] pathway is more likely[154]. Remarkably, alkyne cyclotrimerization reactions can be intercepted with other unsaturated substrates; for example, Obora has shown that thermally stable low-valent Nb catalysts can chemoselectively insert alkenes[155–157] and nitriles[158] to give cross-coupled products[159] (FIG. 4c, right).

Functionalization and defunctionalization

Hydrogenation.

Catalytic hydrogenation of unsaturated substrates is challenging with d^2 early transition metals because of their propensity to promote reductive coupling. Additionally, there are very few examples of direct H_2 activation by d^2 group 5 metals[160–166]. Nonetheless, there are several elegant examples of arene and alkene hydrogenation and alkyne semi-hydrogenation catalysed by d^2 group 5 metals[162,167178].

β-Diketiminate Nb^{III} imido complexes promote remarkably selective semi-hydrogenation of alkynes[176] (FIG. 5a, top). Treatment of $(BDI)Nb(N'Bu)(CO)_2$ (**39**) (BDI = 2,6-diisopropylbenzene-p-diketiminate) with 1-phenyl-1-propyne yields the metallacyclopropene complex **33**, which does not undergo reductive coupling owing to steric encumbrance around the metal centre[179]. Consequently, it was found that **40** can catalyse the semi-hydrogenation of phenylpropyne to Z-p-methylstyrene under H_2/CO. Two mechanistic proposals were made (FIG. 5a, right): through alkyne-CO ligand exchange, followed by σ-bond metathesis of the metallacyclopropene of **40** with H_2 to yield a Nb^V vinyl hydride (**41**), from which C-H reductive elimination then liberates Z-β-methylstyrene and regenerates an arene-bound Nb^{111} (**42**) (path A), or through 1,2-H_2 addition across the imido of **40** to make a Nb amido hydride (**43**), which can then undergo reductive H migration to vinyl amide **44** followed by a-elimination to **42** (path B). The rate and selectivity for semi-hydrogenation are highly CO-dependent, which may provide a tuneable handle in future systems. Higher CO concentration maintained selectivity but slowed the reaction, indicating that CO-alkyne exchange is kinetically relevant. However, lower loadings led to the formation of more fully hydrogenated propylbenzene, indicating that CO also plays a role in efficient product displacement.

Fortier recently described the synthesis of a new masked Ti^{II} synthon, **45** (FIG. 5a, bottom). This complex undergoes a relatively rare example of early transition metal d^2 C-H oxidative addition[160,180194] followed by β-H abstraction to extrude H_2 and make a new cyclometallated complex **46** (REF[195]). Remarkably, this reaction is reversible, opening up the possibility that these complexes might be useful as hydrogenation catalysts. In fact, **45** also performs a unique example of early-transition-metal-promoted transfer hydrogenation[196] (FIG. 5a, bottom left), hydrogenating cyclohexene with concomitant production of **46**, with the ligand serving as the terminal hydrogen donor. This interesting system can also catalytically hydrogenate cyclic alkenes and cyclic dienes, although the mechanism by which this occurs — transfer hydrogenation or a more classical dihydride mechanism — remains unknown.

Dehydrogenation.

There are several examples of C-H oxidative addition to low-valent early transition metals[160,180–194,197,198], including several that lead to stoichiometric dehydrogenation[188–190]. The majority of dehydrogenation reactions promoted by early transition metals are, however, predicated on high-valent, electrophilic metal reactivity, such as 1,2-C-H addition across metal-ligand multiple bonds[199–201]. The first catalytic, selective dehydrogenation of alkanes was recently demonstrated with Ti catalyst **47** [REF.[202]] [FIG. 5b]. This system takes advantage of 1,2-C-H addition of the alkane C-H bond to a Ti alkylidiyne **50**, followed by β-H abstraction of the resultant Ti-alkyl-alkylidene (**51**) to formally reduce Ti, making a new Ti^{11} alkyl-alkene adduct **52** (REFS[40–41–203–204]). Remarkably, this system is rendered catalytic by addition of a methylene transfer agent, phenyldibenzophosphole methylene ylide, $H_2CP(C_{12}H_8)Ph$ (**48**), which serves as an oxidant to reoxidize the Ti^{II} fragment (**53**) back to a Ti^{IV} alkylidene (**54**)[202]. The structure of this reagent is critical, as deleterious phenyl migration from a Ti^{II}-ylide adduct will occur with other simple arylphosphorus ylides[204]. Although turnover numbers in this system are poor and phosphorus ylides are impractical terminal oxidants, this system is remarkable in its selectivity, yielding only terminal alkene products. This selectivity results from the unique mechanism, which — unlike late transition metal alkane dehydrogenation catalysts — does not involve metal hydride species, which could isomerize the alkene.

There are many low-valent Ti and Zr complexes capable of the catalytic dehydrogenation of amine boranes, particularly using metallocene derivatives[205–210]. In a recent elegant application, a $Cp^*_2TiCl_2/{}^nBuLi$ catalytic system has been shown to promote an unusual step-growth dehydropolymerization of $MeNH_2(BH_3)$, enabling the first synthesis of high-molar-mass poly(N-methylaminoborane) by an early transition metal[211]. This system was also successful in the catalytic dehydropolymerization of several other primary amine borane derivatives. Despite computational evidence for a M^{II}/M^{IV} redox mechanism for amine borane dehydrogenation[212], there is conflicting experimental evidence that indicates alternate mechanisms may also be involved. For example, several M^{IV} precatalysts such as $M(NMe_2)_4$ (M = Ti, Zr)[208], $[{}^{i}Pr_2Si(NDIPP)_2]\ Zr(NMe_2)_2\text{-}LiCl(THF)_3$ (DIPP = 2,6-diisopropylphenyl)[213] and $K^5\text{-}(Me_3SiNCH_2CH_2)_2N(CH_2CH_2SiMe_2CH_2)\ Zr$ (REF[196]) may promote dehydrogenation via c-bond metathesis routes, while in other cases, M^{III} metallocene species have been observed in situ[214].

Hydrodefluorination.

C-F bond dissociation energies (BDEs) range from 110 to 130 kcal mol^{-1} fluoro-organics are not easily biodegraded but instead are often incinerated[217],[218]. Thus, there is considerable impetus to design catalytic methods for C-F bond degradation[219],[220]. Although C-F bond activation has been observed across the transition metal series[221–229], early transition metals are exceptionally fluorophilic, making them excellent candidates for hydrodefluorination reactions. There are numerous examples in which low-valent early transition metals can mediate C-F bond activation to generate M-F species, including examples with Ti (REFS[230–233]), Zr (REFS[233–239]), Hf (REF[240]), Nb (REFS[241–243]) and Sc (REF[244]). The challenge in these systems is rendering them catalytic, as the resultant M-F species is often a considerable thermodynamic sink[245].

In the first demonstration of catalytic C-F bond activation by an early metal, Cp_2TiF_2 was shown to defluorinate perfluorinated cycloalkanes to produce perfluorinated arenes in the presence of excess Al^0 with HgCl2 (REF[246]) (FIG. 5c, top). In the same study, it was found that Cp_2ZrF_2 similarly catalyses this reaction in the presence of Mg^0 and $HgCl_2$, although in a rather exothermic fashion. This result was followed by mechanistic work using $Cp^*_2ZrH_2$. Under an atmosphere of H_2, it was found that $Cp^*_2ZrH_2$ reacted with primary, secondary and tertiary C-F bonds to yield the corresponding alkanes and Cp^*_2ZrHF (REF[247]). Intriguingly, mechanistic evidence supported a radical mechanism in which in situ generated Cp^*_2ZrH abstracted F% despite the fact that the relative rate of C-F reactivity was 1° > 2° > 3° — the reverse of the pattern seen in typical radical reactions. In support of the radical mechanism, added reductant increased the rate of 1-fluorohexene hydrodefluorination threefold, while radical inhibitors such as 9,10-dihydroanthracene inhibit the rate of defluorination. Radical clock experiments of $Cp^*_2ZrH_2$ with cyclopropylcarbinyl fluoride provided Cp^*_2ZrHF and ring-opened $Cp^*_2Zr(\text{“Bu})H$ as opposed to methylcyclopropane. It was suggested that the steric bulk of $Cp*_2ZrH_2$ may be the origin of the observed rate trends[237–247–248].

There are also several notable examples of Nb-catalysedhydrodefluorination. Mixtures of $NbCl_5$ and $LiAlH_4$ catalyse the hydrodefluorination of aryl fluorides and benzylic fluorides[249–250] (FIG. 5c, middle). In these reactions, trifluoromethyl groups were reduced fully to methyl groups under mild conditions. In the case of aryl fluoride reductions, it was proposed that the reaction proceeds through a (DME)$NbCl_3$(arene) (DME = 1,2-dimethoxyethane) intermediate that undergoes nucleophilic substitution by hydride, but the mechanism of these reductions has not been fully established. Arnold and Bergman recently examined a more well-defined system for aryl fluoride hydrodefluorination using a d^2 (BDI)Nb^{III}(N′Bu) fragment[251] (FIG. 5c, bottom). Mechanistic studies in this system indicate that (BDI)Nb^{m}(N′Bu)(arene) (**57**) can oxidatively add Ar-F to generate (BDI)Nb^{V}(N′Bu)F(Ar) (**55**), which can be transmetallated with silanes, making a strong Si-F bond and a (BDI)Nb^{V}(N^{f}Bu)H(Ar) species capable of C-H reductive elimination. In both the $NbCl_5$ and (BDI)Nb systems, catalytic turnover is achieved by using a terminal reductant (Si, Al) that is more fluorophilic than Nb.

Catalytic single-electron transfer

Single-electron transfers employing low-valent early transition metal reductants are frequently used in organic synthesis. The Nugent-RajanBabu reagent[24–25], Cp_2TiCl, is used in radical ring-opening-cyclization cascades and is the most common early transition metal reagent for single-electron transfer[252]. These types of cyclization cascades have been used in numerous total syntheses of natural products[23–253–254]. Cp_2TiCl is easily generated via in situ reduction of commercially available Cp_2TiCl_2 by Zn or Mn dust and has recently been touted as a ‘greeN′ reagent for chemical synthesis[255–257]. This reagent typically exists as the chloride-bridged dimer, $[Cp_2TiCl]_2$, and forms the active monomeric species through a solvent-assisted equilibrium[258].

Gansäuer expanded the use ofthe Nugent-RajanBabu reagent in the context of radical ring opening of epoxides by developing a catalytic procedure that uses a weak acid (2,4,6-collidine hydrochloride) to protonate the generated titanium alkoxide (**59**) and a reductant (Zn or Mn) to regenerate Cp_2TiCl (REF[35]) (FIG. 6a, left). 2,4,6-Collidine hydrochloride is an ideal acid for epoxide reactions; it is strong enough to protonate the Ti-alkoxide bonds but weak enough to not open the epoxide ring independently. Furthermore, the liberated 2,4,6-collidene conjugate base is sterically congested, disfavouring association with titanium that would hinder catalysis. In their initial report, Mn was the preferred reductant in this reaction, as the $MnCl_2$ by-product is insufficiently Lewis acidic to promote epoxide ring opening, although later catalytic applications have successfully used Zn. With appropriate solvent and counteranion choice, cationic $[Cp_2Ti]$ fragments can also be used as catalysts[259]. This catalytic single-electron reduction of epoxides has been used to functionalize arenes, alkenes and alkynes[259–263] (FIG. 6a, right). Remarkably, these radical reactions are able to proceed enantioselectively when using large, terpene-derived cyclopentadienyl ligands (**60**) on titanium[263].

Cp_2TiCl can also be used to catalyse redox umpolung reactions for the coupling of nitriles or activated alkenes with carbonyls or imines[73,264–274] (FIG. 6b). These reactions share similar mechanistic features to classical epoxide and azirine ring-opening reactions; owing to the oxophilicity of Ti, treatment of many types of carbonyl derivatives with Ti^{III} species results in the formation of Ti^{IV} carbonyl radicals. These Ti carbonyl radicals can further react with myriad electrophiles[273,275]. In a detailed mechanistic study of a Ti^{III}-catalysed acyloin-type cross-coupling of ketones and nitriles, it was found that a bimolecular and bimetallic radical recombination mechanism that circumvented free radical intermediates was operational[274] (FIG. 6b, bottom). Umpolung-like conjugate additions have also been achieved with hemiaminals, yielding quaternary carbons-a to amines, and coupling or reduction of α,β-unsaturated carbonyls is also possible[276–278].

Combining the above approaches, both Gansauer and Lin have each demonstrated that three-membered ring rupture can also be promoted by a-carbonyl reduction in N-acyl aziridines[279,280] and cyclopropylketones[281] (FIG. 6c). In the case of N-acyl aziridines (**61**), treatment with Ti^{III} sources results in ring opening that, in contrast to typical aziridine ring openings, produces the more substituted carbon radical **62**. These reactions take advantage of the biradical character[282–288] of the resulting Ti^{IV} azaenolate or enolate **62**; radical reductive couplings of the ring-opened azaenolate or enolate with alkene electrophiles can be performed catalytically in the presence of reductant (Mn^0 or Zn^0) and weak organic acid (collidine HBr or NEt_3HCl) to form amines (path A), while redox-neutral [3+2] cycloadditions with electrophilic alkenes can also be achieved in a catalytic fashion (path B).

Cp_2Ti^{III} pinacolates, generated through Cp_2TiClpromoted pinacol coupling of benzaldehyde followed by further reduction, undergo facile deoxygenation to form alkenes. This reaction challenges the classical McMurry coupling mechanism, in which Ti^{II} or Ti^0 complexes were thought to promote carbonyl coupling and/or olefination[289].

Single-electron strategies in small-molecule activation and photoredox catalysis.

Reduced early transition metal complexes have historically been excellent platforms for small-molecule activation because of their strong reduction potentials and propensity to form thermodynamically stable metal-ligand multiple bonds. However, these same features become a challenge when attempting to render these reactions catalytic. There are myriad examples of stoichiometric N_2 activation with low-valent early transition metals. Given that this field has been thoroughly reviewed[4–17], here, we focus on only several examples that highlight emerging new strategies toward catalytic applications of small-molecule activation — in particular, proton-coupled electron transfers (PCETs) in early transition metals and their applications toward N_2 reduction and water oxidation.

Recent work using group 4 metallocene amide derivatives has found PCET to be a promising route to ammonia formation via M-N hydrogenolysis[290,291] (FIG. 7a). This route has the potential to overcome the incredible free energy inefficiency of nitrogen reduction involving separated sources of protons and electrons (for example, $[HOEt_2] + [BArF_{24}] + KC_8$). Experimental and computational studies have demonstrated that coordination of NH_3 to $(\eta^5\text{-}C_5Me_4SiMe_3)_2M$ (M = Ti, Zr) fragments decreases the N-H bond dissociation free energy (BDFE) by >40 kcal mol^{-1} compared with free NH_3. In general, the degree of N-H

BDFE lowering is a function of the early transition metal redox couple, in which higher energy redox couples (for example, Zr^{IV}/Zr^{III} in **64** or Ti^{III}/Ti^{II} in **65**) lead to greater activation than lower energy couples (for example, Ti^{IV}/Ti^{III} in **63**). This allows for thermodynamically favourable PCET to occur from (η^5-C_5Me_5)(py-Ph)RhH (**68**) — which has a weak Rh-H bond (52.3 kcal mol^{-1}) but is nonetheless able to split molecular H_2 — to ($\eta^5Me_4SiMe_3)_2TiCl(NR_2)$ derivatives (R = H, Me, NH_2, NMe_2) (BDFEs ^ 60 kcal mol^{-1}). Using this strategy, the catalytic hydrogenolysis of Ti^{IV} amide complex **66** to the Ti^{III} chloride complex **67** has been realized, opening the possibility of incorporating PCET into a catalytic N_2 reduction cycle with H_2 as the terminal reductant.

Similar to the effects seen with NH_3, coordination of H_2O to $Cp_2Ti^{III}X$ results in dramatically reduced H-OH BDEs ($A_{bde} \approx 50$ kcal mol^{-1}), enabling water to serve as a H-atom donor[292–294]. This important effect can be used in the photochemical splitting of water. For example, ansa-titanocene dihydroxido complexes undergo Ti-O bond homolysis under visible light to form ansa-titanocene monohydroxido complexes and OH radicals[295–297]. This reaction had been observed with non-tethered titanocenes before[298], but the Cp-Ti BDFE is typically smaller than the Ti-O BDFE, leading primarily to loss of Cp in those systems. A catalytic model system for the photochemical splitting of water has been demonstrated using an ansa-titanocene aquo-hydroxo complex **70** (REF [297]) (FIG. 7b). Currently, this process requires TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl) oxyl) to reoxidize the bis(aquo) complex **69** to **70**, which can liberate an OH radical upon irradiation. While this reaction may be catalytic, a turnover number could not be confirmed. In contrast to the above reaction, reaction of Cp^*_2TiOTf with water results in rapid oxidation to $Cp^*_2Ti(OH)(OTf)$ and hydrogen gas without TEMPO additive[299].

Building upon this work showing that Cp_2MX_2 can undergo ligand-to-metal charge-transfer (LMCT) processes to liberate radicals, it has also been shown that early transition metals can be used as sensitizers for single-electron photoredox catalysis. For example, metal photosensitizers have been designed from π-donor ligands on electron-poor Zr centres (FIG. 7c). As Zr^{IV} is a d^0 metal, these complexes use LMCT processes as opposed to the typical metal-to-ligand charge-transfer (MLCT) processes seen in late transition metal photosensitizers such as $[Ru(bpy)_3]^{2}$+ (REF [300]). Zr is considerably less expensive and more earth abundant than the common late metals used in photosensitizers, making it an attractive alternative for catalysis. $Zr(^{Me}PDP)_2$ (^{Me}PDP = 2,6-bis(5-methyl-3-phenyl-1H-pyrrol-2-yl)-pyridine) (**73**) has a visible excitation at 528 nm and a photoemission at 594 nm. Cyclic voltammetry (CV) experiments show a reversible reduction at −2.16 V, while Rehm-Weller analysis estimates an excited-state reduction potential of −0.07 V. This excited-state reduction potential is supported by excited-state quenching using weak organic reductants such as 1,3-dimethyl-2-phenyl-2,3-dihydro-1H-7-methylbenzo-[d]imidazole (^{Me}BIH). Complex **73** is able to catalyse the reductions of ethyl 2-bromo-2,2-difluoroacetate and diethyl maleate to ethyl 2,2-difluoroacetate and diethyl succinate, respectively (FIG. 7c, right). An in-depth study of the homocoupling of benzyl bromide helped support the photoredox mechanism[301].

Group-transfer catalysis

As is the case with small-molecule activation reactions, engendering catalytic reactivity in group-transfer reactions is particularly challenging owing to the strength of M-E multiple bonds. Classical examples such as methylene transfer in the Tebbe olefination result in the formation of strong Ti-O double bonds, precluding practical turnover. Nonetheless, there have been several notable advances toward catalytic oxidative group-transfer reactions, in particular nitrene transfer. Most of the catalytic early transition metal nitrene transfer reactions involve oxidative imination of unsaturated organic functional groups, which stands in contrast to late-transition-metal-catalysed nitrene transfers, which often perform C-H insertions[302–305] or aziridinations[306–308].

Heyduk has developed several Zr and Ta complexes of aminoquinone-derived redox non-innocent ligands[80,309]. In these complexes, multi-electron redox changes needed for group transfer take place on the ligand framework instead of at the metal centre, allowing facile, low-temperature access to imido complexes that can undergo further reactivity such as catalytic nitrene coupling[310,311], imide reduction[312] and oxidative isocyanide imination (FIG. 8a, left). For example, in the (NNN) ZrCl (**74**)-catalysed isocyanide imination reaction, the trianionic (tris)amide $(NNN)^{3-}$ligand undergoes two-electron oxidation by RN_3 to yield the monoanionic $(NNN)^{1-}$imido complex **75**, which can insert isocyanide to form an η^2-carbodiimide **76**. Upon carbodiimide ligand loss, the NNN ligand framework is again reduced to the $(NNN)^{3-}$ form in **74** to close the catalytic cycle[313]. A related Ti system based on a diamide-dimine (dadi) framework has also been reported[82]. These (dadi) Ti complexes can access a large array of ligand oxidation states, thereby realizing a two-electron pathway for catalytic azide carbonylation by **77** (FIG. 8a, right). Productive catalysis hinges on weak CO binding to Ti resulting from the redox non-innocent ligand; one would expect Ti^{II} to exhibit strong CO binding due to backdonation into the C-O π^* orbital, but because the redox events take place on the ligand, the electron density at Ti remains low throughout the catalytic cycle and thus Ti is incapable of strong backdonation.

In contrast to the above examples of overt ligand redox non-innocence in nitrene transfer, there are several recent examples of formally Ti^{II}/Ti^{IV}-catalysed oxidative nitrene transfer reactions. These reactions yield multi-substituted pyrroles from the coupling of alkynes with azobenzene[314,315] or α,β-unsaturated imines and α-iminocyclopropanes from the coupling of alkynes and alkenes with azobenzene[316] (FIG. 8b). The crux of this system is that cooperative metal-ligand effects can also stabilize low-valent metals through backbonding (classical redox non-innocence) into the reagents (alkynes and diazenes) or products (pyrroles and imines), allowing for otherwise challenging reductive events, such as the reductive elimination from **82** to **83**, to occur with relative ease. Although it was initially speculated that azobenzene was a critical reagent for catalytic reoxidation of **83** to **80** through the hydrazido adduct **84**, recent advances have extended this chemistry into other nitrene sources such as azides[317].

Computational analysis has revealed several additional surprising facets of the reductive elimination events that are critical for catalytic turnover in these Ti^{II}/Ti^{IV} reactions[318,319]. In general, it appears that direct reductive coupling of M-C and M-X σ-bonds from intermediates **82** or **88** is unfavourable relative to other reductive pathways. For example, in the pyrrole synthesis, manifold intrinsic bond orbital (IBO) analysis indicates that reductive elimination from the six-membered metallacycle **82** is a π-type electrocyclic ring closure (FIG. 8b, left). By contrast, in the alkene-alkyne coupling reactions, the six-membered metallacycle **88** is semi-saturated (FIG. 8b, right) and thus lacks the requisite π-orbital for electrocyclization. This opens up alternative reductive elimination pathways: p-H elimination to ultimately form α,β-unsaturated imines (**86**) or a pericyclic Kulinkovich-like cyclopropanation to form a-iminocyclopropanes (**87**). It is proposed that the α,β-unsaturated imines are formed through N-H reductive elimination, which has not previously been observed on Ti. Computational studies have proposed a more complex insertion-type pathway for the formation of this product, although experimental evidence for either pathway is currently lacking[320].

In contrast to group 4 metals, group 5 metal imidos tend to be considerably less reactive. To counteract this, efforts have been made to synthesize group 5 systems that electronically saturate the metal *d* orbitals (π-loading), thereby increasing the polarizability of the imido bonds[321]. The re-loaded β-diketiminate (BDI) Nb bis(imido) complex **89** can thus perform a formally N^{III}/Nb^{V}-catalysed nitrene transfer reaction to generate asymmetric dialkylcarbodiimides from azides and isocyanides[322] (FIG. 8c).

Outside of catalytic nitrene transfer, there are also many examples of stoichiometric atom-transfer reactions (As_4 (REF.[323]), S_8 (REFS[324],[325]) and P_4 (REF.[326])). For example, reaction of either P_4 or As_4 with activated zirconocene derivatives results in pnictogen-silicon analogues of benzene[327] and carbon-phosphorous cage compounds[328]. The Cummins group has also extensively studied P_4 transformations[329] and synthesized phosphorous-rich organic clusters mediated by a Nb^{III}/Nb^{V} couple[330].

O-atom transfer is an incredibly challenging target to achieve with oxophilic early transition metals because the strong metal-oxo bond is a thermodynamic sink. In order to circumvent this problem, Nb nitride **90** has been used to perform outer-sphere O-atom transfer from CO_2 (FIG. 8d). CO_2 binds to the terminal anionic nitride in **90**, and the resulting oxide ion in **91** can then be transferred to a RC(O)Z (Z = halide, OAc) acceptor to form **92**, an N-bound cyanate. Subsequent oxidation and reduction steps liberate CO from the bound cyanate in **93**, regenerating **90**. While this system is not catalytic, it remains a rare example of a closed synthetic cycle to achieve CO_2 reduction[331].

Summary and outlook

The field of low-valent early transition metal synthesis, reactivity and catalysis has undergone a resurgence of activity in recent years. Many of these new reactions and applications can be split into three categories: reactions providing a modern twist on classic low-valent organometallic transformations, such as catalytic ring-opening reactions and substrate-directed reductive couplings; reactions that push low-valent early transition metals into new, emerging fields, such as PCET, photoredox catalysis and catalyst-controlled radical reactions; and new modes of low-valent inorganic and organometallic reactivity, such as oxidative nitrene transfer catalysis and reversible end-on Sc^{II} N_2 binding.

Each of these categories illustrates that early transition metals play a rich and evolving role in a broad array of chemical applications, and that there likely remains substantially more to discover as the field of low-valent early metal chemistry is revisited through the lens of modern organometallic chemistry. For example, accessing low-valent intermediates under mild conditions (using, for example, organosilane reductants or photoredox chemistry) is only beginning to have an impact in the field and should help to overcome many of the chemical compatibility issues associated with the strong reductants previously used to access low-valent early transition metals.

While many of the reactions discussed here are catalytic in nature, it would be unwise to neglect the importance of fundamental and stoichiometric reactivity with the early transition metals — not only can these later provide the basis for catalytic reactions (as seen in many of the examples discussed above), but the early metals are incredibly earth abundant, environmentally friendly and inexpensive and often have practical utility even in stoichiometric quantities.

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Inner-sphere reductants

Reagents that act as reductants after first forming a bond to the complex of interest.

Umpolung reactions

Reactions that proceed through polarity inversion of the given functional group.

Redox non-innocent ligands

Ligands bound to a metal complex in which the oxidation state is ambiguous, wherein oxidation or reduction of the ligands may occur in tandem with or instead of metal oxidation or reduction.

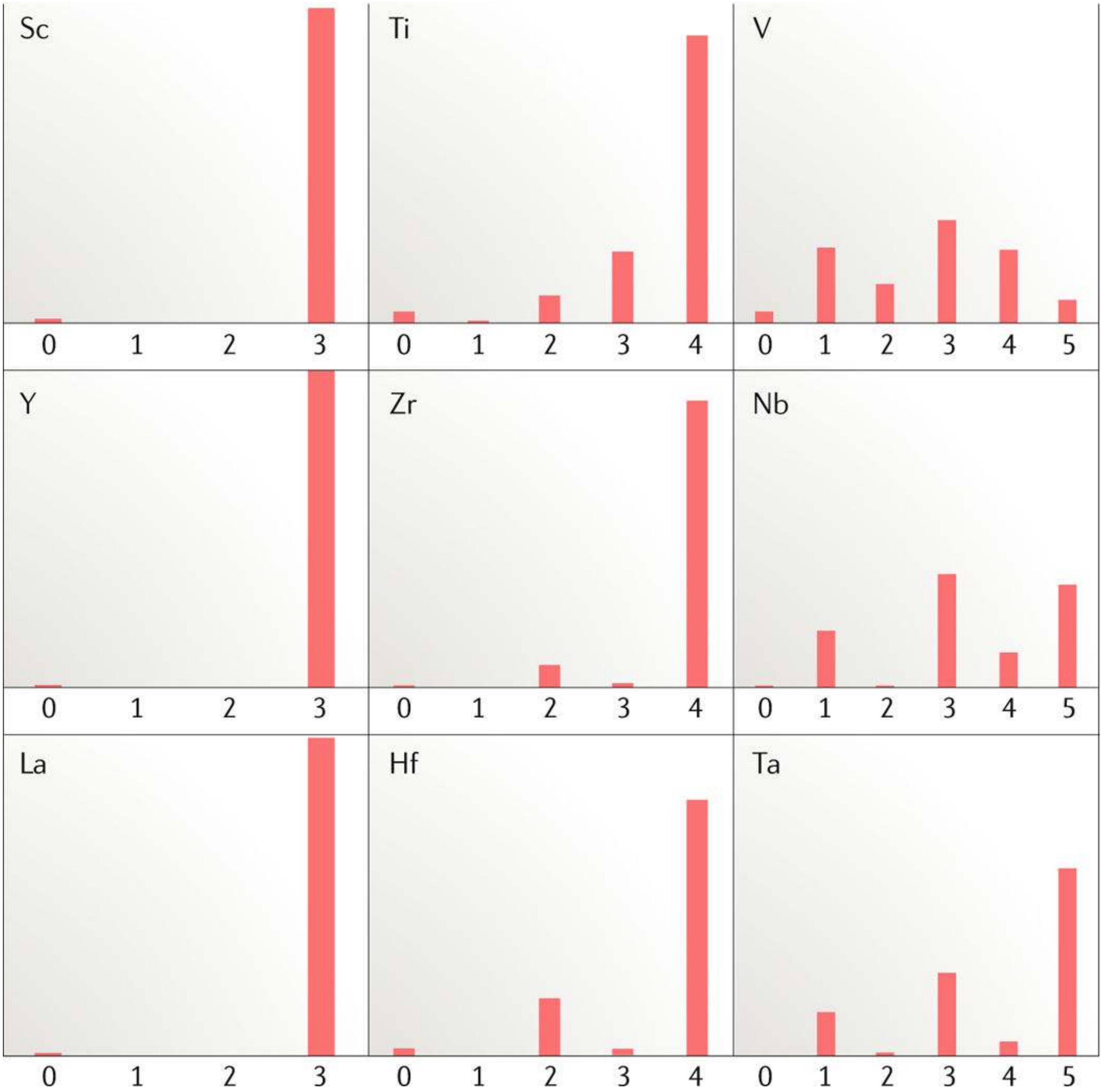


Fig. 1 |. Relative abundance of the valence states of early transition metal organometallic complexes.

Reduced early transition metal complexes become increasingly rare as one proceeds from group 5 to earlier groups and also from period 3 to period 5. Data adapted from REF[26].

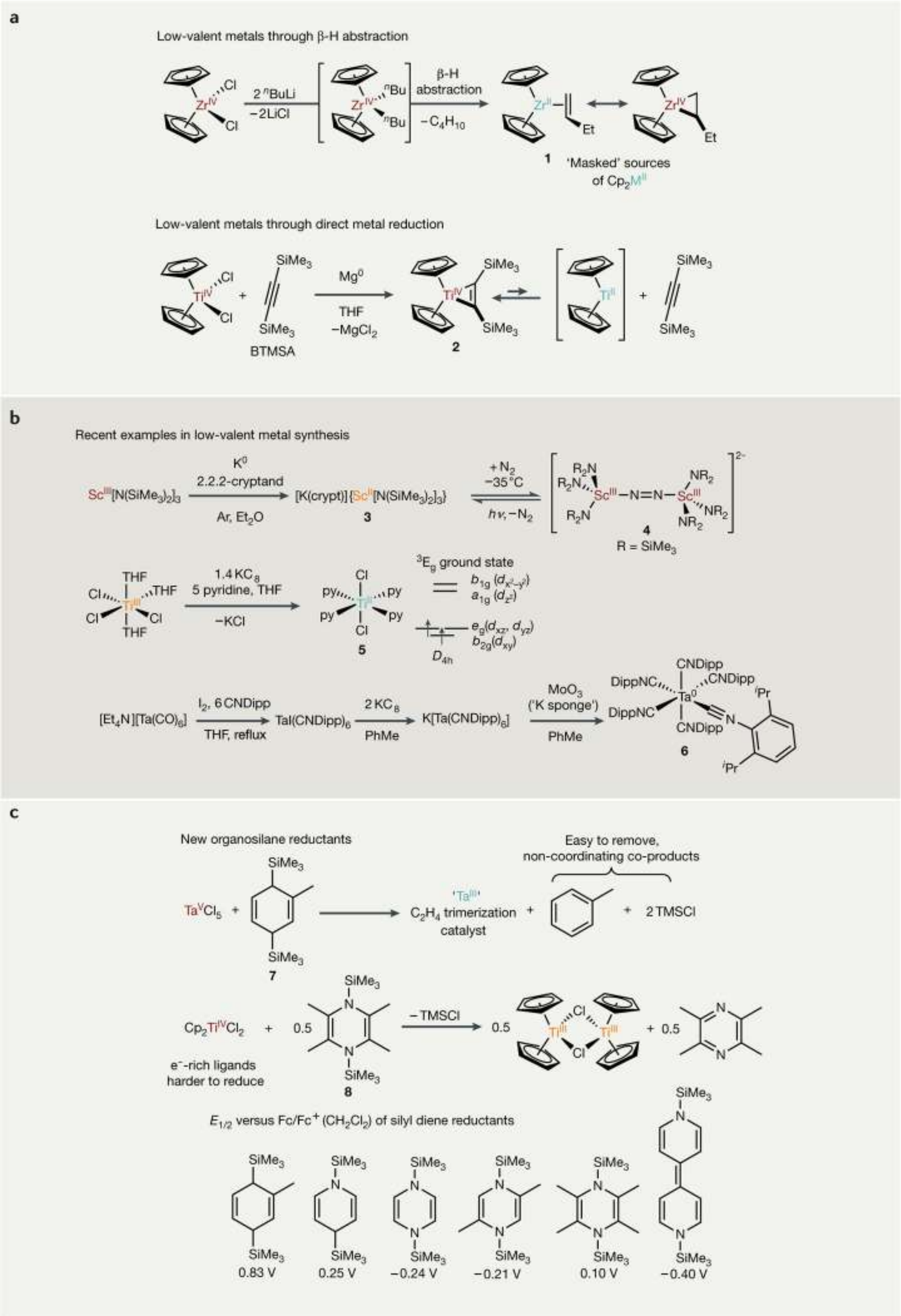


Fig. 2 |. Examples of synthetic routes to low-valent early transition metal complexes.

a | Classical reduction routes involving strong reductants. **b |** Representative examples of modern low-valent metal synthesis. **c |** New organosilane reductants for low-valent metal synthesis and catalysis. These routes demonstrate the diverse array of reduction methods available and the common ability of π-accepting ligands to stabilize low-valent early transition metal complexes. Red-coloured metals are in their highest oxidation state, orange-coloured metals are one-electron reduced, and teal-coloured metals are two-electron reduced. *hv*, irradiation; Dipp, 2,6-diisopropylphenyl; $E_{1/2}$, half-wave potential; Fc, ferrocene; THF, tetrahydrofuran; TMSCl, trimethylsilyl chloride.

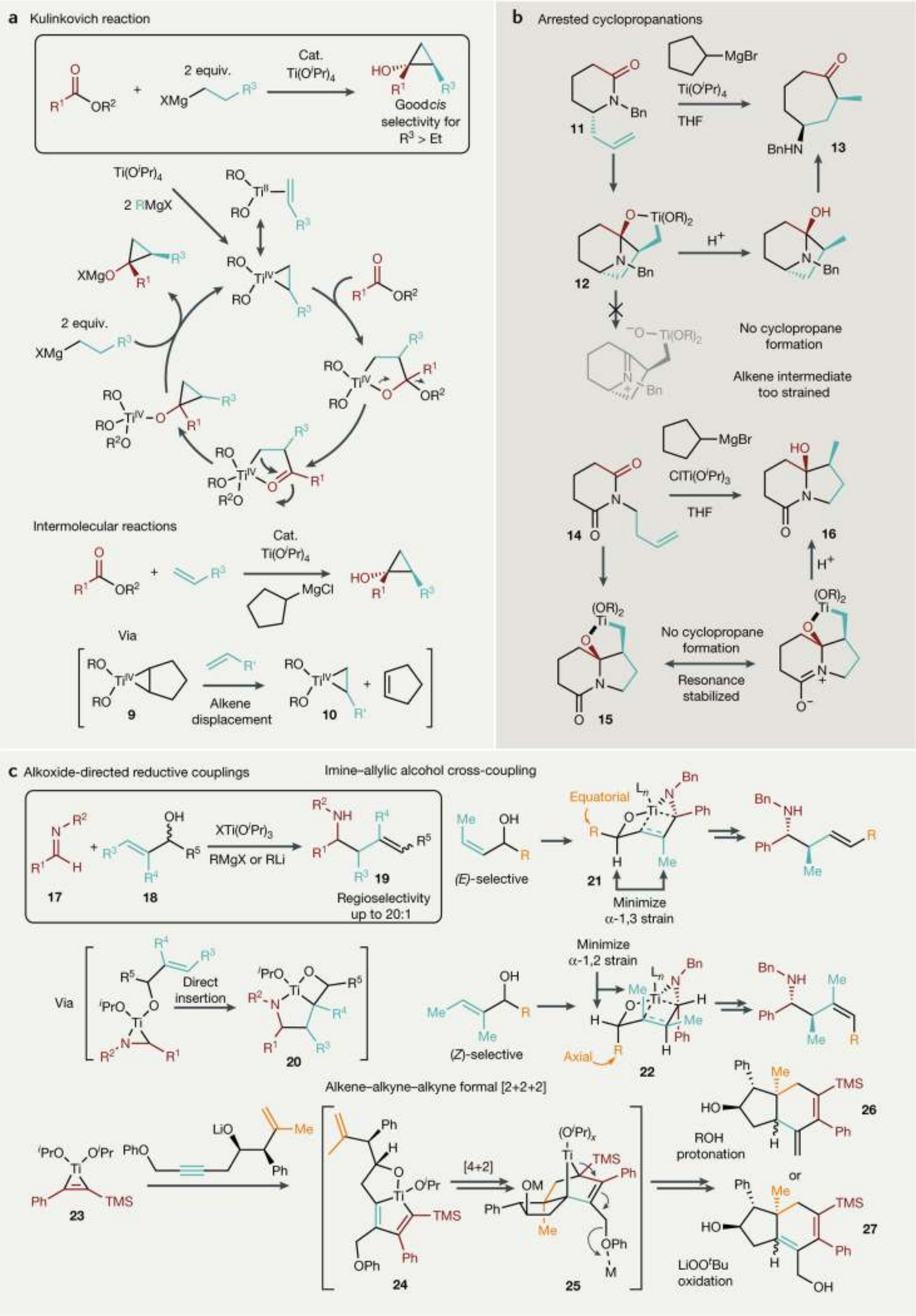


Fig. 3 |. Recent advances in two-electron reductive coupling reactions proceeding through titanacyclopropane and titanacyclopropene intermediates from Ti(O^{i}Pr)$_4$/RM and related species.

a | Catalytic KuLinkovich cydopropanation reactions, in which ester C = O bond insertion into the Ti bond precedes pericycLic metaLLacycLe collapse. **b |** Stoichiometric arrested KuLinkovich-de Meijere-Like cyclopropanations, in which metaLLacycLe collapse is prevented through steric (top) or electronic (bottom) blocking. **c |** Alkoxide-directed regiospecific and stereospecific reductive couplings that bias regiospecific metaLLacycLe formation and subsequent insertion steps through covalent Ti-O bonding. DCE, dichLoroethane; DME, dimethoxyethane; equiv., equivalents; THF, tetrahydrofuran; TMS, trimethyLsiLyL.

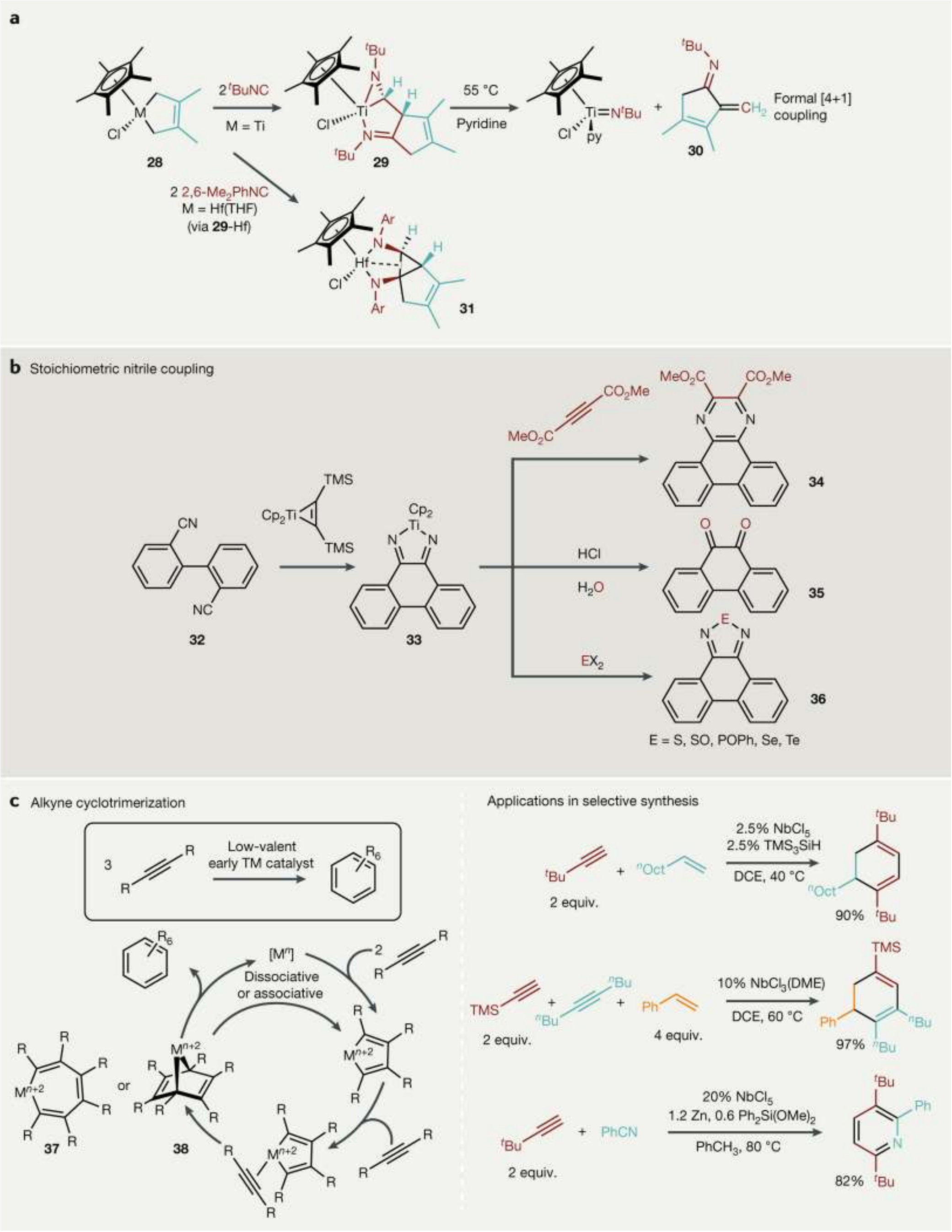


Fig. 4 |. Examples of new reductive coupling reactions.

a | Isocyanide insertion into metaiiacydopentenes can result in imido extrusion and formal [4+1] coupling with Ti, while intermediate products can be isolated with the heavier Hf congener. **b |** Nitrile reductive couplings lead to diazatitanacyclopentadienes that can undergo further reaction to make new **π**-conjugated materials. **c |** A general mechanistic scheme for early-transition-metal-catalysed cyclotrimerization catalysis (left) and new advances in selective heterocyclization catalysed by simple reduced Nb complexes. DCE, 1,2- dichloroethane; DME, 1,2-dimethoxyethane; equiv., equivalents; THF, tetrahydrofuran; TM, transition metal; TMS, trimethylsilyl

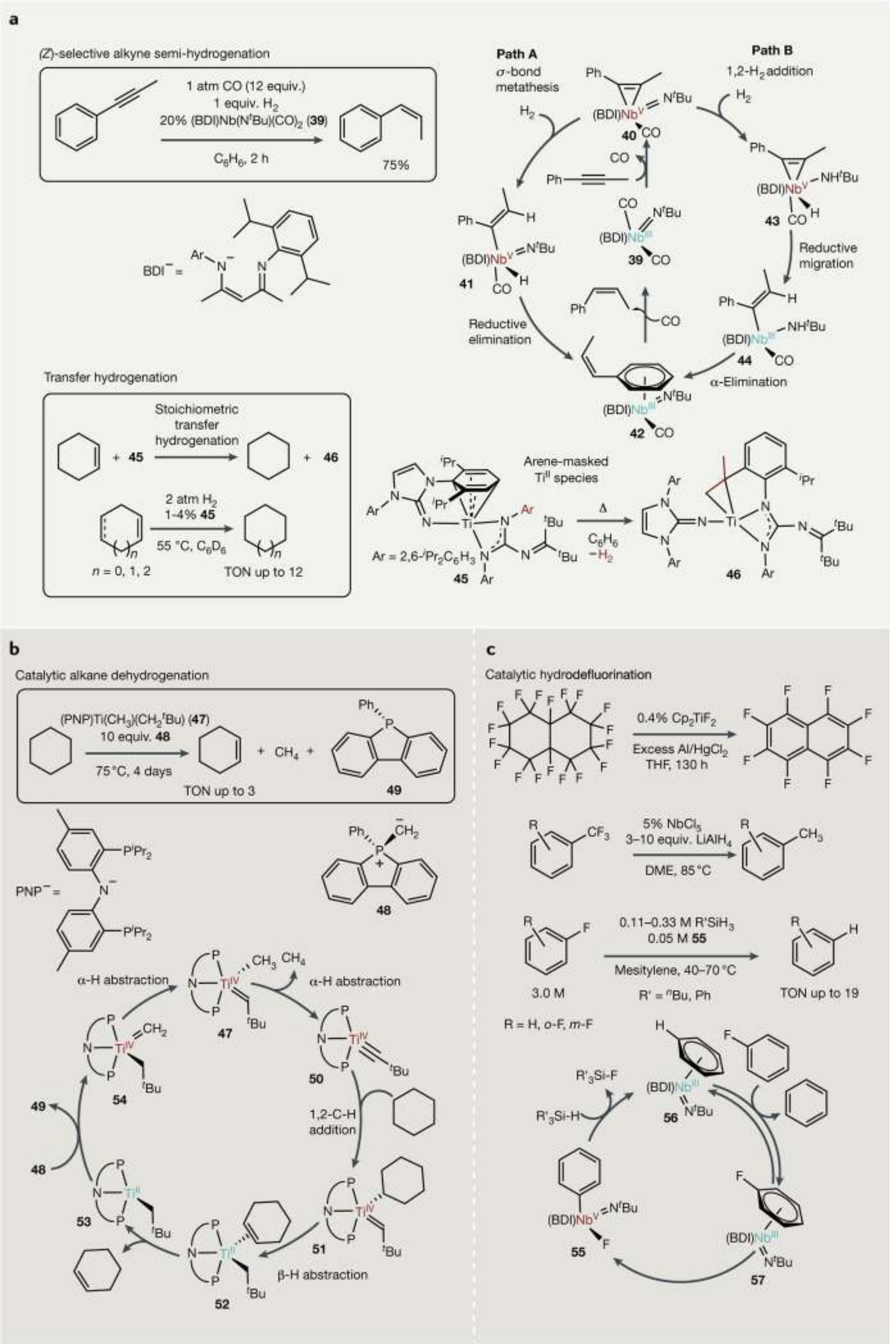


Fig. 5 |. Catalytic (de)hydrofunctionalizations.

a | Well-defined Nb-catalysed (Z)-selective alkyne semi-hydrogenation catalysed by Nb imido complexes (top) and Ti-catalysed transfer hydrogenation (bottom). **b |** Selective, catalytic alkane dehydrogenation using phosphorus ylides as terminal oxidants. **c |** Catalytic examples of hydrodefluorination that take advantage of the formation of strong Al–F or Si–F bonds as a driving force for defluorination. Δ, heat; BDI, β-diimine; DME, dimethoxyethane; equiv, equivalents; THF, tetrahydrofuran; TON, turnover number.

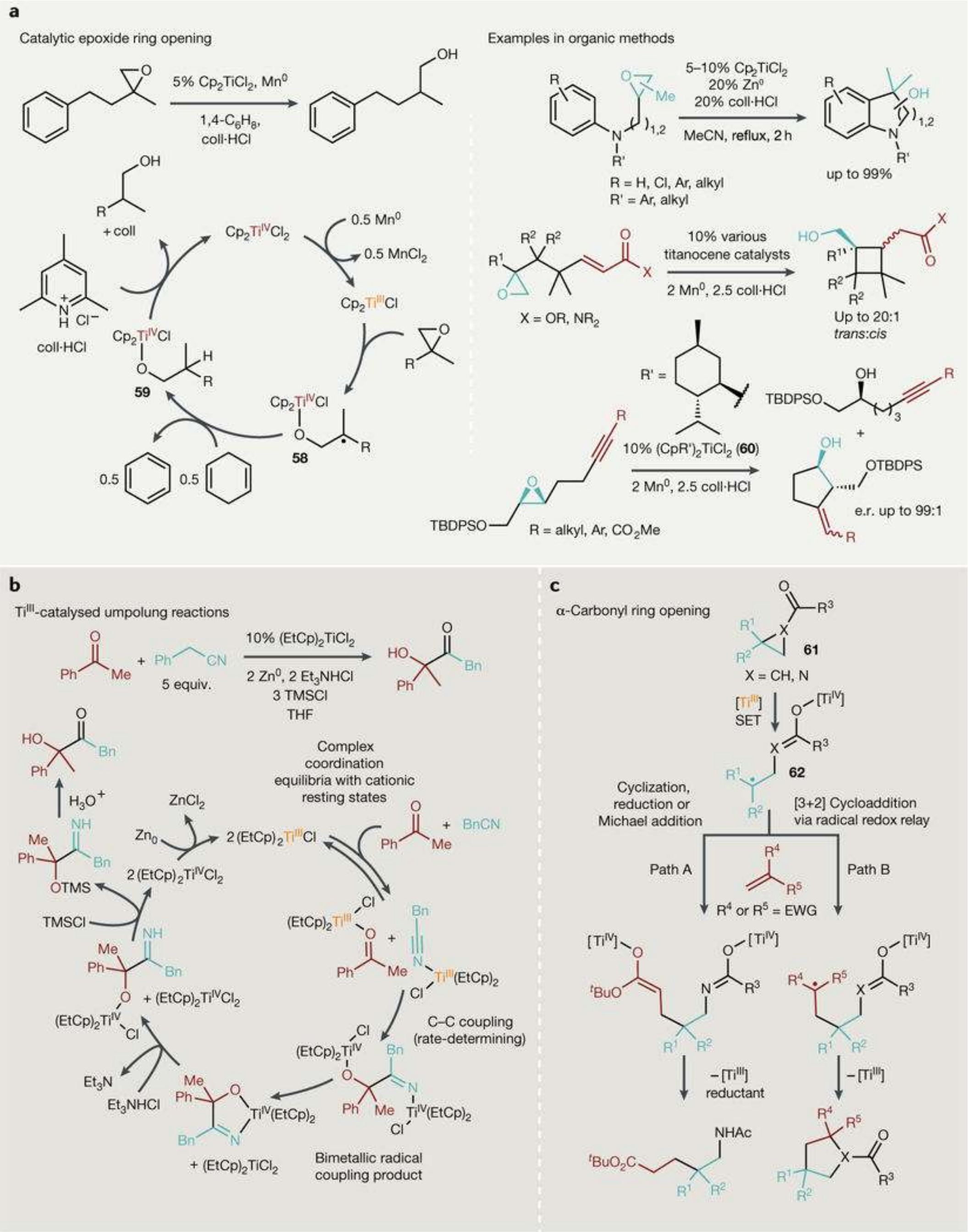
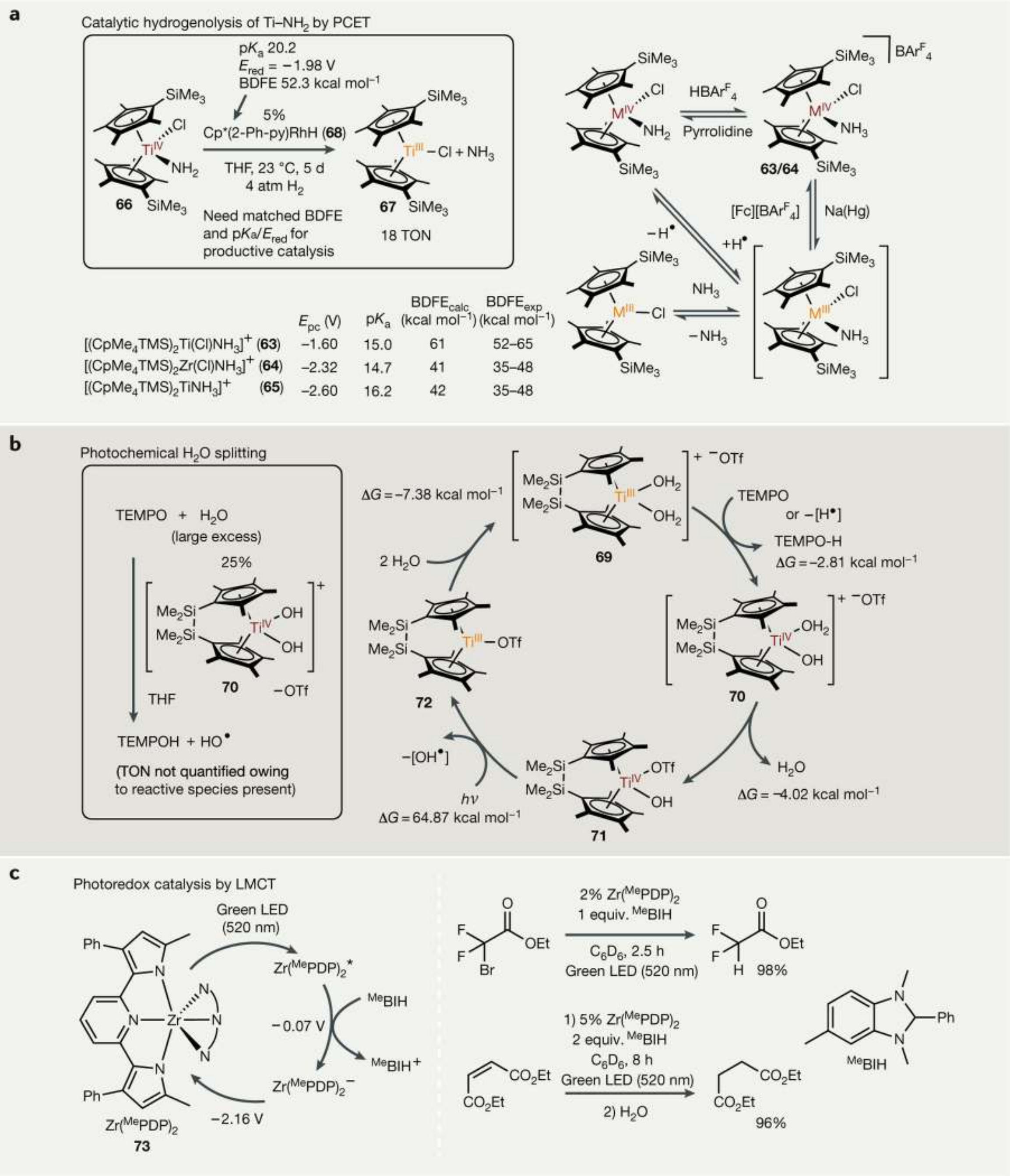


Fig. 6 |. Single-electron processes catalysed by Ti^{III} complexes.

a | Catalytic epoxide ring opening using weak reductants and acids to drive turnover (Left) and examples in selective organic synthesis. **b |** Single-electron umpolung reactions can yield new C-C bonded products through a complex bimetallic radical coupling mechanism. **c |** SingLe-eLectron transfer (SET) from Ti^{III} into carbonyls adjacent to strained rings gives access to several new aLkene coupling reactions including cyclization, Michael addition and [3+2] cycLoadditions. CoLL-HCL, 2,4,6-coLLidine hydrochloride; equiv, equivalents; e.r., enantiomeric ratio; EWG, eLectron-withdrawing group; TBDPS, tert-butyLdiphenylsiLyL; THF, tetrahydrofuran; TMS, trimethyLsiLyL.



	E_{pc} (V)	pK_a	BDFE$_{calc}$ (kcal mol^{-1})	BDFE$_{exp}$ (kcal mol^{-1})
[(CpMe$_4$TMS)$_2$Ti(Cl)NH$_3$]$^+$ (63)	−1.60	15.0	61	52–65
[(CpMe$_4$TMS)$_2$Zr(Cl)NH$_3$]$^+$ (64)	−2.32	14.7	41	35–48
[(CpMe$_4$TMS)$_2$TiNH$_3$]$^+$ (65)	−2.60	16.2	42	35–48

Fig. 7 |. Single-electron strategies in small-molecule activation chemistry.

a | Hydrogenoiysis of metal amides to ammonia via proton-coupled electron transfer (PCET), enabled by coordination-induced weakening of the N-H bond. **b |** Photochemical model of H_2O splitting with Ti^{III} catalysts, again enabled by coordination-induced weakening of O-H bonds. **c |** Photoredox catalysis via ligand-to-metal charge transfer (LMCT) with $(^{Me}PDP)_2Zr$ complexes, in which charge transfer occurs in a direction opposite of state-of-the-art late transition metal photoredox catalysts, which undergo metal-to-ligand charge transfer (MLCT). *hν*, irradiation; BDFE, bond dissociation free energy;

Cp*, $C_5Me_5^-$; E_{pc}, cathodic peak potential; equiv, equivalents; E_{red}, reduction potential; Fc, ferrocene; LED, light-emitting diode; ^{Me}PDP, 2,6-bis (5-methyl-3-phenyl-1H-pyrrol-2-yl)-pyridine; TEMPO, (2,2,6,6-tetramethy[piperidin-1-y[)oxy[; THF, tetrahydrofuran; TMS, trimethylsilyL; TON, turnover number.

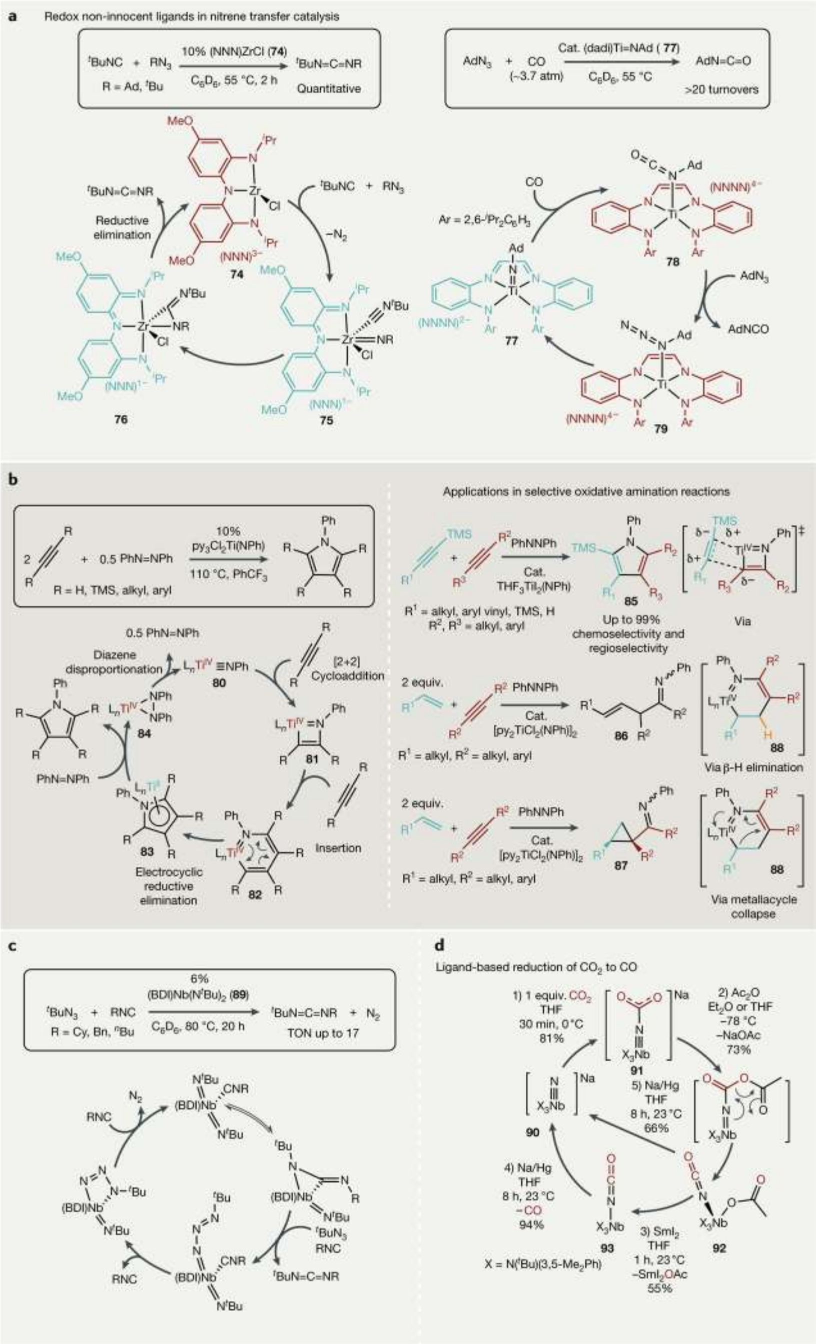


Fig. 8 |. Group-transfer catalysis mediated by early transition metal complexes.

a | Redox non-innocent ligand frameworks enable nitrene transfer reactions by undergoing redox changes at the ligand instead of the metal. **b |** Ti^{II}/Ti^{IV} redox catalytic nitrene transfer in oxidative amination catalysis — a new mechanism for pyrrole formation (left) — and examples in selective synthesis (right). **c |** Nitrene transfer promoted by a **π**-loaded bis(imido)Nb catalyst, which renders the imido fragment more labile than other group 5 imido complexes. **d |** A closed synthetic cycle for ligand-based CO_2 reduction to CO that avoids the formation of strong M-O multiple bonds. BDI, 2,6 diisopropylbenzene-β diketiminate; dadi, diamide-dimine; equiv, equivalents;THF, tetrahydrofuran; TMS, trimethylsilyl; TON, turnover number.