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The roles of Lewis acidic additives in organotransition metal catalysis

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We describe recent examples of prominent reactions in organic synthesis that involve transition metal and Lewis acid cocatalysts. Introducing Lewis acid additives to transition metal catalysis can enable new reactivity or improve activity and selectivity of an existing process. Several studies are highlighted to illustrate the possible roles of Lewis acids in catalytic mechanisms. The uses of Lewis acid additives in bond-breaking catalysis (C–C activation, C–H activation, and hydrogenolysis reactions) and bond-forming catalysis (Au-catalysed alkyne functionalisation, Pd-catalysed C–C and C–N bond formation) are reviewed.

1. Introduction

In pursuit of more efficient organotransition metal catalysis, many chemists have boosted activity and/or selectivity using Lewis acid additives.¹ Significant recent contributions have advanced the mechanistic understanding of transition metal–Lewis acid synergy, and therefore it is timely to provide a concise review of highlights of this area. Out of a broad array of examples in which Lewis acidic additives are used in organometallic catalysis, we present here four classes of Lewis acid effects in catalytic reactions, chosen to highlight a few important ways in which Lewis acids may influence organo-

metallic reactions. This Review is intended as a guide for practitioners who seek to improve catalytic reactions by the addition of additives and to understand the role of additives from a mechanistic perspective. We focus on mechanistic effects of Lewis acids throughout catalytic cycles, including alkylaluminums, alkyl and arylboranes, alkylzincs, and metal halides and triflates (trifluoromethanesulfonate, or OTf) of various cations. These classes of Lewis acids play a role in the cooperative activation of strong bonds, such as in the oxidative addition of C–C and C–H bonds to transition metals, or the hydrogenolysis of C–O and C–N bonds. Lewis acids can also facilitate bond-forming reactions, such as Au-catalysed reactions of alkynes (and related reactions), as well as Pd-catalysed C–C and C–N bond forming reactions.

Lewis acids can play myriad roles within a given transition metal-catalysed reaction (Fig. 1). Some examples in this Review

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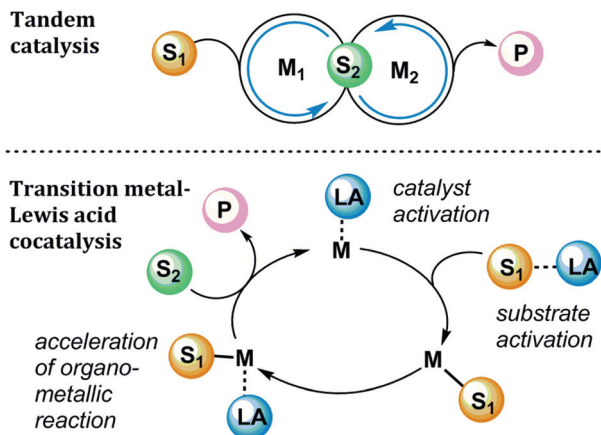


Fig. 1 Generalized mechanism for tandem catalysis (top) and transition metal and Lewis acid cocatalysis (bottom). S_1 , S_2 = substrates; M = metal complex; LA = Lewis Acid; P = product.

will involve tandem catalysis,² in which two discrete catalytic cycles occur simultaneously in a single reaction mixture, where M_1 is a transition metal catalyst and M_2 is an acid catalyst. More complex mechanisms see the involvement of a Lewis acid cocatalyst (LA) upon a single catalytic cycle mediated by a transition metal catalyst (M). In a simplified mechanistic model, the Lewis acid can affect the overall cycle by forming Lewis acid–base adducts with different components of the catalytic reaction.

For example, cooperative substrate–Lewis acid interactions (S_1 –LA) or catalyst–Lewis acid interactions (M –LA) can promote the turnover-limiting step of catalysis or direct the reaction pathway in a selectivity-determining step. In this Review, we will encounter examples of reactions in which the Lewis acid is revealed to take several possible roles, such as activating substrate toward a transition metal centre, accelerating a key elementary organometallic step (*i.e.*, migratory insertion, transmetalation, or reductive elimination), affecting the catalyst activation or deactivation pathways, or promoting the controlled release of a Brønsted acid *in situ*. Here we highlight recent examples that elucidate the numerous possible sources of Lewis acid effects in organometallic catalysis and identify the modes of action of the Lewis acid in different reaction contexts.

One challenge is understanding why a particular Lewis acid is more effective than another in a given reaction. Electrophilic species can be found across the periodic table, and the methods to systematically categorize Lewis acids or measure Lewis acidity are limited.³ In select cases, the behaviour of the Lewis acids can be differentiated. For example, Organ and co-workers⁴ suggest that the different susceptibility of boron Lewis acids to autoxidation can result in different reaction outcomes in Pd and boron-catalysed C–N bond forming reactions. Another example is provided by Marks and co-workers,⁵ who show that the capacity of Pd and metal triflate cocatalysts to affect the hydrogenolysis of ethers is dependent on the effective charge density of the metal triflate cation employed.

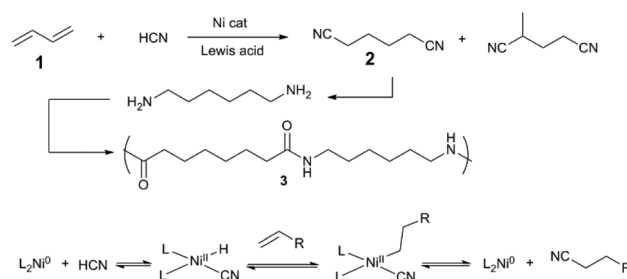
In each section, we highlight synthetic methods enabled by cocatalytic systems, as well as insights into potential modes of cooperativity. There are several methods for rationalising Lewis acid effects observed in catalytic reactions. Density functional theory calculations enable the assessment of the role of Lewis acid–base adducts of substrates and key catalyst intermediates on catalytic reaction pathways, as well as parametrisation of Lewis acids. Experimental insight into catalyst–Lewis acid cooperativity can be ascertained through the isolation of catalytic intermediates or model complexes thereof and assessing their reactivity towards Brønsted or Lewis acids. Lastly, monitoring of reaction rates can confirm an empirical Lewis acid effect and provide insight into possible reaction pathways. Here we piece together these clues to unveil numerous modes of catalyst–Lewis acid interactions in productive catalysis.

2. Cooperative catalyst systems for C–C and C–H bond activation

A representative example of transition metal/Lewis acid cooperative bond activation is DuPont's Adiponitrile Process (Scheme 1),⁶ which is thought to proceed *via* oxidative addition of HCN, Ni–H insertion of diene, and reversible elimination to generate alkylnitrile. In the presence of a Lewis acid cocatalyst (typically, BPh_3), the Ni/phosphine-catalysed hydrocyanation of 1,3-butadiene (**1**) shows increased rate and selectivity for the desired linear adiponitrile (**2**) *versus* branched isomers. Since Lewis acids can promote the oxidative addition of a C–CN bond to Ni(0) – *i.e.*, the microscopic reverse of alkylnitrile-forming reductive elimination – branched nitriles can be thus re-engaged by the catalyst, and again eliminated to form linear **2**. Jones^{7,8} revealed that a cooperative Ni/LA system reacts preferentially with C–CN bonds over activated C–H bonds, *e.g.* in allylcyanide. Together, these early works in cooperative bond activation are the basis for a wide variety of synthetic methods in C–C and C–H bond activation discussed in this section.

2.1 Synthetic methods that apply Ni and Lewis acid cocatalysts

2.1.1. C–C bond activation. Ni and Lewis acid catalysts enable the use of nitriles as electrophiles in C–C bond forming



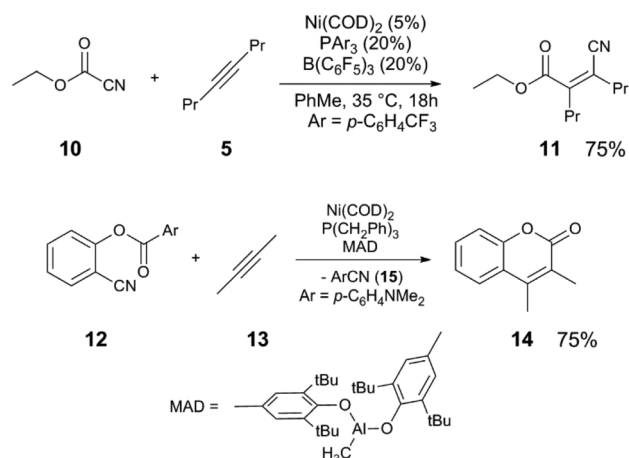
Scheme 1 Hydrocyanation of butadiene *en route* to 6,6-nylon (**3**)⁶ (top) and the mechanism of Ni-catalysed alkene hydrocyanation (bottom).



reactions.^{9,10} Nakao, Hiyama and coworkers¹¹ report the reaction of benzonitrile **4** with 4-octyne (**5**) via Ni(COD)₂/PPhMe₂ and AlMe₂Cl to provide alkenynitrile **6** in 96% yield (Scheme 2). The reaction proceeds by cooperative oxidative addition of the C–CN bond of **4**, followed by migratory insertion of the alkyne into the Ni–C_{Ar} bond, and reductive elimination of alkenynitrile product. The Lewis acid also increases selectivity for C–CN bond cleavage *versus* C–H bond cleavage, as demonstrated in the alkenylation of cyanoindole **7** with **5** to provide the 3-alkenylindole **8** (Scheme 3).¹¹ In the absence of Lewis acid, C–H activation of the indole instead results in 2-alkenylindole **9**, without cleavage of the C–CN bond.

Other nitriles, such as allylnitriles,¹² benzylnitriles,¹³ and alkynynitriles¹⁴ can be employed in similar catalytic scaffolds. Intramolecular versions in which alkenes are used as the coupling partner also have been reported,^{15,16} including variants which include Pd catalysts.^{17–20} The reaction of cyanoester **10**, a more activated electrophile, with **5** to give alkenynitrile **11** uses an electron-poor phosphine PAR^F₃ (Ar^F = 3,5-C₆H₃(CF₃)₂) in combination with Ni(COD)₂ and B(C₆F₅)₃ as the Lewis acid cocatalyst (Scheme 4).²¹ Other C–C bonds can be activated such as in anhydrides,²² cyclopropanes,²³ and esters.²⁴ In the latter example, the reaction of aryl nitrile **12** with 2-butyne (**13**) and catalytic Ni(COD)₂/P(CH₂Ph)₃/MAD (MAD = methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide)) results in sequential C–C bond activation events resulting in formation of coumarin **14** and elimination of aryl nitrile **15**.

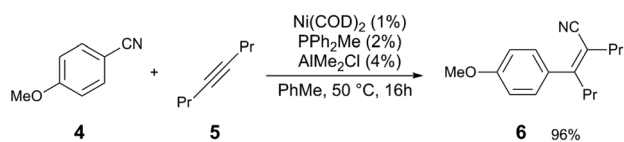
The activation of C(sp³)–CN bonds in unactivated aliphatic nitriles is more challenging, due to lower C–CN reactivity and competing β-hydride elimination of alkylnickel intermediates. These challenges can be overcome using a directing group on the nitrile to kinetically stabilize the resulting alkylnickel inter-



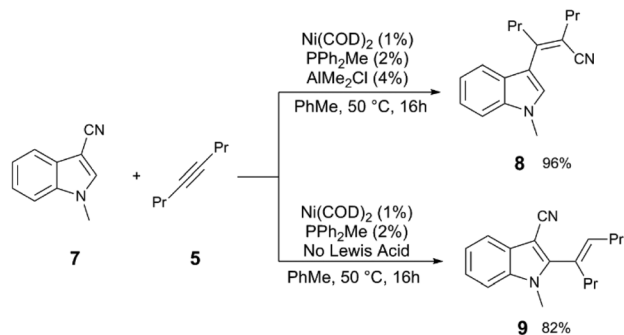
Scheme 4 Alkynylation of cyanoesters²¹ (top) and sequential C–CN and C–CO bond activation to form coumarins²⁴ (bottom).

mediate, and/or using a sterically-demanding ligand to reduce the rate of β-H elimination.²⁵ The pyrrolidine-substituted nitrile **16** and **5** react to give alkenynitrile **17** in 86% yield using a Ni(COD)₂/SPhos/AlMe₃ catalyst mixture (Scheme 5). A clever manifestation of cooperative C(sp³)–CN bond activation is realized by the Morandi group, in which alkylnitriles are used as HCN group transfer reagents (Scheme 6),^{26,27} utilizing the reversibility of the steps in the general alkene hydrocyanation mechanism to drive formation of the desired product without resorting to the use of hazardous HCN. For example, styrene (**18**) and isobutyrylnitrile (**19**) are converted to alkylnitrile **20** and isobutylene (**21**), using Ni(COD)₂/DPE-Phos/AlMe₂Cl; isobutyrylnitrile is selected as HCN transfer agent due to removal of gaseous isobutylene, driving selective formation of the desired product. A subsequent publication from the Morandi group uses a similar method to synthesize aryl nitriles.²⁸

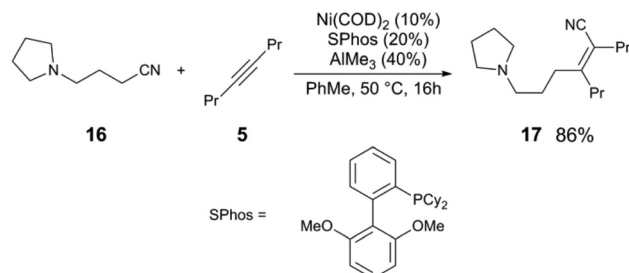
2.1.2. C–H bond activation. Similar catalysts are useful for catalytic C–H functionalisation, including hydroarylation of alkenes and/or alkynes using pyridines,^{29,30} pyridones,³¹ benzamides,³² and sulfonylarenes,³³ as well as the alkenylation of C–H bonds in aldehydes³⁴ and formamides.^{35,36} Regio- and chemodivergent hydroarylation of alkynes is observed as a function of ligand and Lewis acid identity, and demonstrative examples are shown in Scheme 7. In the direct, regioselective



Scheme 2 Ni and Al-catalysed carbocyanation of alkyne with benzonitriles.¹¹

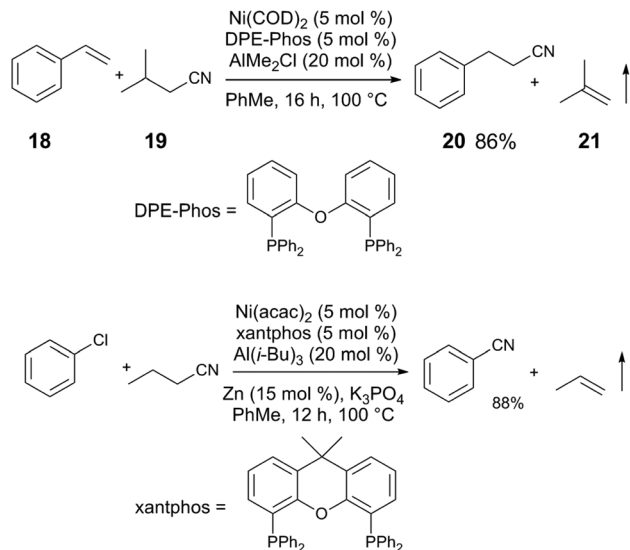


Scheme 3 Divergent reactivity in the Ni and Al-catalysed carbocyanation of alkyne with 3-cyanoindoles.¹¹

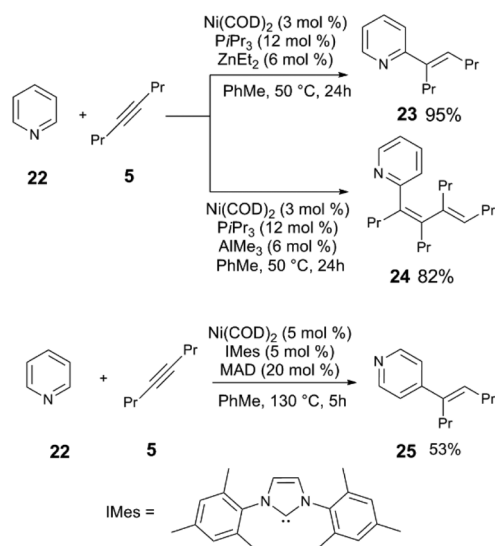


Scheme 5 Activation of alkylnitriles using a directing group.²⁴





Scheme 6 Alkynitriles as HCN transfer agents to alkenes²⁶ (top) and aryl halides²⁸ (bottom).



Scheme 7 Divergent reactivity in the C–H alkylation of heterocycles.^{29,30}

hydroarylation of **5** with pyridine (**22**) via $\text{Ni}(\text{COD})_2/\text{P}^i\text{Pr}_3/\text{LA}$ catalysts, when ZnR_2 ($\text{R} = \text{Me}$ or Ph) is used, the 2-monoalkenylated pyridine (**23**) is formed selectively (96% yield). In contrast, when AlMe_3 is used, the bis-alkenylated pyridine (**24**) is formed selectively (82% yield). A regioselectivity switch is observed when choosing a different catalyst system: the hydroarylation of **5** via $\text{Ni}(\text{COD})_2/\text{IPr}/\text{MAD}$ ($\text{IPr} = 1,3\text{-bis}(2,6\text{-diisopropylphenyl})\text{imidazole-2-ylidene}$) results in alkylation of the 4-position of the arene to yield **25** (70% yield), and similar regioselectivity is observed when this catalyst system is used for the hydroarylation of alkenes.

2.2. The role of the Lewis acid in cyanofunctionalisation and C–H functionalisation

In these reactions, the Lewis acid influences selectivity of C–C and C–H bond activation.^{37–41} Sakaki and coworkers³⁷ investigated the mechanism of the aforementioned dual C–C cleavage reaction of **12** to form the coumarin **14** by computation. An abridged mechanism determined by DFT calculations is depicted in Fig. 2 to reflect key elementary steps of the reaction; the mechanism proceeds by oxidative addition of the arylcyanide to $\text{Ni}(0)$, followed insertion of the alkyne into an arylnickel bond, followed by C–C bond formation and β -aryl elimination, yielding **14** and benzonitrile byproduct **15**. The calculations show that binding of the Lewis acid (which has been simplified from MAD to $\text{Al}(\text{OMe})_3$) at both the cyano and ester groups of the substrate are essential to achieving the two C–C cleavage steps of the reaction. In the presence of two equivalents of Lewis acid, both N-bound and O-bound, the transition state energies for both C–C bond cleavage events are significantly reduced, and moderate activation barriers are found: for C–CN activation, the ΔG^\ddagger is $+14.4 \text{ kcal mol}^{-1}$, and for C–CO activation the ΔG^\ddagger is $+17.3 \text{ kcal mol}^{-1}$, whereas in the absence of any Lewis acid, the barriers are $\Delta G^\ddagger = +44.8 \text{ kcal mol}^{-1}$ and $\Delta G^\ddagger = +23.8 \text{ kcal mol}^{-1}$, respectively. The significant reduction in barrier of C–CN cleavage is attributed to charge transfer from the Ni $3d_\pi$ to the C–CN $\sigma^* + \pi^*$ molecular orbital and increasing population of the LUMO of antibonding character is crucial to C–CN bond cleavage. The

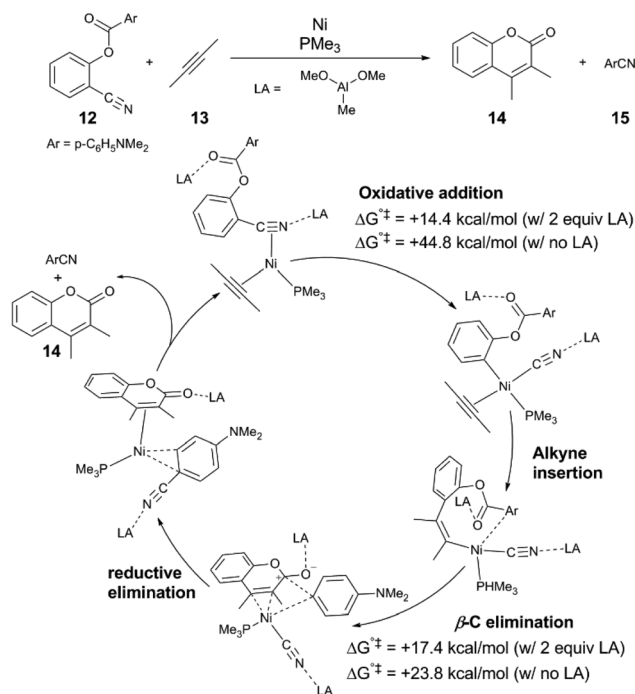


Fig. 2 A proposed mechanism of Ni and Lewis acid-cocatalysed C–CN and C–CO bond activation informed by DFT calculations.³⁷ For the purpose of clarity, isomerization and ligand exchange steps are omitted from the figure.



computations support the experimental result that no conversion of **12** is observed in the absence of Lewis acid.

Another computational study performed by Guan and co-workers³⁸ provides further insight into the regioselectivity observed by Ni/LA catalyst systems. The reaction of fluorinated benzonitrile **26** with 2-butyne (**13**) is investigated using a simplified Ni/DPE-Phos catalyst with BPh₃ cocatalyst. The selectivity of rate-limiting C–CN bond cleavage to yield the alkenynitrile **27** is evaluated in comparison to other competitive bond cleavages (C–H, C–F) in both the presence and absence of BPh₃. In the absence of BPh₃, the energy barriers of C–CN and C–H bond cleavage are similar ($\Delta G^{\ddagger} = +22.0$ kcal mol⁻¹ and $\Delta G^{\ddagger} = +21.2$ kcal mol⁻¹, respectively; Table 1). Upon binding of BPh₃ to **26**, the barrier of C–CN cleavage is reduced to +17.4 kcal mol⁻¹, whereas the barrier of C–H cleavage increases to +28.8 kcal mol⁻¹, confirming that the Lewis acid can increase the kinetic preference for C–CN cleavage *versus* other reactive bonds. The BDEs of the C–H and C–F bonds in the **26**:BPh₃ Lewis acid–base adduct are determined to be similar in free **26**; however, the BDE of the C–CN bond is significantly reduced ($\Delta H = +136.2$ kcal mol⁻¹, free **26**; $\Delta H = +112.7$ kcal mol⁻¹ **26**:BPh₃) upon adduct formation. The results affirm findings in other studies,³⁹ where Lewis acids reduce activation barriers of oxidative addition of cyanoester and alkylnitrile to Ni(0). Lewis acids can also reduce the barrier to migratory insertion of the alkyne into Ni–C bonds.

To summarize, advances in C–C and C–H bond activation have been enabled by cooperative Ni and Lewis acid catalysis, and numerous novel synthetic methods have resulted. A survey of examples indicates dependence of the electron-donating capacity of the ancillary ligand and the electron-withdrawing capacity of the Lewis acid in these catalytic systems strongly dictates the catalyst activity and selectivity. To generalize, the

most obvious role of the Lewis acid in this context is to effect substrate activation, though effects of chemo- and regioselectivity are also identified. In the following sections, the origins of catalyst–Lewis acid cooperativity will be more ambiguous.

3. Hydrogenation of carboxylic acids, esters, amides, and ethers

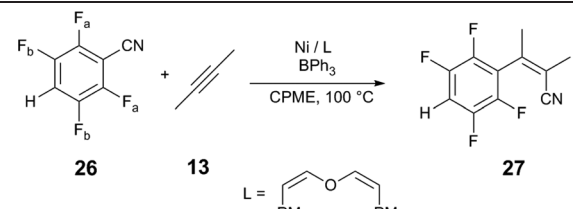
We now turn our attention to the hydrogenation of C–O and C–N bonds, where Lewis acid additives influence activity and selectivity chiefly by acting as source of Brønsted acid. To contextualise the role of Lewis acids as potential sources of Brønsted acids, our discussion begins by exploring the influence of acid additives upon Klankermeyer and Leitner's levulinic acid (**28**) hydrogenation,^{42,43} catalysed by a Ru(acac)₃/1,1,1-Tris(diphenylphosphinomethyl)ethane (triphos) catalyst (Scheme 8). This example represents an advance in hydrogenation of challenging carboxylic acid derivative substrates through the use of a multifunctional catalyst system. The reaction sequence for the conversion of **28** to γ -valerolactone (**29**), 1,4-pentanediol (**30**), and 2-methyltetrahydrofuran (MeTHF, **31**) can be formulated using distinct Ru-catalysed hydrogenation steps and acid-catalysed dehydration steps. The overall performance of the reaction (*i.e.*, activity and selectivity) is highly dependent on both the Ru catalyst (ligand, and counter-anion) and pK_a of the reaction medium. Mechanistic evidence also points to acidic additives influencing catalyst activation and deactivation modes during Ru-mediated reaction steps.^{43,44}

3.1. Ru-Catalysed hydrogenation and Brønsted acid cocatalysis

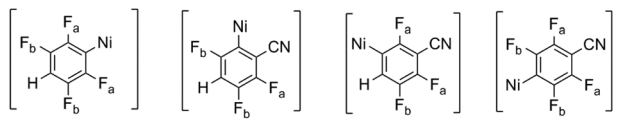
By modifying Klankermeyer and Leitner's catalyst and conditions, the activity and selectivity of the reaction can be dramatically affected.⁴² Ru(acac)₃, tri(octyl)phosphine, and NH₄PF₆ selectively converts **28** to γ -valerolactone (**29**) in >99% yield (Scheme 9), without further reduction of the lactone. In contrast, the use of Ru(acac)₃, triphos, along with a mixed acid system (using a sulfonic acid (aIL) and NH₄PF₆) provides excellent selectivity for the complete reduction of **28** to MeTHF (**31**) in 92% yield.

In the latter reaction, an off-cycle catalyst resting state (triphos)Ru(CO)(H)₂ (**32**) was isolated from the reaction

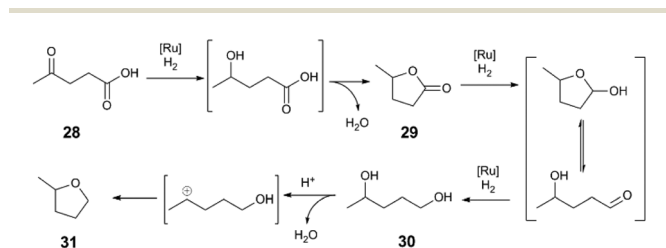
Table 1 Effect of Lewis acids on the Ni-catalysed activation of 2,3,5,6-tetrafluorobenzonitrile³⁸



Possible bond activations: C–CN, C–F, C–H

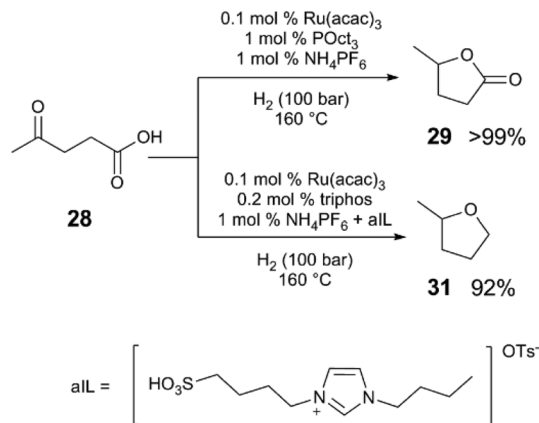


Bond activation	ΔG^{\ddagger} (kcal mol ⁻¹)	ΔG^{\ddagger} w/BPh ₃ (kcal mol ⁻¹)	BDE (kcal mol ⁻¹)	BDE w/BPh ₃ (kcal mol ⁻¹)
C–CN	+22.0	+17.4	+136.2	+112.7
C–F _a	+27.8	+33.1	+125.8	+125.8
C–F _b	+32.8	+43.0	+125.2	+125.0
C–H	+21.2	+28.8	+122.5	+122.8



Scheme 8 Conversion of levulinic acid to 2-methyltetrahydrofuran.⁴²





Scheme 9 Acid-dependent selectivity in the hydrogenative cyclisation of levulinic acid.⁴²

mixture.⁴³ The carbonyl ligand is most likely derived from decarbonylation of aldehyde formed *in situ*. As precatalyst, **32** has lower catalytic activity than the combination of Ru(acac)₃ and triphos, but can be reactivated by adding substrate and/or acid (Fig. 3). The ability of an acid to restore activity is dependent on pK_a, conjugate base identity, and Ru/acid ratio. Acid could react with neutral [Ru(H)₂] to form the non-classical hydride [Ru(H₂)H⁺] (**33**). Subsequent dihydrogen dissociation could then open up a site for substrate binding.

In a related amide hydrogenation, activity of (triphos)Ru(OAc)(H) (**34**), also depends on the Ru/acid ratio.⁴⁴ Stoichiometric reactions of **34** and methanesulfonic acid (MsOH) form a mixture of species depending on equivalents of acid added (Fig. 4), suggesting acid influences catalyst activity by controlling speciation of Ru intermediates. The acidity of the reaction medium influences both metal-mediated and acid-promoted steps in these reaction sequences.

3.2. Hydrogenation reactions enabled by Lewis acid cocatalysis

3.2.1. Ru-Catalysed hydrogenation of carboxylic acid derivatives. Beller has reported several mild hydrogenations of carboxylic acid derivatives *via* transition-metal and Lewis acid cocatalysis.^{45–48} The substitution of Brønsted acid for Lewis acid was first realized in the hydrogenation of carboxylic acids and esters: the conversion of lactone **35** to ether **36** proceeds using the Ru(acac)₃/triphos and Al(OTf)₃ cocatalysts at relatively moderate

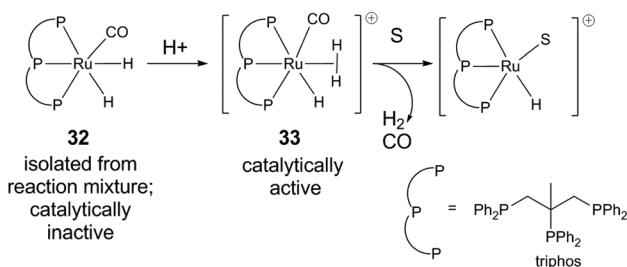


Fig. 3 Catalyst resting state in levulinic acid hydrogenation.⁴³

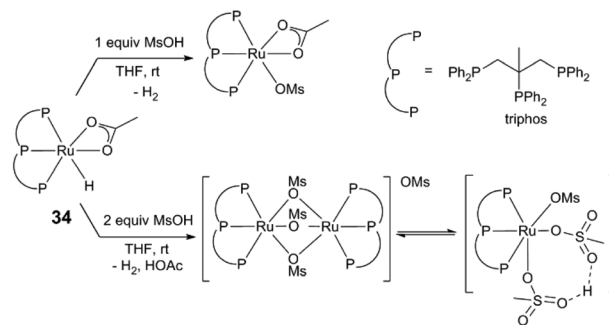
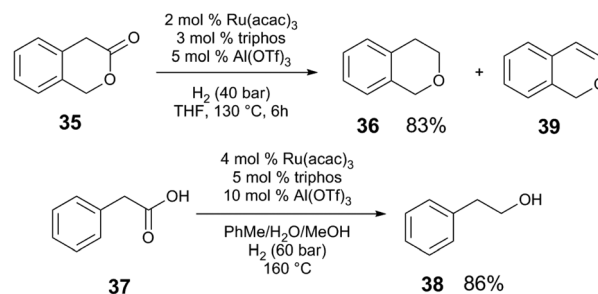


Fig. 4 Reactivity of a Ru(triphos) complex with methanesulfonic acid.⁴⁴

H₂ pressure (15–40 bar).⁴⁵ A similar catalyst mixture converts carboxylic acid **37** to alcohol **38**, although slightly higher pressures of H₂ are necessary (40–60 bar) (Scheme 10).⁴⁶

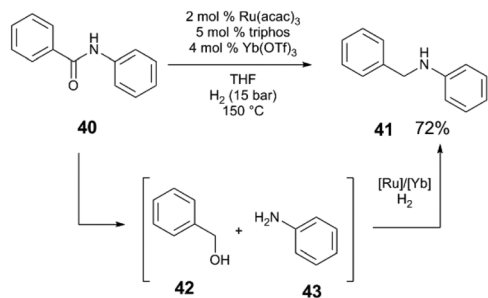
Under lower pressures of H₂, metal triflate cocatalysts greatly outperform Brønsted acids. The hydrogenation of **37** (Scheme 10) does not proceed in the absence of cocatalyst, or with Brønsted acids (MsOH, diphenylphosphate), whereas when Al(OTf)₃ is employed, >99% conversion of **35** is observed with 83% yield of the desired ether product **36**. Although triflic acid (TfOH) also promotes conversion of **35**, poor selectivity of the reaction is observed; a competing elimination from the intermediate acetal provides the enol ether **39** as the major product in 45% yield. Al(OTf)₃ provides much better performance than other Al compounds. Qualitative mechanistic experiments suggest that an off-cycle catalyst resting state is reactivated in the presence of relatively acidic protons, resembling the reactivity of Ru and Brønsted acid cocatalytic systems (section 3.1). The presence of H₂O is important for efficient catalysis; the reaction is suppressed when molecular sieves are added, or when non-polar solvents are used. The authors propose that Al(OTf)₃ is important to generate Brønsted acid *in situ* upon combination with H₂O or alcohols. Like the system reported by Klankermeyer and Leitner, the acid could act to generate the active cationic [RuH⁺] species. Additionally, the weakly-coordinating OTf counteranion of the M(OTf)₃ Lewis acid may play an important role in the reaction, as chloride anions inhibit catalysis.

The Ru(acac)₃/triphos/M(OTf)₃ system also mediates the hydrogenation of secondary amides to amines (Scheme 11) at



Scheme 10 Hydrogenation of esters⁴⁵ (top) and carboxylic acids⁴⁶ (bottom).

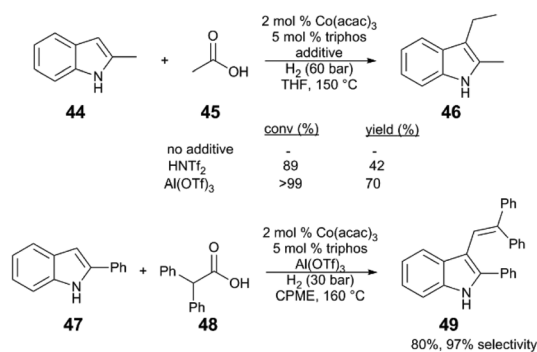
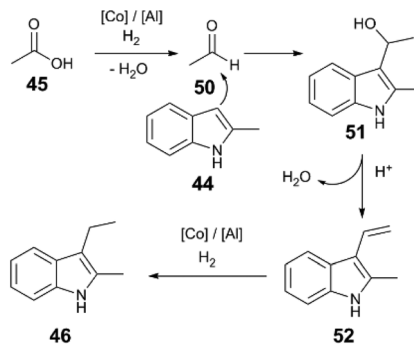


Scheme 11 Hydrogenation of secondary amides.⁴⁷

low pressures of H₂ (5–15 bar).⁴⁷ A screen of acidic additives reveals that in the hydrogenation of amide **40**, Yb(OTf)₃·H₂O cocatalyst provides the highest yield of amine **41** and that again, Lewis acidic metal triflate salts outperform Brønsted acidic cocatalysts under these reaction conditions. The reaction proceeds by initial hydrogenolysis of the amide to benzyl alcohol **42** and aniline **43**, which are observable intermediates. A subsequent condensation reaction between **42** and **43** yields the benzylamine **41**. Control experiments show that both the individual Ru and Yb catalysts are necessary for the condensation reaction to occur, and that H₂, while not necessary for condensation, improves the efficiency of this step.

3.2.2. Co-Catalysed indole alkylation via carboxylic acid hydrogenation. A related example employs a Co(acac)₃/triphos-catalysed tandem carboxylic acid hydrogenation and indole alkylation or alkenylation (Scheme 12).⁴⁸ The reaction only proceeds in the presence of Brønsted or Lewis acid additives. Once again, metal triflate additives provide the best reaction performance, over other Lewis acids (BF₃·Et₂O, B(C₆F₅)₃) or Brønsted acids (HOTf, HNTf₂, MsOH, TfOH). The reaction of indole **44** with acetic acid (**45**) yields the alkylindole **46** in 70% using Al(OTf)₃ as cocatalyst, and in 42% yield using HNTf₂, whereas no conversion is observed in the absence of an acidic cocatalyst. Under similar conditions, reaction of indole **47** with diphenylacetic acid (**48**) yields alkenylindole (**49**) in 80% yield.

A plausible reaction sequence (Fig. 5) starts with Co/Al(OTf)₃-catalysed hydrogenation of acetic acid (**45**) to the respective acetaldehyde (**50**), followed by nucleophilic attack of

Scheme 12 Alkylation of indoles via carboxylic acid hydrogenation.⁴⁸Fig. 5 Proposed mechanism of acetic acid hydrogenation and indole alkylation.⁴⁸

the indole **44** to **51**. Acid-catalysed dehydration of the resulting functionalized indole intermediate **51** generates alkenylated indole **52**; subsequent Co and Al(OTf)₃-catalysed hydrogenation of the alkene yields the desired alkylindole product **46**. Evidence for an alkenylindole intermediate comes from the reaction of α,α-disubstituted carboxylic acid (**48**). Here the major product is alkenylindole **49**, probably because the trisubstituted alkene is unreactive towards successive hydrogenation.

3.2.3. Pd and Lewis acid-catalysed ether hydrogenolysis. Other examples of tandem transition metal and Lewis acid-catalysed hydrogenolysis reactions reveal a distinct role of Lewis acids in promoting C–O bond cleavage.^{49–52} Hydrogenolysis of ether **53** to **54** is achieved with Yb(OTf)₃ and alumina-supported Pd nanoparticles in ionic liquid solvent ([EMIM][OTf], EMIM = 1-ethyl-3-methylimidazolium) (Scheme 13).⁴⁹ The C–O bond cleavage event of **53** to allylphenol **55** is the microscopic reverse of alkene hydroalkoxylation, a reaction catalysed by lanthanide Lewis acids. Indeed, the same catalysts can perform the C–O bond cleavage as well; however, the C–O bond cleavage of **53** is endothermic (ΔH ≈ +14 kcal mol⁻¹). When coupled with Pd-catalysed hydrogenation (ΔH ≈ –25 kcal mol⁻¹) the overall tandem C–O hydrogenolysis becomes exothermic. In this case, the reaction is not accelerated by HOTf, and so the authors propose that Yb(OTf)₃ activates substrate towards C–O bond cleavage, rather than simply generating Brønsted acid *in situ*. The lanthanide metals with smaller ionic radius and greater electrophilicity (*i.e.*, effective charge density) are more effective at promoting the reaction. An experimental screen of lanthanide triflates shows yields correlate with known activation parameters for metal-triflate-catalysed conversion of ethers to enols.⁴⁹

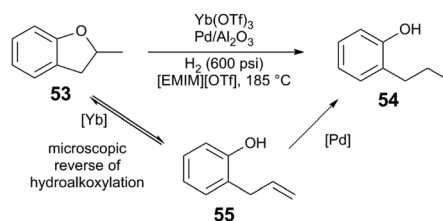
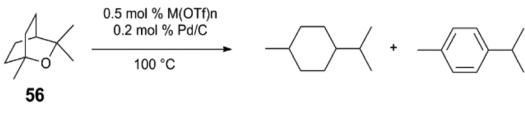
Scheme 13 Hydrogenolysis of ethers.⁴⁹

Table 2 Correlation of ether hydrogenolysis activity and metal triflate effective charge density⁵¹


Acid	Time (min)	Conv. (%)	ρ (eff. charge density)
—	90	—	—
La(OTf) ₃	30	0.2	2.60
Yb(OTf) ₃	30	0.2	2.81
Ce(OTf) ₃	10	5.7	3.44
Sc(OTf) ₃	10	12.4	3.23
Fe(OTf) ₃	10	13.6	3.71
Al(OTf) ₃	10	23.7	3.87
Zr(OTf) ₄	10	33.5	4.29
Hf(OTf) ₄	10	46.0	4.37
HOTf	10	10.4	—

The competency for metal triflates to mediate the key acid-catalyzed C–O bond cleavage step indicates the transition metal Lewis acids are particularly suitable for ether cleavage (Table 2). In the absence of H₂ pressure, the conversion of 1,8-cineole (**56**) is greatest when reacted with 0.5 mol% Zr(OTf)₄ or Hf(OTf)₄ and Pd/C (which has been pre-treated with H₂).⁵¹ Computationally-determined (B3LYP) effective charge density (ρ) of metal triflate Lewis acids tracks with catalytic performance, as determined by conversion and turnover numbers. DFT exploration of the reaction's potential energy surface indicates that C–O bond cleavage of 2-methyltetrahydropyran *via* Yb(OTf)₃ has a higher activation barrier ($\Delta G^\ddagger = +32.4$ kcal mol⁻¹), than when Hf(OTf)₄ is used ($\Delta G^\ddagger = +16.8$ kcal mol⁻¹) – in agreement with experimental observation. The authors propose that the Lewis acid may bind and increase acidity of intermediate alcohols, potentially mitigating side reactions, such as carbocation rearrangement.

Metal triflate Lewis acids are competent cocatalysts to mediate challenging, multi-step hydrogenation reaction sequences catalysed by a variety of different transition metals. In some cases, it is evident that a Lewis acid can promote the formation of a Brønsted acid *in situ*, which may be important to catalyse dehydration steps or other acid-catalysed reactions. It is also evident that Brønsted acids activate catalytic intermediates. As is demonstrated by Pd and metal triflate mediated ether hydrogenolysis, the coupling of two catalyst systems can “leverage” demanding endothermic reactions.

4. Tandem Au(I) catalysis: Lewis acids as Brønsted acids, catalyst activators and reactivators

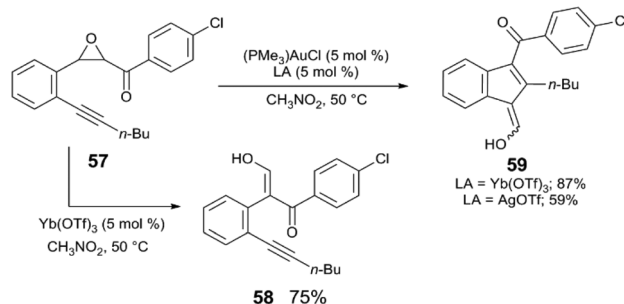
The ability of Lewis and Brønsted acids to form highly-active cationic Au(I) catalysts was noted in the seminal 1998 report by Teles⁵³ on Au-mediated alkyne hydroalkoxylation, a reaction of immense subsequent interest.⁵⁴ Au halide catalyst precursors are typically combined with Ag salts, which are thought to

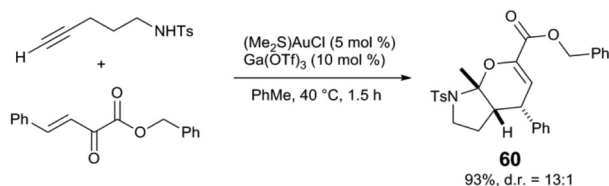
generate catalytically-active cationic Au species. Although the non-innocent role of Ag in such reactions is recognized,⁵⁵ less attention has been afforded to the role of Brønsted or Lewis acids in Au-catalysed reactions.⁵⁶ In similar fashion to the analogy of Ru/Brønsted acid and Ru/Lewis acid cocatalytic systems (sections 3.1 and 3.2), it is useful to consider the potential role of Lewis acids to effect the generation of Brønsted acid *in situ* within the context of Au catalysis (section 4.2). We note that although several Au/Brønsted acid catalysed reactions are known,^{57–61} we present evidence that the action of Lewis acids in some cocatalytic systems are distinct from that of Brønsted acids. Here we summarize recent efforts to understand the mechanism of such cooperative catalytic systems.

4.1. Au and Lewis acid tandem catalysis

First, examples are discussed in which Au and the Lewis acid act synergistically in tandem catalysis. To the best of our knowledge, the first evidence of metal triflate Lewis acids to serve as a catalyst activator in Au-catalysed reactions is the report of Shi,⁶² in which (PMe₃)AuCl and Yb(OTf)₃ catalyse the rearrangement of epoxy alkynes to carbocycles (Scheme 14). In addition to Yb(OTf)₃ acting as an apparent halide abstractor in this reaction, the catalyst is more active when Yb(OTf)₃ is employed rather than when AgOTf is employed. The first step of the reaction involves the ring-opening of epoxy alkyne **57** to the enol alkyne **58**, which is catalysed independently by Yb(OTf)₃ without activation of the alkyne, and the Au-catalysed rearrangement of **57** to the carbocycle **59** occurs in much greater yield with Yb(OTf)₃. The combination of (PMe₃)AuCl and Yb(OTf)₃ generates (PMe₃)Au(OTf) *in situ* – presumably the active form of the catalyst. The authors claim that the mixture of (PMe₃)AuCl and Yb(OTf)₃ provides improved catalytic activity than when (PMe₃)AuCl and AgOTf are used, as well as when pre-formed (PMe₃)Au(OTf) is used under the standard reaction conditions.

Several other synthetic applications have more recently emerged, particularly in cascade reactions where Lewis acids promote steps not catalysed by Au. The groups of Jia and Xu report several synergistic Au and Lewis acid reactions in the synthesis of spirocyclic^{63–65} and fused bicyclic compounds.^{66,67} For example, bicyclic aminal **60** is synthesized *via* a Au-cata-

**Scheme 14** Tandem epoxide ring-opening and cyclisation.⁶²



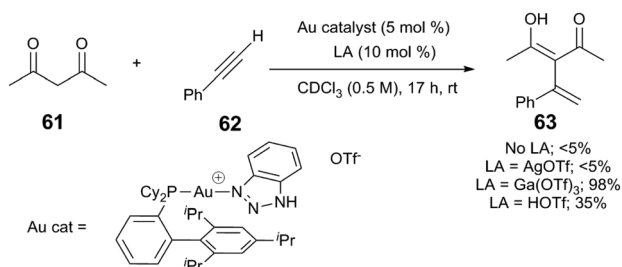
Scheme 15 Tandem intramolecular alkyne hydroamination and inverse electron demand Diels–Alder reaction.⁶⁶

lysed intramolecular alkyne hydroamination followed by an Ga(OTf)₃-catalysed inverse-electron-demand hetero-Diels–Alder cyclisation (Scheme 15).⁶⁶ Analogous Au and Lewis acid tandem reactions are reported to selectively favour spiroaminals⁶³ and spiro-heterocycles⁶⁴ over bicyclic cyclisation patterns. Spiroketals⁶⁵ and fused tricyclic compounds⁶⁷ are also accessible from similar alkyne hydrofunctionalisation/cycloaddition sequences, where the Lewis acid also acts to generate *ortho*-quinonemethides from 2-(hydromethyl)phenol derivatives. Au and Lewis acid-catalysed alkyne hydroamination has also been applied to the synthesis of N-heterocycles such as pyrroles⁶⁸ and indoles.⁶⁹

Lewis acids can also affect Au-mediated steps of the catalytic reaction. In a Au/Ga-cocatalysed intermolecular Nakamura reaction, nucleophilic attack of 1,3-diketone **61** upon phenylacetylene (**62**) yields the alkenylated 1,3-diketone **63** (Scheme 16).⁷⁰ The authors find that (XPhos)Au(TA)(OTf) (TA = 1*H*-benzo[1,2,3]triazole) is only a competent precatalyst in the presence of Ga(OTf)₃; other Lewis acids, such as Zn(OTf)₂, or other cocatalysts such as AgOTf or HOTf, do not cocatalyse the reaction. The authors propose that Ga(OTf)₃ may bind, and therefore, activate the 1,3-dicarbonyl substrate, but may also be critical for the formation of catalytic Brønsted acid.

4.2. Distinguishing between Ag, Brønsted and Lewis acid effects in Au catalysis

Hammond and Xu have comprehensively investigated Brønsted and Lewis acid effects in Au-catalysed reactions.^{71–73} In one study, the effect of cocatalytic additives on Au-catalysed alkyne and allene hydrofunctionalisation reactions was explored.⁷¹ Au catalysis at extremely low catalyst loadings (0.02–0.5 mol%) are strongly influenced by impurities such as halides anions, or basic anions (OH[−] or CO₃^{2−}). The authors



Scheme 16 Alkylation of phenylacetylenes.⁷⁰

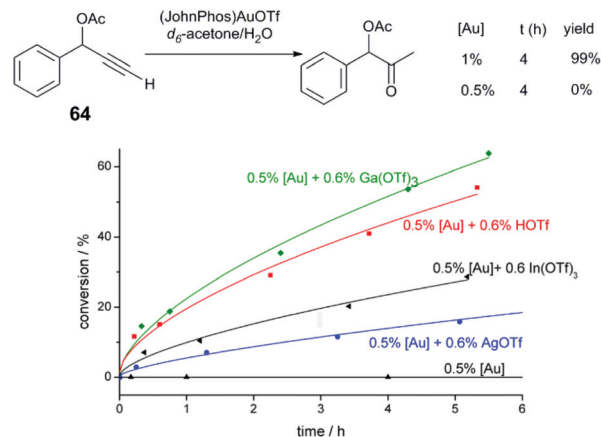


Fig. 6 Effect of acidic additives on the reaction profile of alkyne hydration.⁷² Reprinted with permission. Copyright 2014 American Chemical Society.

explore a series of reactions catalysed under base- and halide-free conditions using precatalysts (JohnPhos)AuOTf (JohnPhos = (2-biphenyl)di-*tert*-butylphosphine) and (PPh₃)AuOTf. In a low-catalyst loading hydration of alkyne **64** (Fig. 6), no catalytic activity is observed in the reaction without co-catalyst; in the reaction with cocatalytic (0.6 mol%) Ga(OTf)₃ or HOTf, the reaction proceeds to high conversion in 12 hours. Ga(OTf)₃ may act as a source of Brønsted acid (HOTf) in this case. But in other reactions, such as the cycloisomerisation of enyne **65** (Fig. 7), cocatalytic HOTf is ineffective, whereas cycloisomerisation proceeds to quantitative yield in 20 min in the presence of In(OTf)₃. On the other hand, in the hydrocarboxylation of hexynoic acid, the reaction is promoted by HOTf, AgOTf, and In(OTf)₃ at an approximately similar rate; here, Ga(OTf)₃ is ineffective.

These examples demonstrate the complexity of catalyst–Lewis acid interactions and their dramatic effect on catalyst

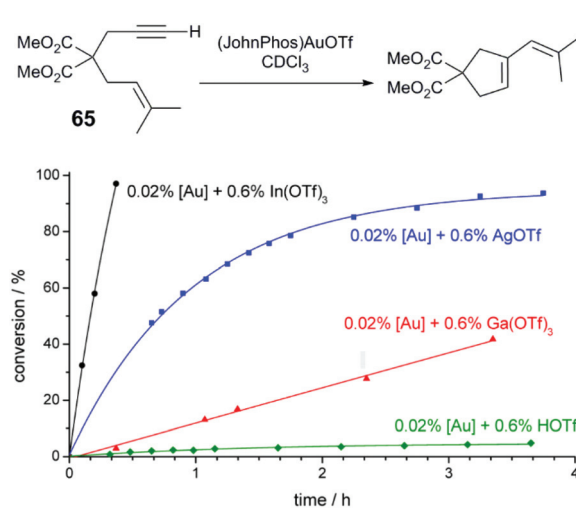


Fig. 7 Effect of acidic additives on the reaction profile of enyne cyclisation.⁷² Reprinted with permission. Copyright 2014 American Chemical Society.



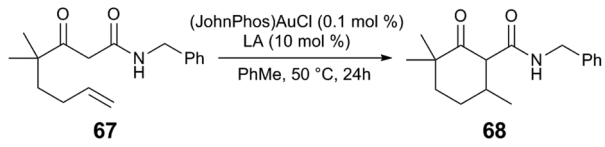
performance. An acidic cocatalyst may regenerate catalytically-active cationic Au deactivated by base or halide impurities. A Brønsted acid-mediated mechanism for catalyst reactivation may proceed by protonolysis of a basic Au species, whereas Lewis acid-mediated catalyst reactivation may involve either anion abstraction or *in situ* generation of HOTf or other Brønsted acids. The authors demonstrate that basic impurities can come from filtration agents or desiccants, such as Celite or 4 Å molecular sieves.

Acid acceleration in Au reactions presumably influence the rate-limiting step in catalysis, but the rate-limiting step in Au catalysis is not always clear.⁷¹ In certain cases protodeauration is believed to be rate-limiting;^{74,75} strong Au–C bonds are generally robust to protonolysis and likely present in on-cycle and off-cycle pathways. Hammond⁷⁵ and Yu⁷⁶ find that protonolysis of heteroarylgold complexes is first order in gold complex and acid, and that the rate depends on the acid pK_a . In protonolysis of heteroarylgold complex **66** the rate is evidently dependent on the acid strength: TfOH yields 100% conversion of **66** in 5 min of reaction, whereas the weaker acid TsOH requires a longer duration (80%, 1 h); HOAc produces no reaction (Scheme 17).⁷⁵ Accelerating turnover-limiting protodeauration is therefore a plausible role for Lewis acids, in addition to decreasing the rate of catalyst deactivation.

As noted previously, Lewis acids can also affect the activation of Au precatalysts by abstracting a coordinating anion. The use of Lewis acids as activators of Au halide precursors has been systematically studied by Gandon and coworkers,^{77–79} who sought alternatives to Ag activation. Ag is thought to form inactive bimetallic Au–Ag⁸⁰ or dimeric Au species,⁸¹ and increase rates of catalyst decomposition; fast, irreversible anion abstraction can actually *slow* catalysis *via* favouring formation of Au(0) or inactive gold species (such as $[L_2Au][X]$).⁷⁷ Decomposition is of special concern in reactions of reducing substrates (alkynes or alkenes) or in reactions requiring elevated temperatures.⁷⁵

Alternative halide abstractors, such as Cu, Zn, In, and Bi Lewis acids, are effective in Au-catalysed hydroalkylation reactions, enyne cyclisations, and other Au catalysis.^{77,78} Unusually low Au loadings are effective in C–C bond forming reactions with Cu cocatalysts. The Au/Cu cocatalyst system also offers the advantage of scalability; for example, the ene- β -ketoamide **67** is transformed into the cyclised product **68** using (L)AuCl and $Cu(OTf)_2$ (80% yield, dr 95 : 5, L = JohnPhos or PPh_3) and

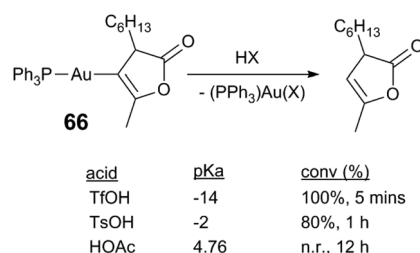
Table 3 Effect of Lewis acids on intramolecular alkene hydroalkylation⁷⁸



Lewis acid	Conv. (%)	Conv. (w/o Au, %)
Sc(OTf) ₃	0	0
Yb(OTf) ₃	0	0
Zn(OTf) ₂	83	0
Al(OTf) ₃	26	16
AlCl ₃	0	0
Ga(OTf) ₃	Trace	12
GaCl ₃	0	0
In(OTf) ₃	100	77
Bi(OTf) ₃	100	38
HOTf	0	0

notably, the reaction only proceeds to <30% conversion when AgOTf is used instead of $Cu(OTf)_2$. Following the speciation of the $(PPh_3)_2AuCl$ precatalyst by ³¹P NMR reveals slow generation of $[(PPh_3)_2Au][OTf]$ upon combination with $Cu(OTf)_2$, presumably *via* unobserved $(PPh_3)_2Au(OTf)$. During catalytic conditions, $Cu(OTf)_2$ may slowly and reversibly abstract the chloride anion from the Au precatalyst, minimising catalyst decomposition by maintaining low concentration of $[LAu][X]$. In a separate report, a screen of Lewis acids at similar reaction conditions (Table 3) indicates that $In(OTf)_3$ and $Bi(OTf)_3$ also promote the hydroalkylation, whereas $Sc(OTf)_3$, $Yb(OTf)_3$, and TfOH are not effective. The Au/LA catalyst system is also useful in Au-catalysed alkyne hydroarylation, enyne cyclisation, and alkyne hydrofunctionalisation reactions.

A Lewis acid can take on numerous possible roles in Au catalysis. The most obvious role is anion abstractor, and sometimes Lewis acids provide improved activity *vs.* the more common Ag activators. The Lewis acid can also generate Brønsted acid *in situ* – thereby affecting Au-centred activation/deactivation pathways, accelerating the turnover-limiting protonolysis of key Au–C intermediates, or initiating acid-catalysed reaction sequences. We note that control experiments are critical when evaluating acid effects in Au catalysis. Several Lewis acids, such as Ga or In compounds, are also π -acids and can sometimes independently catalyse alkyne functionalisation reactions.⁸² Furthermore alkyne functionalisation reactions can also be independently catalysed by Brønsted acids.⁸³



Scheme 17 Protonolysis of an arylgold complex.⁷⁵

5. Enabling transmetalation and reductive elimination with Lewis acids in Pd catalysis

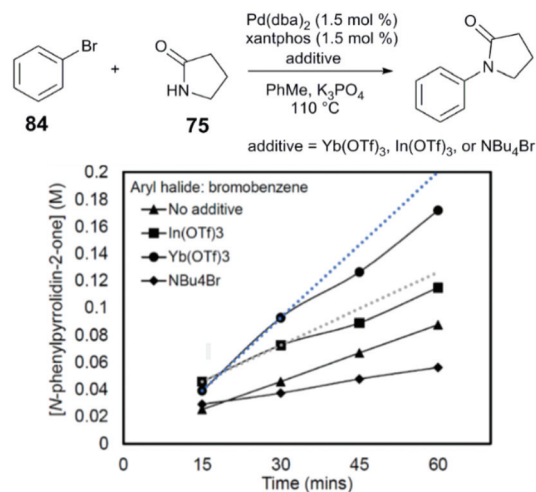
In this section, we will present several examples of Lewis acid additives and their effects in C–C and C–N coupling reactions. Pd coupling reactions are almost always run in the presence of



chloride **80** with **78** catalysed by Pd₂(dba)₃/xantphos yields **78** in only 3% yield. The reaction instead returns >98% yield when Zn(OAc)₂ or Zn(OPiv)₂ is employed as a cocatalyst (60 mol%).

Although the mechanistic proposal by Hartwig and Shen invokes the binding of Lewis acid to a heteroaryl-palladium moiety, this catalyst-Lewis acid interaction is not a requirement for a Lewis acid effect to be observed in C–N coupling reactions. Our group has observed that metal triflate Lewis acids are suitable cocatalysts in Pd catalysis, improving the yield of various *N*-arylamide products.⁸⁹ In a representative example (Scheme 22), the reaction of bromoarene **81** with *N*-methylacetamide (**82**) via Pd(dba)₂/xantphos/Al(OTf)₃ yields the tertiary amide **83** in 89% yield, whereas only 53% yield of **83** is observed in the absence of an Al salt. Based on mechanistic insight and kinetic data, the Lewis acid appears to accelerate the rate-limiting transmetalation step of catalysis. However, deconvolution of key steps of transmetalation is difficult. At the very least, this step includes various reversible pre-equilibria as represented in Fig. 8: (a) halide dissociation from the oxidative addition complex **I**, (b) amide coordination to **II**, (c) dissolution of heterogeneous base (*N*-arylation reactions in the presence of insoluble, inorganic bases can be mass-transfer limited),⁹⁰ and (d) amide deprotonation to yield intermediate **III**.

Measurement of the initial rates of catalysis of the coupling of bromobenzene (**84**) and pyrrolidin-2-one (**78**) indicate that an approximately three-fold acceleration is observed in the presence of Yb(OTf)₃ (1 : 1 Yb : Pd), and that inhibition of catalysis is observed in the presence of exogenous bromide salts (NBu₄Br) (Fig. 9). Our group proposed that the Lewis acid acts to mitigate competitive binding of bromide (a reaction byproduct) and the weakly nucleophilic amide by catalytic halide abstraction from the key Pd intermediate **I**. Indeed, by ³¹P NMR, evidence for the generation of the cationic Pd intermediate [(xantphos)Pd(Ph)]⁺ from the interaction of the oxidative addition complex, (xantphos)Pd(Ph)(Br), with Yb



Scheme 22 *N*-Arylation of a secondary acyclic amide.⁸⁹

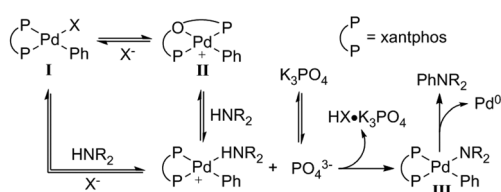


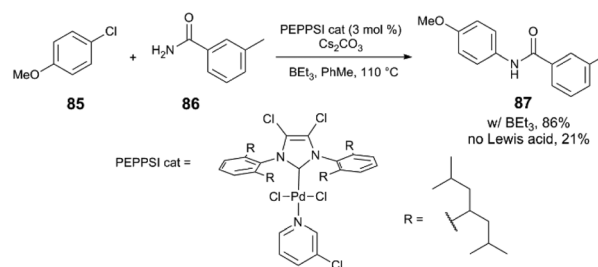
Fig. 8 Proposed mechanism of dehydrohalogenation and amide coordination in Pd-catalysed amide *N*-arylation.⁸⁹ Reprinted with permission. Copyright 2017 American Chemical Society.

Fig. 9 Effect of additives on the initial rate of amide *N*-arylation.⁸⁹ Reprinted with permission. Copyright 2017 American Chemical Society.

(OTf)₃, suggesting that Lewis acids can promote the dissociative pathway in transmetalation represented in Fig. 8.

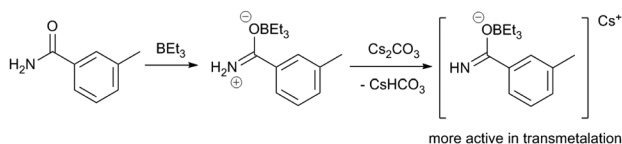
Another example in which a dramatic Lewis acid effect is observed comes from the group of Organ,⁴ where a sterically hindered NHC ligand enables the coupling of aryl halides and primary amides when borane cocatalysts are employed. Unactivated aryl chloride **85** and benzamide **86** react with a PEPPSI-Pd catalyst to yield the secondary amide **87** in quantitative yield with various borane additives (BEt₃, tri(*sec*-butyl) borane, B(C₆F₅)₃), while the product is only obtained in 21% yield in the absence of a borane (Scheme 23). The authors observe different behaviour between the three borane reagents. Whereas alkylboranes undergo autoxidation readily, B(C₆F₅)₃ has stronger B–C bonds and therefore does not undergo immediate reaction with O₂. It is observed that atmospheric contaminants and/or added radical traps affect the catalysis differently depending on which borane is used; for example, reactions that employ BEt₃ do not yield product when the borane is first exposed to air. The authors provide spectroscopic evidence for the formation of borane-amide adducts (Scheme 24), which may be responsible for increasing the nucleophilicity of the amide and thereby facilitating transmetalation.

In these Pd-catalysed reactions, various evidence points to the Lewis acid modulating the reactivity of the key Pd oxidative



Scheme 23 *N*-Arylation of a primary amide.⁴





Scheme 24 Formation of an amidonium boronate complex.⁴

addition intermediates by catalyst-Lewis acid interactions, though Lewis acids of different character are employed (alkylborane, arylborane, zinc salts, or metal triflates, such as $\text{Al}(\text{OTf})_3$ or $\text{Yb}(\text{OTf})_3$) and therefore different possible modes of action of the Lewis acid may be operative. Based on the stoichiometric study by Shen and Hartwig, alkylboranes may increase the rate of reductive elimination *versus* the rate of amido protonolysis. Based on the works of our group and Organ, where delivery of the nitrogen nucleophile to Pd appears to be turnover-limiting, binding of amide may require sequestration of halide, or the generation of a more nucleophilic boron-amidate complex.

6. Conclusions

Lewis acid cocatalysts influence a diverse array of transition metal-catalysed reactions. Through mechanistic insight from a variety of studies, it appears that the predominant roles of the Lewis acid in the described transformations are as follows: (1) to form a Lewis acid base-adduct of the substrate to enable a challenging bond-cleavage event or to provide a thermodynamic driving force for a bond-cleavage event, (2) to modulate the $\text{p}K_{\text{a}}$ of the reaction medium, effect the controlled release of a Brønsted acid *in situ*, or facilitate proton transfer by some means, (3) to affect the coordination sphere of catalyst precursors or key catalyst intermediates by anion abstraction, and in doing so promote catalyst activation, reactivate off-cycle catalyst species, or accelerate slow organometallic elementary steps. In some cases, parametrisation or spectroscopic study has enabled insight into the behaviour of Lewis acidic species. Further mechanistic insight and novel experimental means of Lewis acid parameterisation are crucial for further application and rational design of cocatalytic systems.

Lewis acid additives can provide more active or selective catalysts for existing processes, or enable orthogonal reactivity of catalytic reactions by the Lewis acid-mediated interception of key intermediates. Thus, further development in this area will impact new and existing chemistries alike, and we expect Lewis acids will figure prominently in many further catalytic applications. Additional work in understanding and controlling Lewis acid/organometallic interactions will be instrumental in offering new opportunities in homogeneous catalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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