Evidence That Protons Can Be the Active Catalysts in Lewis Acid Mediated Hetero-Michael Addition Reactions

Tobias C. Wabnitz, Jin-Quan Yu, and Jonathan B. Spencer*[a]

Abstract: The mechanism of Lewis acid catalysed hetero-Michael addition reactions of weakly basic nucleophiles to α,β-unsaturated ketones was investigated. Protons, rather than metal ions, were identified as the active catalysts. Other mechanisms have been ruled out by analyses of side products and of stoichiometric enone–catalyst mixtures and by the use of radical inhibitors. No evidence for the involvement of π-olefin–metal complexes or for carbonyl–metal-ion interactions was obtained. The reactions did not proceed in the presence of the non-coordinating base 2,6-di-*tert*-butylpyridine. An excellent correlation of catalytic activities with cation hydrolysis constants was obtained. Different reactivities of mono- and dicarbonyl substrates have been rationalised. A ^{1}H NMR probe for the assessment of proton generation was established and Lewis acids have been classified according to their propensity to hydrolyse in organic solvents. Brønsted acid-catalysed conjugate addition reactions of nitrogen, oxygen, sulfur and carbon nucleophiles are developed and implications for asymmetric Lewis acid catalysis are discussed.

Keywords: Brønsted acids · enones · hydrolysis · Lewis acids · Michael addition

Introduction

Michael and hetero-Michael addition reactions are amongst the most important bond forming strategies for both carbon–carbon and carbon–heteroatom bonds in organic chemistry. The first reports of hetero-Michael addition reactions date back to 1874 and 1878, when Sokoloff and Latschinoff observed the addition of ammonia to mesityl oxide and Loydl described the reaction of sodium hydroxide with fumaric acid;[1] even before the discovery of the actual Michael addition of carbon nucleophiles by Komnenos in 1883 and the studies of Michael in 1887.[2]

Normally, either the donor or the acceptor component need to be activated in hetero-Michael addition reactions. The classical method to achieve this has been deprotonation of the nucleophile with strong bases. In order to perform the reaction under conditions more compatible with other functional groups, alternative methodologies have been developed. Important advances have been made with Lewis acid catalysts, which activate the acceptor components and allow hetero-Michael addition reactions to proceed under much milder conditions.

Due to the importance of β-amino carbonyl moieties in natural product chemistry and in drug development, syntheses of these compounds by aza-Michael addition reactions have received considerable attention.[3] Lewis acid catalysts based on lanthanide triflates, $FeCl_3$, $InCl_3$, $CeCl_3$/NaI, and platinum group metals have been used and asymmetric versions with chiral complexes of main-group and transition-metal cations have been reported.[4,5] Recently, significant advances in metal-salt-catalysed, intermolecular aza-Michael addition reactions of weakly basic nitrogen nucleophiles such as carbamates, oxazolidinones and oximes to α,β-unsaturated ketones were reported by Kobayashi et al., Banik and Srivastava and by our group. $[Pd(CH_3CN)_2Cl_2]$, $[Pd(CH_3CN)_4](BF_4)_2$,[6] $Cu(OTf)_2$,[7] $Bi(NO_3)_3$,[8] and noble metal chlorides[9] such as $RhCl_3 \cdot 3H_2O$, $ReCl_5$, $PtCl_4 \cdot 5H_2O$, and AuCl were found to be efficient catalysts for these transformations under very mild conditions. However, conclusive evidence for the reaction mechanism has not been presented.

Lewis acid catalysed hetero-Michael addition reactions of alcohols and thiols under nonbasic conditions have also been reported. Achiral oxa-Michael addition reactions mediated by Pd^{II} and Zn^{II} have been described,[10,11] and addition reactions of sulfur nucleophiles have been achieved both with achiral catalysts such as $InBr_3$[12] and $Bi(NO_3)_3$[8] and chiral transition-metal complexes.[13]

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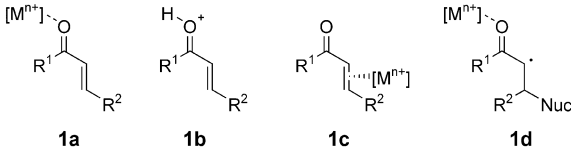
In two very recent communications we described simple protocols for the hetero-Michael addition reactions of nitrogen, oxygen and sulfur nucleophiles mediated by homogeneous[14] or heterogeneous[15] protic acid catalysts. These methods were very general and a wide variety of nucleophiles and acceptors could be used.

We were intrigued that catalysts ranging from $[Pd(CH_3CN)_2Cl_2]$ over noble metal chlorides and $Bi(NO_3)_3$ to strong Brønsted acids could be used for very similar reactions and we suspected common mechanistic principles for all transformations. Herein, we report the first comprehensive investigation of the reaction mechanism of catalytic hetero-Michael addition reactions with weakly basic nucleophiles.

Results and Discussion

Four principal mechanisms can be envisaged for the mode of catalyst action in conjugate addition reactions to enones under nonbasic conditions. Lewis acid mediated activation of the enone towards nucleophilic addition can occur by formation of carbonyl–metal-ion complexes such as **1a**. Similarly, the carbonyl oxygen can be protonated by Brønsted acids, leading to **1b**. Direct interactions between olefinic double bonds and transition-metal catalysts can furnish the activated complexes **1c**. Finally, coordination of metal ions is known to facilitate attack of free radicals on enones, leading to the intermediates **1d**.

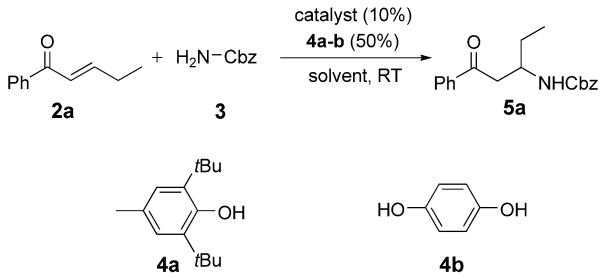


1a **1b** **1c** **1d**

Free radical conjugate addition reactions have been used to create carbon–carbon and carbon–sulfur bonds,[16] but applications of nitrogen nucleophiles are not known. To determine if single-electron-transfer processes are involved, aza-Michael addition reactions of benzyl carbamate (Cbz-NH_2, **3**) and the enone **2a** were carried out in the presence of radical inhibitors such as 3,5-di-tert-butyl-4-hydroxytoluene (BHT) (**4a**) and hydroquinone (**4b**) (Table 1). In agreement with results obtained by Kobayashi et al. for $PtCl_4 \cdot 5H_2O$,[9] reaction rates and yields were virtually unchanged when $[Pd(CH_3CN)_4](BF_4)_2$ and $In(OTf)_3$ were used in the presence or absence of the inhibitors (runs 1–4). Dramatic rate accelerations observed with $Cu(OTf)_2$ (runs 5–7) were due to reduction of Cu^{II} to Cu^{I} by the phenolic inhibitors,[17] accompanied by the liberation of one equivalent of catalytically active triflic acid (TfOH).[14,18] The involvement of free radicals in the catalytic cycle is therefore very unlikely.

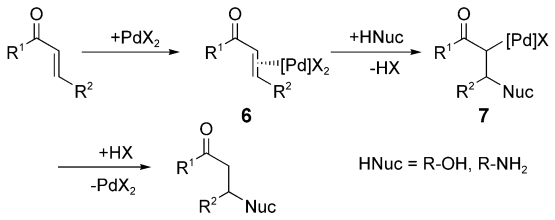
A transition-metal-catalysed pathway proceeding via the π-complexes and α-palladated intermediates **6** and **7,** respectively, was postulated for Pd^{II}-mediated oxa- and aza-Michael addition reactions (Scheme 1).[6,10]

Table 1. Aza-Michael addition reactions in the presence of radical inhibitors.



2a **3** **5a** **4a** **4b**

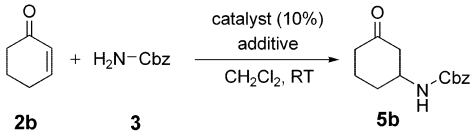
Run	Catalyst	Solvent	Inhibitor	t[h]	Yield[%]
1	$[Pd(CH_3CN)_4](BF_4)_2$	CH_2Cl_2	–	7	97
2	$[Pd(CH_3CN)_4](BF_4)_2$	CH_2Cl_2	**4a**	7	93
3	$In(OTf)_3$	CH_3CN	–	0.5	97
4	$In(OTf)_3$	CH_3CN	**4b**	0.5	94
5	$Cu(OTf)_2$	CH_3CN	–	3	99
6	$Cu(OTf)_2$	CH_3CN	**4a**	0.25	96
7	$Cu(OTf)_2$	CH_3CN	**4b**	0.25	94



Scheme 1. π-Activation of enones by Pd^{II}.

The crucial step in this sequence is the protonolytic cleavage of the palladium–carbon bond. This step is known to be accelerated by phosphine ligands on palladium, the presence of excess halide ions or weak acids.[19] However, the aza-Michael reaction of the carbamate **3** with the enone **2b**, which can be catalysed by $[Pd(CH_3CN)_2Cl_2]$, was completely shut down when $[Pd(PPh_3)_2Cl_2]$ was used or LiCl was added, and no increase in reaction rate was observed in the presence of trifluoroacetic acid (TFA) (Table 2).[14,18]

Table 2. Pd^{II}-catalysed aza-Michael addition reactions under different conditions.

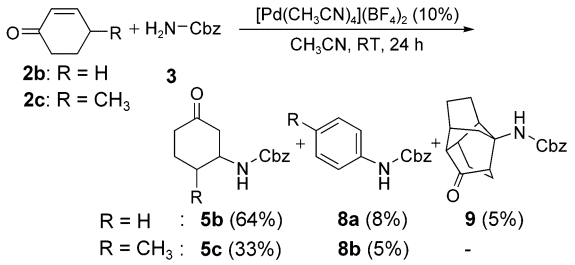


2b **3** **5b**

Run	Catalyst	Additive	t[h]	Yield[%]
1	$[Pd(CH_3CN)_2Cl_2]$	–	24	66
2	$[Pd(PPh_3)_2Cl_2]$	–	48	–
3	$[Pd(CH_3CN)_2Cl_2]$	LiCl (200%)	48	–
4	$[Pd(CH_3CN)_2Cl_2]$	TFA (20%)	24	64

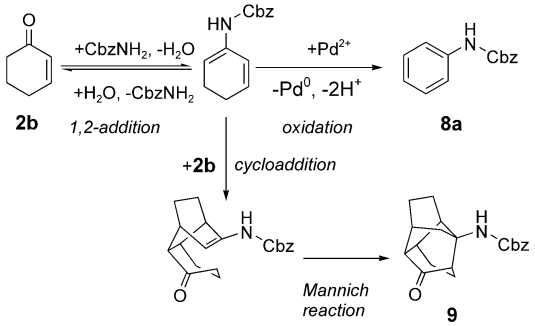
Careful analyses of the $[Pd(CH_3CN)_4](BF_4)_2$-catalysed aza-Michael addition reactions to the cyclohexenones **2b**,**c** in CH_3CN[20] revealed that small quantities of the anilines **8a**,**b** and the tetracyclic compound **9** were formed as side

products (Scheme 2), supporting reaction pathways involving catalytic activation of the carbonyl group. The anilines **8a**,**b** can be formed through 1,2-addition of benzyl carbamate to the acceptor and subsequent oxidation of the enamines by Pd^{II}, as recently demonstrated by Saito et al.[21]



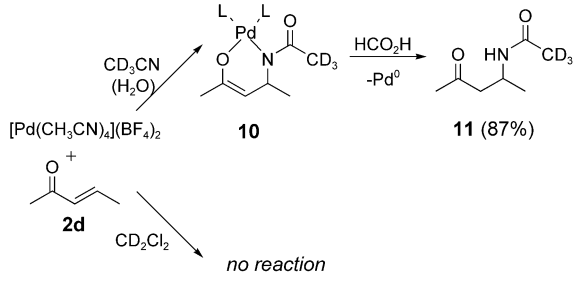
Scheme 2. Formation of side products in the Pd^{II}-catalysed aza-Michael addition reactions.

The structure of the tetracyclic compound **9** was confirmed by X-ray crystallography.[22] The formation of this product is also likely to be initiated by 1,2-attack on the carbonyl group, followed by Diels–Alder (or stepwise conjugate addition reactions) and intramolecular Mannich reactions (Scheme 3).



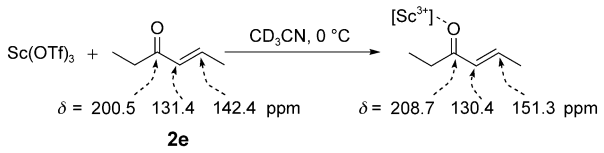
Scheme 3. Postulated routes of side product formation in Pd^{II}-catalysed aza-Michael addition reactions of cyclohexenones.

Attempts to detect the postulated complexes **6** were also made by NMR analysis of stoichiometric mixtures of $[Pd(CH_3CN)_4](BF_4)_2$ and (*E*)-pent-3-en-2-one (**2d**). No substrate–catalyst complexes were detected in CD_2Cl_2. In CD_3CN, a slow Ritter reaction of the enone took place without prior complex formation (Scheme 4). The precise structures of the intermediates could not be determined and chelate complexes such as **10** are tentatively proposed based on the data available. Decomplexation by reduction of Pd^{II} with formic acid gave **11** as the only product.[23,24] None of these results provided evidence for catalytic activation of enones through coordination to the olefinic double bond.



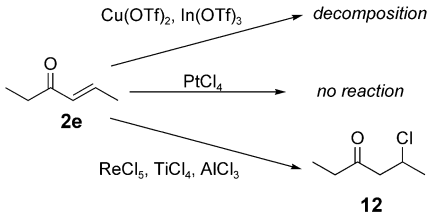
Scheme 4. Stoichiometric enone–Pd^{II} interactions.

Stoichiometric mixtures of other metal salts and enones were also analysed by NMR spectroscopy. $Sc(OTf)_3$, which is a strong, oxophilic Lewis acid but a poor catalyst for the aza-Michael addition reactions of carbamates, did form complexes with the enone **2e** and significant changes in ^{13}C chemical shifts of the enone were detected (Scheme 5). In



Scheme 5. ^{13}C NMR analysis of enone–Sc^{III} complexes.

contrast, when $Cu(OTf)_2$ or $In(OTf)_3$ and the enone **2e** were mixed, no complexes were observed and slow, unselective condensation reactions occurred. Neither complex formation nor decomposition was detected with $PtCl_4$. When $ReCl_5$ was used, release of HCl led to the formation of the β-chloroketone **12**. The same reaction took place when the catalytically inactive chlorides $TiCl_4$ and $AlCl_3$ were used (Scheme 6).

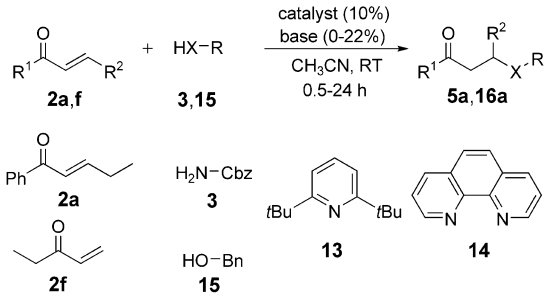


Scheme 6. Enone–metal-salt interactions in CD_3CN at 0 °C.

These NMR experiments did not reveal carbonyl/Lewis acid interactions for active catalysts, but showed that Brønsted acids can be generated. Therefore, investigations aimed at separating Lewis and Brønsted acidity were carried out with the weak base 2,6-di-*tert*-butylpyridine (**13**), which only binds to protons and is unable to coordinate to metal ions due to the bulky *tert*-butyl groups.[25] In the presence of the pyridine **13**, none of the active metal salt catalysts reported to date[6–9] were able to induce conversion in the aza-Michael addition of benzyl carbamate (**3**) to the enone **2a** (Table 3, runs 1–11).

These results strongly suggest that the presence of Brønsted acids is crucial for the reaction. As the release of more than one equivalent of protons per unit Lewis acid is possible through hydrolysis, increased amounts of base **13** were required to suppress the reaction with the easily hydrolysable salts $Fe(ClO_4)_3 \cdot 9H_2O$ and $In(OTf)_3$ (runs 10 and 11). Slow conversion was observed when stoichiometric amounts of dibasic phenanthroline (**14**) were present as a ligand to

Table 3. Inhibition of the metal-salt-catalysed aza- and oxa-Michael addition reactions by nitrogen bases.

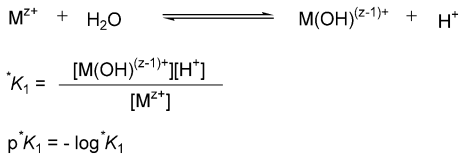


Run	Enone	RXH	Catalyst	Base (amount)	Product	Yield [%]
[a]	**2a**	**3**	MX_n	–	**5a**	80–99
1[b]	**2a**	**3**	$[Pd(CH_3CN)_2Cl_2]$	**13** (11%)	–	–
2	**2a**	**3**	$[Pd(CH_3CN)_4](BF_4)_2$	**13** (11%)	–	–
3	**2a**	**3**	$Cu(OTf)_2$	**13** (11%)	–	–
4	**2a**	**3**	$RhCl_3 \cdot 3H_2O$	**13** (11%)	–	–
5	**2a**	**3**	$ReCl_5$	**13** (11%)	–	–
6	**2a**	**3**	$PtCl_4$	**13** (11%)	–	–
7	**2a**	**3**	AuCl	**13** (11%)	–	–
8	**2a**	**3**	$AuCl_3$	**13** (11%)	–	–
9	**2a**	**3**	$Bi(NO_3)_3 \cdot 5H_2O$	**13** (11%)	–	–
10	**2a**	**3**	$Fe(ClO_4)_3 \cdot 9H_2O$	**13** (22%)	–	–
11	**2a**	**3**	$In(OTf)_3$	**13** (22%)	–	–
12[c]	**2a**	**3**	[d]	**14** (10%)	**5a**	45
13[b]	**2f**	**15**	$Pd(CH_3CN)_2Cl_2$	–	**16a**	85
14[b]	**2f**	**15**	$Pd(CH_3CN)_2Cl_2$	**13** (11%)	–	–

[a] Yields with catalysts in runs 1–11 ranged from 80% ($ReCl_5$) to 99% ($Cu(OTf)_2$) in the absence of bases. [b] In CH_2Cl_2. [c] In CH_3NO_2. [d] $[Pd(phenanthroline)(CH_3CN)_2](BF_4)_2$ was used (no further base added).

Pd^{II}, confirming the Brønsted basic role of the pyridine **13** as an inhibitor (run 12). The identical effect of **13** was observed in Pd^{II}-catalysed oxa-Michael addition reactions of benzyl alcohol (**15**) to the enone **2f** (runs 13 and 14).

For metal salts with weakly coordinating anions, the generation of Brønsted acids through cation hydrolysis in aqueous solution is well-documented and hydrolysis constants ${}^*K_1$ have been obtained for ions of almost all metals in the periodic table (Scheme 7).[26,27] Surprisingly, no systematic studies of catalyst hydrolysis are available for reactions in organic solvents, despite the important implications for Lewis acid mediated transformations.[28]



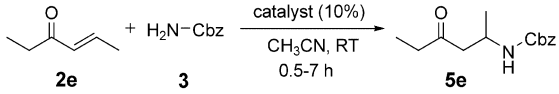
Scheme 7. Description of hydrolysis equilibria using the notation of Sillén and Martell (see ref. [27]).

The aza-Michael addition of benzyl carbamate (**3**) to the enone **2e** was carried out with Lewis acids containing highly cationic metal parts and catalytic activities and hydrolysis constants were compared (Table 4).[26,29–33]

Cations with $p^*K_1 \leq 7.3$ were found to release sufficient amounts of acid to catalyse the reaction and good yields were obtained with Al^{III}, V^{III}, Cr^{III}, $Fe^{II/III}$, Cu^{II}, ZrO^{2+}, Pd^{II}, In^{III}, Hg^{II} and Bi^{III}. In all cases, the reactions were completely suppressed in the presence of the pyridine **13** (22%). Poor conversion was observed with cations in the borderline region $p^*K_1 = 7.7$–9.0 (Zn^{II}, Pb^{II}), while no reaction took place with the weakly hydrolysing cations Li^{I}, Na^{I}, Mg^{II}, Mn^{II}, Co^{II}, Ni^{II}, Ag^{I}, and Cd^{II} ($p^*K_1 > 9.0$). Rare earth triflates induced slightly less conversion than predicted from their hydrolysis constants. No reaction was observed with La^{III} and Sm^{III} and only slow conversion took place with Sc^{III} and Yb^{III}. Apart from these cases, an excellent correlation of p^*K_1 and catalytic activity was obtained.

As p^*K_1 values are only meaningful in aqueous solutions, the presence of protons in organic solutions was verified spectroscopically for all Lewis acids used. The wide separation of ^1H chemical shifts of the pyridine **13** and its conjugated acid **17** allowed the extent of proto-

Table 4. Aza-Michael addition reactions with cationic catalysts.

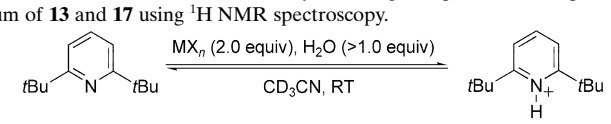


Run	Catalyst	t [h]	Yield	p^*K_1[a]
1	$Li(OTf)$	7	–	13.7
2	$NaClO_4 \cdot H_2O$	7	–	14.6
3	$Mg(ClO_4)_2$	7	–	11.4
4	$Al(ClO_4)_3$	5	93	5.3[b]
5	$Sc(OTf)_3$	7	42	4.8[c]
6	$V(ClO_4)_3 \cdot nH_2O$	5	79	2.4
7	$Cr(ClO_4)_3 \cdot 6H_2O$	5	76	4.0
8	$Mn(ClO_4)_2 \cdot 6H_2O$	7	–	10.6
9	$Fe(ClO_4)_2 \cdot 6H_2O$	7	92	7.1[d]
10	$Fe(ClO_4)_3 \cdot 9H_2O$	1	93	2.7[e]
11	$Co(BF_4)_2 \cdot 6H_2O$	7	–	9.7[d]
12	$Ni(ClO_4)_2 \cdot 6H_2O$	7	–	9.9[d]
13	$Cu(CH_3CN)_4PF_6$	7	–	–[f]
14	$Cu(OTf)_2$	1	81	7.3
15	$Zn(BF_4)_2 \cdot nH_2O$	7	18	9.0
16	$ZrO(ClO_4)_2 \cdot 8H_2O$	2	94	5.1[g]
17	$Pd(CH_3CN)_4(BF_4)_2$	1	76	1.6
18	$AgClO_4 \cdot H_2O$	7	–	11.7
19	$Cd(ClO_4)_2 \cdot nH_2O$	7	–	10.1
20	$In(OTf)_3$	0.5	94	4.0
21	$Sn(OTf)_2$	1	94	3.4[d]
22	$La(OTf)_3 \cdot nH_2O$	7	–	8.5
23	$Sm(OTf)_3$	7	–	7.9
24	$Yb(OTf)_3$	7	20	7.7
25	$Hg(ClO_4)_2 \cdot 3H_2O$	2	91	2.4
26	$Pb(ClO_4)_2 \cdot 3H_2O$	7	16	7.9[h]
27	$Bi(OTf)_3$	0.5	94	1.6

[a] Unless otherwise noted, values were taken from ref. [29] and ref. [26] [b] See ref. [30] [c] See ref. [31] [d] Reported ${}^*K_1$ for Fe^{II}, Co^{II}, Ni^{II}, Sn^{II} vary dramatically; ref. [29] [e] See ref. [32] [f] ${}^*K_1$ immeasurably low. See ref. [26] [g] p^*K_3 given (for $Zr(OH)_3^+ + H^+$). [h] See ref. [33]

nation to be determined easily in the presence of metal salts (Table 5).[34] It was confirmed that protons were liberated from all good catalysts in the presence of one or more equivalents of water (**17**:**13** > 10:1). Without exception, metal salts that did not hydrolyse (**17**:**13** < 1:10) failed to induce conversion in the aza-Michael addition reactions. Notably, protons were released from $[Pd(CH_3CN)_2Cl_2]$ in

Table 5. Brønsted acid detection by assessing the protonation equilibrium of **13** and **17** using ^{1}H NMR spectroscopy.



13 **17**

Extent of protonation	Metal salts
17:**13** > 10:1	$AlCl_3$, $Al(ClO_4)_3$, $Sc(OTf)_3$, $TiCl_4$, $V(ClO_4)_3{\cdot}n\,H_2O$, $Cr(ClO_4)_3{\cdot}6\,H_2O$, $Fe(ClO_4)_2{\cdot}6\,H_2O$, $Fe(ClO_4)_3{\cdot}9\,H_2O$, $Cu(OTf)_2$, $ZrO(ClO_4)_2{\cdot}8\,H_2O$, $RhCl_3{\cdot}3\,H_2O$, $[Pd(CH_3CN)_4](BF_4)_2$, $In(OTf)_3$, $Sn(OTf)_2$, $Sm(OTf)_3$, $Yb(OTf)_3$, $ReCl_5$, $PtCl_4$, $AuCl$[a], $AuCl_3$, $Hg(ClO_4)_2{\cdot}3\,H_2O$, $Pb(ClO_4)_2{\cdot}3\,H_2O$, $Bi(OTf)_3$, $Bi(NO_3)_3{\cdot}5\,H_2O$
equilibrium	$Co(BF_4)_2{\cdot}6\,H_2O$, $Zn(BF_4)_2{\cdot}n\,H_2O$, $[Pd(CH_3CN)_2Cl_2]$[b], $[Pd(phenanthroline)(CH_3CN)_2](BF_4)_2$[c], $La(OTf)_3$
17:**13** < 1:10	$Li(OTf)$, $NaClO_4{\cdot}H_2O$, $Mg(ClO_4)_2$, $Mn(ClO_4)_2{\cdot}6\,H_2O$, $Ni(ClO_4)_2{\cdot}6\,H_2O$, $[Cu(CH_3CN)_4]PF_6$, $Pd(OAc)_2$, $[Pd(CH_3CN)_2Cl_2]$, $AgClO_4{\cdot}H_2O$, $Cd(ClO_4)_2{\cdot}n\,H_2O$

[a] 6.0 equiv used. [b] Suspension in CD_2Cl_2. [c] In CD_3NO_2.

CD_2Cl_2, but not in CD_3CN, in which hydrolysis was hindered due to solvation. This coincides with the observed catalytic activity of $[Pd(CH_3CN)_2Cl_2]$.[35] These experiments also confirmed the ability of rare earth triflates to generate acid, but due to their high affinity to carbonyl groups even in the presence of water, hydrolysis is minimised in catalysis.[36] As expected, $AlCl_3$ and $TiCl_4$ are also readily hydrolysed. However, these salts failed to catalyse the aza-Michael addition reactions due to competitive conjugate addition of HCl (Scheme 6).

A common feature of all active metal salt catalysts is the generation of both protons and weakly nucleophilic counter ions in solution. Catalytically active metal chlorides are able to form complex acids with defined pK_a values, for instance *trans*-$[PtCl_4(H_2O)_2]$ (pK_a = 2.64),[37] $[AuCl_3(H_2O)]$ (pK_a = 2.7), $[RhCl_3(H_2O)_3]$ (pK_a = 4.8)[27] and $[PdCl_2(H_2O)_2]$ (pK_a = 2.1).[29] Re^V can form stable, weakly basic oxohalide complexes such as $[ReCl_4O]^-$.[38] The involvement of these or similar species in $ReCl_5$-mediated aza-Michael addition reactions explains how active acid catalysts can be generated, while yields are reduced due to competitive conjugate addition of HCl (Scheme 3 and Table 3).[39] Although electron-donating ligands reduce the propensity of cations to hydrolyse, diamine–Pd^{II} complexes can still generate acid and a pK_a value of 4.7 has been reported for $[Pd(bipyridine)(H_2O)_2]^{2+}$.[29] AuCl is the only catalyst that cannot directly liberate a Brønsted acid through hydrolysis. However, in the absence of stabilising ligands, AuCl disproportionates in solution, furnishing Au^0 and hydrolysable $AuCl_3$.[40,41]

The origin of water required for hydrolysis must also be addressed. Water can be present as residual moisture or can be released from heteroatom nucleophiles and carbonyl compounds through imine condensation (Scheme 3), or acetal/thioacetal formation. As these reversible processes occur easily under nonbasic conditions, it is virtually impossible to perform the hetero-Michael addition reactions described in the strict absence of water. In addition, in situ drying agents such as molecular sieves led to irreproducible results and could not be used for mechanistic studies as they are known not only to retain water, but also to exchange ions and neutralise acids.[42]

The important aspect of water content was therefore studied by kinetic experiments with Lewis acid catalysts and variable amounts of water. The addition of up to two equivalents of water with respect to the catalyst led to a significant rate increase in the $[Pd(CH_3CN)_4](BF_4)_2$-catalysed aza-Michael addition of the carbamate **3** to the enone **2a** in CD_3CN (Figure 1). Due to its Brønsted basic properties, increased amounts of water caused the reaction to slow down. The same relationship between water content and reaction rate was observed with $PtCl_4$ and also with SbF_5, which forms strongly Brønsted acidic $SbF_5(H_2O)$ upon hydrolysis.[18,43] The rate decrease caused by the action of water as a Brønsted base was also detected with the acid catalyst $HBF_4{\cdot}OMe_2$.[18]

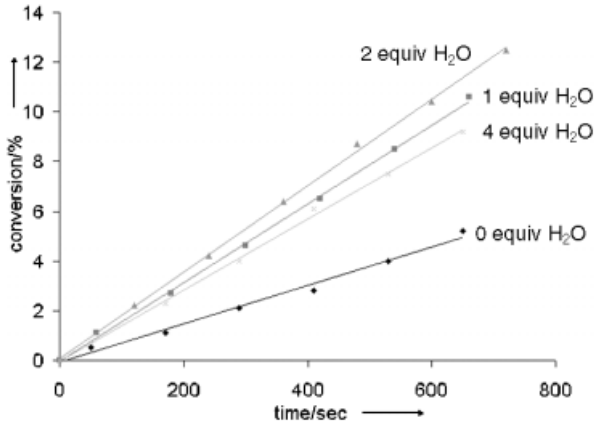
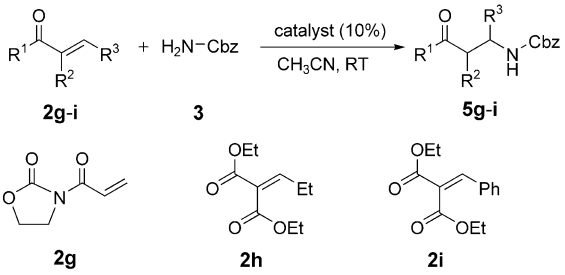


Figure 1. Initial rates (and linear best fits) of $[Pd(CH_3CN)_4](BF_4)_2$-catalysed aza-Michael addition reactions of **3** to **2a** in the presence of varying amounts of water in CD_3CN (15% catalyst).

In a similar manner, other molecules with oxygen functionalities can act as Lewis or Brønsted bases. Earlier studies revealed that no or only reactions takes place when the acid-catalysed aza-Michael addition is carried out in THF, diethyl ether, acetone or ethyl acetate, whereas the reaction is faster in acetonitrile, dichloromethane, and nitromethane.[14]

Dicarbonyl acceptors, such as alkylidene malonates and enoyl oxazolidinones, are known to coordinate more strongly to oxophilic metal ions bearing multiple charges than to protons,[44] forming conformationally rigid catalyst–substrate complexes. Both Brønsted and Lewis acids such as Tf_2NH and $Yb(OTf)_3$ were suitable catalysts for the aza-Michael addition of benzyl carbamate (**3**) to the acceptors **2g** and **h** (Table 6, runs 1–4). However, Tf_2NH and hydrolysable

Table 6. Aza-Michael addition of benzyl carbamate (**3**) to dicarbonyl acceptors.



Run	Acceptor	Catalyst	Product	*t* [h]	Yield [%]
1[a]	**2g**	Tf_2NH[d]	**5g**	72	49
2[a]	**2g**	$Yb(OTf)_3$	**5g**	48	21
3[a]	**2h**	Tf_2NH	**5h**	12	91
4[a]	**2h**	$Yb(OTf)_3$	**5h**	12	87
5	**2i**	Tf_2NH	–	48	–
6	**2i**	$Cu(OTf)_2$	**5i**	48	3
7	**2i**	$In(OTf)_3$	**5i**	48	19
8	**2i**	$Yb(OTf)_3$	**5i**	12	51
9[b]	**2i**	$Yb(OTf)_3$	**5i**	12	21
10[c]	**2i**	$Yb(OTf)_3$	**5i**	48	38

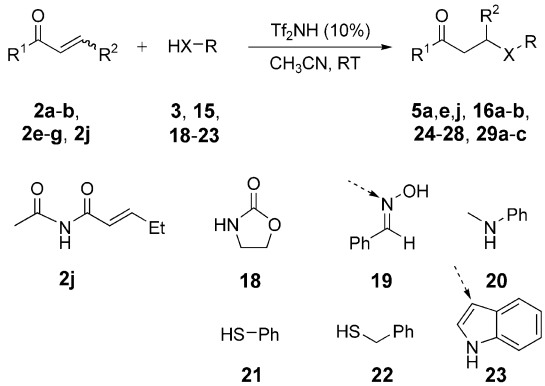
[a] At −20 °C. [b] 2,6-Di-*tert*-butylpyridine (**13**, 11 %) was added. [c] In THF. [d] Tf_2NH = bis(trifluoromethanesulfon)imide.

metal salts such as $Cu(OTf)_2$ or $In(OTf)_3$ turned out to be poor catalysts when benzylidene malonate **2i** was used (runs 5–7). $Yb(OTf)_3$-mediated reactions with **2i**, on the other hand, proceeded even in the presence of the pyridine **13** and THF; this rules out background proton catalysis and confirms Yb^{III} as the active catalyst (runs 8–10). Therefore, Lewis acid catalysed processes involving dicarbonyl compounds such as alkylidene malonates can benefit from minimisation of proton-mediated background reactions.

In combination, these results unambiguously show that protons can be the active catalysts in Lewis acid mediated hetero-Michael reactions to α,β-unsaturated ketones and to some dicarbonyl acceptors. Consequently, Lewis acid catalysts reported for aza- and oxa-Michael addition reactions of weakly basic nucleophiles[6–9,10a,c] were outperformed by homogeneous or heterogeneous Brønsted acid catalysts such as Tf_2NH or Nafion® SAC-13.[14,15] Examples and extensions of this methodology are listed in Table 7. In addition to benzyl carbamate (**3**) (runs 1–3), other nitrogen nucleophiles such as oxazolidin-2-one (**18**), benzaldehyde oxime (**19**) and *N*-methylaniline (**20**) could be used successfully (runs 4–6). Oxa-Michael addition reactions reactions of benzyl alcohol (**15**) could also be catalysed by Brønsted acids (runs 7 and 8) and did not require Pd^{II} catalysts. The same method could be applied to the thiols **21** and **22**, which reacted rapidly in the presence of Tf_2NH (entries 9–10). Similarly, the weakly basic carbon nucleophile indole (**23**) underwent acid-catalysed Michael addition reactions with the enones **2a**, **2e** and **2f** (runs 11–13).

Transformations with similar nucleophiles and acceptors as used in runs 5, 6, 9 and 10 have also been carried out with chiral Lewis acid catalysts.[5g,f,13] The existence of Brønsted acid catalysed pathways has important implications for the development of enantioselective processes. Catalytic enantioselective reactions which are sensitive to proton-mediated background reactions cannot succeed under nonbasic conditions when trace amounts of water cannot be excluded, and when hydrolysable cationic catalysts are used. The impact of hydrolysis can be reduced by employing Lewis basic solvents such as THF or chelating dicarbonyl substrates. Alternatively, the propensity of Lewis acid catalysts to hydrolyse can be lowered by modification of the metal centre with strongly electron-donating ligands or by using cations with a small hydrolysis constants $^*K_1$. To date, Lewis acid catalysed enantioselective aza- and thia-Michael addition reactions to monodentate enones under nonbasic conditions have only been carried out with weakly hydrolysing complexes of Sc^{III} and Cd^{II}.[5h,13b–13c] High *ee*s in addition reactions to chelating acceptors have been achieved

Table 7. Brønsted acid catalysed conjugate addition reactions of nitrogen, oxygen, sulfur and carbon nucleophiles.[a]



Run	Acceptor	RXH	Solvent	Product	*t* [h]	Yield [%]
1	**2a**	**3**	CH_3CN	**5a**	10 min	98
2	**2e**	**3**	CH_3CN	**5e**	10 min	94
3	**2j**	**3**	CH_3CN	**5j**	48	71
4	**2a**	**18**	CH_3CN	**24**	1	94
5[b]	**2g**	**19**	CH_2Cl_2	**25**	10	87
6	**2g**	**20**	CH_3CN	**26**	12	98
7	**2f**	**15**	CH_3CN	**16a**	12	79
8	**2a**	**15**	CH_3CN	**16b**	48	72
9	**2b**	**21**	$CHCl_3$	**27**	2	96
10	**2g**	**22**	CH_2Cl_2	**28**	2	93
11[c]	**2a**	**23**	CH_3CN	**29a**	0.5	95
12[c]	**2e**	**23**	CH_3CN	**29b**	2	88
13	**2f**	**23**	CH_3CN	**29c**	12	98

[a] The dashed arrows indicate the reactive centres of **19** and **23**. [b] Tf_2NH (50 %) was used. [c] At 50 °C.

with chiral catalysts based on Mg^{II}, Ni^{II}, Zn^{II}, Y^{III}, Yb^{III},[5b,d,f,g,13a,13d] or with Al^{III} complexes[5c] bearing strongly basic ligands.[45,46] All these catalysts have only weak tendencies to hydrolyse, confirming the importance of the concept described in this report.[47]

Conclusion

The generation of Brønsted acids through hydrolyis of metal complexes is a known, but often underestimated phenomenon in Lewis acid catalysis. In this report, Brønsted acids have been identified as the active catalysts in hetero-Michael addition reactions to α,β-unsaturated ketones. Acid mediated conjugate addition reactions of weakly basic nitrogen, oxygen, sulfur and carbon nucleophiles have been developed. Aza-Michael addition reactions of benzyl carbamate (**3**) and ^{1}H NMR studies with 2,6-di-*tert*-butylpyridine (**13**) have been used as probes to detect proton liberation from Lewis acids in organic solvents. These investigations provide very useful guidelines for the development of Lewis acid catalysed reactions of mono- and dicarbonyl compounds under nonbasic conditions and are not limited to hetero-Michael addition reactions.

Experimental Section

General: Solvents were distilled from CaH_2 prior to use. Thin-layer chromatography was performed with Merck 60 PF_{254} 0.2 mm plates (glass backed) and Merck 9385 Kieselgel 60 was used for column chromatography. NMR spectra were recorded on Bruker Avance 400 and 500 machines, running at 400 and 500 MHz (^{1}H) or 100 and 126 MHz (^{13}C), respectively. Chemical shifts (in ppm) are reported relative to residual solvent peaks. CD_2Cl_2 (< 0.02% H_2O) and CD_3CN (< 0.05% H_2O) were used as prescored ampoules (0.75 mL). Assignments of ^{1}H and ^{13}C spectra were verified by ^{1}H,^{1}H-COSY, DEPT-135 and ^{1}H,^{13}C-HMQC techniques. Infrared spectra were recorded on a Perkin–Elmer Spectrum One FT-IR as neat solids or liquids. Mass spectra were recorded on a Kratos 890 spectrometer. Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. $Al(ClO_4)_3$,[48] $Cu(CH_3CN)_4PF_6$,[49] $Bi(OTf)_3$[50] and compounds **2a**,[51] **2g**,[52] **2h**[53] and **2i**,[54] were prepared according to literature procedures. $V(ClO_4)_3{\cdot}nH_2O$ was prepared in situ from VCl_3 and $AgClO_4{\cdot}H_2O$. Commercially available materials were used as received, except enones, which were distilled prior to use. The products **5a**,**b**,**e**,**g**,**h** and **16b** have previously been characterised by us[6,14] and full characterisation data for compounds **8a** and **b** have already been reported in the literature.[55]

General procedure (GP1) for catalytic hetero-Michael addition reactions (0.5 mmol scale): The nucleophile (0.75 mmol) and the catalyst (0.05 mmol, 10%) were dissolved in CH_3CN (1 mL). The α,β-unsaturated carbonyl compound (0.5 mmol) was added and the reaction mixture was stirred at ambient temperature and monitored by TLC. When maximum conversion was reached,[56] an excess of silica gel containing 10% Na_2CO_3 was added, the solvent was evaporated and the products were isolated by column chromatography. The nature of the catalyst and deviations from this procedure (such as different solvents, reaction temperatures and reaction scales) are noted in brackets with the individual compounds.

General procedure (GP2) for kinetic experiments: NMR samples containing equal amounts of benzyl carbamate (**3**) (78 mg, 0.52 mmol), catalyst (3%-15%) and CD_3CN (or CD_2Cl_2) (0.75 mL) were prepared from stock solutions. If appropriate, water (or another additive) was added to these samples. The enone **2a** (80 μL, 80 mg, 0.50 mmol) was injected by syringe, the mixtures were shaken and immediately placed into a NMR spectrometer at 25°C. Acquisitions (2 scans) were made at regular intervals. Conversions were determined from the relative intensities of the methyl protons of the enone **2a** ($\delta = 1.10$ ppm in CD_3CN) and the product **5a** ($\delta = 0.92$ ppm in CD_3CN).

General procedure for Brønsted acid detection with 2,6-di-*tert*-butylpyridine: 2,6-Di-*tert*-butypyridine (**13**) (12 μL, 11 mg, 0.05 mmol), metal salt (0.1 mmol) and—when anhydrous metal salts were used—water (0.9 μL, 0.9 mg, 0.05 mmol) were dissolved in CD_3CN (0.75 mL). The relative amounts of **13** and the conjugated acid **17** were determined by ^{1}H NMR spectroscopy. **13**: ^{1}H NMR (400 MHz, CD_3CN): $\delta = 1.33$ (s, 18H; CH_3), 7.16 (d, $J = 7.8$ Hz, 2H; *m*-Ar-*H*), 7.59 ppm (t, $J = 7.8$ Hz, 1H; *p*-Ar-*H*). **17**; ^{1}H NMR (400 MHz, CD_3CN): $\delta = 1.53$ (s, 18H; CH_3), 7.90 (d, $J = 8.2$ Hz, 2H; *m*-Ar-*H*), 8.47 (t, $J = 8.2$ Hz, 1H; *p*-Ar-*H*), 11.21 (br, 1H; N*H*).

Interaction between Sc^{III} and (*E*)-hex-4-en-3-one (2e): $Sc(OTf)_3$ (98 mg, 0.21 mmol) and **2e** (22 μL, 20 mg, 0.20 mmol) were dissolved in CD_3CN (0.75 mL). ^{13}C NMR spectra were recorded at 0°C and stoichiometric complex formation was observed. **2e**: ^{13}C NMR (100 MHz, CD_3CN, 0°C): $\delta = 7.4$, 17.4 (CH_3), 32.4 (CH_2), 131.4, 142.4 (=CH), 200.5 ppm (C=O). $Sc(OTf)_3$+**2e**: ^{13}C NMR (100 MHz, CD_3CN, 0°C): $\delta = 7.6$, 17.8 (CH_3), 32.4 (CH_2), 130.4, 151.3 (=CH), 208.7 ppm (C=O).

***N*-[(*E*)-Pent-2-enoyl]acetamide (2j)**: Sulfuric acid (110 μL, 205 mg, 2.10 mmol) was added to a mixture of (*E*)-pent-2-enoyl amide (2.1 g, 21 mmol) and acetic acid anhydride (20 mL, 210 mmol). The solution was stirred at 80°C for 30 min, volatile components were evaporated in vacuo and the product was isolated as a colourless solid after column chromatography (2.42 g, 82%); $R_f = 0.35$ (PE/EtOAc 1:1); M.p. = 84–85°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.03$ (t, $J = 7.4$ Hz, 3H; CH_2CH_3), 2.22 (dq, $J = 6.5$, 7.4 Hz, 2H; CH_2CH_3), 2.42 (s, 3H; C(O)CH_3), 6.19 (d, $J = 15.4$ Hz, 1H; C(O)C*H*), 7.10 (dt, $J = 6.5$, 15.4 Hz, 1H; C=C*H*), 9.21 ppm (br, 1H; N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.1$ 25.2 (CH_3), 25.5 (CH_2), 122.0, 152.0 (=CH), 165.4, 173.6 ppm (C=O); IR (neat, film): $\tilde{\nu} = 3259$, 3199, 2967, 1726, 1682, 1643, 1500, 1278 cm^{-1}; HRMS (+EI, 70 eV) calcd for: $[C_7H_{11}NO_2]^+$: 141.0790; found: 141.0793 $[M]^+$.

***trans*-3-Benzyloxycarbonylamino-4-methylcyclohexanone (5c)**: Compound **5c** was prepared according to GP1 ($[Pd(CH_3CN)_4](BF_4)_2$, 1.0 mmol scale, 24 h) and was isolated in $dr > 20{:}1$ as a colourless oil (86 mg, 33%). The assignment of *trans*-geometry was based upon the coupling constant between C*H*CH$_3$ and C*H*N, which was determined by ^{1}H–^{1}H homodecoupling experiments at 0°C ($^3J = 10.5$ Hz). R_f 0.24 (PE/diethyl ether 1:3); ^{1}H NMR (500 MHz, $CDCl_3$, 0°C): $\delta = 1.04$ (d, $J = 6.6$ Hz, 3H; CHCH_3), 1.42 (dm, $J = 13.9$ Hz, 1H; C*H*H), 1.78 (dm, $J = 10.5$ Hz, 1H; C*H*CH$_3$), 2.03 (dm, $J = 13.9$ Hz, 1H; C*H*H), 2.22–2.43 (m, 3H; C(O)CH_2, C(O)C*H*H), 2.73 (m, 1H; C(O)CH*H*), 3.59 (dm, $J = 10.5$ Hz, 1H; N*CH*), 4.82 (br, 1H; N*H*), 5.10 (s, 2H; OCH_2), 7.32–7.43 ppm (m, 5H; Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 17.8$ (CH_3), 30.7 (CH_2), 36.6 (CH), 40.4, 47.5 (CH_2), 54.4 (CH), 66.7 (CH_2), 128.1, 128.2, 128.5 (Ar-C), 136.4 (*ipso*-Ar-C), 155.6, 208.7 ppm (C=O); IR (neat, film): $\tilde{\nu} = 3324$, 2957, 2928, 1717, 1680, 1531, 1275, 1251, 1020 cm^{-1}; HRMS [+ESI] calcd for: $[C_{15}H_{19}NO_3Na]^+$: 284.1263; found: 284.1256 $[M+Na]^+$.

Diethyl ester of 2-(benzyloxycarbonylaminophenylmethyl)malonic acid (5i): Compound **5i** was prepared according to GP1 ($Yb(OTf)_3$, 1.0 mmol scale, 12 h) and was isolated as a colourless oil (202 mg, 51%). R_f 0.26 (PE/diethyl ether 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.11$ (t, $J = 7.2$ Hz, 3H; CH_2CH_3), 1.20 (t, $J = 7.2$ Hz, 3H; CH_2CH_3), 3.88 (br, 1H; C(O)C*H*), 4.02–4.19 (m, 4H; CH_2CH$_3$), 5.08 (d, $J = 12.3$ Hz, 1H; OC*H*H), 5.11 (d, $J = 12.3$ Hz, 1H; OCH*H*), 5.54 (dd, $J = 4.2$, 8.7 Hz, 1H; NC*H*), 6.47 (br, 1H; N*H*), 7.21–7.33 ppm (m, 10H; Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 14.3 (CH_3), 54.4, 57.2 (CH), 62.0, 62.4, 67.3 (CH_2), 126.7, 128.1, 128.4, 128.4, 128.8, 129.0 (Ar-C), 136.9, 136.9 (*ipso*-Ar-C), 156.1, 167.3, 168.4 ppm (C=O); IR (neat, film): $\tilde{\nu} = 3344$, 2982, 1725, 1498, 1217, 1020, 696 cm^{-1}; HRMS [+ESI] calcd for: $[C_{22}H_{25}NO_6Na]^+$: 422.1580; found: 422.1602 $[M+Na]^+$.

***N*-[3-(Benzyloxycarbonylamino)pentanoyl]acetamide (5j)**: Compound **5j** was prepared according to GP1 (Tf_2NH, 48 h) and was obtained as a colourless solid (103 mg, 71%). R_f 0.21 (PE/EtOAc 1:1); M.p. 123–125°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 7.4$ Hz, 3H; CH_2CH_3), 1.40–1.52 (m, 2H; CH_2CH$_3$), 2.26 (s, 3H; C(O)CH_3), 2.68–2.73 (m, 2H; C(O)CH_2), 3.95 (m, 1H; NC*H*), 5.05 (s, 2H; OCH_2), 5.32 (br, 1H; N*H*),

7.26–7.33 (m, 5H; Ar-*H*), 9.39 ppm (br, 1H; N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 25.4 (CH_3), 28.3, 42.3 (CH_2), 50.2 (CH), 67.0 (CH_2), 128.3, 128.5, 128.9 (Ar-C), 136.9 (*ipso*-Ar-C), 156.5, 172.7, 172.8 ppm (C=O); IR (neat, film): $\tilde{\nu}$ = 3317, 3144, 2976, 1734, 1709, 1686, 1534, 1245 cm^{-1}; HRMS [+ESI]: calcd for $[C_{15}H_{20}N_2O_4Na]^+$: 315.1321, found: 315.1313 $[M+Na]^+$.

Compound **9** was isolated as a side product in the synthesis of **5b** according to GP1 ($[Pd(CH_3CN)_4(BF_4)_2]$, 1.0 mmol scale) as a colourless solid (17 mg, 5%). Samples from several runs were combined and crystals suitable for X-ray crystallography were obtained from pentane/diethyl ether. R_f 0.35 (PE/diethyl ether 1:3); M.p. 136–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.69 (m, 7H; C*H*$_2$, C*H*), 1.80–1.86 (m, 1H; C*H*H), 1.90–2.01 (m, 4H; C*H*$_2$, C*H*), 2.20–2.28 (m, 1H; C*H*), 2.34 (t, J = 6.2 Hz, 1H; C(O)C*H*), 2.71 (m, 1H; C(O)C*H*), 4.92 (br, 1H; N*H*), 5.05 (s, 2H; OC*H*$_2$), 7.28–7.36 ppm (m, 5H; Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 23.5, 23.5, 23.7 (CH_2), 28.2, 35.8 (CH), 36.1 (CH_2), 37.1, 51.5, 53.4 (CH), 56.7 (C_{quart}), 66.9 (CH_2), 128.6, 128.7, 129.0 (Ar-C), 136.7 (*ipso*-Ar-C), 155.8, 218.9 ppm (C=O); IR (neat, film): $\tilde{\nu}$ = 3304, 3248, 2924, 2855, 1733, 1690, 1535, 1262 cm^{-1}; HRMS [+ESI]: calcd for $[C_{20}H_{23}NO_3Na]^+$: 348.1576; found: 348.1581 $[M+Na]^+$).

(*Z*)-4-(2,2,2-Trideuteroacetylamido)pent-2-en-2-olato palladium(II) complexes (10): The complexes were prepared by dissolving pent-3-en-2-one (**2d**) (21 μL, 18 mg, 0.21 mmol) and $[Pd(CH_3CN)_4(BF_4)_2]$ (100 mg, 0.210 mmol) in CD_3CN (0.75 mL). The starting enone was completely consumed within 2 h and the products were analysed in situ (70:30 mixture). Major species: ^{1}H NMR (400 MHz, CD_3CN): δ = 1.66 (d, J = 6.7 Hz, 3H; CHC*H*$_3$), 1.79 (s, 3H; =CC*H*$_3$), 4.00 (m, 1H; NC*H*), 4.79 ppm (m, 1H; C=C*H*); ^{13}C NMR (100 MHz, CD_3CN): δ = 15.9, 23.0 (CH_3), 53.7 (CH), 101.1 (=CH), 144.8 (=C_{quart}), 166.9 ppm (C=O);[57] Minor species: ^{1}H NMR (400 MHz, CD_3CN): δ = 1.35 (d, J = 6.6 Hz, 3H; CHC*H*$_3$), 1.89 (s, 3H; =CC*H*$_3$), 4.28 (m, 1H; NC*H*), 5.20 ppm (m, 1H; C=C*H*); ^{13}C NMR (100 MHz, CD_3CN): δ = 16.3, 21.5 (CH_3), 43.0 (CH), 102.7 (=CH), 145.4 (=C_{quart}), 171.7 ppm (C=O);[57] IR (mixture, in CD_3CN): $\tilde{\nu}$ = 1734, 1647, 1524, 1197 cm^{-1}; HRMS [+ESI]: calcd for $[C_7H_9D_3NO_2Pd]^+$: 251.0091; found: 251.0089 $[M+H]^+$.[58]

***N*-(1-Methyl-3-oxo-butyl)-2,2,2-trideuteroacetamide (11)**: Formic acid (1.0 mL, 0.80 g, 18 mmol) was added to the solution described in the preparation of the complexes **10**. The mixture was stirred at 50 °C. After 2 h the initially dark orange solution became clear and Pd^0 had precipitated. The solid was filtered off, aqueous Na_2CO_3 (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The product was obtained as a colourless oil (26 mg, 87%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (d, J = 6.3 Hz, 3H; CHC*H*$_3$), 2.14 (s, 3H; C(O)C*H*$_3$), 2.59 (dd, J = 5.7, 16.8 Hz, 1H; C(O)C*H*H), 2.66 (dd, J = 5.0, 16.8 Hz, 1H; C(O)CH*H*), 4.30 (m, 1H; NC*H*), 6.20 ppm (br, 1H; N*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.1, 30.6 (CH_3), 41.9 (CH), 48.7 (CH_2), 169.5, 208.2 ppm (C=O);[57] IR (neat, film): $\tilde{\nu}$ = 3287, 3075, 2927, 1710, 1637, 1546, 1370, 729 cm^{-1}; HRMS [EI, 70 eV] calcd for: $[C_7H_{10}D_3NO_2]^+$: 146.1135; found: 146.1132 $[M]^+$.

***N*-(1-Methyl-3-oxo-butyl)acetamide (H^3-11)**: Compound H^3-**11** was prepared in analogy to compound **11** with CH_3CN as a solvent. The product was obtained as a colourless oil (27 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (d, J = 6.3 Hz, 3H; CHC*H*$_3$), 1.92 (s, 3H; C(O)C*H*$_3$), 2.14 (s, 3H; C(O)C*H*$_3$), 2.60 (dd, J = 5.7, 16.8 Hz, 1H; C(O)C*H*H), 2.67 (dd, J = 5.0, 16.8 Hz, 1H; C(O)CH*H*), 4.30 (m, 1H; NC*H*), 6.14 ppm (br, 1H; N*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.2, 23.4, 30.6 (CH_3), 41.9 (CH), 48.6 (CH_2), 169.4, 208.2 ppm (C=O); IR (neat, film): $\tilde{\nu}$ = 3287, 3084, 2924, 1710, 1648, 1547, 1370, 731 cm^{-1}; HRMS [EI, 70 eV] calcd for: $[C_7H_{13}NO_2]^+$: 143.0946; found: 143.0947 $[M]^+$.

5-Chlorohexan-3-one (12): Compound **12** was prepared by bubbling gaseous HCl through a solution of **2e** (57 μL, 49 mg, 0.5 mmol) in CH_3CN (1 mL) for 10 min. The solvent was evaporated and preparative thin-layer chromatography furnished a colourless oil (22 mg, 34%). The NMR spectra of this compound and of stoichiometric mixtures of **2e** and $AlCl_3$, $TiCl_4$, $ReCl_5$ in CD_3CN were identical. R_f 0.50 (PE/diethyl ether 1:1); ^{1}H NMR (400 MHz, CD_3CN): δ = 0.96 (t, J = 7.0 Hz, 3H; CH_2CH_3), 1.47 (d, J = 6.6 Hz, 3H; CHC*H*$_3$), 2.41 (q, J = 7.0 Hz, 2H; C*H*$_2$CH$_3$), 2.75 (dd, J = 5.1, 17.1 Hz, 1H; C(O)C*H*H), 2.89 (dd, J = 7.8, 17.1 Hz, 1H; C(O)CH*H*), 4.45 ppm (ddq, J = 5.1, 6.6, 7.8 Hz, 1H; C*H*Cl); ^{13}C NMR (100 MHz, CD_3CN): δ = 8.3, 26.2 (CH_3), 37.6, 53.2 (CH_2), 54.2 (CH), 208.3 ppm (C=O); IR (neat, film): $\tilde{\nu}$ = 2961, 1726, 1393, 1250, 1066 cm^{-1}; HRMS [EI, 70 eV] calcd for: $[C_6H_{11}ClO]^+$: 134.0498; found: 134.0494 $[M]^+$.

1-(Benzyloxy)pentan-3-one (16a): Compound **16a** was prepared according to GP1 (Tf_2NH, 1.0 mmol scale, 12 h) and was obtained as a colourless oil (151 mg, 79%). R_f 0.44 (CH_2Cl_2/acetone 30:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (t, J = 7.4 Hz, 3H; CH_2CH_3), 2.49 (q, J = 7.4 Hz, 2H; C*H*$_2$CH$_3$), 2.71 (t, J = 6.3 Hz, 2H; C(O)C*H*$_2$), 3.77 (t, J = 6.3 Hz, 2H; OC*H*$_2$), 4.53 (s, 2H; OC*H*$_2$), 7.30–7.41 ppm (m, 5H; Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.4 (CH_3), 36.4, 42.3, 65.2, 73.0 (CH_2), 127.4, 127.5, 128.2 (Ar-C), 138.0 (*ipso*-Ar-C), 209.6 ppm (C=O); IR (neat, film): $\tilde{\nu}$ = 2975, 2871, 1711, 1454, 1364, 1090, 735 cm^{-1}; HRMS [EI, 70 eV] calcd for: $[C_{12}H_{16}O_2]^+$: 192.1150; found: 192.1155 $[M]^+$.

3-(2-Oxo-oxazolidin-3-yl)-1-phenylpentan-1-one (24): Compound **24** was prepared according to GP1 (Tf_2NH, 1.0 mmol scale, 1 h) and was isolated as a colourless solid (232 mg, 94%). R_f 0.17 (diethyl ether); m.p. 48–50 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.4 Hz, 3H; CH_2CH_3), 1.61–1.78 (m, 2H; C*H*$_2$CH$_3$), 3.12 (dd, J = 5.7, 16.2 Hz, 1H; C(O)C*H*H), 3.33 (dd, J = 7.9, 16.2 Hz, 1H; C(O)CH*H*), 3.57 (dt, J = 2.3, 7.9 Hz, 2H; NC*H*$_2$), 4.07 (m, 1H; NC*H*), 4.21 (t, J = 7.9 Hz, 2H; OC*H*$_2$), 7.42 (dd, J = 7.5, 7.9 Hz, 2H; *m*-Ar-*H*), 7.53 (t, J = 7.5 Hz, 1H; *p*-Ar-*H*), 7.91 ppm (d, J = 7.9 Hz, 2H; *o*-Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 (CH_3), 25.6, 41.4, 43.0 (CH_2), 52.9 (CH), 62.4 (CH_2), 128.4, 129.0, 133.7 (Ar-C), 136.9 (*ipso*-Ar-C), 158.1, 198.3 (C=O); IR (neat, film): $\tilde{\nu}$ = 2963, 2910, 1736, 1686, 1425, 1226, 1057, 756 cm^{-1}; HRMS [+ESI] calcd for $[C_{14}H_{17}NO_3Na]^+$: 270.1106; found: 270.1098 $[M+Na]^+$.

3-[3-(Benzylideneamino)propionyl]-2-oxazolidinone *N*-oxide (25): Compound **25** was prepared according to GP1 (Tf_2NH (50%), in CH_2Cl_2, 10 h) and was obtained as a colourless solid (112 mg, 87%). R_f 0.05 (PE/EtOAc 1:1); m.p. 169–171 °C; ^{1}H NMR (500 MHz, CD_3CN): δ = 3.48 (t, J = 6.3 Hz, 2H; C(O)C*H*$_2$), 3.90 (t, J = 8.3 Hz, 2H; NC*H*$_2$), 4.24 (t, J = 6.3 Hz, 2H; NC*H*$_2$), 4.36 (t, J = 8.3 Hz, 2H; OC*H*$_2$), 7.42–7.48 (m, 3H; *m*-Ar-*H*, *p*-Ar-*H*), 7.74 (s, 1H; N=C*H*), 8.22–8.24 ppm (m, 2H; *o*-Ar-*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 32.5, 42.4, 60.8, 62.8 (CH_2), 128.5, 128.7, 130.6 (Ar-C), 130.6 (*ipso*-Ar-C), 136.3 (N=CH), 154.3, 170.9 ppm (C=O); IR (neat, film): $\tilde{\nu}$ = 2975, 1776, 1761, 1694, 1380, 1214, 1118, 755 cm^{-1}; HRMS [+ESI] calcd for $[C_{13}H_{14}N_2O_4Na]^+$: 285.0851; found: 285.0858 $[M+Na]^+$.

3-[3-(*N*-Methyl-*N*-phenylamino)propionyl]oxazolidin-2-one (26): Compound **26** was prepared according to GP1 (Tf_2NH, 12 h) and was obtained as a colourless oil (122 mg, 98%). R_f 0.29 (diethyl ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.96 (s, 3H; NC*H*$_3$), 3.20 (t, J = 7.1 Hz, 2H; NC*H*$_2$), 3.73 (t, J = 7.1 Hz, 2H; C(O)C*H*$_2$), 3.91 (t, J = 8.3 Hz, 2H; NC*H*$_2$), 4.30 (t, J = 8.3 Hz, 2H; OC*H*$_2$), 6.70 (t, J = 7.1 Hz, 1H; *p*-Ar-*H*), 6.78 (d, J = 8.0 Hz, 2H; *o*-Ar-*H*), 7.22 ppm (dd, J = 7.1, 8.0 Hz, 2H; *m*-Ar-*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 32.6 (CH_2), 38.2 (CH_3), 42.5, 48.3, 62.1 (CH_2), 112.6, 116.7, 129.2 (Ar-C), 149.0 (*ipso*-Ar-C), 153.8, 172.3 ppm (C=O); IR (neat, film): $\tilde{\nu}$ = 2918, 1771, 1690, 1598, 1505, 1385, 1220, 1034 cm^{-1}; HRMS [+ESI] calcd for $[C_{13}H_{16}N_2O_3Na]^+$: 271.1059; found: 271.1062 $[M+Na]^+$.

3-(Phenylsulfanyl)cyclohexan-1-one (27): Compound **27** was prepared according to GP1 (Tf_2NH, in $CHCl_3$, 2 h) and was obtained as a colourless oil (99 mg, 96%). R_f 0.31 (PE/ether 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.70–1.75 (m, 2H; C*H*$_2$), 2.12–2.17 (m, 2H; C*H*$_2$), 2.29–2.40 (m, 3H; C(O)C*H*$_2$, C(O)C*H*H), 2.68 (dd, J = 4.4, 14.3 Hz, 1H; C(O)CH*H*), 3.44 (m, 1H; SC*H*), 7.27–7.33 (m, 3H; *m*-Ar-*H*, *p*-Ar-*H*), 7.42 ppm (d, J = 5.7 Hz, 2H; *o*-Ar-*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.0, 31.2, 40.9 (CH_2), 46.1 (CH), 47.8 (CH_2), 127.8, 129.0 (Ar-C), 133.1 (*ipso*-Ar-C), 133.2 (Ar-C), 208.6 ppm (C=O); IR (neat, film): $\tilde{\nu}$ = 3056, 2943, 1708, 1582, 1438, 1220, 1024, 739 cm^{-1}; HRMS [+ESI] calcd for $[C_{12}H_{15}OS]^+$: 207.0844; found: 207.0848 $[M+H]^+$.

3-[3-(Benzylsulfanyl)propionyl]oxazolidin-2-one (28): Compound **28** was prepared according to GP1 (Tf_2NH, in CH_2Cl_2, 2 h) and was obtained as a colourless oil (124 mg, 93%). R_f 0.27 (ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.74 (t, J = 7.0 Hz, 2H; SC*H*$_2$), 3.20 (t, J = 7.0 Hz, 2H; C(O)C*H*$_2$), 3.76 (s, 2H; Ar-C*H*$_2$), 3.99 (t, J = 8.3 Hz, 2H; NC*H*$_2$), 4.38 (t, J = 8.3 Hz, 2H; OC*H*$_2$), 7.24–7.36 ppm (m, 5H; Ar-*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.6, 35.2, 36.3, 42.5, 62.2 (CH_2), 127.0, 128.5, 128.9 (Ar-C), 138.2 (*ipso*-Ar-C), 153.5, 171.6 ppm (C=O); IR (neat, film):

$\tilde{\nu}$ = 2920, 1770, 1692, 1384, 1200, 1036, 757, 703 cm^{-1}; HRMS [+ESI] calcd for $[C_{13}H_{15}NO_3SNa]^+$: 288.0670; found: 288.0669 $[M+Na]^+$.

3-(1*H*-Indol-3-yl)-1-phenylpentan-1-one (29a): Compound **29a** was prepared according to GP1 (Tf_2NH, 50 °C, 30 min) and was obtained as a colourless oil (131 mg, 95 %). R_f 0.38 (CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.4 Hz, 3H; CH_2CH_3), 1.93–1.99 (m, 2H; CH_2CH_3), 3.41 (dd, J = 7.4, 16.2 Hz, 1H; C(O)CHH), 3.51 (dd, J = 6.3, 16.2 Hz, 1H; C(O)CHH), 3.70 (m, 1H; Ar-CH), 6.98 (s, 1H; *hetero*-Ar-H), 7.18 (dd, J = 7.7, 8.0 Hz, 1H; Ar-H), 7.22 (dd, J = 7.7, 8.0 Hz, 1H; Ar-H), 7.33 (d, J = 8.0 Hz, 1H; Ar-H), 7.45 (dd, J = 6.9, 7.4 Hz, 2H; *m*-Ar-H), 7.56 (t, J = 7.4 Hz, 1H; *p*-Ar-H), 7.76 (d, J = 8.0 Hz, 1H; Ar-H), 7.97 (d, J = 6.9 Hz, 2H; *o*-Ar-H), 8.13 ppm (br, 1H; NH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 12.3 (CH_3), 28.5 (CH_2), 34.7 (CH), 45.0 (CH_2), 111.5 (Ar-C), 119.0 (*ipso*-Ar-C), 119.2, 119.4, 121.5, 121.9 (Ar-C), 126.8 (*ipso*-Ar-C), 128.2, 128.6, 133.0 (Ar-C), 136.7, 137.4 (*ipso*-Ar-C), 200.4 ppm (C=O); IR (neat, film): $\tilde{\nu}$ = 3419, 2963, 1677, 1597, 1456, 1336, 1209, 904 cm^{-1}; HRMS [EI, 70 eV] calcd for $[C_{19}H_{19}NO]^+$: 277.1467; found: 277.1472 $[M]^+$.

5-(1*H*-Indol-3-yl)hexan-3-one (29b): Compound **29b** was prepared according to GP1 (Tf_2NH, 50 °C, 2 h) and was obtained as a colourless oil (95 mg, 88 %). R_f 0.25 (CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, J = 7.4 Hz, 3H; CH_2CH_3), 1.42 (d, J = 7.0 Hz, 3H; $CHCH_3$), 2.40 (q, J = 7.4 Hz, 2H; CH_2CH_3), 2.72 (dd, J = 8.2, 15.8 Hz, 1H; C(O)CHH), 2.94 (dd, J = 6.0, 15.8 Hz, 1H; C(O)CHH), 3.68 (m, 1H; Ar-CH), 6.92 (s, 1H; *hetero*-Ar-H), 7.12 (dd, J = 7.1, 7.8 Hz, 1H; Ar-H), 7.23 (dd, J = 7.1, 7.8 Hz, 1H; Ar-H), 7.32 (d, J = 7.8 Hz, 1H; Ar-H), 7.68 (d, J = 7.8 Hz, 1H; Ar-H), 8.10 ppm (br, 1H; NH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 7.8, 21.3 (CH_3), 27.2 (CH), 39.5, 50.3 (CH_2), 111.4, 119.2, 119.3, 120.3 (Ar-C), 121.1 (*ipso*-Ar-C), 122.9 (Ar-C), 126.3, 136.6 (*ipso*-Ar-C), 211.5 ppm (C=O); IR (neat, film): $\tilde{\nu}$ = 3409, 2973, 1702, 1457, 1339, 1098, 906 cm^{-1}; HRMS [EI, 70 eV] calcd for $[C_{14}H_{17}NO]^+$: 215.1310; found: 215.1319 $[M]^+$.

1-(1*H*-Indol-3-yl)-pentan-3-one (29c): Compound **29c** was prepared according to GP1 (Tf_2NH, 12 h) and was obtained as a colourless solid (98 mg, 98 %). R_f 0.25 (CH_2Cl_2); m.p. 92–94 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, J = 7.3 Hz, 3H; CH_2CH_3), 2.42 (q, J = 7.3 Hz, 2H; CH_2CH_3), 2.84 (t, J = 7.3 Hz, 2H; C(O)CH_2), 3.08 (t, J = 7.3 Hz, 2H; Ar-CH_2), 6.95 (s, 1H; *hetero*-Ar-H), 7.12 (dd, J = 7.7, 8.0 Hz, 1H; Ar-H), 7.22 (dd, J = 7.7, 8.0 Hz, 1H; Ar-H), 7.36 (d, J = 8.0 Hz, 1H; Ar-H), 7.63 (d, J = 8.0 Hz, 1H; Ar-H), 8.06 ppm (br, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.9 (CH_3), 19.6, 36.2, 42.9 (CH_2), 111.3 (Ar-C), 115.4 (*ipso*-Ar-C), 118.8, 119.4, 121.7, 122.1 (Ar-C), 127.3, 136.5 (*ipso*-Ar-C), 211.7 ppm (C=O); IR (neat, film): $\tilde{\nu}$ = 3315, 3059, 2936, 1702, 1331, 1219, 1112, 1046 cm^{-1}; HRMS [EI, 70 eV] calcd for $[C_{13}H_{15}NO]^+$: 201.1154; found: 201.1148 $[M]^+$.

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[58] It is conceivable that one of these species is an oxazine derivative, which can be formed in acid-catalysed Ritter reactions, see ref. [24]

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