Water-accelerated organic transformations

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Rather than quenching all reactive intermediates and arresting the reaction, the addition of catalytic or stoichiometric (1–10 equiv.) quantities of H_2O to organic and organometallic processes can lead to surprisingly beneficial effects on reaction rate, product yield, and regio-, diastereo- and enantioselectivity. A most intriguing aspect of H_2O-promoted transformations is the role that this strong Lewis-base can play in providing a source for more highly Lewis-acidic species. This scenario is most likely operative when H_2O is added to reaction mixtures containing alanes, but organozinc reagents or organocuprates also seem to be transformed accordingly. In addition, the oxide or hydroxide ligand on the metal presents a source for chelation interactions that change aggregation states of organometallics and can provide anchimeric assistance. In many cases, water has been found to be an effective hydrolyzing agent leading to secondary products that serve as catalysts or promoters. In some cases, it has been shown that water provides a quenching agent capable of driving chemical equilibria towards the desired products.

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Introduction

Reports of stoichiometric or sub-stoichiometric quantities of water resulting in significant increases in the rate and/or the enantioselectivity of organic transformations have sporadically appeared in the literature over the past decade. The means by which water acts as an accelerant in many of these processes is often poorly understood or even counterintuitive. Due to the abundance of primary literature and review articles on subjects concerning organic reactions in aqueous media[1] (*i.e.* Diels–Alder, Aldol, Claisen reactions, *etc.*), this review will focus primarily on transformations in which only stoichiometric or sub-stoichiometric amounts of water are necessary to achieve the desired rate enhancement or reaction improvement. Furthermore, the role that water plays is categorized into three distinct classes of activation: (a) water as a hydrolyzing agent leading to secondary products that serve as catalysts or promoters; (b) water used as an internal quenching agent to drive chemical equilibria, and (c) water as a Lewis acid activator or co-activator. This review is not intended to be comprehensive, and in many cases examples have been selected primarily as illustrations of larger and more comprehensive research efforts.

Water as a hydrolyzing agent leading to secondary products that serve as catalysts or promoters

The controlled *in situ* hydrolysis of TMS-Cl in the presence of NaI led to mild conditions for the preparation of internal alkenyl iodides in good yields and stereoselectivities from both terminal and internal alkynes (Scheme 1).[2] While one could speculate
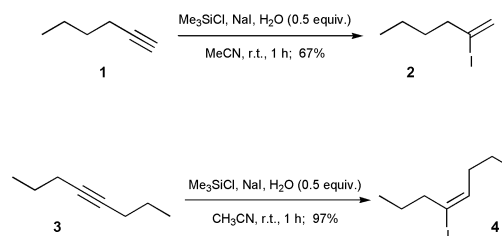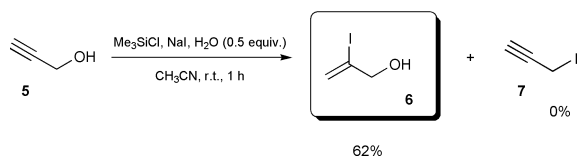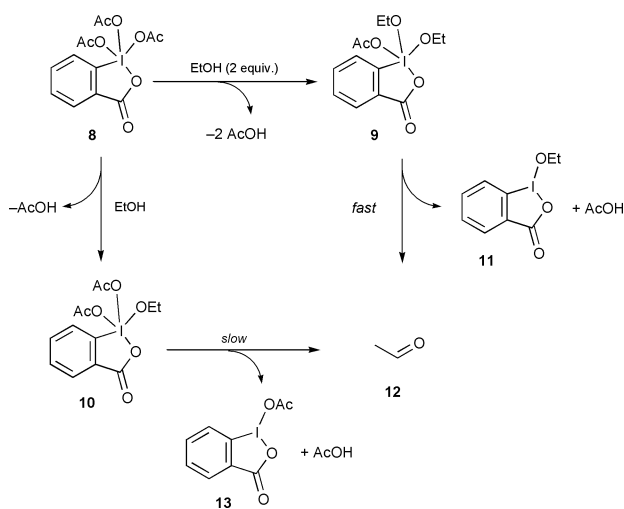

Scheme 1

that a mixture of HCl and HI is formed during the hydrolysis, direct use of an aqueous (57%) HI solution under otherwise identical conditions led mostly to unreacted alkyne.

Acetonitrile was shown to be by far the best solvent for this transformation. The unique selectivity of these mild conditions is highlighted by the clean and stereoselective addition of HI to

prop-2-ynyl alcohol to afford the desired internal alkenyl iodide **6** in 62% yield without any of the undesired prop-2-ynyl iodide (Scheme 2).
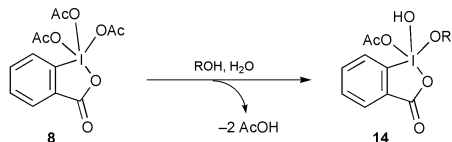

Scheme 2

A related example of this type of H$_2$O-induced reaction acceleration is represented by the Dess–Martin oxidation. After a serendipitous experimental discovery that only 'aged' (2 years) Dess–Martin periodinane (DMP) reagent was consistently effective in a crucial oxidation step in the total synthesis of rapamycin, a study was undertaken in an attempt to elucidate the general inconsistencies in the preparation of the Dess–Martin periodinane reagent, and to address the 'aging' effect. This study led to the observation that the addition of 1 equiv. of water to DMP accelerated the oxidation reaction dramatically.[3] The inspiration for the use of water as an accelerant came from earlier work in which Dess and Martin observed that the rate of oxidation of ethanol could be increased by the addition of a second equivalent of ethanol.[4] Presumably, an intermediate such as **9** shown in Scheme 3 is formed in the latter process.
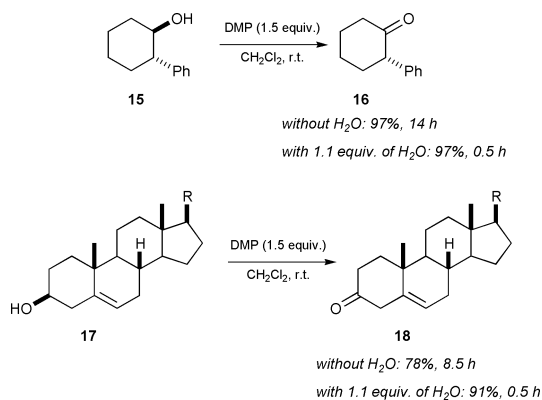

Scheme 3

The increased reactivity of the monoacetate **9** has been ascribed to the difference in basicity of the ethoxy *vs.* the acetoxy substituent. Schreiber and Meyer sought to mimic this effect by replacing an acetoxy group with hydroxide through the addition of one equivalent of H$_2$O (Scheme 4). Indeed, when
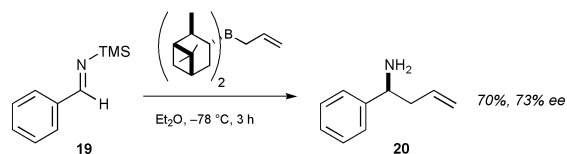

Scheme 4

CH$_2$Cl$_2$ containing 1.1 equiv. of water was added dropwise to the alcohol–DMP mixture, a greatly improved rate of oxidation was observed (Scheme 5). Both *trans*-2-phenylcyclohexanol and cholesterol were oxidized in 30 min to 97 and 91% completion, respectively. Under anhydrous conditions, oxidation of these two alcohols was significantly slower, requiring 14 and 8.5 h, respectively. Furthermore, prolonged reaction times under anhydrous conditions resulted in the decomposition of cholesterol, even in the presence of pyridine as a buffer.

without H$_2$O: 97%, 14 h

with 1.1 equiv. of H$_2$O: 97%, 0.5 h

without H$_2$O: 78%, 8.5 h

with 1.1 equiv. of H$_2$O: 91%, 0.5 h

Scheme 5

The preparation of enantiomerically pure homoallylamines by asymmetric allylboration of imines has generated substantial interest.[5] In 1997, Itsuno and co-workers reported that the (apparently) more reactive *N*-trimethylsilylbenzaldimine could be allylated at lower temperatures (−78 °C) to afford the desired homoallylamines in good yields and in good to excellent ee's (depending on the chiral allylboron reagent used).[6] Using Brown's *B*-allylpinan-3-ylborane reagent,[7] the homoallylic benzylamine could be obtained in 70% yield with an ee of 73% (Scheme 6). In efforts to establish comparative rate data for the

Scheme 6

allylboration of aldimines *vs.* aldehydes, Brown and co-workers subsequently discovered that the reported allylations did not take place under anhydrous conditions, even after a week at room temperature. However, upon aqueous workup of the reaction mixture, a 95% yield of the desired homoallylic amine was obtained.

Surprisingly, this reaction appears to take place quite rapidly upon aqueous workup, but remains dormant in the absence of water. Consequently, cooling the reaction temperature to −100 °C followed by dropwise addition of one equivalent of H$_2$O afforded an improved yield (87%) and a higher ee (94%, Scheme 7).[8] Presumably, H$_2$O is necessary to protodesilylate
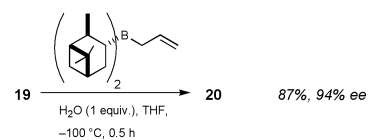
Scheme 7

the aldimine which is rapidly allylated. The improvement in %ee is thought to be due to a controlled, non-exothermic hydrolysis of the imine, allowing the reaction to proceed at much lower temperatures than the previous workup conditions.[9]

Two catalysts for the Mukaiyama aldol condensation, Cp$_2$Ti(OTf)$_2$ and trityl triflate (Ph$_3$COTf), both of which have also been used as Lewis acids for Diels–Alder reactions, have recently been shown to be precursors of the active species in this transformation.[10] Rigorous NMR studies have demonstrated that the hydrolysis of these triflates by trace amounts of H$_2$O leads to the formation of triflic acid, and subsequently, Me$_3$Si–OTf, which is responsible for catalyzing the reaction. The sequence of events that lead to the formation of Me$_3$Si–OTf is shown in Scheme 8. This spontaneous hydrolysis is in-
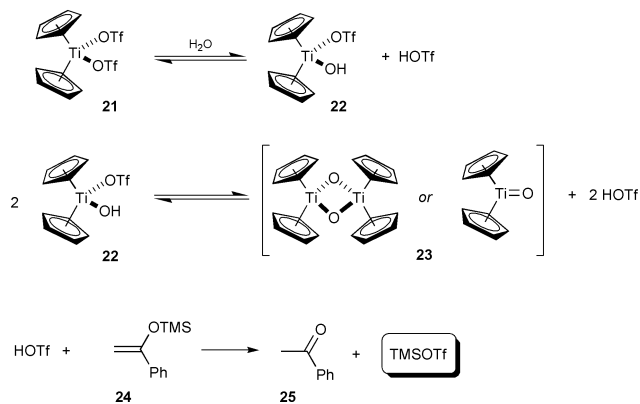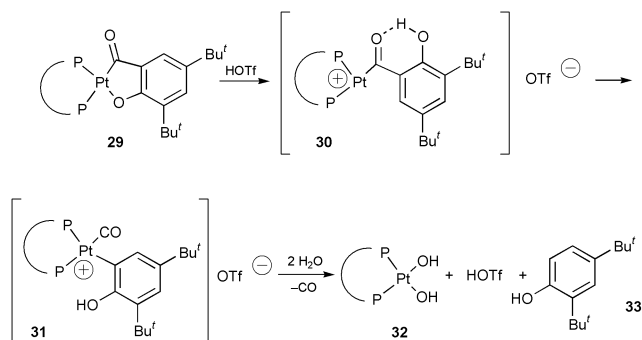
Scheme 8

strumental in explaining why certain chiral $L_2Ti(OTf)_2$ complexes provide racemic products from several substrates and under a broad range of reaction conditions.

An interesting observation was made during attempts to perform a Pt-catalyzed aldol addition of silyl ketene acetals to aldehydes. It was found that both O_2 and H_2O were needed in order to obtain enantiomerically enriched products.[11] Under aerobic and anhydrous conditions, the chiral Pt(II) acyl complex **29** catalyzed the reaction between dimethylketene methyl trimethylsilyl acetal and benzaldehyde at −25 °C. The desired aldol product was obtained after 16 h in a yield of 99% but was formed as a racemic mixture. When the same reaction was conducted in the presence of air, a product with an ee of 35% was obtained. Furthermore, if the reaction mixture was exposed to air and two equivalents of H_2O, the %ee rose to 59% (Scheme 9).

no H₂O, under Ar: 99%, 0% ee

2 equiv. of H₂O, under air: 99%, 59% ee
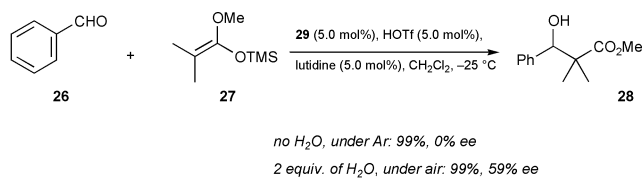
Scheme 9

Based on ^{31}P NMR experiments, the authors of this study speculated that hydrolysis of the salicylaldehyde ligand with two equiv. of H_2O produced the catalytically active dihydroxy platinum complex **32** (Scheme 10).[12] However, further analysis
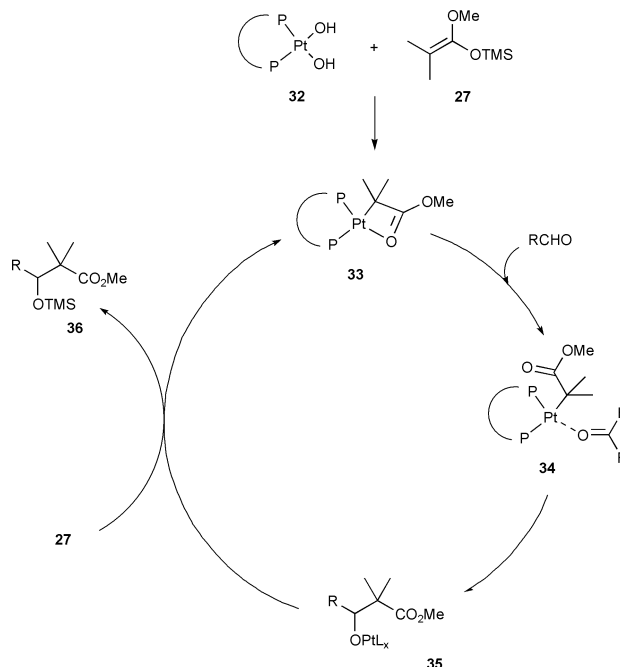
Scheme 10

is needed for verification of the structure of **32** and for the experimental validation of this hypothesis.

In the presence of an excess of the silylketene acetal **27**, the proposed dihydroxy platinum complex **32** was thought to

collapse to a C-bound Pt-enolate. A catalytic cycle that is in agreement with this mechanistic hypothesis is shown in Scheme 11.
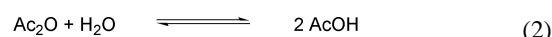
Scheme 11

Water has been postulated to be an essential ingredient in the synthesis of indoles *via* the Pd(0)-catalyzed intramolecular cyclization of alkynes to imines (Scheme 12).[13] The mechanism

via...

*Carbopalladation or Oxidative Addition*
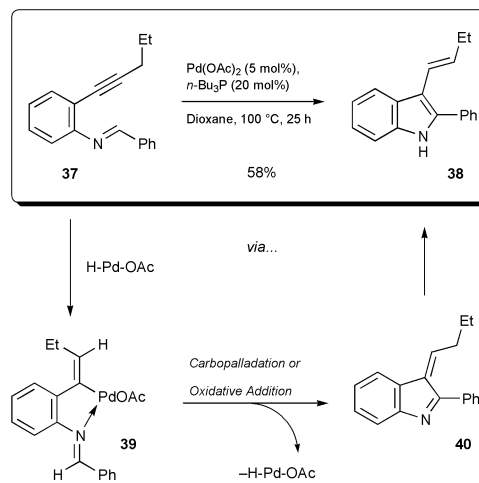
Scheme 12

was thought to involve a regioselective hydropalladation of the alkyne as the first step. The source of Pd-H under these conditions remained unclear.

However, the formation of Pd(0) from the reaction of Bu_3P and $Pd(OAc)_2$ is precedented [eqn. (1)],[14] and, furthermore, the oxidative addition of AcOH to Pd(0) has been reported [eqn. (3)].[15] Although this reaction was performed in dry solvents, it is possible that trace amounts of water were present, thus providing a source for the hydrolysis of Ac_2O [eqn. (2)].

$$Pd(OAc)_2 + Bu_3P \longrightarrow Pd(0) + Bu_3P{=}O + Ac_2O \quad (1)$$

$$Ac_2O + H_2O \rightleftharpoons 2\,AcOH \quad (2)$$

$$Pd(0) + AcOH \rightleftharpoons AcO\text{-}Pd\text{-}H \quad (3)$$

Further evidence for the formation of a Pd-H intermediate *via* this sequence was obtained when 1 equiv. of D_2O was added to

the reaction mixture and the desired indole was obtained in 80% yield (NMR) with 29% deuterium incorporation at C(1) (Scheme 13). Deuterium incorporation at any other position was not observed.
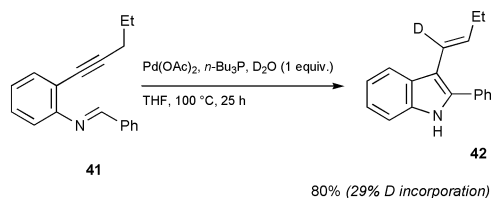

Scheme 13

Water used as an internal quenching agent to drive chemical equilibria

It is well established that silyloxycyclopropanes undergo metal-mediated ring openings to form β-metallo ketones.[16] In 1993, Ryu and co-workers reported their work toward the trapping of the analogous β-Cu(II) keto intermediates with suitable electrophiles such as electron deficient acetylenes. A typical reaction with dimethyl acetylenedicarboxylate (DMAD) is shown in Table 1.[17] Mechanistically, several competing pathways, *i.e.*

Table 1 The effect of additives on the reaction of siloxycyclopropane with Cu(BF$_4$)$_2$ and DMAD
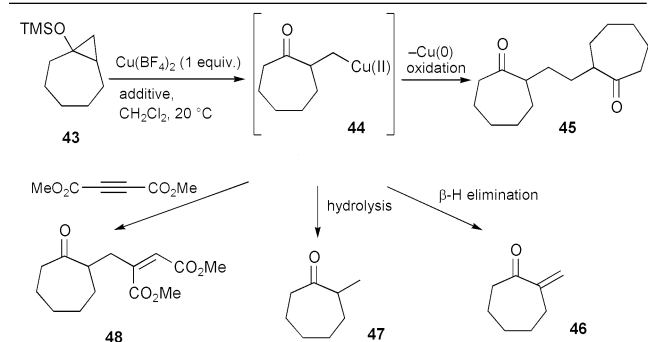
Entry	DMAD/mmol	Additive (mL)	45 (%)	46 (%)	47 (%)	48 (%)
1	1	—	0	2	35	45
2	1	BuOTMS (0.2)	0	4	4	65
3	1.1	BuOTMS (0.2) + H$_2$O (0.02)	0	4	6	73

oxidative homocoupling, β-H elimination and BF$_3$·OEt$_2$-promoted hydrolysis are feasible for this process. Optimal conditions included the use of 0.2 mL of a 10 vol% solution of trimethylsiloxybutane in CH$_2$Cl$_2$ containing one equivalent of H$_2$O (Table 1, entry 3). Trimethylsiloxybutane was used for the suppression of the BF$_3$·OEt$_2$-promoted hydrolysis of the starting silyloxycyclopropane, and the one equivalent of H$_2$O was apparently needed for the protonation of the resulting vinylcopper intermediate. Internal quenching effectively prevented the reversibility of the addition and therefore decreased the lifetime of the β-Cu(II) ketone species that was prone to side reactions such as β-H elimination or oxidative homocoupling. Interestingly, 1,4-addition of the β-Cu(II) ketone intermediate to reactive electrophiles such as DMAD proceeded faster than protonation of the alkyl–copper bond.

Stannyl- and silylcupration of alkynes was shown to be most effective if H$_2$O was used as an internal proton source.[18] Stannylcupration of prop-2-ynyl alcohol **49** was conducted in the presence of protic additives with pK_a values of 4–15.5 (Table 2). Surprisingly, the stannylcuprate was stable at pK_a values above 4, but more acidic additives such as 2,4,6-(NO$_2$)-PhOH (pK_a = 0.3) destroyed the cuprate. When no internal proton source was used (entry 1) the vinylstannane was

Table 2 Effects of proton source on yield and regiochemistry of stannylcupration

| Entry	Additive (equiv.)	Yield (%)	50 (%)	51 (%)	52 (%)
1	—	82	30	0	70
2	MeOH (110)	70	100	0	0
3	PhOH (30)	88	86	14	0
4	AcOH (10)	78	87	13	0
5	2,4-(NO$_2$)$_2$ PhOH (10)	80	85	15	0
6	H$_2$O (10)	97	85	15	0

obtained in good yield but as a 30:70 mixture favoring the thermodynamically more stable *trans*-addition product **52**. Use of protic additives provided the vinylstannane in similar yields but only the *cis*-addition products were obtained. Although greater control of the ratio of 'distal' *vs.* 'proximal' regio-isomers was obtained with MeOH, the best overall yield was obtained when 7–10 equiv. of H$_2$O were used (Table 2, entry 6).[19]

Stannylcupration of enyne **53** is an example where H$_2$O proved to be superior to MeOH, providing the (E)-dienyl-stannane **54** in 80% yield as a single isomer (Scheme 14).

MeOH (110 equiv.)   72%   **54**

H$_2$O (10 equiv.)   80%
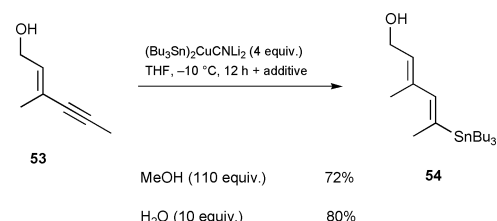
Scheme 14

Similarly, silylcupration of **53** in the absence of any protic quenching agents provided the desired product **55** but with relatively poor regioselectivity (Scheme 15). However, upon

THF, −10 °C, 10 h   95% E/Z = 73:27

THF/H$_2$O (7 equiv.), −10 °C, 10 h   94% E/Z = 100:0
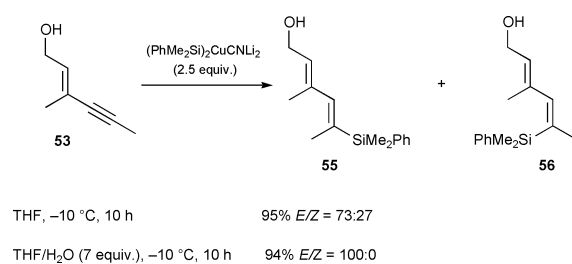
Scheme 15

addition of 7 equiv. of H$_2$O the desired dienylsilane was obtained in 94% yield as a single regioisomer.

H$_2$O was also shown to improve the Barbier addition of *in situ* prepared allylzinc to imines derived from (S)-valine esters (Table 3).[5d] Under anhydrous conditions (entries 1–3), the diastereoselectivity decreased under prolonged reaction times. Therefore, diastereomerically pure products could only be obtained at the expense of lower chemical yields. The authors suspected that the addition was reversible, which would account for the loss of diastereoselectivity under extended reaction times. In attempts to inhibit possible equilibration, the reaction was conducted in the presence of an internal proton source so that protonation of the zinc salt of **25** would lead to an irreversible process. In the presence of 0.7 equiv. of H$_2$O, the desired diastereomerically pure product was indeed obtained in 92% isolated yield after 24 h. Although the rate of addition was decreased by the presence of H$_2$O, the diastereoselectivity improved considerably (Table 3, entries 4 and 5).

Table 3 Effect of H_2O and reaction time on the diastereomeric ratio of **58**

Entry	Additive (equiv.)	Time/h	Product	Yield (%)	dr (%)
1	—	0.5	(S,S)	80	>99:1
2	—	1.5	(S,S)	100	94:6
3	—	32	(S,S)	100	52:48
4	H_2O (0.7)	7	(S,S)	60	100:0
5	H_2O (0.7)	24	(S,S)	92	100:0

A study directed towards the development of conditions favorable for nucleophilic additions to imines in the presence of carbonyl groups demonstrated that the combination of water and $BF_3 \cdot Et_2O$ was a superior catalyst for the selective addition of silyl enolates to imines in the presence of benzaldehyde.[20] $BF_3 \cdot Et_2O$ alone, if used in catalytic amounts, was sufficient to promote the addition of 1-phenyl-1-trimethylsiloxyethane to benzylideneaniline in the presence of 1 equiv. of benzaldehyde (Table 4, entry 2). However, superior results were obtained

Table 4 Imine-selective addition reactions

Entry	$BF_3 \cdot Et_2O$/ equiv.	Additive (equiv.)	Time/h	**59** (%)	**60** (%)
1	1	—	0.5	18	48
2	0.2	—	0.5	60	15
3	0.2	H_2O (0.1)	0.5	92	5
4	0.2	H_2O (1.0)	1	98	1
5	0.2	H_2O (10)	0.5	97	1
6	0.2	H_2O (50)	17	92	0

when 1 equiv. of H_2O was added to the reaction mixture (Table 4, entry 4). The combination of $BF_3 \cdot Et_2O$ and H_2O might form the hydrate which transfers a proton to give H_3O^+ and BF_3OH^-. Activation of the imine by preferential protonolysis could account for the reversal in selectivity.

## Water as a Lewis acid activator or co-activator

Although the Pauson–Khand reaction remains one of the most effective methods for the preparation of cyclopentenones, its scope has been somewhat limited by high temperatures and long reaction times. According to the generally accepted mechanism, the rate-limiting step involves decarbonylation, which generates a free coordination site for the incoming olefin.[21] Many successful attempts at accelerating the reaction by employing various 'hard' Lewis bases as additives have been disclosed. The presence of these 'hard' Lewis bases (*N*-methylmorpholine *N*-oxide,[22a] trimethylamine *N*-oxide,[22a] DMSO,[22b] sulfoxides,[22b] cyclohexylamine and NH_4OH[21c]) is thought to accelerate the decarbonylation step. Water (as a solvent) retarded the reaction.[22c] However, small amounts of H_2O proved to be very effective in accelerating the catalytic variant of the Pauson–Khand reaction.[23] Although H_2O was not the best promoter in this study, it certainly is the cheapest and perhaps most convenient to use (Table 5).

Table 5 The catalytic Pauson–Khand reaction in the presence of various 'hard' Lewis bases

Entry	Additive	CO/atm	**61** (%)	**62** (%)
1	—	7	82	12
2	Cyclohexylamine	7	93	5
3	Diisopropylamine	7	28	64
4	Diisopropylethylamine	7	7	81
5	Benzyl alcohol	7	21	73
6	2-Methoxyethanol	7	71	27
7	Ethylene glycol	7	97	0
8	1,4-Dioxane	7	5	72
9	1,2-Dimethoxyethane	7	0	91
10	1,2-Dimethoxyethane (solvent)	7	78	9
11	1,2-Dimethoxyethane	1	83	5
12	1,2-Dimethoxyethane	3	6	82
13	1,2-Dimethoxyethane	20	0	93
14	H_2O (20 equiv.)	7	33	63
15	H_2O/toluene (1:2)	7	65	21

The cyclization of **63** provides an example where H_2O proved to be a superior additive to DME (Scheme 16).

additive:
DME: 90%
H_2O: 95%

Scheme 16
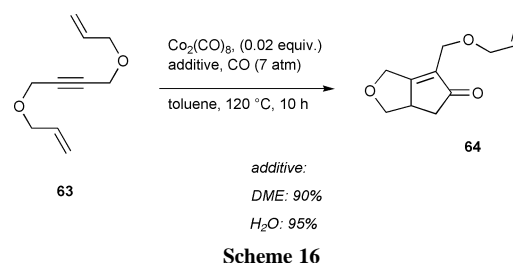
Buono and co-workers recently described a new chiral copper catalyst for the asymmetric addition of dialkylzinc reagents to cyclic enones.[24] Initially, diethylzinc addition to cyclohexenone proceeded in a yield of 55% with an ee of 45% using a new CuI–QUIPHOS catalyst in toluene at −20 °C (Table 6, entry 1).

**Table 6** CuI–QUIPHOS catalyzed addition of Et_2Zn to cyclohexenone

Entry	Solvent	Additive (equiv.)	Yield (%)	Ee (%)
1	Toluene	—	53	45
2	THF	—	53	25
3	CH_2Cl_2	—	55	7
4	1,2-Dichloroethane	—	69	30
5	CCl_4	—	34	7
6	Toluene	H_2O (0.5)	55	6
7	THF	H_2O (0.5)	50	22
8	1,2-Dichloroethane	H_2O (0.5)	55	23
9	Hexane	H_2O (0.5)	0	0
10	CH_2Cl_2	H_2O (0.5)	76	61
11	CH_2Cl_2	$Zn(OH)_2$ (0.1)	64	44
12	CH_2Cl_2	$Zn(OH)_2$ (0.25)	81	53

Attempts to optimize this result by varying the solvent were unsuccessful (entries 1–5). However, a dramatic increase in ee

was observed upon addition of 0.5 equiv. of H_2O. Interestingly, this effect was only observed when CH_2Cl_2 was used as the solvent (Table 6, entries 6–10). The authors proposed that Et_2Zn was hydrolyzed to $Zn(OH)_2$ which supposedly was a stronger, more effective Lewis acid. This hypothesis was tested by adding $Zn(OH)_2$ in place of H_2O (entries 11 and 12). A similar result was obtained when 0.25 equiv. of $Zn(OH)_2$ were used, although further increases in the amount of $Zn(OH)_2$ had deleterious effects.

Apparently, the increased Lewis acidity of the hydrolyzed zinc species activated the carbonyl moiety and, perhaps intramolecularly, provided anchimeric assistance to the approaching Cu species through chelation. This interaction might result in a 'tighter' transition state and higher levels of enantioselectivity (Scheme 17).
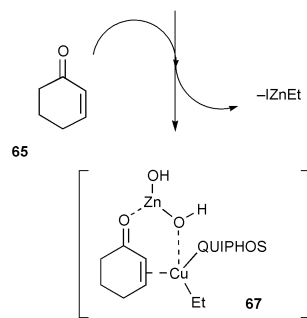
Scheme 17

Although the formation of $Zn(OH)_2$ is plausible, especially since the direct addition of this additive provided results similar to those with H_2O, the formation of alternative agents such as EtZn–O–ZnEt cannot be excluded. The favorable results using $Zn(OH)_2$ could then be explained by the analogous formation of a species such as EtZn–O–Zn–O–ZnEt. We have found that addition of water to a solution of Me_2Zn produces a stronger Lewis acid capable of activating benzaldehyde towards dimethylzinc addition (Scheme 18).[25] This reaction does not proceed to any significant degree in the absence of H_2O.
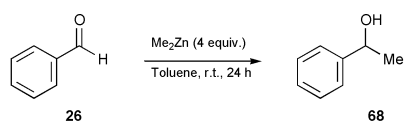
without H_2O: trace

with 1 equiv. of H_2O: 60% (NMR yield)

Scheme 18

Corey and co-workers have observed that the addition of 0.3–0.33 equiv. of H_2O to lithium dimethylcuprate at −78 °C generates a substantially more reactive, and selective agent for conjugate addition to the chiral α,β-enone **69** (Table 7).[26]

The authors speculated that the heightened reactivity upon addition of H_2O arose from the formation of a mixed planar cuprate species as shown in Scheme 19. The exocyclic lithium moiety was described as being 'especially suited for chelate formation with the α'-alkoxy-α,β-enone'.

Shibasaki, Sasai and co-workers have seen a significant improvement in their Yb-BINOL catalyzed asymmetric epoxidations of acyclic enones in the presence of H_2O as an additive.[27,28] Both yields and ee's were greatly affected by the amount of added H_2O. The best results were obtained when 5 equiv. of H_2O were used (Scheme 20). Interestingly, and not necessarily easy to reconcile with the effect of water, the use of 4 Å MS was shown to be critical to obtain optimal results.

Addition of H_2O has also been shown to lead to slightly improved enantioselectivities in the addition of 1-naphthol to pyruvate esters.[29] The chiral 1,4:5,8-dimethano-

Table 7 Diastereoselective organocuprate additions

| Entry	Solvent	Temperature/°C	Additive (equiv.)	Yield (%)	Ratio **70:71**
1	Et_2O	−45	LiI (4)	88	14:1
2	THF	−45	—	80	2.5:1
3	THF	−78	TMS-Cl (5)	>80	2:1
4	Et_2O	−78	H_2O (0.3–0.33)	93–100	16:1
5	Et_2O	−78	H_2O (0.3) + TMS-Cl (5)	>90	33:1
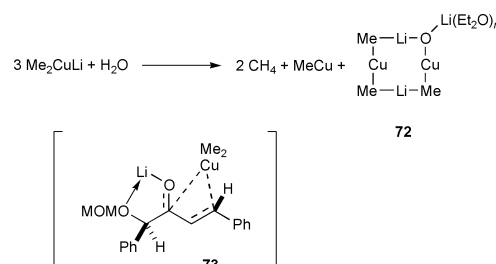
Scheme 19
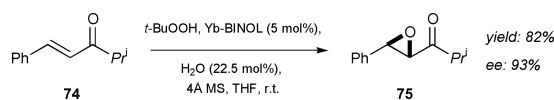
Scheme 20

1,8,10,10,11,11-hexamethyl-1,2,3,4,5,6,7,8-octahydro-4a,4b,8a,9,9a-η-9H-fluorenezirconium trichloride **79** (5 mol%), H_2O (27 mol%) and an excess of ethyl pyruvate in CH_2Cl_2 at −10 °C provided the adduct **78** in 70% yield and with an ee of 89% after 5 h (Table 8). Without H_2O and under otherwise

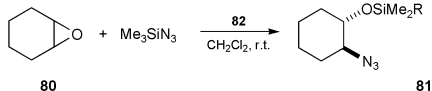**Table 8** Effect of H_2O on yield and ee in the formation of **78**
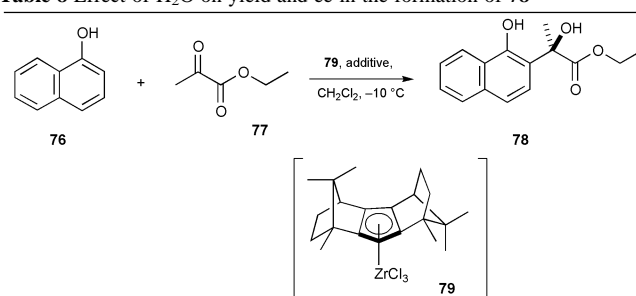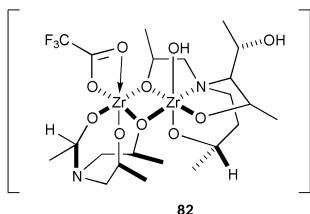
Entry	Additive (equiv.)	Time/h	Conversion (%)	Ee (%)
1	—	2	70	80
2	—	5	85	80
3	—	24	Quant.	72
4	H_2O (0.27)	2	55	89
5	H_2O (0.27)	5	70	89
6	H_2O (0.27)	24	90	84

identical conditions, **78** was obtained in 85% yield with a lower ee of 80%. It is known that $CpZrCl_3$ forms adducts with donor ligands such as THF or DMF to give a stable Zr $d^0/16e^-$ intermediate.[30] Accordingly, it seems possible that two water

molecules coordinate to **79** to provide a related 16e⁻ intermediate. The resulting change in geometry could be responsible for the modest increase in enantiomeric excess. Again, it appears likely that the reversibility of the reaction is partly responsible for the drop in ee under prolonged reaction times. However, unlike the previously discussed reversible addition of allylzinc reagents to imines, the use of water in this case does not appear to inhibit this equilibration as effectively. Alternatively, catalyst decomposition into achiral species can also lead to lower reaction ee's.

Another Zr-catalyzed asymmetric reaction that has been reported to be positively influenced by the presence of water is the Zr-catalyzed enantioselective addition of azide to cyclohexene oxide (Table 9).[31] Both the yield and ee in this process were

Table 9 Enantioselective opening of *meso* epoxides with TMS-azide

Entry	Additive	[Additive]/ [epoxide]	Relative rate	Ee (%)
1	—	—	1.0	84
2	CyOSiMe₂Prⁱ	2.2	2.1	86
3	CyOH	0.19	2.5	85
4	n-C₅H₁₁OH	0.35	2.5	83
5	H₂O	0.63	0	—
6	H₂O	0.32	0.79	79
7	H₂O	0.16	2.2	88
8	H₂O	0.10	2.1	85
9	H₂O	0.073	1.3	85
10	H₂O	0.027	1.3	82
11	4 Å MS	—	0.2	54

increased by addition of silyl ethers, alcohols and H_2O. These additives might be effective in assisting in the catalytic turnover of the Zr-complex.

In 1991, Miyashita and co-workers presented an elegant stereospecific methylation of γ,δ-epoxy acrylates using a trimethylaluminum–H_2O mixture (Scheme 21).[32] Water was
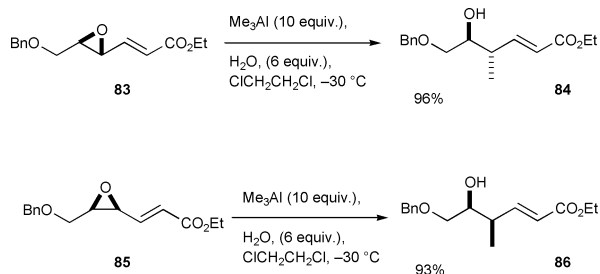
Scheme 21

shown to be critical for this transformation; under anhydrous conditions the reaction did not occur. Furthermore, replacing H_2O with MeOH also resulted in recovered starting material. Both *cis*- and *trans*-epoxides were readily methylated with complete regio- and stereocontrol.[33]

This methodology was successfully applied toward a key intermediate in the formal synthesis of *ent*-tirandamycin B (Scheme 22).[34]
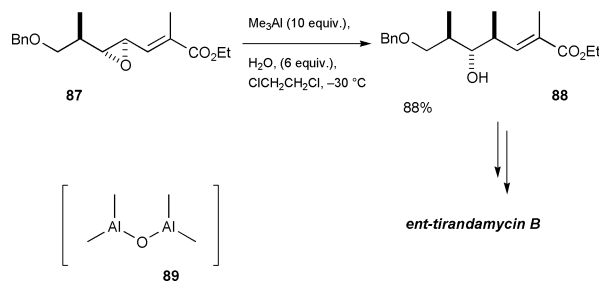

Scheme 22

The bisaluminum-oxo intermediate **89** was proposed to be a reactive intermediate formed by the reaction of H_2O and excess trimethylaluminum in this process. Due to the dual Lewis acid/ nucleophilic nature of this species, its exact role remains unclear. It is possible that **89** behaves both as a strong Lewis acid and/or a more reactive methylating agent.

In a related reaction scheme, a water–Me_3Al mixture was found to be useful for accelerating the zirconocene dichloride-catalyzed methylalumination of alkynes. Addition of 1.5 equiv. of H_2O to 3 equiv. of Me_3Al in the presence of 0.2 equiv. of Cp_2ZrCl_2 generated a much more reactive methylating agent.[35] Methylalumination proceeded quite rapidly under these modified conditions, providing the desired methylated product in quantitative yield (as 97:3 ratio of regioisomers) after 10 min at −78 °C (Scheme 23). In comparison, under standard conditions oct-1-yne was methylated in a 95:5 stereoselectivity after 3 h at room temperature.[36]
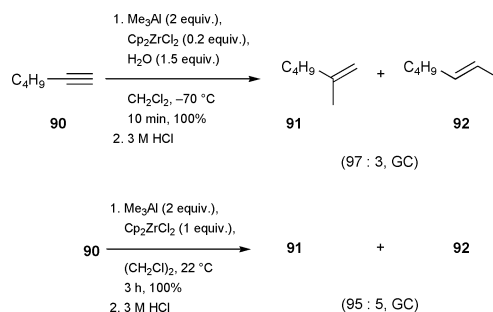
Scheme 23

More recently, this dramatic rate effect of H_2O addition in carbometalation reactions has been extended to the asymmetric methylalumination of terminal alkenes.[37] In 1995, Negishi and Kondakov reported the first asymmetric methylalumination of alkenes using Erker's chiral zirconium catalyst **95**.[38,39] Despite the good to excellent yields and ee's obtained under the original conditions, substrates such as styrene proved quite resistant towards the methylation process, and after 22 days only 30% product was obtained (Scheme 24).[38a] In contrast, a dramatic increase in the reaction rate was achieved by the addition of 1 equiv. of H_2O to 4 equiv. of Me_3Al.[37] The desired product was obtained after 12 h at −5 °C in 73% yield with an ee of 89%. A more quantitative assessment of the rate difference with styrene under the two sets of reaction conditions is shown in Fig. 1. Monitoring the appearance of 2-phenylpropanol at 0 °C by GC revealed that in the presence of 1 equiv. of H_2O the reaction went to >85% completion after 8 h. Without the benefit of water, no trace of 2-phenylpropanol could be detected. Although more elaborate studies have yet to be conducted in order to shed more light on the mechanism of this water-induced acceleration, it is feasible that a species such as **89** is being formed in this process as well. The degree in which MAO (methylaluminoxane) activates Zr-based catalysts in Ziegler–Natta type polymerizations is relatively well known, and yet also poorly understood in a mechanistic sense.[40] In analogy to the effect of MAO in the Ziegler–Natta process, we believe that a reasonable mechanism involves formation of a cationic

Scheme 24
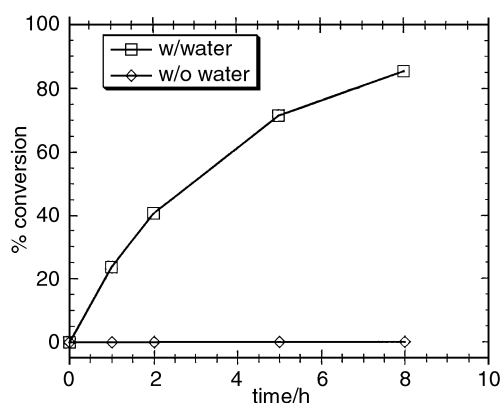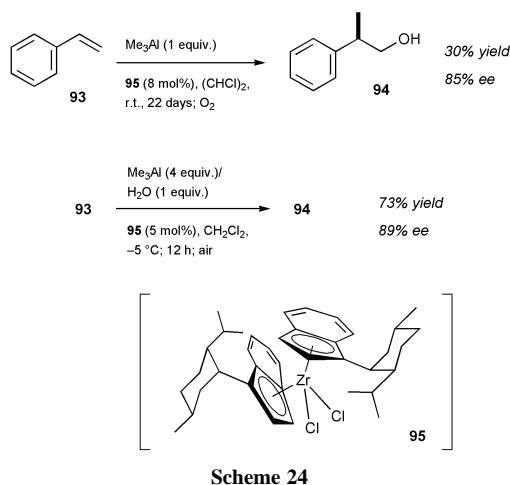
Fig. 1 Rate analysis of the chiral zirconocene-catalyzed methylalumination of styrene at 0 °C using 4 equiv. of trimethylaluminium, 5 mol% of chiral catalyst **95**, and styrene at a 0.17 M concentration in CH_2Cl_2 in the absence and presence of 1 equiv. of H_2O.

zirconocene intermediate formed by ligand (Cl-, or more likely Me-) abstraction from the zirconocene complex by the more Lewis acidic intermediate **89** or a higher molecular weight, more reactive analog thereof that is generated upon addition of H_2O to the reaction mixture.

Conclusions

Maybe one of the most surprising aspects of our survey is the large number of well-documented cases where the addition of catalytic or stoichiometric amounts of H_2O to the reaction mixture of organic and organometallic processes has led to beneficial effects on reaction rate, product yield, and regio-, diastereo- and enantioselectivity. Since, in particular when moisture-sensitive organometallic reagents or Lewis acids are involved, synthetic chemists go to great lengths to avoid traces of water in the reaction mixture, it can only be speculated how many new H_2O-accelerated processes remain to be (re-)discovered, and how many cases of adventitious water effects have played a significant but yet unrecognized role in influencing the course of the reaction. A most intriguing aspect of H_2O-promoted processes is the role that this strong Lewis-base can play in providing the source for transient highly Lewis-acidic species. After a sometimes vigorous exothermic reaction with organometallic derivatives that can only be controlled by careful addition of sub-equimolar quantities of H_2O, the resulting metal oxide or metal hydroxide species is activated at the metal center by the negative inductive effect of the powerful electron-withdrawing oxygen substituent and becomes more

Lewis acidic. This scenario is most likely operative when H_2O is added to reaction mixtures containing alanes. In addition, the oxide or hydroxide ligand on the metal presents a source for chelation interactions that change aggregation states of organometallics and can provide anchimeric assistance. Unfortunately, there is a dearth of mechanistic information regarding the interaction and the actual active species obtained upon reaction of H_2O with reactive organometallics or Lewis acids, and beyond empirical experimentation there is little general information that could be used as a guideline when water-effects might prove beneficial. The situation is a bit more transparent in cases when water is used as a hydrolyzing agent leading to secondary products that serve as catalysts or promoters or when water provides a quenching agent intended to drive chemical equilibria. More often than not, the latter working hypotheses can be tested by preforming the active species, monitoring the reaction mixture spectroscopically, or by a thorough analysis of reaction intermediates and products. In all aspects of water-mediated processes, we are anticipating that chemists will continue to discover surprising new effects and beneficial uses of H_2O as a highly versatile reagent in the organic chemistry tool box.

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