

The new world of organic reactions in water*

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Abstract: Different reactivities and selectivities are observed in water compared with those in organic solvents. In this article, such three examples are described. While ammonia was known not to react in metal-catalyzed allylic amination, palladium-catalyzed allylic amination using aqueous ammonia proceeded to afford primary amines in high yields. Second, allylboronates reacted with aldehydes in aqueous media to afford α -addition adducts exclusively in high yields with high diastereo- and enantioselectivities using $\text{Zn}(\text{OH})_2$ with ligands as catalysts. Finally, it was found that catalytic use of $\text{In}(0)$ was effective for the reactions of allylboronates with ketones in water.

Keywords: allylic amination; allylation; asymmetric catalysis; C–C bond formation; green sustainable chemistry; water.

INTRODUCTION

Organic reactions are usually carried out in organic solvents in modern organic chemistry. It is very rare to use water as the reaction medium, while water is safe, benign, environmentally friendly, and inexpensive compared with organic solvents [1]. In organic reactions in aqueous media, there are two major obstacles to be surmounted. First, many reactive substrates, reagents, and catalysts are decomposed or deactivated by water. Second, most organic substances are insoluble in water. On the other hand, we have investigated organic reactions in water from the standpoint that the most ideal reactions, enzymatic reactions *in vivo*, are carried out in water. Indeed, we have found unique reactivity and selectivity in aqueous media, which are not observed in organic solvents where water plays key roles. In this article, three examples where different reactivities and selectivities are observed in water compared with those in organic solvents are described. It is noted that these three is just examples and just the tip of the iceberg. The author believes that many other examples may exist but have not yet been uncovered [2,3].

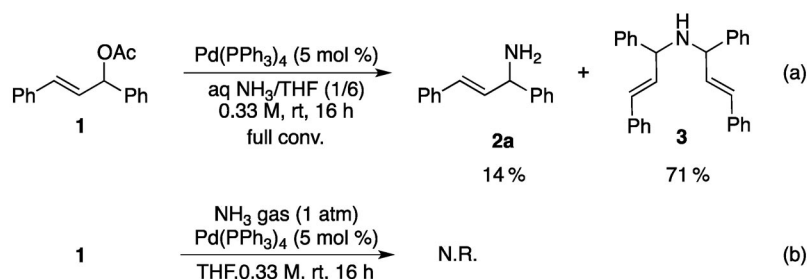
PALLADIUM-CATALYZED ALLYLIC AMINATION USING AQUEOUS AMMONIA

Palladium-catalyzed allylic amination is a well-established method for the synthesis of allyl amines. Indeed, during these three decades, a variety of nitrogen nucleophiles have been developed for this useful transformation [4]. However, although ammonia is one of the most attractive nitrogen sources from a cost and atom economical point of view [5,6], there were no reports on the use of ammonia for metal-catalyzed allylic amination providing primary amines before our first work [7]. Even some authoritative review articles dealing with allylic aminations mentioned that “Ammonia does not react” [4b] or “Ammonia fails to act as an effective nucleophile for π -allylpalladium” [4a]. Due to “the failure of ammonia” [8], a variety of ammonia surrogates such as *p*-toluenesulfonamide [9], phthalimide [10],

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di-*tert*-butyl iminodicarbonate [11], and sodium azide [12] for allylic amination to synthesize primary amines have been reported [13]. In general, the difficulty in using ammonia for metal-catalyzed processes is as follows: (i) many kinds of transition metals are deactivated by ammonia to give stable amine complexes, and (ii) if a reaction forms a primary amine, this product is more reactive than ammonia and causes problematic overreactions.

Based on continuous studies on using ammonia as a nitrogen source for organic synthesis in our laboratory [14], it was found that the reaction of 1,3-diphenylallyl acetate (**1**) with aqueous ammonia in the presence of a catalytic amount of Pd(PPh₃)₄ proceeded with full conversion at room temperature to give 14 % of the primary amine **2a** along with 71 % of the corresponding secondary amine **3** (Scheme 1a). It is noted that these results are contrary to the common knowledge described in review articles. Moreover, ammonia gas did not give the product at all, but aqueous ammonia gave the product (Scheme 1b). Thus, ammonia did not react in the absence of water, but did react in the presence of water [7].



Scheme 1 Allylic amination using gaseous ammonia and aqueous ammonia.

Since the yield of the desired **2a** was low, several reaction conditions were examined using allyl acetate **1** as a model substrate to improve primary/secondary amine selectivity. Changing the aqueous NH₃:THF (tetrahydrofuran) ratio from 1:6 to 1:2 at 0.33 M in order to increase the quantity of ammonia resulted in slight improvement of the selectivity (Table 1, entries 1 and 2). Fortunately, the dilution method was found to be effective for improvement of the selectivity (entries 2–4). Although combination of aqueous NH₃ and nonpolar toluene resulted in no reaction, a polar aprotic solvent such as dimethyl formamide (DMF) or acetonitrile showed similar efficiency (entries 5–8). Among the solvents tested, 1,4-dioxane gave the best result at 0.11 M. Further dilution in the dioxane/aqueous NH₃ system was examined, and it was found that 0.04 M was the critical concentration for this reaction (entries 9–11). At 0.03 M the reaction did not proceed at all probably due to the deactivation of Pd(0) (entry 12). It was assumed that under such high dilution conditions, liberated PPh₃ could not stabilize catalytically active Pd(0). Indeed, by addition of 13 mol % of external PPh₃, which made the total concentration of PPh₃ as same as that in the reaction at 0.04 M, the catalyst completely recovered its catalytic activity, giving the products in good yields (entry 13).

Substrate scope of the present reaction under the optimized conditions was shown in Table 2. Not only 1,3-diaryl- but also dialkyl-allyl acetate can be applied to the present reaction to give the primary amine **2b** in 79 % yield (entry 2). The reaction of cyclic allyl carbonates possessing a variety of substituents such as aryl with both electron-donating and -withdrawing groups, and alkyl at the vinylic positions proceeded with excellent selectivities to afford the corresponding primary amines in yields around 80 % (entries 3–7). The corresponding allyl acetate was found to be unreactive. Under the same conditions in entry 3, the reaction of 2-phenylcyclohexenylallyl acetate proceeded with 38 % conversion to give **2c** in 29 % yield. It should be noted that the presence of substituents at the vinylic position is not the reason for high primary amine selectivity. Moreover, the reaction of the less sterically hindered, simple nitrogen-containing cyclic allyl carbonate gave the desired primary amine **2h** in high

yield with high selectivity (entry 8). Five- and seven-membered cyclic allyl carbonates also reacted smoothly to afford the primary amines in high yields with high selectivities (entries 9–11).

Table 1 Optimization of reaction conditions.

		Pd(PPh ₃) ₄ cat.		→		2a + 3		
1		aq. NH ₃ /solvent, rt						
Entry	Solvent	NH ₃ /Solvent	Conc. (M)	cat. (mol%)	Time (h)	Selectivity (2a/3) ^a	Yield (%) ^b	
							2a	3
1	THF	1/6	0.33	5	16	26/74	14	71
2	THF	1/2	0.33	5	6	28/72	20	66
3	THF	1/2	0.17	5	10	47/53	34	55
4 ^c	THF	1/2	0.11	5	23	59/41	40	42
5	THF	1/2	0.11	10	12	62/36	44	39
6	toluene	1/2	0.11	10	12	–	trace	trace
7	DMF	1/2	0.11	10	12	68/32	48	37
8	acetonitrile	1/2	0.11	10	12	58/42	39	46
9	1,4-dioxane	1/2	0.11	10	12	77/23	61	29
10	1,4-dioxane	1/2	0.06	10	18	83/17	66	22
11	1,4-dioxane	1/2	0.04	10	18	89/11	71	16
12	1,4-dioxane	1/2	0.03	10	18	–	0	0
13 ^d	1,4-dioxane	1/2	0.03	10	18	91/9	73	13

^aMolar ratio of 2a/3 determined by ¹H NMR spectroscopic analysis of crude material.

^bIsolated yield after chromatography. Yield of 3 was based on the half amount of 1.

^c12 % of 1 was recovered.

^d13 mol % of external PPh₃ was added.

Table 2 Allylic amination using aqueous ammonia.

Entry	Substrate	Product (2)	Conditions ^a	Selectivity ^b	Yield (%) ^c
1			a: R = Ph	89/11	71
2			b: R = -(CH ₂) ₂ Ph	93/7	79
3			c: R = Ph	96/4	81
4			d: R = <i>p</i> -MeOC ₆ H ₄ -	94/6	80
5			e: R = <i>m</i> -NO ₂ C ₆ H ₄ -	95/5	80
6			f: R = 3,5-CF ₃ C ₆ H ₃ -	97/3	82
7			g: R = -(CH ₂) ₃ Ph	>99/<1	82
8			h	94/6 ^d	85
9			i: n = 1	94/6	82
10			j: n = 3	93/7	76

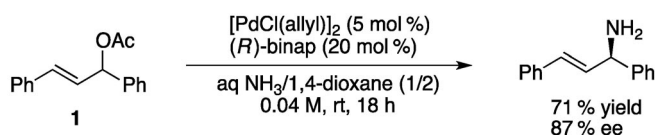
^aA: Table 1, entry 11. B: Table 1, entry 9.

^bMolar ratio of primary/secondary amine determined by ¹H NMR spectroscopic analysis of crude material.

^cIsolated yield of 2 after chromatography.

^dCalculated based on isolated products.

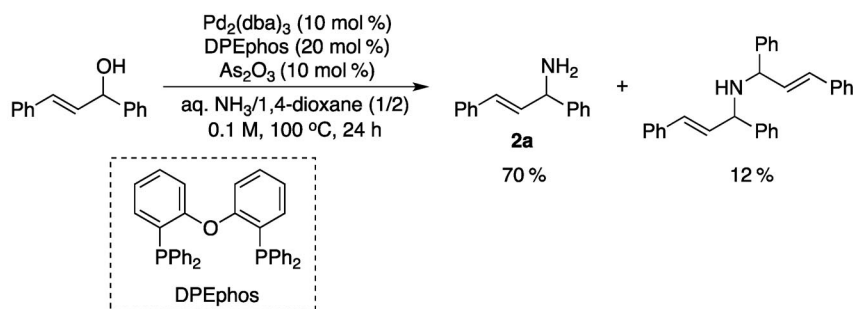
A preliminary investigation on asymmetric variant of this reaction was also conducted. In the presence of catalytic amounts of $[\text{PdCl}(\eta^3\text{-allyl})_2]$ and (*R*)-BINAP, asymmetric allylic amination using aqueous ammonia proceeded to give the corresponding allyl amine in 71 % yield with 87 % ee (Scheme 2). The effective chiral induction observed here suggested that no replacement of the bis-phosphine ligand by ammonia occurred under the present conditions. This is the first example of catalytic asymmetric synthesis using aqueous ammonia as a nitrogen source, although a somewhat large amount of chiral ligand is needed. By using 12 mol % of binap, the reaction did not proceed at all probably due to the same reason discussed in Table 1 (entry 12). An excess ligand may play a role for stabilization of catalytically active Pd(0), and indeed, the use of triphenylphosphine as an additive could decrease the amount of binap to an equimolar amount of Pd(0) [15]. Absolute configuration of the product amine was assigned to be *R* by transformation of the product into the literature known tosyl amine [16]. The sense of stereochemistry in chiral induction was the same as that in the allylic substitution reaction catalyzed by Pd/BINAP complexes [17].



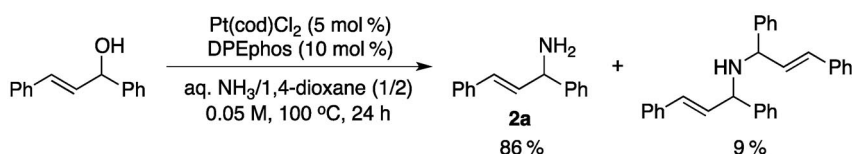
Scheme 2 A preliminary investigation on asymmetric allylic amination using aqueous ammonia.

Thus, palladium-catalyzed allylic amination using aqueous ammonia for the preparation of primary amines has been developed for the first time. It is noteworthy that the use of aqueous ammonia is essential, and that ammonia gas (without water) did not react at all. The first catalytic asymmetric synthesis using aqueous ammonia as a nitrogen source was also demonstrated. Further investigations to clarify the role of water provided from aqueous ammonia are in progress.

While the starting allyl acetates were prepared from allylic alcohols, direct allylic amination from allylic alcohols was possible using $\text{Pd}_2(\text{dba})_3$, DPEphos, and As_2O_3 [18] (Scheme 3) or $\text{Pt}(\text{cod})\text{Cl}_2$ and DPEphos as catalyst (Scheme 4) [19,20]. In both cases, thermal conditions are needed.



Scheme 3 Direct allylic amination from allylic alcohol with Pd.



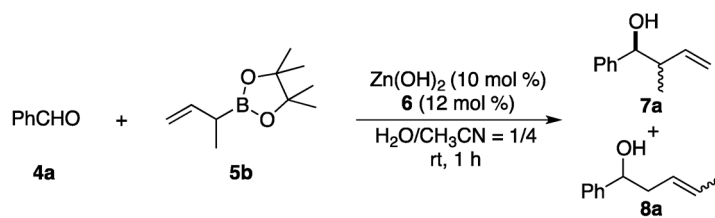
Scheme 4 Direct allylic amination from allylic alcohol with Pt.

ALDEHYDE ALLYLATION WITH ALLYLBORONATES IN AQUEOUS MEDIA

Allylation is one of the most important and widely used C–C bond-forming reactions in organic chemistry. While several allylating reagents have been extensively studied, allylsilanes [21], allylstannanes [22], and allylborons [23–25] are among the most popular species especially from a synthetic utility viewpoint. As for the reactions with aldehydes, allylsilanes and allylstannanes often react in the presence of Lewis acids via acyclic transition states affording *syn*-products predominantly [21,22]. Allylborons are more reactive than allylsilanes and allylstannanes. They react with aldehydes spontaneously *in the absence of a catalyst* via cyclic transition states due to the Lewis acidity of boron, to give *syn*- and *anti*-products depending on the geometry of starting allylborons [23–26]. Lewis acid-catalyzed reactions of allylboronates with aldehydes have also been reported [26]. While boron reagents have been established as one of the most reactive and nontoxic reagents, γ -addition products have been obtained in almost all cases in the reactions with aldehydes [27]. Contrary to this, it was revealed that α -addition products are obtained exclusively by the reactions of allylboronates with aldehydes in the presence of a catalytic amount of zinc hydroxide [Zn(OH)₂] with a ligand in aqueous media [28,29].

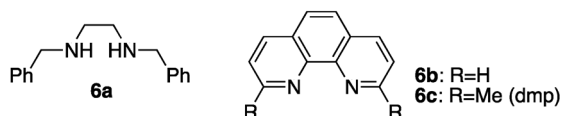
In the presence of 10 mol % of Zn(OH)₂ in H₂O/CH₃CN (1/4), pinacol allylboronate (**5a**) was treated with benzaldehyde. The reaction proceeded smoothly to afford the desired homoallylic alcohol in high yield. However, since it was difficult to distinguish catalyzed and noncatalyzed reactions at this stage, the reaction of α -methyl-substituted allylboronate **5b** with benzaldehyde was then examined (Table 3). When the reaction was carried out *in the absence of Zn(OH)₂*, γ -addition product **8a** was obtained selectively (entry 1, noncatalyzed reaction), while a mixture of α -adduct **7a** and γ -adduct **8a** ($\alpha/\gamma = 45/55$) was produced in the presence of Zn(OH)₂ (entry 2). It was noted that the very rare α -addition product was formed in the presence of Zn(OH)₂, although the selectivities (both α/γ and diastereoselectivity of **7a**) were not high. Various parameters were further examined, and, finally, interesting ligand effects were uncovered. When Zn(OH)₂ was combined with diamine **6a**, the *syn/anti* ratio of **7a** was improved albeit with moderate α/γ selectivity (entry 3). The α/γ selectivity was improved significantly in the presence of Zn(OH)₂ with 2,9-dimethyl-1,10-phenanthroline (**6c**, dmp), and the *syn/anti* ratio was also high (entry 5). Furthermore, when the reaction was conducted in dry CH₃CN, γ -adduct **8a** was obtained exclusively (entry 6). Thus, it was revealed that the use of water is essential for the

Table 3 Effect of Zn(OH)₂, ligands, and water.



Entry	Ligand (6)	Yield (%)	7a/8a	<i>Syn/Anti</i> (7a)
1 ^a	-	77	5/95	-
2	-	81	85/15	69/31
3	6a	81	81/19	96/4
4	6b	84	33/67	78/22
5	6c	82	>98/<2	93/7
6 ^b	6c	61	<2/>98	-

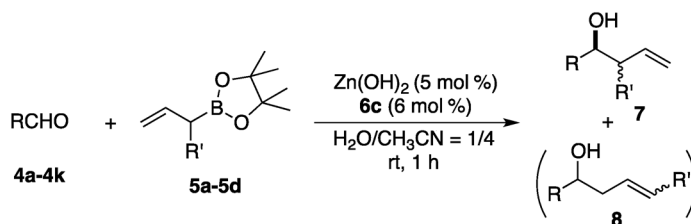
^a In the absence of Zn(OH)₂. ^b In dry CH₃CN.



α -selectivity. In all cases, conversion of **7a** into **8a** or of **8a** into **7a** was not observed. Moreover, no isomerization of **5b** to crotylboronate species occurred under the conditions.

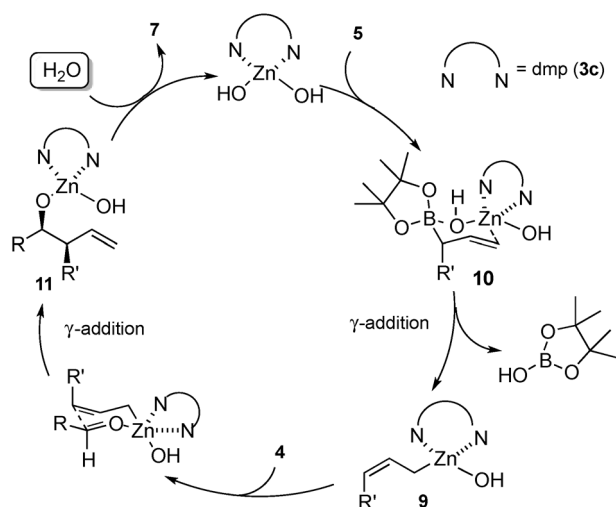
Several aldehydes were then treated with α -substituted allylboronates in the presence of 5 mol % of $\text{Zn}(\text{OH})_2 \cdot \mathbf{6c}$ in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ (1/4) (Table 4). It is noted that in all cases only α -adducts **7** were obtained in high yields. To the best of our knowledge, during a relatively long history of allylboron chemistry, this is a very rare case where α -addition products are obtained exclusively from aldehydes [27,30]. As for the *syn/anti* selectivities of **7**, high *syn*-selectivities were obtained in the reactions of **5a** with aromatic aldehydes (entries 1–7). While the *syn/anti* selectivities decreased slightly for hetero-aromatic aldehydes (entries 8–10), a mixture of *syn*- and *anti*-**7** was obtained from 3-phenylpropion-aldehyde (entry 11). Regarding the α -substituted allylboronates, not only **5b** but ethyl- (**5c**), butyl- (**5d**), and *i*-butyl- (**5e**) substituted allylboronates reacted smoothly to afford α -adducts **7** exclusively in high yields with high *syn*-selectivities (entries 12–14).

Table 4 $\text{Zn}(\text{OH})_2 \cdot \mathbf{6c}$ -catalyzed allylation reactions in aqueous media.



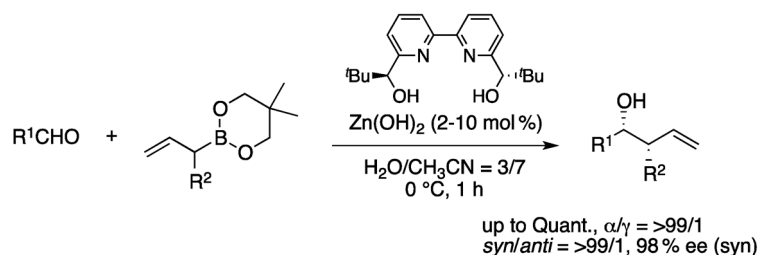
Entry	Aldehyde	5 (R ¹)	Yield (%)	7/8	<i>Syn/Anti</i> (7)
1	4a : R ¹ =H, R ² =H	5b (Me)	83	>98/<2	94/6
2	4b : R ¹ =CH ₃ , R ² =H	5b	85	>98/<2	93/7
3	4c : R ¹ =OCH ₃ , R ² =H	5b	82	>98/<2	93/7
4	4d : R ¹ =NO ₂ , R ² =H	5b	91	>98/<2	96/4
5	4e : R ¹ =Br, R ² =H	5b	92	>98/<2	94/6
6	4f : R ¹ =H, R ² =OCH ₃	5b	92	>98/<2	91/9
7	(1g)	5b	91	>98/<2	97/3
8	(1h)	5b	85	>98/<2	93/7
9	(1i)	5b	84	>98/<2	86/14
10	(1j)	5b	85	>98/<2	77/23
11	Ph(CH ₂) ₂ CHO (1k)	5b	84	>98/<2	50/50
12	4a	5c (Et)	89	>98/<2	89/11
13	4a	5d (Bu)	81	>98/<2	88/12
14	4a	5e (<i>i</i> -Bu)	85	>98/<2	90/10

On the mechanism of this α -selective allylation (Scheme 5), it was assumed that the key was conversion of allylboronates **5** into *Z*-allylzincate species **9** (via **10**, γ -addition), which could immediately react with aldehydes **4** to afford **11** (via γ -addition); thus, two γ -additions could result in providing α -addition products. Water could facilitate regeneration of the zinc catalyst from **11**. Electrospray ionization (ESI)-mass spectra of a mixture of $\text{Zn}(\text{OH})_2$ with **6c** and **5a** (see Table 4) showed a signal that corresponded to **9**, although the position and geometry of the methyl group were unknown. According to the mechanism proposed, it should be noted that the Zn -catalyzed reactions proceed much faster than background (noncatalyzed) reactions [31].



Scheme 5 Assumed catalytic cycle.

This reaction has been applied to asymmetric catalysis using $\text{Zn}(\text{OH})_2$ and a chiral ligand (Scheme 6) [32–34].



Scheme 6 Catalytic asymmetric allylation in aqueous media.

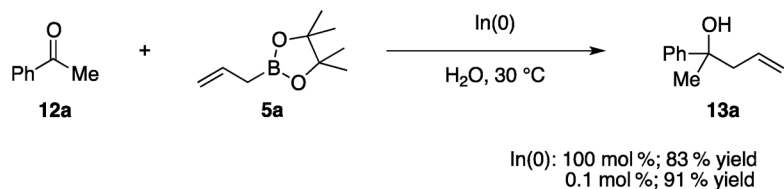
Thus, very rare, α -selective allylation reactions of allylboronates with aldehydes has been achieved. The use of $\text{Zn}(\text{OH})_2$ with ligands as catalysts in aqueous media is a key in these reactions. The role of the ligand and water toward full elucidation of the mechanism of these unique α -selective allylation reactions of allylboronates with aldehydes are under investigation.

CATALYTIC USE OF $\text{In}(0)$ FOR C–C BOND TRANSFORMATIONS IN WATER

There have been remarkable advances in catalytic allylations of ketones [35] using stannanes [36], silanes [37], boron reagents [38], and in situ prepared manganese compounds [39] in combination with various catalysts. Unfortunately, however, these reactions rely on strictly anhydrous conditions and/or on the use of more than 1 equiv of corrosive and/or toxic allylation agents. Moreover, the substrate scope is limited in many cases. With respect to safety and environmental concerns, development of general catalytic allylations of ketones in water is of central importance. The catalytic use of $\text{In}(0)$ was found to be effective for the general catalytic C–C bond transformations in water. While organoindium reagents are known to tolerate various functional groups [40], more than a stoichiometric amount of In metal [41] is typically required in synthesis [40,42–44]. This is the first case that the catalytic use of

In(0) works well in C–C bond formation [45–47]. Here again, water is essential as a solvent, and even no reaction or very sluggish reactions occurred in organic solvents.

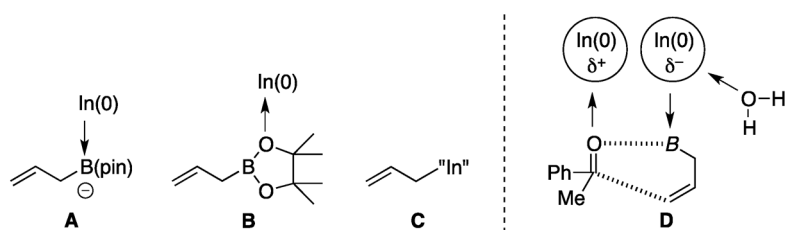
The model study was carried out using acetophenone (**12a**; $R^1 = \text{Ph}$, $R^2 = \text{Me}$) and allylboronate **5a** in water (Scheme 7); the noncatalyzed reaction essentially did not proceed, while the desired product **13a** ($R^1 = \text{Ph}$, $R^2 = \text{Me}$) was obtained in 83 % yield in the presence of 100 mol % of In(0) powder [48]. No undesired compounds such as pinacol coupling-type or reduction products were detectable in the crude reaction mixtures. Surprisingly, the In metal was recovered quantitatively after the reaction. Based on this crucial observation, the catalytic loading could be reduced to as little as 0.1 mol % under rigorously optimized conditions (90 % yield) [49]. It is truly remarkable that this C–C bond formation selectively proceeds with a catalytic amount of In(0), since generally 1–2 equiv of In metal are required for metal-to-In transmetalations [42a,c]. Organic solvents were screened in order to confirm the required presence of water. Under neat conditions, only a trace amount of product **13a** was formed; therefore, it was ruled out that this reaction proceeds in concentrated organic-phase droplets. Moreover, the use of various organic solvents such as *n*-hexane, toluene, THF, dichloromethane (DCM), MeCN, DMF, MeNO₂, dimethyl sulfoxide (DMSO), *t*-BuOH, *n*-BuOH, *i*-PrOH, and EtOH proved to be ineffective; thus, water likely plays a key role in the present reaction. This dramatic solvent effect stands in sharp contrast to In(I) catalysis, in which anhydrous THF was the most efficient solvent [48a].



Scheme 7 In(0)-catalyzed allylation of ketones **12** with **5a** in water.

The independent use of In(I) and In(III) compounds (3 mol %) for the allylation of **12a** with **5a** in water revealed that In(I) was significantly more active than In(III). In(I) readily decomposed upon contact with water to form In(0), which is surmised to be the real catalyst; In(III) is stable in water. A possible boron-to-In transmetalation was examined by using an allylindium species, independently generated in situ from allyl bromide with In(0) (100 mol %) in water; the isolated yield was moderate (40 %). Preliminary ¹H and ¹¹B NMR spectroscopic experiments in D₂O with allylboronate **5a** in the presence of In(0) (100 mol %) indicated substantial decomposition of **5a** in the absence of **12a**; another allyl species could not be identified. NMR spectroscopic monitoring of the In(0)-catalyzed allylation of **12a** with **5a** in D₂O revealed the direct formation of product **13a**; the allylborated ketone (O–B bond) was not detected.

At the current stage, it is believed that simple Lewis base or acid activation of **5a** with In(0) does not play the key role in this catalytic system (Scheme 8, species **A** or **B**). It is proposed that In shows a new type of catalytic activation of both allylboronate and ketone; the key may be the use of water as a small polar protic solvent with a high dielectric constant, being able to activate In(0) as a Lewis base (species **C**). Partial electron transfer from the oxygen lone pair of H₂O to the In metal surface may occur (Lewis base activation). Alternatively, water may be necessary for the stabilization of key intermediates or for the hydrolysis of the assumed O–B bond in the initially formed allylborated ketone. The size, the hydrogen bonding ability, and the proton acidity of the solvent might be critical as well. Thus, In(0) may serve as a surface-activated dual catalyst capable of activating **5a** as a Lewis base and **12a** as a Lewis acid. Alternatively, In(0) may transfer one electron to the boron atom of **5a** (SET) [50], thereby triggering the formation of a reactive allylindium(I) reagent at the metal surface via catalytic transmetalation (species **D**). It is the most likely that the reaction proceeds at the In metal surface.



Scheme 8 Possible mechanism of In(0) catalysis in water.

The scope of ketones **12** was surveyed for this In(0)-catalyzed allylation with **5a** under optimized conditions (Table 5) [49]. As shown in Table 5, high yields were obtained for various aromatic, hetero-aromatic, and aliphatic ketones. Remarkably, both acyclic and cyclic substrates containing various functional groups such as fluoro, bromo, hydroxy, methoxy, and amino groups were tolerated.

Table 5 Scope of ketones **12** for In(0)-catalyzed allylation with **5a** in water.

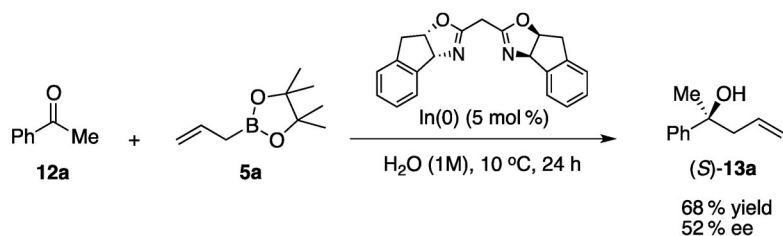
Entry	Ketone 12	Yield (%)	Entry	Ketone 12	Yield (%)
1	12a : R ¹ = Ph, R ² = Me	92	12	12l : R ^{1,2} = -(CH ₂) ₅ -	88
2	12b : R ¹ = 2-F-C ₆ H ₄ , R ² = Me	91	13	12m : R ^{1,2} = -(CH ₂) ₄ -	90
3	12c : R ¹ = 2-Br-C ₆ H ₄ , R ² = Me	98	14	12n : R ^{1,2} = -CH=CH-(CH ₂) ₃ -	82
4	12d : R ¹ = 2-HO-C ₆ H ₄ , R ² = Me	90	15	12o : R ¹ = <i>n</i> -pent, R ² = Me	86
5	12e : R ¹ = 2-MeO-C ₆ H ₄ , R ² = Me	96	16	12p : α -tetralone	90
6	12f : R ¹ = 4-Me-C ₆ H ₄ , R ² = Me	89	17	12q : β -tetralone	99
7	12g : R ¹ = 1-naphthyl, R ² = Me	87	18	12r : R ¹ = 2-thienyl, R ² = Me	95
8	12h : R ¹ = Ph, R ² = Et	95	19	12s : R ^{1,2} = -(CH ₂) ₂ NBn(CH ₂) ₂ -	88
9	12i : R ¹ = Ph, R ² = <i>n</i> -Pr	92	20	12t : R ¹ = 4-pyridyl, R ² = Me	81
10	12j : R ¹ = Ph(CH ₂) ₂ , R ² = Me	97	21	12u : R ¹ = 3-pyridyl, R ² = Me	87
11	12k : R ¹ = 4-MeO-C ₆ H ₄ (CH ₂) ₂ , R ² = Me	95	22	12v : R ¹ = 2-furyl, R ² = Me	82

Moreover, the use of α -methylallylboronate **5b** was examined in order to demonstrate the potential of this In(0)-catalyzed C–C bond formation in water (Table 6). Highly formal α -addition of **5b** to all tested ketones **12** was observed; γ -adducts were not detected. Interestingly, this constitutional selectivity contrasts the exclusive γ -addition of **5b** to carbonyl compounds under Lewis or Brønsted acid catalysis [51] and is consistent with catalytic transmetalation at the In metal surface. Crotylboronates proved to be unreactive in the present reaction system. The corresponding products **14** were obtained with exceptionally high *syn*-diastereoselectivity in high yields. The *anti*-diastereoselectivity for substrate **12e** (Table 6, entry 3) might be explained with bidentate coordination of **12e** to the crotylindium species. These results are remarkable since geometrically pure crotyl reagents are generally required to selectively form these adducts, but with the exception of sporadic reports, diastereoselectivities proved to be modest [36b,37–40].

Table 6 In(0)-catalyzed formal α -addition of **5b** to ketones **12** in water.

Entry	Ketone 12	Yield (%)	α : γ	<i>syn</i> : <i>anti</i>
1	12a : R ¹ = Ph, R ² = Me	99	>99:1	58:1
2	12b : R ¹ = 2-F-C ₆ H ₄ , R ² = Me	93	>99:1	32:1
3	12e : R ¹ = 2-MeO-C ₆ H ₄ , R ² = Me	90	>99:1	1:65
4	12g : R ¹ = 1-naphth, R ² = Me	75	>99:1	84:1
5	12p : α -tetralone	72	>99:1	32:1
6	12u : R ¹ = 3-pyridyl, R ² = Me	91	>99:1	40:1

The catalytic asymmetric allylation of **12a** with **5a** was examined in water by using In(0) combined with a chiral bis(oxazoline) ligand in a molar ratio of 1:1 (Scheme 9). The desired homoallylic alcohol **13a** was isolated in 68 % yield with 52 % ee, which is the best result so far obtained for catalytic asymmetric allylation of **12a** in water. Other more effective methods require strictly anhydrous conditions [36a,c,37–39].

**Scheme 9** Preliminary study of asymmetric In(0) catalysis in water.

Thus, unprecedented catalytic use of In(0) for C–C bond transformations has been discovered. Remarkably, water is required for these general allylations to proceed. Importantly, the In metal catalyst can be recovered and reused without loss of activity. Moreover, the potential of this concept has been demonstrated through highly regio- and diastereoselective reactions and its applicability to asymmetric catalysis in water.

CONCLUSIONS

In the above three examples, the reactions only proceeded in aqueous media or the selectivities were observed only in aqueous media. In all cases, water plays key roles for the reactivities and selectivities. On the other hand, the role of water is not very clear yet at this stage. Looking back on more than 100 years' history of organic chemistry, almost all investigations have been carried out in organic solvents. Now that unique reactivities and selectivities are discovered in water/aqueous media, more extensive studies on organic reactions in water are necessary.

While many basic and advanced textbooks entitled “Organic Chemistry” are now published, those can be read as “Organic Chemistry in Organic Solvents.” New textbooks entitled “Organic Chemistry in Water” will be and should be established. The new books will also cover many enzymatic reactions and amino acid and carbohydrate chemistry, which may lead to real understanding of organic reactions in water. That could be “the new world of organic chemistry.”

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