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ARTICLE

Water promoted allylic nucleophilic substitution reactions of (*E*)-1,3-diphenylallyl acetateReceived 00th January 20xx,
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Transition metal free, water based, greener protocol for allylic alkylation, allylic amination, *O*-allylation of (*E*)-1,3-diphenylallyl acetate is described. The developed methodology is applicable for a wide range of nucleophiles furnishing excellent yields of corresponding products up to 87% under mild reaction conditions. A Distinct effect of water and base is explored for allylic nucleophilic substitution reactions of (*E*)-1,3-diphenylallyl acetate.

Introduction

The transition metal-catalyzed nucleophilic substitution reaction on substrates containing a leaving group at the allylic position is known as the Tsuji-Trost reaction.¹ The Tsuji-Trost reaction is an important reaction in the synthesis of natural products, pharmaceuticals, functional materials and agrochemicals.² Based on nucleophiles involved in the reaction there are number of Tsuji Trost reactions reported (Figure 1) such as allylic alkylation,³ allylic arylation,⁴ allylic amination,⁵ and *O*-allylation⁶. Due to its wide applications Tsuji-Trost reaction is broadly explored for allyl alcohols and activated allyl alcohol derivatives such as allyl halides, allyl carboxylates, allyl ethers, allyl phosphonates and allyl sulfonates etc.⁷ The direct use of allylic alcohol for Tsuji Trost reaction is well explored research area and (*E*)-1,3-diphenylallyl alcohol is most studied substrate. Moreover, recently lewis acid (ZnCl₂, FeCl₃·6H₂O, MoO₂(acac)₂, Re₂O₇ etc.) catalyzed⁸ and metal free protocols⁹ have been reported for allyl alcohols. Similarly, allyl carboxylates are widely explored derivatives of allyl alcohols for Tsuji-Trost protocols and notably (*E*)-1,3-diphenylallyl acetate is one of the most studied derivative.^{3-6,8,10} Despite of impressive progress, the reported protocols have some drawbacks such as the use of expensive metal based catalysts, use of toxic organic solvents, need of additives, high temperatures and harsh reaction conditions. Therefore most of the reported protocols are not according to the principals of green chemistry¹¹ and generates toxic waste which prevents its applicability on industrial scale particularly for

pharmaceutical applications.¹² In this regard, a catalyst free protocol for allylic nucleophilic substitution reactions was reported by Zhang et al. but the reported protocol is substrate specific and only explored for selective example.¹³ Recently Muzart et al. reported water mediated transition metal free protocol for Tsuji Trost reactions of (*E*)-1,3-diphenylallyl acetate.¹⁴ However in the reported protocol along with water; use of toxic organic co-solvent DMF or methanol is necessary. Moreover, it is well known fact that to remove DMF from product a tedious work up procedure is required while methanol itself acts as nucleophile giving corresponding methanol substituted ether (**31**) as a side product. Nevertheless, the reported methods leave room to improve the reaction conditions, broad scope and functional group tolerance. In addition, it is more appealing to develop actual

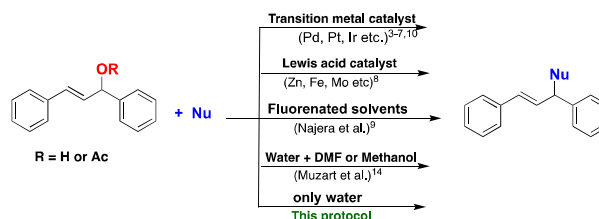


Figure 1. Reported strategies for allylic nucleophilic substitution reactions.

water based protocol because compared to toxic organic solvents water is environmentally benign, safe to handle, readily available and inexpensive solvent. Moreover, recent reports by Qiu et al. on hot water promoted polyene cyclization of π activated alcohols¹⁵, by Mayr et al. on electrophilicities and electrofugalities of 1,3-diaryllallyl cations¹⁶ and by Cozzi et al. on nucleophilic substitutions of secondary alcohols¹⁷ encourage us to investigate possibility for water based protocol for allylic nucleophilic substitution reactions of (*E*)-1,3-diphenylallyl acetate. It should be noted that for (*E*)-1,3-diphenylallyl acetate there is thin boundary line between water mediated allylic nucleophilic substitutions, carbocation based reactions and Tsuji Trost reactions. We believe that our studies might be useful to know insight into

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the effect of catalyst free water mediated allylic nucleophilic substitution reaction on enantiomeric excess for transition metal catalyzed aqueous Tsuji Trost reactions. Particularly our findings are useful for recently reported catalytic bioorganometallic Tsuji Trost protocols which require long reaction time up to 40 hours (because of low concentration of reactants), however achieving higher yields but with low enantiomeric excess or no enantiomeric excess.¹⁸ Therefore in continuation with our interest for developing water based catalytic systems for wide applications,¹⁹ herein we report our studies on transition metal free water promoted allylic nucleophilic substitution reactions of (*E*)-1,3-diphenylallyl acetate.

Result and Discussion

We started our initial experiment with reaction of (*E*)-1,3-diphenylallyl acetate (**1a**) and acetylacetone (**2a**) in presence of base sodium carbonate (Na_2CO_3) in water. Interestingly 68% yield of product **3a** were obtained in 24 hours (Table 1, entry 1), indicating a fast-nucleophilic substitution reaction in water. Next various bases were screened it was observed that compare

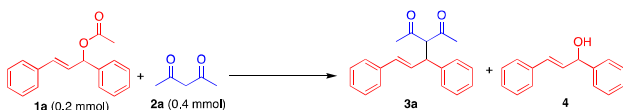


Table 1. Optimization of reaction conditions^a

Entry	Base (equiv)	2a (equiv)	<i>T</i> (°C)	Time h	3a Yield [%] ^b	4 Yield [%] ^b
<i>Effect of base</i>						
1	Na_2CO_3 (2)	2	50	24	68	5
2	K_2CO_3 (2)	2	50	24	57	8
3	Cs_2CO_3 (2)	2	50	24	49	13
4	K_3PO_4 (2)	2	50	24	45	4
5	NaOAc (2)	2	50	24	4	0
6	Et_3N (2)	2	50	24	48	2
7	KOH (2)	2	50	24	79	6
8	NaOH (2)	2	50	24	81	9
9	NaOtBu (2)	2	50	24	87	2
10	---	2	50	24	0	0
<i>Effect of base stoichiometry</i>						
11	NaOtBu (1)	2	50	24	94	0
12	NaOtBu (3)	2	50	24	12	33
13	NaOtBu (4)	2	50	24	0	61
14	NaOtBu (10)	2	50	24	0	83
<i>Effect of stoichiometry of 2a</i>						
15	NaOtBu (1)	1	50	24	70	0
16	NaOtBu (1)	4	50	24	93	0
<i>Effect of temperature</i>						
17	NaOtBu (1)	2	rt	24	13	0
18	NaOtBu (1)	2	40	24	80	0
19	NaOtBu (1)	2	60	24	96	0
<i>Effect of Time</i>						
20	NaOtBu (1)	2	50	27	98	0
21	NaOtBu (1)	2	50	21	89	0
22	NaOtBu (1)	2	50	18	70	0
23	NaOtBu (1)	2	50	15	64	0

^aReaction Conditions: **1a** (0.20 mmol), **2a**, base, water (2 mL), air. ^bGC yield.

to weak bases (Table 1, entries 1-6) strong bases furnish higher yield of **3a** (Table 1, entries 7-9). Among the screened bases sodium *tert*-butoxide which is a non-nucleophilic strong base gave higher yield of **3a** up to 87% (Table 1, entry 9), while in the absence of base reaction did not proceed (Table 1, entry 10). Furthermore, study of base stoichiometry shows interesting results (Table 1, entries 11-14) notably under base-limiting conditions higher yield of **3a** were obtained (Table 1, entry 11). However, use of excess base resulted in exclusively formation product (*E*)-1,3-diphenylallyl alcohol (**4**) which may be formed by hydrolysis of **1a** under basic condition (Table 1, entries 12-14). Afterward we checked the effect of stoichiometry of acetylacetone (**2a**) on reaction outcome (Table 1, entries 11 and 15-16) and it was observed that two equivalences of acetyl acetone (**2a**) is sufficient for higher conversion (Table 1, entry 11). Next temperature was optimized and 50 °C found to be best as 94% yield of **3a** was obtained (Table 1, entry 11 and 17-19). Moreover, time study shows that reaction requires 27 hours for completion however as 94% yields were obtained in 24 hours therefore we performed next experiments for 24 hours. (Table 1, entry 11 and entries 20-23). Next effect of reactants concentration was checked and it was observed that with further increase in

reactants concentration yield of **3a** was decreased (See SI, Table 2).

Afterwards, we studied the change of water pH during the reaction (Table 2), it was observed that after addition of sodium *tert*-butoxide in water; pH increase to 12.5 (Table 2, entry 1). Next after addition of acetylacetone (**2a**) and stirring the reaction mixture for 10-minutes water pH drops up to 8.5 (Table 2, entry 2). As soon as (*E*)-1,3-diphenylallyl acetate (**1a**) is added water pH further drop to 8 (Table 2, entry 3). Interestingly once the reaction started after one hour the pH of water drop to 7.5 and remains 7 to 7.5 until the completion of reaction (Table 2, entries 4 and 5). Therefore, considering the strong basic condition after the addition of base sodium *tert*-butoxide, it is important to follow proper addition pattern to avoid ester hydrolysis of **1a** and for effective generation of corresponding nucleophile of **2a**.

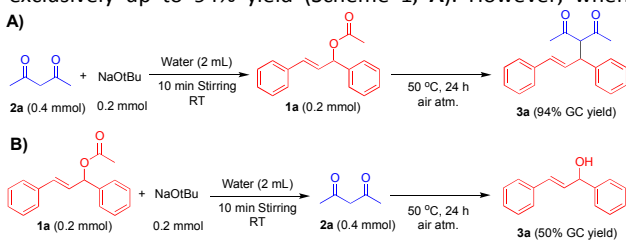
Table 2 Study of pH change during reaction^a

Entry	Reactant addition	pH
1	Water + NaOtBu	12.5
2	Water + NaOtBu + 2a	8.5
3	Water + NaOtBu + 1a + 2a	8
4	After 1 h	7.5
5	After 24 h	7 to 7.5

^aReaction Conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), NaOtBu (0.20 mmol), water (2 mL), 50 °C, 24 h, air. ^bGC yield.

Therefore, next effect of addition pattern was studied which reveal strong influence of addition pattern on outcome of product (Scheme 1). It was observed that in addition sequence

when first acetylacetone (**2a**) is added into a solution of water and sodium *tert*-butoxide, the desired product **3a** formed exclusively up to 94% yield (Scheme 1, A). However, when



addition pattern was changed by first adding (*E*)-1,3-

Scheme 1 Effect of addition pattern

diphenylallyl acetate (**1a**) into a solution of water and sodium *tert*-butoxide (pH 12.5) product **4** formed exclusively by ester hydrolysis of **1a** (Scheme 1, B). This observation confirms that addition pattern is very important for Tsuji Trost type substitution reactions of (*E*)-1,3- of (*E*)-1,3-diphenylallyl acetate (**1a**).

Notably in most of the reported Tsuji Trost protocols reactions were performed in water along with organic co-solvent.^{7,14,18,20} Therefore, we checked the effect of various

Table 3 Effect of solvent on water promoted allylic nucleophilic substitution^a

Entry	Solvent (mL)	3a Yield [%] ^b	Side product Yield [%] ^b
1	Water (2)	94	-
2	Methanol (2)	0	52 (3k)
3	Ethanol (2)	24	62 (3l)
4	n-butanol (2)	7	68 (3m)
5	Isopropanol (2)	19	4 (3n)
6	THF (2)	-	-
7	DMF (2)	-	-
8	Acetonitrile (2)	-	-
9	DMSO (2)	-	-
10	Acetone (2)	-	-
11	Ethyl acetate (2)	-	-
12	1,4-dioxane (2)	-	-
13	Hexane (2)	-	-
14	Diethyl ether (2)	-	-
15	DCM (2)	-	-
16	Benzene (2)	-	-
17	Toluene (2)	-	-
18	Water (1) : Methanol (1)	62	26 (3l)
20	Water (1) : Ethanol (1)	87	13 (3m)
21	Water (1) : <i>N</i> -butanol (1)	25	75 (3n)
19	Water (1) : Isopropanol (1)	92	8 (3o)
22	Water (1) : THF (1)	71	-
23	Water (1) : DMF (1)	96	-
24	Water (1) : Acetonitrile (1)	96	-
25	Water (1) : DMSO (1)	96	-
26	Water (1) : Acetone (1)	96	-
27	Water (1) : Ethylacetate (1)	-	-
28	Water (1) : 1,4-dioxane (1)	96	-
29	Water (1) : Hexane (1)	37	-
30	Water (1) : Diethyl ether (1)	58	-
31	Water (1) : DCM (1)	26	-
32	Water (1) : Benzene (1)	-	-
33	Water (1) : Toluene (1)	-	-

Solvent (2 mL), 50 °C, 24 h, air. ^bGC yield.

polar protic, polar aprotic and non-polar organic solvents with or without water as co-solvent (Table 3). This study leads to observation of distinct effect of water for allylic nucleophilic substitution reaction giving highest yield of product **3a** in water (Table 3, entry 1). It was observed that protic nucleophilic solvents themselves act as nucleophile and leads to the mixture of corresponding ether products **3k-3o** along with expected **3a** product (Table 3, entries 2-5). It should be noted that reaction neither proceeds in polar aprotic solvents (Table 3, entries 6-11) nor in non-polar solvents (Table 3, entries 12-17). However, when water used as co-solvent; to our surprise with most of the organic solvents either completely or partially miscible with water reaction gave excellent yield of **3a** but no reaction was observed in water immiscible organic solvents (Table 3, entries 18-34). However low boiling solvents such as hexane, diethyl ether and DCM partially evaporated during the reaction which ultimately change the ratio of water and and co-solvent therefore resulting in moderate yields of **3a** (Table 3, entries 29-31).

These observations confirm that water indeed a key player in all reactions and use of co-solvent either have no influence or inhibit the reaction. Therefore, the final optimized parameters are (*E*)-1,3-diphenylallyl acetate (**1a**, 0.20 mmol), acetylacetone (**2a**, 0.40 mmol), sodium *tert*-butoxide (0.20 mmol), water (2 mL), 50 °C, 24 h under air atmosphere. Next to check the applicability of protocol for scale up, reaction was performed at 20 mmol scale and product was separated by simple separation of organic layer which results in 71% yield of **3a** (See SI scheme 1). To rule out the possibility of palladium contamination we carried out test experiment by adding ES IPT based fluorescent palladium sensor²⁰ into the reaction mixture and no fluorescence was observed after 24 h confirm no contamination of palladium in the reaction.

Next applicability of the protocol for broad range of substrates were explored (Table 4). First various nucleophiles such as acetylacetone (**2a**), phenol (**2b**), sodium azide (**2c**), indole (**2d**) and benzylamine (**2e**) were screened under optimized reaction conditions and smoothly converted into corresponding products **3a-3e** (Table 4, entries 1-5) conforming broad applicability of our protocol. It's noteworthy to mention that base is not required for reaction with azide, indole, amines and alcohols because their nucleophilicity is sufficient for nucleophilic attack, notably reaction of most of the amines gave full conversion within 16 hours. In order to extend the substrate scope for allylic amination next, we screened broad range of amines under optimized reaction conditions (Table 4, entries 5-10). Interestingly primary amines such as benzylamine (**2e**) and propargylamine (**2f**) gave higher yield of corresponding product **3e** and **3f** (Table 4, entries 5 and 6) while sterically hindered *primary* amines such as isopropylamine (**2g**) and cyclopentylamine (**2h**) gave moderate yield of **3g** and **3h** (Table 4, entries 7 and 8). Moreover, with use of secondary amines a diethylamine (**2i**) lower yield of **3i** were obtained (Table 4, entry 9). Exceptionally morpholine (**2j**) which is also a secondary amine gave higher yield of **3j** (Table 4, entry 10). Then to extend the applicability of protocol for *O*-allylation various *primary*, *secondary* and *tertiary* alcohols were screened. Interestingly, *primary* alcohols such as methanol (**2k**), ethanol (**2l**) and *n*-butanol (**2m**) works best giving moderate yields for **3k**, **3l** and **3m** (Table 4, entries 11-13). However, reactions with bulky alcohols such as *secondary* isopropyl alcohol (**2n**) gave lowest yield of product **3n** (Table 4, entry 14) while *tertiary* butyl alcohol (**2o**) does not give any product (Table 4, entry 15). Therefore, from overall substrate scope study it was observed that increase in bulky groups at nucleophile **2** increases the steric hindrance and results decrease in the yield of corresponding product **3**. Overall with water promoted allylic nucleophilic substitution reactions of (*E*)-1,3 diphenylallyl acetate it is easy to do allylic alkylation, *N*-allylation and *O*-allylation without use of any catalyst or co-solvent.

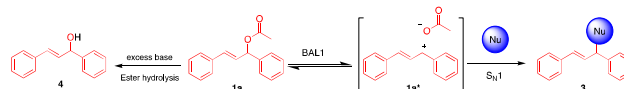
Table 4 Substrate scope study^a

Entry	Nucleophile	Product	Yield [%] ^d
1		3a	87 ^b
2		3b	83 ^b
3	NaN ₃	3c	74
4		3d	78
5		3e	81
6		3f	82
7		3g	74
8		3h	59
9		3i	46
10		3j	86
11	—OH	3k	53
12		3l	74
13		3m	75
14		3n	42
15		3o	0

^aReaction Conditions: **1a** (0.20 mmol), **2** (0.40 mmol), water (2 mL), 50 °C, 24 h, air. ^bBase NaOtBu (0.20 mmol) ^cFor amines reaction stopped at 16 h, ^dIsolated yield

Proposed Mechanism

Based on our studies and as per mechanism proposed by Muzart et al. we believe that reaction proceed via BAL1 followed by S_N1 mechanism.¹⁴ First under aqueous condition (*E*)-1,3-diphenylallyl acetate (**1a**) undergo alkyl oxygen bond cleavage and result in formation of carbocation **1a***. Moreover, formation of carbocation **1a*** is the rate determining step and therefore reaction requires longer reaction time 24 hours. Next in situ **1a*** undergo S_N1 nucleophilic substitution²¹ reaction by attack of nucleophile **2** (**Nu**) giving corresponding product **3**. In addition our studies on reaction pH (Table 2) and addition pattern (Scheme 1) also confirms that under strong basic conditions ester hydrolysis of (*E*)-1,3-diphenylallyl acetate (**1a**) may occurs by acyl oxygen



bond cleavage giving (*E*)-1,3-diphenylallyl alcohol (**4**) as product. This confirms a distinct effect of water and base for allylic nucleophilic substitution reactions of (*E*)-1,3-diphenylallyl acetate (**1a**).

Conclusions

In conclusion, we have developed flexible greener aqueous protocol for conversion of (*E*)-1,3-diphenylallyl acetate into number of allylic products. Reported protocol is promising alternative for toxic metal catalyst based and organic solvent based protocols. We believe that our studies might be useful to know insight into the effect of catalyst free water mediated allylic nucleophilic substitution reaction on enantiomeric excess for catalytic bioorganometallic tsuji trost reactions which requires long reaction time.

Conflicts of interest

There are no conflicts to declare.

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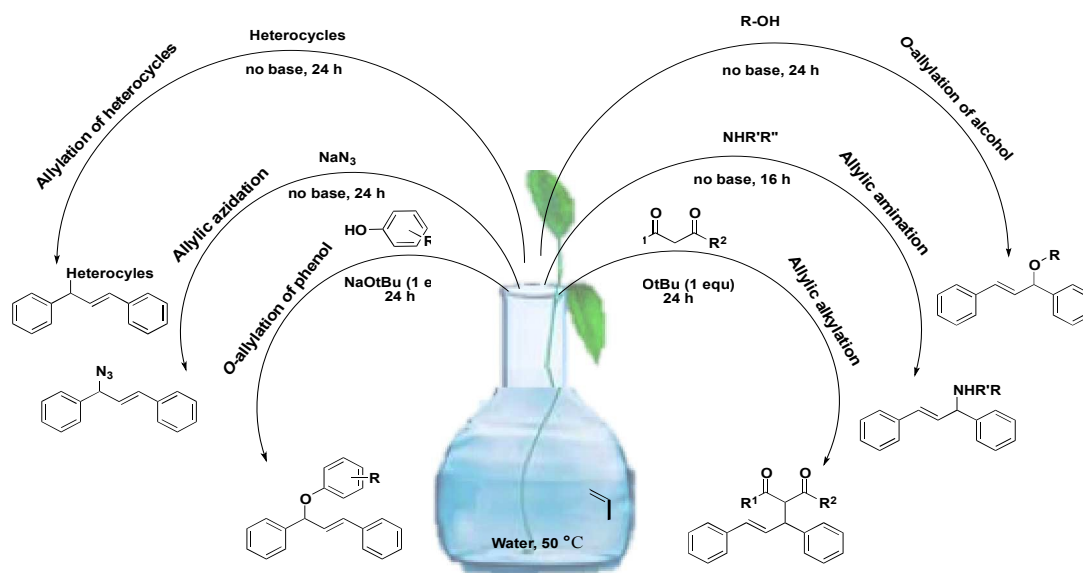
Water promoted allylic nucleophilic substitution reactions of (*E*)-1,3-diphenylallyl acetate

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Transition metal free, reagent free only water based, greener protocol for allylic alkylation, allylic amination, *O*-allylation of (*E*)-1,3-diphenylallyl acetate is described