Organocatalysis "on water". Regioselective [3 + 2]-cycloaddition of nitrones and allenolates†

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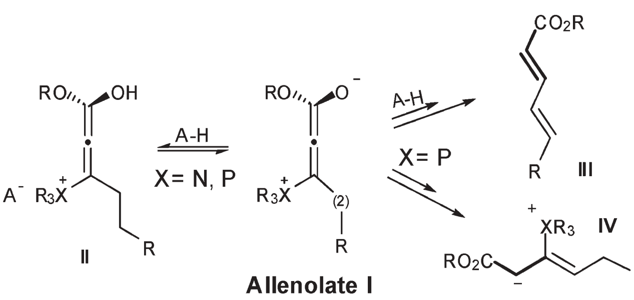
The first example of a regioselective and organocatalyzed 1,3-dipolar cycloaddition reaction between conjugated alkynoates and nitrones "on water" is described.

A plethora of organic reactions are now efficiently performed in water displaying, in some cases, impressive rate accelerations, selectivity, new reactivity and high yields.[1,2] Despite the considerable progress accumulated, the number of organocatalyzed reactions in pure water remains small[3] and therefore there is a clear demand for new, direct and efficient applications.

We[4] and others[5] have shown that the chemical reactivity associated with β-phosphonium or ammonium allenolates **I** is instrumental in dictating the outcome of many interesting chemical processes. In general, these reactive functionalities are generated in an organic medium by the addition of catalytic amounts of tertiary phosphines (X = P) or amines (X = N) to conjugated alkynoates and they display a chemical reactivity profile governed by the nature of the heteroatom located at the β-position (Scheme 1).

Although some examples of generation and reactivity of these allenolates in water were reported early in the seventies,[6] little attention has since been paid to the design and development of efficient aqueous-processed allenolate-driven reactions. In this communication, we report on the first example of the productive utilization of β-phosphonium (or ammonium) allenolates **I** as reactive dipolarophiles in aqueous-processed 1,3-dipolar cycloadditions (1,3-DCRs) (Huisgen reactions).[7]



Scheme 1 Reactivity profile of zwitterionic allenolates generated by addition of tertiary amines or phosphines to conjugated alkynoates.

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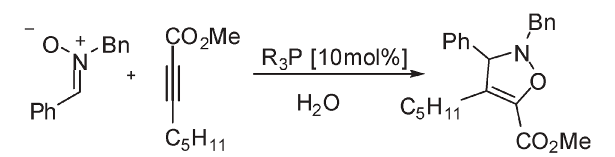
† Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday.

We initiated our studies by examining the ability of triphenylphosphine to catalyze the reaction of the scarcely reactive phenyl *N*-benzylnitrone (**1a**) and methyl 2-octynoate (**2a**) in water. After some experimental work, we found that 2,3-dihydroisoxazole **3aa**‡[8] could be obtained in a modest 10% yield when an aqueous suspension[9] of nitrone, alkynoate and catalyst was vigorously stirred at 40 °C for 48 h. Importantly, product **3aa** was obtained as the sole regioisomer (Table 1, entry 1). Addition of LiCl[10] increased the reaction yield up to a significant 68% (Table 1, entry 3). Once a suitable reaction medium was established, we next performed several experiments to meet the best reaction conditions and the best catalyst (Table 1). It was found that: (1) at least two equivalents of the alkynoate were needed to complete the reaction; (2) both tertiary amines and tertiary phosphines catalyzed the reaction, although with different efficiencies (entries 3–9); (3) no reaction took place in the absence of catalyst (entry 2); (4) addition of LiCl increased the catalytic efficiency (entries 1 and 3); (5) the amount of water was not important as long as enough water was present to fuse the solid nitrone and bring all of the reactants in close contact; (6) the intermediate β-phosphonium allenolates **I** did not rearrange to the corresponding dienoates **III** (Scheme 1);[5] (7) vigorous mixing and a rigorous order of addition of reactants and catalyst were crucial to achieve good results, and finally, (8) no reaction was observed under the same conditions in organic solvents (entries 10–11).

Table 1 1,3-DCR between nitrone **1a** and alkynoate **2a**[a]

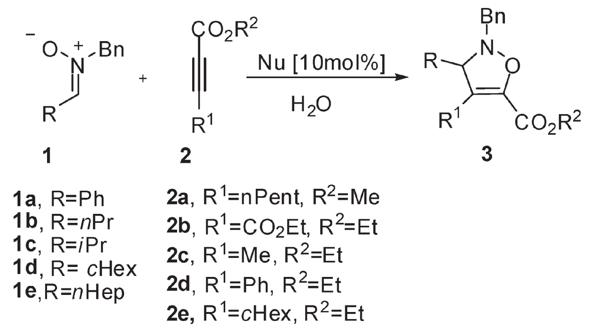


1a **2a** **3aa**

Entry	Solvent	Catalyst	T/°C	Time	Yield[b]
1	H_2O	Ph_3P	40	48 h	10%
2		No catalyst			NR[d]
3	H_2O–LiCl[c]	Ph_3P			68%
4		Et_3N			59%
5		Quinine			57%
6		Quinuclidine			56%
7		DABCO			38%
8		DMAP			36%
9		Isoquinoline			51%
10	Toluene	Ph_3P		24 h	NR[d]
11	CH_2Cl_2	Ph_3P			NR[d]

[a] Nitrone (0.5 mmol), alkynoate (1 mmol), catalyst (0.05 mmol), solvent (1 ml). [b] Yield of isolated, analytically pure product. [c] 3 M solution of LiCl in water. [d] No reaction.

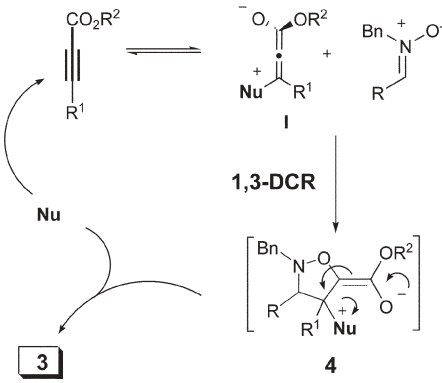
Table 2 Organocatalyzed 1,3-DCR of nitrones **1a–e** and alkynoates **2a–d** "on water"[a]



Entry	Nitrone	Alkyne	LiCl (±)	Catalyst	*T*/°C	Yield[b]
1	**1a**	**2a**	+	Ph_3P[c]	40	68%
2	**1a**	**2b**	−	Ph_3P	RT	99%
3	**1a**	**2c**	−	Ph_3P	RT	35%
			+	Quinuclidine[d]	40	49%
4	**1a**	**2d**	−	Ph_3P	RT	61%
5	**1a**	**2e**	+	Ph_3P	40	71%
6	**1b**	**2a**	−	Ph_3P	RT	81%
7	**1b**	**2b**	−	Ph_3P	RT	95%
8	**1b**	**2c**	−	Et_3N	RT	44%
			−	Quinuclidine	RT	26%
9	**1b**	**2d**	−	Ph_3P	RT	94%
			−	Quinuclidine	40	81%
10	**1b**	**2e**	−	Ph_3P	RT	70%
11	**1c**	**2a**	+	Ph_3P	40	43%
			+	Quinuclidine	40	75%
12	**1d**	**2a**	+	Ph_3P	40	37%
			+	Quinuclidine	40	79%
13	**1e**	**2a**	+	Ph_3P	40	54%
			+	Quinuclidine	40	75%

[a] Reaction conditions: an aqueous (or 3 M LiCl) suspension of nitrone (0.5 mmol in 1 ml) was stirred until the nitrone was completely fused. Alkynoate (0.1 mmol) was added dropwise to the suspension and then the catalyst (10 mol%; 0.05 mmol) was carefully added. The resulting aqueous suspension is vigorously stirred for 12 h at room temperature or 40 °C. Dichloromethane extraction followed by flash chromatography afforded the analytically pure product. [b] Yield of isolated, analytically pure product. [c] 48 h. [d] 20 mol%.

Table 2 shows the scope of this novel aqueous 1,3-DCR with regard to the nitrone and alkynoate. Nitrone **1a**, the most reluctant dipole of the series, reacted with alkynoates **2b** and **2d** at room temperature, in pure water and in the presence of triphenylphosphine to give the cycloadducts **3ab** and **3ad** in good yields (entries 2 and 4). Less reactive alkynoates **2a** and **2e** required the aid of LiCl and heating (entries 1 and 5). Nitrone **1b**, the most reactive dipole of the selected set of nitrones, performed an efficient triphenylphosphine-catalyzed cycloaddition with alkynoates **2a**, **2b** and **2d** to give the corresponding cycloadducts **3ba**, **3bb** and **3bd** in excellent yields (entries 6, 7 and 9). Quinuclidine also proved to be a good catalyst for the reaction of this nitrone with alkynoate **2d**, although heating was required and the efficiency was slightly lower (entry 9). While triphenylphosphine was the best catalyst for reactions involving aromatic nitrone **1a**, quinuclidine displayed a better catalyst activity for the reactions involving aliphatic nitrones **1c–e** (entries 11–13). Alkynoate **2c** exhibited the worst reactivity of all of the assayed alkynoates. Only tertiary amines[11] were able to catalyze, with some efficiency, the 1,3-DCRs involving this alkynoate (entries 3 and 8). In general, the data from Table 2 shows a good tolerance of this 1,3-DCR with regard to the nitrone, alkynoate and catalyst nature.



Scheme 2 Organocatalyzed 1,3-DCR between nitrones **1** and alkynoates **2** "on water".

Three features of this aqueous 1,3-DCR are remarkable. Firstly, reagents do not need to be water-soluble; furthermore, they react when suspended in water ("on water").[9] Secondly, a catalytic amount of allenolate **I** (dipolarophile) forms in water, at 40 °C, with sufficient half-life to react with the nitrone (dipole). Thirdly, the 2,3,4,5-tetrasubstituted 2,3-dihydroisoxazoles **3** are obtained as the sole cycloadducts (complete regioselectivity).[12]

Scheme 2 outlines a plausible catalytic mechanism accounting for the observed results. The catalytic cycle is triggered by the addition of the catalyst (Nu) to an alkynoate to generate the zwitterionic allenolate **I**. Regioselective 1,3-DCR of this dipolarophile intermediate and nitrone affords the zwitterionic cycloadduct intermediate **4**, which incorporates a molecule of each one of the three educts: nitrone, alkynoate and catalyst. Elimination of a molecule of catalyst generates the 2,3-dihydroisoxazole ring **3**, reinitiating the cycle. Remarkably, in spite of the marked electronic and structural differences between tertiary phosphines and amines, they perform the same catalytic task: generation of the reactive dipolarophile allenolate **I**.[13] Preliminary theoretical calculations support the proposed catalytic model with the zwitterionic allenolates **I** acting as the reactive dipolarophiles. The experimentally observed regiochemical outcome is theoretically predicted by the energetically favored nitrone-LUMO controlled 1,3-DCR operating in this cycle.

In summary, we have established the first example of a regioselective and organocatalyzed 1,3-DCR between conjugated alkynoates and nitrones "on water". The scenario described introduces a new catalytic system based on the *in situ* generation of reactive β-phosphonium (or ammonium) allenolates **I** and constitutes a powerful synthetic manifold for the construction of 2,3,4,5-tetrasubstituted 2,3-dihydroisoxazoles **3**. Importantly, these reactive zwitterionic dipolarophile intermediates incorporate a molecule of catalyst directly attached to the reactive double bond and it is expected that this property can be fully exploited by chiral organocatalysts to exercise a measurable effect on the stereoselective course of these 1,3-DCRs. The study of this issue and its application to other related chemical processes are in progress in our lab.

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Notes and references

‡ ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.92 (t, 3H, J = 7 Hz), 1.37 (m, 4H), 1.66 (q, 2H, J = 7.5 Hz), 2.72 (dt, 1H, J = 7.5 and 13.8 Hz), 2.80 (dt, 1H, J = 7.5 and 13.8 Hz), 3.62 (s, 3H), 4.05 (d, 1H, J = 12.8 Hz), 4.33 (d, 1H, J = 12.8 Hz), 5.10 (s, 1H), 7.19 (m, 2H), 7.30 (m, 8H), 7.57 (d, 1H, J = 12.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 22.3, 26.1, 26.7, 31.4, 50.9, 63.6, 72.3, 102.9, 127.2 (2C), 127.6, 127.8, 128.3 (2C), 128.4 (2C), 129.5 (2C), 135.6, 141.6, 165.1, 168.5. IR ($CHCl_3$, cm^{-1}) 1645.9, 1693.3. Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.80; H, 7.33; N, 3.91%. MS, *m/z* (relative intensities) 365 (M+, 3.3), 288 (17.3), 274 (11.8), 211 (12.4), 193 (6), 189 (5), 176 (5.4), 149 (8.5), 131 (5.9), 116 (4.4), 105 (37.2), 91 (100), 77 (13.6).

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