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Dual Reactivity Pattern of Allenolates "On Water": The Chemical Basis for Efficient Allenolate-Driven Organocatalytic Systems

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Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

Abstract: A study of the reactivity pattern associated with zwitterionic allenolates "on water" is reported. This study establishes the chemical basis for two organocatalyzed allenolate-driven reaction networks operating "on water". The first one is a chemodifferentiating three building block (ABB′) three-component reaction (ABB′ 3CR) manifold comprising terminal alkynoates and aldehydes. The manifold produces propargylic enol ethers **3** with higher average efficiency than their homologues in organic solvents. The second one is a novel organocatalytic system elicited by the reaction of alkynoates and nitrones in the presence of tertiary amines or phosphines. While terminal alkynoates afford 2,3,5-trisubstituted 2,3-dihydroisoxazoles **5** and propargylic N-hydroxylamines **6**, internal alkynoates selectively afford the 2,3,4,5-tetrasusbstituted 2,3-dihydroisoxazaole **10**. Importantly, in both cases, the 2,3-dihydroisoxazole ring is obtained as a sole regioisomer.

Keywords: acetylides · allenolates · cycloaddition · organocatalysis · water chemistry

Introduction

An important goal in modern organic chemistry is the development of new, efficient, and environmentally benign synthetic methodologies.[1] Progress toward this goal requires, among other considerations, advanced use of alternative solvents, design of safer chemicals, and development of new atom-efficient catalytic processes.[2] The last decades have witnessed significant advances in these areas, mainly in the development of aqueous organic transformations and organocatalysis. The use of water as solvent offers many advantages. The most obvious are cost, safety, and environmental concerns, but also using water as the unique medium facilitates the experimental procedure, reduces the necessity of tedious protection–deprotection strategies for certain acidic-hydrogen-containing functionalities and allows the direct use of water-soluble molecules without the need for lipophilic derivatizations. Since the seminal finding of Breslow[3] and Grieco[4] on the beneficial effect of water on the rate of the Diels–Alder reactions compared to all organic solvents, the number and type of productive aqueous organic reactions have experienced an enormous increase. Besides Diels–Alder reactions, a wide spectrum of organic reactions are nowadays efficiently performed in water, including pericyclic reactions, reactions of carbanion or carbocation equivalents, reactions of radicals and carbenes, oxidation–reduction reactions, and transition-metal catalysis.[5] Many of these reactions not only display the above-mentioned advantages related with the reaction processing, but they also usually show impressive rate accelerations, better selectivity, new reactivity profiles, and higher yields than their homologues in organic solvents.[6] Remarkably, these beneficial effects are observed even when the reactants are sparingly soluble or insoluble in water. Sharpless has coined this phenomenon as the "on-water effect" to denote graphically this unique reactivity of organic compounds in aqueous suspension.[7]

On the other hand, organocatalysis has emerged as a green complement to metal catalysis with remarkable achievements in enantioselective C–C bond-forming reactions, oxidations, and heterofunctionalizations.[8] Despite the con-

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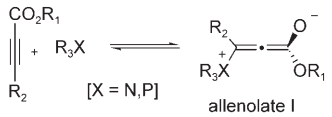
siderable progress accumulated during the last decade, the number of organocatalyzed reactions in pure water remains relatively small and mainly concentrated around a reduced group of reactions including direct aldol,[9] Mannich,[10] Michael-addition,[11] Baylis–Hillman,[12] and cycloaddition reactions.[13] Obviously, not only the number but also the type of reactions need to be increased. This challenge is currently a sought after goal in chemistry and it provides new opportunities for the design and study of new profiles of reactivity and their catalytic implementation. In this article, we give a full account of our study on the reactivity associated with zwitterionic allenolates **I** on water (Scheme 1). Specifically,



Scheme 1. Zwitterionic allenolates **I**.

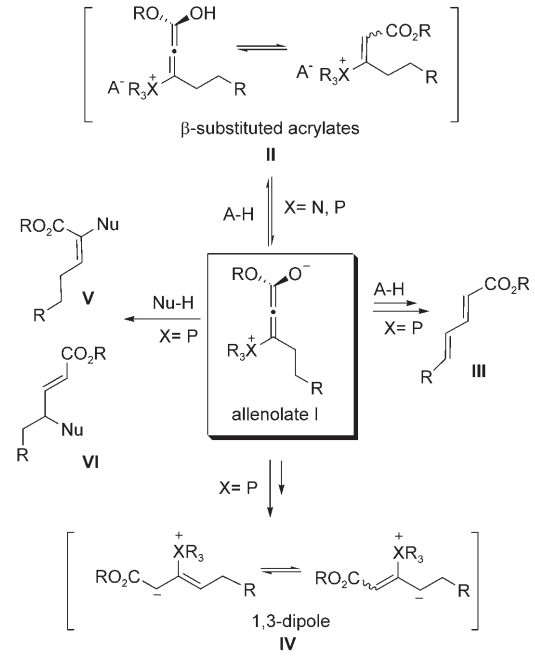
we describe the double reactivity profile displayed by these species when they are generated in situ either in the presence of an electrophile (aldehyde) or an electrophilic 1,3-dipole functionality (nitrone).[14] The results of this study establish the conditions for developing novel and robust allenolate-driven organocatalytic systems operating on water and they set a preliminary chemical scenario for the extension to a possible asymmetric version of these processes.

Results and Discussion

Reactivity profile of allenolates: In general, zwitterionic allenolates **I** display a reactivity profile encoded by the charged heteroatom located at the β-position (Scheme 2). Only the acid–base reaction affording β-substituted acrylates **II** is general for both species.[15] The remaining transformations are specific for the β-phosphonium allenolates.[16–18]

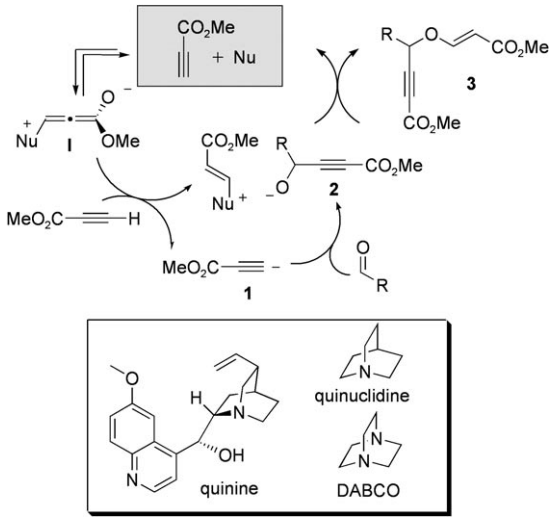
A main advantage that arises from the manner by which the allenolates **I** are generated relies on the subsequent use of these transient reactive zwitterions in a further complexity-generating transformation. We have productively used this property in the construction of highly efficient synthetic manifolds based on the chemodifferentiating three building block (ABB′) three-component reactions (ABB′ 3CRs) of terminal alkynoates and aldehydes or activated ketones.[15,19] Despite of the apparent synthetic potential of this strategy, not many attempts for rational designing and exploration of new possibilities have been achieved.[16b]

Allenolate-driven organocatalytic processes on water: Although some examples of the generation and reactivity of these allenolates in water were reported early in the seventies,[20] little attention has been since paid to the rational design and development of efficient aqueous allenoate-driven reactions. To the best of our knowledge, no systematic studies of their reactivity in water have been accomplished.[14]



Scheme 2. Reactivity profile of zwitterionic allenolates **I** generated by addition of tertiary amines or phosphines on conjugated alkynoates.

Allenolates as bases: **ABB′ 3CRs based on terminal alkynoates and aldehydes**: In organic solvents, terminal alkynoates and aliphatic aldehydes react in the presence of a catalytic amount of tertiary amine to afford propargylic enol ethers **3** through the well established catalytic cycle shown in Scheme 3.[15] The reaction comprises a chemodifferentiating ABB′ 3CR manifold and it is both chemically efficient (56–87%) and atom economical. Either DABCO



Scheme 3. Mechanism for the tertiary amine-catalyzed ABB′ 3CRs of methyl propiolate and aliphatic aldehydes.

(DABCO = 1,4-diazobicyclo[2.2.2]octane), −78 °C) or triethylamine (0 °C) are good catalysts for these reactions. The catalytic manifold is triggered by the Michael addition of the catalyst on the alkynoate to generate the basic allenolate **I** (kinetic reaction), which in turn, generates the ammonium acetylide **1** (thermodynamic reaction). 1,2-Addition on the aldehyde yields the ammonium alkoxide **2**, which in turn, affords propargylic enol ethers **3** and catalyst to restart the cycle (Scheme 3). To our delight and in spite of the charged nature of all of the participating intermediates, this organocatalytic manifold operates on water with higher average chemical efficiency (71–95% yield) than the homologues in organic solvent (Table 1). It is remarkable that the reactivity profile displayed by the terminal alkynoate in the presence of a tertiary amine and an aldehyde in organic media is fully maintained on water.

Table 1. Tertiary amine-catalyzed ABB′ 3CRs of aliphatic aldehydes and methyl propiolate on water.

Entry	R	Catalyst	Product (yield [%])[a]
1	*n*Pr	DABCO	**3a** (50)
2	"	Et_3N	**3a** (15)
3	"	quinuclidine	**3a** (80)
4	"	quinine	**3a** (95)
5	*n*Hex	"	**3b** (71)
6	*n*Dec	"	**3c** (80)
7	$PhCH_2CH_2$	"	**3d** (80)
8	*i*Pr	"	**3e** (97)
9	*c*Hex	"	**3f** (91)

[a] Aldehyde (1 mmol), methyl propiolate (3 mmol), catalyst (0.18 mmol), 6 M LiCl (2 mL), RT, overnight, vigorous stirring.

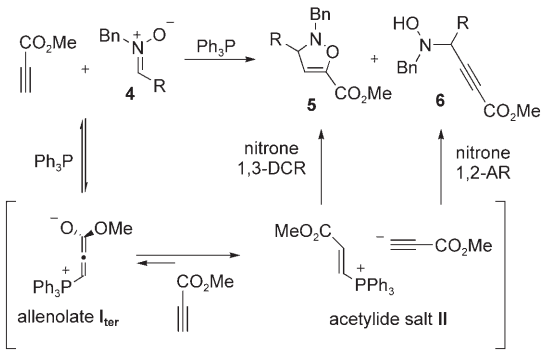
Table 1 shows several examples of this on water organocatalytic ABB′ 3CR. In all of the studied cases, the reaction needed a minimal amount of 1.5 equivalents of the alkynoate to be completed and the addition of LiCl to be effective.[21] With regard to the catalyst, no reaction was observed between aldehydes and methyl propiolate in the absence of catalyst. Among all of the tertiary amines assayed, quinine, a chiral catalyst, gave the best catalytic performance (18 mol%, 85% average yield), but the asymmetric induction was practically zero. Other tertiary amines also catalyzed the reaction, but with worse efficiency (entries 1–4). With regard to the aldehyde, aromatic aldehydes failed to give the reaction. This result is in full accordance with the divergent reactivity displayed by these derivatives in organic media.[22] In contrast, aliphatic aldehydes proved to be excellent materials for these processes. Three general tendencies were observed with regard to the ramification, length, and substitution of the alkyl chain of the aldehyde. Firstly, branching at the α-position significantly increased the efficiency of these processes (compare entries 4–7 with 8 and 9). Secondly, lengthening of the chain mildly decreased the efficiency, but without a clear tendency (compare entries 4, 5 and 6). Thirdly, although the presence of an aromatic ring on the chain would increase the hydrophobicity of the substrate and in turn, the catalytic efficiency, this preassumed beneficial effect was not observed (compare entries 4, 7 and 9). In reverse, a phenyl ring on the chain is less effective than an ethyl group (entries 4 and 7).

With regard to the reaction processing, it was found that a vigorous mixing and a rigorous order of addition of reactants and catalyst are crucial to achieve good and repetitive results, and that the amount of water was not important as long as enough water was present to bring all of the reactants in close contact.

Although the practical consequences of these ABB′ 3CRs manifolds are obvious, the full chemical description of these processes requires more experimental and theoretical work.

Allenolates as dipolarophiles and bases: **the organocatalyzed reaction of alkynoates and nitrones**: Nitrones are very well suited synthetic functionalities because they are stable compounds, which can react as electrophiles to afford N-hydroxylamines or as 1,3-dipoles to give the expected N−O-containing cycloadducts (Huisgen reaction).[23] This bifunctional reactivity has been fully exploited in their metal-catalyzed reactions with alkynes.[24,25] To the best of our knowledge, the aqueous organocatalyzed versions of these reactions has not been accomplished.

We initiated our studies by examining the ability of triphenylphosphine to catalyze the reaction of nitrone **4a** (R = Ph) and methyl propiolate in organic solvent (Scheme 4). Exploratory experiments showed a diminished reactivity of this sparingly soluble nitrone. After some experimental work, we found that triphenylphosphine (10 mol%) in toluene (or benzene, 1 mL) was able to catalyze this reaction, at room temperature, to afford a roughly stoichiometric mixture of the [3+2] cycloadduct **5a**[25,26] and the 1,2-addition product **6a**[24] in very low yield. Dilution or change of solvent (dichloromethane) did not increase the conversion. Although the conversion was extremely low to elicit synthetic interest, the observed chemical outcome was surprising and in some way, unexpected: the reaction network utilizes each and everyone of the latent reactivities of the nitrone and the terminal alkynoate to construct two topologically well differentiated sets of products. When the reaction was performed



Scheme 4. Reaction of nitrones **4** with methyl propiolate in the presence of triphenylphosphine.

on water the same roughly equimolecular mixture of products was obtained but with an impressive increment in yield (90%) and reaction rate. Among other general considerations, it was observed that 1) at least two equivalents of the propiolate were needed to complete the reaction, 2) neither the 1,2-addition reaction (1,2-AR) nor the 1,3-dipolar cycloaddition reaction (1,3-DCR) took place in the absence of the tertiary phosphine, 3) the catalyst charge could be reduced to 1 mol% without detriment to the yield (we used a standard catalyst charge of 5 mol% for better accuracy measurements at the millimolar level), and again, 4) the reaction processing required the same protocol as before.

Table 2 shows the general scope of this reaction with regard to the nitrone substitution. In general, either aromatic or aliphatic nitrones were good substrates for this reaction

Table 2. Reaction of nitrones **4** with methyl propiolate in the presence of triphenylphosphine (5 mol%) on water.[a]

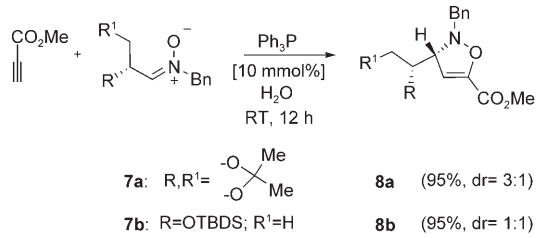
Entry	R	4	Yield [%]	Ratio **5**/**6**
1	Ph	**4a**	90	1:0.90
2	*p*NO_2-Ph	**4b**	91	1:0.93
3	*p*OMe-Ph	**4c**	93	1:0.85
4	*n*Pr	**4d**	95	1:0.83
5	*n*Hex	**4e**	90	1:0.73
6	*i*Pr	**4f**	80	1:0.85
7	*c*Hex	**4g**	80	1:0.77
8	CO_2Me	**4h**	85	1:0.75

[a] Nitrone (1 mmol), methyl propiolate (2.0 mmol), Ph_3P (5% mol), H_2O, RT, vigorous stirring, 12 h.

(entries 1–6 and 7–9). Although the yield was uniformly high in all of the cases, aromatic nitrones **4a–c** displayed a slightly superior average yield than the aliphatic nitrones **4d–h** (92 versus 88%). Both linear and branched aliphatic nitrones afforded products with high yields although with different efficiency (compare entries 4–5 with entries 6 and 7). In the case of the aromatic nitrones, the precise electronic nature of the aromatic ring did not have a measurable influence on the nitrone reactivity (entries 1–3). Other tertiary phosphines and amines, including triethylamine, quinuclidine, isoquinoline, and tributylphosphine, also catalyzed the reaction with similar efficiency and chemical outcomes (results are not shown).

Noteworthy, in all the studied cases, the 1,3-DCRs were completely regioselective affording 2,3-dihydroxazoles **5** as the unique cycloadducts.[27] In addition, although these reactions afford a roughly equimolar mixtures of products **5** and **6**, the latter can be easily and efficiently cyclized to the corresponding 2,3-diydroisoxazoles **5** by reaction with ZnI_2-DMAP.[26]

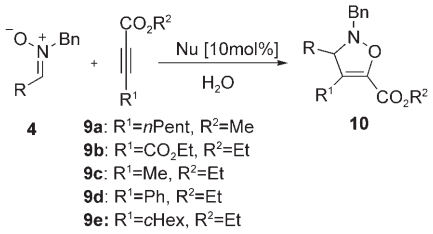
Surprisingly, the reaction of methyl propiolate with the chiral nitrones **7a–b**, bearing an oxygenated function at the α-position, selectively afforded the 1,3-cycloadducts **8a–b** with total regioselectivity (Scheme 5). While the diastereoisomeric ratios were within the expected values for a nitrone-stereocontrolled addition,[23,25,28] the kinetic inhibition of the 1,2-addition pathway was very impressive.[29] Interest-



Scheme 5. Reaction of methyl propiolate with the chiral nitrones **7a–b**, bearing an oxygenated function at the α-position.

ingly, the homologue uncatalyzed cycloaddition of nitrone **7a** and methyl propiolate in refluxing toluene affords cycloadduct **8a** as a 1:1 mixture of diastereoisomers.[28]

Internal alkynoates **9a–e** proved to be excellent substrates for these organocatalytic reactions. Because the corresponding internal allenolates cannot launch the 1,2-addition pathway, only the expected 1,3-DCR cycloadducts **10** were observed. We initiated our studies by examining the ability of triphenylphosphine to catalyze the reaction of the scarcely reactive N-benzyl-phenylnitrone (**4a**, R = Ph) and methyl 2-octynoate (**9a**) on water (Scheme 6). After some experimen-



Scheme 6. Organocatalyzed 1,3-DCR of nitrones **4** and internal alkynoates **9a–e**.

tal work, we found that 2,3-dihydroisoxazole **10aa** could be obtained in a modest 10% yield when an aqueous suspension of nitrone, alkynoate, and catalyst was vigorously stirred at 40°C for 48 h. Importantly, the regioselectivity pattern observed with terminal alkynoates was preserved and the cycloadduct **10aa** was obtained as the sole regioisomer. Table 3 shows the effect of solvent, additives and catalyst on the efficiency of this reaction. In general, we observed 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 efficiency (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), and 5) no reaction was observed under the same conditions in organic solvents (entries 10–11). With regard to the reaction processing, this called for the same precautions mentioned in previous experiments. The reaction showed a wide scope with regard to nitrone and alkynoate (Table 4). Nitrone **4a**, the most reluctant dipole of the series, reacted with alkynoates **9b** and **9d** at room temperature, in pure water, and in the

Table 3. Reaction of nitrone **4a** (R = Ph) with methyl 2-octynoate (**9a**) in the presence of a tertiary amine or phosphine.[a]

Entry	Solvent	Catalyst	T [°C]	t [h]	Yield [%]
1	H_2O	Ph_3P	40	48	10
2	"	no catalyst	"	"	nr[b]
3	H_2O/LiCl[c]	Ph_3P	"	12	68
4	"	Et_3N	"	"	59
5	"	quinine	"	"	57
6	"	quinuclidine	"	"	56
7	"	DABCO	"	"	38
8	"	DMAP[d]	"	"	36
9	"	isoquinoline	"	"	51
10	toluene	Ph_3P	"	24	nr[b]
11	CH_2Cl_2	Ph_3P	"	"	nr[b]

[a] Nitrone (1 mmol), methyl propiolate (2 mmol), catalyst (5 % mol), solvent (1 mL), RT, vigorous stirring. [b] nr = no reaction. [c] Solution of LiCl (3 M) in water. [d] DMAP = 4-dimethylaminopyridine.

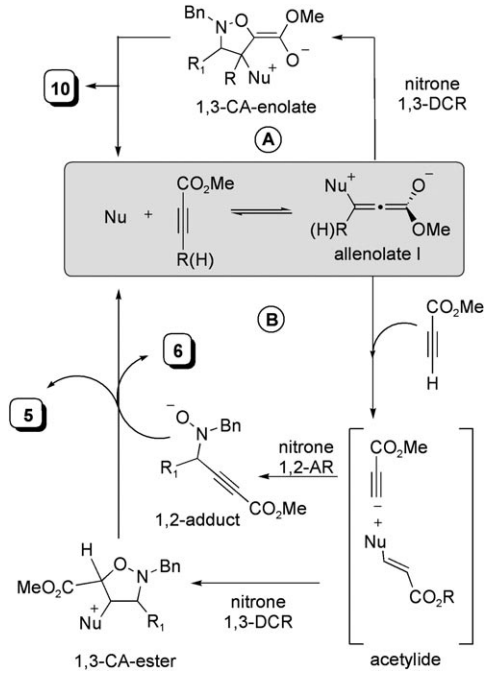
Table 4. Synthesis of 2,3-dihydroisoxazoles **10** by the organocatalyzed 1,3-DCR of selected nitrones **4** and alkynoates **9a–e** on water.[a]

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

[a] Reaction conditions: nitrone (1 mmol), alkynoate (2 mmol), catalyst (10 mol %), water (or aqueous 3 M LiCl solution) (1 mL), vigorous stirring, 12 h, RT or 40 °C. [b] + = LiCl added, – = LiCl not added. [c] 48 h. [d] 20 mol %.

presence of triphenylphosphine to give the cycloadducts **10ab** and **10ad** in good yields (entries 2 and 4). Less reactive alkynoates **9a** and **9e** required the aid of LiCl and heating (entries 1 and 5). Nitrone **4d**, the most reactive dipole of the selected set of nitrones, performed an efficient triphenylphosphine-catalyzed cycloaddition with alkynoates **9a**, **9b**, and **9d** to give the corresponding cycloadducts **10da**, **10db**, and **10dd** in excellent yields (entries 6, 7 and 9). Quinuclidine also proved to be a good catalyst for the reaction of this nitrone with alkynoate **9d**, although heating was required and the efficiency was slightly lower (entry 9). While triphenylphosphine was found to be the best catalyst for reactions involving aromatic nitrone **4a**, quinuclidine displayed a better catalyst activity for the reactions involving aliphatic nitrones **4e–g** (entries 11–13). Alkynoate **9c** exhibited the worst reactivity of all of the assayed alkynoates. Only tertiary amines[30] were able to catalyze, with some efficiency, the 1,3-CDRs involving this alkynoate (entries 3 and 8). Remarkably, in all the cases, the intermediate β-phosphonium allenolates **I** did not rearrange to the corresponding dienoates **III** (Scheme 2).

Scheme 7 outlines a plausible catalytic mechanism accounting for the observed results. Two catalytic cycles **A** and **B** are postulated as a function of the alkynoate substitution.



Scheme 7. Proposed mechanism for the organocatalyzed reaction of nitrones and alkynoates on water.

Internal alkynoates react through the catalytic cycle **A**, which is triggered by the addition of the catalyst (Nu) on alkynoate, to generate the zwitterionic allenolate **I**. Regioselective 1,3-DCR of this dipolarophile intermediate and nitrone **4** affords the corresponding zwitterionic 1,3-cycloadduct–enolate intermediate (1,3-CA–enolate), 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 **10**, 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**.[31] Cycle **B** operates with terminal alkynoates (R = H). It is launched by the formation of allenolate **I** (R = H) which, in the presence of the acidic terminal alkynoate, forms the corresponding acetylide salt. This salt reacts with nitrone **4** as a β-activated acrylate dipolarophile to afford the corresponding charged 1,3-cycloadduct intermediate (1,3-CA–ester), and as a reactive acetylide (1,2-AR) to yield the corresponding anionic 1,2-adduct. The cycle **B** is closed by formation of the 2,3-dihydroisoxa-

zole ring **5** with catalyst regeneration to reinitiate the cycle. While the 1,3-DCR pathway is catalytic, the 1,2-AR is stoichiometric: it consumes acetylide without catalyst regeneration. This pathway survives because the anionic 1,2-adduct intermediate (1,2-adduct) participates in the transformation of the 1,3-CA-ester into dihydroisoxazole derivative **5**, with formation of propargylic N-hydroxylamine **6** together with catalyst regeneration to reinitiate the cycle. Both processes work perfectly coupled in an efficient chemical reaction network able to successfully produce topologically different products **5** and **6**.

Conclusion

The study of the reactivity pattern associated with zwitterionic allenolates **I** on water has been accomplished. These reactivity profiles have been productively exploited in the rational design and development of organocatalyzed allenolate-driven reaction networks operating on water. Specifically, we have explored the chemical basis for a chemo-differentiating ABB′ 3CR manifold comprising terminal alkynoates and aldehydes. The organocatalytic systems elicited by the reaction of alkynoates and nitrones in the presence of tertiary amines or phosphines has also been studied. This work establishes the chemical basis for developing novel and robust allenolate-driven organocatalytic systems operating on water and it sets up the preliminary chemical scenario for the possible extension to its asymmetric version. Such studies are ongoing in our lab and the results will be published in due course.

Experimental Section

General remarks: ^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ were recorded either at 400 and 100 MHz or at 500 and 125 MHz (Bruker Ac 200 and AMX2–500), respectively. FTIR spectra were measured in chloroform solutions by using a Shimadzu IR-408 spectrophotometer. Mass spectra (low resolution) (EI/CI) were obtained with a Hewlett–Packard 5995 gas chromatograph/mass spectrometer. High-resolution mass spectra were recorded with a Micromass Autospec mass spectrometer. Microanalyses were performed with a Fisons Instruments EA 1108 carbon, hydrogen, and nitrogen analyzer. Analytical TLC plates used were E. Merck Brinkman UV-active silica gel (Kieselgel 60 F254) on aluminum. Flash column chromatography was carried out with E. Merck silica gel 60 (particle size less than 0.020 mm) by using appropriate mixtures of ethyl acetate and hexanes as eluent. Starting nitrones **4a–j** were prepared by using standard procedures. All other materials were obtained from commercial suppliers and used as received. The LiCl aqueous solutions were freshly prepared before use. Compounds **3a**,[15c] **3b**,[15c] **3e**,[15c] and **10aa**[14] have been fully described in the indicated references.

General procedure for the synthesis of propargylic enol ethers 3: Careful dropwise addition of methyl propiolate (3.0 mmol) followed by addition of the catalyst (0.18 mmol) to a vigorously stirred suspension of aldehyde (1.0 mmol) in aqueous 6 M LiCl solution (2 mL) resulted in a suspension which was vigorously stirred at room temperature overnight. Extraction with CH_2Cl_2 (×2; in most cases one extraction was enough), drying on Na_2SO_4, concentration, and fast flash chromatography (ethyl acetate/hexanes 20:80) delivered pure propargylic enol ether **3**.

General procedure for the synthesis of 2,3,5-trisubstituted 2,3-dihyroisoxazoles 5 and propargylic N-hydroxylamines 6: Nitrone (1.0 mmol) suspended on water (1 mL) was stirred until completely fused. Methyl propiolate (2.0 mmol) was added dropwise to the suspension and then triphenylphosphine (0.1 mmol) was carefully added. The resulting aqueous suspension was vigorously stirred for 12 h. Extraction with CH_2Cl_2 (×2; in most cases one extraction was enough), drying on Na_2SO_4, concentration, and fast flash chromatography (ethyl acetate/hexanes 20:80) delivered pure compounds **5** and **6**. In those cases in which the 1,2-addition is inhibited (nitrones **7a–b**), a fast percolate through a short plug of silica gel was enough to obtain pure cycloadducts (**8a–b**).

General procedure for the synthesis of 2,3,4,5-tetrasubstituted 2,3-dihyroisoxazoles 10: Nitrone (1.0 mmol) suspended on water (or aqueous 3 M LiCl solution) (1 mL) was stirred until completely fused. Alkynoate (2.0 mmol) was added dropwise to the suspension and then the catalyst (0.1 mmol) was carefully added. The resulting aqueous suspension was vigorously stirred for 12 h at room temperature or at 40 °C. Extraction with CH_2Cl_2 (×2; in most cases one extraction was enough), drying on Na_2SO_4, concentration, and fast flash chromatography (ethyl acetate/hexanes 20:80) delivered analytically pure tetrasubstituted 2,3-dihydroisoxazole **10**.

Methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)tetradec-2-ynoate (3c): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.85 (t, ^3J(H,H) = 6.9 Hz, 3H), 1.23–1.31 (m, 14H), 1.40–1.47 (m, 2H), 1.81–1.91 (m, 2H), 3.68 (s, 3H), 3.76 (s, 3H), 4.60 (d, ^3J(H,H) = 6.4 Hz, 3H), 5.34 (d, ^3J(H,H) = 12.5 Hz, 1H), 7.51 ppm (d, ^3J(H,H) = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.0, 22.6, 24.7, 28.9, 29.2, 29.3, 29.4, 29.5, 31.8, 34.5, 51.2, 52.9, 70.5, 78.5, 83.0, 99.1, 153.1, 159.8, 167.6 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 2242.5, 1715.5, 1645.8, 1625.8 cm^{-1}; MS (70 eV): *m*/*z* (%): 338 (0.7) [M^+], 237 (100), 177 (29), 121 (27), 107 (32), 93 (39), 79 (31), 55 (34); elemental analysis calcd (%) for $C_{19}H_{30}O_5$: C 67.43, H 8.93; found: C 67.64, H 8.72.

Methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-6-phenylhex-2-ynoate (3d): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.12–2.29 (m, 2H), 2.77–2.84 (m, 2H), 3.70 (s, 3H), 3.78 (s, 3H), 4.56 (dd, ^3J(H,H) = 5.8, 7.4 Hz, 1H), 5.35 (d, ^3J(H,H) = 12.5 Hz, 1H), 7.14–7.31 (m, 5H), 7.53 ppm (d, ^3J(H,H) = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 30.7, 36.0, 51.2, 52.9, 69.2, 78.8, 82.6, 99.3, 126.4, 128.4, 128.6, 139.6, 153.0, 159.7, 167.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 2241.9, 1715.9, 1646.3 cm^{-1}; MS (70 eV): *m*/*z* (%): 302 (0.2) [M^+], 248 (12), 141 (20), 118 (8.6), 91 (100); elemental analysis calcd (%) for $C_{17}H_{18}O_5$: C 67.54, H 6.00; found: C 67.42, H 6.13.

Methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-4-cyclohexylbut-2-ynoate (3f): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.08–1.26 (m, 5H), 1.64–1.85 (m, 6H), 3.68 (s, 3H), 3.76 (s, 3H), 4.40 (d, ^3J(H,H) = 5.8 Hz, 1H), 5.34 (d, ^3J(H,H) = 12.5 Hz, 1H), 7.51 ppm (d, ^3J(H,H) = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 25.5, 25.5, 25.9, 28.0, 28.3, 42.1, 51.1, 52.8, 75.3, 79.0, 82.3, 98.9, 153.1, 160.2, 167.6 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 2240.4, 1716.2, 1645.6 cm^{-1}; MS (70 eV): *m*/*z* (%): 280 (1.1) [M^+], 179 (51), 178 (51), 147 (31), 119 (100), 91 (43), 81 (60); elemental analysis calcd (%) for $C_{15}H_{20}O_5$: C 64.27, H 7.19; found: C 64.34, H 7.12.

Methyl 2-benzyl-3-phenyl-2,3-dihydro-5-isoxazolecarboxylate (5a): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.87 (s, 3H), 4.15 (d, ^3J(H,H) = 12.9 Hz, 1H), 4.49 (d, ^3J(H,H) = 12.9 Hz, 1H), 5.10 (d, ^3J (H,H) = 3.0 Hz, 1H), 5.97 (d, ^3J(H,H) = 2.7 Hz, 1H), 7.23–7.42 ppm (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 52.3, 63.0, 72.9, 110.5, 127.3 (2C), 128.4 (4C), 129.5 (4C), 135.4, 140.1, 145.2, 159.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1733.5, 1642.5 cm^{-1}; MS (70 eV): *m*/*z* (%): 295 (14.9) [M^+], 278 (1.8), 264 (1.2), 236 (4.4), 218 (5.1), 204 (31.46), 144 (20.2), 131 (6), 117 (27), 91 (100), 77 (8.6), 65 (9.6); elemental analysis calcd (%) for $C_{18}H_{17}NO_3$: C 73.20, H 5.80, N 4.74; found: C 73.26, H 5.98, N 4.70.

Methyl 2-benzyl-3-(4-nitrophenyl)-2,3-dihydro-5-isoxazolecarboxylate (5b): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.91 (s, 3H), 4.09 (d, ^3J(H,H) = 12.9 Hz, 1H), 4.45 (d, ^3J(H,H) = 12.9 Hz, 1H), 5.19 (d, ^3J(H,H) = 3.0 Hz, 1H), 5.97 (d, ^3J(H,H) = 3.0 Hz, 1H), 7.30–7.33 (m, 4H), 7.41–7.43 (m, 2H), 8.20 ppm (d, ^3J(H,H) = 9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 52.5, 63.1, 71.8, 108.6, 123.5 (2C), 128.2 (2C), 128.6 (2C), 129.5 (2C), 134.5, 146.0, 147.3, 147.5, 159.0; IR ($HCCl_3$): $\tilde{\nu}$ = 1733.5, 1642.5, 1523.3 cm^{-1}; MS (70 eV): *m*/*z* (%): 340 (14.9) [M^+], 332 (0.5), 281 (2.2), 249 (32.5), 218 (3.8), 203 (2.6), 189 (7.2), 116

(5.7), 91 (100), 89 (7.3), 85 (8.0), 84 (12.6), 65 (7.8), 48 (13.9); elemental analysis calcd (%) for $C_{18}H_{16}N_2O_5$: C 63.52, H 4.74, N 8.23; found: C 63.79, H 4.95, N 8.09.

Methyl 2-benzyl-3-(4-methoxyphenyl)-2,3-dihydro-5-isoxazolecarboxylate (5c): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.76 (s, 3H), 3.82 (s, 3H), 4.07 (d, ^3J(H,H) = 12.9 Hz, 1H), 4.40 (d, ^3J(H,H) = 12.9 Hz, 1H), 5.0 (d, ^3J(H,H) = 3.0 Hz, 1H), 5.89 (d, ^3J(H,H) = 3.0 Hz, 1H), 6.81 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.09 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.26–7.36 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 52.3, 55.3, 62.9, 72.5, 110.7, 114.0 (2C), 127.6, 128.3, 128.4 (2C), 129.5 (2C), 132.2, 135.4, 145.2, 159.4 ppm; IR ($HCCl_3$): $\tilde{\nu}$ = 1733.2, 1644.8 cm^{-1}; MS (70 eV): *m*/*z* (%): 325 (11.6) [M^+], 260 (0.3), 234 (34.7), 218 (9.9), 174 (15.6), 147 (23.4), 146 (12.6), 121 (5.9), 91 (100), 77 (7.7), 65 (8.6), 51 (4.6); elemental analysis calcd (%) for $C_{19}H_{19}NO_4$: C 70.14, H 5.89, N 4.31; found: C 70.26, H 5.76, N 4.05.

Methyl 2-benzyl-3-propyl-2,3-dihydro-5-isoxazolecarboxylate (5d): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.75 (t, ^3J(H,H) = 7.4 Hz, 3H), 1.10–1.19 (m, 1H), 1.27–1.40 (m, 2H), 1.42–1.49 (m, 1H), 3.81 (s, 3H), 3.84 (d, ^3J(H,H) = 12.6 Hz, 1H), 3.88–3.91 (m, 1H), 4.28 (d, ^3J(H,H) = 12.6 Hz, 1H), 5.83 (d, ^3J(H,H) = 2.9 Hz, 1H), 7.30–7.37 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 13.6, 18.4, 37.4, 51.2, 62.9, 69.3, 110.8 (2C), 127.6, 128.3 (2C), 129.6 (2C), 135.5, 144.9, 152.6, 159.6; IR ($CHCl_3$): $\tilde{\nu}$ = 1697.9, 1629.1 cm^{-1}; MS (70 eV): *m*/*z* (%): 261 (1.8) [M^+], 243 (1.6), 229 (5.8), 218 (15.8), 91 (100), 71 (11.2), 65 (6.6); elemental analysis calcd (%) for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36; found: C 68.90, H 7.20, N 5.55.

Methyl 2-benzyl-3-hexyl-2,3-dihydro-5-isoxazolecarboxylate (5e): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.82 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.07–1.25 (m, 8H), 1.35–1.47 (m, 2H), 1.42–1.49 (m, 1H), 3.81 (s, 3H), 3.84 (d, ^3J(H,H) = 12.6 Hz, 1H), 3.86–3.90 (m, 1H), 4.28 (d, ^3J(H,H) = 12.3 Hz, 1H), 5.82 (d, ^3J(H,H) = 2.7 Hz, 1H), 7.26–7.37 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 14.0, 22.4, 25.2, 28.8, 31.6, 35.3, 52.2, 62.9, 69.5, 110.9 (2C), 127.6, 128.3 (2C), 129.6 (2C), 135.6, 145.0, 159.6 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1734.9, 1649.9 cm^{-1}; MS (70 eV): *m*/*z* (%): 303 (1.1) [M^+], 285 (0.6), 272 (0.2), 254 (0.2), 244 (1.8), 218 (23.0), 91 (100), 65 (4.2), 55 (3.6); elemental analysis calcd (%) for $C_{18}H_{25}NO_3 \cdot x\,H_2O$: C 71.26, H 8.31, N 4.62; found: C 71.80, H 8.61, N 4.41; HRMS calcd for $C_{18}H_{25}NO_3$: 303.183444; found: 303.182182.

Methyl 2-benzyl-3-isopropyl-2,3-dihydro-5-isoxazolecarboxylate (5f): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.75 (t, ^3J(H,H) = 6.8 Hz, 6H), 1.60–1.62 (m, 1H), 3.68 (dd, ^3J(H,H) = 2.9, 6.4 Hz, 1H), 3.80 (s, 3H), 3.83 (d, ^3J(H,H) = 12.9 Hz, 1H), 3.86–3.90 (m, 1H), 4.27 (d, ^3J(H,H) = 12.9 Hz, 1H), 5.81 (d, ^3J(H,H) = 2.9 Hz, 1H), 7.26–7.37 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 18.1, 18.3, 33.2, 52.2, 63.7, 75.7, 108.9 (2C), 127.7, 128.3 (2C), 129.8 (2C), 135.6, 145.3, 159.6 ppm; IR ($HCCl_3$): $\tilde{\nu}$ = 1733.6, 1652.7 cm^{-1}; MS (70 eV): *m*/*z* (%): 261 (2.4) [M^+], 250 (0.7), 218 (24.0), 202 (3.9), 128 (5.0), 91 (100), 82 (4.5), 65 (6.6), 55 (4.7); elemental analysis calcd (%) for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36; found: C 69.11, H 7.30, N 5.30.

Methyl 2-benzyl-3-cyclohexyl-2,3-dihydro-5-isoxazolecarboxylate (5g): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.73 (qd, ^3J(H,H) = 3.4, 12.2 Hz, 1H), 0.90 (qd, ^3J(H,H) = 3.4, 12.2 Hz, 1H), 1.04–1.19 (m, 3H), 1.31–1.37 (m, 1H), 1.55–1.73 (m, 5H), 3.68 (dd, ^3J(H,H) = 6.5, 8.3 Hz, 1H), 3.79 (s, 3H), 3.80 (d, ^3J(H,H) = 12.9 Hz, 1H), 4.24 (d, ^3J(H,H) = 12.9 Hz, 1H), 5.83 (d, ^3J(H,H) = 3.0 Hz, 1H), 7.26–7.37 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 25.8. 25.9, 26.3 (2C), 28.7, 42.8, 52.2, 63.6, 74.8, 109.2, 127.6, 128.3 (2C), 129.7 (2C), 135.7, 145.0, 152.8, 159.6 ppm; IR ($HCCl_3$): $\tilde{\nu}$ = 1699.0, 1628.4 cm^{-1}; MS (70 eV): *m*/*z* (%): 301 (1.5) [M^+], 242 (1.5), 218 (26.5), 91 (100), 55 (5.6); elemental analysis calcd (%) for $C_{18}H_{23}NO_3$: C 71.73, H 7.69, N 4.65; found: C 71.74, H 7.81, N 4.85.

3-Ethyl 5-methyl 2-benzyl-2,3-dihydro-3,5-isoxazoledicarboxylate (5h): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.22(t, ^3J(H,H) = 7.1 Hz, 3H), 3.82 (s, 3H), 4.07 (d, ^3J(H,H) = 12.9 Hz, 1H), 4.16 (q, ^3J(H,H) = 7.1 Hz, 2H), 4.41 (d, ^3J(H,H) = 12.9 Hz, 1H), 4.68 (d, ^3J(H,H) = 3.0 Hz, 1H), 5.78 (d, ^3J(H,H) = 3.0 Hz, 1H), 7.26–7.37 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 18.4, 37.4, 51.2, 62.9, 69.3, 110.8, 127.6, 128.3 (2C), 129.6 (2C), 135.5, 144.9, 152.6, 159.6 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1733.9, 1716.0, 1627.7 cm^{-1}; MS (70 eV): *m*/*z* (%): 291 (7.5) [M^+], 232 (26.9), 218 (6.8), 204 (3.5), 158 (6.0), 91 (100), 65 (7.3); elemental analysis calcd (%) for $C_{15}H_{17}NO_5$: C 61.85, H 5.88, N 4.81; found: C 61.86, H 5.91, N 4.75.

Methyl 4-[benzyl(hydroxy)amino]-4-phenyl-2-butynoate (6a): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.64 (s, 3H), 4.10 (d, ^3J(H,H) = 12.9 Hz, 1H), 4.37 (d, ^3J(H,H) = 12.9 Hz, 1H), 5.13 (s, 1H), 7.23–7.52 ppm (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 51.2, 63.6, 70.9, 110.5, 127.7 (2C), 128.4 (4C), 129.2 (4C), 135.4, 140.3, 145.3, 152.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3392.9, 2399.9, 1706.4, 1629.5 cm^{-1}; MS (70 eV): *m*/*z* (%): 295 (10.3) [M^+], 288 (9.7), 278 (6.7), 266 (1.6), 264 (1.2), 218 (2.8), 204 (18.0), 144 (5.8), 116 (9.4), 91 (100), 65 (6.4); elemental analysis calcd (%) for $C_{18}H_{17}NO_3$: C 73.20, H 5.80, N 4.74; found: C 73.40, H 5.87, N 4.66.

Methyl 4-[benzyl(hydroxy)amino]-4-(4-nitrophenyl)-2-butynoate (6b): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.65 (s, 3H), 4.09 (d, ^3J(H,H) = 12.9 Hz, 1H), 4.45 (d, ^3J(H,H) = 12.9 Hz, 1H), 5.20 (s, 1H), 7.30–7.33 (m, 4H), 7.42–7.45 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 51.4, 63.7, 70.0, 109.0, 123.5 (2C), 128.2 (2C), 128.6 (2C), 129.2 (2C), 134.5, 147.50, 147.66, 152.9, 163.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3683.7, 2400.0, 1729.4, 1646.2 cm^{-1}; MS (70 eV): *m*/*z* (%): 340 (9.6) [M^+], 323 (2.8), 311 (1.9), 249 (14.2), 234 (2.1), 218 (3.1), 203 (1.7), 136 (20.1), 91 (100), 89 (7.7), 65 (7.7); elemental analysis calcd (%) for $C_{18}H_{16}N_2O_5$: C 63.52, H 4.74, N 8.23; found: C 63.72, H 4.80, N 7.89.

Methyl 4-[benzyl(hydroxy)amino]-4-(4-methoxyphenyl)-2-butynoate (6c): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.65 (s, 3H), 3.76 (s, 3H), 4.07 (d, ^3J(H,H) = 12.9 Hz, 1H), 4.33 (d, ^3J(H,H) = 12.9 Hz, 1H), 5.08 (d, ^3J(H,H) = 1.8 Hz, 1H), 6.80–6.82 (m, 2H), 7.28–7.36 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 51.3, 55.2, 63.6, 70.6, 109.8, 110.8, 113.8 (2C), 127.9, 128.5 (4C), 129.3 (2C), 135.4, 152.6, 159.3, 164.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3392.4, 2399.7, 1700, 1628.4 cm^{-1}; MS (70 eV): *m*/*z* (%): 325 (24.9) [M^+], 308 (5.7), 234 (69.6), 218 (5.6), 206 (6.3), 202 (6.6), 174 (20.3), 160 (10.5), 146 (23.1), 121 (83.4), 104 (8.5), 91 (100), 89 (7.4), 77 (14.2), 65 (13.1), 51 (6.3); elemental analysis calcd (%) for $C_{19}H_{19}NO_4$: C 70.14, H 5.89, N 4.31; found: C 70.29, H 6.08, N 3.87.

Methyl 4-[benzyl(hydroxy)amino]-2-heptynoate (6d): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.79 (t, ^3J(H,H) = 7.4 Hz, 3H), 1.15 (m, 1H), 1.37 (m, 1H), 1.49 (m, 1H), 1.65–1.55 (m, 1H), 3.72 (s, 3H), 3.84 (d, ^3J(H,H) = 12.9 Hz, 1H), 4.04 (dq, ^3J(H,H) = 1.6, 8.8 Hz, 1H), 4.20 (d, ^3J(H,H) = 12.9 Hz, 1H), 7.28–7.32 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 13.7, 18.4, 36.7, 51.2, 63.8, 67.3, 109.3, 127.8, 128.4 (2C), 129.4 (2C), 135.5, 152.6, 164.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3672.8, 2254.2, 1793.9, 1698, 1630 cm^{-1}; MS (70 eV): *m*/*z* (%): 261 (1.9) [M^+], 218 (27.5), 104 (2.5), 91 (100), 77 (2.6), 65 (8.2); elemental analysis calcd (%) for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36; found: C 69.02, H 7.23, N 5.67.

Methyl 4-[benzyl(hydroxy)amino]-2-decynoate (6e): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.84 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.10–1.18 (m, 7H), 1.30–1.34 (m, 1H), 1.45–1.52 (m, 1H), 1.57–1.63 (m, 1H), 3.72 (s, 3H), 3.84 (d, ^3J(H,H) = 12.6 Hz, 1H), 4.04 (dq, ^3J(H,H) = 1.6, 8.8 Hz, 1H), 4.21 (d, ^3J(H,H) = 12.6 Hz, 1H), 7.28–7.32 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 14.0, 22.5, 25.1, 28.9, 31.7, 34.5, 51.2, 63.8, 67.4, 109.2, 127.8, 128.4 (2C), 129.5 (2C), 135.6, 152.6, 164.4 ppm; IR ($HCCl_3$): $\tilde{\nu}$ = 3672.7, 2254.2, 1793.8, 1698.2, 1629.4 cm^{-1}; MS (70 eV): *m*/*z* (%): 303 (1.9) [M^+], 285 (5.3), 228 (8.9), 218 (17.7), 91 (100), 65 (5.3); elemental analysis calcd (%) for $C_{18}H_{25}NO_3 \cdot x\,H_2O$: C 71.26, H 8.31, N 4.62; found: C 71.77, H 8.74, N 4.55; HRMS calcd for $C_{18}H_{25}NO_3$: 303.183444; found: 303.184525.

Methyl 4-[benzyl(hydroxy)amino]-5-methyl-2-hexynoate (6f): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.76 (d, ^3J(H,H) = 6.7 Hz, 3H), 0.82 (d, ^3J(H,H) = 6.7 Hz, 3H), 1.90–1.96 (m, 1H), 3.72 (s, 3H), 3.81 (d, ^3J(H,H) = 12.9 Hz, 1H), 3.98 (dd, ^3J(H,H) = 1.6, 3.2 Hz, 1H), 4.19 (d, ^3J(H,H) = 12.9 Hz, 1H), 7.27–7.39 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 15.8, 19.1, 30.8, 51.2, 64.7, 72.4, 107.5, 127.8, 128.4 (2C), 129.5 (2C), 135.7, 152.9, 164.6 ppm; IR ($HCCl_3$): $\tilde{\nu}$ = 3566.1, 2360.3, 1792.0, 1771.6, 1699.5, 1635.2 cm^{-1}; MS (70 eV): *m*/*z* (%): 261 (0.5) [M^+], 218 (20), 91 (100), 65 (4.7); elemental analysis calcd (%) for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36; found: C 68.93, H 7.21, N 5.22.

Methyl 4-[benzyl(hydroxy)amino]-4-cyclohexyl-2-butynoate (6g): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.07–1.27 (m, 5H), 1.55–1.67 (m, 6H), 3.73 (s, 3H), 3.80 (d, ^3J(H,H) = 12.9 Hz, 1H), 3.94–3.95 (m, 1H),

4.16 (d, ^3J(H,H) = 12.9 Hz, 1H), 7.27–7.39 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 26.0 (2C), 26.3 (2C), 29.6, 40.8, 51.2, 64.5, 72.0, 106.9, 127.7, 128.3 (2C), 129.4 (2C), 135.8, 152.8, 164.6 ppm; IR ($HCCl_3$): $\tilde{\nu}$ = 3392.0, 2362.1, 1699.0, 1628.3 cm^{-1}; MS (70 eV): *m*/*z* (%): 301 (2.4) [M^+], 272 (0.8), 270 (0.7), 218 (31.3), 91 (100), 55 (6.2); elemental analysis calcd (%) for $C_{18}H_{23}NO_3$: C 71.73, H 7.69, N 4.65; found: C 71.69, H 7.90, N 4.65.

5-Ethyl 1-methyl 4-[benzyl(hydroxy)amino]-2-pentynedioate (6h): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.21 (t, ^3J(H,H) = 7.1 Hz, 3H), 3.70 (s, 3H), 4.08 (d, ^3J(H,H) = 12.9 Hz, 1H), 4.16 (m, 2H), 4.35 (d, ^3J(H,H) = 12.9 Hz, 1H), 7.25–7.38 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 13.7, 18.4, 36.7, 51.2, 63.8, 67.3, 109.3, 127.8, 128.4 (2C), 129.4 (2C), 135.5, 152.6, 164.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3399.9, 2400.9, 1737.3, 1633.1 cm^{-1}; MS (70 eV): *m*/*z* (%): 291 (0.5) [M^+], 274 (0.3), 262 (1.5), 232 (0.9), 218 (19.9), 91 (100), 64 (7.0); elemental analysis calcd (%) for $C_{15}H_{17}NO_5$: C 61.85, H 5.88, N 4.81; found: C 61.99, H 5.93, N 4.80.

Methyl (3*R*)-2-benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,3-dihydro-5-isoxazolecarboxylate (8a, major diastereoisomer): $[\alpha]_D^{20}$ = +111.1 (*c* = 0.47 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.26 (s, 3H), 1.28 (s, 3H), 3.69–3.73 (m, 1H), 3.81 (s, 3H), 3.94 (d, ^3J(H,H) = 12.7 Hz, 1H), 3.96–4.0 (m, 2H), 4.21 (dd, ^3J(H,H) = 5.6, 3 Hz, 1H), 4.32 (d, ^3J(H,H) = 12.7 Hz, 1H), 5.69 (d, ^3J(H,H) = 3.0 Hz, 1H), 7.36–7.28 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 24.9, 26.2, 52.4, 53.4, 63.3, 65.4, 71.6, 108.0, 109.6, 128.0, 128.5 (2C), 129.7 (2C), 134.7, 147.1, 159.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3390.0, 2400.1, 1735.3, 1643.7 cm^{-1}; MS (70 eV): *m*/*z* (%): 319 (0.4) [M^+], 304 (1), 262 (0.6), 244 (1.1), 232 (0.2), 218 (19.9), 101 (6.4), 91 (100), 65 (4.7); elemental analysis calcd (%) for $C_{17}H_{21}NO_5$: C 63.94, H 6.63, N 4.39; found: C 64.05, H 6.53, N 4.17.

Methyl (3*S*)-2-benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,3-dihydro-5-isoxazolecarboxylate (8a, minor diastereoisomer): $[\alpha]_D^{20}$ = −117.4 (*c* = 0.39 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.27 (s, 3H), 1.33 (s, 3H), 3.34 (dd, ^3J(H,H) = 8.6, 5.2 Hz, 1H), 3.82 (s, 3H), 3.88 (d, ^3J(H,H) = 12.4 Hz, 1H), 3.92 (dd, ^3J(H,H) = 8.6, 5.6 Hz, 1H), 3.98 (dd, ^3J(H,H) = 7.8, 3.0 Hz, 1H), 4.01 (dt, ^3J(H,H) = 7.8, 5.6 Hz, 1H), 5.93 (d, ^3J(H,H) = 3.0 Hz, 1H), 7.31–7.33 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 25.2, 26.7, 52.4, 63.1, 66.9, 71.6, 108.0, 109.6, 128.1, 128.6 (2C), 129.8 (2C), 134.8, 146.0, 159.3 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3382.3, 2400.1, 1787.6, 1732.1, 1626.4 cm^{-1}; MS (70 eV): *m*/*z* (%): 319 (0.4) [M^+], 304 (1.2), 262 (0.4), 260 (0.4), 244 (1.1), 232 (0.1), 218 (21.0), 101 (6.0), 91 (100), 65 (4.9); elemental analysis calcd (%) for $C_{17}H_{21}NO_5$: C 63.94, H 6.63, N 4.39; found: C 64.05, H 6.38, N 3.90.

(*S*)-Methyl 2-benzyl-3-((1*R*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-2,3-dihydro-5-isoxazolecarboxylate (8b, *syn*): $[\alpha]_D^{20}$ = −258.2 (*c* = 0.31 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.01 (s, 3H), −0.03 (s, 3H), 0.81 (s, 9H), 0.98 (d, ^3J(H,H) = 6.0 Hz, 3H), 3.54 (q, ^3J(H,H) = 6.0 Hz, 1H), 3.81 (s, 3H), 3.89 (d, ^3J(H,H) = 12.6 Hz, 1H), 3.94 (dd, ^3J(H,H) = 5.6, 3.0 Hz, 1H), 4.32 (d, ^3J(H,H) = 12.6 Hz, 1H), 5.75 (d, ^3J(H,H) = 3.0 Hz, 1H), 7.26–7.39 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = −4.8 (2C), 19.7, 25.8 (3C), 51.2, 63.6, 70.4, 75.8, 107.1, 127.7, 128.3, 129.2 (2C), 129.8 (2C), 135.4, 153.9, 159.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3019.1, 2399.9, 1733.8, 1684.0 cm^{-1}; MS (70 eV): *m*/*z* (%): 377 (1.1) [M^+], 362 (0.5), 320 (7.9), 218 (72.3), 159 (7.5), 115 (4.6), 91 (100), 89 (4.6), 73 (27.3), 59 (4.0); elemental analysis calcd (%) for $C_{20}H_{31}NO_4Si$: C 63.62, H 8.28, N 3.71; found: C 63.60, H 8.44, N 3.77.

(*R*)-Methyl 2-benzyl-3-((1*R*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-2,3-dihydro-5-isoxazolecarboxylate (8b, *anti*): $[\alpha]_D^{20}$ = −258.2 (*c* = 0.31 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.01 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 0.98 (d, ^3J(H,H) = 6.0 Hz, 3H), 3.54 (dq, ^3J(H,H) = 7.3, 6.0 Hz, 1H), 3.72 (s, 3H), 3.76 (dd, ^3J(H,H) = 7.3, 3.0 Hz, 1H), 3.87 (d, ^3J(H,H) = 12.7 Hz, 1H), 4.25 (d, ^3J(H,H) = 12.7 Hz, 1H), 5.89 (d, ^3J(H,H) = 3.0 Hz, 1H), 7.26–7.39 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = −4.8, −4.9, 18.6, 25.8 (3C), 51.2, 63.6, 71.3, 75.8, 109.33, 127.7, 128.3, 129.2 (2C), 129.8 (2C), 135.4, 153.9, 159.5 ppm; IR ($HCCl_3$): $\tilde{\nu}$ = 3019.1, 2399.9, 1733.8, 1684.0 cm^{-1}; MS (70 eV): *m*/*z* (%): 377 (1.93) [M^+], 362 (0.5), 320 (12.7), 218 (33.0), 159 (0.9), 101(5.9), 91-(100), 89 (6.1), 73 (26.7), 65 (3.3), 59 (5.6); elemental analysis calcd (%) for $C_{20}H_{31}NO_4Si$: C 63.62, H 8.28, N 3.71; found: C 63.67, H 8.35, N 3.42.

Diethyl 2-benzyl-3-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate (10ab): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.14 (t, ^3J(H,H) = 7.0 Hz, 3H), 1.37 (t, ^3J(H,H) = 7.2 Hz, 3H), 4.07 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.10 (q, ^3J(H,H) = 7.1 Hz, 2H), 4.12 (d, ^3J(H,H) = 13.0 Hz, 1H), 4.44 (d, ^3J(H,H) = 13.0 Hz, 1H), 5.21 (s, 1H), 7.30 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 13.9, 29.6, 60.6, 62.7, 63.5, 72.7, 109.0, 127.3 (3C), 128.0 (3C), 128.5 (2C), 129.4, 134.8, 139.6, 151.9, 159.2, 162.2, 176.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3450, 2399.7, 1715, 1707.8, 1655.9 cm^{-1}; MS (70 eV): *m*/*z* (%): 381 (13) [M^+], 308 (13), 77 (11), 290 (38), 262 (13), 203 (28), 144 (15), 117 (13), 91 (100); elemental analysis calcd (%) for $C_{22}H_{23}NO_5$: C 69.28, H 6.08, N 3.67; found: C 68.9, H 6.47, N 3.40.

Ethyl 2-benzyl-4-methyl-3-phenyl-2,3-dihydroisoxazole-5-carboxylate (10ac): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.02 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.19 (s, 3H), 3.99 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.40 (d, ^3J(H,H) = 12.6 Hz, 1H), 4.11 (d, ^3J(H,H) = 12.6 Hz, 1H), 5.24 (s, 1H), 7.28 (m, 8H), 7.77 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 12.3, 14.12, 59.67, 63.55, 72.63, 103.8, 127.3, 128.0, 129.3, 135.6, 141.5, 164.2, 164.6, 176.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3154.6, 2253.3, 1793.8, 1693.3 cm^{-1}; MS (70 eV): *m*/*z* (%): 323 (7.2) [M^+], 246 (28), 232 (20), 144 (5), 117 (7.1), 91 (100), 77 (11), 65 (12); elemental analysis calcd (%) for $C_{20}H_{21}NO_3$: C 74.28, H 6.55, N 4.33; found: C 74.05, H 6.79, N 4.11.

Ethyl 2-benzyl-3,4-diphenyl-2,3-dihydroisoxazole-5-carboxylate (10ad): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.02 (t, ^3J(H,H) = 7.2 Hz, 3H); 3.99 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.11 (d, ^3J(H,H) = 12.6 Hz, 1H), 4.40 (d, ^3J(H,H) = 12.6 Hz, 1H), 5.24 (s, 1H), 7.28 (m, 13H), 7.77 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 13.9, 60.0 (2C), 63.3 (2C), 73.7, 103.7, 127.3 (2C), 127.8 (3C), 128.2 (3C), 129.9 (3C), 130.1 (2C), 131.1, 135.5, 141.4, 162.1, 163.9 ppm; IR ($HCCl_3$): $\tilde{\nu}$ = 3154.7, 2253.4, 1793.7, 1692.4, 1641.5 cm^{-1}; MS (70 eV): *m*/*z* (%): 385.17 (4.7) [M^+], 308 (16), 294 (30), 167 (11), 105 (71), 91 (100), 77 (29); elemental analysis calcd (%) for $C_{25}H_{23}NO_3$: C 77.90, H 6.01, N 3.63; found: C 77.81, H 6.14, N 3.55.

Ethyl 2-benzyl-4-cyclohexyl-3-phenyl-2,3-dihydroisoxazole-5-carboxylate (10ae): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.21 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.30 (tq, ^3J(H,H) = 13.0, 3.33 Hz, 1H), 1.44 (m, 2H), 1.59 (dq, ^3J(H,H) = 13.0, 3.5 Hz, 2H), 1.77 (m, 1H), 1.91 (m, 4H), 3.49 (tt, ^3J(H,H) = 12.0, 3.3 Hz, 1H), 4.09 (d, ^3J(H,H) = 12.6 Hz, 1H), 4.12 (q, ^3J(H,H) = 7.2 Hz, 1H), 4.16 (q, ^3J(H,H) = 7.1 Hz, 1H), 4.38 (d, ^3J(H,H) = 12.6 Hz, 1H), 5.13 (s, 1H), 7.37 ppm (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 14.1, 25.6 (2C), 25.8 (2C), 29.7, 36.0, 59.5, 63.5, 72.2, 127.0 (2C), 127.7 (2C), 128.2 (2C), 128.4 (2C), 129.5 (2C), 135.6, 141.8, 164.6, 171.5, 176.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 2933.2, 2235.4, 1709.09 cm^{-1}; MS (70 eV): *m*/*z* (%): 391 (33) [M^+], 314 (84), 300 (68), 190 (15), 91 (100), 83 (18); elemental analysis calcd (%) for $C_{25}H_{29}NO_3$: C 76.70, H 7.47, N 3.58; found: C 76.81, H 7.56, N 3.52.

Methyl 2-benzyl-4-pentyl-3-propyl-2,3-dihydro-5-isoxazolecarboxylate (10da): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.77 (t, ^3J(H,H) = 7.4 Hz, 3H), 0.88–0.90 (m, 3H), 1.08–1.16 (m, 1H), 1.3–1.5 (m, 5H), 1.5–1.6 (m, 4H), 2.58 (dt, ^3J(H,H) = 13.9, 7.6 Hz, 1H), 2.72 (dt, ^3J(H,H) = 13.9, 7.6 Hz, 1H), 3.72 (s, 3H), 3.77 (d, ^3J(H,H) = 12.7 Hz, 1H), 3.99 (dd, ^3J(H,H) = 8.8, 2.8 Hz, 1H), 4.15 (d, ^3J(H,H) = 12.7 Hz, 1H), 7.29–7.37 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 13.7, 13.9, 18.5, 22.3, 26.1, 26.6, 31.3, 37.0, 50.9, 53.4, 63.4, 68.6, 102.6, 127.7, 128.4 (2C), 129.6 (2C), 135.9, 165.4, 168.2 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3391.1, 2399.9, 1692.1, 1646.0 cm^{-1}; MS (70 eV): *m*/*z* (%): 331 (2.6) [M^+], 313 (0.3), 288 (26.7), 91 (100), 65 (3.0); elemental analysis calcd (%) for $C_{20}H_{29}NO_3$: C 72.49, H 8.82, N 4.23; found: C 72.57, H 8.57, N 4.02.

Diethyl 2-benzyl-3-propyl-2,3-dihydro-4,5-isoxazoledicarboxylate (10db): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.77 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.11–1.19 (m, 1H), 1.26 (t, ^3J(H,H) = 7.4 Hz, 3H), 1.36 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.35–1.43 (m, 1H), 1.56 (m, 2H), 3.85 (d, ^3J(H,H) = 12.7 Hz, 1H), 4.11 (app t, ^3J(H,H) = 6.4, 5.6 Hz, 1H), 4.28 (d, ^3J(H,H) = 7.2 Hz, 2H), 4.29 (d, ^3J(H,H) = 12.7 Hz, 1H), 4.33 (d, ^3J(H,H) = 7.2 Hz, 2H), 7.27–7.36 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 13.5, 13.8, 14.0, 18.3, 36.2, 62.5, 63.3, 69.0, 108.7, 127.9, 128.4 (2C), 129.6 (2C), 135.0, 151.8, 151.9, 159.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3394.2, 2336.7, 1716.2, 1655.1 cm^{-1}; MS (70 eV): *m*/*z* (%): 347 (2.6) [M^+], 329 (0.7), 304 (20.6),

125 (7.6), 91 (100), 53 (6.6); elemental analysis calcd (%) for $C_{17}H_{21}NO_5$: C 65.69, H 7.25, N 4.03; found: C 65.54, H 7.59, N 3.97.

Ethyl 2-benzyl-4-methyl-3-propyl-2,3-dihydroisoxazole-5-carboxylate (10dc): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 0.78$ (t, $^3J(H,H) = 7.2$ Hz, 3H), 1.16 (m, 2H), 1.18 (t, $^3J(H,H) = 7.2$ Hz, 3H), 1.49 (m, 2H), 2.19 (s, 3H), 3.80 (d, $^3J(H,H) = 12.6$ Hz, 1H), 4.01 (dd, $^3J(H,H) = 8.5$, 2.2 Hz, 1H), 4.15 (d, $^3J(H,H) = 12.6$ Hz, 1H), 4.16 (d, $^3J(H,H) = 7.2$ Hz, 1H), 4.20 (q, $^3J(H,H) = 7.2$ Hz, 1H), 7.32 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 12.3$, 13.7, 14.3, 18.4, 36.8, 59.6, 63.5, 68.7, 103.2, 127.6, 128.3 (2C), 129.5 (2C), 135.8, 164.0, 165.0 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2958.4$, 2360.7, 1698.5, 1654.4 cm^{-1}; MS (70 eV): m/z (%): 289 (0.9) [M^+], 246 (19), 198 (11), 188 (13), 152 (30), 139 (12), 91 (100); elemental analysis calcd (%) for $C_{17}H_{23}NO_3$: C 70.56, H 8.01, N 4.84; found: C 70.68, H 8.09, N 4.48.

Ethyl 2-benzyl-4-phenyl-3-propyl-2,3-dihydroisoxazole-5-carboxylate (10dd): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 0.82$ (t, $^3J(H,H) = 7.4$ Hz, 3H), 1.21 (t, $^3J(H,H) = 7.2$ Hz, 3H), 1.47 (m, 1H), 1.56 (s, 1H), 1.63 (m, 2H), 3.92 (d, $^3J(H,H) = 12.6$ Hz, 1H), 4.16 (dq, $^3J(H,H) = 7.2$, 1.34 Hz, 2H), 4.20 (d, $^3J(H,H) = 6.0$ Hz, 1H), 4.30 (d, $^3J(H,H) = 12.6$ Hz, 1H), 7.37 (m, 8H), 7.75 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 13.7$, 14.1, 18.6, 29.7, 36.9, 59.9, 63.0, 70.0, 103.5, 127.7 (2C), 128.4 (2C), 129.4 (2C), 129.7 (2C), 129.8 (2C), 130.8 (2C), 135.8, 161.9, 164.2 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3018.6$, 2929.3, 1686.0, 1634.3 cm^{-1}; MS (70 eV): m/z (%): 351 (2.1) [M^+], 308 (59), 105 (37), 91 (100), 77 (28), 65 (10); elemental analysis calcd (%) for $C_{22}H_{25}NO_3$: C 75. 19, H 7.17, N 3.99; found: C 74.88, H 7.61, N 3.52.

Ethyl 2-benzyl-4-cyclohexyl-3-propyl-2,3-dihydroisoxazole-5-carboxylate (10de): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 0.75$ (t, $^3J(H,H) = 7.2$ Hz, 3H), 1.15 (m, 4H), 1.27 (t, $^3J(H,H) = 7.2$ Hz, 3H), 1.74 (m, 10H), 3.29 (tt, $^3J(H,H) = 11.8$, 3.1 Hz, 1H), 3.72 (d, $^3J(H,H) = 12.7$ Hz, 1H), 3.95 (dd, $^3J(H,H) = 8.5$, 2.9 Hz, 1H), 4.10 (d, $^3J(H,H) = 12.7$ Hz, 1H), 4.20 (q, $^3J(H,H) = 7.2$ Hz, 2H), 7.31 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 13.7$, 14.0, 25.6, 25.9, 29.6, 29.8, 31.4, 36.9, 37.0, 59.5, 61.7, 63.3, 68.4, 101.2, 127.6, 128.3 (2C), 129.5 (2C), 135.9, 171.3, 176.0 ppm; IR ($HCCl_3$): $\tilde{\nu} = 3020.3$, 2870.2, 1729.0 cm^{-1}; MS (70 eV): m/z (%): 357 (0.5) [M^+], 314 (25), 193 (3), 135 (3.2), 91 (100), 55 (7.8); elemental analysis calcd (%) for $C_{22}H_{31}NO_3$: C 73.95, H 8.74, N 3.92; found: C 74.10, H 8.84, N 3.52.

Ethyl 2-benzyl-3-hexyl-4-pentyl-2,3-dihydroisoxazole-5-carboxylate (10ea): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 0.84$ (t, $^3J(H,H) = 7.2$ Hz, 3H), 0.87 (t, $^3J(H,H) = 7.2$ Hz, 3H), 1.10–1.25 (m, 7H), 1.25–1.35 (m, 5H), 1.37–1.47 (m, 1H), 1.47–1.60 (m, 3H), 2.59 (dt, $^3J(H,H) = 13.8$, 7.6 Hz, 1H), 2.70 (dt, $^3J(H,H) = 13.8$, 7.6 Hz, 1H), 3.71 (s, 3H), 3.77 (d, $^3J(H,H) = 12.7$ Hz, 1H), 3.97 (dd, $^3J(H,H) = 8.9$, 2.6 Hz, 1H), 4.15 (d, $^3J(H,H) = 12.7$ Hz, 1H), 7.32 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 13.8$, 14.0, 22.2, 22.5, 25.2, 26.0, 26.6, 28.9, 31.3, 31.7, 34.7, 50.8, 63.4, 68.7, 127.6, 128.3 (2C), 129.6 (2C), 135.8, 165.4, 168.1, 176.0 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3434.3$, 2929.4, 2360.8, 1703.3, 1647.22 cm^{-1}; MS (70 eV): m/z (%): 373 (8.1) [M^+], 288 (100), 274 (10), 230 (37), 91 (53); elemental analysis calcd (%) for $C_{23}H_{35}NO_3$: C 73.96, H 9.44, N 3.75; found: C 73.98, H 9.49, N 3.88.

Ethyl 2-benzyl-3-isopropyl-4-pentyl-2,3-dihydroisoxazole-5-carboxylate (10fa): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 0.73$ (t, $^3J(H,H) = 6.7$ Hz, 3H), 0.78 (t, $^3J(H,H) = 7.2$ Hz, 3H), 0.87 (t, $^3J(H,H) = 7.2$ Hz, 3H), 1.32 (m, 4H), 1.55 (m, 2H), 1.86 (m, 1H), 2.59 (dt, $^3J(H,H) = 13.8$, 7.6 Hz, 1H), 2.70 (dt, $^3J(H,H) = 13.8$, 7.6 Hz, 1H), 3.71 (s, 3H), 3.74 (d, $^3J(H,H) = 12.6$ Hz, 1H), 3.94 (d, $^3J(H,H) = 3.1$ Hz, 1H), 4.13 (d, $^3J(H,H) = 12.6$ Hz, 1H), 7.31 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 13.8$, 15.8, 19.1, 22.2, 26.1 (2C), 26.7, 31.2, 31.4, 50.7, 64.3, 73.7, 77.2, 127.6, 128.2 (2C), 129.6 (2C), 135.9, 168.5 ppm; IR ($CHCl_3$): $\tilde{\nu} =$ 2958.1, 2360.7, 1702.8, 1646.3 cm^{-1}; MS (70 eV): m/z (%): 331 (1.9) [M^+], 288 (88), 179 (2.9), 91 (100), 65 (7.8), 55 (4.8); elemental analysis calcd (%) for $C_{20}H_{29}NO_3$: C 73.01, H 9.04, N 4.05; found: C 73.15, H 8.87, N 4.34.

Ethyl 2-benzyl-3-cyclohexyl-4-pentyl-2,3-dihydroisoxazole-5-carboxylate (10ga): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 0.87$ (t, $^3J(H,H) = 7.0$ Hz, 3H), 1.10–1.20 (m, 5H), 1.32 (m, 4H), 1.45–1.65 (m, 8H), 2.59 (dt, $^3J(H,H) = 13.8$, 7.6 Hz, 1H), 2.70 (dt, $^3J(H,H) = 13.8$, 7.6 Hz, 1H), 3.71 (s, 3H), 3.72 (d, $^3J(H,H) = 12.6$ Hz, 1H), 3.91 (d, $^3J(H,H) = 3.5$ Hz, 1H), 4.11 (d, $^3J(H,H) = 12.6$ Hz, 1H), 7.31 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 13.8$, 22.2, 26.1 (2C), 26.3 (2C), 26.4, 26.7, 29.7, 31.4, 41.2, 50.8, 64.1, 73.3, 100.1, 127.6, 128.2 (2C), 129.6 (2C), 135.9, 165.6, 168.4 ppm; IR ($HCCl_3$): $\tilde{\nu} = 2927.8$, 2360.7, 2338.4, 1701.4, 1645.9 cm^{-1}; MS (70 eV): m/z (%): 371 (8.5) [M^+], 290 (8.1), 289 (66), 288 (100), 272 (9.6), 166 (3.2), 91 (52); elemental analysis calcd (%) for $C_{23}H_{33}NO_3$: C 74.36, H 8.95, N 3.77; found: C 74.41, H 8.99, N 3.73.

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[30] The experimentally observed bad catalytic activity of the Ph_3P could be due to a phosphorous-driven rearrangement of alkynoate **9c** to ethyl 2,3-butadienoate,[17] a poor dipolarophile and an excellent precursor of phosphorous-containing allylic anions **IV** (see Scheme 2).

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