ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

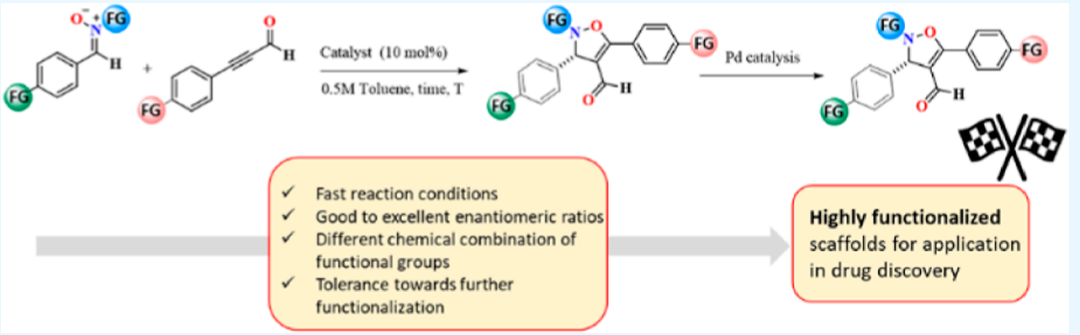
Fast MacMillan's Imidazolidinone-Catalyzed Enantioselective Synthesis of Polyfunctionalized 4-Isoxazoline Scaffolds

Dario Corbisiero, Tommaso Fantoni, Lucia Ferrazzano, Giulia Martelli, Paolo Cantelmi, Alexia Mattellone, Chiara Palladino, Magda Monari, Riccardo Pedrazzani, Alessandra Tolomelli,* and Walter Cabri*

Cite This: *ACS Omega* 2022, 7, 26919−26927

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: The enantioselective 1,3-dipolar cycloaddition of nitrones and arylpropionaldehydes to generate highly functionalized scaffolds for application in drug discovery was herein investigated. The use of a second-generation MacMillan catalyst as hydrochloride salt consistently accelerated the reaction speed, allowing a decrease in the reaction time up to >100 times, still affording 4-isoxazolines with good to excellent enantiomeric ratios at room temperature. As a proof of concept, further functionalization of the isoxazoline core through Pd-catalyzed cross-coupling was performed, generating differently functionalized chemical architectures in high yield.

INTRODUCTION

The introduction of heterocycles as nonclassical motifs is a common approach in the selection of bioisosters for the development of peptidomimetics.[1] Heterocyclic cores contribute to protein recognition by establishing key hydrogen bonds with their counterparts. In addition, in biomimetic design, these versatile scaffolds allow for the efficient modulation of substituents, electronic properties, or dimensions of strategic moieties to increase efficacy.[2] Examining the structures of the top 200 pharmaceuticals by retail sales in 2020[3] revealed that almost 50% of these compounds are small molecules containing at least one heterocycle. In this context, five-membered rings are privileged structures as different topologies and stereochemistries can be easily designed by selecting proper reactions and conditions. For example, 4-isoxazolines[4] exhibit interesting and diverse activities[5] and have been utilized as intermediates in the synthesis of bioactive compounds,[6] thanks to the interactions that both the N−O bond and π system can establish with a biological target.

Following our interest in protein−protein interaction interference, over the last few years, we have designed and synthesized small libraries of ligands of $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrins,[7] which are transmembrane receptors involved in cancer cell angiogenesis. Our synthetic ligands contained 4-isoxazolines as the core of the peptidomimetics, which are further decorated with suitable branches for binding therapeutics and diagnostics.[8]

Successful synthesis of racemic 4-isoxazolines via 1,3-dipolar cycloaddition of nitrones with alkynes[9] and allenes,[10] cycloaddition of oxaziridines with alkynes,[11] cyclization of propargylic *N*-hydroxylamines,[12] conjugate addition of *N*-hydroxylamines to alkylidene acetoacetates,[13] and addition of organometallic reagents to isoxazolium salts[14] has been reported in the literature.

The few reported examples of catalytic asymmetric synthesis primarily involve high loading of expensive and rare metal catalysts[12,15] or organocatalysts in the 1,3-dipolar cycloaddition of nitrones to propargylaldehydes.[16] In view of the insertion of enantiopure isoxazoline scaffolds in molecules with potential

Received: June 3, 2022
Accepted: July 7, 2022
Published: July 20, 2022

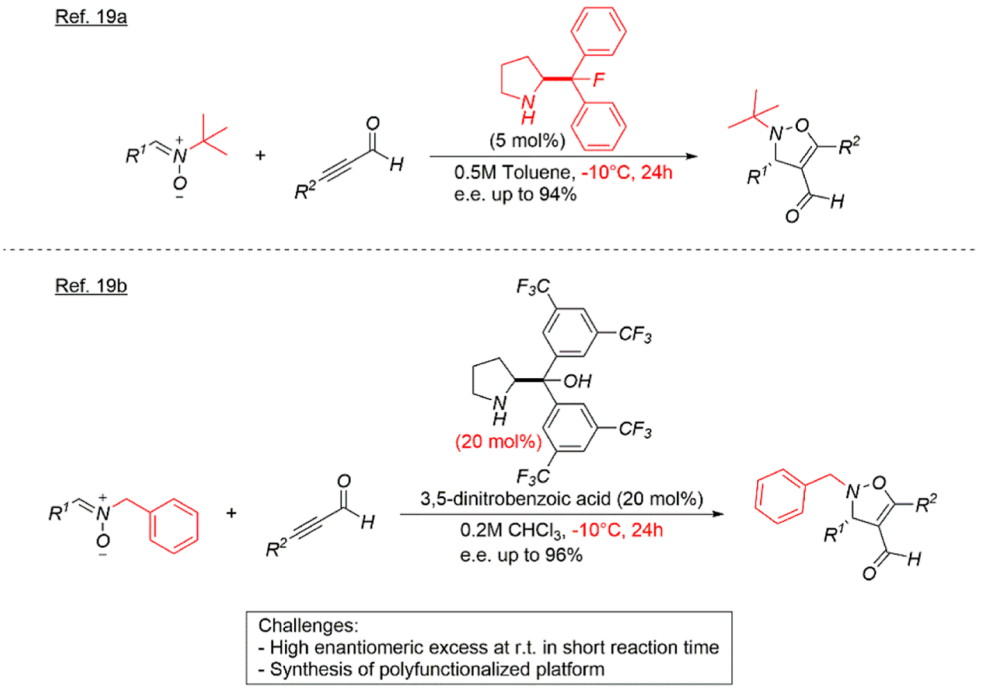
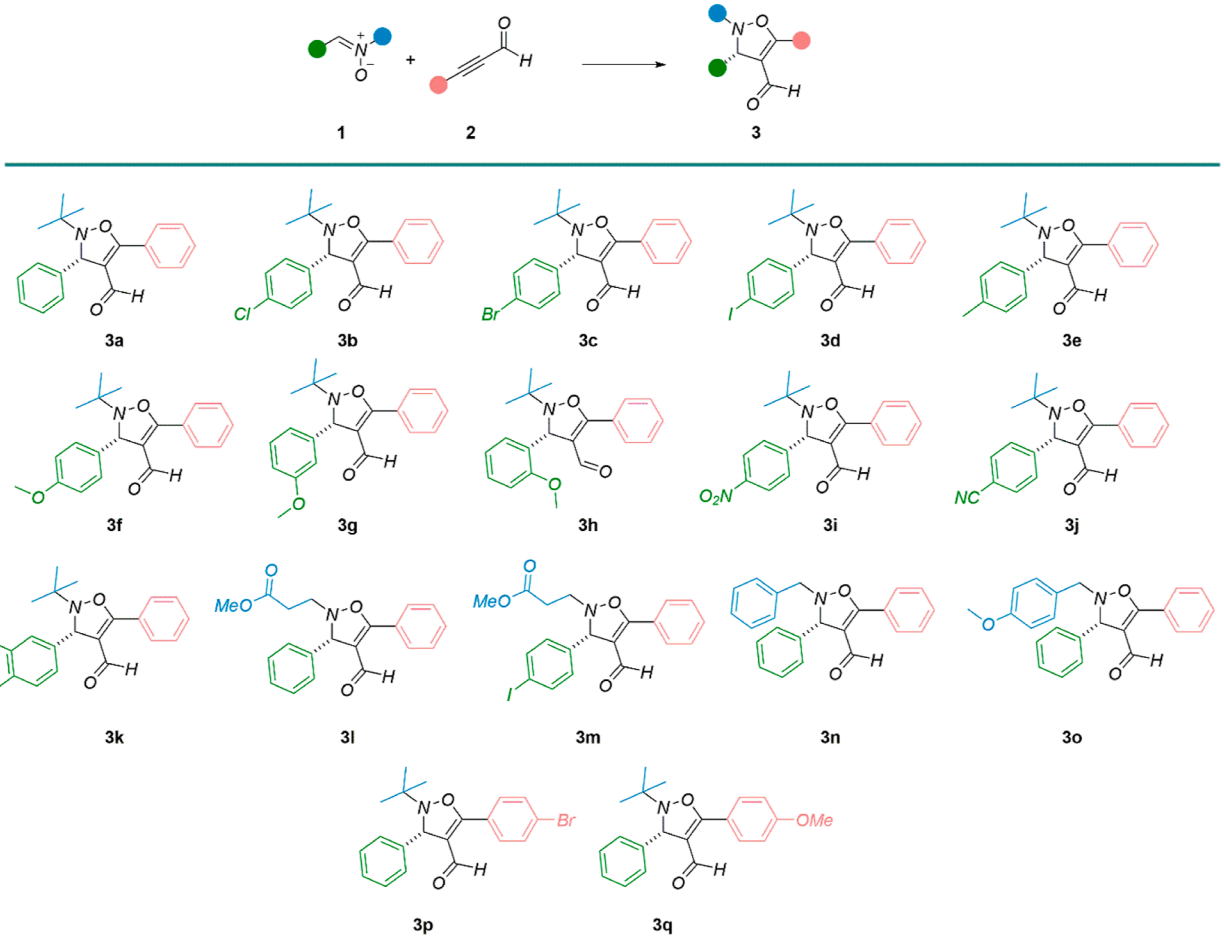


Figure 1. Previously reported approaches for organocatalyzed synthesis of isoxazolines.

Scheme 1. Scope of the 1,3 Dipolar Cycloaddition between Nitrones 1 and Arylpropionadehydes 2



https://doi.org/10.1021/acsomega.2c03477
ACS Omega 2022, 7, 26919−26927

application as drugs,[17] organocatalytic methods are particularly attractive, thanks to the ease of handling the catalysts and the mild reaction conditions.[18]

Reactions between aromatic nitrones and alkynals were independently reported by Alemán[19a] and Sun,[19b] who achieved high enantiomeric excesses on simple substrates by utilizing the aldehyde moiety in the formation of iminium ions with a small selection of organocatalysts. Surprisingly, McMillan's imidazolidinones, which theoretically should generate high enantiomeric excess (e.e.) and more reactive iminium ion species, have generally been discarded in favor of prolinol derivatives (Figure 1).

The main characteristic of proline-like organocatalyzed reactions is that critical evaluation of the uncatalyzed process is necessary because of the high reactivity of the substrates. The enantioselectivity of the protocol is determined from the ability of the catalyst to transfer the chiral information and from the relative speed between the catalyzed and uncatalyzed reactions.

In this work, we explored the use of commercially available MacMillan's catalysts with the target to accelerate the reaction and achieve high yield and enantiomeric ratio (e.r.) by fine-tuning the cycloaddition conditions, in order to identify a versatile and competitive protocol for the synthesis of polyfunctionalized isoxazoline scaffolds. Moreover, further decoration of these building blocks has been explored using Pd-catalyzed reactions, demonstrating the prospective of these heterocycles in generating bioactive molecules.

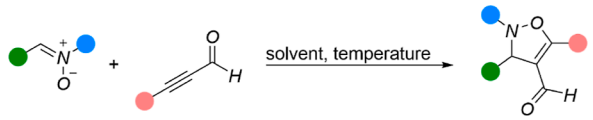
RESULTS AND DISCUSSION

The general scheme and the substrate scope explored in this article are reported in Scheme 1. At first, to succeed in the synthesis of polyfunctionalized isooxazolines **3a−q**, differently substituted nitrones 1a-q and aldehydes **2a−c** were studied in order to evaluate the kinetic impact of the catalyzed and uncatalyzed reactions. As a consequence, nitrones **1a−k**, **1p−q**, and **1n−o** were synthesized starting from *N*-tertbutylhydroxylamine hydrochloride or *N*-benzylhydroxylamine hydrochloride and the corresponding aldehyde, by using a previously described procedure.[20a] On the contrary, the synthesis of nitrones **1l,m** required optimization of the reaction conditions involving the 1,4-addition of the suitable benzaldoxime to methyl acrylate, promoted by ZnI_2 and $BF_3{\cdot}Et_2O$ in a 1:1 mixture (see Supporting Information).[20b]

To obtain reliable conversion data on the 1,3-dipolar cycloaddition, the relative response factor was calculated to correct the HPLC integration ratios between **1** and **3** (see Supporting Information). The uncatalyzed 1,3-dipolar cycloaddition between aromatic nitrones **1** and 3-phenylpropionaldehyde **2** was carried out as a model reaction to evaluate the effects of solvents, substituents, and temperature on reactivity. Table 1 shows selected substrates, whereas the entire screening method is described in the Supporting Information.

Independent from the selected nitrone, the slow uncatalyzed reaction leading to a racemic product had generally a minimal impact on the stereoselective cycloaddition. Only for critical cases (entries 13 and 16, Table 1), conditions leading to lower conversions have been privileged. The reaction between *N*-tertbutyl nitrone **1a** and aldehyde **2**, used to screen the solvents (entries 1−7), showed that a protic solvent like isopropanol accelerated the cycloaddition (entry 4). Regarding the nitrone substituents, the presence of a methoxy group at the para-position in **1f** slightly accelerated the reaction (entry 9). In contrast, the presence of a linear alkyl group on the nitrogen in nitrone **1l** consistently increased the conversion (entry 13).

Table 1. Solvent, Temperature, and Substituents Effects on the Uncatalyzed Reaction between 1 and 2[a]



				conversion (%)		
entry	substrate	T (°C)	solvent	1 h	2 h	4 h
1	**1a**	rt	toluene	4	6	10
2	**1a**	rt	DCM	2	4	7
3	**1a**	rt	THF	5	6	9
4	**1a**	rt	^{i}PrOH	7	11	20
5	**1a**	rt	^{t}BuOAc	5	8	11
6	**1a**	rt	anisole	3	4	7
7	**1a**	rt	DMC	2	3	6
8	**1c**	rt	toluene	4	6	8
9	**1f**	rt	toluene	5	9	14
10	**1h**	rt	toluene	2	6	10
11	**1i**	rt	DCM	1	2	4
12	**1j**	rt	DCM	2	3	4
13	**1l**	rt	toluene	27	48	76
14	**1l**	0	toluene	3	6	12
15	**1l**	−10	toluene	2	3	5
16	**1n**	rt	toluene	11	21	32
17	**1o**	rt	toluene	2	3	5

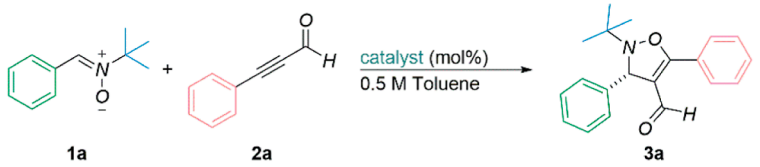
[a]All reactions were carried out with 20 mol % excess of aldehyde, 0.5 M concentration, and the conversion was monitored by HPLC. The reported data are a selection of a more extended screening (see Supporting Information).

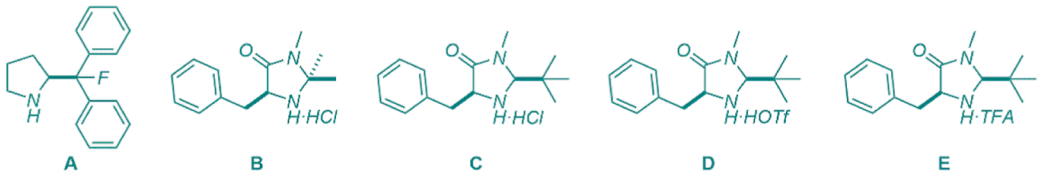
To limit the impact of uncatalyzed cycloaddition on this substrate, the reaction temperature was decreased (entries 14 and 15). In summary, the outcomes shown in Table 1 suggest that (i) protic solvents should be avoided and (ii) the uncatalyzed reaction should be slowed down with linear *N*-alkyl nitrones to generate high e.e.. Toluene generally represents the best solvent in terms of solubility and reaction performance, and for this reason, it was used in subsequent experiments, except for **3i** and **3j**, which were synthesized in DCM due to the poor solubility in toluene of the corresponding nitrones. Different organocatalysts were then screened using cycloaddition between **1a** and **2** as a standard reaction (Table 2) and compared with the results reported in the literature for Jorgensen−Hayashi's catalyst.

Interestingly, in the racemic setup, while the addition of pyrrolidine had a poor effect on the conversion, a more rapid reaction was observed with the corresponding hydrochloride salt (entries 1 and 2). The reaction acceleration observed using pyrrolidine hydrochloride (entry 2) was clearly related to lowering of the LUMO energy due to protonation of the carbonyl, which favors nucleophilic 1,2-addition of the pyrrolidine, as clearly described by Houk and Strozier in 1973.[21] Imidazolidinone catalysts have been successfully applied to LUMO-lowering activation of unsaturated compounds for [3 + 2] dipolar cycloadditions between nitrones and aldehydes[22] and for the [4 + 2] Diels−Alder reactions of unsaturated ketones and dienes.[23] In both cases, a key role of the Brønsted acid cocatalyst was highlighted.[24] Enantioselective cycloaddition catalyzed by the fluorinated Jorgensen−Hayashi's pyrrolidine derivative **A** reportedly generates a 90% e.e. in 24 h at −10 °C

https://doi.org/10.1021/acsomega.2c03477
ACS Omega 2022, 7, 26919−26927

Table 2. Catalyst Screening in the 1,3-Dipolar Cycloaddition between Aromatic Nitrone 1a and 3-Phenylpropionaldehyde 2





entry	Cat (mol %)	T (°C)	t (h)	C[a] (%)	Y[b] (%)	S/R[a]
1	Pyr (10)	rt	24	30		50:50
2	Pyr·HCl	rt	1.5	>99	97	50:50
3[c]	A (5)	−10	24	>99	99	95:5
4	B (10)	−10	24	23	20	89:11
5	C (10)	rt	<0.2	>99	99	97:3
6	D (10)	rt	0.5	>99	96	96:4
7	E (10)	rt	<0.2	>99	99	97:3
8	C (10)	−10	1	>99	99	99:1
9	D (10)	−10	8	>99[d]	95	99:1
10	E (10)	−10	1	>99	99	99:1

[a]Determined by HPLC. [b]Isolated yields. [c]Data from ref 19a. [d]Conversion was 37% after 1 h.

Table 3. Stereoselective 1,3-Dipolar Cycloaddition between 1a−o and 2 Catalyzed by the Second-Generation Macmillan Catalyst[a]

entry	1	solvent	catalyst	T (°C)	t (h)	conversion[b]%	product[c] (yield %)	3[b] S/R
1	**1a**	toluene	**C**	rt	<0.2	>99	**3a** (99)	97/3
2	**1b**	toluene	**C**	rt	4	>99	**3b** (90)	96/4
3	**1c**	toluene	**C**	rt	4	>99	**3c** (92)	95/5
4	**1d**	toluene	**C**	rt	4	>99	**3d** (90)	95/5
5	**1e**	toluene	**C**	rt	<0.2	98	**3e** (91)	99/1
6	**1f**	toluene	**C**	rt	<0.2	>99	**3f** (91)	98/2
7	**1g**	toluene	**C**	rt	<0.2	>99	**3g** (99)	97/3
8	**1h**	toluene	**C**	rt	2	80	**3h** (77)	95/5
9	**1i**	DCM	**C**	rt	4	72	**3i** (68)	95/5
10	**1j**	DCM	**C**	rt	4	70	**3j** (65)	95/5
11	**1k**	toluene	**C**	rt	<0.2	>99	**3k** (99)	98/2
12	**1l**	toluene	**E**	rt	5[d]	>99	**3l** (80)	92/8
13	**1m**	toluene	**E**	rt	5[d]	>99	**3m** (74)	90/10
14	**1n**	toluene	**E**	rt	<0.2	>99	**3n** (99)	91/9
15	**1o**	DCM	**E**	rt	18[d,e]	>99	**3o** (83)	92/8
16	**1b**	toluene	**C**	−10	8	>99	**3b** (92)	97/3
17	**1c**	toluene	**C**	−10	8	>99	**3c** (94)	97/3
18	**1d**	toluene	**C**	−10	8	>99	**3d** (95)	97/3
19	**1h**	toluene	**C**	−10	18	97	**3h** (95)	97/3
20	**1i**	toluene	**C**	−10	18	91	**3i** (85)	97/3
21	**1j**	toluene	**C**	−10	18	92	**3j** (89)	96/4
22	**1l**	toluene	**E**	−10	1.5	>99	**3l** (82)	92/8
23	**1m**	toluene	**E**	−10	4	>99	**3m** (75)	90/10
24	**1n**	toluene	**E**	−10	1	>99	**3n** (99)	93/7
25	**1o**	DMC	**E**	−10	15	>99	**3o** (85)	92/8

[a]All reactions were carried out with 1.2 equiv of **2**, 0.5 M concentration, and 10 mol % catalyst; complete screening is reported in Supporting Information. [b]Determined by HPLC. [c]Isolated yields. [d]The nitrone **1** (0.5 mmol) was added dropwise as 2 M solution within the reported reaction time. [e]The reaction was carried out on the 5 mmol scale.

(entry 3). Surprisingly, the first-generation McMillan catalyst as hydrochloride **B** was inefficient and poorly selective (entry 4). Steric hindrance close to the nitrogen likely had a negative effect on the reaction outcome. However, the situation completely

https://doi.org/10.1021/acsomega.2c03477
ACS Omega 2022, 7, 26919−26927

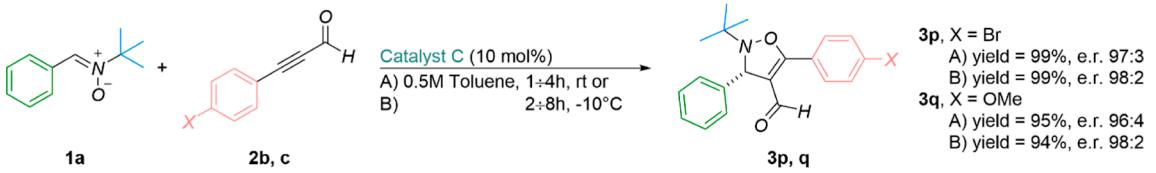


Figure 2. Reaction between nitrone **1a** and alkynals **2b**,**c**.

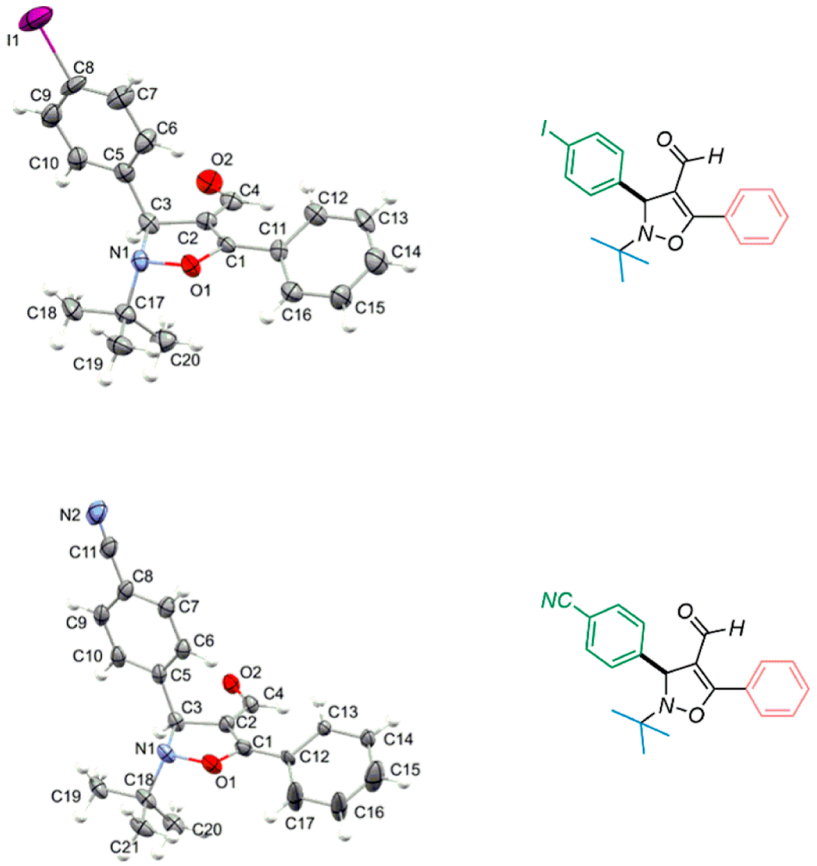


Figure 3. Crystal structures of isoxazolines **3d** and **3j**.

changed moving to the hydrochloride **C**, trifluoromethanesulfonate **D**, or trifluoroacetate **E** of the second-generation McMillan's catalyst (entries 5−10). The cycloadditions catalyzed by **C**, **D**, and **E** were superior in terms of speed and enantioselectivity with respect to the cycloadditions catalyzed by **A** already at room temperature, considering that the reaction time reduced to <0.5 h and the e.r. was always >96/4 in favor of the (*S*) enantiomer (entries 5−7). A further improvement was achieved by lowering the temperature to −10 °C, obtaining **3a** with an e.r. >99/1 with both catalysts (entries 8−10). Even if the reaction with catalyst **E** afforded similar results to those performed with salt **C**, the use of fluorinated compounds should be avoided when efficient alternatives are available. For this reason, we focused on the use of catalyst **C**, making few exceptions for substrates affording unsatisfactory results in terms of yield or e.e. With the goal of developing a useful, scalable, and rapid method for the synthesis of enantiopure isoxazolines as core scaffolds in peptidomimetics, we explored substrate scope by performing reactions on nitrones **1**, bearing different N-protecting groups or aromatic functionalization, and alkynal **2**, as reported in Table 3.

The reaction of **1a−k** with 3-phenylpropiolaldehyde **2** afforded the corresponding isoxazolines **3a−k** with excellent enantiomeric ratios at room temperature (entries 1−11). The introduction of halogens at para-position of the nitrone (**1b−d**) required longer reaction time (4 h) to afford high conversions and yields (entries 2−4) with respect to reference **1a** (entry1). The introduction of electron-donating groups (**1e−g**) or bulky groups (**1k**) provided fast reactions (less than 10 min) with high yields and an almost exquisite stereocontrol (e.r. ≥ 97/3, entries 5−7 and 11). Noteworthy, both *para*- and *meta*-methoxy nitrones (**1f,g**) exhibited similar results, while ortho-derivative (**1h**) decreased the reaction speed, probably because of steric hindrance. For nitrones **1h−j**, in order to increase the e.r. up to 95/5 while avoiding the detrimental effects of uncatalyzed background transformations, it was necessary to stop the reactions after a short time (2−4 h), with a trade off in terms of yield (entries 8−10). As previously mentioned, the introduction of electron-withdrawing groups required a solvent switch from toluene to DCM to improve the solubility of the starting materials (entries 9−10). The introduction of more flexible and less sterically demanding propionate or benzylic substituents on the nitrogen (**1l−o**) afforded **3l−o** with a lower

https://doi.org/10.1021/acsomega.2c03477
ACS Omega 2022, 7, 26919−26927

e.r. (90/10 ÷ 92/8) and yield (74 ÷ 99%; entries 12−15). This can be attributed to the rapid uncatalyzed reaction (entries 13, 16 and 17, Table 1) and to decreased restraint due to free rotation around the C−N bond that affects the catalyst performances. The use of catalyst **E** in combination with slow addition of nitrone was necessary to improve the yield and the stereoselectivity of the synthesis of isoxazolines **3l−3o**. The shift from the hydrochloric acid salt **C** to the trifluoroacetic one **E** of the MacMillan catalyst allowed to avoid e substrate decomposition (entries 12, 13, and 15).

We then explored the temperature effect to limit the uncatalyzed reaction contribution. Following this experimental evidence and tuning the reaction time according to the reaction kinetics, we enhanced the e.r. of halogen derivatives (entries 2−4 vs 16−18), *ortho*-methoxy derivatives (entry 8 vs 19), and electron-withdrawing groups (entries 9 and 10 vs 20 and 21). Interestingly, substrates **1l−o** exhibited almost identical results, in terms of enantiomeric ratios and yields, to the reactions carried out with the slow addition of the nitrone at room temperature (entries 12−15 vs 22−25).

We have also explored the reaction using para-substituted arylpropionaldehydes, namely, the *p*-MeO-Ph and *p*-Br-Ph derivatives. The corresponding isooxazolines **3p** and **3q** have been obtained in high yield and e.r. (Figure 2).

Isooxazoline Configuration Assessment and Reaction Mechanism. To establish the absolute configuration of the newly formed stereocenters, we compared our characterizations with the analytical data reported in the literature. The preferential formation of the (*S*) enantiomer using the (2*S*,5*S*)-imidazolidinone catalyst was confirmed. However, to further assess the stereoselectivity, we directly isolated crystals of isooxazolines **3g** and **3j** and subjected them to X-ray analysis (Figure 3).

The mechanism of the 1,3-dipolar cycloaddition herein explored can be postulated on the basis of the extensive studies reported in the literature on this topic and confirmed by crystallographic data.[25] First, in the LUMO-lowering activation of the unsaturated aldehyde **2**, reversible formation of the iminium ion leads to a preferential (E) geometry, which is reportedly the most-populated geometry for avoiding non-bonding interactions between the unsaturated chain of the activated substrate and the *tert*-butyl substituent of the heterocycle.[26]

As a consequence, the benzyl group on the catalyst framework effectively shields one face of the activated alkyne, leaving the opposite face exposed to the partner reactant. Moreover, this specific class of iminium ions was identified by Mayr as being extremely reactive in comparison with that derived from other organocatalysts.[23,27] In the evaluation of the intermolecular interaction of the reactive iminium species with the nitrone partner, electronically and sterically controlled inductions should be considered. The mechanism of 1,3-dipolar cycloaddition of a nitrone and an unsaturated alkyne was explored only for Jorgensen−Hayashi's catalyst-derived iminium ions.[19] Considering the information collectively, it is plausible to explain the excellent enantioselectivity observed through a pseudoexo-anti-approach, which minimizes the repulsion between the positively charged nitrogen atoms while avoiding the hindrance of the tertbutyl imidazolidone chain (Figure 4).

Isooxazoline Functionalization via Cross-Coupling. The choice of proper substituents on the phenyl ring was designed to open access to isooxazoline decoration. Compounds **3d** and **3m**, bearing an iodine on the aromatic ring, were

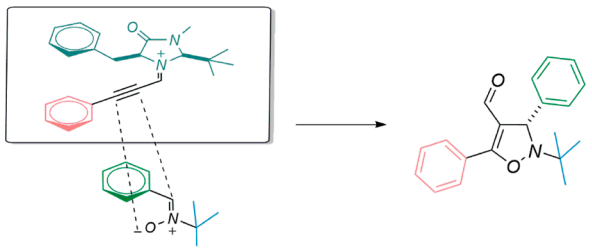


Figure 4. Plausible iminium−nitrone approach leading to (S)-isoxazoline stereochemistry.

identified as useful reagents for Pd-catalyzed cross-coupling reactions[28] (Scheme 2). To verify if the conditions required for cross-coupling reactions could have an impact on isooxazoline enantiopurity, we subjected **3d** to basic conditions (3 or 10 equiv of TEA) and high temperature (70 °C) for 3 h. These experiments allowed to establish that the e.e. of **3d** was maintained even after treatment under harsh conditions (see Supporting Information for more details). On the basis of these results, the Heck reaction[29] between **3m** and tertbutyl acrylate was performed in the presence of TEA and 2 mmol % Pd precatalyst in toluene at 40 °C. Under these conditions, product **4** was isolated in 82% yield after 16 h, providing a scaffold with three functionalizable branches bearing two orthogonal ester groups. On the same substrate, the Heck−Cassar−Sonogashira reaction (HCS)[30] performed using Heck−Cassar conditions with a small excess of phenylacetylene afforded compound **5** in 71% yield. For the more stable *N*-tertbutyl−substituted isooxazoline **3d**, the Sonogashira protocol with trimethylsilylacetylene, including CuI as a cocatalyst, afforded compound **6** in 94% yield in 1 h at room temperature.

CONCLUSIONS

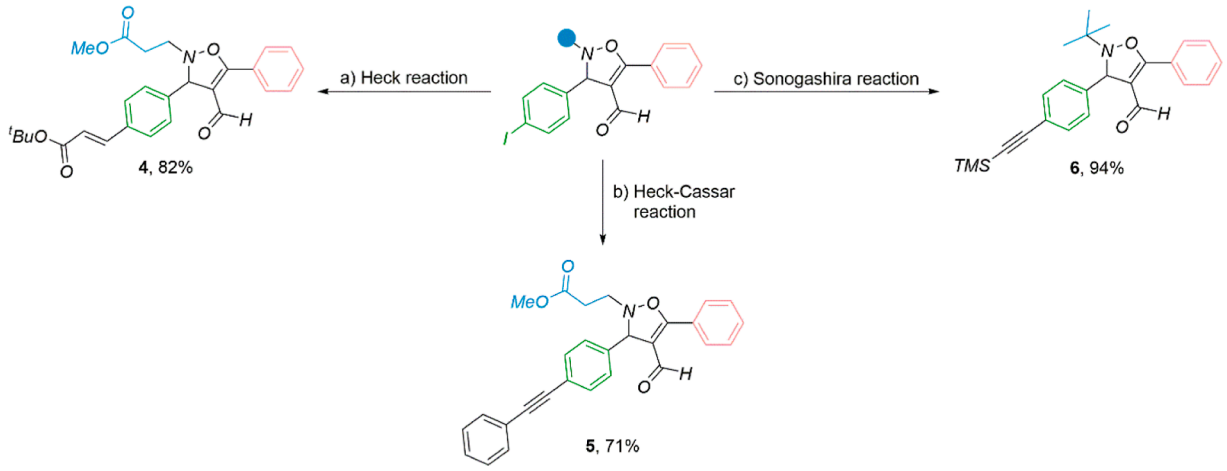
The organocatalyzed 1,3-dipolar cycloadditions proved to be sensitive not only to temperature and solvent but also primarily to the selected catalyst. The best results in terms of reaction speed and e.r. were achieved using the second-generation MacMillan catalyst with a Brønsted acid cocatalyst. The hydrochloride catalyst **C** markedly accelerated the reaction in comparison to the literature data, decreasing the reaction time up to >100 times and affording the final products with high enantioselectivity by controlling non-stereoselective uncatalyzed reactions. The reaction was compatible with several functional groups. The good results observed in HCS and Heck Pd-catalyzed cross-coupling reactions confirmed the possible use of these isooxazolines as scaffolds for the development of polyfunctionalized platforms in bioactive peptidomimetic design. The mild reaction conditions and the fast transformation observed with some substrates can open access to the development of flow organocatalyzed 1,3-dipolar cycloadditions.

EXPERIMENTAL SECTION

General Methods. Commercial reagents (reagent grade, >99%) were used as received without additional purification. Solvents were commercially available and used after degasification. ^{1}H and ^{13}C NMR spectra were recorded using an Agilent-Technologies-Varian INOVA 400 MHz instrument with an $^{1}H/^{19}F/X$ 5-mm PFG ATB broadband probe, VT, single, double, and triple resonance, *z*-axis pulsed-field gradients, and a customized variable-temperature probe. Chemical shifts (δ) are reported in ppm relative to residual solvent signals

https://doi.org/10.1021/acsomega.2c03477
ACS Omega 2022, 7, 26919−26927

Scheme 2. Functionalization of Isooxazolines 3d,m via Cross-Coupling Reactions[a]



[a]Reagents and conditions: (a) **3m** (0.2 mmol), tert-butylacrylate (1.5 equiv), TEA (1.1 equiv), $Pd(PPh_3)_2Cl_2$ (2 mol %), toluene (0.5 M), 40 °C, 16 h. (b) **3m** (0.2 mmol), phenylacetylene (1.5 equiv), TEA (1.1 equiv), $Pd(PPh_3)_2Cl_2$ (2 mol %), toluene (0.5 M), 40 °C, 16 h. (c) **3d** (0.2 mmol), trimethylsilylacetylene (1.5 equiv), TEA (1.1 equiv), $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (1 mol %), toluene (0.5 M), r.t., 1 h.

($CHCl_3$, 7.27 ppm for 1H NMR and CDCl3, 77.16 ppm for ^{13}C NMR). Optical rotations were measured on a SCHMIDT + HAENSCH UniPol L-1000 polarimeter. Flash column chromatography was performed using silica gel Merk-60 (230−400 mesh). HPLC−MS analyses were recorded with an Agilent 1260 InfinityLab instrument. Column: Zorbax SB-C18, particle size: 5 μm, pore size: 100 Å, length: 250 mm, and internal diameter: 4.6 mm. Mobile phase: H_2O/CH_3CN, and the e.r. was determined by HPLC employing a Daicel Chiralpack IC column (hexane/isopropanol mobile phase).

General Procedure for the Synthesis of Nitrones 1l,m. To an oven-dried 10 mL Schlenk flask purged with N_2, the proper oxime and methyl acrylate (2.0 equiv) were dissolved in dry toluene (0.50 M). Zinc iodide (30 mol %) and boron trifluoride diethyl etherate (30 mol %) were then added, and the flask was closed with a plug, and the reaction mixture was heated at 60 or 80 °C overnight (depending on the selected acrylate). The solvent was evaporated, and the crude reaction product was dissolved in DCM and filtered through a short Celite pad. The crude product was then purified by column chromatography over silica gel to give the desired products, **1l−m**, in 65−72% yield.

1l: Yellow sticky oil: yield = 72%. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.21−8.18 (m, 2H), 7.62 (s, 1H), 7.39−7.30 (m, 3H), 4.24 (t, J = 6.2 Hz, 2H), 3.60 (s, 3H), 2.99 (t, J = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.4, 138.9, 131.3, 129.6, 129.3, 128.4, 61.4, 51.9, 31.3. LC−MS−ESI: rt 9.61 min, m/z 208.0 [M + 1], 437.1 [2M + 23].

General Procedure for the Synthesis of 2,3-Dihydroisoxazoles 3a−q. The catalyst C or E was prepared by dissolving the commercial catalyst in minimal amount of dry Et_2O, and an acidic solution of HCl in dry Et_2O (1 M, 1.0 equiv) or TFA was added, respectively. The mixtures were stirred for 10 min and dried under vacuum to afford the desired catalyst as an off-white solid.

In a round-bottom flask, nitrones **1a−q** and catalyst (10 mol %) were dissolved in toluene (0.5 M). The solution was then kept at rt or at −10 °C, and aldehyde **2** (1.2 equiv) was added. The conversion was evaluated by HPLC-UV analysis at 210 nm, and after complete consumption of **1**, the reaction crude was directly purified by flash chromatography to give the desired product **3a−q** in 45−99% yield.

3a: Yellow solid: yield = 99%. mp 96−98 °C. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.69 (s, 1H), 7.73−7.70 (m, 2H), 7.61−7.57 (m, 1H), 7.54−7.50 (m, 4H), 7.37−7.33 (m, 2H), 7.29−7.24 (m, 1H), 5.60 (s, 1H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 185.2, 169.1, 142.7, 132.2, 129.2, 129.1, 128.5, 127.6, 127.4, 126.3, 117.9, 66.2, 62.0, 25.1. The e.r. was determined by HPLC using a Chiralpak IC column (hexane/iPrOH [90:10]), flow rate 1.0 mL/min, τ_{minor} = 7.0 min, and τ_{major} = 8.8 min (e.r. = 1:99 at −10 °C and e.r = 3:97 at r.t). $[\alpha]20D$ = 427.1 (c 1.0 in CH_2Cl_2). LC−MS−ESI: rt 18.15 min, m/z 308.0 [M + 1], 637.2 [2M + 23].

Crystallographic Analysis. The X-ray intensity data were collected on a Bruker Apex II CCD diffractometer. Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in three sets of 20 exposures, collected in three different ω regions, and eventually refined against all data. A full sphere of reciprocal space was scanned by 0.5° ω steps. SMART3 software was used for collecting frames of data, indexing reflections, and determining lattice parameters. The collected frames were then processed for integration using the SAINT program,[31] and an empirical absorption correction was applied using SADABS.[32] The structures were solved by direct methods (SIR 2014)[33] and subsequent Fourier syntheses and refined by full-matrix least-squares on F2 (SHELXTL)[34] using anisotropic thermal parameters for all non-hydrogen atoms. The aromatic, methyl, methylene, and methine hydrogen atoms were placed at calculated positions, refined with isotropic thermal parameters U(H) = 1.2 Ueq(C), and allowed to ride on their carrier carbons. The structure of **3j** showed a phenyl disordered over two orthogonal positions with relative occupancies of 0.65 and 0.35.

Crystal data and experimental details of the data collection for **3d** and **3j** are reported in the Supporting Information. Molecular drawings were generated using Mercury.[35] Crystallographic data were deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 2100934 and 2100935. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/getstructures.

https://doi.org/10.1021/acsomega.2c03477
ACS Omega 2022, 7, 26919−26927

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c03477.

$^{1}H/^{13}C$ NMR, crystallographic data, and chiral HPLC analysis of all products and reaction kinetics (PDF)

Crystal data and structure refinement (ZIP)

■ AUTHOR INFORMATION

Corresponding Authors

Alessandra Tolomelli − *Department of Chemistry, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy;* orcid.org/0000-0003-4202-1136; Email: alessandra.tolomelli@unibo.it

Walter Cabri − *Department of Chemistry, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy;* orcid.org/0000-0001-7865-0474; Email: walter.cabri@unibo.it

Authors

Dario Corbisiero − *Department of Chemistry, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy;* orcid.org/0000-0002-5818-1786

Tommaso Fantoni − *Department of Chemistry, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy*

Lucia Ferrazzano − *Department of Chemistry, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy;* orcid.org/0000-0002-7083-2211

Giulia Martelli − *Department of Chemistry, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy;* orcid.org/0000-0001-7563-4954

Paolo Cantelmi − *Department of Chemistry, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy;* orcid.org/0000-0001-8796-6825

Alexia Mattellone − *Department of Chemistry, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy;* orcid.org/0000-0002-7867-2267

Chiara Palladino − *Department of Chemistry, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy;* orcid.org/0000-0001-8245-9584

Magda Monari − *Department of Chemistry, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy*

Riccardo Pedrazzani − *Department of Chemistry, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c03477

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We kindly acknowledge Alma Mater Studiorum-University of Bologna for financial support. We thank Prof. Piergiorgio Cozzi and Prof. Andrea Gualandi for useful discussions. Fondazione CarisBo is gratefully acknowledged for project funding (#18668 "Tecnologie avanzate per il controllo e lo sviluppo di molecole innovative per la salute"). MIUR is kindly acknowledged for project funding (PRIN 2020−2020833Y75_004 "synthesis and biomedical applications of tumor-targeting peptidomimetics and conjugates").

■ REFERENCES

(1) Kumari, S.; Carmona, A. V.; Tiwari, A. K.; Trippier, P. C. Amide Bond Bioisosteres: Strategies, Synthesis, and Successes. *J. Med. Chem.* **2020**, *63*, 12290−12358.

(2) Gomtsyan, A. Heterocycles in drugs and drug discovery. *Chem. Heterocycl. Compd.* **2012**, *48*, 7−10.

(3) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87*, 1348−1349. https://njardarson.lab.arizona.edu/content/top-pharmaceuticals-poster

(4) (a) Pinho e Melo, T. M. V. D. 4-Isoxazolines: Scaffolds for Organic Synthesis. *Eur. J. Org. Chem.* **2010**, *2010*, 3363−3376. (b) Chukanov, N. V.; Reznikov, V. A. The chemistry of 2,3-dihydroisoxazole derivatives. *Russ. Chem. Bull.* **2011**, *60*, 379−399.

(5) Habeeb, A. G.; Praveen Rao, P. N.; Knaus, E. E. Design and Synthesis of 4,5-Diphenyl-4-isoxazolines: Novel Inhibitors of Cyclooxygenase-2 with Analgesic and Antiinflammatory Activity. *J. Med. Chem.* **2001**, *44*, 2921−2927.

(6) Chandrasekhar, B.; Ahn, S.; Ryu, J. S. Stereoselective Synthesis of a Ceramide Transporter Protein (CERT)-Dependent Ceramide-Trafficking Inhibitor, (1R,3S)-HPA-12, via Gold(I)-Catalyzed Cyclization of a Propargylic N-Hydroxylamine. *Synthesis* **2017**, *49*, 1569−1574.

(7) Tolomelli, A.; Gentilucci, L.; Mosconi, E.; Viola, A.; Dattoli, S. D.; Baiula, M.; Spampinato, S.; Belvisi, L.; Civera, M. Development of Isoxazoline-Containing Peptidomimetics as Dual $\alpha v\beta 3$ and $\alpha 5\beta 1$ Integrin Ligands. *ChemMedChem* **2011**, *6*, 2264−2272.

(8) Ferrazzano, L.; Corbisiero, D.; Potenza, E.; Baiula, M.; Dattoli, S. D.; Spampinato, S.; Belvisi, L.; Civera, M.; Tolomelli, A. Side chain effect in the modulation of $\alpha v\beta 3/\alpha 5\beta 1$ integrin activity via clickable isoxazoline-RGD-mimetics: development of molecular delivery system. *Sci. Rep.* **2020**, *10*, 7410.

(9) Libuori, A.; Ottana, R.; Romeo, G.; Sindona, G.; Uccella, N. Regioselective formation of 4-isoxazolines from n-aryl nitrones and alkynes. *Tetrahedron* **1988**, *44*, 1247−1253.

(10) Padwa, A.; Bullock, W. H.; Kline, D. N.; Perumattam, J. Heterocyclic synthesis via the reaction of nitrones and hydroxylamines with substituted allenes. *J. Org. Chem.* **1989**, *54*, 2862−2869.

(11) Videtta, V.; Perrone, S.; Rosato, F.; Alifano, P.; Tredici, S. M.; Troisi, L. Condensed Oxaziridine-Mediated [3+2] Cycloaddition: Synthesis of Polyhetero-bicyclo Compounds. *Synlett* **2010**, *18*, 2781−2783.

(12) Chandrasekhar, B.; Ahn, S.; Ryu, J.-S. Synthesis of 4-Isoxazolines through Gold(I)-Catalyzed Cyclization of Propargylic N-Hydroxylamines. *J. Org. Chem.* **2016**, *81*, 6740−6749.

(13) Benfatti, F.; Bottoni, A.; Cardillo, G.; Gentilucci, L.; Monari, M.; Mosconi, E.; Stenta, M.; Tolomelli, A. Synthesis of Ethyl 5-Hydroxyisoxazolidine-4-carboxylates via Michael Addition/Intramolecular Hemiketalisation. *Eur. J. Org. Chem.* **2008**, *2008*, 6119−6127.

(14) Domínguez, E.; Ibeas, E.; de Marigorta, E. M.; Palacios, J. K.; SanMartin, R. A Convenient One-Pot Preparative Method for 4,5-Diarylisoxazoles Involving Amine Exchange Reactions. *J. Org. Chem.* **1996**, *61*, 5435−5439.

(15) Honda, K.; Mikami, K. Asymmetric "Acetylenic" [3+2] Cycloaddition of Nitrones Catalyzed by Cationic Chiral PdII Lewis Acid. *Chem.—Asian J.* **2018**, *13*, 2838−2841.

(16) Hashimoto, T.; Maruoka, K. Recent Advances of Catalytic Asymmetric 1,3-Dipolar Cycloadditions. *Chem. Rev.* **2015**, *115*, 5366−5412.

(17) (a) Han, B.; He, X.-H.; Liu, Y.-Q.; He, G.; Peng, C.; Li, J.-L. Asymmetric organocatalysis: an enabling technology for medicinal chemistry. *Chem. Soc. Rev.* **2021**, *50*, 1522−1586. (b) Alemán, J.; Cabrera, S. Applications of asymmetric organocatalysis in medicinal chemistry. *Chem. Soc. Rev.* **2013**, *42*, 774−793. (c) Hughes, C. D. L. Applications of Flow Chemistry in Drug Development: Highlights of Recent Patent Literature. *Org. Process Res. Dev.* **2018**, *22*, 574−584.

(18) (a) *Comprehensive Enantioselective Organocatalysis - Catalysts, Reactions, and Applications*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2013. (b) Juaristi, E. Recent developments in next generation (S)-proline-derived chiral organocatalysts. *Tetrahedron* **2021**, *88*, 132143.

(19) (a) Alemán, J.; Fraile, A.; Marzo, L.; Garcia Ruano, J. L.; Izquierdo, C.; Diaz-Tenderob, S. Enantioselective Synthesis of 4-Isoxazolines by 1,3-Dipolar Cycloadditions of Nitrones to Alkynals Catalyzed by Fluorodiphenylmethylpyrrolidines. *Adv. Synth. Catal.* **2012**, *354*, 1665−1671. (b) Cai, X.; Wang, C.; Sun, J. Organocatalytic Enantioselective Dipolar [3+2] Cycloadditions of Acetylenic Aldehydes with Nitrones for the Formation of Chiral 4-Isoxazolines. *Adv. Synth. Catal.* **2012**, *354*, 359−363.
(20) (a) Morales, S.; Guijarro, F. G.; Alonso, I.; García Ruano, J. L.; Cid, M. Dual Role of Pyrrolidine and Cooperative Pyrrolidine/Pyrrolidinium Effect in Nitrone Formation. *ACS Catal.* **2016**, *6*, 84−91. (b) Nakama, K.; Seki, S.; Kanemasa, S. A new synthetic access to N-alkylated nitrones through Lewis acid-catalyzed conjugate additions of aldoximes. *Tetrahedron Lett.* **2001**, *42*, 6719−6722.
(21) Houk, K. N.; Strozier, R. W. New Radical Allylation Reaction of Iodides. *J. Am. Chem. Soc.* **1973**, *95*, 4094.
(22) Jen, W. S.; Wiener, J. J.; MacMillan, D. W. C. New Strategies for Organic Catalysis: The First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition. *J. Am. Chem. Soc.* **2000**, *122*, 9874−9875.
(23) (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels−Alder Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243−4244. (b) Brazier, J. B.; Gibbs, T. J. K.; Rowley, J. H.; Samulis, L.; Yau, S. C.; Kennedy, A. R.; Platts, J. A.; Tomkinson, N. C. O. Improving catalyst activity in secondary amine catalysed transformations. *Org. Biomol. Chem.* **2015**, *13*, 133−141.
(24) Cozzi, P. G.; Gualandi, A.; Mengozzi, L.; Wilson, C. M. Sustainable Catalysis: Without Metals or Other Endangered Elements, Part 2, *RSC Green Chemistry*, 41st ed.; North, M.; Royal Society of Chemistry, 2016; Chapter 18, pp 164−195.
(25) (a) Northrup, A. B.; MacMillan, D. W. C. The First General Enantioselective Catalytic Diels−Alder Reaction with Simple α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **2002**, *124*, 2458−2460. (b) Gordillo, R.; Carter, J.; Houk, K. N. Theoretical Explorations of Enantioselective Alkylation Reactions of Pyrroles and Indoles Organocatalyzed by Chiral Imidazolidinones. *Adv. Synth. Catal.* **2004**, *346*, 1175−1185. (c) Seebach, D.; Grošelj, U.; Badine, D. M.; Schweizer, W. B.; Beck, A. K. Isolation and X-Ray Structures of Reactive Intermediates of Organocatalysis with Diphenylprolinol Ethers and with Imidazolidinones. *Helv. Chim. Acta* **2008**, *91*, 1999−2034.
(26) (a) Austin, J. F.; MacMillan, D. W. C. Enantioselective Organocatalytic Indole Alkylations. Design of a New and Highly Effective Chiral Amine for Iminium Catalysis. *J. Am. Chem. Soc.* **2002**, *124*, 1172−1173. (b) Gothelf, K. V.; Jørgensen, K. A. Asymmetric 1,3-Dipolar Cycloaddition Reactions. *Chem. Rev.* **1998**, *98*, 863−910.
(27) Mayr, H.; Lakhdar, S.; Maji, B.; Ofial, A. R. A quantitative approach to nucleophilic organocatalysis. *J. Org. Chem.* **2012**, *8*, 1458−1478.
(28) Seechurn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085.
(29) Cabri, W.; Candiani, I. Recent Developments and New Perspectives in the Heck Reaction. *Acc. Chem. Res.* **1995**, *28*, 2−7.
(30) (a) Ferrazzano, L.; Martelli, G.; Fantoni, T.; Daka, A.; Corbisiero, D.; Viola, A.; Ricci, A.; Cabri, W.; Tolomelli, A. Fast Heck−Cassar−Sonogashira (HCS) Reactions in Green Solvents. *Org. Lett.* **2020**, *22*, 3969−3973. (b) Fantoni, T.; Bernardoni, S.; Mattellone, A.; Martelli, G.; Ferrazzano, L.; Cantelmi, P.; Corbisiero, D.; Tolomelli, A.; Cabri, W.; Vacondio, F.; Ferlenghi, F.; Mor, M.; Ricci, A. Palladium Catalyst Recycling for Heck-Cassar-Sonogashira Cross-Coupling Reactions in Green Solvent/Base Blend. *ChemSusChem* **2021**, *14*, 2591−2600.
(31) *SMART & SAINT Software Reference Manuals*, version 5.051 (Windows NT Version); Bruker Analytical X-ray Instruments Inc.: Madison, WI, 1998.
(32) Sheldrick, G. M. *SADABS-2008/1—Bruker AXS Area Detector Scaling and Absorption Correction*; Bruker AXS: Madison, Wisconsin, USA, 2008.
(33) Burla, M. C.; Caliandro, R.; Carrozzini, B.; Cascarano, G. L.; Cuocci, C.; Giacovazzo, C.; Mallamo, M.; Mazzone, A.; Polidori, G. Crystal structure determination and refinement via SIR2014. *J. Appl. Crystallogr.* **2015**, *48*, 306−309.
(34) Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71*, 3−8.
(35) Macrae, C. F.; Sovago, I.; Cottrell, S. J.; Galek, P. T. A.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G. P.; Stevens, J. S.; Towler, M.; Wood, P. A. Mercury 4.0: from visualization to analysis, design and prediction. *J. Appl. Crystallogr.* **2020**, *53*, 226−235.

https://doi.org/10.1021/acsomega.2c03477
ACS Omega 2022, 7, 26919−26927