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

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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 bioisosteres 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 20203 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 stereoisomers can be easily designed by selecting proper reactions and conditions. For example, 4-isoxazolines5 exhibit interesting and diverse activities5 and have been utilized as intermediates in the synthesis of bioactive compounds,5 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 αvβ3 and α5β1 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 alkynes9 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 salts14 has been reported in the literature.

The few reported examples of catalytic asymmetric synthesis primarily involve high loading of expensive and rare metal catalysts12,15 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
Figure 1. Previously reported approaches for organocatalyzed synthesis of isoxazolines.

Scheme 1. Scope of the 1,3 Dipolar Cycloaddition between Nitrones 1 and Arylpropiondehydes 2
application as drugs, organocatalytic methods are particularly attractive, thanks to the ease of handling the catalysts and the mild reaction conditions.

Reactions between aromatic nitrones and alkynals were independently reported by Aleman and Sun, 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 general scheme and the substrate scope explored in this article are reported in Scheme 1. At first, to succeed in the synthesis of polyfunctionalized isoaxazolines 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-tert-butylhydroxylamine hydrochloride or N-benzhydrylamine hydrochloride and the corresponding aldehyde, by using a previously described procedure. 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$_3$·Et$_2$O in a 1:1 mixture (see Supporting Information).

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).

### RESULTS AND DISCUSSION

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### Table 1. Solvent, Temperature, and Substituents Effects on the Uncatalyzed Reaction between 1 and 2

| 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     | PrOH   | 7   | 11  | 20  |
| 5     | 1a        | rt     | ‘BuOAc | 5   | 8   | 11  |
| 6     | 1a        | rt     | anisole| 3   | 4   | 7   |
| 7     | 1a        | rt     | toluene| 4   | 6   | 8   |
| 8     | 1c        | rt     | toluene| 5   | 9   | 14  |
| 9     | 1f        | rt     | toluene| 2   | 6   | 10  |
| 10    | 1h        | rt     | toluene| 1   | 2   | 4   |
| 11    | 1i        | rt     | DCM    | 2   | 3   | 4   |
| 12    | 1j        | rt     | DCM    | 2   | 3   | 5   |
| 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   |

“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).”

contrast, the presence of a linear alkyl group on the nitrogen in nitrone 11 consistently increased the conversion (entry 13).

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 Jørgensen–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 corresponding diazo compound, as clearly described by Houk and Strozier (2013).

Imidazolidinone catalysts have been successfully applied to LUMO-lowering activation of unsaturated compounds for [3 + 2] dipolar cycloadditions between nitrones and aldehydes and for the [4 + 2] Diels–Alder reactions of unsaturated ketones and dienes. In both cases, a key role of the Brønsted acid cocatalyst was highlighted. Enantioselective cycloaddition catalyzed by the fluorinated Jørgensen–Hayashi’s pyrrolidine derivative A reportedly generates a 90% e.e. in 24 h at −10 °C.
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 (%) | Y (%) | S/R |
|-------|-------------|--------|-------|-------|-------|-----|
| 1     | Pyr (10)    | rt     | 24    | 30    | 50:50 |     |
| 2     | Pyr·HCl     | rt     | 1.5   | >99   | 97    | 50:50|
| 3     | 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   | 95    | 99:1|
| 10    | E (10)      | −10    | 1     | >99   | 99    | 99:1|

"Determined by HPLC. bIsolated yields. cData from ref 19a. dConversion was 37% after 1 h.

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

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

"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. bDetermined by HPLC. cIsolated yields. dThe nitrone 1 (0.5 mmol) was added dropwise as 2 M solution within the reported reaction time. eThe 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
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-phenylpropionaldehyde 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 (1i–o) afforded 3l–o with a lower
The choice of proper substituents on the phenyl ring was the hindrance of the tertbutyl imidazolidone chain (Figure 4). Considering the information collectively, it is plausible to uncatayzed 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 vs 9 and 10 vs 20 and 21). Interestingly, substrates II−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 isoaxazolines 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 (2S,5S)-imidazolidinone catalyst was confirmed. However, to further assess the stereoselectivity, we directly isolated crystals of isoaxazolines 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. 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.

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 MacMillan catalyst with a Brønsted acid cocatalyst. The hydrochloride catalyst Cassar conditions 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 enantiomeric excess.

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 Cassar conditions 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 enantiomeric excess.

EXPERIMENTAL SECTION

General Methods. Commercial reagents (reagent grade, >99%) were used as received without additional purification. Solvents were commercially available and used after degasification. 1H and 13C NMR spectra were recorded using an Agilent-Technologies-Varian INOVA 400 MHz instrument with an 1H/13F/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

![Figure 4](image-url). Plausible iminium−nitrone approach leading to (S)-isoaxazoline stereochemistry.
Scheme 2. Functionalization of Isooxazolines 3d,m via Cross-Coupling Reactions*4

“Reagents and conditions: (a) 3m (0.2 mmol), tert-butylacrylate (1.5 equiv), TEA (1.1 equiv), Pd(PPh₃)₃Cl (2 mol %), toluene (0.5 M), 40 °C, 16 h. (b) 3m (0.2 mmol), phenylacetylene (1.5 equiv), TEA (1.1 equiv), Pd(PPh₃)₃Cl (2 mol %), toluene (0.5 M), 40 °C, 16 h. (c) 3d (0.2 mmol), trimethylsilylacetylene (1.5 equiv), TEA (1.1 equiv), Pd(PPh₃)₃Cl (2 mol %), toluene (0.5 M), 16 h.

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

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ASSOCIATED CONTENT

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

Crystal data and structure refinement (ZIP)


correlated to 1H/13C NMR, crystallographic data, and chiral HPLC analysis of all products and reaction kinetics (PDF)

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Notes

The authors declare no competing financial interest.

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