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Enantioselective Synthesis of 4-Isoxazolines by 1,3-Dipolar Cycloadditions of Nitrones to Alkynals Catalyzed by Fluorodiphenylmethylpyrrolidines

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Dedicated to Dr. Rosario Martín Ramos on the occasion of her retirement.

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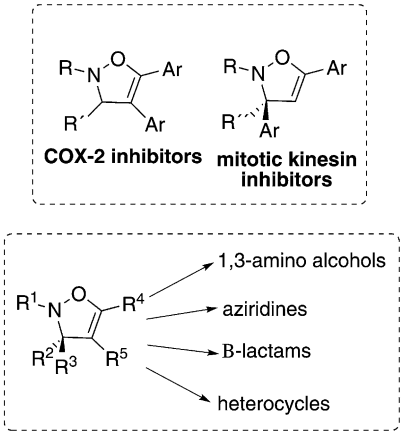
Abstract: The first organocatalytic enantioselective 1,3-dipolar reaction between nitrones and alkynals catalyzed by (*S*)-2-(fluorodiphenylmethyl)pyrrolidine to give 4-isoxazolines (2,3-dihydroisoxazoles) with high enantiomeric excess, excellent yields and low catalyst loading (1–5 mol%) is presented. The catalytic loading could be reduced to 1 mol% with only slight increases in reaction times.

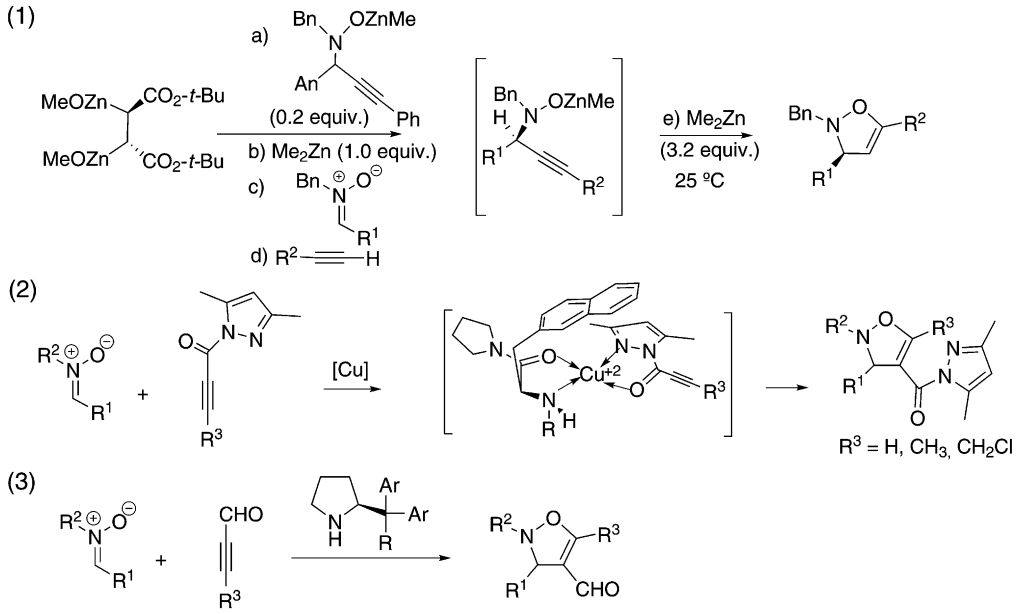
Keywords: [3+2]cycloaddition reactions; 2,3-dihydroisoxazoles; iminium ions; 4-isoxazolines; organocatalysis



Scheme 1. Usefulness of 4-isoxazolines.

4-Isoxazolines or 2,3-dihydroisoxazoles[1] are compounds exhibiting interesting pharmacological properties (anti-inflamatory action[2] and mitotic kinesin inhibition[3]), along with other biological activities.[4] They have also been used as synthons for preparing 1,3-amino alcohols,[5] aziridines,[6] β-lactams[7] and a wide variety of heterocycles (Scheme 1).[8]

Several approaches have been developed for the synthesis of these compounds in racemic form,[9] with the 1,3-dipolar cycloadditions of nitrones with alkynes being one of the most successfully used despite problems with the regioselectivity.[9a] By contrast, very few methods concerning the asymmetric synthesis of these compounds have been reported (most of them starting from chiral pool molecules),[10] with only two of them involving nitrones and being enantioselective.[7a,11] The first method consists of the asymmetric addition of alkynylzinc reagents to nitrones in the presence of (*R*,*R*)-tartrate as ligand, and the subsequent cyclization of the resulting zinc intermediate [Eq. (1), Scheme 2].[11] This method is not very practical though because of the required laborious experimentation. The second method is related to asymmetric 1,3-dipolar cycloadditions of nitrones and propioloylpyrazoles catalyzed by copper[7a] [Eq. (2), Scheme 2]. The scope of this method is limited to $R^3 = H$, Me, CH_2Cl and requires the incorporation of the acylpyrazole moiety (which is later transformed into other functionalities) to coordinate the metal forming the rigid intermediate that is responsible of the activation of the triple bond as well as the stereoselectivity. To the best of our knowledge, no organocatalytic[12] version of this reaction has been reported, despite the fact that catalysts able to interact covalently and non-covalently with different EWG-activated triple bonds are well known.[13] This fact suggests that the main difficulties in the stereoselective control



Scheme 2. Enantioselective approaches for preparing 4-isoxazolines [Eqs. (1) and (2)] and the present work Eq. (3).

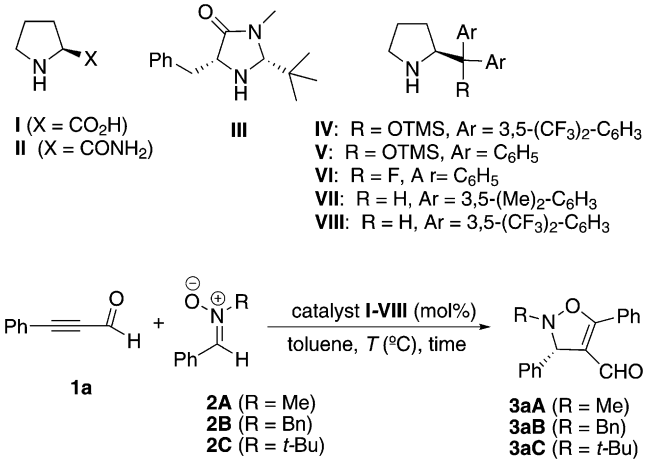
of the cycloaddition of nitrones to activated alkynes will be related with finding the proper catalyst to promote restrictions in the many possible approaches of the nitrone to the linear triple bond. In this work, we describe our efforts toward finding such a catalyst, which allowed us to achieve the first highly efficient organocatalytic method for obtaining 4-isoxazolines by 1,3-dipolar reaction of nitrones and alkynals under aminocatalysis [Eq. (3), Scheme 2].[13a]

As the model reaction for optimization, nitrone **2A** was exposed to alkynal **1a** in the presence of different secondary amine catalysts **I–VIII** (Table 1). First, we confirmed that the reaction takes place at room temperature even in the absence of catalyst (entry 1, Table 1), demonstrating that the alkynals are sufficiently reactive at room temperature. This reaction gave racemic **3aA** and required 5 days to proceed to completion. Since this background reaction could decrease the enantiomeric excess, we decided to stop the rest of the reactions with this nitrone (**2A**)[14] after 24 h in case that the catalyst could decrease its activity. Incomplete conversion and low enantiomeric ratios were found with proline (**I**) and prolinamide (**II**) (entries 2 and 3). The use of MacMillan's catalyst (**III**) and Jørgensen–Hayashi's catalysts (**IV** and **V**) provided full conversion but poor enantiomeric ratios (entries 4–6). Toluene was used as solvent in all these reactions, but the change to THF, DCE or CH_2Cl_2 did not improve these results (see the Supporting Information for details). Interestingly, when the OTMS group of the Jørgensen–Hayashi catalysts (**IV** and **V**) was substituted by fluorine (**VI**) or hydrogen (**VII**, **VIII**), the enantiomeric ratios were improved (entries 7–9), with the best results obtained using catalyst **VIII**, which provided a complete conversion after 24 h and 81:19 enantiomeric ratio (entry 9).

Next, we examined the influence of increasing the size of R (nitrone) on the stereoselectivity. Nitrones **2B** and **2C** bearing benzyl and *tert*-butyl groups joined to nitrogen, respectively, were interesting for the larger size. Reactions of **2B** (R = Bn) showed a complete conversion under catalysis of **VI** and **VII** (also with **VIII**), indicating a higher reactivity than **2A** (compare entries 10 and 11 with 7 and 8). Moreover, the best enantiomeric ratios in reactions of **2B** with **1a** were obtained using catalyst **VI** (compare entries 10–12). Therefore, this reaction was studied at lower temperature (0 °C) and the *er* was increased to 88:12 (entry 13). Less important were the results obtained using other temperatures and solvents (see the Supporting Information). The use of the commercially available nitrone **2C** (R = *t*-Bu) gave even better results (entries 14–17) with **VI**. The obtained stereoselectivity was higher than with **2B** (compare entries 12 and 14), slightly improved when the temperature was lowered (compare entries 14–16), and was maintained by decreasing the catalyst loading to 5% (entry 17) or even 1% (entry 18), although in the latter case the reaction required 4 days for completion. The enantiomeric ratio decreased when 0.5 mol% of **VI** was used (entry 19). We observed unaltered starting materials with the use of an acid co-catalyst (TFA) (entry 20), whereas the use of benzoic acid gave full conversion, and the obtained *ee* was similar to the previous one (compare entries 17 and 21).

The scope of this reaction was investigated using the optimized reaction conditions in entry 17 (Table 1). Results obtained for different aryl-substi-

Table 1. Representative screening results for the catalyzed reactions of nitrones **2A–C** with the alkynal **1a**.[a]



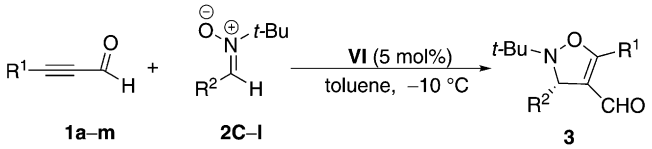
Entry	Cat (mol%)	2-R	Temp. [°C]/Time [h]	Conversion [%][b]	*er*[c]
1	–	**2A**-Me	r.t./12	100	-
2	**I** (20 mol%)	**2A**-Me	r.t./24	44	55:45
3	**II** (20 mol%)	**2A**-Me	r.t./24	30	52:28
4	**III** (20 mol%)	**2A**-Me	r.t./24	>99	64:36
5	**IV** (20 mol%)	**2A**-Me	r.t./24	>99	55:45
6	**V** (20 mol%)	**2A**-Me	r.t./24	>99	55:45
7	**VI** (20 mol%)	**2A**-Me	r.t./24	60	75:25
8	**VII** (20 mol%)	**2A**-Me	r.t./24	70	70:30
9	**VIII** (20 mol%)	**2A**-Me	r.t./24	>99	81:19
10	**VI** (20 mol%)	**2B**-Bn	r.t./24	>99	85:15
11	**VII** (20 mol%)	**2B**-Bn	r.t./24	>99	70:30
12	**VIII** (20 mol%)	**2B**-Bn	r.t./24	>99	70:30
13	**VI** (20 mol%)	**2B**-Bn	0/24	>99	88:12
14	**VI** (20 mol%)	**2C**-*t*-Bu	r.t./24	>99	90:10
15	**VI** (20 mol%)	**2C**-*t*-Bu	−10/24	>99	95:5
16	**VI** (10 mol%)	**2C**-*t*-Bu	−10/24	>99	96:4
17	**VI** (5 mol%)	**2C**-*t*-Bu	−10/24	>99	95:5
18	**VI** (1 mol%)	**2C**-*t*-Bu	0/96	>99	95:5
19	**VI** (0.5 mol%)	**2C**-*t*-Bu	0/120	>99	88:12
20	**VI** (5 mol%)[d]	**2C**-*t*-Bu	−10/24	n.r.[e]	–
21	**VI** (5 mol%)[f]	**2C**-*t*-Bu	−10/24	>99	95:5

[a] All reactions were performed on a 0.2-mmol scale in 0.4 mL of solvent and stopped at the indicated time
[b] Conversion was determined by ^{1}H NMR.
[c] Enantiomeric ratio was determined by chiral HPLC.
[d] Reaction carried out with a 5 mol% of TFA.
[e] No reaction.
[f] Reaction carried out with a 5 mol% of $PhCO_2H$.

tuted (**1a–h**), alkyl-substituted (**1i–l**) and alkenyl-substituted (**1m**) alkynals with nitrones **2C–2I** (all of them *N-tert*-butyl derivatives) are collected in Table 2. These reactions were performed on a 0.2-mmol scale, except for the entry 2 which was carried out on a 2.0-mmol scale, affording **3aC** in 84% isolated yield without any significant erosion of the stereoselectivity (compare entries 1 and 2). Enantioselectivity and reactivity were exceptionally unaffected by the incorporation of electron-donating (**1b–1d**, entries 3–5) or electron-withdrawing (**1e–1h**, entries 6–9) groups on the aromatic ring of the arylalkynals. The reaction of 2-octynal (**1i**) with **2C** was slower (5 days) and gave lower yield (58%) than that of arylalkynals (24 h and >80% yield), but the high stereoselectivity was maintained (entry 10). The incorporation of a secondary alkyl group (**1j**) strongly decreased the reactivity (5 days, entry 11), whereas substrates with tertiary alkyl groups (**1k**) did not react (entry 12), which was also the case for the TMS derivative **1l** (entry 13). Remarkably, enynals (**1m**) evolved with good yields and excellent *er* (entry 14).

Finally, we studied the behavior of different *N-tert*-butylnitrones.[15] The introduction of electron-donat-

Table 2. Scope of the reaction of nitrones **2C–I** with alkynals **1a–m** under catalysis with **VI**.[a]



1a–m 2C–I 3

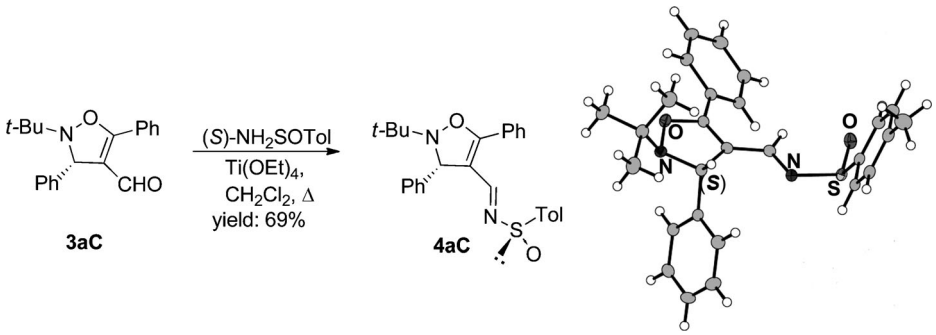
Entry	R^1/R^2	Yield [%]: Product	*er* [%][b]
1	Ph-**1a/**Ph-**2C**	>99: **3aC**	95:5
2	Ph-**1a/**Ph-**2C**	84:[c] **3aC**	96:4
3	*p*-MeC_6H_4-**1b/**Ph-**2C**	90: **3bC**	95:5
4	*p*-$MeOC_6H_4$-**1c/**Ph-**2C**	>99: **3cC**	95:5
5	*p*-(*t*-Bu)C_6H_4-**1d/**Ph-**2C**	99: **3dC**	95:5
6	*p*-BrC_6H_4-**1e/**Ph-**2C**	85: **3eC**	90:10
7	*p*-F-C_6H_4-**1f/**Ph-**2C**	96: **3fC**	95:5
8	3,5-$(CF_3)_2C_6H_3$-**1g/**Ph-**2C**	80: **3gC**	94:6
9	3,4-$(Cl)_2C_6H_3$-**1h/**Ph-**2C**	99: **3hC**	92:8
10	*n*-pentyl-**1i**[e]**/**Ph-**2C**	58: **3iC**	90:10
11	cyclohexyl-**1j**[e]**/**Ph-**2C**	56: **3jC**	92:8
12	*t*-Bu-**1k/**Ph-**2C**	n.r.	–
13	TMS-**1l/**Ph-**2C**	n.r.	–
14	cyclohexenyl-**1m/**Ph-**2C**	72: **3mC**	97:3
15[d]	Ph-**1a/***p*-$MeOC_6H_4$-**2D**	90: **3aD**	94:6
16[d]	Ph-**1a/***p*-MeC_6H_4-**2E**	69: **3aE**	94:6
17[d]	Ph-**1a/***p*-ClC_6H_4-**2F**	80: **3aF**	93:7
18[d]	Ph-**1a/***o*-$MeOC_6H_4$-**2G**	90: **3aG**	88:12
19[d]	Ph-**1a/***p*-CNC_6H_4-**2H**	89: **3aH**	83:17
20[d]	Ph-**1a/**PhCH=CH-**2I**	96: **3aI**	87:13

[a] All reactions were performed on a 0.2-mmol scale in 0.4 mL of solvent and stopped after 24 h.
[b] Enantiomeric ratio was determined by chiral HPLC (see Supporting Information).
[c] This reaction was carried out in a 2.0-mmol scale.
[d] This reaction was carried out with 5 mol% of catalyst **IV**.
[e] This reaction was stopped after 5 days.

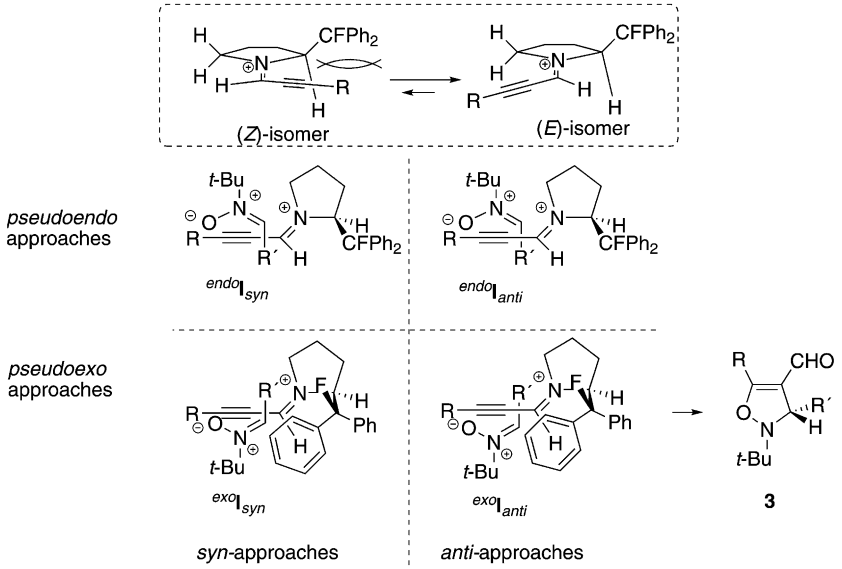
ing (**2D** and **2E**) and weakly electron-withdrawing (**2F**) groups did not affect the reactivity and stereoselectivity (entries 15–17). However, enantiomeric ratios were not as good when the substituents occupied the *ortho* position (**2G**, entry 18) or were strongly electron-withdrawing (**2H**, entry 19). Alkenyl nitrone **2I** (R^2 = PhCH=CH-) also underwent the reaction with slightly lower stereoselectivity (entry 20).

The absolute configuration of 4-isoxazolines (**3**) was deduced from that of the *N*-sulfinylimine **4aC** [obtained by reaction of **3aC** with (*S*)-*p*-tolylsulfinamide, Scheme 3], which after crystallization could be unequivocally assigned by X-ray diffraction studies.[16]

In order to explain the obtained results, we propose the stereochemical course indicated in Scheme 4. The iminium intermediate resulting from reaction of alkynals **2** with catalyst **VI** could adopt *E* or *Z* configurations around the C=N bond, which should be in equilibrium in solution.[17] On the basis of the steric situation, diastereoisomer *E* should be the more stable



Scheme 3. Synthesis and ORTEP diagram of compound **4aC**.



Scheme 4. Proposal for the approach of the nitrone to the iminium ion.

one, because it lacks the interactions of the alkynyl with the $CFPh_2$ group, but it is not easy to conclude whether the stability difference between them excludes participation of the *Z* isomer in the reaction.

At the triple bond, only the π-bond conjugated with the C=N is activated enough for reaction with the dipole. Thus, four approaches of the nitrone to the *E* isomer (the same would be true for the *Z*) are possible. Two of them correspond to the *pseudoendo* approaches to each face of the reactive π bond (*syn* or *anti* with respect to the $CFPh_2$ group at the catalyst), and the other two to the *pseudoexo* approaches (Scheme 4). The *pseudoendo* approaches ($^{endo}\mathbf{I}_{syn}$ and $^{endo}\mathbf{I}_{anti}$) should be strongly destabilized by electrostatic repulsion of the positively charged nitrogens. The *pseudoexo* approach $^{exo}\mathbf{I}_{syn}$ is likely less stable than the $^{exo}\mathbf{I}_{anti}$ because of the steric interactions whenever one of the phenyl groups at the catalyst is oriented as indicated in Scheme 4. The evolution of the $^{exo}\mathbf{I}_{anti}$ approach would produce compounds **3**, which are the major products obtained in the reactions we have studied.[18]

This analysis, despite satisfactorily predicting the experimental results, is based on two assumptions that are not entirely evident: first, the exclusion of the *Z*-isomers as participating species in the reaction; and second, the arrangement of one of the phenyl groups at the catalyst hindering the *syn* approach of the nitrone. In order to clarify these two points, we decided to calculate the relative stability of the geometric isomers *E* and *Z* in their three possible conformations around the C–C bond supporting the fluorinated substituent of the catalyst. To this end, we performed theoretical calculations using the *Gaussian 09* code.[19] The simulations were carried out with density functional theory (DFT), in particular using the B3LYP functional[20] in combination with the 6-31++G(d,p) basis. We first optimized the geometry of the *E* and *Z* iminium ions formed by reaction of the catalyst **VI** with the alkynal **1a**. We have considered the three starred conformations for the *Z*-iminium (first file, Figure 1) and *E*-iminium (second file, Figure 1). Over the geometry obtained for these six isomers, we performed single point energy calculations with a more accurate level of theory B3LYP/6-311++G(3df,2p). Relative energies shown in Figure 1 include zero-point energy correction [ZPE computed with the 6-31++G(d,p)] basis set and solvent effects (toluene) using the polarizable continuum model (PCM).[21] According to these calculations, the *E*-iminium ion is clearly favored with respect to the Z isomer. Also, rotamer 3, shown in Scheme 4 for predicting the stereochemical course of the reactions, is the most populated. Therefore we can conclude that the model proposed in Scheme 4 is supported by theoretical calculations indicated in Figure 1. The higher stability of rotamer 3 could be attributed to electrostatic attractions between the positively charged nitrogen and the electon-rich fluorine[22] (also stabilizing rotamer 2) and to steric effects.

In conclusion, we have presented the first organocatalytic enantioselective 1,3-dipolar reaction between arylnitrones and alkynals catalyzed by (*S*)-2-(fluorodiphenylmethyl)pyrrolidine (**VI**) to yield 4-isoxazolines (2,3-dihydroisoxazoles). It takes place in 1–2 days with high enantiomeric excess, excellent yields and low catalyst loading (1–5 mol%). The reaction is efficient with alkenyl, aryl (regardless the electronic character of the substituents), and primary or secondary alkyl alkynals. Other 1,3-dipolar and Diels–Alder re-

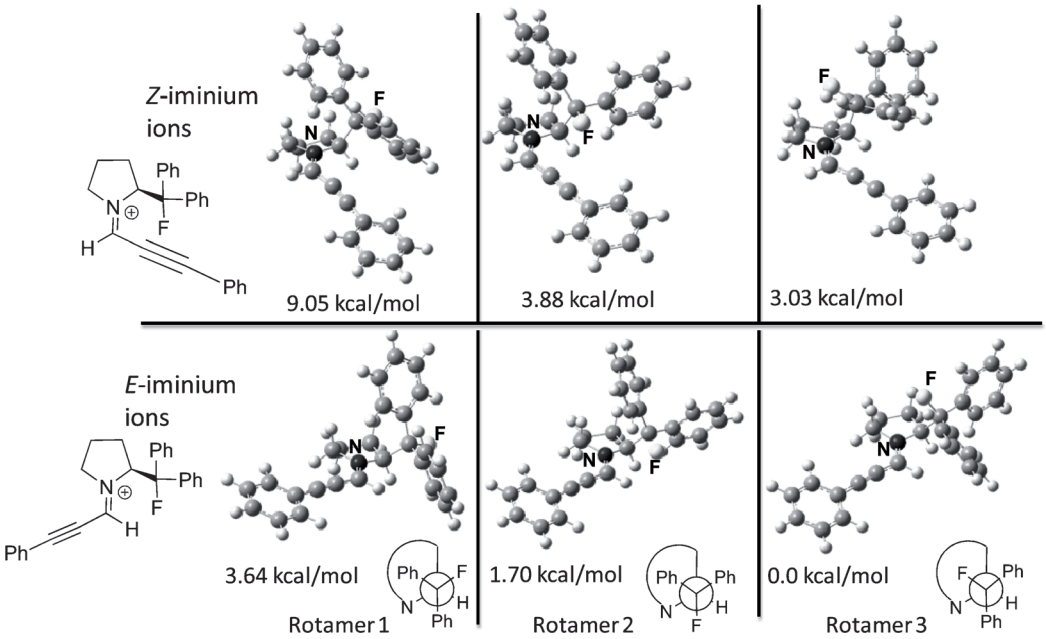


Figure 1. Different conformations of the alkynal iminium ion.

actions of alkynals catalyzed by **VI** are currently being studied in our group.[23]

Experimental Section

General Methods

NMR spectra were acquired on a Bruker 300 spectrometer, running at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired in the broad-band decoupled mode. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Flash column chromatography was performed using silica gel Merk-60 (230–400 mesh). The *ee*s were determined by HPLC employing a Daicel Chiralpack IC column.

General Procedure for the Synthesis of 2,3-Dihydroisoxazoles (3)

To a cooled (0/−10 °C) solution of 0.20 mmol of nitrone (**2A–I**) and 0.04 mmol of catalyst **VI** (5 mol%) in 0.4 mL of toluene, 0.24 mmol of aldehyde (**1a–m**) were added. When the reaction was completed, the crude product was evaporated, analyzed by ^{1}H NMR and the product **3** was isolated by flash chromatography (see the Supporting Information).

Acknowledgements

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References

[1] For reviews about 4-isoxazolines, see: a) T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* **2010**, 3363; b) J. P. Freeman, *Chem. Rev.* **1983**, *83*, 241; c) P. Grünanger, P. Vita-Finzi, *Isoxazolines*, in: *The Chemistry of Heterocyclic Compounds*, (Eds.: E. C. Taylor, A. Weissberger), John Wiley & Sons, **1991**, Vol. 49, chapter 2, pp 416–647.

[2] a) A. C. Habeeb, P. N. Praveen Rao, E. E. Knaus, *J. Med. Chem.* **2001**, *44*, 2921; b) R. D. Cramer, R. J. Jilek, S. Guessregen, S. J. Clark, B. Wendt, *J. Med. Chem.* **2004**, *47*, 6777.

[3] M. E. Fraley, R. M. Garbaccio, G. D. Hartman, *PCT Int. Appl.* WO2006/023440, 43, **2006**.

[4] a) J. M. Atienza, D. Susanto, C. Huang, A. S. McCarty, J. Colicelli, *J. Biol. Chem.* **1999**, *274*, 4839; b) A. I. Hubich, T. A. Zheldakova, T. V. Chernikhova, E. V. Koroleva, F. A. Lakhvich, M. V. Sholukh, *Biochem. Biophys. Res. Commun.* **2006**, *341*, 357.

[5] a) V. Mancuso, C. Hootelé, *Tetrahedron Lett.* **1988**, *29*, 5917; b) P. Macours, J. C. Braekman, D. Daloze, *Tetrahedron* **1995**, *51*, 1415; c) P. Aschwanden, L. Kærnø, R. W. Geisser, F. Kelinbeck, E. M. Carreira, *Org. Lett.* **2005**, *7*, 5741.

[6] For the synthesis of aziridines from 4-isoxazolines, see: a) T. Ishikawa, T. Kudok, J. Yoshida, A. Yashura, S. Manabe, S. Saito, *Org. Lett.* **2002**, *4*, 1907; b) N. Wada,

K. Kaneko, Y. Ukaji, K. Inomata, *Chem. Lett.* **2011**, *40*, 440.

[7] a) A. Sakakura, M. Hori, M. Fushimi, K. Ishihara *J. Am. Chem. Soc.* **2010**, *132*, 15550. b) Terminal alkynes react with nitrones under copper catalysis affording isoxazolines which *in situ* evolve into β-lactams, see: D. A. Evans, F. Kelibeck, M. Rueping, *Asymmetric Synthesis – The Essentials*, (Eds.: M. Christmann, S. Braese), Wiley-VCH, Weinheim, **2007**, p 72, and references cited therein.

[8] See, for example, a) A. M. Gonzáles-Nogal, M. Calle, *Tetrahedron* **2009**, *65*, 5472. For tetrasubstituted pyrroles, see: b) S. M. M. Lopes, C. M. Nunes, T. M. V. D. Pinho e Melo, *Tetrahedron* **2010**, *66*, 6078; c) see also ref.[1a]

[9] See, e.g.: a) A. Liguori, R. Ottana, G. Romeo, G. Sindona, N. Uccella, *Tetrahedron* **1988**, *44*, 1247; b) A. Padwa, D. N. Kline, K. F. Koehler, M. Matzinger, M. K. Venkatramanan, *J. Org. Chem.* **1987**, *52*, 3909; c) A. Padwa, W. H. Bullock, D. N. Kline, J. Perumattam, *J. Org. Chem.* **1989**, *54*, 2862; d) A. Padwa, M. Matzinger, Y. Tomioka, M. K. Venkatramanan, *J. Org. Chem.* **1988**, *53*, 955; e) G. Broggini, G. Zecchi, *Gazz. Chim. Ital.* **1996**, *126*, 479; f) T. M. V. D. Pinho e Melo, *Curr. Org. Chem.* **2009**, *13*, 1406; g) M. Buchlovic, S. Man, K. Kislitsõn, C. Mathot, M. Potácek, *Tetrahedron* **2010**, *66*, 1821.

[10] Starting from a chiral amine, see: a) D. François, A. Maden, W. V. Murray, *Org. Lett.* **2004**, *6*, 1931; from chiral nitrones, see: b) F. Cantagrel, S. Pinet, Y. Gimbert, P. Y. Chavant, *Eur. J. Org. Chem.* **2005**, 2694; c) F. Busqué, P. de March, M. Figueredo, J. Font, T. Gallagher, S. Milán, *Tetrahedron: Asymmetry* **2002**, *13*, 437; d) L. Bruché, A. Arnone, P. Bravo, W. Panzeri, C. Pesenti, F. Viani, *Eur. J. Org. Chem.* **1999**, 1665.

[11] W. Wei, M. Kobayashi, Y. Ukaji, K. Inomata, *Heterocycles* **2009**, *78*, 717.

[12] In constrast, the aminocatalytic 1,3-dipolar reactions of nitrones with acroleins to obtain isoxazolidines have been widely used and the factors controlling the access of the nitrones to the two prochiral faces of the iminium intermediates are well established, see: a) W. S. Jen, J. J. M. Wienr, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874; b) S. S. Chow, M. Navalainen, C. A. Evans, C. W. Johanner, *Tetrahedron Lett.* **2007**, *48*, 277; c) S. Karlsson, H.-E. Högberg, *Eur. J. Org. Chem.* **2003**, 2782; d) M. Lemay, J. Trant. W. W. Ogilvie, *Tetrahedron* **2007**, *63*, 11644; e) for a general review in 1,3-dipolar reactions, see: H. Pellissier, *Tetrahedron* **2007**, *63*, 3235.

[13] During the evaluation of this manuscript a related work was published, see: a) X. Cai, C. Wang, J. Sun *Adv. Synth. Catal.* **2012**, *354*, 359–363. For leading references on the activation of alkynals, see: b) S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606; c) X. Zhang, S. Zhang, W. Wang, *Angew. Chem.* **2010**, *122*, 1523; *Angew. Chem. Int. Ed.* **2010**, *49*, 1481; d) J. Alemán, A. Núñez, L. Marzo, V. Marcos, C. Alvarado, J. L.García Ruano, *Chem. Eur. J.* **2010**, *16*, 9453; e) J. Alemán, C. Alvarado, V. Marcos, A. Nunez, J. L. García Ruano, *Synthesis* **2011**, 1840.

[14] Nitrone **2C** did not show any background reaction at room temperature, 0 °C and −10 °C at 1, 3 and 5 days.

[15] In these cases, the *er*s were slighgly better when catalyst **IV** was used instead of catalyst **VI** (see the Supporting Information for further details).

[16] CCDC 852722 contains the supplementary crystallographic data (see the Supporting Information for more details) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-(1223)-336-033, e-mail: deposit@ccdc.cam.ac.uk].

[17] For a study iminium ions of α,β-unsaturated aldehydes, see: C. Sparr, W. B. Schweizer, H. Martín Senn, R. Gilmour, *Angew. Chem.* **2009**, *121*, 3111; *Angew. Chem. Int. Ed.* **2009**, *48*, 3065.

[18] The model indicated in Scheme 4 suggests that the stereochemical course of these reactions, and therefore their enantioselectivity, is not depending on the substituent joined to the nitrogen of the nitrone, but we have checked that reactions with *N-t*-Bu nitrone (**2C**) are much more enantioselective than those with *N*-methyl nitrone (**2A**). In order to clarify this question we studied the composition of the uncatalyzed reaction mixtures (**1a**+**2A**) and (**1a**+**2C**) at −10 °C after 24 h (the usual time for the reactions in Table 2). In the first case, the formation of racemic **3aA** has taken place, with a conversion degree around 50%, whereas in the second one only trazes of **3aC** can be detected by NMR. This would explain the decrease of the enantioselectivity observed in uncatatalyzed reactions of **1a** with **2A**.

[19] M. J. Frisch et al., *Gaussian 09 (Revision B.01)*, Gaussian, Inc., Wallingford CT, **2010**.

[20] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1998**, *37*, 785.

[21] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999.

[22] A significant contribution of the *gauche* effect (hyperconjugative electron donation from the σ orbital of the C–H bond to the parallel, low-lying antiboding orbital of the C–F bond [σC–H→σ*C–F]) cannot be disregarded. This interaction has been proposed by Gilmour et al. for explaining a similar conformational behavior of the iminium intermediates formed by **VI** and α,β-unsaturated aldehydes (see ref.[17]). They found that **VI** is a better organocatalyst than other non-fluorinated amines of similar structure in some reactions of α,β-unsaturated aldehydes (epoxidation). They attributed this behavior to the fact that the *gauche* effect provides an extra degree of torsional rigidity to the intermediate iminium, which improves the stereoselctive control.

[23] A preliminary attempt at deprotection of the *N-tert*-butyl-4-isoxazolines was not successful: treatment of **3aC** with 5% HCl at room temperature and at 50 °C did not give the desired product.

