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Azomethine Ylides from Nitrones: Using Catalytic *n*-BuLi for the Totally Stereoselective Synthesis of *trans*-2-Alkyl-3-Oxazolines

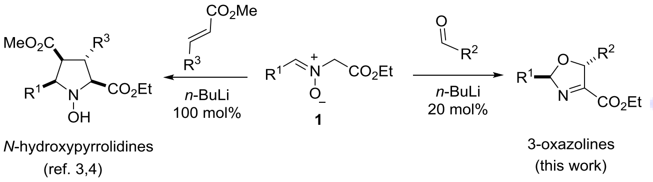
Veronica Juste-Navarro,[a] Ignacio Delso,[b] Tomás Tejero[a] and Pedro Merino*[a]

Dedicated to Prof. Miguel Yus for his contribution to the field of organolithium chemistry

Abstract: The cycloaddition of azomethine ylide *N*-oxides (nitrone ylides) with aldehydes provides 3-oxazolines in a complete stereoselective way in the presence of a catalytic amount of *n*-butyllithium. The process involves an initial nucleophilic attack to the aldehyde followed by intramolecular oxygen addition to the nitrone moiety and lithium-assisted elimination of water regenerating the catalytic species. Various Li-based catalytic systems are possible and the self-generated water is required for continuing the catalytic cycle. The best results are observed with 20 mol% of *n*-butyllithium in contrast to the use of stoichiometric amounts that inhibit the catalyzed rate. Experimental, spectroscopic and computational mechanistic studies have provided evidences of lithium ion catalysis and allowed rationalizing the several competing catalytic processes.

The chemistry of azomethine ylides has been extensively studied in the past.[1] In particular, *N*-metalated azomethine ylides have received considerable attention because of their utility in asymmetric catalytic reactions.[2] We have reported the use of a novel class of azomethine ylides derived from nitrones **1** (azomethine ylide *N*-oxides or nitrone ylides) in a tandem Michael-Mannich reaction with α,β-unsaturated esters to provide *N*-hydroxypyrrolidines in excellent yields and complete stereoselectivity (Scheme 1).[3] The reaction required stoichiometric amounts of *n*-BuLi to generate the ylide and the lithium ion was required for activating the reagents in both steps.[4]

Organolithium compounds have been extensively employed as bases in stoichiometric amount for metalation reactions,[5] but their use as catalysts, other than in polymerization reactions,[6] is an ongoing research challenge.[7] Although several catalytic processes involving lithium salts have already been documented for lithium chloride,[8] lithium bromide,[9] lithium perchlorate[10] and, in a less extent, lithium hydroxide,[11] to date, there is only one report dealing with the use of an organic alkali metal compound in catalytic reactions.[12] In continuation of our work on the reactivity of nitrone ylides with electrophiles we have investigated the reaction with aldehydes and found that using catalytic amounts of *n*-BuLi, 3-oxazolines are obtained in good yields and complete selectivity (Scheme 1).[13]



Scheme 1. Reactivity of *N*-(ethoxycarbonylmethyl) nitrones **1** precursors of nitrone ylides.

3-Oxazolines are heterocyclic systems of interest,[14] difficult to be prepared, and no methods are reported for the stereoselective synthesis of 2,5-disubsututited derivatives. In contrast to well-established methods for accessing 2-oxazolines,[15] the preparation of isomeric 3-oxazolines (2,5-dihydrooxazoles) have received far less attention.[16] Taking into account a retrosynthetic analysis considering the fragments which join to form the heterocyclic nucleus (Figure 1), all these methods belong to C + OC$_2$N approach. Very recently, Zhong and co-workers developed an acid-promoted formal [3+2] cycloaddition between donor-acceptor oxiranes and nitriles,[17] the only method representing a COC + CN approach.

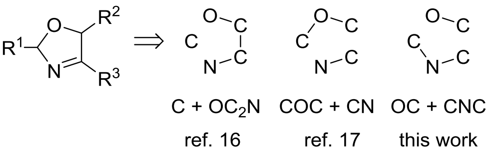


Figure 1. Retrosynthetic approaches for 3-oxazolines

Herein, we report a novel and efficient catalytic stereospecific synthesis of *trans*-2-alkyl-5-substituted-3-oxazolines based on an OC + CNC approach (Figure 1). Various catalytic systems, all of them based on a lithium salt, are possible. Among them, *n*-BuLi provided the best results acting as an efficient pre-catalyst. To the best of our knowledge, this is the first method that describes a catalytic synthesis of substituted 3-oxazolines in a complete stereoselective way and uses aldehydes as starting materials. A rationale based on DFT computational studies is provided for explaining both the stereoselectivity and the catalytic cycles involved in the reaction.

The synthetic approach started by preparing novel *C*-alkyl nitrones **1** following the methodology previously reported by us.[18] Initially we screened reaction conditions developed in our group for nitrone ylides.[3] Optimization studies are given in Table 1.

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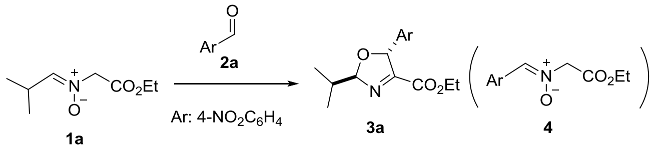
Table 1. Synthesis of 3-Oxazolines **3**. Optimization of Reaction Conditions



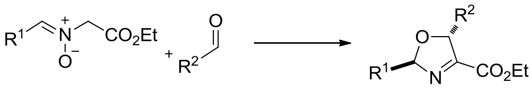
entry	Base (eq)	Li salt (eq)	T (ºC)	t (h)	solvent	Yield (%)[a]
1	Et_3N (1.0)	LiBr (1.0)	25	24	MeCN	80
2	Et_3N (1.0)	LiBr (1.0)	0	72	MeCN	72
3	Et_3N (1.0)	LiBr (1.0)	50	6	MeCN	70
4	Et_3N (1.0)	LiBr (1.0)	25	24	CH_2Cl_2	68
5	Et_3N (1.0)	LiBr (1.0)	25	24	DMSO	36
6	Et_3N (1.0)	CuBr (1.0)	25	24	MeCN	15[b]
7	Et_3N (1.0)	LiOAc (1.0)	25	24	MeCN	60
8	DBU (1.0)	LiBr (1.0)	25	24	MeCN	91
9	DABCO (1.0)	LiBr (1.0)	25	24	MeCN	94
10[b]	DABCO (1.0)	LiBr (1.0)	25	24	MeCN	10[c]
11	DABCO (1.0)	LiBr (0.5)	25	24	MeCN	88
12	DABCO (1.0)	LiBr (0.2)	25	24	MeCN	46
13	DABCO (0.5)	LiBr (1.0)	25	24	MeCN	90
14	DABCO (0.5)	LiBr (0.5)	25	24	MeCN	92
15	DABCO (0.2)	LiBr (0.2)	25	48	MeCN	30(30)
16	LiOH (1.0)		25	12	MeCN	87(8)
17[b]	LiOH (1.0)		25	12	MeCN	10[c]
18	LiOH (1.0)		25	12	EtOH	68
19	LiOH (0.5)		25	12	MeCN	80(15)
20	LiOH (0.2)		25	4 d	MeCN	10(50)
21	LiOH (0.1)		25	4 d	MeCN	n.r.[c]
22	*n*-BuLi (1.0)		-80	24	THF	<10[c]
23	*n*-BuLi (1.0)		rt[d]	12	THF	74
24	*n*-BuLi (1.0)		-40[d]	4	THF	40[c]
25	*n*-BuLi (0.5)		-40[d]	4	THF	90
26	*n*-BuLi (0.2)		-40[d]	4	THF	90[e]
27	*n*-BuLi (0.1)		-40[d]	24	THF	68

[a] Only the trans-isomer was obtained. When compound **4** was also obtained the yield is given in brackets. [b] The reaction was conducted in the presence of 4 Å MS. [c] Starting materials were recovered. [d] *n*-BuLi was added at -80ºC and after 5 min the reaction was warmed to the stated temperature. [e] An identical result was obtained by carrying out the reaction at -80ºC to rt

The use of stoichiometric amounts of triethylamine and LiBr (entry 1) led exclusively to *trans*-3-oxazoline **3a**, the elimination product of the initially expected *N*-hydroxypyrrolidine.[19] The reaction can be carried out at 0 ºC and 50º C for longer and shorter reaction time, respectively, with minimum loss of yield (entries 2 and 3). On the other hand, both the use of solvents different from acetonitrile (entries 4 and 5) and lithium salts different from LiBr (entries 6 and 7) caused evident decreasing of the yield. Changing the base to DBU (entry 8) or DABCO (entry 9) improved considerably the yield to more than 90%. However, when the reaction was carried out in the presence of molecular sieves (entry 10) the reaction showed a conversion of only 10% after 24 h, the starting materials being recovered unaltered. We studied the possibility of using catalytic amounts of base and/or lithium salt (entries 11-15) and found that 50 mol% of both DABCO and LiBr led to the same result that stoichiometric amounts. Unfortunately, decreasing to 20 mol% led to a considerably loss of yield (30%) and formation of undesired nitrone **4** as a result of transoximation between the starting nitrone **1a** and aldehyde **2a**, through hydrolysis of the former. In this context, we did not observed cross-reactivity between **4** and **2a**. Next, we consider the possibility of integrating both base and lithium in the same species and found that LiOH promotes the reaction in 87% yield (entry 16) although a 8% of **4** was obtained. Again the presence of molecular sieves blocked the reaction (entry 17). To increase the solubility of LiOH, ethanol was tested as a solvent but lower yield was obtained (entry 18). The use of catalytic amounts led to increased transoximation or no reaction (entries 19-21). When *n*-BuLi was used at low temperature the reaction did not progress after 24 h (entry 22) but warming slowly the reaction up to ambient temperature during 12 h the yield increased to 74% (entry 23). In an attempt of adjusting the reaction conditions we check the reaction after warming up to -40ºC during 4 h (entry 24). At this time, only a yield 40% was observed and starting materials were recovered indicating that the reaction had not finished. On the other hand, the use of substoichiometric amounts of *n*-BuLi (entry 25) led to a clean reaction in high chemical yield under the same conditions, revealing a faster rate of the reaction. By decreasing *n*-BuLi to 20 mol%, the same result was obtained (entry 26), no transoximation being observed. With lower amounts of *n*-BuLi the reaction required more time (entry 27) but still 68% chemical yield was obtained. In all cases, the *trans*-isomer was the only observed product. The structure of compound **3a** was confirmed by X-ray crystallography.[20] At this point, it became evident that the process was catalytic involving lithium species and that different mechanisms should operate under stoichiometric and catalytic conditions.

The optimized reaction conditions (20 mol% BuLi) were applied to various nitrones and aldehydes (Table 2). For the purpose of comparison the reactions were also carried out with 50 mol% DABCO / LiBr (Table 1, entry 14) and identical results were obtained. Thus, both reaction conditions can be equally used. The reaction proceeded smoothly for nitrones **1a-d** with both aliphatic and aromatic aldehydes. In the case of aromatic aldehydes with electron-donating groups (Table 2, entries 4 and 5) and α,β-unsaturated aldehydes (Table 2, entries, 10, 11 and 17) additional reaction time was needed for achieving good chemical yield. With the latter it existed the possibility of 1,4-addition but it was never observed.

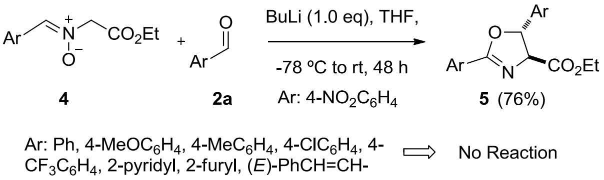
Table 2. Synthesis of 3-Oxazolines **5**. Scope of the reaction.[a]



entry	R^1	R^2	1	2	3	Yield (%)[b]
1	*i*-Pr	4-$NO_2C_6H_4$	**1a**	**2a**	**3a**	90 (92)
2[c]	*i*-Pr	4-$NO_2C_6H_4$	**1a**	**2a**	**3a**	74 (70)
3	*i*-Pr	Ph	**1a**	**2b**	**3b**	89 (90)
4[d]	*i*-Pr	4-MeC_6H_4	**1a**	**2c**	**3c**	78 (69)
5[e]	*i*-Pr	4-$MeOC_6H_4$	**1a**	**2d**	**3d**	75 (64)
6	*i*-Pr	*i*-Pr	**1a**	**2e**	**3e**	86 (82)
7	*i*-Pr	*i*-Bu	**1a**	**2f**	**3f**	88 (89)
8	*i*-Pr	cyclopentyl	**1a**	**2g**	**3g**	89 (85)
9	*i*-Pr	$PhCH_2$	**1a**	**2h**	**3h**	93 (91)
10[d]	*i*-Pr	(*E*)-MeCH=CH	**1a**	**2i**	**3i**	78 (71)
11[d]	*i*-Pr	(*E*)-PhCH=CH	**1a**	**2j**	**3j**	69 (53)
12	*i*-Bu	4-$NO_2C_6H_4$	**1b**	**2a**	**3k**	93 (90)
13	*i*-Bu	Ph	**1b**	**2b**	**3l**	88 (85)
14	cyclohexyl	4-$NO_2C_6H_4$	**1c**	**2a**	**3m**	92 (90)
15	cyclohexyl	Ph	**1c**	**2b**	**3n**	90 (87)
16	cyclohexyl	*i*-Pr	**1c**	**2e**	**3o**	78 (80)
17[d]	cyclohexyl	(*E*)-MeCH=CH	**1c**	**2i**	**3p**	72 (68)
18	cyclopentyl	4-$NO_2C_6H_4$	**1d**	**2a**	**3q**	92 (89)
19	cyclopentyl	Ph	**1d**	**2b**	**3r**	90 (86)
20	*i*-Pr	2-piridyl	**1a**	**2k**	**3s**	86 (89)
21	*i*-Pr	2-furyl	**1a**	**2l**	**3t**	92 (90)

[a] Reactions were run using nitrones **1** (0.5 mmol scale) and 1.0 eq of aldehyde **2** in the stated solvent (0.5 M) unless otherwise indicated. Conditions A: 20 mol% BuLi, THF, -80º C to -40ºC, 4 h. Conditions B: 50 mol% DABCO, 50 mol% LiBr, MeCN, rt, 24 h. [b] Isolated yield after purification by column chromatography; values corresponding to conditions A. Isolated yields corresponding to conditions B are given between brackets Only the trans-isomer was obtained. [c] Reaction was run in 6.0 mmol scale (1.04 g of nitrone). [d] Reaction was run for 36 h. [e] Reaction was run for 48 h..

Although *C*-alkyl nitrones afforded good reactivity, there still remained limitations on the substrate. When *C*-aryl nitrones were used we did not observe any reactivity, illustrating the well-known fact that *C*-aryl nitrones are less reactive than *C*-alkyl nitrones.[21] The lack of reactivity was also observed for heteroaryl nitrones (*C*-(2-pyridyl) and *C*-(2-furylyl)) and α,β-unsaturated nitrone derived from cinnamalehyde. Indeed, only in the favorable case of nitrone **4** and aldehyde **2a** we observed the formation of a product in good yield after 48 h (Scheme 2).[22] However, that product was confirmed to be the corresponding 2-oxazoline **5** by X-ray crystallography.[20] The formation of **5** is possibly due to a migration of the double bond as a consequence of the stabilization by conjugation with the aromatic ring.[23]



Scheme 2. Exceptional reaction of nitrone **4** with aldehyde **2a**.

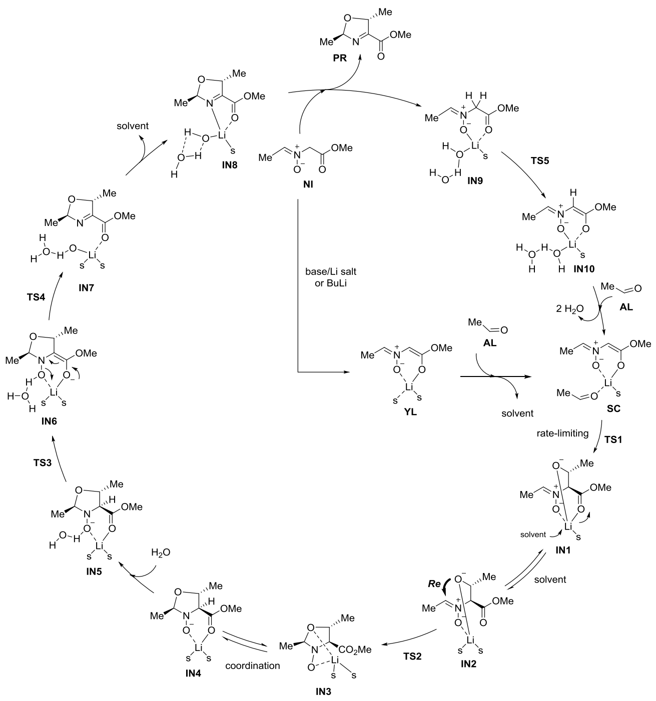
We also initiate preliminary studies on the chiral version of the reaction. Unfortunately only negative results were obtained. The reaction in the presence of 20 mol% (-)-sparteine only 6 %ee. The use of a chiral lithum alkoxide derived from (*R*)-BINOL (20 mol%) and *n*-BuLi (20 mol%) afforded great amounts of transoximation (30% of **3a** and 45% of **4**) in a similar way to LiOH and no chiral induction (10% ee for **3a**) was observed.

In our previous work with α,β-unsaturated esters and *C*-aryl nitrones like **4** we demonstrated that the reaction was stepwise by isolating the initial Michael intermediate;[3] further computational studies[4] corroborated the mechanism providing the *N*-hydroxypyrrolidine as the final product of the reaction. On the contrary, for the reaction between **1a** and **2a**, which can be conducted under catalytic conditions, any attempt of isolating either an intermediate or the *N*-hydroxypyrrolidine precursor from 3-oxazoline **3** failed. These observed differences together with the fact that molecular sieves blocked the reaction, demonstrating that water is necessary, and the observation that the reaction is faster with substoichiometric amounts of *n*-BuLi prompted us to investigate the mechanism of the reaction computationally and by NMR spectroscopy.

We modelled the reaction between nitrone **NI** and aldehyde **AL** catalyzed by *n*-BuLi considering the formation of the corresponding nitrone ylide **YL** as the first step. Several approaches are possible for the reaction between ylide **YL** and aldehyde **AL**. A comprehensive study of all the possible pathways has been carried out at M06-2X/6-311+G(d,p)/PCM=THF level of theory using geometries optimized at M06-2X/6-31G(d)/PCM=THF level. Further discussion will only refer to the preferred pathway leading to the *trans*-isomer (for the complete computational analysis see Supporting Information).

Once the ylide is formed, the aldehyde coordinates the lithium atom to form the starting complex **SC** in which both reagents are activated. The catalytic cycle, illustrated in Scheme 3, starts from **SC** which is the most stable intermediate in the cycle. The most favorable **TS1** leads to **IN1** with a barrier of ΔG = 5.0 kcal/mol which resulted to be the rate-limiting step. Further exchange of a solvent molecule is favored by 14.6 kcal/mol giving rise to **IN2** which evolves through the preferred *Re* attack

(**TS2** located 1.3 kcal/mol below the ground state) to **IN3**. Exchange of coordination in this intermediate formed **IN4** (7.3 kcal/mol more stable) which can be transformed into **IN6** through a 1,3-H shift.



Scheme 3.. Catalytic cycle for Li-catalyzed synthesis of 3-oxazolines

The prototropy observed between **IN4** and **IN6** can take place through an intramolecular transition state (located 10.8 kcal/mol above the ground state, not shown in Scheme 3; see SI) or the more stable **TS3** (located 14.2 kcal/mol below the ground state) after formation of **IN5**, involving a water molecule generated in the last step of the catalytic cycle. Under catalytic conditions only the first round of the cycle takes place through the above mentioned intramolecular transition state higher in energy, at which time water is produced and the catalytic cycle carries on through **IN5** and **TS3**.

In agreement with this hypothesis, the use of molecular sieves should reduce drastically the rate of the reaction as indeed, it is observed experimentally. When equimolar amounts of base/LiBr are used, the reaction is completed in one round and in this case, the prototropy in **IN4** can be facilitated by the protonated base, also through a bimolecular process. In the case of using equimolar amounts of *n*-BuLi, transformation of **IN4** should account through the intramolecular transition state (1,3-H shift), higher in energy (see SI). This justifies the reduced rate of the reaction observed with 1.0 eq of *n*-BuLi. After formation of **IN6** from **IN5**, the reaction proceeds through **TS4** located at -21.6 kcal/mol below the ground state to form intermediate **IN7** which after releasing a solvent molecule provides **IN8**.

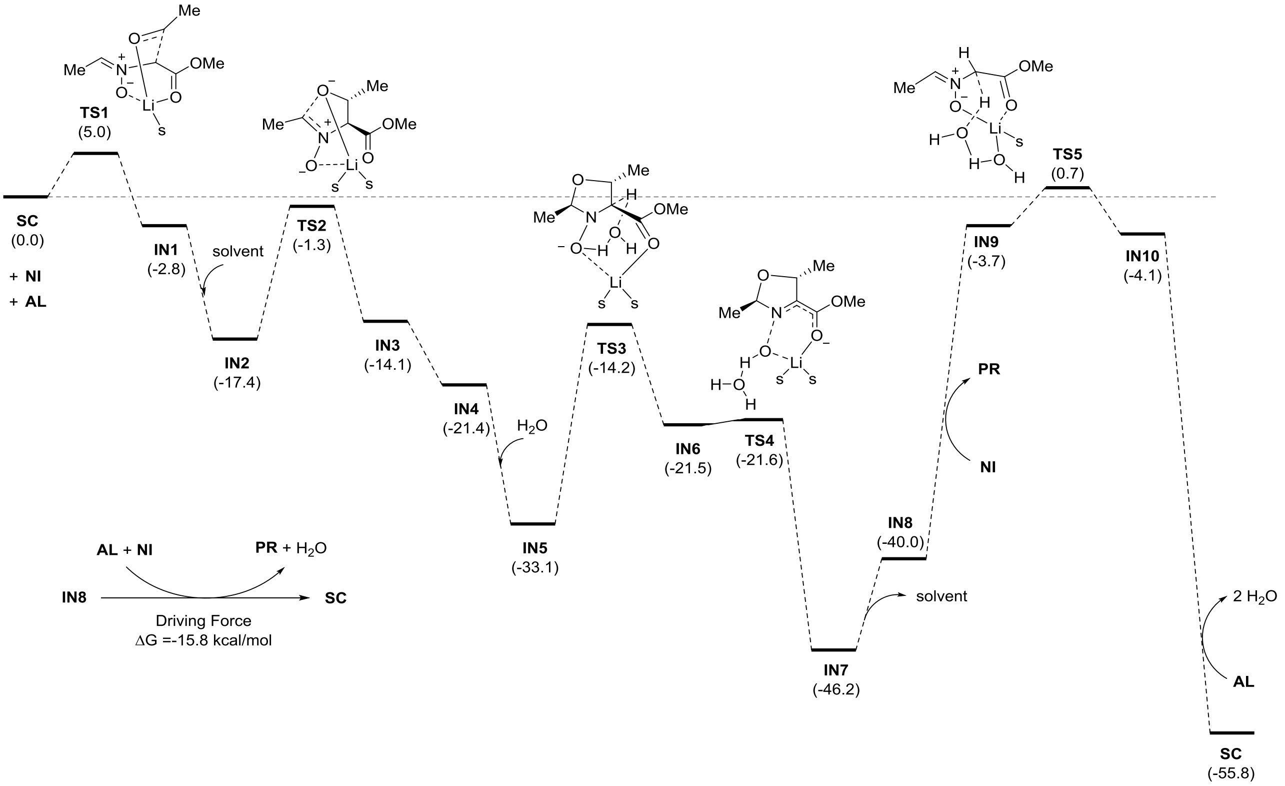


Figure 2. Energy surface for the reaction between **1** and **2** catalyzed by *n*-BuLi. The most stable route corresponding to the formation of *trans*-**3** is shown

Figure 2 illustrates the energy profile for the formation of the only observed *trans*-3-oxazoline **PR** and completion of the catalytic cycle. The driving force of the catalytic cycle illustrated in Scheme 2 is determined by the regeneration of **SC** from **IN8** (through **IN9, TS5** and **IN10**) with concomitant release of the final product and two molecules of water (actually only one is produced per round). This final catalyst-turnover step involves a favored energy ($\Delta G = -15.8$ kcal/mol) for the reaction of **1** (**NI**) with **2** (**AL**).

NMR experiments using 0.2 eq of *n*-BuLi recording the complete reaction in real time showed the presence of the final product **3a** without any addition of a proton source, confirming that an *N*-hydroxypyrrolidine could not be a real intermediate.

However, when the reaction mixture was maintained at -80ºC both nitrone and aldehyde are consumed immediately giving rise to signals that are in agreement with the formation of **IN4** (see SI). This intermediate demonstrated to be stable at -80ºC for 4h, the formation of **3a** being observed after warming at -40ºC. Since the use of 1.0 eq of *n*-BuLi does not allow the formation of water in the catalytic cycle an alternative -and more energetic-path have to be present, as indeed it is (see SI). By using 0.2 eq of n-BuLi, warming at -40ºC is enough for completing the reaction in 4 h. demonstrating the faster pathway illustrated in Scheme 3 in which assistance of a water molecule render lower in energy the corresponding **TS3** (in the alternative path where water is not involved, alternative **TS3'** is, indeed, 5.8 kcal/mol higher in energy). Thus, both computational and spectroscopic studies are in complete agreement with the experimental observations.

In summary, a lithium-catalyzed route towards 3-oxazolines starting from novel azomethine ylide *N*-oxides (nitrone ylides) and aldehydes has been developed. Actually, lithium contributes to facilitate elimination of water, which serves to push the catalytic cycle forward. The combination of a base and a lithium salt or the use of *n*-BuLi serve as a pre-catalyst to initiate the catalytic cycle which is self-sufficient until starting materials are consumed. The only species formally regenerated in the catalytic cycle are the lithium atom, which, of course, must be solvated/coordinated along the whole cycle and the water, which might be considered to have an autocatalytic role. These results demonstrate that a lithium ion can act as a catalyst confirming previous computational results of Saa and Capo.[8e] Notably, an excess of water or the use of lithium salts like LiOH promote undesired nitrone hydrolysis leading to a transoximation making the use of catalytic amounts of *n*-BuLi a unique system for the progress of the reaction (using DABCO/LiBr is also possible but below 50 mol% transoximation is also observed). The same problem arises for the asymmetric version of the reaction when a chiral lithium alkoxide is used as a base. Both spectroscopic and computational studies are in agreement with the experimental observations showing a faster reaction with substoichiometric amounts of *n*-BuLi than with equimolar amounts. Also, those studies explain the necessity of water for the progress of the reaction at low temperature. Further studies directed to other lithium-catalyzed reactions with nitrone ylides including cataytyic asymmetric versions of the reaction are currently in progress in our laboratories.

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Keywords: Azomethine ylides • Nitrones • 3-Oxazolines • Lithium Catalysis • DFT calculations

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3927-3933.) but oxazolidines were obtained and either low diastereoselectivities were obtained with benzaldimines or a weak acid catalyst was required with benzophenone-derived imines. The presence of the oxygen atom in ylides derived from **1** is crucial for the obtention of 3-oxazolines.

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[19] Apparently, compound **3a** might be formed through dehydration of the corresponding *N*-hydroxypyrrolidine which was the initially expected product in a similar way to the reaction between nitrone ylides and unsaturated esters (see ref. 3). However, such hydroxylamine is never formed (see below)

[20] The authors have deposited the atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. Deposition numbers are as follows: **3a**, CCDC 1444429; **3f**, CCDC 1444430. The coordinates can be obtained on request from the Director, Cambridge Crystallographi Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. For ORTEP graphics see Supporting Information.

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[22] Any other combination of nitrone and aldehyde gave no reaction, proving that both the aldehyde (for the first step) and the nitrone (for the second step) must be activated by the presence of electronwithdrawing groups .

[23] In addition to conjugation as a driving force it should be note that 2-oxazolines are more stable than 3-oxazolines

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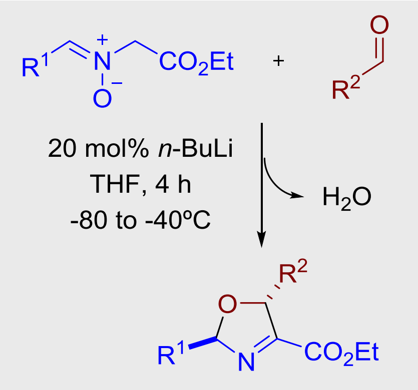
The reaction between nitrone ylides and aldehydes in the presence of catalytic amounts of *n*-BuLi provides 3-oxazolines with complete *trans*-selectivity. DFT calculations allow rationalizing the role of self-generated water for the progress of the catalytic cycle



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