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Synthesis of 3,6-Dihydro-2*H*-[1,2]-Oxazines from Nitroarenes and Conjugated Dienes, catalyzed by Palladium/Phenanthroline Complexes and employing Phenyl Formate as a CO Surrogate

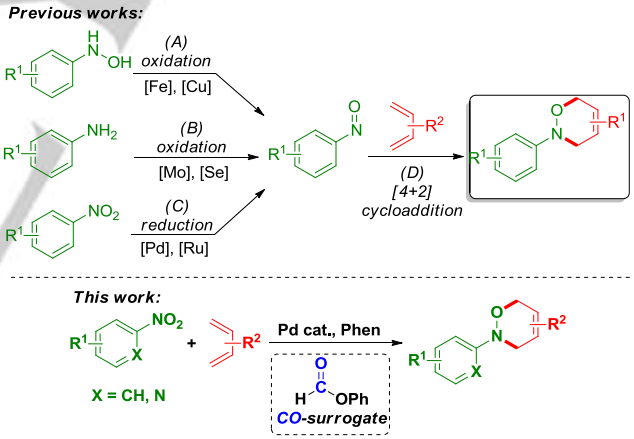
Mohamed A. EL-Atawy,[a] Dario Formenti,[b] Francesco Ferretti,[b] and Fabio Ragaini[b]*

Abstract: Palladium/phenanthroline catalyzed reduction of nitroarenes by the carbon monoxide generated in situ by decomposition of phenyl formate affords the corresponding nitrosoarene. The latter are trapped by conjugated dienes to give the corresponding 3,6-dihydro-2*H*-[1,2]-oxazines (hetero Diels-Alder adducts). Many functional groups are well tolerated. Yields are higher than those obtainable by any previously reported method, including the direct reaction of the diene with the pure nitrosoarene. The reaction can be performed in a single standard glass pressure tube, without the need for autoclaves or high-pressure CO lines.

Introduction

Heterocyclic compounds belonging to the oxazines family are structural motifs present in various natural products, life science molecules and, in general, biologically active compounds.[1] Within this family, 1,2-oxazines represent an interesting class, for both their roles as bioactive molecules[1a, 2] and synthetic intermediates. In fact, the weakness of the N-O bond makes the 1,2-oxazine scaffold useful for further functionalization, allowing to obtain numerous other structures. The synthesis and reactivity of 1,2-oxazines have been reviewed many times,[1a, 2a, 3] so that a complete list of the investigated reactions is not possible here. We just mention that the selective transformation of 1,2-oxazines to cyclic or acyclic aminoalcohols or aminosugars,[4] oxazepinones,[5] and pyrroles[3b, 6] are significant examples of how these heterocycles play a pivotal role in synthetic chemistry.

The hetero Diels-Alder [4+2] cycloaddition reaction between nitrosoarenes and dienes (Path (D), Scheme 1) is the classic approach for the preparation of 1,2-oxazines bearing an aryl ring on the nitrogen atom and the field has extensively been reviewed.[1a, 3a-g, 7] However, this transformation is limited by the reduced availability and relatively low stability of nitroso compounds, which are also well-known cancer promoters. A more convenient alternative is represented by the domino reaction sequence in which the nitrosoarene intermediate is catalytically produced *in-situ* from more stable and easily available starting materials and subsequently trapped by the diene in the cycloaddition reaction. Oxidation of hydroxylamines (Scheme 1, Path (A)) is typically employed to this aim when acylnitroso compounds are desired, but the low stability of *N*-arylhydroxylamines makes this approach less convenient for the latter substrates and we are aware of only one paper in which the synthesis of *N*-aryloxazines was pursued by this protocol.[8] In other cases, *N*-aryloxazines were obtained by this way only in the contest of mechanistic studies (to prove the formation of free nitrosoarenes).[9] A more interesting approach involves the use of arylamines and organic or inorganic peroxides (Path (B)).[10]



Scheme 1. Synthetic approaches for the preparation of the 1,2-oxazine scaffold..

The preparation of 1,2-oxazines from nitroarenes can be a valuable approach because of the wide commercial availability and stability of the substrates (Path (C), Scheme 1). Several years ago one of us reported that both ruthenium/Ar-BIAN (Ar-BIAN = *bis*(aryl)acenaphthenequinonediimine)[11] and palladium/Phen (Phen = 1,10-phenanthroline)[12] complexes catalyze this reaction when CO is used as reductant for the nitro group.[13] Although ruthenium complexes afforded only moderate yields due to the competitive formation of allylic amines, very good selectivities towards 1,2-oxazines could be obtained by using the palladium/phenanthroline catalyst. However, in both cases, the use of pressurized CO is a drawback since it requires the use of high-pressure equipment and CO lines and the presence of the corresponding safety measures, limiting its

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application as a practical synthetic method by most research groups.

In the last decades, much attention has been paid to the development of methods that allow to avoid the use of gaseous CO in carbonylation reactions, employing molecules capable of releasing CO *in-* or *ex-situ*.[14] Very recently, we reported that phenyl formate can be used as a stable and effective CO source for the reductive cyclization of various nitro compounds affording important heterocycles.[15] No elaborate catalyst or ligand was necessary and commercially available or easily prepared $Pd(CH_3CN)_2Cl_2$ and phenanthroline were employed. In that paper we focused our attention to the preparation of indoles; however we demonstrated that the proposed protocol can be as well applied to the synthesis of other heterocycles. Herein, we report the application of this reaction to the synthesis of a variety of 3,6-dihydro-2*H*-[1,2]-oxazines, highlighting how phenyl formate allows obtaining higher yields than those previously achieved with any of the previously reported synthetic methods.

Results and Discussion

The single experiment for the synthesis of an oxazine by the palladium/phenanthroline catalyzed reaction of nitrobenzene and 2,3-dimethylbutadiene reported in our preliminary communication on the use of phenyl formate as a CO source[15] had given an excellent yield (97%), but a relatively large excess of the diene (16 equiv. with respect to nitrobenzene) had been used. Thus, we first attempted decreasing the amount of diene and we were pleased to find that the excess diene can be reduced fourfold without essentially affecting the isolated yield of the oxazine (96 %, Table 1, entry 1). Given this excellent result, we decided not to attempt to further optimize the experimental conditions and used these to investigate the substrate scope of the reaction (Table 1).

The effect of changing the substituents on the nitroarene was first tested by employing 2,3-dimethylbutadiene as a constant counterpart. 4-Fluoro (**1b**), chloro (**1c**) and bromo (**1d**) substituted nitrobenzene gave the corresponding oxazine in almost quantitative yield (entries 2-4). This was not an obvious results because palladium/phenanthroline complexes are known to catalyze the Heck reaction.[16] Thus, a competitive activation of the carbon-halogen bond may have occurred, at least in the case of the bromo derivative, also taking into account that the presence of the strongly electronwithdrawing nitro group activates the C-X bond towards oxidative addition.

Nitroarenes 3,5-disubstituted with electronwithdrawing chloro (**1e**) or trifluoromethyl (**1f**) groups also gave the oxazine in excellent yields (entries 5 and 6). Among other electronwithdrawing groups, methoxycarbonyl (**1g**) was also well-tolerated (entry 7). This result is interesting because the 4-methoxycarbonylphenyl group can be removed by Birch reduction. Relevant to the chemistry here described, the oxazine derived from the reaction of isoprene and 4-methoxycarbonyl-nitrosobenzene has been previously dehydrated to the corresponding pyrrole by irradiating it with UV light and the aryl group removed by Birch reduction to give the N-H pyrrole in high yields.[6b]

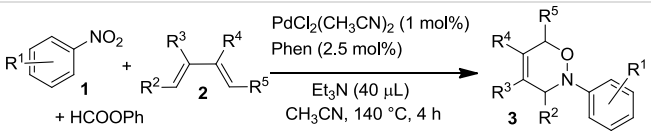
On the contrary, only a low isolated yield was achieved when using 4-nitrobenzamide (**1h**, entry 8). It should be recalled that nitroarenes are readily carbonylated to diaryl ureas when reacted with arylamines[13a, 13e, 17], a reaction that is efficiently catalyzed by palladium/phenanthroline complexes,[18] and that amides have been shown to be able to enter this reaction in place of amines, affording acyl ureas.[19] So a competition with another reaction is expected in this case, which may also give oligomeric products if the nitro and amido groups of the so formed acyl urea are involved in further reactions of the same kind.

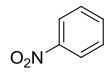
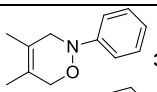
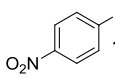
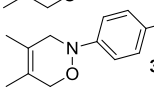
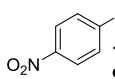
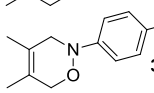
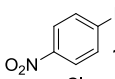
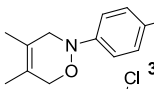
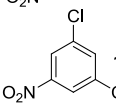
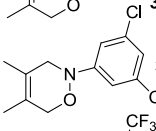
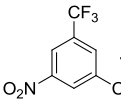
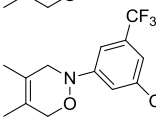
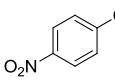
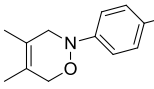
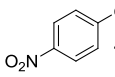
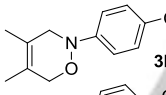
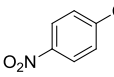
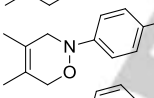
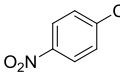
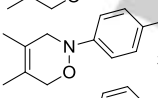
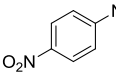
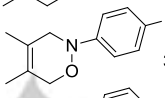
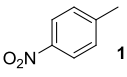
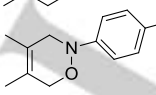
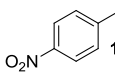
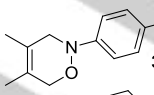
When the reaction was performed under the standard conditions starting from 4-nitrobenzoic acid (**1i**), a product was isolated in a moderate yield that turned out to be the phenyl ester of the expected oxazine (**3ia'**, entry 9). Clearly, the phenol formed as a byproduct of the formate decomposition reentered the reaction. In order to isolate the oxazine having the free carboxylic acid (**3ia**), we repeated the reaction and subjected the crude reaction mixture to a basic hydrolysis step before the work-up. However, most of the nitroarene remained unreacted. Suspecting a deactivation of the triethylamine, required to decompose phenyl formate,[15] due to its protonation by the carboxylic group, we repeated the reaction by adding an amount of triethylamine such that it could completely deprotonate the carboxylic group and still leave an unreacted amine amount equal to the standard one (entry 10). A better 40% yield of **3ia** was obtained, which was anyway lower than that achieved for the corresponding methyl ester **3ga**. The reason appears to be the deprotonation of the carboxylic group, which transform it from an electronwithdrawing to an electrondonating group, thus retarding the reaction and decreasing its efficiency (see later). 1,4-Dinitrobenzene (**1j)** may in principle yield a bis-oxazine, but under the present reaction conditions only the mono oxazine (**3ja**) could be isolated as a clean compound in 88% yield, without further reduction of the second nitro group (entry 11).

Moderately donating alkyl groups (methyl (**1k**), ethyl (**1l**), and isopropyl (**1m**), entries 12-14) were well tolerated, but a strongly donating methoxy group (**1n**) was not (entry 15). This was not completely unexpected, since a poor or no yield of the final product was obtained when a methoxy group was present on the aryl ring for other amination and heterocyclization reactions of nitroarenes in several cases,[11a, 20] including the synthesis of oxazines,[11b, 12] although good results were obtained in other cases.[21] The rationale for this behavior is based on two points:

a) The initial reduction step of nitroarenes by metal complexes has been shown to be an electron transfer from the metal complex to the nitro group in all the cases in which this step has been experimentally analyzed.[22] Electrondonating substituents make this reduction more difficult and slow down the reaction in all cases in which the initial reduction is the r.d.s. of the cycle. This has been unequivocally shown to be the case by kinetic measurements in at least two cases,[11a, 21c] but is likely a much more frequent eventuality, if not the rule, for reductive cyclization reactions of nitroarenes in the presence of carbon monoxide.

Table 1. Substrate scope.

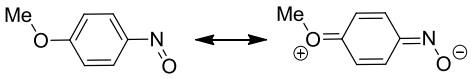


Entry[a]	1	2	3	Yield {%}[b]
1	 **1a**	 **2a**	 **3aa**	96
2	 **1b**	 **2a**	 **3ba**	99
3	 **1c**	 **2a**	 **3ca**	98
4	 **1d**	 **2a**	 **3da**	99
5	 **1e**	 **2a**	 **3ea**	88
6	 **1f**	 **2a**	 **3fa**	96
7	 **1g**	 **2a**	 **3ga**	86
8	 **1h**	 **2a**	 **3ha**	25
9	 **1i**	 **2a**	 **3ia'**	32
10	 **1i**	 **2a**	 **3ia**	40[c]
11	 **1j**	 **2a**	 **3ja**	88
12	 **1k**	 **2a**	 **3ka**	72
13	 **1l**	 **2a**	 **3la**	87
14	**1m**	**2a**	**3ma**	95
15	**1n**	**2a**	**3na**	trace
16	**1o**	**2a**	**3oa**	15
17	**1p**	**2a**	**3pa**	82
18	**1q**	**2a**	**3qa**	77
19	**1r**	**2a**	**3ra**	76
20	**1s**	**2a**	**3sa**	58
21	**1t**	**2a**	**3ta**	trace
22	**1b**	**2b**	**3bbA** / **3bbB**	78 (**A**/**B** = 5.0:1)[d]
23	**1b**	**2c**	**3bcA** / **3bcB**	62 (**A**/**B** = 2.9:1)[d]
24	**1b**	**2d**	**3bdA** / **3bdB**	89 (**A**/**B** = 0.75:1)
25	**1b**	**2e**	**3be**	n.d.
26	**1b**	**2f**	**3bf**	n.d.
27	**1b**	**2g**	**3bg**	n.d.
28	**1b**	**2h**	**3bh**	79[e]
29	**1b**	**2i**	**3bi**	87[f]

[a] Experimental conditions: nitroarene 0.54 mmol, $Pd(CH_3CN)_2Cl_2$ 1 mol %, Phen 2.5 mol %, diene 4 equiv, HCOOPh 2.2 mmol, Et_3N 0.27 mmol, 140 °C. Reactions were performed in an ACE Pressure Tube. [b] Yields refer to isolated products. [c] Et_3N 0.81 mmol, t = 6 h. The reaction mixture was hydrolyzed before the chromatographic purification. [d] The ratio between the two isomers was determined by ^1H NMR on the isolated product. [e] 8 equiv. of **2h** were employed with respect to **1b**. [f] 6 equiv. of **2i** were employed with respect to **1b**.

b) The following cyclization proceeds from the intermediately formed nitrosoarene, which acts as an electrophile.[23] Electrondonating groups usually make even this step less efficient. A favorable effect of a methoxy group on the cyclization step has been attributed at least in one case to the high stabilizing effect of this group on radical species that may be formed as intermediates during the cyclization.[24]

In the present case, the first point is surely operating, since a lot of unreacted **1n** was still present at the end of the reaction. Moreover, even the second aspect is important, as the nitrosoarene is involved in a hetero Diels-Alder reaction and the latter is well known to proceed the better the lower is the level of the orbitals of the dienophile.[25] The presence of a *para* methoxy group on the aryl ring of nitrosobenzene allows a quinonoid resonance form for **1n**, where the nitroso group gain a negative charge and loses its double bond, making it unsuitable to undergo a Diels-Alder reaction (Scheme 2).[26]



Scheme 2. Resonance forms of 4-nitrosoanisole.

Although no resonance structure can be drawn in the case of 4-nitrobenzoate anion, it is clear that the deprotonation of **1i** by triethylamine both decreases the reactivity of the nitro compound and the tendency of the intermediately formed nitroso arene to be involved in a hetero Diels-Alder reaction, thus explaining the low yield obtained with this substrate.

The problem of getting an oxazine having an oxygen atom on the para position of the aryl ring could be partly solved by employing an acetylated nitrophenol (**1o**, entry 16). In this case, the desired oxazine was obtained, albeit in a low yield.

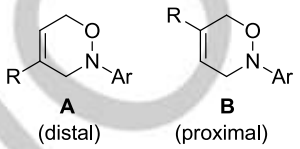
Very interestingly, the protocol was compatible with the presence of two functional groups, cyano (**1p**) and formyl (**1q**), which may themselves be involved into a Diels-Alder reaction (entries 17-18). In particular, the formation of **3qa** is noteworthy. This product would likely not be obtainable starting from the corresponding aniline under oxidizing conditions and the corresponding nitroso compound, though known, requires several delicate synthetic steps to be prepared.[27]

The presence of a sterically large bromide atom in the ortho position of the nitroarene (**1r**) still allowed the reaction to afford high yields of the oxazine (entry 19).

As far as heteroaromatic nitro compounds are concerned, the electron poor pyridine ring (**1s**) allowed the reaction to proceed efficiently, but the electron rich thiophene (**1t**) did not (entries 20 and 21). The low reactivity of **1t** can be explained by the same reasons discussed above for electron rich nitroarenes. It is worth recalling that 2- nitrosopyridine has been employed is several cases as a substrate in enantioselective reactions of nitrosoarenes with different substrates, including the asymmetric hetero Diels-Alder reaction.[3e, 3g, 25c, 28] The possibility of obtaining the same kind of products starting from the commercially available nitropyridine suggests that an enantioselective version of the present reaction may be developed in the future.

Having investigated in depth the effect of substituents on the nitroarene, we investigated the effect of changing the diene. 4-Fluoronitrobenzene (**1b**) was employed as a reference nitroarene.

Two isomers (distal and proximal) can be obtained for the oxazines derived from isoprene (**2b**) (Scheme 3). The formation of these isomers has been previously investigated both from an experimental[3c, 3f] and a theoretical[29] point of view.



Scheme 3. Resonance forms of 4-nitrosoanisole.

Both isomers were obtained with a prevalence of the electronically favored one (**3bbA/3bbB** = 5.0:1, entry 22). A similar result was obtained when using myrcene (**2c**) as the diene (**3bcA/3bcB** = 2.9:1, entry 23), but the two isomers were formed in closer amounts.

A diene in which one of the two olefinic double bonds is internal, 1,3-pentadiene (**2d**) still allowed the reaction to proceed efficiently (entry 24). Again two isomers were formed, but in this case the proximal isomer prevailed (**3bdA/3bdB** = 0.75:1) in accord with what expected based on the literature for related oxazines.[7c, 30] However, when dienes were employed in which both double bonds are internal (**2e-g**) only trace amounts of the corresponding oxazines could be detected (entries 25-27). One problem is that in these cases the formation of the oxazine is reversible at high temperature[11b] and the accumulated nitrosobenzene can be involved in side reactions, among which the formation of azoxyarenes appears to predominate in our system. However, a second problem was the low nitroarene conversion when these dienes were employed as substrates. We will come back to this point in the following.

We were glad to find that our protocol is compatible with a functionalized diene such as 2,3-dimethoxydiene (**2h**, entry 28). In the corresponding oxazine (**3bh**) all four carbon atoms of the diene moiety are substituted with an oxygen or nitrogen atom, which may easily be subject to further elaboration to give a variety of products, such as azasugars analogues.[4c].

Finally, even unsubstituted butadiene can be employed (**2i**, entry 29). Given the gaseous nature of this diene at ambient temperature and pressure, the reaction protocol had to be slightly changed (see the experimental part). The diene/nitroarene ratio was also increased to 6, to account for the fact that a larger fraction of it is in the gas phase during the reaction.

Having investigated the substrate scope, we performed some additional experiments in order to assess the potentialities of the reaction.

First, the synthesis of **3aa** was repeated working on a ten-fold larger scale. In this case, we used a Teflon-coated autoclave having a c.a. 140 mL free volume space to perform the reaction.

The isolated yield (871 mg, 95%) is essentially the same as in the smaller scale experiment, showing that the reaction can be scaled-up without losses in efficiency.

Since, depending on the respective substitution patterns, dienes can be more expensive than nitroarenes, we also performed a reaction in which a twofold excess of nitroarene was present with respect to the diene. The desired oxazine was again obtained, although with a somewhat reduced yield of 68%.

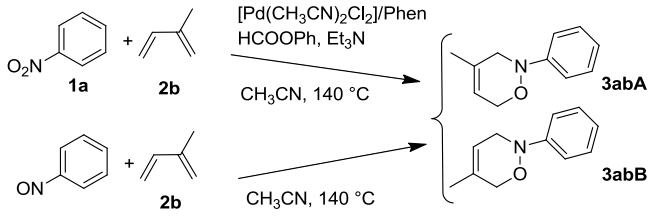
A comparison between the oxazine yields obtained with the present protocol and those previously obtained by other procedures clearly shows the advantages of our method. In particular:

1) Yields are higher than those previously reported by us using the nitroarene + diene approach and with pressurized carbon monoxide as the reductant.[11b, 12] This is especially noteworthy when the comparison with a very similar palladium/phenanthroline catalytic system is made.[12] The only exception to this rule is the reaction run in the presence of an excess of diene with respect to the nitroarene. In this case, it is likely that the lower yield in the present work is due to a partial polymerization of the diene, which decreases the amount of the limiting reagent. This side reaction was less important in the previous work because of the lower temperature employed (100 °C instead of 140 °C) and of the higher effective CO pressure (10 bar in the previous work. The actual CO pressure during the reaction under the presently employed conditions is not known, but it is surely much lower). Carbon monoxide competes with the diene for coordination to the metal and should inhibit the palladium-catalyzed polymerization of the olefin.
2) Except for the cases in which the present protocol failed, the yields obtained employing it are, to the best of our knowledge, always higher than those obtained by direct reaction of the corresponding nitrosoarenes with dienes. For example, the highest isolated yield reported in the literature for the reaction of nitrosobenzene with **2a** to give **3aa** is 80%.[31] It may appear odd that a higher yield is obtained by generating nitrosoarenes in situ than by using the pure compound. However, it should be recalled that nitrosoarenes are in equilibrium in solution with their dimeric form and that the dimer is not inactive. A common byproduct is the azoxyarene derived from the starting nitrosoarene. This may derive from a reduction reaction of the dimer (azoarenedioxide). We also observed the formation of this byproduct in those experiments that gave poor yields. Moreover, some evidence has been provided already more than 50 years ago that the main byproduct of the reaction between *m*- or *p*-nitro-nitrosobenzene and **2a** is the hetero Diels-Alder adduct of the corresponding nitrosoarene dimer with the diene.[32] Although the identity of this byproduct has not been reinvestigated in more recent years, the importance of the monomer-dimer equilibrium on the selectivity even of other reactions involving nitrosoarenes has been stressed more recently.[3e] In our protocol, the nitrosoarene is slowly generated and immediately consumed, so that its concentration is very low at any time and this surely prevents significant accumulation of dimers.
3) The yields obtained with our method also favorably compare with those obtained for the corresponding products by the previously mentioned oxidative protocol starting from arylamines and hydrogen peroxide, in the presence of molybdenum[10b] or selenium[10c] catalysts (e.g. for **3ca** NMR yields of 95% and 90% were reported with the two systems, which however respectively lowered to 51% and 63% upon isolation of the product, compared to a 98% isolated yield in our case). However, we acknowledge that the oxidative protocol works at room temperature and this, analogously to the direct reaction of nitrosoarenes and dienes, allows obtaining the hetero Diels-Alder adducts of dienes such as 1,4-diphenylbutadiene and cyclohexadiene for which our protocol failed due to reversibility of the adduct formation at high temperature.[33]

As far as the reaction mechanism is concerned, we recall that we had provided kinetic and mechanistic evidence that the allylic amination of unfunctionalized olefins by nitroarenes under carbon monoxide pressure and catalyzed by ruthenium complexes with Ar-BIAN ligands involves the initial coordination of the olefin before the rate-determining reaction with the nitroarene.[11a] Preliminary coordination of the olefin to the metal was also identified by Srivastava and Nicholas when studying the activity of $[CpFe(CO)_2]_2$ for the same reaction.[34] We proposed the same olefin pre-coordination for the analogous reaction of dienes, which, in addition to allylic amines, also produced oxazines.[11b] In the case of the palladium-catalyzed reaction, the absence of any allylic amine and the close ratio between the distal, **A**, and proximal, **B**, isomers of the oxazine derived from the catalyzed reaction of isoprene and nitrobenzene and that observed after a traditional reaction between the same diene and nitrosobenzene had pushed us to suggest that free nitrosobenzene was involved as the aminating agent and that the diene was entering the reaction only at the hetero Diels-Alder stage.[12] However, the slower catalytic reaction when sterically hindered dienes are employed warrants a reconsideration of this view. Indeed, if the diene only enters the reaction at a later stage with respect to a rate-determining reaction of the metal complex with the nitroarene, than a complete nitroarene conversion should be observed in all cases and steric hindrance should only affect selectivity. This is not the case. Thus a mechanism in which coordination of the diene precede the reaction with the nitroarene seems more likely.

To further elucidate the role of the diene during the reaction, we reinvestigated the distal/proximal selectivity by comparing the outcome of a reaction run with the present protocol with that of a standard hetero Diels-Alder reaction employing a nitrosoarene as reagent. To this aim, we performed a catalytic reaction between isoprene and nitrobenzene to give **3abA/3abB** and compared the obtained selectivity with that achieved by reacting nitrosobenzene and isoprene in the same solvent and at the same temperature (the same pressure tube was employed to avoid the boiling of the solvent), but in the absence of any other reagent. To prevent any selective loss of one of the two isomers,

in this case the reaction mixture was analyzed by NMR before any purification (Scheme 4).



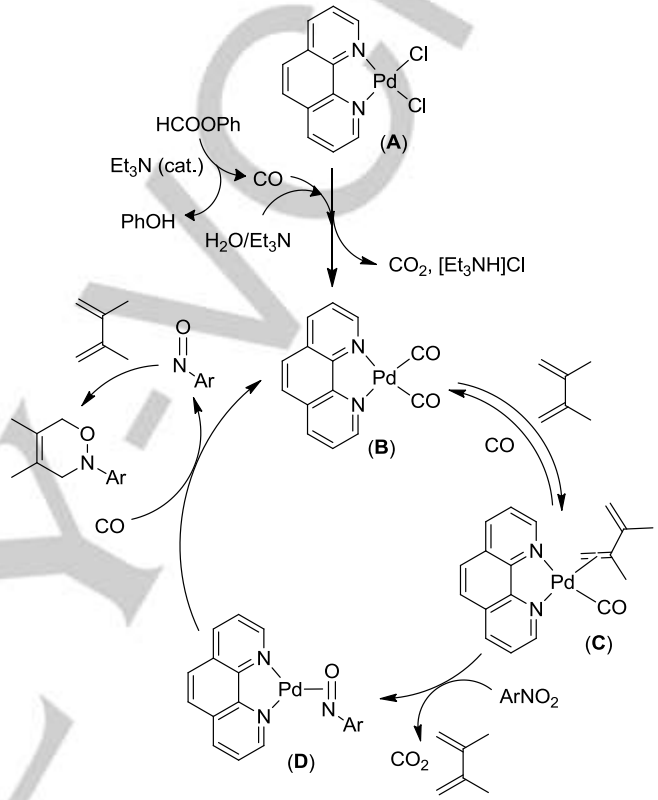
From **1a** and **2b**: **A**/**B** = 88:12, yield 65%
From PhNO and **2b**: **A**/**B** = 87:13, yield 38%

Scheme 4. Comparison between the distal/proximal selectivities observed with the present protocol and a standard hetero Diels-Alder reaction. For the experimental conditions of the former reaction, see the caption to Table 1. The nitrosobenzene reaction was run under the same conditions, but without the catalyst, formate and Et_3N. Both yields and ratio between the two isomers were determined by ^1H NMR on the crude reaction mixture.

3abA and **3abB** were formed in a 88:12 ratio from the catalytic reaction and in a 87:13 ratio from the standard hetero Diels-Alder reaction. Such close results suggests that the cycloaddition step is occurring outside the coordination sphere of the metal even under the conditions of the present study.

At this stage and also considering the known coordination chemistry of nitrosoarenes,[3e, 35] the most likely reaction pathway is that shown in scheme 5.

The complex $[Pd(Phen)Cl_2]$ (**A**) is formed from $[Pd(CH_3CN)_2Cl_2]$ and Phen upon mixing in solution.[36] Reduction of this complex by carbon monoxide, probably with the involvement of trace amounts of water and the help of triethylamine, produces a zerovalent palladium carbonyl complex (**B**).[37] To justify the effect of the olefin on the reaction rate, the latter should be in equilibrium with an olefin complex (**C**), which is the species reacting with the nitroarene. This is exactly what it has been shown to occur in the ruthenium[11] and iron systems[34] discussed before. As previously mentioned, the activation of nitroarenes occurs by a single electron transfer from the metal to the nitroarene. Complex **C** is surely more electron rich than complex **B** and this fact explains the slower observed rate when the diene is too sterically hindered to stably coordinate to the metal. The reaction is then proposed to proceed by formation of a nitrosoarene complex (**D**). Although all previous attempts to isolate a palladium nitrosoarene complex with phenanthroline or other nitrogen ligands have failed,[38] all known [formally] zerovalent palladium nitrosoarene complexes are tricoordinate.[35b, 35c, 35g] This implies that the diene must leave the coordination sphere of the metal. Release of the nitrosoarene in solution and its off-metal hetero Diels-Alder reaction with the diene complete the cycle. This hypothesis explains both the rate acceleration by non-sterically hindered dienes and the almost coincidence of the **A**/**B** ratios when the outcome of a catalytic reaction is compared with that of a traditional reaction starting from nitrosobenzene. However, it should be noted that the instability of type **D** complexes implies that they are highly reactive. Thus, a direct involvement of such complexes in the cycloaddition step cannot be dismissed at the moment. Mechanistic studies are in progress to definitely assess this point, though the instability of zerovalent carbonyl complexes with nitrogen ligands makes the design of experiments giving a clear-cut conclusion difficult.



Scheme 5. Proposed reaction mechanism.

Conclusions

In the present work we have shown that 3,6-dihydro-2*H*-[1,2]-oxazines, versatile substrates for further transformations, can be obtained by reduction of nitroarenes in the presence of conjugated dienes, employing phenyl formate as a CO surrogate. The methods presents several advantages with respect to previously reported alternatives:

1) No need exists to synthesize toxic and unstable precursors such as nitrosoarenes or arylhydroxylamines. On the contrary, nitroarenes are the cheapest and more widely available nitrogen-containing aromatic compounds.
2) Yields are higher than those obtained by any previous synthetic strategy including the direct reaction of a nitrosoarene with the diene and the use of nitroarenes under pressurized CO.
3) No autoclave or pressurized CO lines are necessary. Pressure tubes or flasks are cheap and available in volumes from 1 mL to at least half a liter.

4) A variety of substituents is tolerated, including easily oxidizable ones, such a free formyl group, which would not be compatible with protocols employing strongly oxidizing agents.
5) Phenyl formate and the produced phenol are little toxic if compared with most alternative CO surrogates. The availability of phenyl formate even on large scale makes its use compatible with larger scale preparations even from an economic point of view.
6) The catalyst and ligand are commercially available and cheap when compared respectively with other palladium sources and most phosphine ligands typically employed in other catalytic systems.

These features collectively make the presently described protocol a useful tool for the synthesis of 1,2-oxazines and of the products derived thereof both at a laboratory and the production scale.

Experimental Section

General procedures

Unless otherwise stated, all reactions and manipulations were performed under a dinitrogen atmosphere using standard Schlenk apparatus. All glassware and magnetic stirring bars were kept in an oven at 120 °C for at least two hours and let to cool under vacuum before use. CH_3CN and Et_3N were dried by distillation over CaH_2. Phenyl formate was prepared following a procedure reported in the literature.[14j] Isoprene, myrcene and nitrobenzene were distilled before use. The two dienes were then stored under dinitrogen at 4 °C. 1,10-Phenanthroline (Phen) was purchased as hydrate (Sigma-Aldrich). Before use, it was dissolved in CH_2Cl_2, dried over Na_2SO_4 followed by filtration under a dinitrogen atmosphere and evaporation of the solvent *in vacuo*. Phen was weighed in the air but stored under dinitrogen to avoid water uptake. Deuterated solvents were purchased from Sigma-Aldrich. $CDCl_3$ was filtered on basic alumina and stored under dinitrogen over 4 Å molecular sieves. All other reagents were commercially available and were used as received. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded at room temperature on a Bruker AC 300 FT, an Avance Bruker DPX 300, or on a Bruker Avance DRX 400 spectrometers.

Reactor

The reactor in which the reaction is performed has a special importance. We routinely employed a ~18 mL ACE pressure tube. This tube, also available in many other dimensions or as flasks for larger volumes, is provided either with a "front" or with a "back" "seal". The former corresponds to a FETFE® O-ring sitting below the threads of the PTFE bushing. In the latter, the O-ring sits on top of the threads. In both cases, the weak point of the system is the O-ring itself. With the solvent and reagents employed in our study, the O-ring completely degraded after at most a few reactions if not at the first use. Changing the O-ring material to Viton or even to Karlez did not solve the problem. However, we found that if a "front seal" setting is employed, it is possible to remove the O-ring and still no leakage is observed. This way, the solvent only comes in contact with glass or PTFE. Other brands also commercialize pressure tubes that may be conveniently employed.

Catalytic reactions

The reaction was performed under dinitrogen atmosphere. To avoid weighing very small amounts of $PdCl_2(CH_3CN)_2$ and phenanthroline, stock solutions of these reagents were prepared by dissolving respectively 28 mg of the former reagent in 20 mL dry CH_3CN (to give a 5.4×10^{-3} M solution) and 48.7 mg Phen in 20 mL dry CH_3CN (to give a 1.35×10^{-2} M solution). An ~18 mL ACE pressure tube (see above) was placed in a Schlenk tube having a wide mouth and the tube was evacuated and filled with dinitrogen three times. Then, in a nitrogen flush, were added at RT the nitroarene (0.540 mmol), the diene (2.16 mmol), phenyl formate (240 µl, 2.20 mmol), the catalyst stock solution (1.00 mL, corresponding to a catalyst amount of 1.40 mg, 0.00540 mmol), the Phen stock solution (1.00 mL, corresponding to a ligand amount of 2.44 mg, 0.0135 mmol), acetonitrile (8.0 mL) and finally triethylamine (40 µL). The pressure tube was closed and transferred to an oil bath preheated at 140 °C. When 1,3-butadiene was used, it was condensed into a Schlenk flask containing 15 mL of CH_3CN by cooling with a dry-ice/acetone bath and kept cold, avoiding freezing of the solvent. The amount of condensed diene (1.80 g, 33.2 mmol) was determined by weighing the flask before and after condensation. The butadiene stock solution (1.5 mL corresponding to a diene amount of 3.32 mmol) was transferred while cold by mean of a syringe to the reactor immediately before closing it. The reaction mixture was heated at 140 °C with continuous stirring for 4 hrs. Then the tube was lifted from the oil bath and allowed to cool to room temperature. The reaction mixture was evaporated to dryness using a rotary evaporator and the crude purified by column chromatography on silica. In general, any dimer or oligomer of the diene eluted first, followed by the oxazine. Only in the case of the reaction between **1b** and **2h** did 4-fluoroazoxybenzene eluted before the oxazine.

Products characterization

4,5-Dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]-oxazine (3aa). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane/ethyl acetate 98:2 + 1% Et_3N). Yield = 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 10.6 Hz, 2H), 7.19 – 7.11 (m, 2H), 7.02 (t, J = 9.7 Hz, 1H), 4.35 (s, 2H), 3.69 (s, 2H), 1.76 (s, 3H), 1.67 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.85, 129.19, 125.38, 122.75, 122.66, 116.29, 72.44, 56.75, 16.33, 14.06 ppm. $C_{12}H_{15}NO$ requires C, 76.16; H, 7.99; N, 7.40% Found: C, 76.40; H, 7.89; N, 7.20%

2-(4-Fluorophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (3ba). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane/ethyl acetate 98:2 + 1% Et_3N). Yield = 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 – 7.07 (m, 2H), 7.05 – 6.93 (m, 2H), 4.32 (s, 2H), 3.60 (s, 2H), 1.73 (s, 3H), 1.64 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.08 (d, *J* = 240.8 Hz), 147.15, 125.36, 122.69, 118.25 (d, *J* = 7.8 Hz), 115.72 (d, *J* = 22.4 Hz), 72.50, 57.42, 16.40, 14.01 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -121.74 ppm. $C_{12}H_{15}NO$ requires C, 76.16; H, 7.99; N, 7.40% Found: C, 76.40; H, 7.89; N, 7.20%. $C_{12}H_{14}FNO$ requires: C, 69.55; H, 6.81; N, 6.76%. Found: C, 69.80; H, 6.90; N, 6.60%.

2-(4-Chlorophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (3ca). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane/ethyl acetate 98:2 + 1% Et_3N). Yield = 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 4.32 (s, 2H), 3.63 (s, 2H), 1.73 (s, 3H), 1.64 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.32, 129.13, 127.63, 125.38, 122.43, 117.53, 72.43, 56.55, 16.30, 14.05 ppm. $C_{12}H_{14}ClNO$ requires: C, 64.43; H, 6.31; N, 6.26%. Found: C, 64.14; H, 6.52; N, 6.30%.

2-(4-Bromophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (3da).Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 99%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 1H), 4.31 (s, 2H), 3.62 (s, 2H), 1.73 (s, 3H), 1.64 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.44, 131.64, 124.98, 122.01, 117.44, 114.63, 72.01, 55.96, 15.90, 13.66 ppm. $C_{12}H_{14}BrNO$ requires: C, 53.75; H, 5.26; N, 5.22%. Found: C, 53.90; H, 5.00; N, 5.01%.

2-(3,5-Dichlorophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (3ea). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 88%. ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 1.8 Hz, 2H), 6.93 (t, J = 1.8 Hz, 1H), 4.30 (s, 2H), 3.63 (s, 2H), 1.73 (s, 3H), 1.64 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.29, 135.55, 125.36, 122.02, 121.79, 114.04, 72.49, 55.53, 16.23, 14.07 ppm. $C_{12}H_{13}Cl_2NO$ requires: C, 55.83; H, 5.08; N, 5.43%. Found: C, 56.03; H, 5.30; N, 5.24%.

2-(3,5-Bis(trifluoromethyl)phenyl)-4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (3fa). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 96%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 2H), 7.44 (s, 1H), 4.35 (s, 2H), 3.74 (s, 2H), 1.77 (s, 3H), 1.67 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.63, 132.48 (q, $^2J_{F-C}$ = 33.0 Hz), 125.45, 123.84 (q, $^1J_{F-C}$ 272.7 Hz).121.78 , 115.72 – 114.66 (m), 72.58 , 55.39 , 16.08 , 13.94 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.37 ppm. $C_{14}H_{13}F_6NO$ requires: C, 51.70; H, 4.03; N, 4.31%. Found 52.10; H, 4.25; N, 4.15%.

Methyl 4-(4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazin-2-yl)benzoate (3ga). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 86%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 4.31 (s, 2H), 3.86 (s, 3H), 3.72 (s, 2H), 1.72 (s, 3H), 1.63 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.95, 153.64, 130.75, 124.89, 122.70, 121.77, 113.91, 54.48, 51.76, 15.81, 13.68 ppm. $C_{14}H_{17}NO_3$ requires: C, 68.00; H, 6.93; N, 5.66%. Found: C, 68.30; H, 7.15; N, 5.50%.

4-(4,5-Dimethyl-3,6-dihydro-2*H*-[1,2]-oxazin-2-yl)benzamide (3ha). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 25%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 4.32 (s, 2H), 3.73 (s, 2H), 1.75 (s, 3H), 1.65 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.44, 133.54, 125.35, 121.88, 120.01, 114.83, 104.00, 72.43, 54.39, 16.21, 14.11 ppm. $C_{13}H_{16}N_2O_2$ requires: C, 67.22; H, 6.94; N, 12.06%. Found: C, 67.33; H, 6.98; N, 11.85%.

Phenyl 4-(4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazin-2-yl)benzoate (3ia'). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 32%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.30 – 7.09 (m, 5H), 4.36 (s, 2H), 3.79 (s, 2H), 1.77 (s, 3H), 1.66 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.50, 151.52, 131.88, 129.80, 126.03, 125.33, 122.23, 122.13, 114.28, 72.41, 54.69, 16.25, 14.12 ppm. Three quaternary carbon were not detected. $C_{19}H_{19}NO_3$ requires: C, 73.77; H, 6.19; N, 4.53%. Found: C, 73.60; H, 6.23; N, 4.80%.

4-(4,5-Dimethyl-3,6-dihydro-2*H*-[1,2]-oxazin-2-yl)benzoic acid (3ia). For this reaction, 1.54 equiv. of Et_3N were added instead of 0.54 to neutralize the starting acid and guarantee activation of phenyl formate. The reaction time was also increased to 6 h. At the end of the reaction, acetonitrile and excess diene were evaporated *in vacuo*. The residue was dissolved in ethanol (10 mL) and 3 mL of an aqueous 2 M KOH solution was added. The reaction mixture was stirred overnight and then washed with CH_2Cl_2 (3 × 10 mL). The aqueous layer was separated, neutralized with conc. HCl (0.5 mL) and the formed solid was collected by filtration. The pure product was obtained as a colorless solid after column chromatography (methylene chloride/methanol = 98:2 as the eluent). Yield = 40%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 4.34 (s, 2H), 3.77 (s, 2H), 1.76 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 171.45, 154.59, 131.93, 125.30, 122.12, 121.86, 114.17, 72.39, 54.62, 16.22, 14.11. $C_{13}H_{15}NO_3$ requires: C, 66.94; H, 6.48; N, 6.00%. Found: C, 66.60; H, 6.78; N, 6.80%.

4,5-Dimethyl-2-(4-nitrophenyl)-3,6-dihydro-2*H*-[1,2]-oxazine (3ja). Obtained as a pale yellow solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 88%. ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 9.3 Hz, 2H), 7.05 (d, J = 9.3 Hz, 2H), 4.33 (s, 2H), 3.79 (s, 2H), 1.75 (s, 3H), 1.65 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.78, 141.34, 125.71, 125.24, 121.71, 113.54, 72.48, 53.81, 16.14, 14.13 ppm. $C_{12}H_{14}N_2O_3$ requires: C, 61.53; H, 6.02; N, 11.96%. Found: C, 61.33; H, 6.22; N, 11.73%.

4,5-Dimethyl-2-(p-tolyl)-3,6-dihydro-2*H*-[1,2]-oxazine (3ka). Obtained as a colorless solid oil after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 72%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.6 Hz, 2H), 4.34 (s, 2H), 3.64 (s, 2H), 2.32 (s, 3H), 1.75 (s, 3H), 1.65 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.19, 131.91, 129.33, 124.97, 122.47, 116.32, 72.02, 56.82, 20.68, 15.95, 13.65 ppm. $C_{13}H_{17}NO$ requires: C, 76.81; H, 8.43; N, 6.89%. Found: C, 76.91; H, 8.55; N, 6.79%.

2-(4-Ethylphenyl)-4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (3la). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 87%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.04 (m, 4H), 4.37 (s, 2H), 3.68 (s, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.77 (s, 3H), 1.68 (s, 3H), 1.27 ppm t, J = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.83, 138.74, 128.57, 125.40, 122.91, 116.76, 72.47, 57.22, 28.61, 16.38, 16.19, 14.09 ppm. $C_{14}H_{19}NO$ requires: C, 77.38; H, 8.81; N, 6.45%. Found: C, 77.70; H, 8.95; N, 6.35%.

2-(4-Isopropylphenyl)-4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (3ma). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 95%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 4.33 (s, 2H), 3.64 (s, 2H), 2.88 (p, J = 6.9 Hz, 1H), 1.74 (s, 3H), 1.65 (s, 3H), 1.25 (s, 3H), 1.23 ppm (s, 3H). 13C NMR (75 MHz, $CDCl_3$) δ 148.79, 143.47, 127.09, 125.37, 122.90, 116.73, 72.47, 57.22, 33.83, 24.49, 16.35, 14.06 ppm. $C_{15}H_{21}NO$ requires: C, 77.88; H, 9.15; N, 6.05%. Found: C, 78.12; H, 9.46; N, 5.85%.

4-(4,5-Dimethyl-3,6-dihydro-2*H*-[1,2]-oxazin-2-yl)phenyl acetate (3oa). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 15%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 9.0 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 4.32 (s, 2H), 3.64 (s, 2H), 2.28 (s, 3H), 1.73 (s, 3H), 1.64 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.36, 122.64, 122.09, 117.29, 72.45, 57.01, 21.52, 16.32, 14.06 ppm. $C_{14}H_{17}NO$ requires: C, 68.00; H, 6.93; N, 5.66%. Found: C, 68.31; H, 6.99; N, 5.50%.

4-(4,5-Dimethyl-3,6-dihydro-2*H*-[1,2]-oxazin-2-yl)benzonitrile (3pa). Obtained as a colorless solid after column chromatography (gradient

elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 82%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 9.0 Hz, 2H), 7.08 (d, J = 9.0 Hz, 2H), 4.31 (s, 2H), 3.73 (s, 2H), 1.74 (s, 3H), 1.65 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.05, 133.13, 124.94, 121.49, 119.59, 114.44, 103.60, 72.02, 53.99, 15.79, 13.70 ppm. $C_{13}H_{14}N_2O$ requires: C, 72.87; H, 6.59; N, 13.07%. Found: C, 72.65; H, 6.43; N, 13.18%.

4-(4,5-Dimethyl-3,6-dihydro-2*H*-[1,2]-oxazin-2-yl)benzaldehyde (3qa). Obtained as a tan solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 77%. ^1H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.7 Hz, 2H), 4.33 (s, 2H), 3.78 (s, 2H), 1.75 (s, 3H), 1.65 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.27, 154.96, 131.70, 130.10, 125.27, 121.98, 114.27, 72.42, 54.20, 16.20, 14.13 ppm. $C_{13}H_{15}NO_2$ requires: C, 71.87; H, 6.96; N, 6.45%. Found: C, 71.93; H, 6.82; N, 6.30%.

2-(2-Bromo-5-methylphenyl)-4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (3ra). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 76%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 1.5 Hz, 1H), 6.83 (dd, J = 8.3, 1.7 Hz, 1H), 4.39 (s, 2H), 3.60 (s, 2H), 2.32 (s, 3H), 1.73 (s, 3H), 1.66 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.63, 138.62, 133.36, 127.49, 124.99, 123.16, 121.35, 114.43, 72.95, 57.31, 21.59, 16.37, 14.10 ppm. $C_{13}H_{16}BrNO$ requires: C, 55.33; H, 5.72; N, 4.96%. Found: C, 55.01; H, 5.53; N, 4.88%.

4,5-Dimethyl-2-(pyridin-2-yl)-3,6-dihydro-2*H*-[1,2]-oxazine (3sa). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 58%. ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 4.9 Hz, 1H), 7.69 – 7.53 (t, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.94 – 6.70 (t, 1H), 4.34 (s, 2H), 4.06 (s, 2H), 1.77 (s, 3H), 1.64 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.34, 147.82, 137.96, 124.18, 123.12, 116.80, 110.38, 72.12, 52.02, 16.18, 14.11 ppm. $C_{11}H_{14}N_2O$ requires: C, 69.45; H, 7.42; N, 14.73%. Found: C, 69.35; H, 7.34 N, 14.81%.

2-(4-Fluorophenyl)-5-methyl-3,6-dihydro-2*H*-[1,2]-oxazine (3bbA) and 2-(4-fluorophenyl)-4-methyl-3,6-dihydro-2*H*-2-(4-fluorophenyl)-4-methyl-3,6-dihydro-2*H*-[1,2]-oxazine-oxazine (3bbB). Obtained as a pale yellow oil after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 78% (6.3:1). $^1H\{^{19}F\}$ NMR (300 MHz, $CDCl_3$) δ 7.11 (m, 2H, both isomers), 7.02 (m, 2H, both isomers), 5.63 (s, 2H, both isomers), 4.47 (s, 2H, *distal* isomer), 4.38 (s, 2H, *proximal* isomer), 3.73 (s, 2H, *proximal* isomer), 3.63 (s, 2H, *distal* isomer), 1.81 (s, 3H, *distal* isomer), 1.72 (s, 3H, *proximal* isomer) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.10 (d, *J* = 240.9 H, both isomers), 147.11 (both isomers), 133.90 (*proximal* isomer), 131.04 (*distal* isomer), 120.15 (*distal* isomer), 118.28 (d, $^3J_{F\text{-}C}$ = 7.8 Hz, *proximal* isomer), 118.24 (d, J = $^3J_{F\text{-}C}$ = 7.8 Hz, *distal* isomer), 117.45 (*proximal* isomer), 115.74 (d, $^2J_{F\text{-}C}$ = 22.5 Hz), 115.73 (d, $^2J_{F\text{-}C}$ = 22.1 Hz), 72.52 (*proximal* isomer), 68.99 (*distal* isomer), 57.12 (*distal* isomers), 53.06 (*proximal* isomer), 20.59 (*distal* isomers), 18.45 (*proximal* isomer) ppm. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ -121. 41 (both isomers) ppm. $C_{11}H_{12}FNO$ requires: C, 68.38; H, 6.26; N, 7.25%. Found: C, 68.59; H, 6.37; N, 7.28%.

2-(4-Fluorophenyl)-4-(4-methylpent-3-en-1-yl)-3,6-dihydro-2*H*-[1,2]-oxazine (3bcA) and 2-(4-fluorophenyl)-5-(4-methylpent-3-en-1-yl)-3,6-dihydro-2*H*-[1,2]-oxazine (3bcB). Obtained as a pale yellow oil after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 62% (2.5:1). $^1H\{^{19}F\}$ NMR (400 MHz, $CDCl_3$) δ 7.13 (m, 2H), 7.06 – 6.90 (m, 2H), 5.73 – 5.50 (s, 1H), 5.16 (s, 1H), 4.51 (s, 2H), 4.43 (s, 2H), 3.76 (s, 2H), 3.68 (s, 2H), 2.26 – 2.04 (m, 4H), 1.73 (s, 3H), 1.65 (s, 3H). Expect for the peaks at 4.43 and 3.76 ppm, all the other signals are ascribed to both the isomers. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.76 (d, $^1J_{F\text{-}C}$ = 241.5 Hz, both isomers), 146.93 (both isomers), 137.50 (*minor* isomer), 134.66 (*major* isomer), 132.22 (both isomers), 123.64 (both isomers), 119.36 (*major* isomer), 117.96 (d, $^3J_{F\text{-}C}$ = 7.8 Hz, *major* isomer), 117.83 (d, $^3J_{F\text{-}C}$ = 7.6 Hz, *minor* isomer), 116.50 (*minor* isomer), 115.38 (d, $^2J_{F\text{-}C}$ = 22.3 Hz, *major* isomer), 114.97 (d, $^2J_{F\text{-}C}$ = 22.1 Hz, *minor* isomer), 71.35 (*minor* isomer), 68.68 (*major* isomer), 55.88 (*major* isomer), 52.72 (*minor* isomer), 34.47 (*major* isomer), 32.56 (*minor* isomer), 26.16 (both isomers), 25.75 (both isomers), 17.81 (both isomers) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -121.43 (*major* isomer), -121.54 (*minor* isomer) ppm. $C_{16}H_{20}FNO$ requires: C, 73.35; H, 7.71; N, 5.36%. Found: C, 73.69; H, 7.57; N, 5.48%.

2-(4-Fluorophenyl)-3-methyl-3,6-dihydro-2*H*-[1,2]-oxazine (3beA) and 2-(4-fluorophenyl)-6-methyl-3,6-dihydro-2*H*-1,2-oxazine (3bdB). Obtained as a pale yellow oil after column chromatography (hexane:AcOEt = 9:1 + 1% Et_3N). Yield = 89%. $^1H\{^{19}F\}$ NMR (300 MHz, $CDCl_3$) δ 7.18 – 6.90 (m, 4H, both isomers), 6.01 – 5.75 (m, 2H, both isomers), 4.81 – 4.66 (m, 1H, *major* isomer), 4.57 – 4.27 (m, 2H, *minor* isomer), 4.07 – 3.92 (m, 1H, *minor* isomer), 3.87 – 3.55 (m, 1H, *major* isomer), 1.34 (d, J = 6.7 Hz, 3H, *major* isomer), 1.06 ppm (d, J = 6.6 Hz, 1H, *minor* isomer). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.97 (d, $^1J_{F\text{-}C}$ = 241.1 Hz, *minor* isomer), 158.67 (d, $^1J_{F\text{-}C}$ = 240.6 Hz, *major* isomer), 147.01 (d, $^4J_{F\text{-}C}$ = 2.5 Hz, *major* isomer), 145.24 (d, $^4J_{F\text{-}C}$ = 2.6 Hz, *minor* isomer),131.24 (*major* isomer), 129.57 (*minor* isomer), 125.07 (*minor* isomer), 122.68 (*major* isomer), 119.66 (d, $^3J_{F\text{-}C}$ = 7.8 Hz, *minor* isomer), 117.67 (d, $^3J_{F\text{-}C}$ = 7.8 Hz, *major* isomer), 115.46 (d, $^4J_{F\text{-}C}$ = 22.3 Hz, *minor* isomer), 115.42 (d, $^2J_{F\text{-}C}$ = 22.4 Hz, *major* isomer), 74.18 (major isomer) , 68.90 (*minor* isomer), 56.59 (*minor* isomer), 52.24 (*major* isomer), 19.05 (*major* isomer), 15.10 ppm (*minor* isomer). $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ -121. 91(both isomers) ppm. $C_{11}H_{12}FNO$ requires: C, 68.38; H, 6.26; N, 7.25%. Found: C, 68.00; H, 5.89; N, 7.33%.

2-(4-Fluorophenyl)-4,5-dimethoxy-3,6-dihydro-2*H*-[1,2]-oxazine (3bh). Obtained as a colorless solid after column chromatography (gradient elution from hexane to hexane /ethyl acetate 98:2 + 1% Et_3N). Yield = 79%. $^1H\{^{19}F\}$ NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, J = 9.1, 4.8 Hz, 2H), 7.00 (t, J = 8.7 Hz, 2H), 4.39 (s, 2H), 3.77 (s, 2H), 3.75 (s, 3H), 3.75 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.96 (d, *J* = 242.0 Hz), 145.94, 135.81, 133.64 , 118.04 (d, *J* = 7.7 Hz), 115.44 (d, *J* = 22.4 Hz), 66.76 , 58.96 , 58.82 , 52.89 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -120.79 ppm. $C_{12}H_{14}FNO_3$ requires**:** C, 60.24; H, 5.90; N, 5.85. Found: C, 60.64; H, 5.91; N, 5.85

2-(4-Fluorophenyl)-3,6-dihydro-2*H*-[1,2]-oxazine (3bi). Obtained as a colorless solid after column chromatography (hexane:AcOEt = 9:1 + 1% Et_3N). Yield = 87%. $^1H\{^{19}F\}$ NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.06 (m, 2H), 7.06 – 6.91 (m, 2H), 6.06 – 5.84 (m, 2H), 4.72 – 4.41 (m, 2H), 3.88 – 3.68 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.82 (d, $^1J_{F\text{-}C}$ = 240.9 Hz), 146.95 (d, $^4J_{F\text{-}C}$ = 2.5 Hz), 126.22, 123.15, 117.91 (d, $^3J_{F\text{-}C}$ = 7.8 Hz), 115.46 (d, $^2J_{F\text{-}C}$ = 22.4 Hz), 69.26, 53.07 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -121.39 ppm. $C_{10}H_{10}FNO$ requires: C, 67.03; H, 5.63; N, 7.82%. Found: C, 67.13; H, 5.70; N, 7.99.

1,2-Bis(4-fluorophenyl)diazene 1-oxide (bis-4-fluoroazoxybenzene). ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, J = 9.2, 4.8 Hz, 2H), 8.26 (dd, J = 9.2, 5.4 Hz, 2H), 7.18 (q, J = 8.0 Hz, 4H). Spectroscopic data are in accordance with those published in the literature.[39]

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