JOC Article

Synthesis of Oxazines and *N*-Arylpyrroles by Reaction of Unfunctionalized Dienes with Nitroarenes and Carbon Monoxide, Catalyzed by Palladium−Phenanthroline Complexes

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The reaction between an unfunctionalized conjugated diene and a nitroarene under CO pressure and at 100 °C, catalyzed by $[Pd(Phen)_2][BF_4]_2$ (Phen = 1,10-phenanthroline), affords the corresponding hetero-Diels−Alder adduct (oxazine) in up to 91% yields in one pot. If the reaction mixture is then heated to 200 °C, the oxazines are converted into the corresponding *N*-arylpyrroles in good yields. Pressures as low as 5 bar can be employed, and 0.08% catalyst is sufficient to effect the transformation. The reaction can be equally run by employing the nitroarene or the diene as limiting agent and works well for nitroarenes bearing either electron-withdrawing or mildly electron-donating substituents. A moderate steric hindrance on the nitroarene (*o*-methyl) is well tolerated, but 1,4-disubstituted-1,3-dienes are not suitable substrates.

Introduction

The synthesis of pyrroles[1] has been the focus of much attention in recent years. The synthesis of hetero-Diels−Alder adducts derived from nitrosoarenes as dienophiles (oxazines) has also been investigated, since these products have pharmacological activity themselves or can be easily transformed into other products.[2] However, their usual synthesis requires the intermediate isolation of nitroso compounds, which is problematic, although an approach has also been reported in which oxidation of an aromatic amine in the presence of a diene results in the trapping of the intermediately formed nitrosoarene to give the hetero-Diels−Alder adducts in one pot.[3,4] Several synthetic approaches are available for the synthesis of pyrroles, but few of them are applicable to *N*-arylpyrroles.[1,5] Moreover, most synthetic methods give best results for pyrroles bearing one or two substituents in the 2 and 5 positions.[5] On the contrary, the procedure here reported is best suited for pyrroles which are only substituted in the 3 and 4 positions.We have recently reported[6,7] a new synthetic way to produce allylic amines, employing a simple unactivated olefin and an aromatic nitro compound as the aminating reagent, under reducing conditions (CO pressure). The reaction was catalyzed by $Ru_3(CO)_{12}$ in the presence of Ar-BIAN ligands (Ar-BIAN = bis(arylimino)acenaphthene). It is important to note that the reaction does not produce salts as byproducts. The production of such byproducts is becoming increasingly unacceptable for industrial processes. Nicholas and co-workers have reported on a similar reaction.[8] When we applied the same catalytic system to 1,3-dienes, in addition to the expected allylic amine, two other products were formed: the hetero-Diels−Alder adduct derived from the intermediate nitrosoarene and the diene and the *N*-arylpyrrole.[9] It was shown that the hetero-Diels−Alder adduct (oxazine) and the allylic amine are independent primary products of the reaction, but the pyrrole derives from further reaction of the adduct (Scheme 1).

Despite its novelty, the ruthenium-catalyzed reaction still presents several drawbacks when applied to the

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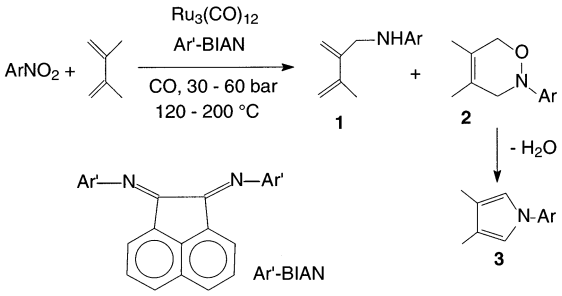
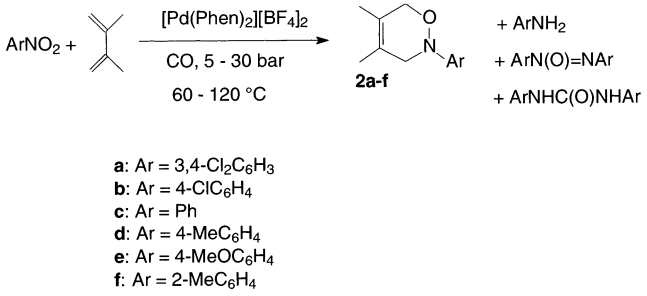
SCHEME 1





(1)

synthesis of oxazines and pyrroles: (a) Yields are only moderate to good (40−60%). (b) Usually a 1 mol % amount of $Ru_3(CO)_{12}$ has to be employed. (c) A large excess of diolefin must be employed with respect to the nitroarene to reach the best results. (d) Steric hindrance is not tolerated either on the nitroarene or on the diene. (e) A CO pressure of 40 bar must be applied, requiring the use of a metal autoclave.

Our group has been active for many years in the field of the carbonylation reactions of nitroarenes to afford isocyanates, carbamates, and ureas.[10] At the moment, the most active catalytic system for these last reactions is based on the use of palladium−phenanthroline complexes.[10−12] Here we report that palladium−phenanthroline complexes are also very active and selective catalysts for the reaction of nitroarenes with 1,3-dienes, affording oxazines and pyrroles.

Results and Discussion

Synthesis of Oxazines: Optimization of the Experimental Conditions. The complex $[Pd(Phen)_2][BF_4]_2$ (Phen = 1,10-phenanthroline) catalyzes the reaction of nitrobenzene with 2,3-dimethylbutadiene under CO pressure at 60−120 °C to selectively afford the hetero-Diels-Alder adduct 2-phenyl-4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (**2c**). Byproducts of the reaction are aniline and azo- and azoxybenzene. Diphenylurea is usually formed in small amounts but becomes the main byproduct when the reaction is run in methanol or methanol-containing solvent mixtures (eq 1).

An extensive optimization of the reaction conditions has been carried out, employing nitrobenzene and 2,3-dimethylbutadiene as substrates. The results of all the experiments are reported in Table 1. Only the general trends are discussed, and a reference is given to the relevant entries in Table 1. It should be noted that the conversion of most reactions was intentionally kept below 100% to be able to evidence any effect on both reaction rate and selectivity.

The most important observations are the following:

(a) The catalytic system is much more active than the ruthenium-based one previously reported, and a catalytic ratio of 1200 (rather than 30!) can be currently employed (corresponding to 0.08 mol % catalyst).

(b) No or only trace amounts of allylic amine are formed.

(c) Solvent: Methanol, the solvent commonly employed in the carbonylation reactions to yield carbamates, can be used even for the present reaction, but conversion and selectivity increase if increasing amounts of the less polar toluene are added to the solvent mixture (with a corresponding decrease in the methanol amount) up to the point in which the catalyst become insoluble in the reaction mixture and the reaction stops completely (entries 1−6). THF and DMF, however, gave better results, with the second affording a faster reaction (entries 13, 15).

(d) Additives: The addition of Et_3N to the reaction mixture increases the rate of the reaction in methanol/toluene (entries 8, 9, 11) and, to a lower extent, in THF (entries 13, 16, 32, 37−40), but the effect is not observable for the reaction in DMF, where conversion is complete anyway (entries 33, 34). The effect on the selectivity is small, with a maximum for a 100:1 Et_3N/Pd mol ratio (entries 32, 37−40). Clearly, DMF is a basic enough solvent not to require any additional base. In the presence of the amine, the rate of the reaction in THF becames almost equivalent to the one in DMF, with a slightly higher selectivity (entries 32, 33). Since DMF is more difficult to separate after the reaction, the combination THF/Et_3N was preferred in this study. In the presence of Et_3N, diethyl ether gave a selectivity even slightly higher than THF (entries 32, 35) but at a much reduced rate. Methylene chloride, on the other hand, is not a suitable solvent, affording a very low conversion and only trace amounts of oxazine (entry 36). The addition of an acid (benzoic acid) to the reaction mixture slowed the reaction (entries 51, 52), although the effect on selectivity was small. In the absence of diolefins, acids are known to increase the rate of carbonylation reactions of nitroarenes.[11,12]

(e) Olefin amount: The reaction rate is higher if a larger excess of olefin is present (entries 16−18, 20, 23, 25, 26), but the effect on selectivity is negligible as long as the olefin is present in at least a 2:1 molar amount with respect to the nitroarene. In the absence of any olefin (entry 20), the reaction was very slow; azo- and azoxybenzene and diphenylurea were formed as principal products, but a small amount (5% selectivity) of the trimer of phenyl isocyanate (1,3,5-triphenyl-[1,3,5]triazinan-2,4,6-trione) was also detected and quantified by HPLC.

(f) CO pressure: For reactions run at a 1200:1 catalytic ratio, the ideal CO pressure is 10 bar (entries 4, 8, 17−

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TABLE 1. Reactions between 2,3-Dimethylbutadiene and $PhNO_2$, Catalyzed by $[Pd(phen)_2](BF_4)_2$[a]

entry	Phen/Pd	$PhNO_2$/Pd mol ratio	Et_3N/Pd mol ratio	diene/mL	solv	solv vol/mL	T/°C	t/h	P_{CO}/bar	$PhNO_2$ conv %[b,c]	oxazine (**2c**) sel %[d,e]	$PhNH_2$ sel %[c,d]	PhN=NPh sel %[c,d]	PhN(O)NPh sel %[c,d]	$(PhNH)_2CO$ sel %[d,e]
1	16	1200		1	tol	9	120	6	60	1.3	0	<1	<1	<1	<1
2[j]	16	1200		1	MeOH/ tol	1:8	120	6	60	13.7	66.3	<1	<1	<1	36.2
3[j]	16	1200		1	MeOH/tol	2.5:6.5	120	6	60	20.0	56.7	<1	<1	<1	26.5
4[j]	16	1200		1	MeOH/ tol	4.5:4.5	120	6	60	54.5	52.7	<1	<1	8.2	15.6
5[j]	16	1200		1	MeOH/tol	6.5:2.5	120	6	60	44.3	51.6	<1	<1	7.5	10.7
6[j]	16	1200		1	MeOH	0	120	6	60	42.7	52.2	<1	<1	8.0	14.2
7[j]	16	1200		2	MeOH/tol	4:4	120	6	60	72.9	55.7	<1	<1	12.6	16.6
8[j]	16	1200		1	MeOH/tol	4.5:4.5	120	6	30	54.6	54.3	<1	<1	9.9	9.1
9[j]	16	1200	100	1	MeOH/tol	4.5:4.5	120	6	30	67.6	54.8	<1	<1	6.6	3.5
10[j]	16[g]	1200	100	1	MeOH/tol	4.5:4.5	120	6	30	59.7	52.6	<1	<1	6.9	6.2
11[j]	16	1200	200	1	MeOH/tol	4.5:4.5	120	6	30	74.8	57.8	<1	<1	6.2	7.2
12[j]	16	1200	200	2	MeOH/tol	4:4	120	6	30	89.9	53.8	<1	<1	2.5	11.2
13	16	1200		2	THF	10	120	6	30	75.7	58.3	3.4	0.9	7.6	f
14	16	1200		2	THF + DMP[i]	10	120	6	30	74.4	56.4	3.4	<1	5.6	f
15	16	1200		2	DMF	10	120	6	30	94.9	58.6	5.9	<1	5.9	f
16	16	1200	200	2	THF	10	120	6	30	94.0	54.8	3.5	1.6	7.1	f
17	16	1200	200	1.5	THF	10	120	6	30	88.5	54.8	3.7	<1	<1	f
18	16	1200	200	1.5	THF	10	120	6	10	95.6	68.7	3.8	1.8	7.7	f
19	16	1200	200	1.5	THF	10	120	6	5	86.8	57.4	3.6	0.6	3.5	f
20[l]	16	1200	200		THF	10	120	6	10	16.2		5.2	10.5	18.3	f
21	16	1200	200	1.5	THF	20	120	6	10	100	66.0	4.5	7.6	2.4	f
22	16	1200	200	1.5	THF	30	120	6	10	100	70.8	3.7	4.8	3.7	f
23	16	600	200	1.5	THF	30	120	6	10	100	79.3	3.1	3.0	3.5	f
24	16	300	200	1.5	THF	30	120	6	10	100	80.8	2.7	1.8	2.1	f
25	16	600	200	0.75	THF	30	120	6	10	100	67.0	4.2	6.6	3.9	f
26	16	600	200	2	THF	30	120	6	10	100	83.5	f	f	f	f
27	16	600	200	2	THF	30	80	6	10	100	73.5	3.0	3.0	7.4	f
28	16	600	200	2	THF	30	100	6	10	99.0	85.5	2.0	1.7	4.9	f
29	16	600	200	2	THF	30	110	6	10	100	84.5	2.2	1.9	2.5	f
30	16	300	200	2	THF	30	60	6	10	86.0	67.6	2.4	<1	4.8	f
31	16	600	200	2	THF	30	100	3	10	98.8	83.1	2.0	1.3	3.7	f
32	16	600	200	2	THF	30	100	1.5	10	87.9	76.9	3.2	<1	<1	f
33	16	600		2	DMF	30	100	1.5	10	100	72.6	8.4	<1	<1	f
34	16	600	200	2	DMF undist	30	100	1.5	10	100	70.2	6.4	1.5	<1	f
35	16	600	200	2	Et_2O	30	100	1.5	10	27.5	80.5	2.3	<1	<1	f
36	16	600	200	2	CH_2Cl_2	30	100	1.5	10	7.8	<1	<1	<1	<1	f
37	16	600	300	2	THF	30	100	1.5	10	86.1	75.8	3.1	<1	4	f
38	16	600	100	2	THF	30	100	1.5	10	87.7	79.0	2.2	<1	2.5	f
39	16	600	50	2	THF	30	100	1.5	10	93.0	76.2	2.6	1.3	8.6	f
40	16	600		2	THF	30	100	1.5	10	85.0	76.2	3.3	1.0	6.8	f
41	32	600	100	2	THF	30	100	1.5	10	97.8	74.4	2.9	2.2	5.0	f
42	24	600	100	2	THF	30	100	1.5	10	94.8	77.7	2.3	1.2	2.7	f
43	10	600	100	2	THF	30	100	1.5	10	71.9	76.0	1.7	<1	2.1	f
44	16	600	100[n]	2	THF	30	100	1.5	10	92.5	74.5	0.9	<1	1.9	f
45	16	600	100	2	THF	30	100	6	10	99.6	83.0	1.9	1.4	3.5	f
46	16	600	100	2	THF	30	100	6	5	99.9	86.5	1.4	1.8	2.7	f
47	16	900	100	2	THF	30	100	6	10	98.5	79.5	2.2	1.1	1.4	f
48	32	1200	200	2	THF	30	100	6	10	70.5	90.6	1.6	<1	1.4	f
49[k]	32	1200	200	2	THF	30	100	10	10	99.5	80.5	2.6	1.3	3.7	f
50[k]	16	600	100	2	THF	30	100	0.75	10	34.8	f	1.3	<1	2.5	f
51[h]	16	600		2	THF	30	100	6	10	97.9	84.0	1.1	1.2	5.1	f
52[h]	16	600		2	THF	30	100	1.5	10	51.6	65.0	2.9	<1	0.9	f
53[m]	18	600	100	2	THF	30	100	6	10	22.5	90.2	4.6	<1	<1	f

[a] Experimental conditions: $[Pd(Phen)_2][BF_4]_2$ = 4.5 mg, 7.0×10^{-3} mmol. tol = toluene. [b] Calculated with respect to the starting nitroarene. [c] Measured by GC. [d] Calculated with respect to reacted nitroarene. [e] Measured by ^1H NMR, employing 2,4-dinitrotoluene as an internal standard or by HPLC, with benzophenone as an internal standard. [f] Not determined. [g] Employing $[Pd(TMPhen)_2][BF_4]_2$ (TMPhen = 3,4,7,8-tetramethyl-1,10-phenanthroline) and TMPhen in place of the unsubstituted compounds. [h] Without Et_3N but in the presence of PhCOOH (mol ratio PhCOOH/Pd = 100). [i] DMP = 2,2-dimethoxypropane (0.5 mL). [j] In the presence of methanol, small amounts (1−6% selectivity) of methyl phenylcarbamate were also detected. [k] $[Pd(Phen)_2][BF_4]_2$ = 2.25 mg, 3.5×10^{-3} mmol. [l] The trimer of phenyl isocyanate was also formed (selectivity. 5%). [m] $Pd(dba)_2$ (7.0×10^{-3} mmol) was employed as catalyst in place of $[Pd(Phen)_2][BF_4]_2$. [n] Bu_3N was employed instead of Et_3N.

19) both in term of conversion and selectivity. However, the worse results obtained at 5 bar have turned out to result from an excessive CO consumption with respect to the available amount. When two reactions are compared, conducted with a lower nitrobenzene amount (entries 45, 46), the results obtained at 5 and 10 bar are almost indistinguishable, with the lower pressure affording an even slightly better performance. This point is very important, since 5−10 bar is a pressure that can be withstood even by glass autoclaves of the kind commonly employed to effect hydrogenation reactions and that are much more widespread in common organic synthesis laboratories than are metal autoclaves. Thus, the synthetic utility of the method is greatly enhanced. Use of 1 atm of CO (in a common flask) was attempted. However, for this specific reaction we also had to lower the reaction temperature to 60 °C to avoid boiling of the solvent and of the olefin, and at this low temperature and pressure the reaction did not proceed at all. The increase in conversion on lowering the pressure below 60 bar is surprising, since exactly the reverse occurs in the absence of the diene.[12] At the moment, the best explanation for

this observation is that the diene must coordinate to the palladium center and a competition exists between the diene and CO.

(g) Solvent amount: Increasing the solvent amount from 10 to 30 mL slightly increases rate and selectivity, but the effect is at the limits of the experimental error (entries 18, 21, 22).

(h) Temperature: The temperature at which the best selectivity is achieved is 100 °C, but temperatures up to 120 °C are also suitable. Higher temperatures must be avoided, since under these conditions the oxazine starts to decompose into the pyrrole. At 60 °C the conversion was not complete even if the amount of starting nitrobenzene was halved (entries 26−30).

(i) Ligand: All palladium−phenanthroline-based catalysts need an excess of ligand to be stable under the reaction conditions. Under the conditions reported, the best molar ratio Phen/Pd is 16 (entries 38, 41−43), but the amount is not crucial, provided it is not decreased too much. We note that, on the basis of our experience in using the same catalytic system for carbonylation reactions, the absolute concentration of the phenanthroline ligand is more relevant than the molar ratio with palladium. So the value for the phenanthroline concentration should be kept constant if the palladium amount or the volume are changed rather than the Phen/Pd ratio. Use of 3,4,7,8-tetramethyl-1,10-phenanthroline as ligand gave very similar results, with an even slightly lower conversion (entries 9, 10) and was not investigated further. In the absence of the diene, tetramethylphenanthroline affords better conversion than simple Phen.[10−12]

(j) Base: Apart from Et_3N, Bu_3N was also tried (entries 38, 44). The results were similar, with Et_3N giving a slightly better selectivity.

(k) In some cases, we purified the diene by distillation over sodium before use, but the results are essentially indistinguishable from those obtained with the unpurified diene.

(l) Addition of an internal drying agent (2,2-dimethoxypropane) to the reaction mixture also gave indistinguishable results, indicating that the source of the hydrogen giving rise to the aniline and urea byproducts is not adventitious water (entries 13, 14).

(m) Catalytic ratio: The selectivity increases if the catalytic ratio is lowered from 1200 to 600 but is essentially unaffected by further lowering of the nitrobenzene amount (entries 22−24). The effect is due to the high nitrobenzene concentration in the experiment run at the 1200:1 catalytic ratio. If the same ratio is obtained by halving the catalyst amount, with respect to the experiment with a 600:1 ratio, rather than doubling the nitrobenzene amount, the selectivities are comparable, even if the reaction slows down and a complete conversion is not achieved in 6 h. To reach the same conversion, the reaction time must be increased to 10 h, but the selectivity decreases at such a long reaction time, probably because the oxazine starts to decompose (see also later; entries 45, 47−49)

(n) When the reaction is carried out for 1.5 h instead of 6 h, the conversion is often very high, but the selectivity in oxazine is lower than for the corresponding reaction run for a longer time. This implies that either a relatively stable intermediate or a reversibly formed byproduct is initially obtained that later converts to the oxazine. We have failed to identify this intermediate, but it is apparently not nitrosobenzene, since it was not detected (by GC) in the reaction mixture after a 45 min reaction (entry 50).

TABLE 2. Synthesis of Oxazines from 2,3-Dimethylbutadiene and Different Nitroarenes[a]

nitroarene	$ArNO_2$ conv %[b,c]	$ArNH_2$ sel %[c,d]	oxazine sel %[d,e]
$PhNO_2$	99.6	2.1	83.0 (**2c**)
$PhNO_2$[f]	99.0	2.0	85.5 (**2c**)
4-$ClC_6H_4NO_2$	96.6	4.0	81.9 (**2b**)
3,4-$Cl_2C_6H_3NO_2$	92.0	7.6	80.5 (**2a**)
4-$MeC_6H_4NO_2$	90.8	4.6	91.4 (**2d**)
2-$MeC_6H_4NO_2$	91.3	2.9	83.3 (**2f**)
4-$MeOC_6H_4NO_2$	7.5	1.7	traces (**2e**)

[a] Experimental conditions: $[Pd(Phen)_2][BF_4]$ = 4.5 mg, 7.0×10^{-3} mmol, molar ratios Pd/Phen/Et_3N/$ArNO_2$ = 1:16:100:600, 2,3-dimethylbutadiene = 2 mL, in THF (30 mL) under CO (10 bar) at 100 °C for 6 h. The main byproducts are azo- and azoxyarenes and diarylureas, which were detected but not quantified by GC-MS. [b] Calculated with respect to the starting nitroarene. [c] Measured by GC. [d] Calculated with respect to reacted nitroarene. [e] Measured by ^1H NMR. [f] Et_3N/Pd = 200.

(o) When $Pd(dba)_2$ was employed as catalyst in place of $[Pd(Phen)_2][BF_4]_2$ ($PhNO_2$:Pd = 600, 6 h) the reaction stopped at a 22.5% conversion of nitrobenzene and formation of metallic palladium was clearly observed. The selectivity in oxazine remained high, 90.2% (entry 53). When $[Pd(Phen)_2][BF_4]_2$ is employed as catalyst, the initial palladium(II) complex is surely reduced to the zerovalent state during the reaction.[10] Thus, it appears that the BF_4^- anion has a role in stabilizing the so-formed complex, although at the moment is not clear how it operates.

Use of Different Nitroarenes. The scope and limitations of the reaction in eq 1 were examined by using a series of different nitroarenes, with 2,3-dimethylbutadiene as the reference diene, employing ^1H NMR spectroscopy to quantify the oxazine and gas chromatography for the analysis of the nitroarene and aniline. The results are reported in Table 2.

Both electron-withdrawing and mildly electron-donating substituents are tolerated, but with the strongly electron-donating *p*-methoxy group, no oxazine was obtained. Quite importantly, a moderate steric hindrance on the nitroarene (*o*-methyl group) is well tolerated. More severe steric hindrance has not been examined yet. In the case of the ruthenium-based system, use of *o*-nitrotoluene resulted in only trace amounts of the oxazine. The ruthenium catalyst also gave a much decreased selectivity even for *p*-nitrotoluene. There are two reasons for the poor results obtained with *p*-methoxynitrobenzene. The first is that the first step of the activation of a nitroarene by a transition metal complex is always an electron transfer from the metal to the nitroarene[10] and this transfer is more difficult in the presence of electron-donating substituents. The second is that under CO pressure a competition exists between the hetero-Diels−Alder reaction and a carbonylation reaction to afford diarylureas (or even carbamates, when the reaction is run in methanol). The hetero-Diels−Alder reaction is known to be disfavored by electron-donating substituents on the aryl ring,[13] whereas the reverse occurs for the carbonylation reaction.

TABLE 3. Synthesis of Oxazines from Different Dienes[a]

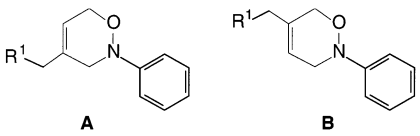
nitroarene	diene	catal/mg	THF/mL	$PhNO_2$/Pd mol ratio	diene/ mmol	*t*/h	$ArNO_2$ conv %[b,c]	$ArNH_2$ sel %[c, d]	oxazine sel %[d,e]
$PhNO_2$	isoprene	4.5	30	600	17.7	6	93.0	1.1	70.5 (**4A**) 11.8 (**4B**)
4-$ClC_6H_4NO_2$	1,4-diphenylbutadiene	1.5	10	300	5.9	10	75.5	8.8	*f*
$PhNO_2$	myrcene	4.5	30	600	17.7	6	94.1	2.0	42.4 (**5A**) 15.1 (**5B**)
4-$ClC_6H_4NO_2$	cyclohexadiene	1.5	10	600	5.9	6	88.1	15.0	traces

[a] Experimental conditions: catalyst $[Pd(Phen)_2][BF_4]_2$, molar ratios Pd/Phen/Et_3N/$ArNO_2$/diene = 1:16:100:600:2520, under CO (10 bar) at 100 °C for 6 h. 4-Chloroazo- and 4-chloroazoxybenzene were detected, but not quantified, by GC-MS. [b] Calculated with respect to the starting nitroarene. [c] Measured by GC. [d] Calculated with respect to reacted nitroarene. [e] Measured by ^1H NMR. [f] Not detected.

Use of Different Olefins. Apart from 2,3-dimethylbutadiene, isoprene, myrcene, 1,4-diphenylbutadiene, and 1,3-cyclohexadiene were also tested as diolefins (Table 3).

Use of 1,4-diphenylbutadiene gave low conversions and only trace amounts of hetero-Diels−Alder adduct, which is at least partly due to a reversibility in the formation of the hetero-Diels−Alder adduct at high temperature. We have previously observed this reversibility by heating the adduct obtained by reaction of nitrosobenzene with 1,4-diphenylbutadiene.[9] With cyclohexadiene a high conversion was observed, but again only trace amounts of the desired adduct were observed by GC-MS.

Two adducts (**A** and **B**) are possible from the reaction between nitrobenzene and isoprene or myrcene. The formation of one isomer with respect to the other in the reaction of nitrosoarenes with dienes has been previously investigated both from an experimental and a theoretical point of view.[2,14]



R^1 = H: **4A,B**
R^1 = $CH_2CH{=}C(CH_3)_2$: **5A,B**

Only isomer **A** has been said to be obtained by reaction of isoprene (R^1 = H) with either nitrosobenzene[15] or *p*-chloronitrosobenzene.[16] Under our conditions, reaction of nitrobenzene with isoprene gave indeed **4A** as the largely dominating isomer, as determined by comparison of the ^1H NMR spectrum with the one reported in the literature for this compound, but some low-intensity signals were also present, which could not be attributed to any known compound and which are close to the ones of **4A** and can be attributed to the previously undetected minor isomer **4B**. We thus reexamined the uncatalyzed hetero-Diels−Alder reaction of nitrosobenzene with 2,3-dimethylbutadiene and again observed the same pattern of signal as for the catalytic reaction. Separation of **4A** from **4B** could not be achieved by column chromatography, but a complete attribution of the corresponding NMR signals could be made by bidimensional NMR spectroscopy (see Experimental Section). The minor isomer is about 7% of the major one in both the products of the catalytic reaction and in the one employing nitrosobenzene as substrate. In the case of myrcene, both isomers **5A,B** have been reported[15] and were indeed observed even in our reaction, in a closer ratio with respect to the isoprene-derived compounds.[17] The lower yields in the myrcene-derived oxazine is due to the formation of relevant amounts of phellandrene, the corresponding furane, which was detected, although not quantified, by GC-MS. We have previously observed the formation of 2,3-dimethylfurane in the thermal decomposition of 2,3-dimethylbutadiene derived oxazines,[7] but this product is usually formed in very low yields and at higher temperatures. Why loss of aniline from **5** is so easy is not obvious at this stage.

We have previously mentioned that use of an atmospheric CO pressure with 2,3-dimethylbutadiene limited the temperature to 60 °C and no reaction was observed. Since myrcene has a relatively high boiling point, a reaction was also run at atmospheric CO pressure and 100 °C (DMF as solvent) by using this olefin and nitrobenzene as substrates. However, the reaction was very slow and even after 25 h only 33% nitrobenzene had been converted, with a 35% selectivity in oxazine.

Use of Excess Nitroarene. During this and previous works in this field, we have always operated in the presence of an excess of diolefin with respect to the nitroarene. However, in most cases the diene is more expensive than the nitroarene and the number of commercially available 1,3-dienes is much more limited. Thus, it would be important to be able to maximize the yield with respect to the diolefin. To this aim, we have performed a reaction employing a 2-fold molar amount of nitroarene with respect to the diene.[18] Since the excess diene is evaporated with the solvent, values for conversion and selectivity cannot be separately given, but the oxazine yield with respect to the starting 2,3-dimethylbutadiene was 90.5%. Note that the selectivity value is surely higher, since no dimers or oligomers of the diene

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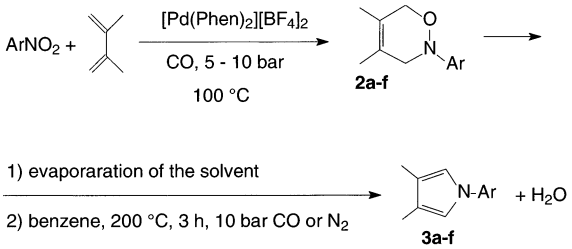
(17) A similar situation is observed when *p*-$ClC_6H_4NO_2$ is employed as substrate instead of $PhNO_2$. Preliminary data indicate that both isomers are again formed from isoprene (selectivity %: 66.5 (**A**); 6.7 (**B**)) and myrcene (selectivity %: 45.2 (**A**); 17.5 (**B**)). However, the corresponding compounds have not been isolated and fully characterized and evidence is based only on the ^1H NMR spectra of the crude mixtures and their similarity with the ones of the nitrobenzene-derived products.

(18) $PhNO_2$, 1.027 g, 8.342 mmol; 2,3-dimethylbutadiene, 0.476 mL, 348.8 mg, 4.218 mmol; $[Pd(Phen)_2][BF_4]_2$, 4.5 mg, 7.03×10^{-3} mmol; mol ratios 1:16:100:600 Pd/Phen/Et_3N/butadiene; 100 °C; P_{CO} = 10 bar; in 30 mL of THF for 6 h.

could be detected. Conversion of the nitroarene was 85.8%, and the amount reacted in excess with respect to the diene was transformed mainly into azoxybenzene. This result is very interesting, since it opens the way to the use of very expensive or difficult to synthesize dienes. Such a development would be inconceivable for the ruthenium-catalyzed reaction, where a large excess of diene is necessary for the reaction to proceed.

Synthesis of *N*-Arylpyrroles. In our previous paper,[9] we reported that when the catalytic reaction between a nitroarene and 2,3-dimethylbutadiene in the presence of $Ru_3(CO)_{12}$/Ph-BIAN was performed at 200 °C, the initially formed oxazine **2** was transformed into the corresponding *N*-arylpyrrole **3** and in some cases this transformation was almost quantitative. The formation of pyrroles by decomposition of hetero-Diels−Alder adducts is not unprecedented.[1f,2a,19] When we performed a reaction under the same conditions of the experiments in Table 1, but at 200 °C, extensive oligomerization of the diene occurred. Palladium−phenanthroline complexes containing a coordinated alkyl group are known to be active catalysts for olefin polymerization.[20] Apparently, at 200 °C a species active in this reaction can be formed under our reaction conditions. It should be stressed that at 100 °C, on the other hand, only trace amounts of a dimer of dimethylbutadiene and no higher oligomer can be detected by GC-MS in the crude reaction mixture. The best procedure we found to obtain the pyrrole consists of a two steps−one pot protocol (eq 2).



(2)

The reaction was first performed at 100 °C similarly to what is reported in Table 1; then the autoclave was vented and the solution evaporated in vacuo in the same glass liner in which the reaction is performed. At this point toluene was added as solvent and the reaction mixture was placed again in the autoclave and heated at 200 °C for 3 h. Pressure has to be applied even in this second stage to avoid boiling of the solvent, but it is indifferent to apply a CO or a dinitrogen pressure. Since the excess diene has been eliminated in the evaporation step, no oligomers are formed. The results of a series of reactions performed by this protocol are reported in Table 4.

Contrary to ruthenium-catalyzed reactions, pyrrole selectivities are lower than the corresponding oxazine ones, although it must be noted that the absolute yields reported in this paper are anyway higher than the previously reported ones. We have previously observed that the ruthenium/Ar-BIAN system also catalyzes the transformation of the oxazine into the pyrrole. The present palladium system, however, does not appear to do the same. In an attempt to increase the yield of the transformation from **2** to **3**, we have added $Ru_3(CO)_{12}$ and Ph-BIAN to the reaction mixture either since the beginning or after the first step and at different CO pressures, but worse results were obtained in any case. The presence of the palladium−phenanthroline system appears to interfere with the ruthenium-catalyzed reaction.

TABLE 4. Synthesis of *N*-Arylpyrroles[a]

nitroarene	$ArNO_2$ conv %[b,c]	$ArNH_2$ sel %[c,d]	pyrrole (**3**) sel %[d,e]
$PhNO_2$	100	14.1	66.0 (**3c**)
4-$ClC_6H_4NO_2$	92.9	12.2	55.6 (**3b**)
4-$ClC_6H_4NO_2$[f]	90.2	13.1	53.2 (**3b**)
3,4-$Cl_2C_6H_3NO_2$	98.3	21.2	43.8 (**3a**)
4-$MeC_6H_4NO_2$	95.3	10.0	48.4 (**3d**)
2-$MeC_6H_4NO_2$	96.9	2.7	51.5 (**3f**)

[a] Experimental conditions: $[Pd(Phen)_2][BF_4]_2$ = 4.5 mg, 7.0 × 10^{-3} mmol, molar ratios Pd/Phen/Et_3N/$ArNO_2$ = 1:16:100:600, 2,3-dimethylbutadiene = 1 mL, in THF (30 mL) under CO (10 bar) at 100 °C for 6 h, followed by evaporation of the solvent and then 200 °C for 3 h in benzene (30 mL) under either CO or N_2 (10 bar). The main byproducts are azo- and azoxyarenes and diarylureas, which were detected but not quantified by GC-MS. [b] Calculated with respect to the starting nitroarene. [c] Measured by GC. [d] Calculated with respect to reacted nitroarene. [e] Measured by ^1H NMR. [f] 2,3-Dimethylbutadiene = 2 mL.

Conclusions

In this paper we have reported a new catalytic system for the synthesis of hetero-Diels−Alder adducts (oxazines) and *N*-arylpyrroles from nitroarenes, unactivated diolefins, and CO. Selectivities are generally good, and it should also been considered that alternative synthetic approaches usually require several steps. In the case of hetero-Diels−Alder adducts, the traditional synthesis requires the isolation of a nitrosoarene, whose preparation often affords lower yields than the global reaction reported here and is much more experimentally demanding. Moreover, even the anilines employed in most syntheses are normally prepared by reduction of the corresponding nitroarenes, so that a further step is avoided. Last but not least, the present synthesis does not produce salt byproducts, a feature that is very important in the light of possible industrial applications.

In this work we employed commercially available dienes, but it is useful to recall that much progress has recently been done in the synthesis of a range of 2,3-disubstituted-1,3-dienes by the metathesis reactions of mono- or disubstituted alkynes with ethylene, catalyzed by the Grubbs' catalyst, $RuCl_2(PCy_3)_2(=CHPh)$, or by related complexes.[21]

At the moment, we have not yet performed a mechanistic study of this reaction. However, the fact that no allylic amine is formed and the similar ratio **4A**/**4B** found for the catalytic reaction of nitrobenzene with 2,3-

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dimethylbutadiene and for the uncatalyzed reaction of the same diene with nitrosobenzene strongly point toward a mechanistic picture in which nitrobenzene is reduced to nitrosobenzene and the latter then reacts with the diene in an off-metal reaction. Dehydration of the oxazine to pyrrole also appears to be a purely organic reaction under the present conditions.

With respect to the previously reported ruthenium-catalyzed reaction: (a) The selectivity in oxazine has been improved from 40−60% to 80−90%. The selectivity in pyrrole has also been improved, although not to such a large extent. (b) The metal loading has been decreased from 3% to 0.08%. (c) Pressure has been lowered from 40 to 5 bar, thus allowing for the use of a glass autoclave. (d) A moderate steric hindrance on the nitroarene is now tolerated, whereas it was not in the case of the ruthenium catalyzed reaction. Substrates with a larger steric hindrance have not been tested yet. (e) A lower molar excess of diene is required with respect to the nitroarene, and equally good results are obtained if the situation is reversed by operating with an excess of nitroarene. (f) The only aspect in which no progress was made is the use of 1,4-disubstituted dienes, which are still unsuitable substrates for this reaction.

Experimental Section

General Procedure. For the general procedure see ref 9. In addition, $[Pd(Phen)_2][BF_4]_2$ was prepared by either of two methods reported in the literature.[22]

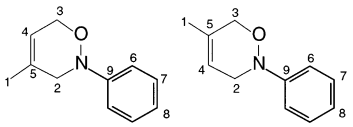
Catalytic Reactions. Catalytic reactions were performed as previously described.[7] Reagents amounts are given in the tables. Those reactions that were repeated showed nitroarene conversion and selectivities to be reproducible within ±1% and ±2%, respectively. When both HPLC and ^{1}H NMR were employed to quantify the oxazine, the two independently obtained values always agreed within ±2%.

Identification of the Organic Products of Catalysis. The byproducts azo- and azoxybenzene, diphenylurea, and all anilines are commercial products and were identified by comparison of their CG or HPLC chromatograms and GC-MS spectra with those of authentic samples. 1,3,5-Triphenyl-[1,3,5]-triazinan-2,4,6-trione[23] and all oxazines and pyrroles prepared in this work have been previously reported in the literature (**2a**,[9] **2b**,[3] **2c**,[24] **2d**,[25] **2e**,[18] **2f**,[25] **3a**,[9] **3b**,[26,27] **3c**,[26,27] **3d**,[26,27] **3e**,[26,27] **3f**,[28] **4A**,[15] **5A,B**[15]), with the exception of the minor isomer **4B**. Some additional spectroscopic data can be found in ref 9, together with some hints about products separation. In the following, the ^{1}H NMR spectrum is anyway reported for some of these compounds when these data were not available in the literature or the present spectrum is of significantly better quality than the published one.

2f: ^{1}H NMR ($CDCl_3$, 298 K) δ, ppm, 1.67 (s, 3 H), 1.75 (s, 3 H), 2.36 (s, 3H), 3.54 (s, 2 H), 4.32 (s, 2 H), 7.0−7.5 (m, 4 H).

3f: ^{1}H NMR ($CDCl_3$, 298 K) δ, ppm, 2.19 (s, 6 H), 2.35 (s, 3H), 6.61 (s, 2 H), 7.1−7.42 (m, 4 H).

4A,B: Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.11; H, 7.59; N, 7.67. The attribution of the NMR signals of the two inseparable isomers has been made by a two-dimensional ^{13}C−^{1}H NMR spectrum (HMQC with BIRD). The carbon atoms are numbered as in the following scheme. The signals due to the aryl groups of the two isomers in both the ^{1}H and ^{13}C spectra overlap completely. The signal due to the C^5 carbon of **4B** was too weak to be confidently assigned.



4A **4B**

4A: ^{1}H NMR ($CDCl_3$, 298 K) δ, ppm, 1.83 (s, 3 H, CH_3), 3.71 (s, 2 H, −CH_2N−), 4.50 (pss, br, 2 H, −CH_2O−), 5.65 (pss br, 1 H, C=C−*H*), 7.02 (t, J = 7.3 Hz, 1 H, *H-para*), 7.15 (d, J = 8.6 Hz, 2 H, *H-ortho*), 7.33 (dd, J_1 = 8.6, J_2 = 7.3 Hz, 2 H, *H-meta*); ^{13}C NMR ($CDCl_3$, 298 K) δ, ppm, 20.6 (C^1), 56.5 (C^2), 68.9 (C^3), 120.2 (C^4), 131.1 (C^5), 116.2 (C^6), 129.2 (C^7), 122.8 (C^8), 150.8 (C^9).

4B: ^{1}H NMR ($CDCl_3$, 298 K) δ, ppm, 1.75 (s, 3 H, CH_3), 3.80 (pss br, 2 H, −CH_2N−), 4.40 (s, 2 H, −CH_2O−), 5.65 (pss, br, 1 H, C=C−*H*), 7.02 (t, J = 7.3 Hz, 1 H, *H-para*), 7.15 (d, J = 8.6 Hz, 2 H, *H-ortho*), 7.33 (dd, J_1 = 8.6, J_2 = 7.3 Hz, 2 H, *H-meta*); ^{13}C NMR ($CDCl_3$, 298 K) δ, ppm, 18.5 (C^1), 52.4 (C^2), 72.5 (C^3), 117.5 (C^4), 116.2 (C^6), 129.2 (C^7), 122.8 (C^8), 150.8 (C^9).

5A: ^{1}H NMR ($CDCl_3$, 298 K) δ, ppm, 1.64 (d, J = 1.4 Hz, 3 H), 1.72 (s, 3H), 2.0−2.3 (m, 4H), 3.75 (s, 2H), 4.53 (d, J = 1.8 Hz, 2H), 5.14 (m, 1H), 5.67 (s br, 1H), 6.9−7.4 (m, 5H).

5B: ^{1}H NMR ($CDCl_3$, 298 K) δ, ppm, 1.64 (d, J = 1.4 Hz, 3 H), 1.72 (s, 3H), 2.0−2.3 (m, 4H), 3.84 (s br, 2H), 4.45 (s, 2H), 5.14 (m, 1H), 5.67 (s br, 1H), 6.9−7.4 (m, 5H).

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