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Synthesis of 4,5-Dihydroisoxazoles by Condensation of Primary Nitro Compounds with Alkenes by Using a Copper/Base Catalytic System

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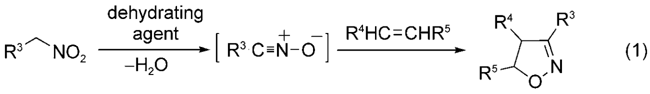
Abstract: A new procedure for the synthesis of 4.5-dihydroisoxazoles by condensation of primary nitro compounds with olefins by using a copper/base catalytic system is described. The catalytic effect of copper(II) salts is evidenced by comparison of the reaction rates. Thus, activated nitro compounds react faster than with organic catalysis by tertiary amines, whereas nitroalkanes, unable to condense with dipolarophiles in the presence of the base alone, undergo the reaction on addition of a copper(II) catalyst. The observed occurrence of induction periods in most reactions is ascribed to an equilibrium preceding the rate-determining step, and gives a hint as to the proposed reaction mechanism. The results indicate that this method might be of practical and general utility for synthetic practice.

Keywords: catalysis · copper · cycloaddition · dihydroisoxazoles · nitro compounds

Introduction

1,3-Dipolar cycloadditions are a powerful method for assembling heterocyclic rings with high regio- and stereocontrol.[1] Primary nitro compounds are extensively used as starting materials for the synthesis of 4,5-dihydroisoxazoles via intermediate nitrile oxides;[2] on treatment with various reagents, such as aryl isocyanates,[3–9] inorganic[10,11] and organic[12–15] chlorides or organic anhydrides,[16,17] in the presence of a dipolarophile and often a base, the isoxazole derivatives are produced besides the discarded material derived from the reagent employed [Eq. (1)].[18] From the same nitro compounds, 4,5-dihydroisoxazoles can also be prepared via alkyl[19,20] or silyl[21,22] nitronates by cycloaddition and subsequent elimination of alcohol or silanol, respectively.

On the other hand, dehydration of primary nitro compounds with the production of isoxazole derivatives has also been observed as a side process during the radical addition of nitro compounds to alkenes caused by Mn^{III} salts. "Activated" nitro compounds (α-nitroketones, nitroacetamides[23] or nitroacetates),[24,25] on treatment with an alkene and Mn^{III}, according to the reported rationalisation, follow two parallel reaction paths: the intermediate Mn^{III} nitronate reacts with the alkene to give either the expected radical addition or the dehydrated cycloadduct. In the first reaction, Mn^{III} behaves as a monoelectronic oxidant, in the other, as a dehydrating agent.[25]



(1)

We have recently reported a convenient procedure for the condensation of primary nitro compounds with alkynes (to isoxazoles) or alkenes (to isoxazolines) under base catalysis.[26–29] This method avoids the use of a dehydrating agent, but requires a catalytic amount of a suitable organic base instead, such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1-methylimidazole. This process appears to occur without the formation of intermediate nitrile oxides and it can be regarded as a condensation process [Eq. (2), EWG = electron-withdrawing group], in which cycloaddition of the intermediate dipole (nitronate) precedes water release. The use of a catalytic organic base instead of stoichiometric polluting

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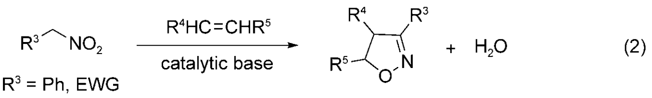
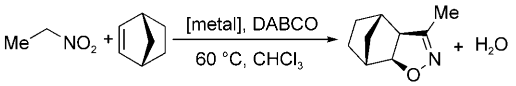
reagents makes this procedure more benign towards the environment and represents another step forward towards atom economy.[30]



However, the reaction is applicable to "activated" nitro compounds (nitroacetate derivatives, α-nitroketones or phenylnitromethane) but fails with nitroalkanes.[26–29] Thus, on treatment of norbornene (0.3 M in $CHCl_3$) with nitroethane and DABCO (molar ratio 1:2.5:0.5) at 60°C for 72 h, no condensation was observed by ^{1}H NMR spectroscopic analysis (Table 1, entry 1). In this paper, we describe a new method leading to substituted 4,5-dihydroisoxazoles based on a copper/base catalytic system. This catalytic system is able to catalyse the condensation of a broad range of nitroalkanes with different functionalised dipolarophiles.

Table 1. Catalytic activities of selected metal salts or complexes in the reaction of norbornene with nitroethane.[a]



Entry[a]	Metal	t [h]	Conv. [%][b]
1	none	72	0
2[c]	$Cu(OAc)_2$	72	0
3	$[Ni(PPh_3)_4]$	72	trace
4	$Cu(OAc)_2$	20 (40)	45 (55)
5	$Cu(OTf)_2$	20	52
6	$Cu(CF_3CO_2)_2$	20 (40)	47 (56)
7	$Pd(OAc)_2$	20	10

[a] Reactions were carried out by using nitroethane/norbornene/DABCO/[metal] in a 2.5:1:0.5:0.05 molar ratio. See the Experimental Section for details. [b] Conversions are based on ^{1}H NMR spectroscopic analysis. [c] No base was used.

Abstract in Italian: *E' descritta una nuova procedura sintetica per la preparazione di 4,5-diidroisossazoli attraverso la condensazione di nitrocomposti primari con olefine. Il metodo si basa sull'utilizzo di un sistema catalitico costituito da rame(II) accompagnato da una base organica. L'effetto catalitico dei sali di rame(II) è stato evidenziato confrontando le velocità di conversione per alcune reazioni modello. Infatti, i nitrocomposti attivati reagiscono più velocemente che non in sola presenza di ammine terziarie mentre i nitroalcani, i quali non condensano con i dipolarofili in presenza della sola base, reagiscono per aggiunta di rame(II). Queste reazioni di condensazione hanno mostrato la presenza di tempi d'induzione variabili in funzione dei substrati e della tipologia di rame utilizzata. Il tempo d'induzione è imputabile a pre-equilibri che precedono lo stadio lento della reazione e sono in accordo con il meccanismo di reazione proposto. I risultati ottenuti mostrano che questo metodo è pratico e di utilità generale per la sintesi organica.*

Results and Discussion

The mentioned reaction between norbornene and nitroethane was assumed as a model: in view the above previous results, various metal salts or complexes were added to this mixture (0.05 molar ratio with respect to the dipolarophile) and the eventual conversion into the condensation product verified after 20 h. No conversion was observed upon addition of the following salts or complexes: AgOAc, AgOTf, $Co(OAc)_2$, $Eu(OAc)_3$, $Fe(OTs)_3$, $FeCl_2$, $La(OTf)_3$, $MgBr_2$, $Ni(OAc)_2$, $[Pt(PPh_3)_4]$, $[PtCl_6H_2]$, $Rh(OAc)_2$, bis(tricyclohexylphosphine)benzylidine ruthenium(IV) chloride, $Sc(OTf)_3$ and $Yb(OTf)_3$. Yet encouragingly, results were obtained by addition of a nickel complex or salts of copper and palladium (Table 1). Among them, it was found that only copper salts gave significant conversions without counter-anion effects (Table 1, entries 4–6).

The reaction conducted with copper(II) acetate in the absence of base showed no conversion (Table 1, entry 2). A trace of product was observed with the $[Ni(PPh_3)_4]$ complex, after 72 h, along with traces of other unidentified compounds (Table 1, entry 3).

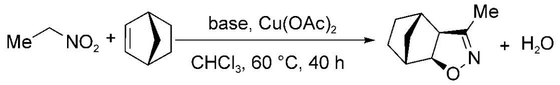
As concerns the use of palladium complex, a further experiment was needed to possibly identify other products. In fact Trost et al. reported a Pd^0-catalysed cycloalkylation of nitro compounds to isoxazoline-2-oxide.[31] The reaction with palladium(II) acetate (Table 1, entry 7) was then repeated on a larger scale and deeply examined, but only the 4,5-dihydroisoxazole cycloadduct was found.[32] It turned out that copper(II) salts are excellent catalysts for these reactions. Thus, the sluggish reaction between ethyl nitroacetate and styrene with DABCO under the reported conditions gave a 50 % conversion of dipolarophile into the corresponding cycloadduct after 40 h, with an induction period of 16–18 h. However, on addition of 5 % copper(II) acetate, the conversion reaches 60 % after 8 h (see further discussions).

The effect is even more dramatic in the reaction of nitropentane with methyl acrylate, which gives no cycloadduct after 40 h in the presence of *N*-methylpiperidine (NMP), but affords 100 % cycloadduct after the same period if 5 % of copper(II) acetate is added to the mixture. Preliminary results have been published before the present work was complete.[33]

Assuming as a model the reaction of norbornene and nitroethane mentioned above, a screening of bases was carried out, in which DABCO was replaced by various bases, in the presence of 0.05 equivalents of copper(II) acetate: the conversion of dipolarophile into product after 40 h is reported in Table 2.

The reaction in general fails with heteroaromatic bases (Table 2, entries 1–3 and 5) with the sole exception of 1-methylimidazole (entry 4). Low conversions are observed with secondary amines, such as diethylamine and piperidine

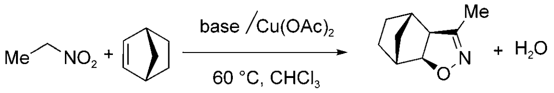
Table 2. Catalytic activities of various bases in the reaction of norbornene with nitroethane promoted by copper(II) acetate.



Entry[a]	Base	pK_{BH^+}[b]	Conv. [%][c]
1	2,2′-bipyridine	4.40	0
2	pyridine	5.23	0
3	2-DMAP[d]	7.00	0
4	1-methylimidazole	7.01	44 (33)
5	imidazole	7.18	0
6	4-methylmorpholine	7.41	27 (19)
7	$Me_2NCH_2NMe_2$	7.67	37 (19)
8	4-(1-pyridinyl)morpholine	7.97	46 (43)
9	1,4-dimethylpiperazine	8.61	82 (68)
10	1,2-dimethylimidazole	8.86	59 (49)
11	$Me_2NCH_2CH_2NMe_2$	8.86	26 (22)
12	4-DMAP[e]	9.52	54 (48)
13	4-(1-pyrrolidinyl)pyridine	9.58	58 (52)
14	*n*BuMe$_2$N	9.83	87 (64)
15	$Me_2N(CH_2)_3NMe_2$	9.88	92 (60)
16	*i*PrMe$_2$N	9.91	74 (64)
17	NMP	9.91	95 (94)
18	1-ethylpiperidine	9.99	100 (84)
19	Et_3N	10.62	78 (62)
20	1-methylpyrrolidine	10.62	85 (82)
21	cyclohexyldimethylamine	10.72	71 (53)
22	Et_2NH	10.76	32 (30)
23	quinuclidine	10.87	76 (66)
24	*i*Pr$_2$EtN	10.98	46 (33)
25	piperidine	11.24	31 (31)
26	tropane	11.56	– (90)[f]
27	proton sponge	12.40	70 (52)
28	DBU[g]	13.27	– (84)[f]
29	MTBD[h]	14.37	– (83)[f]
30	TBD[i]	14.47	74 (71)

[a] Reactions were carried out by using nitroethane/norbornene/base/Cu(OAc)$_2$ in a 2.5:1.0:0.5:0.05 molar ratio. See the Experimental Section for more details. [b] Calculated by using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (1994–2007 ACD/Labs). [c] The reported conversions are based on ^{1}H NMR spectroscopic analysis. In brackets the conversion observed after 20 h. [d] 2-Dimethylaminopyridine. [e] 4-Dimethylaminopyridine. [f] Excess nitroethane was completely deomposed after 20 h, therefore the conversion could no longer increase. [g] 1,8-Diazabicyclo[5.4.1]undec-7-ene. [h] 7-Methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene. [i] 1,5,7-Triazabicyclo[4.4.0]dec-5-ene.

Table 3. Optimisation of reaction conditions: base/metal molar ratio and concentration of dipolarophile.[a]



Entry	Base	Base/Cu(OAc)$_2$	Norbornene [mM]	Conv. [%][b]
1	NMP	1:0.05	304	100
2	NMP	0.5:0.05	304	94 (92)
3	NMP	0.2:0.05	304	65
4	NMP	0.1:0.05	304	56
5	NMP	0.05:0.05	304	44
6	NMP	1:0.05	608	100 (100)
7	NMP	0.5:0.05	608	98 (92)
8	NMP	0.2:0.05	608	72 (68)
9	NMP	0.1:0.05	608	59 (56)
10	NMP	0.05:0.05	608	41 (30)
11	DBU	1:0.05	304	82 (78)
12	DBU	0.5:0.05	304	83 (84)
13	DBU	0.2:0.05	304	76 (70)
14	DBU	0.1:0.05	304	66 (58)
15	DBU	0.05 0.05	304	51 (42)

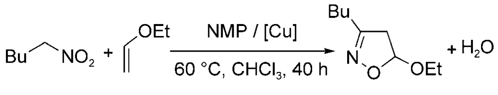
[a] Reactions were carried out by using nitroethane/norbornene in a 2.5:1.0 molar ratio. See the Experimental Section for more details. [b] The reported conversions are based on ^{1}H NMR spectroscopic analysis.

(entries 22 and 25). No definite trend is apparent with other bases, as the results are not related to their strength, to H-bonding ability or to the presence of more than one basic centre.[28] Since very strong bases cause faster decomposition of nitroethane, NMP (entry 17) has been chosen for further experiments. This base, tetramethylpropanediamine and 1-ethylpiperidine (entries 15 and 18, respectively) represent the right balance in terms of high conversion and low decomposition of nitroethane.

The effect of the base/copper ratio and of reagent concentrations on the above model reaction was investigated next (Table 3). The conversion observed after 40 h (0.3 M norbornene (1 equiv) in $CHCl_3$; + nitroethane, 2.5 equiv + copper(II) acetate, 0.05 equiv) decreases as the equivalents of NMP are reduced from one equivalent (entry 1, 100 %) to 0.5 (entry 2, 94 %) and then to 0.05 equivalents (entry 5, 44 %), without significant change when the solution is more concentrated (entries 6–10, 0.6 M). A similar trend is observed with a stronger base, such as DBU (entries 11–15). However, at low base concentrations, decomposition of nitroethane was not severe; therefore, prolonged reaction times ensure complete conversion. These results indicate that the best molar ratio is in the range of 0.5–0.2 base/0.05 copper.

To establish the influence of the copper source on the process, a different dipolarophile/dipole pair was chosen. A less-reactive dipolarophile, such as ethyl vinyl ether, and a more-stable nitroalkane, such as nitropentane (see later), was utilised to fine-tune the reaction conditions. The percentage conversion of dipolarophile after established intervals was evaluated in the presence of different copper sources (Table 4).

Table 4. Influence of the copper source on the condensation of nitropentane with ethyl vinyl ether. Conversion into product by using an excess of nitropentane.[a]



Entry	[Cu]	Conv. [%][b]	Entry	[Cu]	Conv. [%][b]
1	Cu(OAc)$_2$	62 (52)	6	Cu(OTf)$_2$	53 (48)
2	CuOAc	71 (51)			
3	Cu$^{0[c]}$	75 (55)	7	CuO	0
4	Cu$^{0[d]}$	63 (62)	8	$CuCl_2$	58 (55)
5	CuI	48 (45)	9	Cu(CF$_3$CO)$_2$	56 (50)

[a] Reactions were carried out by using nitropentane/ethyl vinyl ether/NMP/[Cu] in a 2.5:1.0:0.5:0.05 molar ratio. See the Experimental Section for more details. [b] Conversions are based on ^{1}H NMR spectroscopic analysis. In brackets: conversion after 20 h. [c] Powder. [d] Wire.

The oxidation state has apparently no influence on the reaction course (CuO is unable to dissolve in the reaction medium). This is ascribed to the easy oxidation of the metal or of Cu^{I} to Cu^{II} by atmospheric oxygen in the presence of both the base and nitro compound. In fact, no significant oxidation is observed in the presence of only one reagent: they are both required, the nitro compound providing the acidity and the amine bringing the salt in solution. An experiment with both the reagents and copper powder under an argon atmosphere showed a negligible reaction progress. The anion moderately affects the conversion attained after 40 h; however, in early reaction stages, a significant influence on the induction period has been observed (see further discussions, Figure 2).

The catalytic effect of copper(II) on the condensation of primary nitro compounds with dipolarophiles has been evidenced by plotting the observed percentage conversion of dipolarophile into product versus time for two model reactions: 1) ethyl nitroacetate (**1e**) with styrene (**3**) (Figure 1) and 2) nitropentane (**1c**) with methyl acrylate (**6**) (Figure 2).

The graphs refer to different catalytic systems, affecting both the reaction rate (slope) and the induction period. Thus, Figure 1 shows the progress of the reaction of ethyl nitroacetate and styrene with four catalytic systems: 1) DABCO/copper powder, 2) DABCO/copper(II) triflate, 3) DABCO/copper(II) acetate and 4) DABCO alone (Figure 1a–d, respectively). Initial reaction rates decrease in the order listed above and are attained after induction periods of a few minutes for (a), about 0.5 h for (b) and (c) and 24 h for (d). These are better appreciated in the bottom graph of Figure 1, in which the early reaction stages are shown on an enlarged time scale.

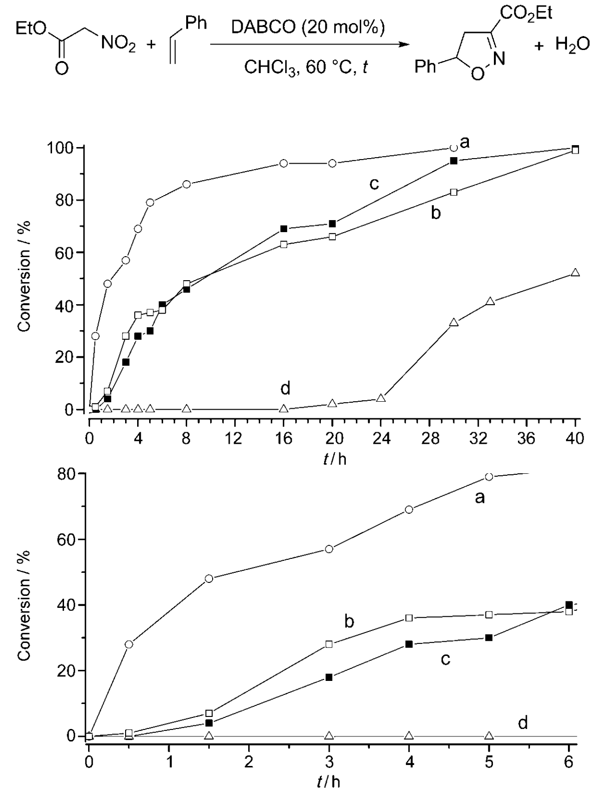


Figure 1. Conversion plots versus time for the condensation of ethyl nitroacetate (**1e**) and styrene (**3**). At the top: conversion plots in the absence of copper (d, △), in presence of 5 mol % of copper (a, ○), copper(II) triflate (b, □) and copper(II) acetate (c, ■). The markers indicate the times at which the samples were taken and the lines merely serve as a guide to the eye. At the bottom: enlarged early stages. See the Experimental Section for details.

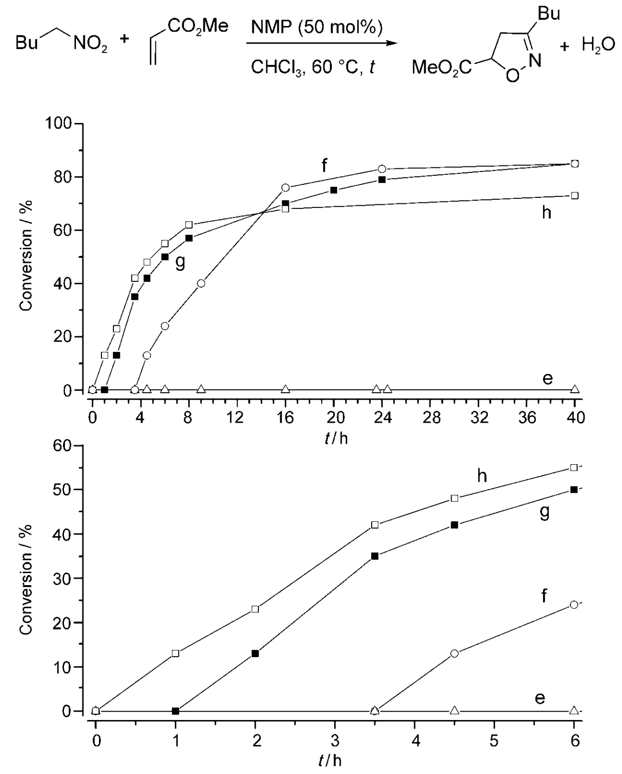
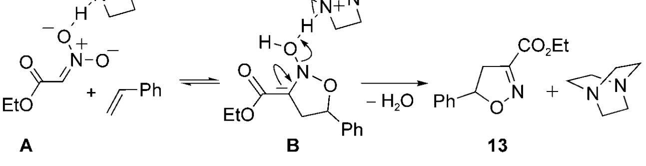


Figure 2. Conversion plots versus time for the condensation of nitropentane (**1c**) and methyl acrylate (**6**). At the top: conversion plots in absence of copper (e, △), in presence of 5 mol % of copper(II) triflate (h, □), copper(II) acetate (g, ■) and copper (f, ○). The markers indicate the times at which samples were taken and the lines merely serve as a guide to the eye. At the bottom: enlarged early stages. See the Experimental Section for details.

The long induction period observed in the absence of copper can be explained by the reaction sequence reported in Scheme 1.[29] Since formation of the H-bonded salt **A** is very fast, the induction time observed in this reaction (Figure 1) appears to be required for the intermediate cyclo-



Scheme 1. Mechanism for the DABCO-catalysed condensation of ethyl nitroacetate and styrene.

adduct **B** to reach a steady concentration before the rate-determining dehydration step to **13** attains its maximum rate.

When Cu^{II} is present in the catalytic system, we might assume an analogous reaction sequence with copper(II) coordination replacing the H-bond. The presence of Cu^{II} in the catalytic system causes an increase of the maximum reaction rate and a dramatic drop of the induction period. The lack of induction time observed when Cu^0 is employed (only a few minutes are needed for the metal to get oxidised, Figure 1a) suggests that copper(II) chelate salts of ethyl nitroacetate are the reacting species.[34] The reaction rate (slope) is greatly enhanced (almost 50% conversion in 90 min): cycloaddition might become the rate-determining step without significant equilibration, water release being faster. When copper is supplied as the triflate (Figure 1b) or acetate (Figure 1c), the observed induction time (about 1 h in both cases) is possibly required for the anions to attain equilibrium in Cu^{II} coordination, thus affecting both the cycloaddition step (induction time) and the loss of water (reaction rate). Owing to the higher stability of the Cu^{II} chelate salt of ethyl nitroacetate relative to triflate and acetate, the difference between these salts is barely detected (Figure 1b,c).

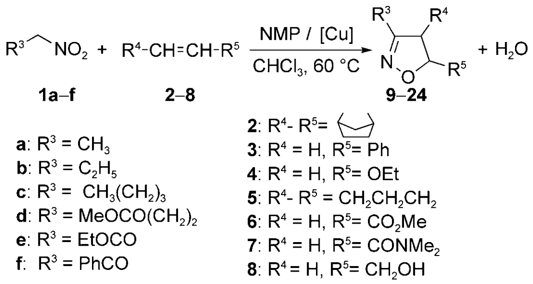
As already pointed out, nitroalkanes do not condense with dipolarophiles in the presence of the base alone. Thus, the model reaction of 1-nitropentane with methyl acrylate, in the presence of NMP or of DABCO does not give any cycloadduct after 40 h (Figure 2e). If copper powder (0.05 equiv) is added to the reaction mixture, the reaction begins after about 4 h, as shown by the plot of the percentage conversion versus time (Figure 2f). The induction time might reasonably be ascribed to the oxidation of Cu^0, which is much slower with nitropentane than with nitroacetate, due to the difference in acid strength and in salt stability. However, the same reaction, on addition of 0.05 equivalents of nitroacetate (**1e**) to 1-nitropentane (**1c**, 1 equiv) showed no significant change in the induction period.

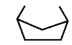
The other graphs, referred to different copper(II) salts, show induction times varying with the anion and reasonably depending on the equilibria preceding the rate-determining step. Moreover, Cu^{II} might be coordinated to the dipolarophile too. In fact, poorer results are obtained from reactions of nitropentane with sluggish dipolarophiles that are unable to coordinate with Cu^{II} (Table 5, entries 4, 7, and 11).

The catalytic effect of Cu^{II} on additions of nitronates[35,36] or of silyl nitronates[37] is well documented. In the present condensation, there is evidence that coordination with Cu^{II} catalyses the cycloaddition step and the loss of water as well.[38]

Synthetic applications: With optimised conditions in hand, the substrate scope and limits of the reaction were explored by using a broad spectrum of alkenes with different structures and electronic demands as well as various nitro compounds (Table 5).

Table 5. Reactions of nitro compounds **1a–f** with various alkenes **2–8** in the presence of a copper/base catalytic system.[a]

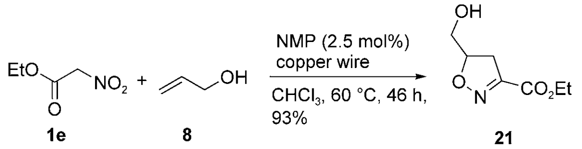


Entry	R^3	R^4	R^5	Product	Yield [%][b]
1	Me			**9**	90
2	*n*Bu			**10**	99
3	EtOCO			**11**	99
4[c]	*n*Bu	H	Ph	**12**	61
5	EtOCO	H	Ph	**13**	97
6[c]	$MeO_2C(CH_2)_2$	H	Ph	**14**	74
7[c]	*n*Bu	$-CH_2CH_2CH_2-$		**15**	17, 27[d]
8	Me	H	CO_2Me	**16**	89
9	Et	H	CO_2Me	**17**	87
10	*n*Bu	H	CO_2Me	**18**	93
11	*n*Bu	H	OEt	**19**	62
12	*n*Bu	H	$CONMe_2$	**20**	90
13	EtOCO	H	CH_2OH	**21**	95
14[c]	*n*Bu	H	CH_2OH	**22**	80
15	PhCO	H	Ph	**23**	95
16	PhCO	H	$CONMe_2$	**24**	99

[a] Reaction conditions: nitro compound (1.06 mmol), alkene (0.424 mmol), NMP (0.084–0.212 mmol), copper or copper(II) acetate (5 mol% with respect to the alkene), $CHCl_3$ (1.4 mL). See the Experimental Section for details. [b] Isolated yield, determined on the analytically pure product and based on the dipolarophile. [c] Copper or copper(II) acetate, 10 mol% with respect to the alkene. [d] The reaction was carried out at 80 °C.

With a reactive dipolarophile, such as norbornene, the yields of isoxazolines from activated and non-activated nitro compounds (Table 5, entries 1–3). With a less-reactive dipolarophile, such as styrene, differences, in terms of yield, have been found between activated and non-activated nitro compounds: ethyl nitroacetate (**1e**) (entry 5, 97%) gives a higher yield than 1-nitropentane (**1c**) (entry 4, 61%) or methyl 4-nitrobutanoate (**1d**) (entry 6, 74%). The same behaviour is observed with allyl alcohol (**8**) (95 vs. 80%, entries 13 and 14, respectively). Nitroalkanes show similar results (entries 8, 9 and 10) in reactions with the acrylate **6**: a better yield is obtained with nitropentane than with nitroethane as a result of extensive decomposition of the latter. Cyclopentene (**5**) with nitropentane gives the cycloadduct **15** in poor yield. (entry 7, 17%) even forcing the reaction conditions (80 °C, 27%). It is worth noting that when a free hydroxy group is present in the dipolarophile neither catalyst deactivation nor side reactions of the alcohol are observed (entries 13 and 14). This outcome allows the incorporated unprotected hydroxy group to function as handle for further synthetic elaborations. The observed reactivities qualitatively accord with the reactivity sequences reported for benzonitrile oxide and for *N*-methyl-*C*-phenyl nitrone towards different olefins: in fact, cyclopentene corresponds to very low reactivity values.[40] This agreement supports the analogy of these 1,3-dipoles with the nitronate, involved in the cycloaddition depicted in Scheme 1. As a copper source for the catalytic system, either copper(II) acetate or copper metal (as powder or wire)[39] can be used. The latter are especially practical (a small piece of copper metal as a wire or turnings is all that needs to be added to the reaction mixture) and convenient for reactions involving oxygenated dipolarophiles.[41]

Finally, we scaled-up, as a representative process, the reaction of ethyl nitroacetate (**1e**) with allyl alcohol (**8**) [Eq. (3)].



1e **8** **21**

(3)

For the sake of practicality, copper wire was used. In preliminary experiments, copper wire was added to the mixture of other reagents, then removed when the solution turned pale green, in order to limit over dissolution of the metal. However, considering that the amount of dissolved copper is dependent on the amount of base, if we use only 2.5 mol% of base, the copper wire can be left as long as the reaction is complete and partial decomposition of nitro acetate is thus avoided. This operating procedure allows the excess of the nitro acetate **1e** to be lowered to 1.2 equivalents relative to the dipolarophile. The reaction carried out with 4 mmol of dipolarophile proceeded with efficiency and product **21** was isolated in 93% yield together with traces of the corresponding 4-substituted regioisomer.

Conclusion

We have developed an efficient procedure based on a [Cu]/NMP catalyst, which provides a route for the synthesis of 4,5-dihydroisozazoles from nitro compounds. This method is the first general catalytic process of condensation between nitro compounds and alkenes. The process uses a cheap and commercially available catalyst, and does not require the exclusion of oxygen or the use of meticulously dried solvents to protect the catalytic system. New methodologies for the facile synthesis of 4,5-dihydroisoxazoles enhance their attractiveness as a platform for the synthesis of complex molecules. The recognition that condensation between nitro compounds and dipolarophiles can be promoted or accelerated by a copper/base catalytic system offers unique mechanistic insights with implications for the further development of highly active and enantioselective catalysts. Studies are underway to extend the applications of this reaction.

Experimental Section

General methods: Chromatographic separations were performed on silica gel 60 (40–6.3 μm) with analytical grade solvents, driven by a positive pressure of air; R_f values refer to TLC (visualised with UV light, permanganate or anisaldehyde stain) carried out on 25 mm silica-gel plates (Merck F254), with the same eluent indicated for the column chromatography. For gradient column chromatography, R_f values refer to the more polar eluent. Solvent removal was performed by evaporation on a rotavap at room temperature. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercuryplus 400 spectrometer (operating at 400 MHz for ^{1}H and 100.58 MHz for ^{13}C NMR) unless otherwise stated. The ^{1}H NMR spectroscopic data are reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). The multiplicities of the ^{13}C NMR spectroscopic signals and assignments were determined by means of gHSQC and gHMBC experiments. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: $\delta = 7.24$ for ^{1}H and 77.0 ppm for ^{13}C NMR spectra). EI (electron impact) mass spectra (at an ionising voltage of 70 eV) were obtained by using a Shimadzu QP5050A quadrupole-based mass spectrometer. Ion mass/charge ratios (m/z) are reported as values in atomic mass units followed by the intensities relative to the base peak in parenthesis. IR spectra were recorded with a Perkin–Elmer 881 spectrophotometer. Elemental analyses were obtained by using an Elemental Analyser Perkin–Elmer 240C apparatus. All compounds were named with Autonom (Beilstein Information Systems) and modified where appropriate.

Materials: Commercially available (Lancaster or Aldrich) nitro compounds (nitroethane, nitropropane, nitropentane, ethyl nitroacetate and methyl 4-nitrobutanoate) and organic bases were used as supplied. $CHCl_3$ (ethanol free) was filtered through a short pad of potassium carbonate just before use. Allyl alcohol was distilled before use. Metal salts of Rh, Cu, Ag, Ni, Pt and Pd were used without treatment. The copper wire was freshly activated just before the use by rapid treatment with 20% aq. nitric acid, and was then washed and dried. Copper powder was purchased from Fluka and used without further purification.

Determination of the catalytic activities of different metal salts (Table 1): Various metal salts were screened in a homemade apparatus in which 6–8 reactions were carried out simultaneously in sealed tubes. The metal salt (0.0212 mmol) was suspended in $CHCl_3$ (1.4 mL). Nitroethane (**1a**; 76 μL, 1.06 mmol), norbornene (**2**; 40 mg, 0.424 mmol) and DABCO (24 mg, 0.212 mmol) were added consecutively and the mixture heated at 60 °C. After 20 h, a portion was withdrawn, diluted in $CDCl_3$ (0.6 mL) and the ^{1}H NMR spectrum was recorded (Varian Gemini 200 MHz). The percentage conversion was evaluated by integrating the Norb-H proton signal of the cycloadduct **9** (m, $\delta = 2.49$ ppm) and the ethylenic protons of norbornene (**2**) (s, $\delta = 5.90$ ppm). Formation of cycloadduct **9** was assumed to be the only process involving norbornene.

Reaction between nitroethane and norbornene in the presence of DABCO/Pd(OAc)$_2$: $Pd(OAc)_2$ (9.5 mg, 0.0425 mmol) was suspended in $CHCl_3$ (2.8 mL). Nitroethane (**1a**; 153 μL, 2.12 mmol), norbornene (**2**; 80 mg, 0.85 mmol) and DABCO (48 mg, 0.425 mmol) were added consecutively and the mixture heated at 60 °C for 20 h. The mixture was then concentrated and the resulting residue showed a spot with the same R_f as an authentic sample of **9** (hexane/diethyl ether 1:1, $R_f = 0.48$). The residue was then dissolved in diethyl ether (15 mL), washed with HCl 5% (3 × 15 mL), brine (3 × 15 mL) and the organic layer dried (sodium sulphate). The solvent was evaporated to afford **9** (8 mg, 12%) as a clear oil.

Determination of the activities of different base/copper(II) acetate catalytic systems (Table 2): Various base/$Cu(OAc)_2$ catalytic systems were screened by using the apparatus mentioned above. Copper(II) acetate (3.9 mg, 0.0212 mmol) was suspended in $CHCl_3$ (1.4 mL). Nitroethane (**1a**; 76 μL, 1.06 mmol), norbornene (**2**; 40 mg, 0.424 mmol) and the base (0.212 mmol) were added consecutively and the mixture heated at 60 °C. After 20 and 40 h, a portion was withdrawn, diluted in $CDCl_3$ (0.6 mL) and the ^{1}H NMR spectrum recorded (Varian Gemini 200 MHz). The percentage conversion was evaluated by integrating the CHC=N or Norb-H proton signal of the cycloadduct **9** (d, $\delta = 2.93$ or 2.49 ppm, respectively) and the ethylenic protons of norbornene (**2**) (s, $\delta = 5.90$ ppm). Formation of cycloadduct **9** was assumed to be the only process involving norbornene.

Optimisation of reaction conditions by varying the base/metal ratio and dipolarophile concentration (Table 3): NMP/$Cu(OAc)_2$ and DBU/Cu-

(OAc)$_2$ catalytic systems were screened considering their ratio at different concentrations of dipolarophile by using the same apparatus as above. Copper(II) acetate (3.9 mg, 0.0212 mmol) was suspended in CHCl$_3$ (1.4 or 0.7 mL). Nitroethane (**1a**; 76 μL, 1.06 mmol), norbornene (**2**; 40 mg, 0.424 mmol) and the base (0.424, 0.212, 0.085, 0.0424 or 0.0212 mmol) were added consecutively and the mixture was heated at 60 °C. After 20 and 40 h, reaction mixtures were analysed as reported above. The percentage conversion was evaluated as above (Table 2).

Influence of the copper source on the condensation of nitro compounds with dipolarophiles (Table 4): Different copper sources (see Table 4) were screened by using the same apparatus as before. A copper salt, powder (0.0212 mmol) or a piece of copper wire was suspended in CHCl$_3$ (1.4 mL). Nitropentane (**1c**; 130 μL, 1.06 mmol), ethyl vinyl ether (**4**; 41 μL, 0.424 mmol,) and NMP (26 μL 0.212 mmol) were added consecutively and the mixture heated at 60 °C. After 40 h, a portion was withdrawn, diluted in CDCl$_3$ (0.6 mL) and the ^{1}H NMR spectrum recorded (Varian Gemini 200 MHz). The percentage conversion was evaluated by integrating the 5-H proton signal of the cycloadduct **19** (d, $\delta = 5.44$ ppm) and the ethylenic protons of ethyl vinyl ether (**4**) (dd, $\delta = 6.42$ ppm). Formation of cycloadduct **19** was assumed to be the only process involving ethyl vinyl ether.

Determination of dipolarophile conversion as a function of time for different catalytic systems (Figures 1 and 2): Various catalytic systems were screened in the usual apparatus. The samples were analysed by using a ^{1}H NMR spectroscopic technique.

Preparation of samples (Figure 1): A mother reaction mixture was prepared by dissolving ethyl nitroacetate (**1e**; 1.656 g, 2.5 equiv), styrene (**3**; 0.531 g, 1.0 equiv) and DABCO (0.114 g, 0.2 equiv) in CHCl$_3$ (25.07 g) at room temperature; then eight sample reactions were obtained by weighing 2.333 g of the mother mixture. Each sample was then heated at 60 °C directly or after the addition of copper powder (1.4 mg) or copper(II) acetate (3.9 mg). Reactions were carried out simultaneously in sealed tubes in the usual apparatus and screened at different times.

Conversion evaluation: An aliquot portion (80 μL) was diluted with CDCl$_3$ (0.6 mL). After addition of [D$_6$]DMSO ($\approx$30 μL) and trifluoroacetic acid ($\approx$4 μL) the ^{1}H NMR spectrum was recorded (Varian Gemini 200 MHz) and the percentage conversion was evaluated by integrating the 4-H proton signal of the cycloadduct **13** (dd, $\delta = \approx 3.10$ ppm), combined with the signal of 5-H from cycloadduct **13** (dd, $\delta = \approx 5.7$ ppm) and the ethylenic protons of styrene (**3**) (m, $\delta = 5.55$–5.70 ppm).

Preparation of samples (Figure 2): Nitropentane (**1c**; 1.493 g, 2.5 equiv), methyl acrylate (**6**; 0.439 g, 1.0 equiv), NMP (0.31 g, 0.5 equiv) and CHCl$_3$ (25.07 g) were mixed at room temperature. Then, eight sample reactions were obtained by weighing 2.271 g of the above mother mixture, which was treated as above.

Conversion evaluation: An aliquot portion (80 μL) was diluted with CDCl$_3$ (0.6 mL), the ^{1}H NMR spectrum was recorded (Varian Gemini 200 MHz) and the percentage conversion was evaluated by integrating the 5-H proton signal of the cycloadduct **18** (m, $\delta = \approx 4.98$ ppm) and the ethylenic protons of methyl acrylate (**6**) (m, $\delta = 5.76$–5.88 ppm).

General procedure for the preparation of isoxazolines 9–24: Nitro compound (1.06 mmol), dipolarophile (0.424 mmol) and NMP were added in sequence to a suspension of either Cu(OAc)$_2$ or copper powder in CHCl$_3$ (1.4 mL). The stirred mixture, which had been heated in a sealed tube at 60 °C (unless otherwise stated), turned light green and became clear after 10–20 min (less than 5 min for activated nitro compounds). Stirring was then maintained for the indicated time. After this time, the solvent was removed and the residue was dissolved in CH$_2$Cl$_2$ (10 mL); silica gel (200 mg) was added to the mixture and the solvent evaporated. The silica gel with the adsorbed product was loaded onto the top of a column of silica gel and purified by chromatography with the indicated eluent.

Isoxazoline 9 (5-methyl-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-4-ene): Nitroethane (**1a**; 76 μL), norbornene (**2**; 40 mg), NMP (26 μL, 0.212 mmol) and copper powder (1.3 mg, 0.0212 mmol) gave after 20 h and chromatographic purification (hexane/diethyl ether 2:1, $R_f = 0.25$) **9** as a clear oil, which turned to clear pale yellow on standing (58 mg, 90 %). ^{1}H NMR: $\delta = 1.00$–1.22 (m, 3H; Norb-*H*), 1.38–1.58 (m, 3H; Norb-*H*), 1.88 (s, 3H; C*H*$_3$), 2.32 (m, 1H; Norb-*H*), 2.49 (m, 1H; Norb-*H*), 2.93 (d, $J = 8.0$ Hz, 1H; C*H*C=N), 4.39 ppm (d, $J = 8.0$ Hz, 1H; C*H*ON); ^{13}C NMR: $\delta = 11.9$ (q; *C*H$_3$), 22.6 (t; Norb-*C*), 27.2 (t; Norb-*C*), 32.0 (t; Norb-*C*), 38.0 (d; Norb-*C*), 42.8 (d; Norb-*C*), 60.6 (d; *C*C=N), 86.1 (d; *C*ON), 155.4 ppm (s, *C*=N); IR (CDCl$_3$): $\tilde{\nu} = 2964$, 2877, 1630, 1455, 1436, 1384, 1331 cm^{-1}; MS (EI): *m*/*z* (%): 151 (36) $[M]^+$, 131 (10), 109 (8), 84 (68), 67 (100); elemental analysis calcd (%) for C$_9$H$_{13}$NO (151.21): C 71.49, H 8.67, N 9.26; found: C 71.19, H 9.02, N 9.31.

Isoxazoline 10 (5-butyl-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-4-ene): Nitropentane (**1c**; 130 μL), norbornene (**2**; 40 mg), NMP (26 μL, 0.212 mmol) and copper powder (1.3 mg, 0.0212 mmol) gave after 40 h and chromatographic purification (hexane, then hexane/diethyl ether 10:1, $R_f = 0.26$) **10** as a colourless oil (81 mg, 99 %). ^{1}H NMR: $\delta = 0.88$ (t, $J = 14.0$ Hz, 3H; C*H*$_3$), 0.99–1.24 (m, 3H; C*H*$_2$CH$_3$, Norb-*H*), 1.24–1.43 (m, 3H; C*H*$_2$C=N, Norb-*H*), 1.42–1.61 (m, 4H; C*H*$_2$C=N, Norb-*H*), 2.08–2.18 (m, 1H; C*H*$_2$CH$_2$CH$_3$), 2.24–2.38 (m, 2H; Norb-*H*, C*H*$_2$CH$_2$CH$_3$), 2.44–2.48 (m, 1H; Norb-*H*), 2.95 (d, $J = 8.3$ Hz, 1H; C*H*C=N), 4.35 ppm (d, $J = 8.3$ Hz, 1H; C*H*ON); ^{13}C NMR: $\delta = 13.7$ (q; *C*H$_3$), 22.4 (t; *C*H$_2$CH$_3$), 22.6 (t; Norb-*C*), 26.3 (t; *C*H$_2$C=N), 27.2 (t; Norb-*C*), 28.3 (t; *C*H$_2$CH$_2$CH$_3$), 32.0 (t; Norb-*C*), 38.1 (d; Norb-*C*), 42.8 (d; Norb-*C*), 59.3 (d; *C*HC=N), 85.9 (d; *C*ON), 158.8 ppm (s; *C*=N); IR (CDCl$_3$): $\tilde{\nu} = 2961$, 2875, 1619, 1456 cm^{-1}; MS (EI): *m*/*z* (%): 193 (13) $[M]^+$, 178 (3), 164 (30), 151 (100), 126 (22), 67 (54); elemental analysis calcd (%) for C$_{12}$H$_{19}$NO (193.29): C 74.57, H 9.91, N 7.25; found: C 74.27, H 10.28, N 7.07.

Isoxazoline 11 (3-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-4-ene-5-carboxylic acid ethyl ester): Ethyl nitroacetate (**1e**; 118 μL), norbornene (**2**; 40 mg), NMP (10 μL, 0.0845 mmol) and Cu(OAc)$_2$ (3.9 mg, 0.0212 mmol) gave after 20 h and chromatographic purification (hexane then hexane/diethyl ether 3:1, $R_f = 0.25$) **11** as a clear oil (88 mg, 99 %). Elemental analysis calcd (%) for C$_{11}$H$_{15}$NO$_3$ (209.2): C 63.14, H 7.23, N 6.69; found: C 62.94, H 7.41, N 7.07; the spectral data are identical to those previously reported.[28]

Isoxazoline 12 (3-butyl-5-phenyl-4,5-dihydroisoxazole): Nitropentane (**1c**; 130 μL), styrene (**3**; 49 μL), NMP (26 μL, 0.212 mmol) and Cu(AcO)$_2$ (7.7 mg, 0.0424 mmol) gave after 40 h and chromatographic purification (hexane, then hexane/diethyl ether 3:1, $R_f = 0.29$) **12** as a colourless liquid (53 mg, 61 %). ^{1}H NMR: $\delta = 0.91$ (t, $J = 7.4$ Hz, 3H; C*H*$_3$), 1.30–1.40 (m, 2H; C*H*$_2$CH$_3$), 1.50–1.58 (m, 2H; C*H*$_2$CH$_2$CH$_3$), 2.36 (t, $J = 7.8$ Hz, 2H; C*H*$_2$C-3), 2.87 (dd, $J = 8.0$, 17.0 Hz, 1H; 4-H), 3.33 (dd, $J = 10.8$, 17.0 Hz, 1H; 4-H), 5.13 (dd, $J = 8.0$, 10.8 Hz, 1H; 5-H), 7.12–7.18 ppm (m, 5H; Ph-*H*); ^{13}C NMR: $\delta = 13.6$ (q; *C*H$_3$), 22.3 (t; *C*H$_2$CH$_3$), 27.3 (t; *C*H$_2$C-3), 28.4 (*C*H$_2$CH$_2$CH$_3$), 45.3 (t; C-4), 81.1 (d; C-5), 125.6 (d, 2C; Ph-*C*) 127.9 (d; Ph-*C*), 128.6 (d, 2C; Ph-*C*), 141.3 (s; Ph-*C*), 158.5 ppm (s; C-3); IR (CDCl$_3$): $\tilde{\nu} = 2959$, 2931, 1624, 1597, 1548, 1493, 1456, 1466, 1432 cm^{-1}; MS (EI): *m*/*z* (%): 203 (6) $[M]^+$, 161 (51), 144 (27), 104 (100); elemental analysis calcd (%) for C$_{13}$H$_{17}$NO (203.28): C 76.81, H 8.43, N 6.89; found: C 76.71, H 8.59, N 7.06.

Isoxazoline 13 (ethyl 5-phenyl-4,5-dihydro-3-isoxazolecarboxylate): Ethyl nitroacetate (**1e**; 118 μL), styrene (**3**; 49 μL), NMP (10 μL, 0.0845 mmol) and copper powder (1.3 mg, 0.0212 mmol) gave after 20 h and chromatographic purification **13** (hexane/diethyl ether 2:1, $R_f = 0.26$) as a colourless oil. Before chromatographic purification the crude material was dissolved in diethyl ether (15 mL) and saturated NaCO$_3$ (15 mL) was added. The mixture was vigorously stirred for 30 min and then the organic layer was washed with brine (3 × 15 mL), dried (sodium sulphate) and concentrated under reduced pressure (90 mg, 97 %). Elemental analysis calcd (%) for C$_{12}$H$_{13}$NO$_3$ (219.24): C 65.74, H 5.98, N 6.39; found: C 65.46, H 6.01, N 6.51; the spectral data are identical to those previously reported.[28]

Isoxazoline 14 (methyl 3-(5-phenyl-4,5-dihydro-3-isoxazolyl)propanoate): Methyl 4-nitrobutanoate (**1d**; 136 μL), styrene (**3**; 49 μL), NMP (26 μL, 0.212 mmol) and copper powder (1.3 mg, 0.0212 mmol) gave after 112 h and chromatographic purification (hexane, then hexane/diethyl ether 2:3, $R_f = 0.27$) **14** as a yellow oil (73 mg, 74 %). ^{1}H NMR: $\delta = 2.60$–2.72 (m, 4H; C*H*$_2$CH$_2$CO, CH$_2$C*H*$_2$CO), 2.90 (dd, $J = 17.0$, 8.0 Hz, 1H; 4-H), 3.36 (dd, $J = 17.0$, 10.8 Hz, 1H; 4-H), 3.67 (s, 3H; OC*H*$_3$), 5.53 (dd, $J = 8.0$, 10.8 Hz, 1H; 5-H), 7.26–7.38 ppm (m, 5H; Ph-*H*); ^{13}C NMR: $\delta = 23.2$ (t; CH$_2$*C*H$_2$C=O), 30.4 (t; *C*H$_2$CH$_2$C=O), 45.7 (t; C-4), 51.8 (q; O*C*H$_3$), 81.6

(d; C-5), 125.7 (d, 2C; Ph-*C*), 128.0 (d; Ph-*C*), 128.6 (d, 2C; Ph-*C*), 141.0 (s; Ph-*C*), 156.9 (s; C-3), 172.7 ppm (s; *C*=O); IR ($CDCl_3$): $\tilde{\nu}=3032$, 2954, 2840, 1733 (C=O), 1623, 1603, 1552, 1494, 1438, 1366, 1339 cm^{-1}; MS (EI): *m*/*z* (%): 233 (51) $[M]^+$, 232 (28), 202 (39) $[M-OMe]^+$, 200 (37), 174 (12) $[M-CO_2Me]^+$, 156 (51), 104 (100), 91 (20), 77 (33) $[Ph]^+$; elemental analysis calcd (%) for $C_{13}H_{15}NO_3$ (233.26): C 66.94, H 6.48, N 6.00; found: C 66.64, H 6.77, N 6.04.

Isoxazoline 15 (3-butyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole)

Experiment conducted with copper acetate at 60°C: A sealed tube was charged with copper(II) acetate (7.7 mg, 0.0424 mmol) suspended in $CHCl_3$ (1.4 mL). Nitropentane (**1c**; 130 μL, 1.06 mmol), cyclopentene (**5**; 37.5 μL, 0.424 mmol) and NMP (52 μL, 0.424 mmol) were then added consecutively and the mixture heated at 60°C. The solution was left stirring for 40 h. After this time, the solvent was removed and the residue dissolved in CH_2Cl_2 (10 mL); silica gel (200 mg) was added to the mixture and the solvent evaporated. The silica gel with the adsorbed product was loaded onto the top of a column of silica gel and purified by chromatography (hexane, then hexane/diethyl ether 4:1, $R_f=0.25$) to provide the product **15** as a clear pale-yellow oil (12 mg, 17%).

Experiment conducted with copper powder at 80°C: A sealed tube was charged with copper powder (2.7 mg, 0.0424 mmol) suspended in $CHCl_3$ (1.4 mL). Nitropentane (**1c**; 130 μL, 1.06 mmol), cyclopentene (**5**; 37.5 μL, 0.424 mmol) and NMP (52 μL, 0.424 mmol) were then added consecutively and the mixture heated at 80°C. The clear solution was left stirring for 60 h. After this time, the solvent was removed and the residue purified as above to give the product **15** as a clear pale-yellow oil (19 mg, 27%). ^{1}H NMR: $\delta=0.90$ (t, $J=7.4$ Hz, 3H; CH_3), 1.16–1.22 (m, 2H; CH_2CH_3), 1.23–1.70 (m, 6H; Bu-*H*, Cp-*H*), 1.79–1.84 (m, 1H; Cp-*H*), 2.00–2.08 (m, 1H; Cp-*H*), 2.10–2.20 (m, 1H; CH_2C=N), 2.30–2.40 (m, 1H; CH_2C=N), 3.52 (t, $J=7.8$ Hz, 1H; *CH*C=N), 4.97 ppm (dd, $J=5.0$, 8.8 Hz, 1H; *CH*CON); ^{13}C NMR: $\delta=13.7$ (q; CH_3), 22.4 (t; CH_2CH_3), 23.3, (t; Cp-*C*), 26.1 (t; CH_2C=N), 28.4, (t; $CH_2CH_2CH_3$), 30.2 (t; Cp-*C*), 35.9 (t; Cp-*C*), 54.3 (d; *C*C=N), 85.4 (d; *C*ON), 159.9 ppm (s; *C*=N); IR ($CDCl_3$): $\tilde{\nu}=2959$, 2872, 1620, 1548, 1466, 1435 cm^{-1}; MS (EI): *m*/*z* (%): 167 (6) $[M]^+$, 152 (2) $[M-Me]^+$, 138 (22) $[M-Et]^+$, 125 (100), 108 (16), 93 (40); elemental analysis calcd (%) for $C_{10}H_{17}NO$ (167.25): C 71.81, H 10.24, N 8.37; found: C 71.91, H 10.42, N 8.20.

Isoxazoline 16 (methyl 3-methyl-4,5-dihydro-5-isoxazolecarboxylate): Nitroethane (**1a**; 76 μL), methyl acrylate (**6**) (39 μL), NMP (26 μL, 0.212 mmol) and $Cu(AcO)_2$ (3.9 mg, 0.0212 mmol) gave after 40 h and chromatographic purification (hexane, then hexane/diethyl ether 1:2, $R_f=0.24$) **16** as pale-yellow oil (54 mg, 89%). ^{1}H NMR: $\delta=1.98$ (m, 3H; CH_3), 3.19 (dm (doublet of multiplets), $J=8.0$ Hz, 2H; 4-H), 3.75 (s, 3H; OCH_3), 4.96 ppm (dd, $J=8.0$, 9.8 Hz, 1H; 5-H); ^{13}C NMR: $\delta=12.6$ (q; CH_3), 42.4 (t; C-4), 52.7 (q; OCH_3), 77.04 (d; C-5), 154.8 (s; C-3), 170.9 ppm (s; *C*=O); IR ($CDCl_3$): $\tilde{\nu}=2956$, 2925, 2850, 1741 (C=O), 1633, 1551, 1437, 1386, 1325 cm^{-1}; MS (EI): *m*/*z* (%): 143 (2) $[M]^+$, 112 (2) $[M-OMe]^+$ 84 (72) $[M-CO_2Me]^+$, 56 (100); elemental analysis calcd (%) for $C_6H_9NO_3$ (143.14): C 50.35, H 6.34, N 9.79; found: C 50.16, H 6.60, N 10.05.

Isoxazoline 17 (methyl 3-ethyl-4,5-dihydro-5-isoxazolecarboxylate): Nitropropane (**1b**; 94 μL, 1.06 mmol), methyl acrylate (**6**; 39 μL), NMP (26 μL, 0.212 mmol) and $Cu(AcO)_2$ (3.9 mg, 0.0212 mmol) gave after 40 h and chromatographic purification (hexane then hexane/diethyl ether 5:3, $R_f=0.15$) **17** as a pale-yellow oil (58 mg; 87%). ^{1}H NMR: $\delta=1.14$ (t, $J=9.2$ Hz, 3H; CH_3), 2.35 (q, $J=9.2$ Hz, 2H; CH_2CH_3), 3.19 (d, $J=9.6$ Hz, 2H; 4-H), 3.75 (s, 3H; OCH_3), 4.94 ppm (t, $J=9.$ 6 Hz, 1H; 5-H); ^{13}C NMR: $\delta=10.7$ (q; CH_3), 20.8 (t; CH_2CH_3), 40.8 (t; C-4), 52.6 (q; OCH_3), 76.8 (d; C-5), 159.4 (s; C-3), 171.0 ppm (s; *C*=O); IR ($CDCl_3$): $\tilde{\nu}=2979$, 2955, 1739 (C=O), 1626, 1602, 1461, 1438 cm^{-1}; MS (EI): *m*/*z* (%): 157 (2) $[M]^+$, 140 (2), 126 (1) $[M-OMe]^+$, 98 (84) $[M-CO_2Me]^+$, 70 (100); elemental analysis calcd (%) for $C_7H_{11}NO_3$ (157.17): C 53.50, H 7.05, N 8.91; found: C 53.88, H 7.13, N 8.53.

Isoxazoline 18 (methyl 3-butyl-4,5-dihydro-5-isoxazolecarboxylate): Nitropentane (**1c**; 130 μL), methyl acrylate (**6**; 39 μL), NMP (26 μL, 0.212 mmol) and copper powder (1.3 mg, 0.0212 mmol) gave after 40 h and chromatographic purification (hexane, then hexane/diethyl ether 4:3, $R_f=0.22$) **18** as a colourless oil (73 mg, 93%). Elemental analysis calcd (%) for $C_9H_{15}NO_3$ (185.22): C 58.36, H 8.16, 4, N 7.56; found: C 57.98, H 8.33, N 7.68; the spectral data are identical to those previously reported.[33]

Isoxazoline 19 (3-butyl-5-ethoxy-4,5-dihydroisoxazole): Four preparations were carried out by using identical reaction conditions but with different catalytic systems.

1) A sealed tube was charged with $Cu(AcO)_2$ (3.9 mg, 0.0212 mmol) suspended in $CHCl_3$ (1.4 mL). Nitropentane (**1c**; 130 μL, 1.06 mmol), ethyl vinyl ether (**4**; 41 μL 0.424 mmol) and NMP (26 μL, 0.212 mmol) were then added consecutively and the mixture was heated at 60°C. The resulting solution was left stirring for 40 h. The solvent was then removed and the residue dissolved in CH_2Cl_2 (10 mL). Silica gel (200 mg) was added to the mixture and the solvent evaporated. The silica gel with the adsorbed product was loaded onto the top of a column of silica gel and purified by chromatography (hexane then hexane/diethyl ether 10:1, $R_f=0.15$) to give the product **19** as a clear oil, which turned yellow on standing (41 mg, 56%).
2) The reaction was repeated by using 1-ethylpiperidine instead of NMP to give 38 mg of **19** (52%).
3) A sealed tube was charged with copper powder (1.3 mg, 0.0212 mmol) suspended in $CHCl_3$ (1.4 mL). Nitropentane (**1c**; 130 μL, 1.06 mmol), ethyl vinyl ether (**4**; 41 μL, 0.424 mmol) and NMP (26 μL, 0.212 mmol) were then added consecutively and the mixture heated at 60°C. The resulting solution was left stirring for 40 h, then worked-up as for **1** to give the product **19** as a clear oil, which turned yellow on standing (45 mg, 62%).
4) The reaction was repeated by using 1-ethylpiperidine instead of NMP to give **19** (43 mg, 59%). ^{1}H NMR: $\delta=0.89$ (t, $J=7.4$ Hz, 3H; CH_3), 1.16 (t, $J=7.2$ Hz, 3H; OCH_2CH_3), 1.32–1.40 (m, 2H; CH_2CH_3), 1.48–1.59 (m, 2H; $CH_2CH_2CH_3$), 2.32–2.38 (m, 2H; CH_2C-3), 2.70 (dd, $J=1.6$, 7.6 Hz, 1H; 4-H), 2.96 (dd, $J=6.6$, 17.6 Hz, 1H; 4-H), 3.46–3.54 (m, 1H; OCH_2CH_3), 3.77–3.85 (m, 1H; OCH_2CH_3), 5.44 ppm (dd, $J=1.6$, 6.6 Hz, 1H; 5-H); ^{13}C NMR: $\delta=13.6$ (q; CH_3), 15.0 (q; OCH_2CH_3), 22.3 (t; CH_2CH_3), 27.3 (t; CH_2C-3), 28.4 (t; $CH_2CH_2CH_3$), 43.7 (t; C-4), 63.4 (t; OCH_2), 101.9 (d; C-5), 159.4 ppm (s; C-3); IR ($CDCl_3$): $\tilde{\nu}=2960$, 2932, 1620, 1457 cm^{-1}; MS (EI): *m*/*z* (%): 171 (<1) $[M]^+$, 156 (1) $[M-Me]^+$, 142 (7) $[M-Et]^+$, 129 (87), 126 (9) $[M-OEt]^+$, 97 (44), 72 (62), 57 (100); elemental analysis calcd (%) for $C_9H_{17}NO_2$ (171.238): C 63.13, H 10.01, N 8.18; found: C 62.97, H 9.94, N 8.05.

Isoxazoline 20 (3-butyl-4,5-dihydroisoxazole-5-carboxylic acid dimethylamide): Nitropentane (**1c**; 130 μL), dimethyl acrylamide (**7**; 43.8 μL), NMP (26 μL, 0.212 mmol) and $Cu(AcO)_2$ (3.9 mg, 0.0212 mmol) gave after 20 h and chromatographic purification (hexane, then hexane/diethyl ether 1:10, $R_f=0.25$) **20** as a colourless oil, which turned pale-yellow on standing (76 mg, 90%). ^{1}H NMR: $\delta=0.87$ (t, $J=7.6$ Hz, 3H; CH_3), 1.26–1.36 (m, 2H; $CH_2CH_2CH_3$), 1.48–1.56 (m, 2H; $CH_2CH_2CH_3$), 2.31 (t, $J=7.6$ Hz, 2H; CH_2C-3), 2.90 (dd, $J=10.9$, 17.0 Hz, 1H; 4-H), 2.94 (s, 3H; NCH_3), 3.11 (s, 3H; NCH_3), 3.67 (dd, $J=7.2$, 17.0 Hz, 1H; 4-H), 5.12 ppm (dd, $J=7.2$, 10.9 Hz, 1H; 5-H); ^{13}C NMR: $\delta=13.6$ (q; CH_3), 22.2 (t; CH_2CH_3), 26.9 (t; CH_2C-3), 28.2 (t; $CH_2CH_2CH_3$), 35.9 (q; NCH_3), 37.1 (q; NCH_3), 38.9 (t; C-4), 76.6 (d; C-5), 158.5 (s; C-3), 167.7 ppm (s; *C*=O); IR ($CDCl_3$): $\tilde{\nu}=2960$, 2933, 2874, 1649 (C=O), 1602, 1499, 1417, 1404 cm^{-1}; MS (EI): *m*/*z* (%) 198 (4) $[M]^+$, 181 (3), 168 (4), 167 (20), 126 (77), $[M-CONMe_2]^+$, 72 (100); elemental analysis calcd (%) for $C_{10}H_{18}N_2O_2$ (198.26): C 60.58, H 9.15, N 14.13; found: C 60.49, H 9.45, N 13.93.

Isoxazoline 21 (5-hydroxymethyl-4,5-dihydroisoxazole-3-carboxylic acid ethyl ester): Ethyl nitroacetate (**1e**); 118 μL), allyl alcohol (**8**; 29 μL), NMP (10 μL, 0.0845 mmol) and copper powder (1.3 mg, 0.0212 mmol) gave after 16 h and chromatographic purification (hexane, then hexane/diethyl ether 1:4, $R_f=0.24$) **21** as a clear viscous liquid (70 mg, 95%). Elemental analysis calcd (%) for $C_7H_{11}NO_4$ (173.17): C 48.55, H 6.40, N 8.09; found: C 48.81, H 6.47, N 8.39; the spectral data are identical to those previously reported.[29]

Isoxazoline 22 ((3-butyl-4,5-dihydroisoxazol-5-yl)methanol): Nitropentane (**1c**; 130 µL), allyl alcohol (**8**; 29 µL), NMP (26 µL, 0.212 mmol) and copper powder (1.3 mg, 0.0212 mmol) gave after 40 h and chromatographic purification (hexane, then hexane/diethyl ether 1:6, $R_f = 0.28$) **22** as a pale-yellow oil (54 mg, 80%). ^{1}H NMR: $\delta = 0.90$ (t, $J = 7.2$ Hz, 3H; CH_3), 1.29–1.40 (m, 2H; $CH_2CH_2CH_3$), 1.48–1.56 (m, 2H; $CH_2CH_2CH_3$), 2.05 (brs, 1H; OH), 2.31 (t, $J = 7.6$ Hz, 2H; CH_2C-3), 2.77–2.83 (m, 1H; 4-H), 2.90–2.97 (m, 1H; 4-H), 3.50–3.56 (m, 1H; CH_2OH), 3.70–3.76 (m, 1H; CH_2OH), 4.59–4.66 ppm (m, 1H; 5-H); ^{13}C NMR: $\delta = 13.7$ (q; CH_3), 22.3 (t; CH_2CH_3), 27.3 (t; CH_2C-3), 28.4 (t; $CH_2CH_2CH_3$), 38.4 (d; C-4), 63.8 (t; CH_2OH), 79.7 (t; C-5), 159.6 ppm (s; C-3); IR (CDCl$_3$): $\tilde{\nu} = 3590$ (OH), 2958, 2931, 2873, 1622, 1456, 1434 cm^{-1}; MS (EI): m/z (%): 157 (4) $[M]^+$, 126 (28) $[M-CH_2OH]^+$, 115 (66), 69 (72), 57 (100); elemental analysis calcd (%) for $C_8H_{15}NO_2$ (157.21): C 61.12, H 9.62, N 8.91; found: C 61.04, H 9.29, N 9.22.

Isoxazoline 23 (phenyl (5-phenyl-4,5-dihydroisoxazol-3-yl)methanone): Benzoylnitromethane (**1f**; 175 mg), styrene (**8**; (49 µL), NMP (10 µL, 0.0845 mmol) and copper powder (1.3 mg, 0.0212 mmol) gave after 40 h and chromatographic purification (hexane, then hexane/diethyl ether 10:1, $R_f = 0.24$) **23** as a colourless oil (101 mg, 95%). Elemental analysis calcd (%) for $C_{16}H_{13}NO_2$ (251.28): C 76.48, H 5.21, N 5.57; found: C 76.07, H 4.90, N 5.87; the spectral data are identical to those previously reported.[27]

Isoxazoline 24 (3-benzoyl-4,5-dihydroisoxazole-5-carboxylic acid dimethylamide): Benzoylnitromethane (**1f**; 175 mg), dimethyl acryl amide (**7**; 44 µL), NMP (10 µL, 0.0845 mmol) and copper powder (1.3 mg) gave after 20 h and chromatographic purification (petroleum ether, then petroleum ether/ethyl acetate 1:1, $R_f = 0.24$) **24** as a pale-yellow oil (104 mg, 99%). ^{1}H NMR: $\delta = 3.00$ (s, 3H; CH_3), 3.18 (s, 3H; CH_3), 3.44 (dd, $J = 11.7$, 17.8 Hz, 1H; 4-H), 4.06 (dd, $J = 7.6$, 17.8 Hz, 1H; 4-H), 5.42 (dd, $J = 7.6$, 11.7 Hz, 1H; 5-H), 7.40–7.46 (m, 2H; Ph-H_{meta}), 7.54–7.59 (m, 1H; Ph-H_{para}), 8.12–8.16 ppm (m, 2H; Ph-H_{ortho}); ^{13}C NMR: $\delta = 36.1$ (q; CH_3), 36.5 (t; C-4), 37.2 (q; CH_3), 78.9 (d; C-5), 128.3 (d; 2C; Ph-C_{meta}), 130.3 (d, 2C; Ph-C_{ortho}), 133.6 (d; Ph-C_{para}), 135.6 (s; Ph-C_{ipso}), 157.9 (s; C-3), 166.4 (s; $Me_2NC{=}O$), 185.8 ppm (s; $PhC{=}O$); IR (CDCl$_3$): $\tilde{\nu} = 3064$, 2940, 1658 (C=O), 1599, 1586 cm^{-1}; MS (EI): m/z (%): 246 (<1) $[M]^+$, 216 (2), 174 (12) $[M-CONMe_2]^+$, 105 (100) $[PhCO]^+$, 77 (52) $[Ph]^+$, 72 (74); elemental analysis calcd (%) for $C_{13}H_{14}N_2O_3$ (246.26): C 63.40, H 5.73, N 11.38; found: C 63.20, H 5.85, N 11.38.

Scale-up for the reaction between ethyl nitroacetate (1e) and allyl alcohol (8): Formation of isoxazoline 21: A sealed 50 mL schlenk tube containing freshly activated copper wire was charged with allyl alcohol (**8**; 0.247 g, 4.24 mmol), ethyl nitroacetate (**1e**; 0.678 g, 5.08 mmol), NMP (0.0105 g, 0.106 mmol) and CHCl$_3$ (14 mL), and the mixture was heated at 60 °C. The resulting solution was left stirring for 46 h. After this time, the solvent was removed and the residue dissolved in CH$_2$Cl$_2$ (50 mL). Silica gel (2 g) was added to the mixture and the solvent evaporated. The silica gel with the adsorbed product was loaded onto the top of a column of silica gel and purified by chromatography (petroleum ether then diethyl ether/petroleum ether 4:1, $R_f = 0.24$) to give isoxazoline **21** (686 mg, 93%) as a viscous clear liquid containing as little as 3% of ethyl 4-(hydroxymethyl)-4,5-dihydro-3-isoxazolecarboxylate. Elemental analysis calcd (%) for $C_7H_{11}NO_4$ (173.17): C 48.55, H 6.40, N 8.09; found: C 48.15, H 6.37, N 8.35; the spectral data are identical to those previously reported.[29]

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[1] a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, New Jersey, **2003**; b) *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley, New York, **1984**.

[2] a) D. Giomi, F. M. Cordero, F. Machetti in *Comprehensive Heterocyclic Chemistry III* (Eds.: A. Katritzky, C. Ramsden, E. Scriven, R. Taylor), Elsevier **2008**; b) V. Jäger, P. A. Colinas in ref. 1a), Chapter 6; c) J. Mulzer, *Organic Synthesis Highlights*; VCH, Weinheim, **1991**; d) K. B. G. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH, New York, **1988**, Chapter 5; e) P. Caramella, P. Grünanger, in ref. 1b), Chapter 3.

[3] Phenylisocyanate: T. Mukaiyama, T. Hoshino, *J. Am. Chem. Soc.* **1960**, *82*, 5339–5342.

[4] For selected recent applications of phenylisocyanate see: a) K. N. Fleming, R. E. Taylor, *Angew. Chem.* **2004**, *116*, 1760–1762; *Angew. Chem. Int. Ed.* **2004**, *43*, 1728–1730; b) T. Rosenau, C. Adelwöhrer, A. Hofinger, K. Mereiter, P. Kosma, *Eur. J. Org. Chem.* **2004**, 1323–1329; c) M. Prakesch, D. Grée, R. Grée, J. Carter, I. Washington, K. N. Houk, *Chem. Eur. J.* **2003**, *9*, 5664–5672; d) K.-H. Park, M. M. Olmstead, M. J. Kurth, *Synlett* **2003**, 1267–1270; e) E. V. Koroleva, Ya. M. Katok, T. V. Chernikova and F. A. Lakhvich, *Chem. Heterocycl. Compd.* **2003**, *39*, 918–924; *Khim. Geterotsikl. Soedin.* **2003**, *7*, 1060–1066; f) F. S. Pashkovskii, Ya. M. Katok, E. M. Shchukina, E. V. Koroleva, F. A. Lakhvich, *Russ. J. Org. Chem.* **2006**, *42*, 230–237; *Zh. Org. Khim.* **2006**, *42*, 246–253; g) A. Kadowaki, Y. Nagata, H. Unob. A. Kamimura, *Tetrahedron Lett.* **2007**, *48*, 1823–1825; h) E. V. Koroleva, Y. M. Katok, F. A. Lakhvich, *Natsyyanal'nai Akademii Navuk Belarusi, Seryya Khimichnykh Navuk* **2000**, *3*, 70–74; *Chem. Abstr.* **2000**, *134*, 131337; i) J. Siu, I. R. Baxendale, R. A. Lewthwaite, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 3140–3160; j) R. Clayton, C. A. Ramsden, *Synthesis* **2005**, 2695–2700.

[5] Tolylene 2,4-diisocyanate: M. G. Leslie-Smith, R. M. Paton, N. Webb, *Tetrahedron Lett.* **1994**, *35*, 9251–9254.

[6] 1,4-Phenylene diisocyanate: V. Jäger, I. Müller, *Tetrahedron* **1985**, *41*, 3519–3528.

[7] For recent selected examples that use 1,4-phenylene diisocyanate see: a) M. Lemaire, N. Veny, T. Gefflaut, E. Gallienne, R. Chênevert, J. Bolte, *Synlett* **2002**, 1359–1361; b) K. S.-L. Huang, E. H. Lee, M. M. Olmstead, M. J. Kurth, *J. Org. Chem.* **2000**, *65*, 499–503.

[8] 4-Chlorophenyl isocyanate: A. P. Kozikowski, P. D. Stein, *J. Am. Chem. Soc.* **1982**, *104*, 4023–4024.

[9] For selected recent applications of 4-chlorophenyl isocyanate see: a) W. Itano, T. Ohshima, M. Shibasaki, *Synlett* **2006**, 3053–3056; b) A. Sekine, N. Kumagai, K. Uotsu, T. Ohshima, M. Shibasaki, *Tetrahedron Lett.* **2000**, *41*, 509–513; c) S. Ghorai, R. Mukhopadhyay, A. P. Kundu, A. Bhattacharjya, *Tetrahedron* **2005**, *61*, 2999–3012; d) P. A. Wade, H. Le, N. V. Amin, *J. Org. Chem.* **2002**, *67*, 2859–2863; e) J. Sengupta, R. Mukhopadhyay, A. Bhattacharjya, M. M. Bhadbhade, G. V. Bhosekar, *J. Org. Chem.* **2005**, *70*, 8579–8582.

[10] Phosphorus oxychloride: a) G. B. Bachman, L. E. Strom, *J. Org. Chem.* **1963**, *28*, 1150–1152; b) J. E. McMurry, *Org. Synth.* **1973**, *53*, 59–62.

[11] a) I. Akritopoulou-Zanze, V. Gracias, J. D. Moore, S. W. Djuric, *Tetrahedron Lett.* **2004**, *45*, 3421–3423; b) S. Chimichi, M. Boccalini, B. Cosimelli, F. Dall'Acqua, G. Viola, *Tetrahedron* **2003**, *59*, 5215–5223.

[12] Acetyl chloride: a) E. Kaji, K. Harada, S. Zen, *Chem. Pharm. Bull.* **1978**, *26*, 3254–3256; b) K. Harada, E. Kaji, S. Zen, *Chem. Pharm. Bull.* **1980**, *28*, 3296–3303.

[13] Ethyl chloroformate/triethylamine and benzenesulphonyl chloride/triethylamine: T. Shimizu, Y. Hayashi, H. Shibafuchi, K. Teramura, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2827–2831.

[14] For selected applications of *p*-toluensulphonyl chloride see: a) S. Kwiatkowski, M. Langwald, *Monatsh. Chem.* **1986**, *117*, 1091–1093; b) P. E. Pigou, C. J. Stirling, *J. Chem. Soc. Perkin Trans. 2* **1988**, 725–730.

[15] Thionyl chloride Y.-J. Chen, C.-N. Li, *J. Chin. Chem. Soc.* **1993**, *40*, 203–207; *Chem. Abs.* **1993**, *119*, 180693.

[16] Acetic anhydride/sodium acetate: A. Mckillop, R. J. Kobylecki, *Tetrahedron* **1974**, *30*, 1365–1371; for recent examples see: a) S. Spyroudis, N. Xanthopoulou, *J. Org. Chem.* **2002**, *67*, 4612–4614; b) B. Alcaide, P. Almendros, E. Sáeza, *Arkivoc* **2004**, 137–152.

[17] Di *tert*-butyldicarbonate/4-dimethylaminopyridine: a) Y. Basel, A. Hassner, *Synthesis* **1997**, 309–312; for recent selected examples see: b) T. Itoh, M. Watanabe, T. Fukuyama, *Synlett* **2002**, 1323–1325; c) S. Chandrasekhar, A. Raza, M. Venkat Reddy, J. S. Yadav, *J. Comb. Chem.* **2002**, *4*, 652–655; d) D. Enders, A. Haertwig, J. Runsink, *Eur. J. Org. Chem.* **1998**, 1793–1802; e) P. Mayo, T. Hecnar, W. Tam, *Tetrahedron* **2001**, *57*, 5931–5941.

[18] For other dehydrating agents see: a) *N*,*N*-diethylaminosulfur trifluoride (DAST) and Methyl *N*-(triethylammoniosulphonyl)carbamate (Burgess salt): N. Maugein, A. Wagner, C. Mioskowsi, *Tetrahedron Lett.* **1997**, *38*, 1547–1550; b) *p*-toluensulphonic acid: T. Shimizu, Y. Hayashi, K. Teramura, *Bull. Chem. Soc. Jpn.* **1984**, 57, 2531–2534; c) 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) G. Giacomelli, L. De Luca, A. Porcheddu, *Tetrahedron*, **2003**, *59*, 5437–5440; d) Hydrotalcite/iodine. A. Cwik, Z. hell, A. Fuchs, D. Halmai, *Tetrahedron Lett.* **2005**, *46*, 6553–6566.

[19] a) V. A. Tartakovskii, I. E. Chlenov, S. S. Smagin, S. S. Novikov, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1964**, 549; *Izv. Akad. Nauk SSSR, Ser. Khim.* **1964**, *3*, 583–584; *Chem. Abs.* **1964**, *60*, 90803; b) V. A. Tartakovskii, S. S. Smagin, I. E. Chlenov, S. S Novikov, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1965**, 534–536; *Izv. Akad. Nauk SSSR, Ser. Khim.* **1965**, 552–554.

[20] For other selected examples see: a) S. Kanemasa, S. Kaga, E. Wada, *Tetrahedron Lett.* **1998**, *39*, 8865–8868; b) V. F. Rudchenko, V. N. Voznesenskii, R. G. Kostyanovskii, *Chem. Heterocycl. Compd.* **1991**, *27*, 96–102; *Khim. Geterotsikl. Soedin.* **1991**, *1*, 114–121; c) O. A. Ivanova, E. M. Budynina, E. B. Averina, T. S. Kuznetsova, N. S. Zefirov, *Synthesis* **2006**, 706–710.

[21] a) K. B. G. Torssell, O. Zeuthen, *Acta Chem. Scand. B* **1978**, *32*, 118–124; b) S. C. Sharma, K. B. G. Torssell, *Acta Chem. Scand. B* **1979**, *33*, 379–383; c) S. H. Andersen, N. B. Das, R. D. Jørgensen, G. Kjeldsen, J. S. Knudsen, S. C. Sharma, K. B. G. Torssell, *Acta Chem. Scand. B* **1982**, *36*, 1–14.

[22] For recent examples see: a) T. Gefflaut, C. Martin, S. Delor, P. Besse, H. Veschambre, J. Bolte, *J. Org. Chem.* **2001**, *66*, 2296–2301; b) Q. Cheng, T. Oritani, T. Horiguchi, Q. Shi, *Eur. J. Org. Chem.* **1999**, 2689–2693; c) C. Soucy, J.-É. Lacoste, L. Breau, *Tetrahedron Lett.* **1998**, *39*, 9117–9120.

[23] R. Warsinsky, E. Steckhan, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2027–2037.

[24] C.-P. Chuang, Y.-L. Wu, M.-C. Jiang, *Tetrahedron* **1999**, *55*, 11229–11236.

[25] B. B. Snider, Q. Che, *Tetrahedron* **2002**, *58*, 7821–7827.

[26] L. Cecchi, F. De Sarlo, F. Machetti, *Tetrahedron Lett.* **2005**, *46*, 7877–7879.

[27] L. Cecchi, F. De Sarlo, C. Faggi, F. Machetti, *Eur. J. Org. Chem.* **2006**, 3016–3020.

[28] L. Cecchi, F. De Sarlo, F. Machetti, *Eur. J. Org. Chem.* **2006**, 4852–4860.

[29] F. Machetti, L. Cecchi, E. Trogu, F. De Sarlo, *Eur. J. Org. Chem.* **2007**, 4352–4359.

[30] a) B. M. Trost, *Science* **1991**, *254*, 1471–1477; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281.

[31] B. M. Trost, L. Li, S. D. Guile, *J. Am. Chem. Soc.* **1992**, *114*, 8745–8141.

[32] P. M. Khan, R. Wu, K. S. Bisht, *Tetrahedron* **2007**, *63*, 1116–1126.

[33] L. Cecchi, F. De Sarlo, F. Machetti, *Synlett* **2007**, 2451–2453.

[34] A. Corsico Coda, G. Desimoni, A. Gamba, G. Invernizzi, P. P. Righetti, P. F. Seneci, G. Tacconi, *Gazz. Chim. Ital.* **1985**, *115*, 111–118.

[35] C. Christensen, K. Juhl, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 4875–4881.

[36] M. Bandini, F. Piccinelli, S. Tommasi, A. Umani-Ronchi, C. Ventrici, *Chem. Commun.* **2007**, 616–618.

[37] K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **2001**, *123*, 5843–5844.

[38] A complete study of the mechanism will be reported in due course.

[39] For selected processes utilising copper metal as catalyst/reagent source see: 1,3-dipolar cycloadditions of azides and alkynes (Huisgen reaction): a) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210–216; b) P. Appukkuttan, W. Dehaen, V. V. Fokin, E. van der Eycken, *Org. Lett.* **2004**, *6*, 4223–4225; coupling of aryl halides (Ullmann–Jourdan reaction): c) W. Boomgaarden, F. Vögtle, M. Nieger, H. Hupfer, *Chem. Eur. J.* **1999**, *5*, 345–355; d) R. Csuk, A. Barthel, C. Raschke, *Tetrahedron* **2004**, *60*, 5737–5750; coupling of aryl halides and alkyl halides e) J. K. Park, H. G. Lee, C. Bolm, B. M. Kim, *Chem. Eur. J.* **2005**, *11*, 945–950; decarboxylation: f) D. B. Boger, M. D. Mullican, *J. Org. Chem.* **1984**, *49*, 4033–4044; aza-Michael addition: g) A. K. Verma, R. Kumar, P. Chaudhary, A. Saxena, R. Shankar, S. Mozumdar, R. Chandra, *Tetrahedron Lett.* **2005**, *46*, 5229–5232; h) K. R. Reddy, N. S. Kumar, *Synlett* **2006**, 2246–2250; peptide nanotube preparation: i) J. Couet, J. D. J. S. Samuel, A. Kopyshev, S. Santer, M. Biesalski, *Angew. Chem.* **2005**, *117*, 3361–3365; *Angew. Chem. Int. Ed.* **2005**, *44*, 3297–3301. Allylic amination of olefins: j) R. S. Srivastava, *Tetrahedron Lett.* **2003**, *44*, 3271–3274.

[40] See reference [2d], Chapter 1, p. 45.

[41] For recent applications of hydroxyalkylisoxazolines see: a) N. Becker, E. M. Carreira, *Org. Lett.* **2007**, *9*, 3857–3858; b) D. Muri, N. Lohse, E. M. Carreira, *Angew. Chem.* **2005**, *117*, 4104–4106; *Angew. Chem. Int. Ed.* **2005**, *44*, 4036–4038.

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