A Domino Copper-Catalyzed C–N and C–O Cross-Coupling for the Conversion of Primary Amides into Oxazoles

Kerstin Schuh (née Müller), Frank Glorius*

Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Straße, 35032 Marburg, Germany
Fax +49(6421)2825629; E-mail: glorius@chemie.uni-marburg.de

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Abstract: A variety of oxazoles can efficiently be prepared, in a single step and in good yield, from primary amides and 1,2-dihaloalkenes using copper-catalysis. This new method allows the regioselective formation of a range of substituted oxazoles. The required 1,2-dihaloalkenes can be prepared by simple treatment of alkynes with elemental bromine or iodine.

Key words: oxazoles, C–N and C–O cross-coupling, copper, cyclization, domino reaction, heterocycles

The oxazole ring is an important structural motif present in a vast number of natural and unnatural compounds. Many different methods for the synthesis of this moiety have been developed, amongst which, cyclocondensation methods such as the Robinson–Gabriel cyclocondensation of α-acylamino ketones are the most popular. However, in many cases, rather harsh conditions for dehydrogenation are required and, therefore, there is a constant need for additional methods for the synthesis of more sensitive oxazoles. Herein, we report an efficient copper-catalyzed formation of oxazoles from 1,2-dihaloalkenes and primary amides, based on cross-coupling reactions.

We aimed for a novel, one-pot synthesis of oxazoles 1. Based on our experience with cross-coupling reactions, we planned to build up the oxazole ring with two successive C–N/C–O bond formations from an alkene component 3 and a primary carboxylic acid amide 4 (Scheme 1); ideally both steps being catalyzed by the same transition-metal catalyst. A related strategy has been successfully used by us and others in the synthesis of benzoxazoles from ortho-dihalobenzenes, thus complementing the traditional synthetic approaches to benzoxazoles. The copper-catalyzed amidation of aryl halides, developed by Buchwald et al., represents a powerful transformation and has found widespread applications. Furthermore, the use of alkenyl halides as substrate was also reported. Consequently, our retrosynthetic analysis comprised of the copper-catalyzed formation and cyclization an halide-substituted enamides 2 (Scheme 1) and, ideally, two successive C–N/C–O bond formations incorporated in a domino process.

Scheme 1 Oxazole synthesis by successive C–N/C–O bond formations

1,2-Dihalogenated olefins 3 are the key synthetic intermediates of this new oxazole synthesis. Fortunately, these olefins can easily be prepared by the reaction of terminal or internal alkynes with bromine or iodine in dichloromethane at ambient temperature, resulting in 1,2-dihalogenated olefins in good yields (Table 1). The stereochemistry of the products obtained were determined by comparison of the NMR data with literature values. In many cases, the E-product was formed predominantly, with the two iodinated olefins 3b and 3d being exclusively E-configured. In contrast, silylated olefin 3e was obtained nearly exclusively as the Z-isomer (entry 6).

As a starting point for our investigation, 1,2-dibromophenylethylene (3a) was reacted with benzamide under copper catalysis. Copper(I) iodide, N,N′-dimethylethlyenediamine (DMEDA), potassium carbonate, toluene and heating (110 °C), conditions previously employed in the synthesis of benzoxazoles by us, were found to be optimal. It is important to note that it was beneficial to degas the solvent in order to avoid butadiyne products resulting from oxidative coupling. The highest yields were obtained...
when 10 mol% of the copper catalyst were employed. Under these conditions, an 11:1 ratio of regioisomeric 2,5- and 2,4-diphenyloxazole was obtained in 70% yield (Table 2, entry 1). Using the diiodo- instead of the dibromo-substituted phenylethylene resulted in an equimolar mixture of the two regioisomeric products (entry 2).

A variety of different primary amides was reacted with 1,2-dibromophenylethylene (3a) under the same conditions (Table 2). With substituted aromatic amides, comparably good results were obtained (entries 3–5). Aliphatic amides reacted as well, although with somewhat lower yields (entries 6–12). In these cases, part of the reduced yield was due to the formation of diamidation side-products.

Again, using 1,2-diiodophenylethylene (3b) instead of the dibromo derivative 3a (entry 7) led to a change in the ratio of regioisomeric products (entry 8). In the latter case, the temperature was gradually increased from 40 °C to 110 °C. Investigation by means of GC-MS revealed that the enamide corresponding to the 2,4-disubstituted oxazole was formed at 40 °C already, whereas the enamide of the 2,5-disubstituted oxazole needed increased temperatures and formed at 80 °C. In addition, the former enamide cyclized at a temperature of 80 °C, whereas the latter enamide cyclization required heating at 110 °C. This observation of enamide intermediates by GC-MS en route to the cyclization products was not observed in the case of benzoxazoles.6● Discontinuation of this reaction after 21 hours (instead of 45 h for complete conversion), allowed the isolation of 22% of the enamide intermediate product. This intermediate cyclized smoothly under standard conditions resulting in the desired product in 93% yield (Scheme 3). Interestingly, the reaction of acrylamide with 1,2-diiodo-1,2-diphenylethylene resulted in

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>X</th>
<th>Olefin</th>
<th>E/Z</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>Br</td>
<td>3a</td>
<td>63:37</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>H</td>
<td>I</td>
<td>3b</td>
<td>100:0</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>n-Hex</td>
<td>H</td>
<td>I</td>
<td>3d</td>
<td>77:23</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>n-Hex</td>
<td>H</td>
<td>Br</td>
<td>3e</td>
<td>1:99</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>SiMe3</td>
<td>Br</td>
<td>3f</td>
<td>17:83</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>Ph</td>
<td>Br</td>
<td>3g</td>
<td>61:39</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>CO2Me</td>
<td>CO2Me</td>
<td>Br</td>
<td>3h</td>
<td>44:56</td>
<td>72</td>
</tr>
</tbody>
</table>

a Determined by GC-MS.
b Isolated yield.
the predominant formation of the 2,4-disubstituted oxazole (entry 12).

Using dibromoalkenes as starting materials, a strong preference for the formation of the 2,5-disubstituted oxazoles was observed, whereas with diiodoalkenes greatly diminished selectivities were obtained. In the former case, the amide attacks the less sterically hindered position of the alkene. The more reactive diiodo-substituted olefins, however, react rather unselectively at both of the two alkene positions.

Intriguingly, \(E\), \(Z\) - or mixtures of \(E\) - and \(Z\)-configured dihalogenated olefins all reacted to form the desired oxazole products. In some cases, an isomerization of \(E\)- and \(Z\)-configured substrates was observed under the reaction conditions. However, no indication of isomerization of the \(E\)-configured diiodinated olefins was observed.\(^8\)

Thus, an isomerization prior to enamide formation does not seem to be a prerequisite for oxazole formation.

Dibromooctene (3c) has a much lower propensity to undergo oxidative homo-coupling. In addition, it is less reactive than the 1,2-dibromophenylethylene (3a) and therefore higher reaction temperatures (130 °C) were required for the enamide to cyclize (Table 3). Again, the formation of 2,5-disubstituted oxazoles was favored (entry 1). Use of the diiodo-substituted substrate still resulted in the predominant formation of the 2,5-disubstituted oxazole (entry 2).

### Table 3 Reaction of Primary Amides with Dibromooctene (3c)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product ratio</th>
<th>Oxazole</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>8:1</td>
<td>Ij</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>(3:1)</td>
<td>Ij</td>
<td>(42)</td>
</tr>
<tr>
<td>3</td>
<td>4-HNC6H4</td>
<td>14:1</td>
<td>Ik</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu</td>
<td>9:1</td>
<td>II</td>
<td>30</td>
</tr>
</tbody>
</table>

\(^a\) Results obtained with 1,2-diido-o-hexylethene (3d) are shown in brackets.

\(^b\) 2,5- to 2,4-Oxazole ratio determined by GC-MS.

\(^c\) Isolated combined yield.

### Table 4 Reaction of Benzamide with 1,2-Dibrominated Tetrasubstituted Alkenes

<table>
<thead>
<tr>
<th>Entry R</th>
<th>R1</th>
<th>R2</th>
<th>Oxazole</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>SiMe3</td>
<td>1m</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph</td>
<td>1n</td>
<td>24</td>
</tr>
<tr>
<td>3(^b)</td>
<td>CO2Me</td>
<td>CO2Me</td>
<td>1o</td>
<td>12</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield.

\(^b\) K3PO4 (3 equiv) was used as base.

A number of amides and amide derivatives, as well as 1,2-dihalogenated olefins did not provide oxazoles under these conditions (Figure 1); however, 1,2-dibrominated tetrasubstituted alkenes did undergo this transformation (Table 4). Since methods for the regioselective formation of 2,4,5-trisubstituted oxazoles are especially desirable, it was pleasing to find that 1,2-dibromo-1-trimethylsilyl-2-phenylethylene (3e) reacted highly regioselectively to give one oxazole only (entry 1); the other regioisomer could not be detected. Acid mediated cleavage of the trimethylsilyl group of this oxazole product (p-TsOH, MeOH, r.t.) allowed for the selective formation of 2,4-diphenyl oxazole in 91% yield. This route is complementary to the results reported in Table 2 and Table 3, since it provides ready access to the isomer previously formed as the minor isomer. 1,2-Dibromo-1,2-diphenylethylene can also react with benzamide to form the desired oxazole product, albeit with reduced yield (entry 2). Presumably, this is due to a reversal of the formation of the olefin substrate back to tolane and bromine. Hydroxy-substituted olefin 3h did not provide any product.

In summary, we have developed a new copper-catalyzed method for the regioselective, single-step preparation of 2,5-disubstituted oxazoles from readily available 1,2-dihalogenated olefins and primary amides. Many functional groups such as halides, amino-, methoxy- and silyl groups...
were tolerated. In addition, use of a silylated olefin allowed the selective preparation of 2,4-disubstituted oxazoles after acid mediated protodesilylation. The required dihalogenated olefins were easily prepared in high yields from the corresponding alkynes by treatment with bromine or iodine.

Chemicals were purchased in commercially available qualities (puriss., p.a. or purum) from Fluka, Aldrich, Acros, Lancaster and Merck and were used without further purification. Solvents toluene and CH₂Cl₂ were of technical quality and were distilled and dried over CaH₂. Solvents for extractions and column chromatography were of technical quality and were distilled prior to use. Molecular sieves (4 Å) were activated by microwave irradiation (3 × 3 min). For flash chromatography, Merck silica gel 60 (230–400 mesh) was used. NMR spectra were recorded on an ARX 300 or DRX 400 spectrometer (Bruker) in CDCl₃; chemical shifts (δ) are given in ppm relative to TMS, and coupling constants (J) are given in Hertz. For IR, a Bruker IFS 88 was used, with wavenumbers given in cm⁻¹. For MS (EI, 70 eV), a Varian CH7 was used and for HRMS, a Finnigan LTQ FT or TSQ 700 was used.

Synthesis of Oxazoles; General Procedure

K₂CO₃, CuI and amide were weighed into a vial under air. The vial was evacuated and filled with argon, followed by the addition of diiodomethylene (23.2.99 mmol, 2.99 equiv), CuI (19.8 mg, 0.10 mmol, 0.10 equiv) and DMEDA (21.5 mL, 0.21 mmol, 0.21 equiv). The products were obtained after purification by flash chromatography. The solvent was removed under reduced pressure and the products were purified by flash chromatography.

2,4-Diphenyloxazole and 2,5-Diphenyloxazole (1a)

The general procedure described above (reaction time: 13 h) was followed using 1,2-dibromoethane (3 mL) and Et₃N-impregnated silica to give 2,5-Diphenyloxazole (22 mg, 8%) in a 11:1 ratio (GC-MS).

2-(4-Methoxyphenyl)-5-phenyloxazole

Yield: 41 mg, 19%; pale-yellow solid; Rf = 0.34 (pentane–EtOAc, 15:1).

IR (KBr): 2962 (w), 1670 (w), 1586 (w), 1553 (s), 1488 (s), 1446 (s), 1339 (m), 1290 (w), 1262 (m), 1157 (w), 1123 (m), 1069 (s), 1022 (m), 929 (m), 782 (m), 755 (s), 718 (s), 705 (w), 691 (m) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.5, 1.6 Hz, 1 H, HCO, and 2,5-Diphenyloxazole (1a) in a 1:1 ratio (GC-MS).

2,4-Diphenyloxazole

Yield: 80 mg (36%); pale-yellow solid; Rf = 0.34 (pentane–EtOAc, 15:1).

IR (KBr): 2962 (w), 1670 (w), 1586 (w), 1553 (s), 1488 (s), 1446 (s), 1339 (m), 1290 (w), 1262 (m), 1157 (w), 1123 (m), 1069 (s), 1022 (m), 929 (m), 782 (m), 755 (s), 718 (s), 705 (w), 691 (m) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 8.15–8.11 (m, 2 H, HCAr,2-Ph), 7.98 (s, 1 H, HCO), 7.85–7.82 (m, 2 H, HCAr,4-Ph), 7.51–7.41 (m, 5 H, HCAr), 7.34 (tt, J = 7.5, 1.2 Hz, 1 H, HCAr,4-Ph).

13C NMR (75 MHz, CDCl₃): δ = 162.0 (OCH₃H), 151.2 (Cq), Cq, 133.4, 131.2, 130.4, 128.1, 126.5, 125.7 (all Cq).

HRMS (EI): m/z (%) = 221 (56) [M⁺], 191 (52), 165 (9), 105 (23), 89 (100), 77 (19), 63 (26), 51 (17), 39 (17), 28 (28).

HRMS (ESI): m/z (%) = 221 (56) [M⁺], 191 (52), 165 (9), 105 (23), 89 (100), 77 (19), 63 (26), 51 (17), 39 (17), 28 (28).

Synthesis of 2,4-Diphényloxazol and 2-(4-Methoxyphenyl)-5-Phenylloxazole (1b)

The general procedure described above (reaction time: 24 h) was followed using dibromophenylethylene (3a; 259 mg, 0.99 mmol, 1.00 equiv), 4-methoxybenzamide (165 mg, 1.09 mmol, 1.00 equiv), K₂CO₃ (411 mg, 2.97 mmol, 3.00 equiv), Cu (18.8 mg, 0.10 mmol, 0.10 equiv) and DMEDA (21.5 mL, 0.20 mmol, 0.20 equiv). The products were obtained after purification by flash chromatography (pentane–EtOAc, 10:1) on Et₃N-impregnated silica to give 2,4-bib and 2,5-bib in a 1:21 ratio (GC-MS).

2-(4-Methoxyphenyl)-5-Phenylloxazole

Yield: 153 mg (62%); pale-yellow solid; Rf = 0.16 (pentane–EtOAc, 10:1).

IR (KBr): 2968 (w), 2840 (w), 1610 (s), 1589 (w), 1469 (s), 1460 (w), 1442 (w), 1418 (w), 1350 (m), 1301 (s), 1251 (s), 1173 (m), 1154 (w), 1107 (w), 1024 (s), 828 (m), 762 (m), 736 (m), 687 (m) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 8.06–8.03 (m, 2 H, HCAr,2-Ph), 7.71–7.68 (m, 2 H, HCAr), 7.45–7.40 (m, 3 H, HCAr, HCN), 7.31 (tt, J = 7.5, 1.6 Hz, 1 H, HCAr,4-Ph), 7.00–6.97 (m, 2 H, HCAr), 3.85 (s, 3 H, OCH₃).

13C NMR (75 MHz, CDCl₃): δ = 161.3 (Cq), 161.2 (Cq), 150.6 (Cq), 128.8 (Cq), 128.1 (2 × Cq), 127.9 (Cq), 124.0 (Cq), 123.2 (Cq), 120.2 (Cq), 114.2 (Cq), 55.3 (OCH₃).

HRMS (EI): m/z (%) = 251 (100) [M⁺], 236 (5), 181 (5), 77 (6), 28 (27).

HRMS (ESI): m/z (%) = 251 (100) [M⁺], 236 (5), 181 (5), 77 (6), 28 (27).

HRMS (EI): m/z (%) = 251 (100) [M⁺], 236 (5), 181 (5), 77 (6), 28 (27).

HRMS (ESI): m/z (%) = 251 (100) [M⁺], 236 (5), 181 (5), 77 (6), 28 (27).

HRMS (EI): m/z (%) = 251 (100) [M⁺], 236 (5), 181 (5), 77 (6), 28 (27).

HRMS (EI): m/z (%) = 251 (100) [M⁺], 236 (5), 181 (5), 77 (6), 28 (27).
Yield: 150 mg (61%); pale-yellow solid; Rf = 0.18 (pentane–EtOAc, 10:1).

IR (KBr): 3444 (br s), 3099 (w), 3053 (w), 2924 (w), 1644 (w), 1601 (w), 1475 (s), 1446 (m), 1398 (m), 1357 (m), 1263 (m), 1232 (m), 1122 (w), 1075 (s), 1009 (m), 943 (w), 932 (m), 914 (w), 833 (s), 762 (s), 736 (s), 694 (s), 657 (w), 540 (w) cm⁻¹.

HRMS (EI): calcd for C₁₇H₁₂NO: 246.0919; found: 246.0920.

The general procedure described above (reaction time: 14 h) was followed using dibromophenylethylene (3a; 260 mg, 0.99 mmol, 1.0 equiv) and K₂CO₃ (415 mg, 3.00 mmol, 3.03 equiv), CuI (18.8 mg, 0.10 mmol, 0.10 equiv) and DMEDA (22 μL, 0.20 mmol, 0.20 equiv). The products were obtained after purification by flash chromatography (pentane–EtOAc, 30:1) to give 2,4-IE and 2,5-IE in a 1:20 ratio (GC-MS).

2-Styryl-4-phenyloxazole and 2-Styryl-5-phenyloxazole (1c)
The general procedure described above (reaction time: 14 h) was followed using dibromophenylethylene (3a; 260 mg, 0.99 mmol, 1.0 equiv), cinnamide (220 mg, 1.49 mmol, 1.50 equiv), K₂CO₃ (415 mg, 3.00 mmol, 3.03 equiv), CuI (18.8 mg, 0.10 mmol, 0.10 equiv) and DMEDA (22 μL, 0.20 mmol, 0.20 equiv). The products were obtained after purification by flash chromatography (pentane–EtOAc, 30:1) to give 2,4-IE and 2,5-IE in a 1:20 ratio (GC-MS).

2-Styryl-5-phenyloxazole
Yield: 150 mg (61%); pale-yellow solid; Rf = 0.18 (pentane–EtOAc, 10:1).

IR (KBr): 3444 (br s), 3099 (w), 3053 (w), 2924 (w), 1644 (w), 1601 (w), 1475 (s), 1446 (m), 1398 (m), 1357 (m), 1263 (m), 1232 (m), 1122 (w), 1075 (s), 1009 (m), 943 (w), 932 (m), 914 (w), 833 (s), 762 (s), 736 (s), 694 (s), 657 (w), 540 (w) cm⁻¹.

HRMS (EI): calcd for C₁₇H₁₂NO: 246.0919; found: 246.0920.

2-Styryl-4-phenyloxazole
Yield: 25 mg (10%); pale-yellow solid; Rf = 0.17 (pentane–EtOAc, 30:1).

IR (KBr): 3051 (w), 1659 (w), 1635 (w), 1605 (w), 1520 (s), 1479 (m), 1445 (m), 1357 (m), 1286 (w), 1161 (w), 1132 (w), 1074 (w), 1062 (w), 972 (s), 941 (m), 909 (w), 830 (m), 754 (s), 688 (s), 501 (s) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.90 (s, 1 H, HCO), 7.80–7.77 (m, 2 H, H₂Ar), 7.61–7.55 (m, 3 H, H₂Ar, HCN), 7.46–7.32 (m, 6 H, H₂Ar, HCN), 7.02 (d, J = 16.2 Hz, 1 H, HCN).

13C NMR (75 MHz, CDCl₃): δ = 161.1 (OC=O, 150.9 (OC=O), 135.8, 135.6, 129.1, 128.9, 128.4, 127.9, 127.2, 124.2, 123.7, 113.9 (C-CN). MS (EI): m/z (%) = 246 (100) [M⁺], 115 (23), 77 (18), 28 (59).

HRMS (EI): m/z calcd for C₁₇H₁₂NO: 246.0921; found: 246.0920.

2-(4-Bromophenyl)-4-phenyloxazole and 2-(4-Bromophenyl)-5-phenyloxazole (1d)
The general procedure described above (reaction time: 14 h) was followed using dibromophenylethylene (3a; 263 mg, 1.00 mmol, 1.00 equiv), formamide (60 μL, 1.51 mmol, 1.51 equiv), K₂CO₃ (415 mg, 3.00 mmol, 3.00 equiv), CuI (38.9 mg, 0.20 mmol, 0.20 equiv) and DMEDA (44 μL, 0.40 mmol, 0.40 equiv). In contrast to the general procedure, formamide was added after the addition of toluene. The product was obtained after purification by flash chromatography (pentane–EtOAc, 10:1). 4-Phenylloxazole was not isolated. 2,4-IE and 2,5-IE were obtained as a mixture in a ratio of 1:10 (GC-MS).

Yield: 47 mg (32%); pale-yellow oil; Rf = 0.18 (pentane–EtOAc, 10:1).

IR (KBr): 3131 (w), 3062 (w), 2926 (w), 1703 (s), 1600 (w), 1506 (m), 1485 (m), 1449 (m), 1315 (w), 1273 (m), 1177 (w), 1105 (m), 1023 (w), 942 (m), 916 (w), 824 (w), 763 (s), 714 (m), 692 (s), 641 (s) cm⁻¹.

HRMS (EI): m/z calcd for C₁₅H₁₀NOBr: 298.9946; found: 298.9947.

2-(4-Bromophenyl)-4-phenyloxazole
Yield: 26 mg (9%); colorless solid; Rf = 0.23 (pentane–EtOAc, 30:1).

IR (KBr): 2924 (w), 1719 (w), 1475 (s), 1446 (m), 1399 (m), 1263 (m), 1232 (w), 1122 (w), 1075 (s), 1009 (m), 943 (w), 932 (m), 914 (w), 833 (s), 762 (s), 736 (s), 694 (s), 657 (w), 540 (w) cm⁻¹.

HRMS (EI): m/z calcd for C₁₅H₁₀NOBr: 298.9946; found: 298.9958.

5-Phenylloxazole (1e)
The general procedure described above (reaction time: 13 h) was followed using dibromophenylethylene (3a; 263 mg, 1.00 mmol, 1.00 equiv), formamide (60 μL, 1.51 mmol, 1.51 equiv), K₂CO₃ (415 mg, 3.00 mmol, 3.00 equiv), CuI (38.9 mg, 0.20 mmol, 0.20 equiv) and DMEDA (44 μL, 0.40 mmol, 0.40 equiv). In contrast to the general procedure, formamide was added after the addition of toluene. The product was obtained after purification by flash chromatography (pentane–EtOAc, 10:1). 4-Phenylloxazole was not isolated. 2,4-IE and 2,5-IE were obtained as a mixture in a ratio of 1:10 (GC-MS).

Yield: 47 mg (32%); pale-yellow oil; Rf = 0.18 (pentane–EtOAc, 10:1).
2-Methyl-4-phenyloxazole and 2-Methyl-5-phenyloxazole (1f)

Synthesis with dibromophenylethylene: The general procedure described above (reaction time: 24 h) was followed using dibromophenylethylene (3a; 278 mg, 1.06 mmol, 1.0 equiv), acetamide (75.4 mg, 1.28 mmol, 1.21 equiv), CuI (41.1 mg, 0.22 mmol, 0.21 equiv) and DMEDA (44 μL, 0.40 mmol, 0.40 equiv). Purification by flash chromatography (pentane–EtOAc, 30:1) in a ratio of 1:8 (GC-MS).

Yield: 33 mg (21%); pale-yellow solid; 2-Methyl-4-phenyloxazole was not isolated.

Synthesis with diiodophenylethylene: The general procedure described above (reaction time: 45 h) was followed using diiodophenylethylene (3a; 357 mg, 1.00 mmol, 1.0 equiv), acetamide (66.1 mg, 1.12 mmol, 1.12 equiv), CuI (41.5 mg, 0.21 mmol, 0.20 equiv). Purification by flash chromatography (pentane–EtOAc, 10:1) gave 2.4-If and 2.5-If in a 1:10 ratio (GC-MS). 2-Methyl-5-phenyloxazole (81 mg, 48%) was obtained as a colorless solid. 2-Methyl-4-phenyloxazole was not isolated.

Yield: 33 mg (21%); pale-yellow solid; 2-Methyl-4-phenyloxazole was not isolated.

2-Propyl-4-phenyloxazole and 2-Propyl-5-phenyloxazole (1g)

The general procedure described above (reaction time: 24 h) was followed using dibromophenylobenzene (3a; 263 mg, 1.00 mmol, 1.0 equiv), butyramide (116 mg, 1.14 mmol, 1.15 equiv), K2CO3 (411 mg, 2.97 mmol, 3.0 equiv) and DMEDA (22 μL, 0.20 mmol, 0.20 equiv). Purification by flash chromatography (pentane–EtOAc, 30:1–10:1) gave 2.4-1g and 2.5-1g in a ratio of 1:8 (GC-MS).

Yield: 74.2 mg (40%); colorless oil; Rf = 0.21 (pentane–EtOAc, 10:1).

IR (film): 3061 (w), 2965 (s), 2934 (m), 2874 (w), 1697 (s), 1578 (w), 1557 (m), 1489 (m), 1382 (w), 1274 (w), 1198 (w), 1134 (m), 1083 (m), 1054 (w), 1026 (w), 967 (w), 942 (w), 762 (s), 692 (s) cm⁻¹.

HRMS (EI): m/z = 187 (37) [M⁺], 170 (159), 100 (103), 77 (89), 77 (45), 51 (8), 32 (16), 28 (100).

2-tert-Butyl-4-phenyloxazole and 2-tert-Butyl-5-phenyloxazole (1h)

The general procedure described above (reaction time: 62 h) was followed using dibromophenylobenzene (3a; 259 mg, 0.99 mmol, 1.0 equiv), pivalamide (116 mg, 1.14 mmol, 1.15 equiv), K2CO3 (411 mg, 2.97 mmol, 3.0 equiv) and DMEDA (22 μL, 0.20 mmol, 0.20 equiv). The product was obtained after purification by flash chromatography (pentane–EtOAc, 30:1–10:1).

Yield: 112 mg (56%); colorless oil; Rf = 0.24 (pentane–EtOAc, 10:1).

IR (film): 3448 (w), 3061 (w), 2972 (s), 2932 (w), 1715 (w), 1590 (m), 1566 (m), 1478 (m), 1449 (m), 1396 (w), 1367 (w), 1294 (w), 1247 (w), 1140 (m), 1110 (m), 1071 (w), 942 (m), 743 (s), 693 (s) cm⁻¹.
**Conversion of Primary Amides into Oxazoles**

1H NMR (300 MHz, CDCl3): δ = 7.63–7.60 (m, 2 H, HCAr), 7.42–7.37 (m, 2 H, HCAr), 7.32–7.26 (tt, J = 7.5, 1.2 Hz, 1 H, HCN), 7.21 (s, 1 H, HCN), 1.45 [s, 9 H, (CH3)3].

13C NMR (75 MHz, CDCl3): δ = 168.5 (OC=N), 159.9 (OC=C), 128.9 (2 × HCAr), 128.5 (Cq), 127.9 (Cq), 124.2 (2 × HCAr), 123.4 (Cq), 121.4 (Cq).

MS (EI): m/z (%) = 171 (90) [M]+, 143 (12), 116 (32), 105 (19), 90 (21), 77 (78), 63 (9), 51 (24), 39 (24), 32 (15), 28 (100).

HRMS (EI): m/z calcd for C11H9NO: 171.0685; found: 171.0686.

**2-Phenyl-4-hexyloxazole and 2-Phenyl-5-hexyloxazole (1j) from Di-bromo-1-octene**

The general procedure described above (reaction time: 13 h) was followed using 1,2-dibromo-1-octene (3d; 266 mg, 0.99 mmol, 1.00 equiv), benzamide (132 mg, 1.08 mmol, 1.09 equiv), K2CO3 (408 mg, 2.95 mmol, 2.98 equiv), Cu (19.2 mg, 0.10 mmol, 0.10 equiv) and DMDMA (22 μL, 0.20 mmol, 0.20 equiv). In contrast to the general procedure, the reaction was performed at 130 °C.

Purification by flash chromatography (hexane/Et2O 1:1) gave 2,4-i-J (1 mg, 9%) and 2,5-i-J (134 mg, 59%) as pale-yellow liquids in a 1:8 ratio (GC-MS).

**2-Phenyl-4-hexyloxazole and 2-Phenyl-5-hexyloxazole (1j) from (E)-Diido-1-octene**

The general procedure described above (reaction time: 24 h) was followed using 1,2-diido-1-octene (3d; 359 mg, 0.99 mmol, 1.00 equiv), benzamide (134 mg, 1.10 mmol, 1.11 equiv), K2CO3 (415 mg, 3.00 mmol, 3.04 equiv), Cu (20.1 mg, 0.11 mmol, 0.11 equiv) and DMDMA (24 μL, 0.22 mmol, 0.22 equiv). In contrast to the general procedure, the reaction was performed at 130 °C.

Purification by flash chromatography (pentane–EtOAc, 30:1) gave 2,4-i-J (26 mg, 11%) and 2,5-i-J (68 mg, 31%) in a 1:3 ratio (GC-MS).

**2-Phenyl-5-hexyloxazole**

Pale-yellow liquid; Rf = 0.10 (pentane–EtOAc, 30:1).

IR (film): 3396 (br s), 3064 (s), 2925 (m), 2856 (m), 1634 (s), 1598 (w), 1489 (w), 1478 (m), 1385 (w), 1278 (m), 1187 (w), 1072 (w), 917 (s), 761 (m), 696 (s), 606 (m), 567 (m), 503 (s), 465 (s), 430 (m), 398 (s), 360 (m), 334 (m), 310 (s), 287 (m), 263 (m), 248 (m), 224 (m), 200 (s), 180 (m), 164 (m), 140 (m), 124 (m), 108 (m), 92 (m), 76 (s), 63 (m), 52 (s), 39 (m), 27 (w), 19 (w).

HRMS (EI): m/z calcd for C11H9NO: 171.0682; found: 171.0683.

**2-Phenyl-4-hexyloxazole**

Pale-yellow liquid; Rf = 0.47 (hexane–EtOAc, 10:1).
IR (film): 3429 (w), 3064 (w), 2928 (s), 2857 (m), 1689 (w), 1590 (m), 1555 (m), 1486 (m), 1467 (m), 1450 (m), 1378 (w), 1345 (m), 1286 (w), 1103 (m), 1062 (m), 1023 (w), 934 (m), 778 (m), 713 (s), 691 (s) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 8.04–8.01 (m, 2 H, HCAr), 7.47–7.41 (m, 4 H, HCAr, HCO), 2.60 [t, J = 7.7 Hz, 2 H, CH₂(CH₃)₃CH₂CH₂], 1.73–1.63 [m, 2 H, CH₂CH₂(CH₃)₂CH₂], 1.41–1.25 [m, 6 H, CH₂CH₂(CH₃)₂CH₂], 0.91–0.87 (m, 3 H, CH₃).

13C NMR (75 MHz, CDCl₃): δ = 161.3 (OC=O), 142.7 (C=O), 133.8 (HCO), 130.0 (HCAr). 128.7 (2 × HCAr), 31.6, 29.0, 28.4, 26.5, 22.6, 14.0 (CH₃).

MS (EI): m/z (%) = 229 (18) [M⁺], 207 (20), 149 (15), 137 (15), 125 (15), 113 (15), 101 (15), 99 (15), 41 (9), 28 (18).

HRMS (EI): m/z calcd for C₁₅H₂₃NO: 229.1470; found: 229.1468.

2-(4-Aminophenyl)-4-hexyloxazole and 2-(4-Aminophenyl)-5-hexyloxazole (1k)
The general procedure described above (reaction time: 38 h) was followed using 1,2-dibromo-1-octene (3c: 270 mg, 1.00 mmol, 1.00 equiv), pivalamide (112 mg, 1.10 mmol, 1.10 equiv), K₂CO₃ (416 mg, 3.01 mmol, 3.01 equiv), Cu (38.4 mg, 0.20 mmol, 0.20 equiv) and DMEDA (54 μL, 0.50 mmol, 0.50 equiv). Purification by flash chromatography (pentane) on Et₂O-saturated silica gave 2.4-1l and 2.5-1l in a 1:9 ratio (GC-MS). 2-(tert-Butyl)-4-hexyloxazole (2,4-I) was not isolated.

Yield: 62 mg (30%); colorless oil; Rf₁ = 0.14 (pentane–EtOAc, 10:1).

IR (film): 3438 (w), 3118 (w), 2960 (s), 2831 (s), 2860 (m), 1693 (w), 1607 (w), 1563 (m), 1346 (w), 1307 (v), 1262 (w), 1214 (w), 1142 (s), 1113 (m), 1030 (m), 975 (m), 820 (m), 751 (w), 728 (w) cm⁻¹.

HRMS (EI): m/z calcd for C₁₅H₂₀ON₂: 244.1576; found: 244.1578.

5-(Trimethylsilyl)-2,4-diphenyloxazole (1m)
The general procedure described above (reaction time: 21 h) was followed using 1,2-dibromo-1-trimethylsilyle-2-phenylethylene (3e: 295 mg, 0.88 mmol, 1.00 equiv, melted), benzamidane (134 mg, 1.10 mmol, 1.25 equiv), K₂CO₃ (417 mg, 3.01 mmol, 3.45 equiv), Cu (19.8 mg, 0.10 mmol, 0.11 equiv) and DMEDA (22 μL, 0.20 mmol, 0.23 equiv). Purification by flash chromatography (pentane–EtOAc, 50:1) gave 2.4-1m. No 2.5-1m was detected (GC-MS).

Yield: 143 mg (56%); colorless solid; Rf₁ = 0.19 (pentane–EtOAc, 50:1).

IR (KBr): 2924 (m), 1587 (w), 1554 (w), 1486 (m), 1446 (m), 1336 (m), 1253 (m), 1138 (w), 1082 (w), 1067 (w), 1025 (w), 976 (m), 919 (m), 845 (s), 779 (w), 761 (m), 720 (m), 687 (m), 634 (m) cm⁻¹.

IR (film): 3438 (w), 3192 (w), 2960 (s), 2831 (s), 2860 (m), 1693 (w), 1607 (w), 1563 (m), 1346 (w), 1307 (v), 1262 (w), 1214 (w), 1142 (s), 1113 (m), 1030 (m), 975 (m), 820 (m), 751 (w), 728 (w) cm⁻¹.

HRMS (EI): m/z calcd for C₁₅H₂₀ON₂S: 249.1236; found: 249.1227.

2.4,5-Trimphenyloxazole (1n)
The general procedure described above (reaction time: 44 h) was followed using 1,2-dibromo-1,2-diphenylethylene (3f: 340 mg, 1.01 mmol, 1.00 equiv), benzamidane (136 mg, 1.11 mmol, 1.10 equiv), K₂CO₃ (422 mg, 3.05 mmol, 3.02 equiv), Cu (20.5 mg, 0.11 mmol, 0.10 equiv) and DMEDA (24 μL, 0.22 mmol, 0.22 equiv). In contrast to the general procedure, the olefin was weighed into the vial with the other solids. The product was obtained after purification by flash chromatography (pentane–EtOAc, 100:1).

Yield: 70 mg (24%); colorless solid; Rf₁ = 0.20 (pentane–EtOAc, 100:1).
IR (KBr): 3054 (w), 1704 (w), 1600 (w), 1552 (w), 1501 (w), 1486 (m), 1447 (m), 1365 (w), 1326 (w), 1244 (w), 1086 (w), 1069 (m), 1054 (w), 1023 (m), 965 (m), 769 (s), 728 (m), 714 (m), 693 (s), 607 (w) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 8.20–8.17 (m, 2 H, HC₅Ar), 7.77–7.69 (m, 4 H, HC₆Ar), 7.52–7.35 (m, 9 H, HC₆Ar).

13C NMR (75 MHz, CDCl₃): δ = 160.1 (OC=N), 145.6, 136.8, 132.6, 130.3, 129.0, 128.7, 128.6, 128.5, 128.2, 128.1, 127.4, 126.6, 126.5 (all CAr).

MS (EI): m/z (%): 297 (100) [M⁺], 269 (11), 165 (88), 105 (10), 89 (20), 77 (16), 63 (8), 51 (6), 28 (27).

HRMS (EI): m/z calcd for C₁₃H₁₁NO₅: 297.0632; found: 297.0632.

Dimethyl-2-Phenoxazol4,5-dicarboxylate (1o)
The general procedure described above (reaction time: 48 h) was followed using 2,3-dimorobut-2-enedimethylether (3g: 47 mg, 1.58 mmol, 1.45 equiv), benzamide (133 mg, 1.09 mmol, 1.00 equiv), CuI (20.5 mg, 0.11 mmol, 0.10 equiv) and DMEDA (24 μL, 0.22 mmol, 0.20 equiv). In contrast to the general procedure, K₂PO₄ (694 mg, 3.27 mmol, 3.00 equiv) was used as base. The product was obtained after purification by flash chromatography (hexane–EtOAc, 5:1).

Yield: 33 mg (12%); pale-yellow solid; Rf = 0.09 (hexane–EtOAc, 5:1).

IR (KBr): 2955 (w), 1760 (s), 1606 (w), 1533 (m), 1481 (m), 1441 (m), 1349 (s), 1324 (m), 1301 (m), 1263 (m), 1225 (s), 1138 (m), 1092 (s), 1073 (m), 965 (w), 828 (m), 794 (m), 769 (m), 719 (s), 692 (m) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 5.78–5.76 (m, 3 H, HC₅Ar), 4.00 (s, 3 H, CH₃), 3.99 (s, 3 H, OCH₃).

13C NMR (75 MHz, CDCl₃): δ = 162.5 (C=O, 81.0 (C=O), 157.2 (OC=O), 141.9 (OC=O), 137.3 (OC=O), 132.1 (HC₆Ar), 128.9 (2 × HC₆Ar), 127.5 (2 × HC₆Ar), 125.4 (HC₅Ar), 52.9 (OCH₃), 52.8 (OCH₂).

MS (EI): m/z (%) = 261 (49) [M⁺], 202 (100), 174 (34), 146 (14), 115 (6), 105 (14), 89 (6), 77 (19), 51 (6), 28 (11).

HRMS (EI): m/z calcd for C₁₃H₁₁NO₅: 261.0627; found: 261.0632.

1,2-Dibromophenylethylene (3a)³
To a solution of phenylacetylene (4.45 g, 43.6 mmol, 1.05 equiv) in CH₂Cl₂ (150 mL) was added a solution of Br₂ (6.55 g, 41.0 mmol, 1.00 equiv) in CH₂Cl₂ (250 mL). After stirring at rt. for 2 h, aq Na₂S₂O₅ (100, 300 mL) was added and the organic layer was separated, washed with H₂O (2 × 200 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The product was recrystallized (MeOH) to give 3a.

Yield: 11.7 g (65%); colorless product; Rf = 0.32 (pentane).

1H NMR (300 MHz, CDCl₃): δ = 7.30–7.27 (m, 5 H, HC₆Ar), 7.19 (s, 1 H, HC₅Ar).

13C NMR (75 MHz, CDCl₃): δ = 143.1 (HC₆Ar), 128.9 (HC₅Ar), 128.4 (HC₆Ar), 96.2 (Cq,vin), 80.7 (Cq,vin).

1,2-Dibromo-1-octene (3d)¹
To a solution of I₂ (10.23 g, 40.3 mmol, 1.00 equiv) in CH₂Cl₂ (200 mL) was added a solution of 1-octyne (4.87 g, 44.2 mmol, 1.10 equiv) in CH₂Cl₂ (100 mL). After stirring at r.t. for 69 h, aq Na₂S₂O₅ (10%, 300 mL) was added and the organic layer was separated, washed with H₂O (2 × 200 mL), dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography (hexane) gave the product 10.

Yield: 13.4 g (91%); reddish liquid; Rf = 0.45 (hexane).

1H NMR (300 MHz, CDCl₃): δ = 6.80 (s, 1 H, HC₅Ar), 2.50 (t, J = 6.0 Hz, 2 H, CH₂CH₃), 1.54 (quint, J = 6.6 Hz, 2 H, CH₂CH₃), 1.36–1.29 (m, 6 H, 3 × CH₃), 0.93–0.88 (m, 3 H, CH₃).

13C NMR (75 MHz, CDCl₃): δ = 104.4 (Cq,vin), 78.9 (HC₅Ar), 44.7, 31.6, 28.1, 27.8, 22.5, 14.1 (all CH₃).

1,2-Dibromo-1-(trimethylsilyl)-2-phenylethylene (3e)¹
A solution of 1-(trimethylsilyl)-2-phenylethylene (1.70 g, 9.75 mmol, 1.00 equiv) in CH₂Cl₂ (20 mL) was cooled to −10 °C and a solution of Br₂ (9.3 mL, 97.7 mmol, 1.00 equiv) in CH₂Cl₂ (c = 1.05 mol/L) was added. The reaction mixture was stirred at −10 °C for 30 min then allowed to warm to r.t., concentrated under reduced pressure and the residue was purified by flash chromatography (pentane) to give 3e.

Yield: 2.26 g (69%); colorless solid; Rf = 0.40 (pentane); EIZ = 1.99 (GC-MS).

1H NMR (300 MHz, CDCl₃): δ = 7.56–7.46 (m, 5 H, HC₆Ar, Z), 7.07 (s, 1 H, HC₅Ar, E).

13C NMR (75 MHz, CDCl₃): δ = 138.1 (Cq,vin, Z), 137.0 (Cq,vin, E), 131.1 (HC₅Ar, Z), 129.4 (HC₅Ar, E + Z), 129.1 (HC₅Ar, E), 128.5 (HC₆Ar, Z), 128.2 (HC₆Ar, E), 127.7 (HC₅Ar, Z), 121.3 (HC₅Ar, E), 108.8 (HC₅Ar, Z), 103.0 (HC₅Ar, E).

(E)-1,2-Diiodophenylethylene (3b)³
To a solution of phenylacetylene (5.16 g, 50.5 mmol, 1.00 equiv) in CH₂Cl₂ (150 mL) was added a solution of I₂ (12.8 g, 50.4 mmol, 1.00 equiv) in CH₂Cl₂ (350 mL), dropwise, over 1 h. After stirring at r.t. for 2.5 h, aq Na₂S₂O₅ (10%, 300 mL) was added and the organic layer was separated, washed with H₂O (200 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The product was recrystallized (MeOH) to give 3b.

Yield: 11.7 g (65%); colorless product; Rf = 0.32 (pentane).

1H NMR (300 MHz, CDCl₃): δ = 7.30–7.27 (m, 5 H, HC₆Ar, Z), 7.19 (s, 1 H, HC₅Ar).

13C NMR (75 MHz, CDCl₃): δ = 143.1 (HC₆Ar), 128.9 (HC₅Ar), 128.5 (HC₆Ar), 96.2 (Cq,vin), 80.7 (Cq,vin).

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Yield: 7.36 g (76%); colorless solid; \( R_f = 0.43 \) (pentane–EtOAc, 5:1). To give residue was purified by flash chromatography (pentane–EtOAc, 17 h, the solution was concentrated under reduced pressure and the residue was purified by flash chromatography (pentane–EtOAc, 10:1).

\[ 13C \text{ NMR (75 MHz, CDCl}_3\]: } 162.6 (C=O), 162.5 (C=O), 125.0 (C\text{vin}, Z), 112.6 (C\text{vin}, E), 53.8 (CH\text{OH}), 53.6 (CH\text{OH}).

**Dimethyl 2,3-Dibromobut-2-enedicarboxylate (3g)\textsuperscript{12}**

To a solution of \( \text{Br}_2 \) (6.00 g, 37.5 mmol, 1.04 equiv) in \( \text{CH}_2\text{Cl}_2 \) (160 mL) was added a solution of dimethyl acetylenedicarboxylate (3.62 mmol, 1.00 equiv) in \( \text{CH}_2\text{Cl}_2 \) (35 mL). After stirring at r.t. for 17 h, the solution was concentrated under reduced pressure and the residue was purified by flash chromatography (pentane–EtOAc, 5:1) to give 3h.

Yield: 7.36 g (76%); colorless solid; \( R_f = 0.43 \) (EtOAc, 5:1); \( R_f = 0.43 \) (GC-MS).

**References**


7. Parameters screened: Ligands: DMEDA (optimal), rac-1,2-diaminocyclohexane (lower conversion, more side products), phenantroline (no reaction); bases: K\textsubscript{2}CO\textsubscript{3} (optimal), K\textsubscript{3}PO\textsubscript{4} (lower conversion, more side products), Cs\textsubscript{2}CO\textsubscript{3} (lower conversion), Et\textsubscript{3}N and NaOAc (no reaction). Reaction temperature: <110 °C conversion was found to be incomplete; solvents: toluene (optimal), chlorobenzene (lower conversion), t-BuOH, dioxane (much lower conversion), DMF (no conversion).

8. In a series of experiments, a range of olefins were heated at 110 °C with and without Cu and DMEDA. Whereas (E)-1,2-diodophenylethylene did not isomerize to the Z-isomer, an isomerization of 1,2-dibromophenylethylene was obtained in cases of older substrates or if small amounts of bromine were added. Bromine-catalyzed isomerizations of dihaloalkanes have previously been described, see: Uemura, S.; Okazaki, H.; Okano, M. J. Chem. Soc., Perkin Trans. 1 1978, 1278.