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Cyclisation of Alkynyl Alcohols and Carboxylic Acids Mediated by N-Heterocyclic Carbene Copper(I) Complexes

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Abstract: The cyclisation of alkynyl alcohols and carboxylic acids in the presence of a $[Cu(NHC)_2]X$ complex is reported. The reactions were carried out in technical grade toluene in the presence of air with a catalyst that is readily accessible. N-Heterocyclic carbenes are recognised for stabilising metal centres in a range of oxidation states, and this work further supports that NHCs can also be used as activation sites in air and moisture stable yet active catalysts.

Keywords: Copper; N-Heterocyclic Carbene; Hydrofunctionalisation; Enol Ether; Lactone

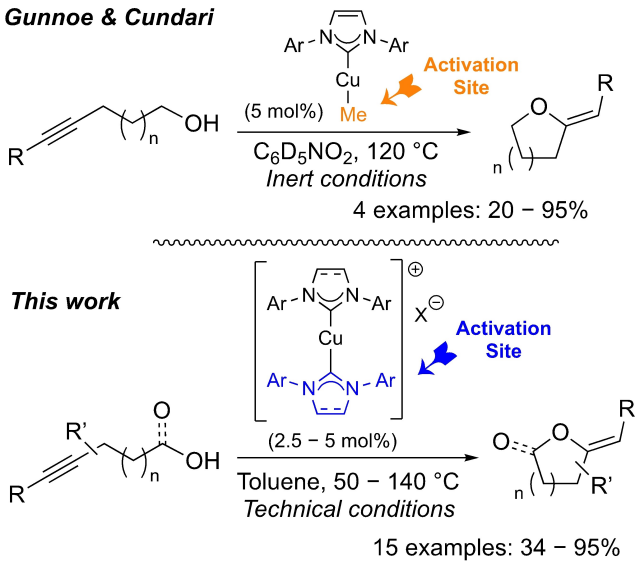
Introduction

The addition of X–H bonds across alkynes and alkenes is a fundamental transformation in organic synthetic chemistry that gives access to important heterocycles when carried out intramolecularly.[1,2] Cyclic enol ethers and lactones are important motifs on their own right due to their unique reactivity and recurring appearance in biologically active compounds.[3–6] These can be efficiently prepared with 100% atom economy thanks to the intramolecular reaction of alcohols and carboxylic acids with unsaturated carbon–carbon bonds using metal catalysis. Powerful as they are, these reactions often suffer from regioselectivity issues (endo/exo selectivity) and require rare precious metals or elaborated ligands.[7] Palladium or rhodium remain popular choices for these reactions, but gold catalysts have lately gained predominance in the field allowing for both inter and intramolecular reactions, often under mild reaction conditions.[8,9] Actually, the pioneering report from Teles on the addition of alcohols to alkynes is often credited as the spark that led to the enormous popularity of gold catalysis in the beginning of the century.[10]

Other metals in Group 11 have received comparatively little attention in this context. It is noteworthy that reported silver-mediated hydroalkoxylations employ simple silver salts (sometimes stoichiometrically),[11,12] while ancillary ligands are crucial for the reported catalytic activities with gold(I) and copper(I) systems. We were particularly interested in copper, the most abundant and inexpensive metal of the Group, and while phosphine or diamine ligands have been used in copper-mediated reactions,[13] it was the work by Gunnoe and Cundari that got our attention. They reported the cyclisation of alkynyl alcohols (and amines) in the presence of a copper(I) complex bearing an N-heterocyclic carbene (Scheme 1).[14,15] A handful of alcohols were reacted in deuterated nitrobenzene at 120 °C to obtain the exo-cyclisation products selectively.

Most [CuX(NHC)] complexes (X = halogen) are stable towards air and moisture, however, copper-methyl derivatives used in this work are highly sensitive and therefore the reported reactions had to be carried out under inert conditions, a recurring feature in these cyclisations. Since the role of the methyl ligand is to drive the formation of the main catalytically active species with release of methane, we

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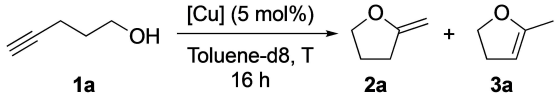
Scheme 1. Activation of [Cu(NHC)] systems for cyclisation reactions.

hypothesized that an alternative activation might be possible starting from a stable copper complex. Our previous work on related $[Cu(NHC)_2]X$ complexes proved that NHC ligands stabilise the metal centre, making the corresponding complexes indefinitely stable under ambient conditions. Moreover, one of them might also act as an activation site in catalytic processes. Thus, we disclosed that this second NHC ligand can be displaced by a weakly nucleophilic base in the hydrosilylation of carbonyl compounds,[16] or behave as an internal base in Click CuAAC reactions.[17] Herein we present the application of such activation strategy to the cyclisation of alkynyl alcohols and carboxylic acids with $[Cu(NHC)_2]X$ catalysts under technical conditions and without any additive.

Results and Discussion

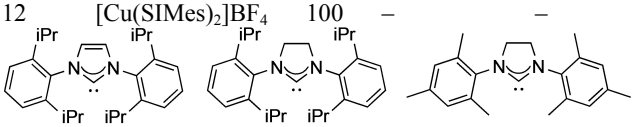
We completed our optimisation studies with commercially available pent-4-ynol **1a** (Table 1). These tests were carried out in technical grade deuterated toluene due to the volatility of the desired cyclised products. No precautions to exclude moisture or oxygen were taken in any of these experiments. Only products issue of an exo-dig cyclisation were detected in the reaction mixtures by ^{1}H NMR, although **2a** underwent partial isomerisation to endocyclic enol ether **3a** in some cases. No conversion was observed at room temperature, but 73% yield and excellent selectivity were observed at 80 °C with $[Cu(IPr)_2]BF_4$ as catalyst (Table 1, entry 4). This result could be further improved by raising the reaction temperature to 100 °C (Table 1, entries 4 and 7). Both the ligand and the type

Table 1. Catalyst screening for the cyclisation of pent-4-ynol.[a]



1a **2a** **3a**

Entry	[Cu]	T (°)	Yield (%)[b]	Ratio[b]
1	[CuCl(IPr)]	RT	–	–
2	$[Cu(IPr)_2]BF_4$	RT	–	–
3	[CuCl(IPr)]	80	–	–
4	$[Cu(IPr)_2]BF_4$	80	73	>19:1
5	[CuCl(IPr)]	100	–	–
6[c]	[CuCl(IPr)]	100	19	8:1
7	$[Cu(IPr)_2]BF_4$	100	89	>19:1
8	$[Cu(IPr)_2]BF_4$	140	87	>19:1
9	$[Cu(IPr)_2]PF_6$	100	23	>19:1
10	$[Cu(SIPr)_2]BF_4$	100	75	10:1
11	$[Cu(SIPr)_2]PF_6$	100	25	10:1
12	$[Cu(SIMes)_2]BF_4$	100	–	–



[a] Reaction conditions: **1a** (0.4 mmol), [Cu] (5 mol%) in toluene-d8 (0.5 mL).
[b] ^{1}H NMR yields and ratios are the average of two independent reactions and were calculated with respect to 1,3,5-trimethoxybenzene as internal standard.
[c] Reaction with KO*t*Bu (5 mol%).

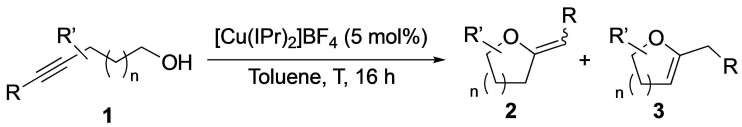
of complex were found critical for the catalytic performance. No reaction was observed with neutral [CuCl(IPr)] even at 100 °C and using a saturated version of the IPr ligand led to a significant drop both in yield and selectivity (SIPr, Table 1, entries 10 and 11). Only traces of **2a** were obtained with a complex bearing two SIMes ligands and complexes with a BF_4 counterion systematically outperformed those with PF_6 instead (Table 1, entries 6 and 8–11). Furthermore, when [CuCl(IPr)] was activated with KO*t*Bu, only a poor yield of 19% was observed (Table 1, entry 6). Preliminary experiments with $[Cu(NCMe)_4]BF_4$ and copper complexes bearing PPh_3 or diamine ligands only led to the recovery of the starting alcohol. No decomposition was observed in any of these experiments.

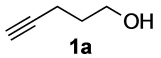
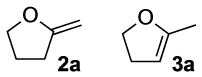
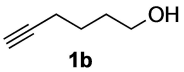
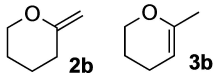
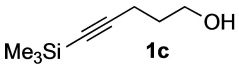
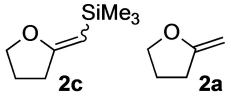
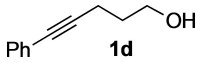
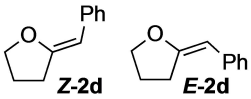
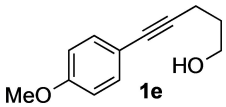
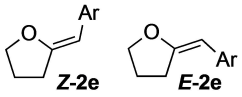
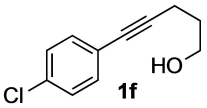
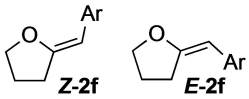
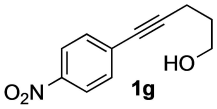
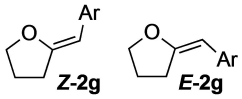
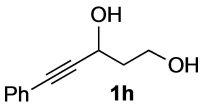
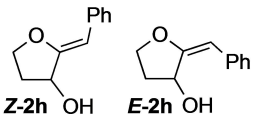
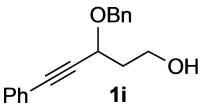
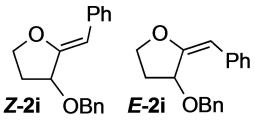
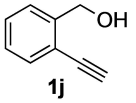
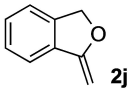
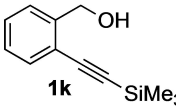
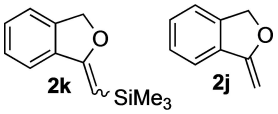
With $[Cu(IPr)_2]BF_4$ as the catalyst of choice, we next explored the scope of the cyclisation of alkynyl alcohols. Five and six membered rings were successfully prepared and different substitutions were well tolerated both at the acetylenic and propargylic positions (Table 2). However, substrates bearing a trimethylsilyl group on the alkyne underwent either partial or total desilylation under these reaction conditions (Table 2, entries 3 and 11) and benzodihydrofurans could be formed in moderate yields, but they

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Table 2. $[Cu(IPr)_2]BF_4$-mediated cyclisations of alkynyl alcohols.[a]



Entry	Alcohol **1**	Reaction Products	T (°C)	Yield (%)[b]	Ratio (%)[c]
1	 **1a**	 **2a** **3a**	100	(89)	>19/1
2	 **1b**	 **2b** **3b**	100 140	(20) (83)	9:1 **3b** only
3	 **1c**	 **2c** **2a**	100	(25)	**2a** only
4	 **1d**	 ***Z*-2d** ***E*-2d**	100 140	(81) 88 (90)	>19:1 >19:1
5	 **1e**	 ***Z*-2e** ***E*-2e**	100 140	(71) 46, **Z** (72)	2:1 5:1
6	 **1f**	 ***Z*-2f** ***E*-2f**	100 140	70 (69) (78)	5:1 9:1
7	 **1g**	 ***Z*-2g** ***E*-2g**	100 140	73 (85) 87 (89)	19:1 5:1
8	 **1h**	 ***Z*-2h** ***E*-2h**	140	73	**Z** only
9	 **1i**	 ***Z*-2i** ***E*-2i**	100 140	78 (71) (77)	7:1 5:1
10	 **1j**	 **2j**	100 140	(34) (22)	– –
11	 **1k**	 **2k** **2j**	80 100	(30) (34)	1.5:1 1:1

[a] Reaction conditions: **1** (0.4 mmol), $[Cu(IPr)_2]BF_4$ (5 mol%) in toluene (0.5 mL) or toluene-d8 for volatile substrates.
[b] Isolated yields, ^{1}H NMR yields shown in brackets are the average of two independent reactions and were calculated with respect to 1,3,5-trimethoxybenzene as internal standard.
[c] Ratios in the crude reaction mixture.

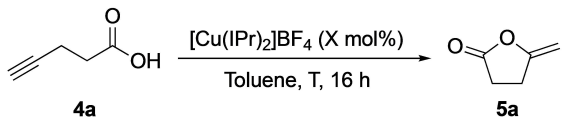
could not be isolated as they decomposed on silica gel, even when pacified with NEt_3 (Table 2, entries 10 and 11).

In general, when incomplete conversions were observed after 16 h, higher temperatures were sometimes beneficial, but comparable results were obtained with higher copper loadings (10 mol%). No starting alcohol was recovered in any of these reactions, which were again completely regioselective. It is worth mentioning that both *E*/*Z* and exocyclic/endocyclic (**2**/**3**) isomerisations of this family of enol ethers have previously been reported[18] and they appear to be

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Table 3. Catalyst screening for the cyclisation of pent-4-ynoic acid.[a]



Entry	[Cu] (mol%)	T (°C)	Recov. (%)[b]	Yield (%)[b]
1	5	100	–	63
2	5	80	–	54
3	2.5	60	–	79
4	2.5	50	–	93
5	2.5	40	88	5
6	5	40	69	18
7[c]	5	80	–	–
8	0	100	>95	–

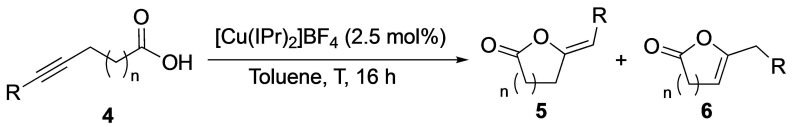
[a] Reaction conditions: **4a** (0.4 mmol), $[Cu(IPr)_2]BF_4$ (2.5 mol%) in toluene (0.5 mL).
[b] ^{1}H NMR recoveries and yields are the average of two independent reactions and were calculated with respect to 1,3,5-trimethoxybenzene as internal standard.
[c] $[Cu(NCMe)_4]BF_4$ as catalyst.

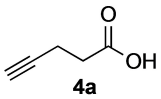
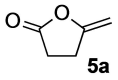
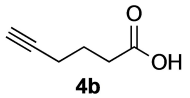
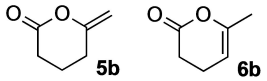
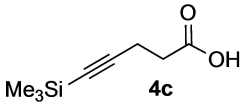
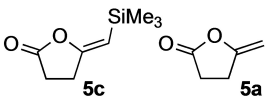
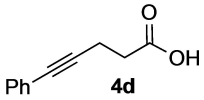
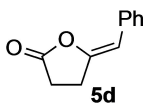
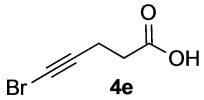
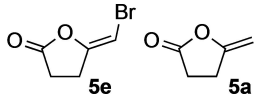
dictated by the substrate itself since no general trend was observed between the reaction temperature and product selectivity. Geometrical isomers were not separable by column chromatography but *E* isomers appeared to undergo partial decomposition during the purification step, which often led to an enrichment in the geometrical ratio in isolated products.

Next, we explored the related cyclisation of carboxylic acids (Table 3). The optimised conditions for the cyclisation of **1a** (see Table 1, entry 6) led to 63% of expected lactone **5a** together with significant decomposition (Table 3, entry 1). Hence, milder conditions were tested and 2.5 mol% of the copper catalyst at 50 °C were found optimal (Table 3, entry 4). Only decomposition was obtained with a simple copper salt and no reaction was observed in the absence of metal even at 100 °C (Table 3, entries 7 and 8).

Higher reaction temperatures were required, however, for the formation of six-membered lactones or the reaction of internal alkynes which only produced *Z*-isomers under these reaction conditions (Table 4). Different substituents at the acetylenic position were well tolerated, although significant desilylation was

Table 4. $[Cu(IPr)_2]BF_4$-mediated cyclisations of alkynyl carboxylic acids.[a]



Entry	Carboxylic Acid **4**	Reaction Products	T (°C)	Recov. (%)[b]	Yield (%)[b]	Ratio (%)[c]
1	 **4a**	 **5a**	50	–	88 (93)	–
2	 **4b**	 **5b** **6b**	50 100 100[d] 140	<95 – – –	(>5) (63) 75 (77) (83)	– **5b** only **5b** only 4:1
3	 **4c**	 **5c** **5a**	100 100[d]	39 12	(45) 59, **5a** (78)	1:2 1:4
4	 **4d**	 **5d**	80 100	40 –	(34) 88 (97)	– –
5	 **4e**	 **5e** **5a**	100	>5	80 (86)	19:1

[a] Reaction conditions: **4** (0.4 mmol), $[Cu(IPr)_2]BF_4$ (2.5 mol%) in toluene (0.5 mL).
[b] Isolated yields. ^{1}H NMR recoveries refer to unreacted starting material and ^{1}H NMR yields shown in brackets are the average of two independent reactions and were calculated with respect to 1,3,5-trimethoxybenzene as internal standard.
[c] Ratios in the crude reaction mixture.
[d] 5 mol% [Cu].

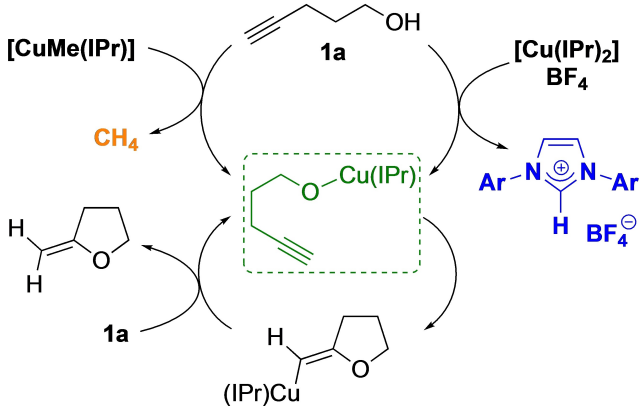
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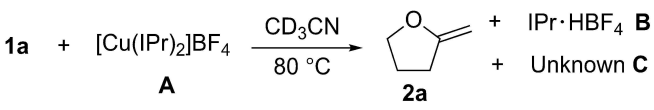
again observed with a TMS derivative (Table 4, entry 3). The cyclisation of bromoalkyne **4e** also led to partial debromination, but only as a minor product and brominated lactone **5e** could still be isolated in high yield (Table 4, entry 5).

Cyclisations with many transition metal systems, including those based on gold(I) catalysts, are accepted to involve the π-coordination of the metal to the alkyne to facilitate the nucleophilic addition of the O–H group.[1] However, in their report on the intramolecular hydroalkoxylation of alkynes,[14a] Gunnoe and Cundari reported extensive mechanistic work with complementary computational and experimental results supporting the formation of a copper-alkoxide as key intermediate in a pathway akin to that proposed for lanthanide systems.[19] Starting from [CuMe(IPr)], the corresponding alkoxide would be formed with release of methane and undergo alkyne insertion leading to a cyclised vinyl copper intermediate that would release the final product upon protonation (Scheme 2).

We hypothesised that the same intermediate could be accessible from $[Cu(IPr)_2]BF_4$ with concomitant formation of an equivalent of the corresponding imidazolium salt (Scheme 2). Hence, we attempted the stoichiometric reaction of **1a** and $[Cu(IPr)_2]BF_4$ in toluene-d8 at 80 °C, but only formation of enol ether **2a** could be evidenced due to the low solubility of the copper complex at this concentration. We then decided to use CD_3CN instead since comparable results could be obtained in the model reaction.[20] This stoichiometric reaction was carried out at 80 °C and ^1H NMR spectra were recorded every 30 min for 8 h in the presence of 1,3,5-trimethoxybenzene as internal standard (Scheme 3).[21] Under these concentrated conditions, the reaction only proceeded to 20% of **2a** after 8 h, but the formation of IPr·HBF_4 could be confirmed by comparison with an actual sample. Indeed, three different species with an IPr moiety in a 1:1:1 ratio were clearly detected by NMR, the starting $[Cu(IPr)_2]BF_4$, IPr·HBF_4 and a third unknow species that could be the resting state of the catalyst.



Scheme 2. Postulated mechanism for copper(I)-mediated hydroalkoxylations.



Scheme 3. Stoichiometric reaction.

It has been reported that for terminal alkynes it is thermally favoured to initiate the complex activation by the formation of a copper–acetylide intermediate that would then isomerise to the required copper alkoxide.[14a,22] There was no indication of formation of a copper acetylide in our stoichiometric reaction and no yellow colouring was ever observed in any reaction with a terminal alkynes, unlike in past reactions where this and other cationic NHC complexes were tested in azide-alkyne cycloaddition reactions.[17]

Finally, the proposed mechanism explains the regioselectivity of the reaction compared to other d-block metals but the stereochemistry of the final alkene products needs to be considered as well. With [CuMe(IPr)] as catalyst under inert conditions, only *Z*-alkenes were observed in the crude reaction mixtures.[14a] This was rationalised by an isomerisation step during the final protonolysis leading to the most stable isomer. In our reactions with alcohols, ***Z*-2** derivatives remained the major if not the only reaction products. However, an erosion of the stereoselectivity of the reaction was noticeable with non negligible amounts of ***E*-2** derivatives formed in some cases (Table 2). This might be attributed to reactions being conducted under technical conditions where not only the starting alkyne, but also water might participate in the protonolysis step.

Conclusions

We have demonstrated that NHC ligands can be used as activation sites in copper(I) complexes to access catalytically active species. While temperatures around 100 °C or higher might still be required (less so for the formation of lactones), reactions can be carried out in technical grade solvents and without any precautions to preclude the presence of water or oxygen. The convenience of the present catalytic system goes well beyond the reaction conditions for the cyclisations and it also applies to the catalysts themselves. $[Cu(IPr)]BF_4$ is commercially available, but also readily accessible from the corresponding air stable imidazolium salt, IPr·HBF_4 and $[Cu(NCMe)_4]BF_4$.[23] In contrast [CuMe(IPr)] requires the isolation of free IPr and the two more reactions, first coordination with CuOAc, followed by treatment with $AlMe_2(OEt)$.[24]

Also, our results further support the formation of a copper–alkoxide intermediate in these reactions origi-

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nally postulated by Gunnoe and Cundary and no evidence for π-coordination of the alkyne, or formation of a copper acetylide were found.

Experimental Section

All reactions were carried out in air using technical solvents without any precautions to exclude moisture or oxygen, unless stated otherwise. Commercially available reagents were used as received without further purification. Column chromatography and TLC were performed on silica gel (Kieselgel 60), using UV light and a potassium permanganate dip to visualise the starting materials and products. Pacified silica was prepared by submerging silica gel into petroleum ether containing 2% v/v trimethylamine overnight. Infrared spectra were recorded in reciprocal centimetres (cm^{-1}) using a FT-IR ATR spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, toluene-d_8 or CD_3CN on Bruker AVANCE 400 spectrometers (^1H: 400 MHz and ^{13}C: 100 MHz) at 25 °C. Chemical shifts, δ, are given in ppm relative to tetramethylsilane (0.00 ppm), $CDCl_3$ (77.0 ppm), toluene-d_8 (137.5, 128.9, 128.0, 125.1, 20.4 ppm). The multiplicity is given as br, s, d, t, q and m for broad, singlet, doublet, triplet, quartet and multiplet. High resolution mass spectra were recorded on either a Micromass Autospec Premier, Micromass LCT Premier or a VG Platform II spectrometer using ESI techniques at the Mass Spectrometry Service of Imperial College London. $[Cu(NHC)_2]X$[23] and [CuCl(IPr)][25] were prepared using reported procedures.

General Procedure A – Cyclisation of alkynyl Alcohols in NMR scale reactions

The reaction substrate (0.4 mmol), $[Cu(IPr)_2]BF_4$ (19 mg, 0.02 mmol, 5 mol%), trimethoxybenzene (~3–4 mg) and toluene-d_8 (0.5 mL) were introduced in a J-Young NMR tube and heated at 80–140 °C for 16 h before cooling down to room temperature. Reported ^1H NMR yields are the average of two independent experiments and were calculated with respect to 1,3,5-trimethoxybenzene (6.12 & 3.35 ppm in toluene-d8) as the internal standard.

General procedure B – Cyclisation of alkynyl alcohols

The reaction substrate (0.4 mmol), $[Cu(IPr)_2]BF_4$ (19 mg, 0.02 mmol, 5 mol%) and toluene (0.5 mL) were introduced in a 10 mL microwave vial, sealed and heated at 80–140 °C for 16 h before cooling down to room temperature. The reaction mixture was filtered through Celite and washed with ethyl acetate (2 mL). The resulting solution was concentrated under reduced pressure and the crude product purified by column chromatography. Product ratios in the crude mixture are reported in Tables 2 and 4.

2-Methylenetetrahydrofuran (2a)

Following general procedure A with **1a** (34 mg, 0.4 mmol) and $[Cu(IPr)_2]BF_4$ (8 mg, 0.01 mmol, 2.5 mol%) at 100 °C, the formation of **2a** and **3a** was observed (89%, **2a**/**3b** > 19:1). Spectroscopic data for the title compounds is in accordance with the literature.[11a] 5-Methyl-2,3-dihydrofuran **3a** was quantified using a triplet at 4.07 ppm. ^1H NMR (400 MHz, toluene-d_8): δ 4.43 (br s, 1H), 3.85 (br s, 1H), 3.66 (t, J = 7.4 Hz, 2H), 2.17–2.10 (m, 2H), 1.41 (q, J = 7.4 Hz, 2H).

2-(4-Methoxybenzylidene)tetrahydrofuran (2e)

Following general procedure B with **1e** (76 mg, 0.4 mmol) at 140 °C and after purification by column chromatography (EtOAc/petroleum ether = 1:39 with 2% Et_3N) **2e** was isolated as a white solid (35 mg, 46%, *Z*/*E* > 19:1). Spectroscopic data for ***Z*-2e** is in accordance with the literature.[26] The *E* isomer was quantified by comparison with the literature (triplet at 4.17 ppm in $CDCl_3$).[27] R_f = 0.32 (EtOAc/petroleum ether = 1:19); ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.20 (s, 1H), 4.30 (t, J = 7.0 Hz, 2H), 3.79 (s, 3H), 2.70 (t, J = 7.0 Hz, 2H), 2.02 (q, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 132.2, 130.6, 128.3, 113.8, 96.4, 72.1, 55.4, 31.0, 24.6.

General procedure C – Cyclisation of alkynyl carboxylic acids

The alkynyl carboxylic acid (0.4 mmol), $[Cu(IPr)_2]BF_4$ (2.5 mol%) and toluene (0.5 mL) were introduced in a 10 mL microwave vial, sealed and heated at 50–100 °C for 16 h before cooling down to room temperature. The reaction mixture was filtered through Celite and washed with ethyl acetate (2 mL). The resulting solution was concentrated under reduced pressure and the crude product purified by column chromatography.

5-Methylenedihydrofuran-2(3*H*)-one (5a)

Following general procedure C from **4a** (39 mg, 0.4 mmol) at 50 °C, the title compound was isolated by column chromatography as a colourless oil (35 mg, 88%). Spectroscopic data for the title compound is in accordance with the literature. R_f = 0.25 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, $CDCl_3$): δ 4.76–4.71 (m, 1H), 4.34–4.29 (m, 1H), 2.93–2.84 (m, 2H), 2.73–2.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 155.6, 88.8, 27.9, 25.0.

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