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# Gold(I)-Catalysed Cyclisation of Alkynoic Acids: Towards an Efficient and Eco-Friendly Synthesis of γ-, δ- and ε-Lactones

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**Abstract:** The improved synthesis of γ-, δ- and ε-lactones using a dinuclear N-heterocyclic carbene (NHC)-gold(I) catalyst is reported. This solvent-free process provides access to γ- and δ-lactones in high regio- and stereoselectivity. Reactions were performed at low catalyst loadings and without the need for any additives. The use of a digold pre-catalyst provides a new synthetic route to functionalised ε-lactones, poorly accessible using previous methodologies.

**Keywords:** gold catalysis; lactones; low catalyst loading; N-heterocyclic carbenes; solvent-free conditions

Lactones are structurally simple molecules and recurrent motifs in natural product skeletons (Figure 1).[1] These cyclic compounds possess a wide variety of biologically relevant functions, from quorum sensing signalling in bacteria,[2] to enzyme inhibition through suicidal ring opening of the lactone core.[3] Furthermore, their *anti*-biofouling capabilities have led to valuable applications as biomimetic materials.[4] Thus, it is clear that lactones are of exceptional importance not only as industrially relevant structures, but also as potential targets of antibacterial and antitumour drugs.

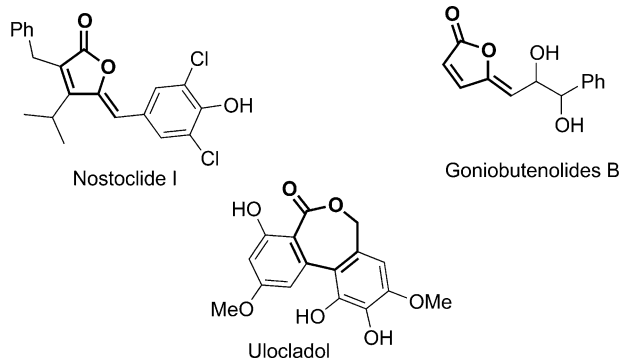
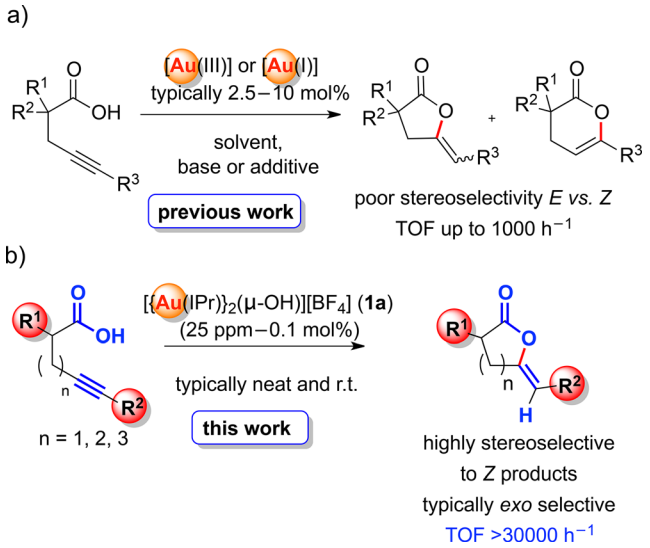



**Figure 1.** Selected lactone-containing natural products.

Hence, the development of straightforward methodologies to address the synthesis of these important structural motifs has attracted increased attention over the past decades. An efficient and atom-economical approach relies on the use of a transition-metal (TM) catalyst-mediated cyclisation of alkynoic acids,[5] through the activation of triple bonds by a Lewis acidic centre and an intramolecular nucleophilic attack from the carboxylate moieties. Previous procedures have been reported using Pd,[6] Rh,[7] Hg,[8] Cu[9] and Ag[10] complexes.

Among other TMs, gold-based catalysts have assumed a pivotal role for this transformation as a result of their high affinity to π-systems.[11] Although gold(I)- or gold(III)-catalysed cyclisation reactions (Scheme 1a) have proven highly effective,[12] these still present some significant drawbacks: (i) the use of high catalyst loadings, (ii) the need for additives, such as co-catalysts and bases in stoichiometric or catalytic quantities, (iii) formation of side-products and undesired by-products and (iv) a lack of regio- and stereocontrol.

While the synthesis of γ- and δ-lactones is well documented, reports disclosing efficient strategies toward the formation of ε-lactones remain scarce.[12c,13] Among the few reports towards these lactones, the best result achieved was reported by Pale and coworkers,[12c] where AuCl salt (10 mol%) and a catalytic amount of $K_2CO_3$ were used to enable the synthesis of caprolactone in 25% yield, only after a prolonged reaction time (48 h)!



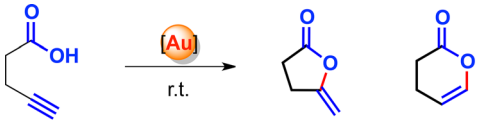

**Scheme 1.** Gold-catalysed hydrocarboxylation of alkynes.

With the aim of improving and developing straightforward and atom-economical synthetic methodologies, we recently reported an intermolecular hydrocarboxylation of alkynes using a mild and efficient N-heterocyclic carbene (NHC) gold(I)-catalysed process.[14] In particular, the air- and moisture-stable digold complex [{Au(IPr)}$_2$(μ-OH)][BF$_4$][15] **1a** has been shown to be highly effective in this transformation, allowing access to a diverse range of substituted enol ethers, with low catalyst loading (as low as 0.5 mol%).

Complex **1a** has been previously postulated to dissociate in solution into two monogold(I) fragments: (i) [Au(IPr)][BF$_4$] acting as a Lewis acid for the activation of the alkyne and (ii) the Brønsted base fragment [Au(IPr)(OH)] **1b**[16] deprotonating the pro-nucleophilic carboxylic acid (**1b** can deprotonate compounds with p$K_a$(DMSO) up to 30.3 p$K_a$ units).[17] Thus, following up on the successful intermolecular hydrocarboxylation of alkynes, we present here a highly efficient regio- and stereoselective (NHC)-gold-catalysed cyclisation to γ-, δ- and ε-alkylidene-lactones (Scheme 1b).

Our studies began by subjecting 4-pentynoic acid **2a** to various NHC-Au(I) catalysts. Using 0.5 mol% catalyst loading of **1a**, a 64% conversion into lactone **3a** was observed by $^1$H NMR spectroscopy after only 30 minutes (Table 1, entry 1). Using 1 mol% of the mononuclear gold complex **1b** (in order to account for the same amount of metal) a similar conversion of 60% was observed after the same reaction time (entry 2). These initial attempts were performed in toluene (10 M) at room temperature. Importantly, cyclisation occurred in a completely *exo*-regioselective manner, while the formation of the *endo* cyclised product **4a**, allowed by Baldwin's rules,[18] was not observed. Catalysts **1a** and **1b** performed remarkably well, allowing cyclisation of **2a** to be completed in solvent-free conditions using 0.2 and 0.4 mol%, respectively, within *5 minutes* (entries 3 and 4).[19] Under the same conditions, cationic [Au(IPr)(ACN)][BF$_4$] (ACN = CH$_3$CN) (**1c**)[20] gave 50% conversion (entry 5). To our delight, a further decrease in catalyst loading was possible; indeed with 25 ppm ($2.5\times10^{-5}$ mol%) of **1a**, 98% conversion of **3a** (entry 6) was obtained in 1 h and the final product could be isolated in 92% yield.

**Table 1.** Optimisation for the cyclisation of alkynoic acids.




2a 3a 4a not observed

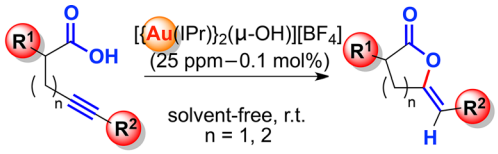
| Entry[a] | Catalyst (mol%) | Solvent | Time (min) | Conversion (%)[b] |
|---|---|---|---|---|
| 1 | **1a** (0.5) | PhCH$_3$[c] | 30 | 64 |
| 2 | **1b** (1) | PhCH$_3$[c] | 30 | 60 |
| 3 | **1a** (0.2) | none | 5 | >99 |
| 4 | **1b** (0.4) | none | 5 | >99 |
| 5 | **1c** (0.4) | none | 5 | 50 |
| 6 | **1a** (25 ppm) | none | 60 | 98 (92) |

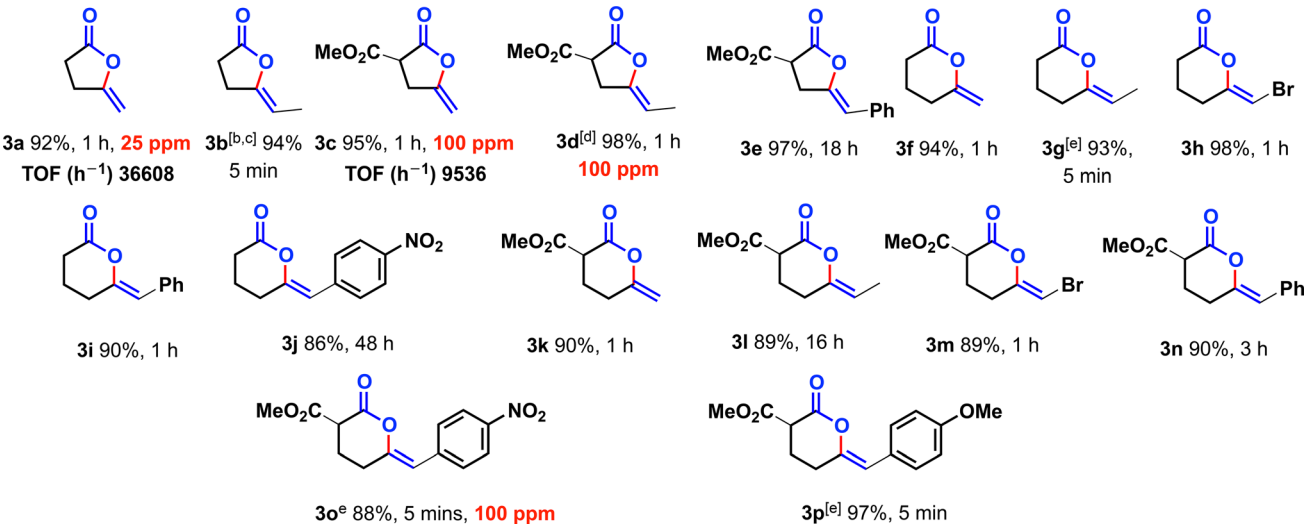
[a] *Reaction conditions:* 0.5 mmol of **2a**, room temperature, [Au] 25 ppm to 1 mol%.
[b] Calculated by $^1$H NMR spectroscopy using pivalaldehyde as internal standard (10 μL, 0.092 mmol), isolated yield (%) in parentheses.
[c] 10 M.

With the optimised conditions in hand, the versatility of the protocol was explored. The catalyst loading of **1a** was varied from 25 ppm to a maximum of 0.1 mol% for more demanding substrates. As summarised in Table 2, the transformation could be applied to differently substituted alkynoic acids with good to excellent isolated yields, ranging from 86 to 98%. Moreover, the purification process was found to be economical and practical since column chromatography proved unnecessary. In fact, a highly convenient filtration followed by pentane wash was sufficient to afford the final lactones in high purity. The process was found to be highly stereoselective, furnishing the *Z*-isomers in all cases, as commonly observed for Au-catalysed processes.[11,21]

High regioselectivity for the *exo* cyclisation was also observed for most substrates. Exceptions were found when internal alkynes bearing a methyl group were used, as in the case of **2b** and the β-alkynoic malonate derivative **2d**, for which the *endo*-dig-cyclisation reaction was competitive with the *exo*-cyclisation, as previously reported.[12c,e] Thus, products **3b** and **3d** were isolated in 94 and 98% yields with an *exo*:*endo* ratio of 7:1 and 4:1, respectively. Interesting-

**Table 2.** Scope for γ- and δ-enol-lactones.




[a] *Reaction conditions:* 0.25–0.5 mmol of substrate, 0.1 mol% of **1a**, room temperature, isolated yield (%).
[b] Ratio **3b**:**4b** 7:1.
[c] Ratio **3b**:**4b** 1:1.7, 0.2 mol% of **1b**.
[d] Ratio **3d**:**4d** 4:1.
[e] At 65 °C.

ly, when using 0.2 mol% of **1b** as pre-catalyst in the formation of **3b**, the ratio between **3b**:**4b** was reversed to 1:1.7. With this same catalyst **1b**, reversal in selectivity was not observed for the cyclisation of **2d**. Substitution into the α-position with an ester enhanced the outcome of the reaction, due to the Thorpe–Ingold effect that forces the reacting termini, the carboxylic acid and the alkyne, to be in closer proximity.[22] Product **3c** was isolated in 95% yield with a catalyst loading of only 100 ppm, after 1 h. Moreover, an internal alkyne bearing a phenyl group was also converted in excellent yield under the reaction condition (**3e**).

The cyclisation of hexynoic acid derivatives was examined next with product **3f** being isolated from 5-hexynoic acid in 94% yield within 1 h. A methyl substituent at the terminal position of the alkynoic acid had no influence on the stereoselectivity and **3g** was formed within 5 min and isolated in 92% yield. Internal alkynes bearing a bromine atom, a phenyl group and a *p*-$NO_2$ substituted aryl were all suitable substrates for this transformation (**3h**–**3j**, 86–98% isolated yields).[23]

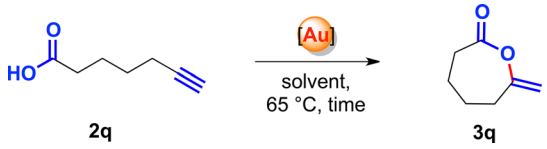
α-Carbomethoxy-substituted hexynoic acids were also investigated. Both terminal alkynes and internal alkynes could be subjected to the cyclisation reaction, affording products **3k**, **3l** and **3m** in good to excellent yields. Moreover, aryl substituents were well-tolerated giving **3n** (90%), **3o** (88%) and **3p** (97%). Specifically, **3o** was obtained with only 100 ppm catalyst loading while performing the reaction at a higher temperature (65 °C).

Under the optimal reaction conditions, the cyclisation process was found to be extremely efficient: the cyclisation of **2a** into **3a** occurred with a TOF (turnover frequency) greater than 36000 $h^{-1}$! The conversion of **2c** into **3c** has a TOF of 9538 $h^{-1}$.

Finally, more challenging substrates were tested: 6-heptynoic acid **2q** was reacted under the optimised conditions, with a slightly higher catalyst loading (0.5 mol%). Cyclisation to give **3q** occurred at room temperature under solvent-free conditions, but a low conversion (18%) was observed (Table 3, entry 1). The formation of undesired side-products was observed by $^1$H NMR spectroscopy, tentatively assigned as dimers or oligomers, formation of which would be entropically favoured under the solvent-free conditions. Increasing the temperature to 65 °C did not lead to any improvement, both in conversion and decrease of undesired products (entry 2).

We reasoned that performing the reaction in a suitable solvent would favour the intramolecular pathway.

**Table 3.** Optimisation for the synthesis of ε-lactone **3q**.




**2q** **3q**

| Entry[a] | Catalyst (mol%) | Solvent (M) | Conversion (%) [b] |
|---|---|---|---|
| 1 | **1a** (0.5) | none | 18[c,d] |
| 2 | **1a** (0.5) | none | 18[d] |
| 3 | **1a** (0.5) | toluene (0.5) | 0 |
| 4 | **1a** (0.5) | THF (0.25) | 18[d] |
| 5 | **1a** (1) | $CH_2Cl_2$ (0.25) | >99 (78) |
| 6 | **1b** (2) | $CH_2Cl_2$ (0.25) | 52 |

[a] *Reaction conditions:* 0.5 mmol of **2q**, solvent or solvent-free, 65 °C, 400 rpm stirring, 18 h, sealed vessels.
[b] Calculated by $^1$H NMR spectroscopy using pivalaldehyde as internal standard (10 μL, 0.092 mmol), isolated yields in parentheses (%).
[c] Room temperature.
[d] Side-product formation confirmed by $^1$H NMR spectroscopy.

Therefore, the reaction was performed in toluene (0.5 M, entry 3) at higher net dilution, which proved successful for the cyclisation of γ-alkynoic acids. However, the reaction did not proceed for **2q** and a solvent of higher polarity had to be employed, together with higher dilution: specifically, using THF (0.25 M), conversions similar to the solvent-free conditions were found (18%), but side-products were still observed (Table 3, entry 4). Despite this, we could observe a clean and complete conversion of **2q** into the ε-lactone in $CH_2Cl_2$ (0.25 M) at 65 °C with a catalyst loading of 1 mol%. Thus, in sealed tube reactions, **3q** could be isolated in 78% yield (entry 5). Under the same reaction conditions, using 2 mol% of **1b** did not give satisfactory results, with low conversions and formation of side-products observed (entry 6).

The reactivity of various other heptynoic acids was explored (Figure 2). Full conversion toward the formation of ε-lactones **3r** and **3s** was observed under the optimized reaction conditions. Compound **3r** was obtained in 91% isolated yield by increasing the catalytic charge of **1a** to 2 mol%. The process could tolerate a bromine substituent in the terminal position of the alkyne, affording **3s** in 80% isolated yield using 2 mol% catalyst after a reaction time of 24 h.[24] The process afforded the *Z*-stereoisomer of **3s**, as confirmed by single diffraction X-ray analysis of suitable crystals of **3s**.[25]

As a possible rationale for the results obtained, based on previous literature suggestions, a mechanism

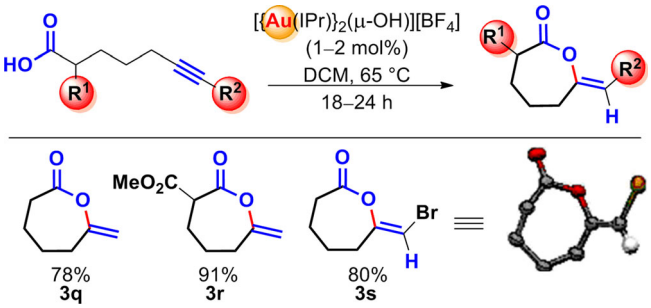
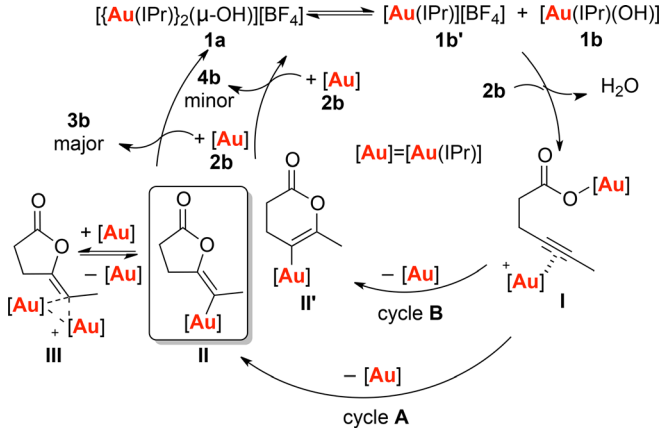



**Figure 2.** General scheme for the Au(I)-catalysed cyclisation of ε-lactones. Thermal ellipsoid representation of **3s** showing 50% probability. Most H atoms are omitted for clarity. Selected torsion angles (deg): O1–C7–C8–Br8 4.5(2)°.

can be proposed for the cyclisation of alkynoic acids (Scheme 2).[14,21a,26] Dissociation of pre-catalyst **1a**, [{Au(IPr)}$_2$(μ-OH)][$BF_4$], into **1b**, [Au(IPr)(OH)], and **1b′**, [Au(IPr)][$BF_4$], can be considered the first step. Furthermore, the formation of **1b** and **1b′** can help to rationalise the high conversions obtained using **1b** as a sole pre-catalyst, although, the latter was not found to be as efficient as **1a**.




**Scheme 2.** Proposed reaction mechanism.

Activation of the alkyne and the acid by the gold fragments, **1b** and **1b′**, can then occur, to form intermediate **I**. From this dinuclear species, the cyclisation proceeds next *via* an intramolecular *anti*-periplanar nucleophilic addition of the activated acid to the π-activated alkyne moiety,[11] with slippage of one gold fragment to the less electrophilic carbon atom and release of the second. Nucleophilic attack proceeds mainly in the regioselective *exo*-cyclisation mode and leads to vinylgold intermediates **II**[27] (Scheme 2, cycle **A**). Considering the results obtained for substrates **3b** and **3d**, **II′** might be formed (cycle **B**), that account for the observed *endo*-cyclisation products **4b** and **4d**. Following this, final protodeauration gives the major *exo*-product **3b** and the minor *endo*-product **4b**. The vinylgold species might furthermore react with the

previously released cationic gold fragment, so to form *gem*-diaurated species, such as **III**,[27e,28] which could be rather a resting state of the catalytic cycle as previously observed for Au-catalysed transformations.[29]

Therefore, in order to gain insight into the mechanism,[30] we followed the conversion of **2a** into **3a** catalysed at different concentrations of **1a**, ranging from 200 to 1000 ppm, in $CDCl_3$.[31] The reaction exhibited first-order dependence to **2a**.[32] A first-order dependence with respect to **1a** is determined, with slight deviation from linearity at lower catalyst concentrations that might suggest a more complex mechanistic picture. These initial results suggest that cooperative catalysis might not be solely operative for this intramolecular transformation.[33]

Finally, the dinuclear gold(I) complex **1a** proved essential for the synthesis of ε-lactones, which suggests that a different mechanism may indeed be at play in the intramolecular cyclization of heptynoic acids.

In conclusion, an efficient and improved synthesis of γ-, δ- and ε-lactones has been presented. The process provides access to a wide range of molecules in a highly regio- and stereoselective manner. The methodology satisfies some basic principles of green chemistry: where no need of additives is required, solvent-free conditions are used and extremely low catalyst loadings (down to 25 ppm) are employed. The rather mild reaction conditions compared to previous methodologies open the way to explore even more complex structures. Further investigations are being carried out in order to shed light on the activation mode and reaction mechanism of the transformation. Efforts aimed at widening the scope to other applications are ongoing in our laboratories.

## Experimental Section

### General Procedure for the Gold-Catalysed Cyclisation of Alkynoic Acids

In a scintillation vial, the alkynoic acid (0.25–1 mmol) and $[\{Au(IPr)\}_2(\mu\text{-}OH)][BF_4]$ **1a** (25 ppm–1 mol%) or [Au(IPr)(OH)] **1b** (0.2 mol%), were stirred in absence of solvent or in $CH_2Cl_2$ at room temperature or 65 °C (400 rpm). The reaction was monitored by $^1H$ NMR spectroscopy or GC until complete cyclisation of the alkynoic acid (5 min–48 h). After the reaction was completed the mixture was diluted with $Et_2O$ or pentane (*ca.* 1 mL), filtered through a short plug of $MgSO_4$ and concentrated under vacuum. The residue was then purified by pentane washing (3×5 mL) to afford the corresponding product.

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## References

[1] a) K.-H. Lee, G. K. Rice, I. H. Hall, V. Amarnath, *J. Med. Chem.* **1987**, *30*, 586–588; b) X.-p. Fang, J. E. Anderson, C.-j. Chang, J. L. McLaughlin, *Tetrahedron* **1991**, *47*, 9751–9758; c) X. Yang, Y. Shimizu, J. R. Steiner, J. Clardy, *Tetrahedron Lett.* **1993**, *34*, 761–764; d) W. F. a. S. Schulz, *Comprehensive Natural Products Chemistry*, Vol. 8, Elsevier, Amsterdam, **1999**; e) D. J. Faulkner, *Nat. Prod. Rep.* **2001**, *18*, 1R–49R; f) S. Schulz, S. Hotling, *Nat. Prod. Rep.* **2015**, *32*, 1042–1066.

[2] M. A. Churchill, H. Sibhatu, C. Uhlson, in: *Quorum Sensing*, Vol. 692, (Ed.: K. P. Rumbaugh), Humana Press, **2011**, pp 159–171.

[3] I. K. Monika, J. P. Balbina, *Mini-Rev. Med. Chem.* **2005**, *5*, 73–95.

[4] a) M. Teplitski, J. B. Robinson, W. D. Bauer, *Mol. Plant-Microbe Interact.* **2000**, *13*, 637–648; b) H. Lade, D. Paul, J. H. Kweon, *BioMed Res. Int.* **2014**, *2014*, 25.

[5] a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3160; b) N. T. Patil, R. D. Kavthe, V. S. Shinde, *Tetrahedron* **2012**, *68*, 8079–8146; c) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* **2008**, *108*, 3174–3198.

[6] a) C. Lambert, K. Utimoto, H. Nozaki, *Tetrahedron Lett.* **1984**, *25*, 5323–5326; b) D. Bouyssi, J. Gore, G. Balme, *Tetrahedron Lett.* **1992**, *33*, 2811–2814; c) A. Arcadi, A. Burini, S. Cacchi, M. Delmastro, F. Marinelli, B. R. Pietroni, *J. Org. Chem.* **1992**, *57*, 976–982; d) J. Garcia-Alvarez, J. Diez, C. Vidal, *Green Chem.* **2012**, *14*, 3190–3196; e) R. Rossi, F. Bellina, M. Biagetti, A. Catanese, L. Mannina, *Tetrahedron Lett.* **2000**, *41*, 5281–5286; f) N. Nebra, J. Monot, R. Shaw, B. Martin-Vaca, D. Bourissou, *ACS Catal.* **2013**, *3*, 2930–2934; g) N. Conde, R. SanMartin, M. T. Herrero, E. Domínguez, *Adv. Synth. Catal.* **2016**, *358*, 3283–3292.

[7] a) T. B. Marder, D. M. T. Chan, W. C. Fultz, J. C. Calabrese, D. Milstein, *J. Chem. Soc. Chem. Commun.* **1987**, 1885–1887; b) D. M. T. Chan, T. B. Marder, D. Milstein, N. J. Taylor, *J. Am. Chem. Soc.* **1987**, *109*, 6385–6388.

[8] a) M. Yamamoto, *J. Chem. Soc. Chem. Commun.* **1978**, 649–650; b) G. A. Krafft, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1981**, *103*, 5459–5466; c) A. Jellal, J. Grimaldi, M. Santelli, *Tetrahedron Lett.* **1984**, *25*, 3179–3182.

[9] C. Sun, Y. Fang, S. Li, Y. Zhang, Q. Zhao, S. Zhu, C. Li, *Org. Lett.* **2009**, *11*, 4084–4087.

[10] a) P. Pale, J. Chuche, *Tetrahedron Lett.* **1987**, *28*, 6447–6448; b) J. A. Marshall, M. A. Wolf, E. M. Wallace, *J. Org. Chem.* **1997**, *62*, 367–371; c) R. Rossi, F. Bellina, C. Bechini, L. Mannina, P. Vergamini, *Tetrahedron* **1998**, *54*, 135–156; d) V. Dalla, P. Pale, *N. J. Chem.* **1999**, *23*, 803–805.

[11] A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449.

 

[12] a) H. Harkat, J.-M. Weibel, P. Pale, *Tetrahedron Lett.* **2006**, *47*, 6273–6276; b) E. Genin, P. Y. Toullec, S. Antoniotti, C. Brancour, J.-P. Genêt, V. Michelet, *J. Am. Chem. Soc.* **2006**, *128*, 3112–3113; c) H. Harkat, A. Y. Dembelé, J.-M. Weibel, A. Blanc, P. Pale, *Tetrahedron* **2009**, *65*, 1871–1879; d) E. Tomás-Mendivil, P. Y. Toullec, J. Díez, S. Conejero, V. Michelet, V. Cadierno, *Org. Lett.* **2012**, *14*, 2520–2523; e) E. Tomás-Mendivil, P. Y. Toullec, J. Borge, S. Conejero, V. Michelet, V. Cadierno, *ACS Catal.* **2013**, *3*, 3086–3098.

[13] a) T. Wakabayashi, Y. Ishii, K. Ishikawa, M. Hidai, *Angew. Chem.* **1996**, *108*, 2268–2269; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2123–2124; b) S. Matsubara, K. Kawamoto, K. Utimoto, *Synlett* **1998**, 267–268; c) H. Imagawa, Y. Fujikawa, A. Tsuchihiro, A. Kinoshita, T. Yoshinaga, H. Takao, M. Nishizawa, *Synlett* **2006**, *2006*, 0639–0641; d) N. Á. Espinosa-Jalapa, D. Ke, N. Nebra, L. Le Goanvic, S. Mallet-Ladeira, J. Monot, B. Martin-Vaca, D. Bourissou, *ACS Catal.* **2014**, *4*, 3605–3611.

[14] S. Dupuy, D. Gasperini, S. P. Nolan, *ACS Catal.* **2015**, *5*, 6918–6921.

[15] R. S. Ramón, S. Gaillard, A. Poater, L. Cavallo, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2011**, *17*, 1238–1246.

[16] S. Gaillard, J. Bosson, R. S. Ramón, P. Nun, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2010**, *16*, 13729–13740.

[17] I. I. F. Boogaerts, S. P. Nolan, *J. Am. Chem. Soc.* **2010**, *132*, 8858–8859.

[18] J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, 734–736.

[19] See the Supporting Information for solvent screening.

[20] P. de Frémont, N. Marion, S. P. Nolan, *J. Organomet. Chem.* **2009**, *694*, 551–560.

[21] a) Y. Oonishi, A. Gómez-Suárez, A. R. Martin, S. P. Nolan, *Angew. Chem.* **2013**, *125*, 9949–9953; *Angew. Chem. Int. Ed.* **2013**, *52*, 9767–9771; b) R. M. P. Veenboer, S. Dupuy, S. P. Nolan, *ACS Catal.* **2015**, *5,* 1330–1334.

[22] a) R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc. Trans.* **1915**, *107*, 1080–1106; b) C. K. Ingold, *J. Chem. Soc. Trans.* **1921**, *119*, 305–329.

[23] 6-(4-Methoxyphenyl)hex-5-ynoic acid did not cyclise under the optimised condition, even after extended reaction time, higher catalyst loading and higher temperature.

[24] Aryl substituents on the alkyne were not tolerated, as well as 7-octynoic acid.

[25] Suitable crystals were grown by slow diffusion of hexane into a saturated solution of **3s** in $Et_2O$. CCDC 1471000 (**3s**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[26] A. Gómez-Suárez, Y. Oonishi, A. R. Martin, S. V. C. Vummaleti, D. J. Nelson, D. B. Cordes, A. M. Z. Slawin, L. Cavallo, S. P. Nolan, A. Poater, *Chem. Eur. J.* **2016**, *22*, 1125–1132.

[27] a) F. Mohr, L. R. Falvello, M. Laguna, *Eur. J. Inorg. Chem.* **2006**, *2006*, 833–838; b) J. A. Akana, K. X. Bhattacharyya, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2007**, *129*, 7736–7737; c) L.-P. Liu, B. Xu, M. S. Mashuta, G. B. Hammond, *J. Am. Chem. Soc.* **2008**, *130*, 17642–17643; d) N. Marion, S. P. Nolan, *Chem. Soc. Rev.* **2008**, *37*, 1776–1782; e) D. Weber, M. A. Tarselli, M. R. Gagné, *Angew. Chem.* **2009**, *121*, 5843–5846; *Angew. Chem. Int. Ed.* **2009**, *48*, 5733–5736; f) A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 971–975; g) A. S. K. Hashmi, A. M. Schuster, S. Gaillard, L. Cavallo, A. Poater, S. P. Nolan, *Organometallis* **2011**, *30*, 6328–6337.

[28] R. BabaAhmadi, P. Ghanbari, N. A. Rajabi, A. S. K. Hashmi, B. F. Yates, A. Ariafard, *Organometallics* **2015**, *34*, 3186–3195.

[29] a) G. Seidel, C. W. Lehmann, A. Fürstner, *Angew. Chem.* **2010**, *122*, 8644–8648; *Angew. Chem. Int. Ed.* **2010**, *49*, 8466–8470; b) T. J. Brown, D. Weber, M. R. Gagné, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2012**, *134*, 9134–9137; c) A. S. K. Hashmi, I. Braun, P. Nösel, J. Schädlich, M. Wieteck, M. Rudolph, F. Rominger, *Angew. Chem.* **2012**, *124*, 4532–4536; *Angew. Chem. Int. Ed.* **2012**, *51*, 4456–4460; d) A. Zhdanko, M. E. Maier, *Organomet.* **2013**, *32*, 2000–2006; e) J. Preindl, K. Jouvin, D. Laurich, G. Seidel, A. Fürstner, *Chem. Eur. J.* **2016**, *22*, 237–247.

[30] Stoichiometric experiments of **1a** and **2b** in $CDCl_3$ led to immediate full conversion into **3b**. No traces of a detectable intermediate could be observed.

[31] The $^1$H NMR spectroscopic data were acquired in $CDCl_3$ for practical reasons, although the reaction was slower than under solvent-free conditions.

[32] See the Supporting Information for full experimental details of the kinetic experiments.

[33] A. Zhdanko, M. E. Maier, *Chem. Eur. J.* **2014**, *20*, 1918–1930. *We are currently exploring the mechanistic landscape of this transformation.*