RESEARCH ARTICLE doi.org/10.1002/adsc.202500062

ADVANCED SYNTHESIS & CATALYSIS

Efficient Synthesis of Amino Lactones via Copper-catalysed Alkene Aminooxygenation

Martina Casciotti,[a] José M. Muñoz-Molina,[a,*] Tomás R. Belderrain,[a,*] and Pedro J. Pérez[a,*]

[a] Laboratorio de Catálisis Homogénea, Unidad Asociada al CSIC, CIQSO-Centro de Investigación en Química Sostenible and Departamento de Química, Universidad de Huelva, 21007 Huelva, Spain
E-mail: jose.molina@dqcm.uhu.es; trodri@dqcm.uhu.es; perez@dqcm.uhu.es

Manuscript received: January 19, 2025; Revised manuscript received: March 16, 2025;
Version of record online: April 14, 2025

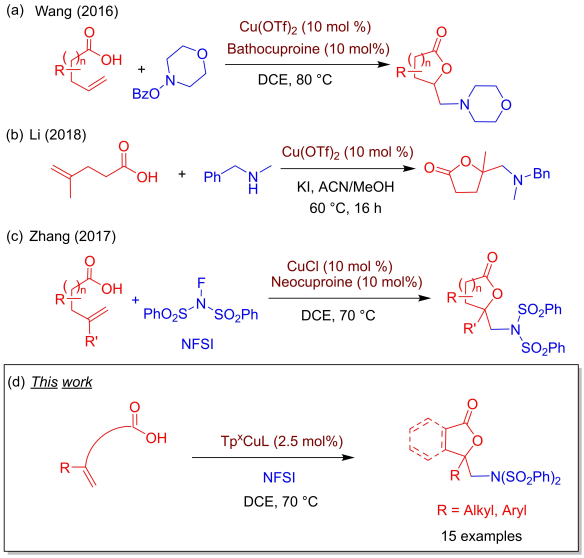
Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202500062

Abstract: The synthesis of 5–7 membered oxygenated heterocycles by intramolecular aminooxygenation of unsaturated alkenes using commercially available N-fluorobenzenesulfonimide as amination reagent and $Tp^{iPr2}Cu(NCCH_3)$ as precatalyst is reported. With unsaturated aliphatic carboxylic acids, the corresponding lactones are obtained from moderate to almost quantitative yields employing a catalyst loading of 2.5 mol% under mild conditions, whereas 2-vinylbenzoic acids originate lower yields.

Keywords: amination; copper catalysis; radical reactions; lactones; C–N bond formation

1. Introduction

Aminolactones are widespread motifs in diverse natural[1] and synthetic biologically active compounds,[2] as they can be transformed into other valuable products.[1a,3] During the last decade, significant efforts have been made toward the development of new and practical methods for the synthesis of such oxygen-containing heterocycles.[4] One of the most versatile methods consists in the metal-catalyzed alkene difunctionalization.[5] Among the reported examples, the copper-catalyzed electrophilic functionalization of unsaturated carboxylic acids has attracted great interest. Wang described the copper-catalyzed aerobic amino-lactonization reaction using previously prepared *O*-benzoylhydroxylamine as the electrophilic amination agent (Scheme 1a).[6] Thus, Li reported the aerobic copper-catalyzed oxyamination of alkenes using electron-rich amines and equimolar amounts of potassium iodide (KI) as additive (Scheme 1b).[7] Interestingly, Zhang reported the copper-catalyzed synthesis of aminolactones using commercially available *N*-fluorobenzenesulfonimide (NFSI) as an amination



Scheme 1. Copper-catalysed electrophilic amino-lactonization reactions.

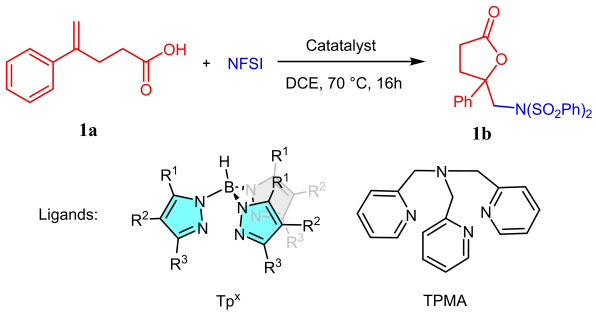
reagent (Scheme 1c).[8] A high yield of 90%, was described for the substrate 2-(2-methylallyl)benzoic acid with a 10 mol% of copper catalyst loading.

Our group has described the synthesis of pyrrolidines and piperidines via intramolecular C – H amination of *N*-alkyl-*N*-fluorosulfonamide using complex [Tp^{iPr2}Cu(NCMe)] as the well-defined precatalyst [Tp^{iPr2} = hydrotris(3,5-diisopropyl-1-pyrazolyl) borate],[9] operating at low catalyst loadings (1 mol%). With this precedent in mind, we wondered if the complexes Tp^{x}CuL[10] (L = solvent) could catalyze the reaction of unsaturated carboxylic acids and NFSI. To our delight, we have found that an array of aminolactones can be prepared with this strategy improving the yields and the reaction conditions reported to date upon using such Tp^{x}CuL catalysts (Scheme 1d).

2. Results and Discussion

Benchmark reaction of 4-phenylpent-4-enoic acid with NFSI. To test the catalytic capabilities of Tp^{x}CuL complexes in the synthesis of amino lactones we chose the 4-phenylpent-4-enoic acid, **1 a**, as the model substrate to be reacted with 1.5 equiv. of NFSI in the presence of catalytic amounts of the complexes shown in Table 1. We decided to start our studies with this unsaturated aliphatic carboxylic acid since Zhang and co-workers[8] reported a 67% yield in the case of **1 a** and a 48% in the case of 5-phenylhex-5-enoic acid, **2 a**, using a catalytic loading of 10 mol% (CuCl/neocuproine). In the absence of any copper species, the mixture of **1 a** and NFSI heated at 70 °C for 16 h did not provide the cyclization product **1 b** (entry 1). Then a series of five experiments were run, only differing in the copper complex added as potential catalyst (entries 2–6). Several trispyrazolylborate ligands bearing electron donating, electron withdrawing, alkyl or aryl substituents at the pyrazolyl rings were employed. The best results were obtained with [Tp^{iPr2}Cu(NCMe)], similarly to the results described for the synthesis of pyrrolidines and piperidines by intramolecular aliphatic C-H functionalization reaction of *N*-fluorosulfonamides.[9b] Importantly, the use of these Tp^{x}CuL catalysts allowed for notably reducing the catalyst loading by a four-fold factor to as low as 2.5 mol% in contrast to the previously described systems (Scheme 1). For the sake of comparison, we also tested an in situ generated copper catalyst bearing the neutral ligand TPMA (TPMA = tris(2-pyridylmethyl)amine),[11] however the yield was significantly lower (entry 7) than those obtained with Tp^{x}CuL complexes. Other conditions of temperature, solvent or stoichiometry may affect the reaction outcome (see SI).

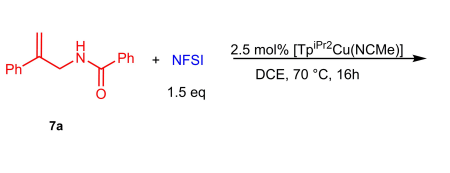
Table 1. Copper-catalysed aminolactonization reactions: catalyst screening and optimization.



Entry	Catalyst	Yield (%)[b]
1	–	n. d.[c]
2	[Tp*Cu]$_2$	80
3	Tp^{iPr2}Cu(NCMe)	97[d]
4	Tp^{Ms}Cu(THF)	77
5	Tp$^{(CF3)2,Br}$Cu(NCMe)	74
6	Tp^{Br3}Cu(NCMe)	80
7	CuI/TPMA	54

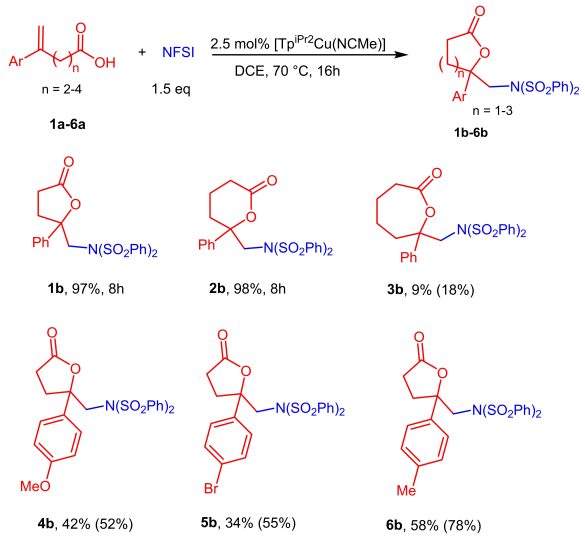
[a] Reaction conditions: **1 a** (0.2 mmol), catalyst (2.5 mol%), and NFSI (0.3 mmol) in DCE (1 mL) at 70 °C under N_2 for 16 h.
[b] Yields obtained by ^{1}H NMR spectroscopy of the reaction mixture (acetophenone as internal calibration standard).
[c] Not detected by ^{1}H NMR. [d]8 h reaction time.

Substrate scope and limitations. **(a) Aliphatic carboxylic acids**. Once the previous catalyst screening led to the identification of Tp^{iPr2}Cu(NCMe) as the best choice, we faced the use of several unsaturated aliphatic carboxylic acids for their conversion into the corresponding cyclization products. Scheme 2 displays the different substrates studied. Both 2.5 and 10 mol% catalyst loadings were used, the results with the latter not being significantly higher, probably as a consequence of catalyst deactivation with time that makes useless the use of larger amounts of catalyst. The six membered ring **2 b** was obtained in almost quantitative yield, whereas yield decreased in the case of the **3 b**. The *para*-substituted 4-aryl-4-enoic acids underwent the cyclization reaction affording the corresponding lactones in moderate yields (**4 b-6 b**), indicating a certain electronic influence of the substituent in *para* position of the aryl ring. We also applied the use of this methodology to the synthesis of oxazoline derivative **7 b** (Eq. (1)), that was obtained in a 55% yield with 2.5 mol% of catalyst.

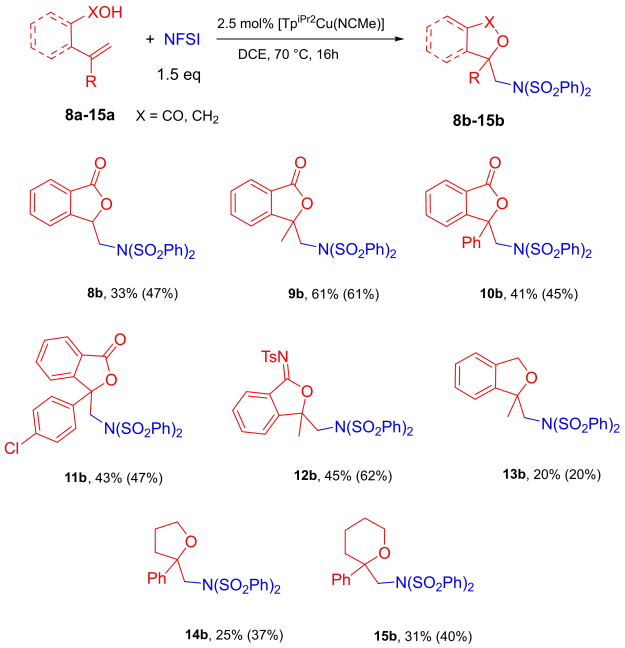


(1)

(b) 2-Vinyl benzoic acid and alcohols. After the results with aliphatic carboxylic acids, we moved onto substrates such as 2-vinyl benzoic acid (**8 a-12 a**) and



Scheme 2. Scope of the amino lactonization reaction of unsaturated aliphatic carboxylic acids as substrates. Reaction conditions: substrate (0.2 mmol), NFSI (0.3 mmol), catalyst (0.005 mmol), in DCE (1 mL) at 70 °C for 16 h. Yields obtained by ^{1}H NMR spectroscopy of the reaction mixture (acetophenone as internal calibration standard). Yields in brackets correspond to a 10 mol% catalyst loading.

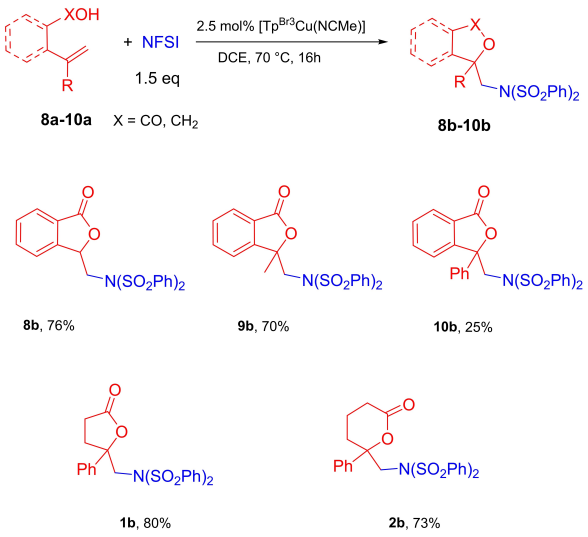


Scheme 3. Amino lactonization reaction of 2-vinylbenzoic acid derivatives (**8a**–**12a**) and alcohols (**13a**–**15a**). Reaction conditions: substrate (0.2 mmol), NFSI (0.3 mmol), catalyst (0.005 mmol), in DCE (1 mL) at 70 °C for 16 h. Yields obtained by ^{1}H NMR spectroscopy of the reaction mixture (acetophenone as internal calibration standard). Yields in brackets correspond to a 10 mol% catalyst loading.

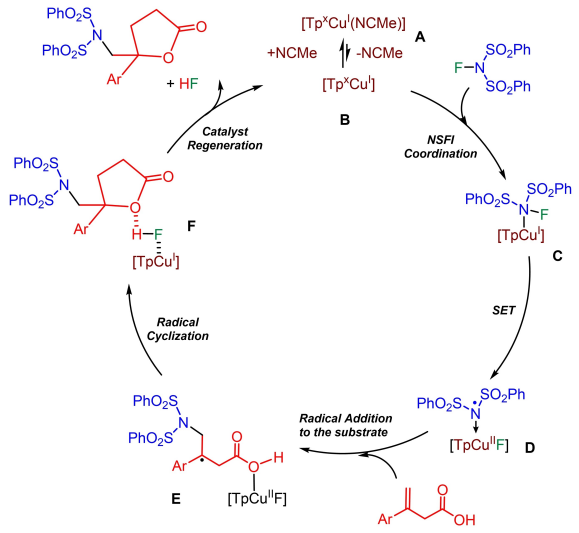
alcohols (**13a-15a**) (Scheme 3). With a 2.5 mol% of catalyst loading, corresponding lactones were obtained with low to moderate yields, albeit comparable to previously reported examples.[8] Yields generally improved upon increasing catalyst loading to 10 mol%. However, the fact that this improvement is not linear points toward catalyst deactivation with time.

Some literature precedents pointed to a potential catalyst deactivation due to protonation of the trispyrazolylborate ligand.[12] Trofimenko and coworkers described the synthesis of the $[(Tp^{Cy}H)CuCl_2]$ complex by the reaction of $[Tp^{Cy}Tl]$ with $CuCl_2{\bullet}2H_2O$.[13] Fujisawa and coworkers reported that the reaction of $[\{Tp^{iPr}Cu^{II}\}(\mu\text{-}OH)]_2$ with tetrachlorocatechol leads to the formation of $(Tp^{iPr}H)Cu^{II}(catCl_4)$ ($catCl_4$ = tetrachlorocatecholate) which contains the Tp^{iPr} ligand with one of the pyrazolyl rings protonated.[14] Moreover, the group of Singh described the protonation of the Tp^{iPr2} in the case of the dinuclear manganese complex $[Tp^{iPr2}Mn^{II}(\mu\text{-}OH)]_2$ by reaction with an excess of benzoic acid gives $[Tp^{iPr2}Mn\text{-}(\mu\text{-}OBz)_3\text{-}Mn(Tp^{iPr2}H)]$.[15] To test if a similar process occurs in the case of $Tp^{iPr2}Cu(NCCH_3)$, we have carried out the reaction of this complex with three equiv. of 2-vinylbenzoic acid, **8a**, but protonation of the pyrazole was not observed. However, the reaction of $Tp^{iPr2}Cu(NCCH_3)$ complex with 3 equiv. of NFSI and, subsequently, 3 equiv. of **8a**, afforded a green solid which IR spectrum shows relevant absorptions at 3135 and 2534 cm^{-1}. The former corresponds to a protonated pyrazolyl ring and is similar to that described by Fujisawa[14] for a related Tp^x-protonated copper complex (3142 cm^{-1}). The band at 2534 cm^{-1} is associated to the B–H moiety and appears shifted toward higher energy region compared to the band of the non-protonated precursor as previously described by Trofimenko.[13] Thus, protonation of a Cu(II) species during catalysis decreases the amount of active catalysts, explaining the decrease in the yields compared to those with the less acidic aliphatic carboxylic acids.

Being determined that the origin of the loss of activity is related with the protonation of the Tp^{iPr2} ligand, we reasoned that decreasing the electron density at the ancillary ligand would make it less prone to protonation. Such decrease in basicity may be reached upon using a Tp^x ligand with electron-withdrawing groups at the pyrazolyl rings. Toward that end, we employed the ligand Tp^{Br3},[10] with the electron-withdrawing bromine substituents. Under our standard conditions (Scheme 4), employing the acids **8a-10a** and 2.5 mol% of catalyst loading, yields improved significantly in the case of **8b** in comparison with $Tp^{iPr}Cu(NCCH_3)$ (from 33% to 76%) and it was also higher in the case of **9b** (70%). The catalytic performance of $Tp^{Br3}Cu(NCCH_3)$ is maintained even at higher temperature. Thus at 100 °C, **8b** was obtained



Scheme 4. Amino lactonization reaction of 2-vinylbenzoic acid derivatives (**8a**–**10a**) and carboxylic acids (**1a**–**2a**) with $Tp^{Br3}Cu(NCCH_3)$ as catalyst. Reaction conditions: substrate (0.2 mmol), NFSI (0.3 mmol), catalyst (0.005 mmol), in DCE (1 mL) at 70 °C for 16 h. Yields obtained by ^1H NMR spectroscopy of the reaction mixture (acetophenone as internal calibration standard).

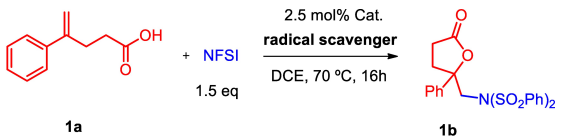


Scheme 6. Mechanistic proposal.

with an 83% yield (see SI). In the case of the unsaturated carboxylic acids **1a** and **2a** the corresponding lactones, **1b** and **2b**, were obtained in high yields (80 and 73%, respectively), although lower than those obtained with $Tp^{iPr}Cu(NCCH_3)$ as catalyst.

Mechanistic proposal. Control experiments in the presence of the radical scavengers TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] or BHT (2,6-di-t-butyl-hydroxytoluene) were carried out under the standard conditions (Scheme 5). In both cases, the formation of the amino lactone **1b** is prevented, assessing the intermediacy of radical species. This is in agreement with our previous contributions on the synthesis of pyrrolidines and piperidines by intramolecular C – H amination of *N*-fluoride amides.[9]

Based on previous work involving N–F bond activation (which included experimental and DFT calculations)[9] and data available, Scheme 6 contains a mechanistic proposal for this transformation. The first step consists in the decoordination of acetonitrile from the catalyst precursor (**A**) followed by N-coordination of the NFSI (**C**). Subsequently, N–F bond cleavage takes place via a single electron transfer (SET) from Cu to the N–F bond (**D**). Substrate incorporation takes place through addition of the radical to the C=C bond, leading to alkyl-radical (**E**). At this stage, cyclization takes place, and intermediate **F**, where the Tp^xCu moiety, the HF and the lactone are associated, is proposed based on previous calculations.[9] From here, the three molecules dissociate to re-start the catalytic cycle, releasing the lactone and one equiv. of HF. Since the catalyst is not protonated by the acidic reactant, requiring also NFSI, we also propose that HF is the responsible for catalyst deactivation.



Entry	Radical scavenger	**1b** (%)[b]
1	TEMPO	5
2	BHT	n.r.

Scheme 5. Control experiments in the presence of radical traps.

3. Conclusions

We have shown that $Tp^{iPr2}Cu(NCCH_3)$ acts as an efficient catalyst in the synthesis of amino lactones, cyclic ethers and oxazoline by intramolecular amino-oxygenation of several alkenyl-containing acids or alcohols. Depending on the nature of the acid, yields varied from moderate to very high employing the less frequent catalyst loading of 2.5 mol% for previous reports in the literature for these transformations. This protocol must be intended as complementary to that previously reported by Zhang, since depending of the nature of the substrate the catalytic outcome is maximized with one or the other.

Experimental Section

All air – and moisture – sensitive manipulations were carried out with standard Schlenk techniques under nitrogen atmos-

phere or in a glovebox (MBRAUN UNILAB). Solvents were purchased from commercial sources, dried by distillation under nitrogen atmosphere using the suitable drying agent and deoxygenated immediately before their use. Reagents were acquired from Merck and used without any further purification. The copper catalysts were synthesized by literature procedures.[16,17,18,19,20,21] NMR spectra were recorded on the NMR spectra were recorded on Bruker Avance III HD 400 and 500 MHz spectrometers. FT-IR spectra were collected on a Nicolet IR200 FTIR spectrometer. High resolution mass spectroscopy experiments were carried out at the Centre for Research in Sustainable Chemistry (CIQSO) of the University of Huelva.

General Catalytic Procedure: Into a glovebox, a 25 mL Schlenk tube was charged with 0.2 mmol of substrate, 0.005 mmol of $Tp^{iPr2}Cu(NCMe)$ (2.5 mol%), and dissolved with 0.5 mL of 1,2-DCE. After 5 minutes, 0.3 mmol of NFSI (1.5 eqiv.) was added followed by addition of 0.5 mL of 1,2-DCE. The tube was sealed and heated to 70 °C. After 16 h, the reaction mixture was cooled down to room temperature, the solvent was removed under reduced pressure and the residue redissolved in ethyl acetate. The obtained solution was filtered over neutral aluminium oxide and dried over vacuum. Then, 23 µL of acetophenone (0.2 mmol) was added as an internal standard.

Spectroscopic and analytical data of compounds **1b-15b** are provided in the Supporting Information.

Acknowledgements

We are grateful for financial support from the Ministerio de Ciencia e Innovación (PID2020-113797RB–C21). We also thank Junta de Andalucía (P18-1536-RT and P20-00348) and Universidad de Huelva (P.O.Feder UHU202053).

References

[1] a) J. F. De Bernardis, D. L. Arendsen, J. J. Kyncl, D. J. Kerkman, *J. Med. Chem.* **1987**, *30*, 178–184; b) C. Kaiser, C. J. Spagnuolo, T. C. Adams, V. H. Audia, A. C. Dupont, H. Hatoum, V. C. Lowe, J. C. Prosser, B. L. Sturm, L. Noronha-Blob, *J. Med. Chem.* **1992**, *35*, 4415–4424; c) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576; d) S. Kobayashi, K. Kamiyama, M. Ohno, *J. Org. Chem.* **1990**, *55*, 1169–1177; e) I. Triandafillidi, M. Raftopoulou, A. Savvidou, C. G. Kokotos, *ChemCatChem* **2017**, *9*, 4120–4124; f) B. Wei, K. W. Li, Y. C. Wu, S. Q. Tong, R. J. Song, *Synthesis.* **2020**, *52*, 3855–3864.

[2] a) M. O. Karlsson, B. Dahlström, S.-Å. Eckernäs, M. Johansson, A. T. Alm, *Eur. J. Clin. Pharmacol.* **1990**, *39*, 275–279; b) H. Hoff, H. Drautz, H. P. Fiedler, H. Zaehner, J. E. Schultz, W. Keller-Schierlein, S. Philipps, M. Ritzau, A. Zeeck, *J. Antibiot.* **1992**, *45*, 1096–1107; c) Putcha, K. M. Danzer, L. R. Kranich, A. Scott, M. Silinski, S. Mabbett, C. D. Hicks, J. M. Veal, P. M. Steed, B. T. Hyman, P. J. McLean, *J. Pharmacol. Exp. Ther.* **2010**, *332*, 849–857.

[3] O. Kitagawa, T. Hanano, K. Tanabe, M. Shiro, T. Taguchi, *J. Chem. Soc. Chem. Commun.* **1992**, 1005–1007.

[4] a) Z. Wu, M. Hu, J. Li, W. Wu, H. Jiang, *Org. Biomol. Chem.* **2021**, *19*, 3036–3054; b) R.-J Song, B. Wei, K.-W. Li, Y.-C. Wu, S.-Q. Tong, *Synthesis* **2020**, *52*, 3855–3865.

[5] a) C. Liu, J. Wu, X. Tan, J. Zhang, W. Wu, H. Jiang *ACS Catal.* **2023**, *13*, 11339–11344; b) E. J. Alexanian, C. Lee, E. J. Sorensen *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691; c) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 7179–7181; d) T. deHaro, C. Nevado, *Angew. Chem. Int. Ed.* **2011**, *50*, 906–910; e) R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 8069–8077; f) G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*,451–454; g) T. J. Donohoe, G. H. Churchill, K. M. P. Wheelhouse, P. A. Glossop, *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 8025–8028; h) L. V. Desai, M. S. Sanford, *Angew. Chem. Int. Ed.* **2007**, *46*, 5737–5740; i) S. R. Chemler, S. D. Karyakarte, Z. M. Khoder, *J. Org. Chem.* **2017**, *82*, 11311–11325; j) K. Muñiz, A. Iglesias, Y. W. Fang, *Chem. Commun.* **2009**, 5591–5593; k) A. Padwa, A. C. Flick, C. A. Leverett, T. Stengel, *J. Org. Chem.* **2004**, *69*, 6377–6386; l) S. Beaumont, V. Pons, P. Retailleau, R. Doddand, P. Dauban, *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 1634–1637.

[6] a) B. N. Hemric, A. W. Chen, Q. Wang, *J. Org. Chem.* **2019**, *84*, 1468–1488; b) B. N. Hemric, K. Shen, Q. Wang, *J. Am. Chem. Soc.* **2016**, *138*, 5813–5816.

[7] a) F. Wu, S. Stewart, J. P. Ariyarathna, W. Li, *ACS Catal.* **2018**, *8*, 1921–1925; b) F. Wu, J. P. Ariyarathna, N. E. Alom, N. Kaur, W. Li, *Org. Lett.* **2020**, *22*, 884–890.

[8] J. Xie, Y. W. Wang, L. W. Qi, B. Zhang, *Org. Lett.* **2017**, *19*, 1148–1151.

[9] a) J. M. Muñoz-Molina, D. Bafaluy, I. Funes-Ardoiz, A. De Aguirre, F. Maseras, T. R. Belderrain, P. J. Pérez, K. Muñiz, *Organometallics* **2022**, *41*, 1099–1105; b) D. Bafaluy, J. M. Muñoz-Molina, I. Funes-Ardoiz, S. Herold, A. J. de Aguirre, H. Zhang, F. Maseras, T. R. Belderrain, P. J. Pérez, K. Muñiz, *Angew. Chem. Int. Ed.* **2019**, *58*, 8912–8916.

[10] J. M. Muñoz-Molina, T. R. Belderrain, P. J. Pérez, *Coord. Chem. Rev.* **2019**, *390*, 171–189.

[11] This type of catalytic systems is commonly used in ATRP (Atom Transfer Radical Polymerization) and ATRA (Atom Transfer Radical Addition) reactions. As a recent contribution see: F. Lorandi, M Fantin, H. Jafari, A. Gorczynski, G. Szczepaniak, S. Dadashi-Silab, A. A. Isse, K. Matyjaszewski *J. Am. Chem. Soc.* **2023**, *145*, 21587–21599 and references therein.

[12] a) S. Reinartz, P. S. White, M. Brookhart, J. L. Templeton, *Organometallics* **2000**, *19*, 3854–3866; b) S. Reinartz, P. S. White, M. Brookhart, J. L. Templeton, *J. Am. Chem. Soc.* **2001**, *123*, 12724–12725; c) C. M. Norris, S. Reinartz, P. S. White, J. L. Templeton, *Organometallics* **2002**, *21*, 5649–5656; d) N. M. West, N. S. Reinartz,

P. S. White, J. L. Templeton, *J. Am. Chem. Soc.* **2006**, *128*, 2059–2066.
[13] A. L. Rheingold, B. S. Haggerty, S. Trofimenko, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1983–1985.
[14] K. Fujisawa, T. Ono, M. Okamura, *Inorganics* **2020**, *8*, 37.
[15] U. P. Singh, R. Singh, S. Hikichi, M. Akita, Y. Moro-oka, *Inorg. Chim. Acta* **2000**, *310*, 273–278.
[16] K. Fujisawa, T. Ono, Y. Ishikawa, N. Amir, Y. Miyashita, K. Okamoto, N. Lehnert, *Inorg. Chem.* **2006**, *45*, 1698–1713.
[17] A. Caballero, M. M. DÍaz-Requejo, T. R. Belderrain, M. C. Nicasio, S. Trofimenko, P. J. Pérez, *J. Am. Chem. Soc.* **2003**, *125*, 1446–1447.
[18] C. Mealli, C. S. Arcus, J. L. Wilkinson, T. J. Marks, J. A. Ibers, *J. Am. Chem. Soc.* **1976**, *98*, 711–718.
[19] J. L. Schneider, S. M. Carrier, C. E. Ruggiero, V. G. Young, W. B. Tolman, *J. Am. Chem. Soc.* **1998**, *120*, 11408–11418.
[20] R. Gava, A. Olmos, B. Noverges, T. Varea, E. Álvarez, T. R. Belderrain, A. Caballero, G. Asensio, P. J. Pérez, *ACS Catal.* **2015**, *5*, 3726–373.
[21] A. Olmos, A. Pereira, T. R. Belderrain, P. J. Pérez, *Synthesis* **2018**, *50*, 3333–3336.