ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Alcazar, E. Palao, E. Lopez, A. de la Hoz, A. Diaz and I. Torres Moya, *Chem. Commun.*, 2020, DOI: 10.1039/D0CC02734K.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/D0CC02734K

COMMUNICATION

Formation of quaternary carbons through cobalt-catalyzed C(sp³)-C(sp³) Negishi cross-coupling.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Eduardo Palao,[a] Enol López,[b] Iván Torres-Moya,[b] Antonio de la Hoz,[b] Ángel Díaz-Ortiz,[b] Jesús Alcázar*[a]

Formation of all-carbon-substituted quaternary carbons is a key challenge in organic and medicinal chemistry. We report a cobalt-catalyzed C(sp³)-C(sp³) cross-coupling that allows for the introduction of benzyl, heteroarylmethylzinc and allyl groups to halo-carbonyl substrates. The cross-coupling reaction is selective for C(sp³)- over C(sp²)-halides, in contrast to most used catalytic metals, and allows access to novel scaffolds of pharmaceutical interest. NMR mechanistic studies suggest the presence of Co(0) complexes as catalytic species.

Escaping flatland is a clear requirement in drug discovery with the aim of improving success rate.[1] In order to increase the C(sp³) fraction in bioactive molecules new procedures for alkyl-alkyl cross-coupling are required. Despite the evolution in this field the formation of all-carbon-substituted quaternary carbon atoms remains a complex challenge.[2]

In the last few years, several Ni and Pd catalysed alkyl-alkyl cross-coupling reactions have been described in literature.[3] Their scope of these transformations is rather limited due to β-hydrogen elimination side reactions.[4] Recently cobalt has appeared as an inexpensive and less toxic alternative for cross-coupling.[5] However, alkyl-alkyl bond formation using cobalt remains a challenge. The first Co-catalysed C(sp³)-C(sp³) coupling was reported by Cahiez and co-workers using Grignard reagents as nucleophiles.[6] The methodology allows the preparation of secondary and tertiary carbon centres and shows limited functional group tolerance.

In the context of Drug Discovery projects, the development of methods with wide functional group tolerance is essential for the functionalization of advanced synthesis intermediates and drug candidates. Organozinc reagents are known to be more functional group tolerant nucleophiles than Grignard ones,[7] and

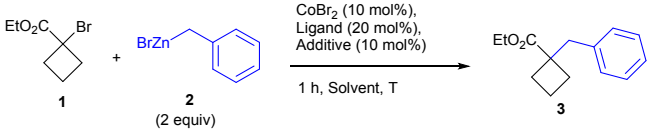


Table 1. Optimization of reaction conditions.

Entry	Ligand	Solvent	T(ºC)	**3:1** ratio[a]
1[b,c]	dppf	DMF	rt	25:75
2[c,d]	dppf	DMF	rt	45:55
3[d]	dppf	DMF	40	48:52
4[d]	dppf	DMF/THF	40	65:35
5[d]	dppf	Toluene/THF	40	16:84
6[d]	dppf	THF	40	6:94
7	dppf	DMF/THF	40	97:3 (45%)
8	**dppe**	**DMF/THF**	**40**	**100:0 (55%)**
9[e]	dppe	DMF/THF	40	94:6
10	dppp	DMF/THF	40	100:0 (49%)
11	dppb	DMF/THF	40	41:59
12	Xantphos	DMF/THF	40	40:60
13	Josiphos	DMF/THF	40	100:0 (38%)
14	Symphos	DMF/THF	40	50:50
15	Binap	DMF/THF	40	6:94
16	$(Et)_2P$-Et-$P(Et)_2$	DMF/THF	40	1:99
17	dppbz	DMF/THF	40	27:73
18	-	DMF/THF	40	4:94
19[f]	-	DMF/THF	40	0:100

[a]Reaction progression as **3**/**1** ratio by GC/MS, isolated yields in brackets; [b]Zn as additive; [c]Overnight reaction: [d]Mg as additive; [e]$CoBr_2$ (5 mol%); [f]Reaction in the absence of $CoBr_2$.

for instance, Knochel and co-workers reported recently the use of aryl zinc reagents in cobalt catalysed C(sp²)-C(sp³) coupling with α-bromolactones for the preparation of tertiary carbon centers.[8a] This prompted us to explore the reactivity of organozinc reagents under cobalt catalysis for preparation of C(sp³)-C(sp³) bonds, specifically focusing on the formation of all-carbon-substituted quaternary centres that remains a challenge in organic and medicinal chemistry. In the course of our investigations Knochel et al. published the first cobalt

[a] *Discovery Chemistry, Janssen Research and Development, Janssen-Cilag, S.A., C/ Jarama 75A, Toledo, Spain. E-mail: jalcazar@its.jnj.com.*
[b] *Facultad de Ciencias y Tecnologías Químicas, Universidad de Castilla-La Mancha, Ciudad Real, Spain.*
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

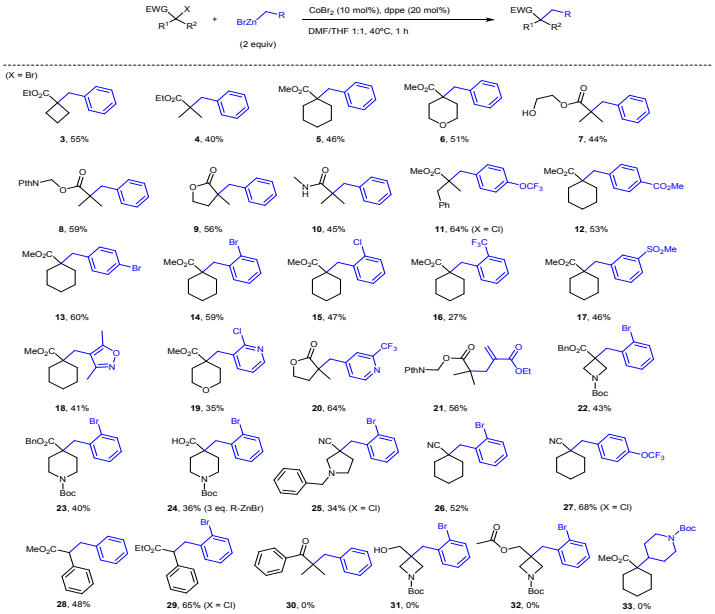
View Article Online
DOI: 10.1039/D0CC03734K

catalysed Negishi type C(sp^3)-C(sp^3) coupling with primary and secondary alkyliodides.[8b]

For our initial screening of reaction conditions, we selected ethyl 1-bromocyclobutane-1-carboxylate **1** and benzylzinc bromide **2** as model substrates and $CoBr_2$ as cobalt source (Table 1). As we anticipated that cobalt(II) was not going to be the active catalytic species, we investigated its reduction to Co(I) or Co(0) using zinc or magnesium additives.[9] Initial reaction with Zn(0) as additive showed 25:75 conversion to **3** (Entry 1), however the use of Mg(0) improved this conversion (Entry 2). Increasing the temperature to 40°C resulted in a slightly increased 48:52 conversion (Entry 3).

Solvent screening showed that a mixture of DMF/THF (1:1) provided the best results (Entries 3-6). To our surprise, in the absence of additive a 97:3 conversion was observed and product **3** was isolated in 45% yield (Entry 7). A variety of ligands with different electronic and coordinating properties were then tested (Entries 7-17 and supporting information). Bidentate phosphorus ligands with diaryl substitution pattern (Entry 8), and bite angles between 85°-93° (Entries 7, 8, 10 and 13) resulted in better conversions.[10] From all ligands dppe was the best performing leading to product **3** in 55% of isolated yield (Entry 8). Triarylphosphines (Entries 15 and 17) failed to work despite the appropriate bite angle (see supporting info), suggesting that electron density around phosphorous atoms may play an important role in the reaction outcome. An attempt to reduce the catalyst loading to 5% was slightly detrimental for the reaction conversion (Entry 9). The importance of both ligand and catalyst was confirmed performing the corresponding blank experiments (Entries 18 and 19).

Scheme 1. Scope of cobalt catalysed cross-coupling.



Conditions described in Table 1, Entry 8 were chosen as optimal and used to explore the reaction scope (Scheme 1). First, different tertiary α-bromo esters were studied. The reaction conditions were compatible with cyclic and acyclic halogenated derivatives and coupling products **3**-**6** were obtained in moderate yields. The transformation was also compatible with the presence of heteroatoms either at the alkyl substituents **6** or at the ester alkoxy group **7**,**8**. Thus hydroxy- (**7**) and phthalimide-containing (**8**) esters were isolated in 44 and 59% yield respectively. Cyclic esters were suitable coupling partners and lactone **9** could be isolated in 56% yield**.** Interestingly, secondary amides underwent the Co-catalyzed Negishi-type coupling affording the corresponding product in comparable yield (**10**, 45% vs **4**, 40%).

To expand the reaction scope a set of diverse organozinc reagents was prepared following our previously published protocol.[11] Different benzyl zinc bromides were compatible with the reaction. Among these groups it is noteworthy to highlight the compatibility with halogenated derivatives which would allow further derivatization of the phenyl ring in the reaction products **13**-**15**. Furthermore, electron rich (**18**) or electron deficient (**19**-**20**) heteroarylmethylzinc bromides were successfully used in this transformation providing the desired products in practical yields. More complex organozinc derivatives, such as those containing an α,β-unsaturated ester, were also fruitful partners in this transformation, as demonstrated with the preparation of compound **21**.

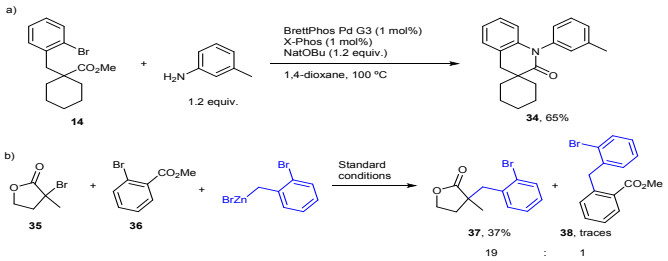
Next, we evaluated the reactivity of an array of heterocyclic scaffolds of common use in medicinal chemistry. In this regard, four to six membered cyclic amine bromoesters yielded the corresponding coupling compounds **22**-**26** in satisfactory yields. Interestingly, a carboxylic acid function did not affect the reaction outcome and compound **24** was obtained in comparable yield to the match-pair ester **23**. A pyrrolidine derivative (**25**) was prepared from the commercially available bromocyano precursor, highlighting the ability of the nitrile group to promote this transformation. This finding prompted us to explore additional cyano-substituted precursors as an alternative to carboxyl group. Gladly the nitrile derivatives **26** and **27** were obtained in satisfactory yields. Noteworthy, chloro derivatives could also be successfully used in the reaction and derivatives **11**, **25**, **27** and **29** were isolated in moderate to good yields (34-68%), broadening the scope in terms of suitable halogenated derivatives. Compound **24** was scaled up at gram scale for a side reaction study. A reproducible isolated yield was obtained (37%), being dehalogenation (16%) and β-elimination (13%) the main side products observed (see supporting information).

In addition to the formation of quaternary carbons, this chemistry was tested for the preparation of tertiary carbon centers. As proof of our concept, 2-halogenated-2-phenylacetates were reacted with benzyl zincbromides under

standard conditions. Interestingly, compounds **28** and **29** were successfully prepared in reasonable yields. However, the reaction did not provide the desired compound when α-bromoester group was replaced by ketone, alcohol and acetyl moieties (**30**-**32**). Reaction also failed when a non-benzylic alkylzinc was used (**33**). Probably this class of organozinc reagents are no able to reduce Co(II) and no effective reaction was observed.

As mentioned above, the fact that the reaction is compatible with halogenated benzyl zinc derivatives provides opportunities for further derivatization of the coupling products. For instance, the spiroquinolone **34** could be prepared in 65% yield from compound **14** after Buchwald coupling with 3-methylaniline followed by intramolecular cyclization (Scheme 2a). This exemplifies the value of this chemistry to access novel scaffolds of pharmaceutical interest.

Scheme 2. Applications of cobalt catalysed cross-coupling: a) preparation of



scaffolds of pharmaceutical interest; b) chemoselectivity of cobalt-catalysed cross-coupling reaction.

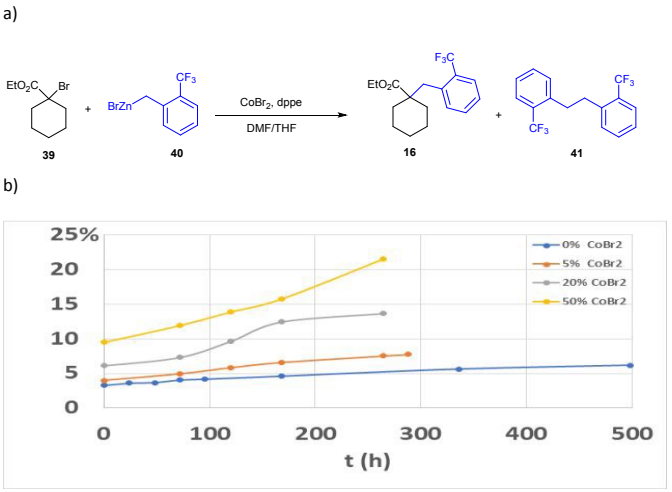
Furthermore, to study the chemoselectivity of the reaction, a competitive study with a mixture of a bromoalkyl (**35**) and bromoaryl (**36**) esters was performed (Scheme 2b). Gratifyingly, analysis of the reaction crude showed compound **37**, product from $C(sp^3)$-$C(sp^3)$ pathway, was largely favored over compound **38** coming from the $C(sp^3)$-$C(sp^2)$ process in competition (ratio **37:38** 19:1). This result illustrates the value of cobalt catalysis for alkyl-alkyl cross couplings over traditional catalytic process involving Pd,[12] Ni[13] or Fe[14] organometallic complexes.

In order to shed some light on the reaction mechanism two approaches were followed: use of radical traps to study the potential involvement of radical processes and NMR kinetic studies aiming to identify the active catalytic species.

BHT and 1,1-dipheylethene were selected as radical traps as other typical reagents used for this purpose, such as TEMPO, are not compatible with the use of organzinc reagents.[15] Neither BHT nor 1,1-diphenylethene quenched the reaction, which suggests a non-radical pathway, although this cannot be completely ruled out (see Scheme S2 in Supporting Information). However, when ethyl 2-bromo-2-cyclopropylacetate was used as a radical clock reagent,[16] the corresponding ring opened product was obtained in low yield. This suggest the presence of radicals in the course of the reaction (see Scheme S3 supporting information).

Figure 1. NMR studies: a) Reaction used for mechanistic studies; b) Evolution of compound 40 at different concen-trations of CoBr2.

View Article Online
DOI: 10.1039/D0CC02734K



^{19}F-NMR. dppe + 2 eq. **39** + $CoBr_2$ to give 1,2-bis(2-trifluoromethyl)phenylethane **40**.

In order to identify the catalytic species involved in the reaction mechanism ^{19}F-NMR and ^{31}P-NMR experiments were performed. For this study the cross coupling reaction of 2-(trifluoromethyl)benzylzinc bromide **40** with ethyl 1-bromo-1-cyclohexylcarboxylate **39** to give the coupling product **16** was chosen (Figure 1a). Experiments were performed in a mixture of non-deuterated DMF/THF to identify and assign the signals corresponding to the reagents, possible products and by-products of the reaction (Figures S1-S6 in Supporting Information). This study showed that products **16** and 1,2-bis(2-trifluoromethyl)phenylethane **41**, a common by-product from the oxidation of the organozinc reagent with different metals, are formed in the reaction. Interestingly the dimer of the organozinc reagent (**41**) formed relatively fast in the mixture and the signals of product **16** started to increase after the signals of the dimer became stable. This suggests an activation step is needed for to the formation of the catalytic complex (Figure S8 in Supporting information). It should be noted that due to the quadrupolar character of ^{59}Co, signals became broad preventing their proper integration.[17]

To determine the relationship between the formation of **41** with the catalyst loading and to stop the reaction at the formation of the catalytic complex a new set of experiments was performed in the absence of the alkyl bromide **39**. Recording ^{19}F-NMR in the presence of 0, 5, 20 and 50 mol% of $CoBr_2$ it was observed that the amount of **41** increased with the concentration of the metal salt. These results suggest a redox process between the organozinc derivative **40** and Co(II) leading to a reduced form of the metal (Figure 1b). The ^{31}P-NMR spectra contained a new phosphorous signal at δ= 37.97 ppm (Figure S8 in Supporting Information). Comparison of the chemical shift observed for this signal with the one of coordination of dppe with $Co(CO)_2Cp$ (δ= 28.96 ppm, Figure S9 in Supporting Information) and the previously reported dppe complex with $Co_4(CO)_{12}$ (δ= 29.9, 30.6 ppm)[18] suggests the potential presence of Co(0) species in the reaction media. Chemical shifts for dppe Co(I) complexes are described at lower fields (δ> 50 ppm).[19]

Conclusions

In summary, a new cobalt catalyzed C(sp^3)-C(sp^3) Negishi cross-coupling protocol has been developed leading to all-carbon-substituted quaternary carbon centers in an effective manner. Reaction was performed under mild conditions and did not require the use of any additives other than the reagents and the catalytic complex. The use of mono-organozinc reagents broaden the scope of the reaction as they can be easily prepared in flow and added directly into the reaction. Regarding the tertiary alkyl halide, different electron withdrawing groups such as esters, amides, nitriles and carboxylic acids are tolerated. The catalytic system showed strong preference for halides on sp^3 hybridized carbon atoms over typical aryl bromides, a reversed behavior compared to most used cross-coupling metals. This fact allowed the access of interesting intermediates for the synthesis of novel useful scaffolds for medicinal and organic chemists. ^{19}F-NMR and ^{31}P-NMR mechanistic studies suggest the involvement of radicals as well as Co(0) complexes in the catalytic cycle. Additional studies to fully elucidate the reaction mechanism are ongoing and will be matter of future publications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgment

Authors want to thank Dr. Andrés Trabanco for his comments during the preparation of this manuscript and Dr. Carlos Martinez for his help in the purification of clock reaction product.

Notes and references

1 (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752; (b) T. Tsukamoto, *ACS Med. Chem. Lett.*, 2013, **4**, 369.

2 (a) J. M. Smith, J. H. Harwood and P. S. Baran, *Acc. Chem. Res.*, 2018, **51**, 1807; (b) J. Christoffers, and A. Baro, *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, 2005; (c) K.W. Quasdorf and L.E. Overman, *Nature*, 2014, **516**, 181.

3 (a) J. Choi and G. C. Fu, *Science*, 2017, ***356***, eaaf7230; (b) J. B. Diccianni and T. Diao, *Trends Chem.*, 2019, **1**, 830; (c) M. R. Netherton and G. C. Fu, *Palladium-Catalyzed Cross-Coupling Reactions of Unactivated Alkyl Electrophiles with Organometallic Compounds*; in *Palladium in Organic Synthesis*, J. Tsuji (Ed.), Springer, Berlin, 2005, p. 85; (d) L. C. McCann, H. N. Hunter, J. A. C. Clyburne and M. G. Organ, *Angew. Chem., Int. Ed*., 2012, **51**, 7024; (e) N. Hadei, G. T. Achonduh, C. Valente, C. J. O'Brien and M. G. Organ, *Angew. Chem., Int. Ed.*, 2011, **50**, 3896; (f) G. M. Schwarzwalder, C. D. Matier and G. C. Fu, *Angew. Chem., Int. Ed.*, 2019, **58**, 3571; (g) X. Mu, Y. Shibata, Y. Makida and G. C. Fu, *Angew. Chem., Int. Ed.*, 2017, **56**, 5821; (h) V. B. Phapale, E. Buñuel, M. García-Iglesias and D. J. Cárdenas, *Angew. Chem., Int. Ed.*, 2007, **46**, 8790; (i) A. Wilsily, F. Tramutola, N. A. Owston and G. C. Fu, *J. Am. Chem. Soc.*, 2012, **134**, 5794; (j) H. Huo, B. J. Gorsline and G.C. Fu, *Science*, 2020, **367**, 559; (k) H. Gong and M. R. Gagn, *J. Am. Chem. Soc.*, 2008, **130**, 12177; (l) H. Gong, R. Sinisi and M. R. Gagn, *J. Am. Chem. Soc.*, 2007, **129**, 1908.

4 (a) S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299; (b) L. M. Martínez-Prieto, E. Ávila, P. Palma, E. Álvarez and J. Cámpora, *Chem. Eur. J.*, 2019, **21**, 9833.

5 (a) G. Cahiez and A. Moyeux, *Chem. Rev.*, 2010, **110**, 1435; (b) W. M. Czaplik, M. Mayer and A. Jacobi von Wangelin, *Synlett*, 2009, 2931; (c) S. Gülak, O. Stepanek, J. Malberg, B. R. Rad, M. Kotora, R. Wolf and A. Jacobi von Wangelin, *Chem. Sci.*, 2013, **4**, 776; (d) J. Mao, F. Liu, M. Wang, L. Wu, B. Zheng, S. Liu, J. Zhong, Q. Bian and P. J. Walsh, *J. Am. Chem. Soc.*, 2014, **136**, 17662; (e) F. Liu, J. Zhong, Y. Zhou, Z. Gao, P. J. Walsh, X. Wang, S. Ma, S. Hou, S. Liu, M. Wang, M. Wang and Q. Bian, *Chem. Eur. J.*, 2018, **24**, 2059; (f) L. Thomas, F. H. Lutter, M. S. Hofmayer, K. Karaghiosoff and P. Knochel, *Org. Lett.*, 2018, **20**, 2441; (g) V. Koch, M. M. Lorion, E. Barde, S. Bräse, J. Cossy, *Org. Lett.*, 2019, **21**, 6241; (h) F. H. Lutter, L. Grokenberger, P. Spieβ, J. M. Hammann, K. Karaghishoff, P. Knochel, *Angew. Chem. Int. Ed.,* 2020, **59**, 5546; (i) C. Gosmini, J.-M. Bégouin and A. Moncomble, *Chem. Commun.*, 2008, 3221; (j) C. E. I. Knappke, S. Grupe, D. Gärtner, M. Corpet, C. Gosmini and A. J. von Wangelin, *Chem. Eur. J.*, 2014, **20**, 6828¸(k) X.-Q., Hao, C., Wang, S.-L., Liu, X., Wang, L., Wang, J.-F., Gong and M.-P. Song, *Org. Chem. Front.*, 2017, **4**, 308; (l) C. Wang, N. Li, W.-J. Zhu, J.-F. Gong and M.-P. Song, *J. Org. Chem.*, 2019, **84**, 191.

6 G. Cahiez, C. Chaboche, C. Duplais, A. Giulliani, A. Moteux, *Adv. Synth. Catal.*, 2008, **350**, 1484.

7 A. D. Dilman and V. V. Levin, *Tetrahedron Lett.*, 2016, **57**, 3986.

8 (a) M. S. Hofmayer, A. Sunagatullina, D. Brösamlen, P. Mauker and P. Knochel, *Org. Lett.*, 2020, **22**, 1286; (b) F. H. Lutter, L. Grokenberger, M. Benz and P. Knochel, *Org. Lett.*, 2020, DOI: 10.1021/acs.orglett.0c00795.

9 (a) W. Xu, J. H. Pek and N. Yoshikai, *Adv. Synth. Catal.*, 2016, **358**, 2564; (b) M. R. Friedfeld, H. Zhong, R. T. Ruck, M. Shevlin and P. J. Chirik, *Science*, 2018, **360**, 888.

10 P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek and P. Dierkes, *Chem. Rev.*, 2000**, 100***,* 2741.

11 (a) N. Alonso, L. Z. Miller, J. de M. Muñoz, J. Alcázar and D. T. McQuade, *Adv. Synth. Catal.*, 2014, **356**, 3737; (b) L. Huck, M. Berton, A. de la Hoz, A. Díaz-Ortiz and J. Alcázar, *Green Chem*., 2017, **19**, 1420; (c) M. Berton, L. Huck and J. Alcázar, *Nat. Protoc.*, 2018, **13**, 324.

12 A. Biffis, P. Centomo, A. Del Zoto, M. Zecca, *Chem. Rev.*, 2018, **118**, 2249.

13 S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299.

14 A. Piontek, E. Bisz and M. Szostak, *Angew. Chem. Int. Ed.*, 2018, **57**, 11116.

15 (a) I. Adiaj, A. Fontana, M. V. Gomez, A. de la Hoz and J. Alcázar, *Angew. Chem. Int. Ed.*, 2018, **57**, 8473; (b) I. Abdiaj, L. Huck, J. M. Mateo, A. de la Hoz, M. V. Gomez, A. Díaz-Ortiz and J. Alcázar, *Angew. Chem. Int. Ed.*, 2018, **57**, 13231.

16 Y. Zhou, L. Wang, G. Yuan, S. Liu, X. Sun, C. Yuan, Y. Yang, Q. Bian, M. Wang and J. Zhong, *Org. Lett*., 2020, DOI: 10.1021/acs.orglett.0c01557

17 J. Chan and S. Auyeung. *Cobalt-59 NMR spectroscopy*; in *Annual Reports on NMR Spectroscopy. 41* G. Webb (Ed.) Academic Press, London, 2000, pp. 1.

18 S. Aine, A. Gobette, G. Jannon and B. Osella, *J. Organomet. Chem.*, 1986, **309**, C51.

19 C. Loubser, H. M. Roos and S. Lotz, *J. Organomet. Chem.*, 1991, **402**, 393.

