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A direct fixation of CO_2 for isotopic labelling of hydantoins using iodine–phosphine charge transfer complexes†

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Herein, we report a method for the isotopic labelling of hydantoins directly from CO_2 by means of trimethyl-λ^5-phosphine diiodide mediated carbonyl insertion. The method is suitable for ^{13}C-labelling of diverse substrates and was implementated for ^{11}C-labelling in PET-imaging facilities for the synthesis of radiotracers. Isolated yields of 90% and radiochemical yields of 89% were achieved for hydantoin containing drug candidates in formulation within 30 min with high molar activity (>400 MBq nmol^{-1}).

Carbon dioxide is an attractive C_1 building block with a wide scope of applications for isotopic labelling of drug molecules for pharmacological studies.[1] The advent of imaging mass spectrometry has created a new need for ^{13}C-labelled drug molecules, *e.g.* for the determination of receptor occupancy and identification of metabolites in target tissues.[2] While imaging MS has high resolution, the destructive nature of MS requires tissue samples to be taken post mortem, which is not always an option in drug development. Instead, non-invasive positron emission tomography imaging (PET) with carbon-11 (^{11}C) labelled isotopologues provide an optimal companion for high resolution imaging MS suitable for living subjects. Since carbon is practically ubiquitous in pharmaceuticals and biomolecules, isotopic substitution of a ^{nat}C atom for a $^{11/13}$C-label offers an elegant solution to obtain complementary labelled compounds with identical properties for both methods. Direct fixation of $^{13}CO_2$ has been demonstrated before, albeit with long reaction times incompatible with our goal for use with both ^{11}C and ^{13}C.[3] Due to the short half-life of ^{11}C (20.4 minutes), radiolabelling, purification, and quality control (QC) of ^{11}C-radiotracers must be implemented within minute time-frames in close proximity to the PET site.[1] In this light, it is advantageous to utilise the primary cyclotron product [^{11}C]CO_2 obtained from proton bombardment of ^{14}N in presence of O_2 for labelling rather than secondary labelling agents.[4–11] Remaining challenges of [^{11}C]CO_2 are the low reactivity and solubility in organic solvents as well as the limited options for process design in typical PET centres.[6]

To study assets from Autifony's development pipeline we encountered a need for a direct and rapid method to isotopically label hydantoin-based drug candidates using the available synthetic precursor. We sought a carbonyl insertion method with CO_2 at low partial pressure to bring the reactivity of phosgene to typical PET production sites involved in multicentre trials. In contrast to most literature methods this calls for trace $^{11}CO_2$ in an He atmosphere. Metal catalysts were not an option as the need for metal determination by ICP-MS prior to release to satisfy cGMP guidelines had to be avoided. One particularly effective strategy to fixate CO_2 between N-atoms is the use of phosphinimines[11] to activate anilines to undergo a pericyclic reaction with [^{11}C]CO_2 to form aryl isocyanates.[9,11,14] Isocyanates readily react with vicinal N-atoms to form hydantoins without the need for strong bases (Scheme 1), which was deemed advantageous to preserve chirality.

The synthesis of ^{11}C-labelled asymmetric ureas from *N*-aryl-triphenylphosphinimines and [^{11}C]CO_2 is a powerful method albeit limited by lack of shelf-stable or commercially available phosphinimines.[11] Due to a general susceptibility to hydrolysis only a few *N*-aryl-triphenylphosphinimines have been described. *N*-Alkyl phosphinimines are virtually absent from literature for lack of the stabilizing resonance effects of the aromatic siblings.[9b,12–15] By use of the Staudinger degradation phosphinimines are obtained *in situ* from electron-withdrawing

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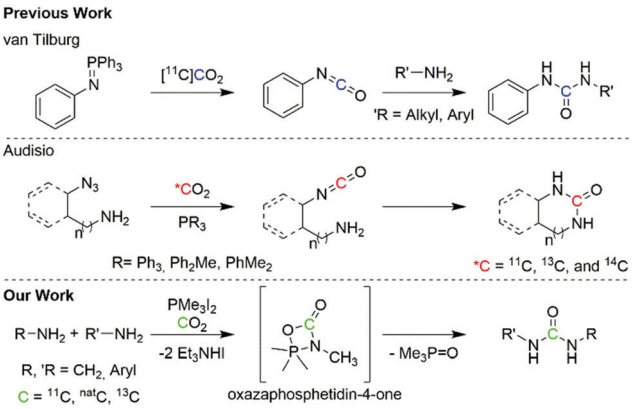


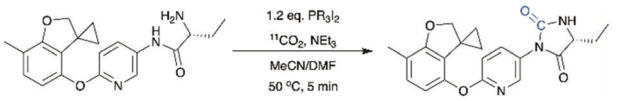
Scheme 1 Recent methods for the incorporation of CO_2.

azide groups in the substrate to direct the phosphinimine formation.[11,14] However, in our case amine-to-azide conversion had to be dismissed for risk of racemisation and need of new synthetic intermediates. With both, isolation and degradation, out of question, we resorted to generation of labile phosphinimines *in situ* from primary aliphatic amines in the new approach described here. This allowed for using available intermediates without the need for any new GMP synthesis. Key to this novel method is an iodine-trimethyl-λ^5-phosphine charge-transfer complex for direct access to aliphatic phosphinimines. As only aromatic examples have been used ever since the discovery of the phosphinimine, this work is the first instance of use of their aliphatic siblings in synthesis.[13,16]

Firstly, we devised a method to prepare the complex fresh from iodine and phosphines. Which proved to be most effective, reliable, and straightforward, providing access to previously undescribed P-I complexes in solid form. An excess of phosphine was found to suppress the formation of iodophosphonium triiodide, which forms in presence of excess I_2. With phosphine in excess, two signals are observed *via* $^{31}P\{^1H\}$ NMR spectroscopy indicating the presence of two isomers. These isomers are consistent with the literature most likely representing the axial trigonal-bipyramidal complex and a linear arrangement containing an I–I bond.[17] The phosphine diiodide charge-transfer complexes generated *in situ* were found to effectively promote carbonyl insertion in feasibility studies in radiochemistry. Automation of all process steps including HPLC and formulation on Synthra radiosynthesis modules allowed for employing $^{11}CO_2$ to rapidly screen the effect of individual reagents. In initial base screening experiments, triethylamine (NEt_3) gave the highest radioactivity yield, stronger bases were omitted to avoid inversion of the 2-aminobutyramide.

Investigating the role of the phosphine revealed that sterically hindered phosphines were not particularly suitable, presumably due to a combination of stability and reactivity. Steric demand of phosphines is expressed in Tolman cone angles (θ).[18] PPh_3 (θ = 145) had the widest angle that still gave yield, albeit only traces. The larger $P(NMe_2)_3$ (θ = 157) and PCy_3 (θ = 170) did not yield product.[19] As the cone angle decreases, we start to see higher yields as shown with PMe_2Ph, (θ = 122)

Table 1 Effect of various phosphines on cyclisation of **18** with $[^{11}C]CO_2$[a]



Entry	Phosphine	RCY	Tolman cone angle (θ)[18]
1	PMe_3	33.4% ± 6.6 (n = 3)	118
2	PBu_3	21.4% ± 12.3 (n = 3)	132
3	PPr_3	12.4% ± 0.4 (n = 2)	132
4	PMe_2Ph	2.0% ± 0.7 (n = 2)	122
5	PCy_3	0%	170
6	PPh_3	Trace	145
7	$P(NMe_2)_3$	0%	157
8	$P(OMe)_3$	0%	107
9	$P(OPh)_3$	0%	128

5 min, NEt_3, DMF/MeCN, RCY – isolated yield after HPLC. [a] Precursor dissolved in MeCN and NEt_3 was added to a reaction vessel. The PR_3I_2 reagent was added to the reaction vessel containing the starting material and the mixture was sparged with He (3 min at 25 mL min^{-1}). $[^{11}C]CO_2$ was added over 30 s at 15 mL min^{-1}. After heating to 50 °C for 5 min, the mixture was diluted with 0.1% aqueous TFA (1:1, v/v) and injected into an HPLC system. Compounds were isolated by SPE extraction on an Oasis HLB cartridge and elution in 9% EtOH in water for injection.

giving a RCY of only 2.0% (Table 1, entry 4). Using alkyl phosphines with decreasing size maximized the yield as seen with PPr_3, PBu_3, and PMe_3, with 12.4%, 21.4%, and the highest 33.4% yields, respectively (Table 1, entries 1–3). We surmised that the larger steric hindrance of these phosphines in relation to PMe_3 (θ = 118) complicates a concerted step forming the 1,3,2-oxazaphosphetidin-4-one intermediate with CO_2, thus allowing for evasion of the CO_2 from the reaction mixture. The sterics of phosphine play a key role in the reactivity between the phosphine-diiodide electrophile and the amine.

Presumably due to the hindrance of a nucleophilic attack by RNH_2 so that formation of the phosphinimine (Scheme 1) becomes less likely with increasing steric demand of the phosphine. We found this to be less of an issue in presence of $^{13}CO_2$ at equal stoichiometry or when employing excess natural carbon dioxide at a partial pressure of 1 bar. However, slow rates of reaction may impede no-carrier added $[^{11}C]CO_2$ chemistry opening for alternative reaction pathways instead of CO_2 fixation. $[^{11}C]CO_2$ is present at low partial pressure and will evade from the reaction mixture if not fixated rapidly. For efficient retention in the reaction mixture the radionuclide must be trapped at low temperature. These factors create a peculiar reaction condition wherein traces of n.c.a. $[^{11}C]CO_2$ are to be engaged. Starting materials are employed in a stoichiometric excess of *e.g.* 10^4 : 1 relative to $[^{11}C]CO_2$. Consequentially, reactions rates become independent of starting material consumption and depend only on the chemical activity (concentration) of trace CO_2. As the CO_2 must be trapped in a rapid reaction before it evades, the observation that low θ corresponds to high fixation of $[^{11}C]CO_2$ in the product can be connected to faster reaction rates. Presumably this is owed to much lower steric hindrance of the concerted, pericyclic reaction between the P═N and O═C molecular orbitals. It can be

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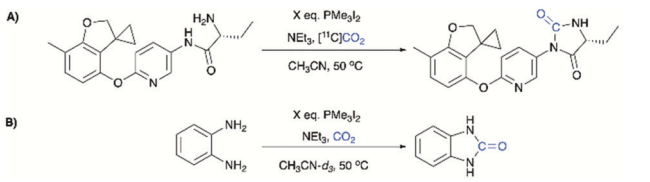
Table 2 Stoichiometric effects of PMe_3I_2 on both $[^{11}C]CO_2$ and CO_2[a]



Entry	I_2 equiv.	[i]RCY[b]	[ii]NMR yield
1	0.5	20.6% ± 0.1 (n = 2)	—
2	1.0	48.7% ± 7.1 (n = 2)	—
3	1.2	48.3% ± 4.1 (n = 3)	37% ± 22 (n = 3)
4	1.5	27.2% ± 2.8 (n = 2)	—
5	2.1	36.1% ± 0.3 (n = 2)	45% ± 8 (n = 3)
6	3.5	—	83% ± 20 (n = 3)
7	4	—	92% ± 10 (n = 6)
8	4.5	—	90% ± 17 (n = 3)

RCY; isolated radiochemical yield. [a] Precursor dissolved in MeCN and NEt_3 was added to a reaction vessel. The PR_3I_2 reagent was then added to the reaction vessel containing the starting material and the mixture was sparged with He (3 min at 25 mL min^{-1}). $[^{11}C]CO_2$ was added over 30 s at 15 mL min^{-1}. After heating to 50 °C for 5 min, the mixture was diluted with 0.1% aqueous TFA (1 : 1, v/v) and injected into a built-in HPLC system. Compounds were isolated by SPE extraction on an Oasis HLB cartridge and elution in 9% EtOH in water for injection. [b] $^{11}CO_2$ is trapped in the reaction vessel at low temperature (>95% trapping at −40 °C), unreacted material outgases rapidly with heating. Increasing the chemical activity of $^{11}CO_2$ in the reaction by a more reactive precursor that requires lower temperature is key to high RCY.

seen that the less stable aliphatic phosphines react sufficiently fast, which most likely due to lability of the intermediates. In contrast, PPh_3 slowly forms a much more stable imine, resulting in a combination that does not react fast enough with n.c.a. $[^{11}C]CO_2$. PMe_3Br_2 and PMe_3ICl were also made and tested, but produced no yield. On investigation of the incubation time before the addition of $[^{11}C]CO_2$ to the mixture, we found that immediate addition produced less than 1% isolated RCY, 17% RCY were obtained after 10 min. The optimal activation time was 5 min before delivery of $[^{11}C]CO_2$ providing an average RCY of 20% without fully optimized conditions. This incubation time allowed for purging the mixture with He to remove $^{nat}CO_2$ prior to radionuclide delivery to improve molar activity. MeCN was the solvent of choice, providing slightly higher RCY than the DMF–MeCN mixture used for initial screenings.[SI]

The reagent stoichiometry was investigated with $[^{11}C]CO_2$ under optimized conditions. Firstly, with 0.5 equivalents (Table 2, entry 1i) was low yielding. Increasing the equivalents, we were able to achieve moderate yields of 48% with both 1.0 and 1.2 equivalents (Table 2, entries 2i and 3i). Further increasing the equivalents resulted in lower yields (Table 2, entries 4i and 5i). This plateau of yield is thought to be caused by the sub-stoichiometric amounts of $[^{11}C]CO_2$ available and the lifetime of the phosphinimine.

To test if the reaction is limited by the concentration of $[^{11}C]CO_2$ we investigated the reaction in the presence of excess $^{nat}CO_2$ in an air-tight vessel to prevent evasion. Starting with 1.2 eq. (Table 2, entries 3ii) we obtained slightly lower yields than the experiments with ^{11}C. Increasing the equivalents to 2.1 (Table 2, entry 5ii) resulted in improved yield. Further increasing the equivalents to 3.5 provided a yield of 83% (Table 2, entry 6ii). At 4 and 4.5 equivalents we obtained the maximum yields around 90% (Table 2, entries 7ii and 8ii). Careful monitoring of these studies by NMR revealed that the stoichiometric excess of PMe_3I_2 required to obtain high yields was due to the hydrolysis of the phosphinimine. We saw near complete conversion of PMe_3 to PMe_3 oxide in the presence of moisture while starting material was not consumed completely. This implied that the amine consumed several equivalents of PMe_3I_2 to cycle through phosphinimine only to be hydrolysed back to amine and PMe_3O, slowly depleting the reagent. At stoichiometric conditions in presence of excess H_2O, the competing hydrolysis of the phosphinimine intermediate is faster than CO_2 capture. The reaction is halted once the charge transfer complex is consumed, resulting in poor yields. Therefore, it is essential that precautions are taken to avoid excess moisture. This was achieved by adding molecular sieves to NMR solvents, using oven-dried glassware, and working with an excess of PMe_3I_2 complex to mitigate the effect of hydrolysis.

As we noted the broad synthetic applicability of the new method under stoichiometric conditions we decided to use it for carbon-13 labelling. A variety of model substrates (Fig. 1) were tested to further investigate both NMR conversion and isolated yields of carbon-13 labelled products.

Under optimized conditions substrate **1** gave quantitative NMR conversion to **1a** and an isolated yield of the isotopically labelled analogue **1b** of 76%. Compound **2** was made in 48% conversion isolated in 26%, owed to the hygroscopic starting material. Compound **3** gave a conversion of 81% but proved difficult to isolate in high yields obtaining only 66%. There was no conversion with substrates **4**, **5**, and **6**. This is thought to be due to the formation of a six membered ring. For example, instead of **4** the starting material would allow for cyclisation of a 2,2,2-trimethyl-2,3-dihydro-2λ^5-pyrido[2,3-*d*][1,3,2]diazaphosphinin-4(1*H*)-one. Substrate 7 provided

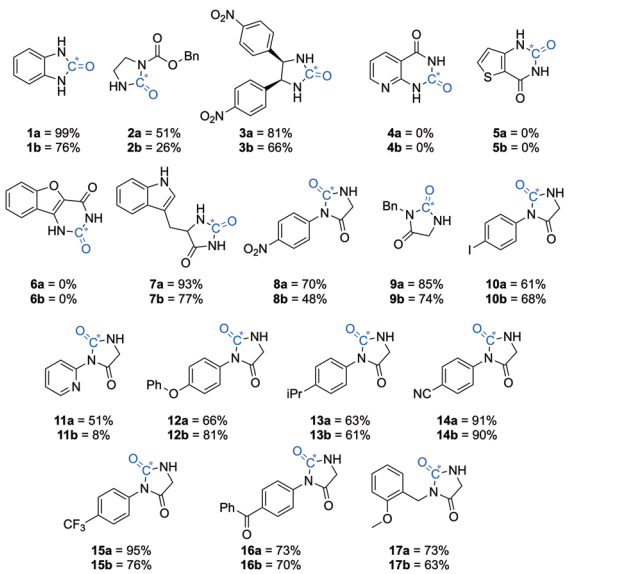


Fig. 1 Results for the direct incorporation of $*CO_2$; (a) NMR yield from $^{nat}CO_2$ and (b) isolated yield of the carbon-13-labelled compound.

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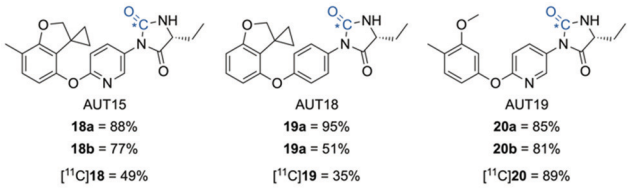

Fig. 2 Isotopic labelling and radiolabelling of drug candidates using $[^{11}C]CO_2$ (a) NMR yield (b) isolated yield with ^{13}C.

the excellent conversion of 93% and was isolated in 77%. The hydantoins **8** and **9** were isolated in moderate yields of 48% and 74%, respectively. Hydantoin **10** was formed and isolated in over 60% yield while **11** showed 51% yield by NMR but was isolated in 8%. Substrate **12** was isolated in 81% while **13** provided both a moderate conversion and isolated yield. Compounds **14** and **15** gave very high conversions and were isolated in 90% and 76%. **16** was isolated in a yield of 70% from an NMR conversion of 73%. **17** provided 73% by NMR and 63% were isolated. With the substrate scope established, the method showed a convincing performance for labelling of the target hydantoins. The carbon-13 labelled Autifony assets **18–20** were isolated in 77% (**18**), 51% (**19**), and 81% (**20**) (Fig. 2).

Radiolabelling of the chiral K_{V3} modulators **18–20** in moderate to excellent yield with $[^{11}C]CO_2$ with retention of the stereocenter.[SI] In the case of $[^{11}C]$**18**, a radiochemical yield of 49% and a molar activity (A_M) of 218 MBq nmol^{-1} was obtained. $[^{11}C]$**19** and $[^{11}C]$**20** were obtained in an RCY of 35% and 89% and in a A_M of 194–417 MBq nmol^{-1} at the time of injection into subjects. A Synthra synthesis module allowed for complete automation of the process. Purified and formulated $[^{11}C]$**18–20** were delivered to the PET scanner within 35 minutes from the end nuclide production and released for use within 2 half-lives.

In conclusion, we report a rapid method for direct synthesis of hydantoins from CO_2 which was found suitable for labelling with carbon-13 in high yields. The preliminary usefulness of this method for translation into carbon-11 labelling of a series of K_{V3} modulators was equally successful. Through the new method we were able to utilize existing GMP precursors for the radiosynthesis of tracers for imaging studies. Key to activating aliphatic substrates is the decreased steric hindrance of the PMe_3, allowing for very fast formation of phosphinimine intermediates and subsequent cyclisation to the hydantoin ring in presence of CO_2. The rapid nature of the reaction provided high yields with sub-stoichiometric ^{11}C with an activity incorporation sufficient for PET imaging. High isolated yields were obtained for direct synthesis with ^{13}C on a wider substrate scope, which bodes well for labelling of various hydantoins.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) B. H. Rotstein, S. H. Liang, M. S. Placzek, J. M. Hooker, A. D. Gee, F. Dolle, A. A. Wilson and N. Vasdev, *Chem. Soc. Rev.*, 2016, **45**, 4708–4726; (*b*) G. Antoni, *J. Labelled Compd. Radiopharm.*, 2015, **58**, 65–72.
2 (*a*) S. R. Ellis, E. Hall, M. Panchal, B. Flinders, J. Madsen, G. Koster, R. M. A. Heeren, H. W. Clark and A. D. Postle, *J. Lipid. Res.*, 2021, **62**, 100023; (*b*) A. Thomen, N. Najafinobar, F. Penen, E. Kay, P. P. Upadhyay, X. Li, N. T. N. Phan, P. Malmberg, M. Klarqvist, S. Andersson, M. E. Kurczy and A. G. Ewing, *ACS Nano*, 2020, **14**, 4316–4325; (*c*) A. R. Buchberger, K. DeLaney, J. Johnson and L. Li, *Anal. Chem.*, 2018, **90**, 240–265.
3 (*a*) M. Xu, A. R. Jupp, M. S. E. Ong, K. I. Burton, S. S. Chitnis and D. W. Stephan, *Angew. Chem., Int. Ed.*, 2019, **58**, 5707–5711; (*b*) M. Xu, A. R. Jupp and D. W. Stephan, *Angew. Chem., Int. Ed.*, 2017, **56**, 14277–14281; (*c*) F. Shi, Y. Deng, T. SiMa, J. Peng, Y. Gu and B. Qiao, *Angew. Chem., Int. Ed.*, 2003, **42**, 3257–3260; (*d*) M. J. Fuchter, C. J. Smith, M. W. Tsang, A. Boyer, S. Saubern, J. H. Ryan and A. B. Holmes, *Chem. Commun.*, 2008, 2152–2154.
4 J. P. Bow and P. J. Riss, *Chem. Methods*, 2020, **1**, 139–141.
5 (*a*) J. M. Hooker, A. T. Reibel, S. M. Hill, M. J. Schueller and J. S. Fowler, *Angew. Chem., Int. Ed.*, 2009, **48**, 3482–3485; (*b*) P. J. Riss, S. Lu, S. Telu, F. I. Aigbirhio and V. W. Pike, *Angew. Chem., Int. Ed.*, 2012, **51**, 2698–2702; (*c*) A. Del Vecchio, F. Caille, A. Chevalier, O. Loreau, K. Horkka, C. Halldin, M. Schou, N. Camus, P. Kessler, B. Kuhnast, F. Taran and D. Audisio, *Angew. Chem., Int. Ed.*, 2018, **57**, 9744–9748.
6 C. Taddei and A. D. Gee, *J. Labelled Compd. Radiopharm.*, 2018, **61**, 237–251.
7 A. K. Haji Dheere, N. Yusuf and A. Gee, *Chem. Commun.*, 2013, **49**, 8193–8195.
8 K. Horkka, K. Dahl, J. Bergare, C. S. Elmore, C. Halldin and M. Schou, *ChemistrySelect*, 2019, **4**, 1846–1849.
9 (*a*) V. Babin, A. Sallustrau, O. Loreau, F. Caille, A. Goudet, H. Cahuzac, A. Del Vecchio, F. Taran and D. Audisio, *Chem. Commun.*, 2021, **57**, 6680–6683; (*b*) HBr salts of triphenylphosphinimines with simple aliphatic N-substituents were reported when a previous version of this manuscript was under review, see:U. S. Ismailani, M. Munch, B. A. Mair and B. H. Rotstein, *Chem. Commun.*, 2021, **57**, 5266–5269.
10 A. V. Mossine, A. F. Brooks, I. M. Jackson, C. A. Quesada, P. Sherman, E. L. Cole, D. J. Donnelly, P. J. Scott and X. Shao, *Bioconjugate Chem.*, 2016, **27**, 1382–1389.
11 E. W. van Tilburg, A. D. Windhorst, M. van der Mey and J. D. M. Herscheid, *J. Labelled Compd. Radiopharm.*, 2006, **49**, 321–330.
12 M. Köhn and R. Breinbauer, *Angew. Chem., Int. Ed.*, 2004, **43**, 3106–3116.
13 (*a*) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, 1919, **2**, 635–646; (*b*) H. Zimmer, M. Jayawant and P. Gutsch, *J Org. Chemi.*, 1970, **35**, 2826–2828; (*c*) L. Horner and H. Oediger, *Liebigs Ann.*, 1959, **627**, 142–162; (*d*) P. Molina, M. Alajarin and A. Arques, *Synthesis*, 1982, 596–597.
14 A. Del Vecchio, A. Talbot, F. Caille, A. Chevalier, A. Sallustrau, O. Loreau, G. Destro, F. Taran and D. Audisio, *Chem. Commun.*, 2020, **56**, 11677–11680.
15 (*a*) R. Appel, W. Büchner and E. Guth, *Liebigs Ann.*, 1958, **618**, 53–58; (*b*) R. Appel and A. Hauss, *Angew. Chem.*, 1959, **71**, 626.
16 C. Jiang and D. W. Stephan, *Dalton Trans.*, 2013, **42**, 630–637.
17 (*a*) W.-W. du Mont, M. Bätcher, S. Pohl and W. Saak, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 912–913; (*b*) F. Ruthe, *Chem. Commun.*, 1997, 1947–1948; (*c*) P. Deplano, S. M. Godfrey, F. Lsaia, C. A. McAuliffe, M. L. Mercurp and E. F. Trogu, *Chem. Ber.*, 1997, **130**, 299–305.
18 (*a*) C. A. Tolman, *J. Am. Chem. Soc.*, 1970, **92**, 2956–2965; (*b*) C. A. Tolman, *Chem. Rev.*, 1977, **77**, 313–348.
19 N. Yamazaki, F. Higashi and T. Iguchi, *Tetrahedron Lett.*, 1974, **15**, 1191–1194.

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