A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Iridium-Catalyzed Hydrochlorination and Hydrobromination of Alkynes via Shuttle Catalysis

Authors: Peng Yu, Alessandro Bismuto, and Bill Morandi

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201912803
Angew. Chem. 10.1002/ange.201912803

Link to VoR: http://dx.doi.org/10.1002/anie.201912803
http://dx.doi.org/10.1002/ange.201912803

WILEY-VCH

10.1002/anie.201912803

RESEARCH ARTICLE

WILEY-VCH

Iridium-Catalyzed Hydrochlorination and Hydrobromination of Alkynes *via* Shuttle Catalysis

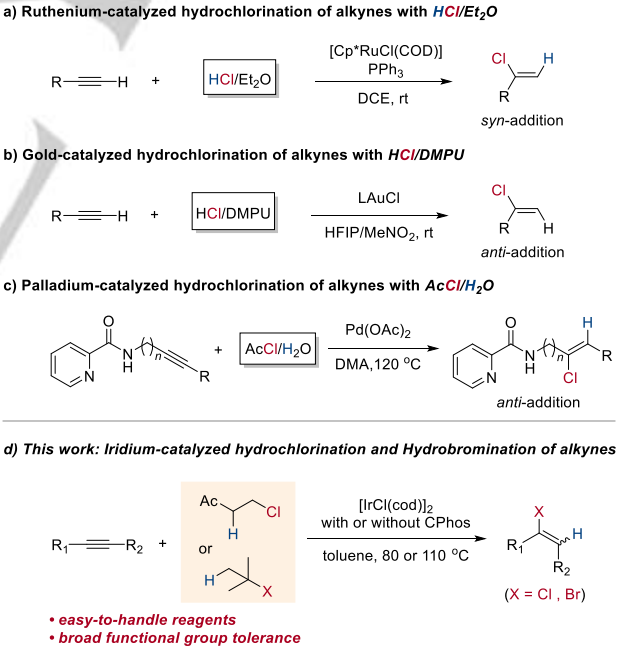
Peng Yu,[a,b] Alessandro Bismuto[a] and Bill Morandi*[a,b]

Abstract: Herein, we describe two different methods for the synthesis of vinyl halides *via* a shuttle catalysis-based iridium-catalyzed transfer hydrohalogenation of unactivated alkynes. The use of 4-chlorobutan-2-one or *tert*-butyl halide as donors of hydrogen halides has allowed to perform this transformation in the absence of corrosive reagents, such as hydrogen halides or acid chlorides, thus largely improving the functional group tolerance and safety profile of these reactions compared to the state-of-the-art. This, has granted access to alkenyl-halide compounds containing acid sensitive groups, such as tertiary alcohols, silyl ethers and acetals. The synthetic value of those methodologies has been demonstrated by gram-scale synthesis where low catalyst loading could be achieved.

Introduction

Alkenyl halides have found widespread application in organic synthesis.[1] Among them, vinyl chlorides have gained increasing attention in recent years due to their significant synthetic utility and occurrence in natural products, pharmaceuticals and agrochemicals.[2] Moreover, vinyl chlorides have emerged as efficient coupling partners in cross-coupling reactions, such as the Suzuki−Miyaura coupling reaction[3] and the Buchwald−Hartwig amination.[4] Thus, the development of methods for the preparation of vinyl chlorides is of great synthetic significance. Vinyl chlorides are generally accessed from carbonyl compounds[5] or alkynes.[6] Although a catalytic process using carbonyl compounds as starting materials has been realized,[5h] the requirement for toxic phosphorus reagents like PCl_5[5a,5b] or $POCl_3$[5d] or a large excess of $CrCl_2$[5c] limits their applications in complex molecule synthesis.

The catalytic synthesis of vinyl chlorides from broadly accessible alkynes is a powerful alternative to the traditional synthetic methods. A first approach, carbochlorination, the addition of a C–Cl bond across an alkyne, mostly involves acid chlorides as reagents.[6] The second approach, alkyne hydrochlorination,[7] a reaction which requires otherwise harsh conditions in the absence of a catalyst, provides a powerful and complementary strategy to transform alkynes into vinyl chlorides. However, most of the catalytic hydrochlorination methods rely on corrosive and acidic HCl as a reagent,[8] leading to a limited functional group tolerance (Scheme 1). For example, Dérien and co-workers have reported a ruthenium-catalyzed hydrochlorination of alkynes with HCl (Scheme 1a),[9] and Hammond, Xu and co-workers have recently employed HCl (as a DMPU/HCl adduct) in a gold-catalyzed reaction (Scheme 1b).[10] However, the use of HCl as a reagent inherently limits the functional group tolerance of these methods. A palladium-catalyzed directed anti-hydrochlorination of unactivated alkynes has recently been realized by Engle and co-workers (Scheme 1c).[11] Through the introduction of a bidentate directing group, they could efficiently control the regioselectivity of the transformation. This method is, however, limited to the synthesis of vinyl chloride products that have a suitably positioned amino group for the introduction of the directing group. The use of an acid chloride as HCl precursor also limits the functional group tolerance of this reaction. Thus, the discovery of a functional group tolerant catalytic hydrochlorination still remains a challenge in organic synthesis. Herein, we report an iridium-catalyzed transfer hydrochlorination and hydrobromination of alkynes using 4-chlorobutan-2-one and *tert*-butyl chloride/bromide as a formal HX donor, a feature that allows for an unusually broad functional group tolerance in the synthesis of vinyl halide species (Scheme 1d). Furthermore, it also represents a rare example of hydro functionalization of unactivated internal alkynes by a simple iridium catalyst.



Scheme 1. Context of the work.

Results and Discussion

Evaluation of the halide donor. Recently, our group reported several reactions that addressed safety problems associated with the use of hazardous and toxic reagents, such as HCN-free hydrocyanation,[12] cyanide-free cyanation of aryl chloride[13] and CO/HCl-free hydrochlorocarbonylation.[14] These reactions

[a] Dr. Peng Yu, Dr. A. Bismuto, Prof. Dr. B. Morandi
Laboratorium für Organische Chemie ETH Zürich
Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland

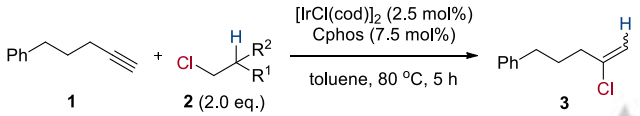
[b] Dr. Peng Yu, Prof. Dr. B. Morandi
Max-Planck-Institut für Kohlenforschung
Kaiser-Wihelm-Platz 1, 45470 Mülheim an der Ruhr, Germany
E-mail: bill.morandi@org.chem.ethz.ch

[†] Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.

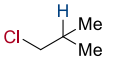
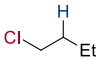
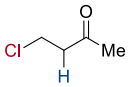
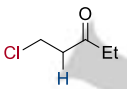
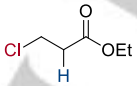
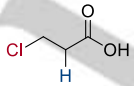
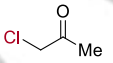
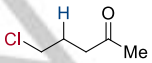
10.1002/anie.201912803

proceed *via* a shuttle catalysis[15] paradigm wherein a chemical moiety is transferred between two stable organic molecules. Accordingly, we sought a suitable catalytic system that could enable an HCl molecule to be formally transferred between a simple alkyl chloride and an alkyne without any direct use of corrosive HCl. We initially explored reagents that are similar in structure to those we employed in previous examples of shuttle catalysis by reacting with a simple aliphatic terminal alkyne **1**.[15] We started our investigations with iridium catalysts because of their expected high reactivity toward the oxidative addition of C–X bonds.[16] Unfortunately, both isobutyl chloride (table 1, entry 1) and butyl chloride (table 1, entry 2) did not show any reactivity probably due to the inertness of the C–Cl bond. Interestingly, the use of *tert*-butyl chloride (**2c**) as the donor of HCl was found to give trace amount of vinyl chloride product (**3**) under these conditions (table 1, entry 3), however together with some decomposition product. We next reasoned that the installation of a polar group at a neighbouring position on the reagent backbone could possibly facilitate the initial activation step through either coordination of a metal and/or

Table 1: Exploring the reagent for the transfer hydrochlorination of alkynes.[a]



1 **2** (2.0 eq.) **3**

Entry	2		3 (%)[b]
1	**2a**		0
2	**2b**		0
3	**2c**		0 (trace)[c]
4	**2d**		85
5	**2e**		75
6	**2f**		0
7	**2g**		15
8	**2h**		0
9	**2i**		trace

[a] **1** (0.1 mmol), **2** (0.2 mmol), $[IrCl(cod)]_2$ (2.5 mol%), CPhos (7.5 mol%), toluene (0.25 mL) at 80 °C, 5 h. [b] NMR yields using dibromomethane as an internal standard. [c] **2c** (1.0 mmol), toluene (0.5 mL) at 110 °C, 12 h.

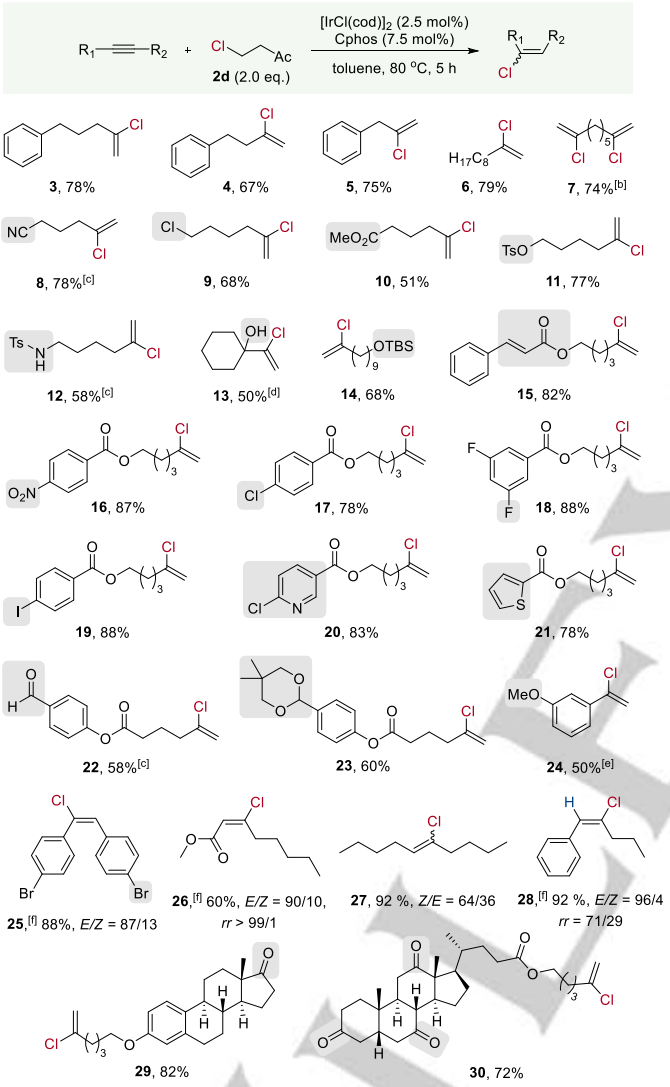
electronic activation of the C–Cl bond. Through the evaluation of several reagents and catalysts (see SI for the optimization), we found 4-chlorobutan-2-one (**2d**), which contains an acyl group on the *β* carbon relative to the chlorine atom, as a suitable donor of HCl for the transfer hydrochlorination of pent-4-yn-1-ylbenzene (**1**).

The ideal catalytic system for this transformation emerged as a combination of $[IrCl(cod)]_2$ as precursor and CPhos as a ligand at 80 °C in toluene, giving rise to **3** as a single regioisomer in 85% yield (table 1, entry 4). To the best of our knowledge, this is the first example of an iridium-catalyzed hydrochlorination reaction. Moreover, the alkene by-product, methyl vinyl ketone, was obtained in 87% yield, a result which strongly suggests that the reaction proceeds through shuttle catalysis. A similar reagent 1-chloropentan-3-one (**2e**) also showed high reactivity under the same conditions, leading to the vinyl chloride (**3**) in 75% yield (table 1, entry 5). Among those reagents bearing various carbonyl groups, only the one containing a carboxylic acid (**2g**) showed limited reactivity in this hydrochlorination reaction, delivering the vinyl chloride (**3**) in 15% yield (table 1, entry 7). As expected, the reagent which lacks *β* hydrogens did not react under the conditions (table 1, entry 8). A reagent bearing the acyl group on the γ carbon to the chlorine atom (**2h**) was also tested in the reaction. However, only trace amount of product was detected, which further demonstrated the beneficial effect of the acyl group on the reactivity of the chloride reagent (table 1, entry 9).

Hydrochlorination using 4-chlorobutan-2-one. With 4-chlorobutan-2-one (**2d**) as the optimized reagent, we then moved to explore the substrate scope of this iridium-catalyzed transfer hydrochlorination reaction. As illustrated in table 2, a wide variety of alkyne derivatives could successfully undergo hydrochlorination reaction using our system to give the corresponding vinyl chlorides in good yield. Initially, we focused on the evaluation of aliphatic terminal alkynes. A broad range of functional groups including nitriles (**8**), chlorides (**9**), esters (**10**), amines (**12**), nitro (**16**), aryl chloride (**17**) or aryl iodide (**19**), fluorides (**18**), aldehyde (**22**) and ketone (**29**) were tolerated. Likewise, *α*, *β*-unsaturated esters, which serve as an important building block in organic synthesis, were tolerated under the reaction conditions (**15**). Interestingly, a substrate bearing two terminal alkyne moieties could undergo successful hydrochlorination reaction giving the product containing two vinyl chloride moieties (**7**). To our delight, acid sensitive functional groups such as tertiary alcohols (**13**), silyl ethers (**14**) and acetals (**23**), which are usually not tolerated by other methods employing hydrochloric acid as a reagent, remained untouched during the reaction, showcasing the excellent functional group tolerance of our methodology. Alkynes containing heterocycles such as pyridine and thiophene reacted smoothly, leading to the corresponding vinyl chlorides in 83% and 78% yield respectively (**20**, **21**). It is worth noting that alkynes derived from natural products such as estrone and cholic acid could also be efficiently converted to the corresponding vinyl chlorides in high yields (**29**, **30**), further demonstrating the diversity and practicality of this novel protocol. An aromatic terminal alkyne was subsequently evaluated and improved yield of product were obtained using Ruphos as the ligand (**24**). Next, we were pleased to find that slightly modifying our protocol, both a

symmetric diarylethyne (**25**) and an asymmetric internal alkyne (**26, 28**) could be converted to the corresponding vinyl chlorides in good selectivity. In the case of symmetric aliphatic internal alkynes, excellent yield of product was obtained, but in a low *Z/E* ratio of 64:36 (**27**). In contrast, an ester-substituted alkyne led to product formation with high yield, regio- and stereoselectivity (**26**).

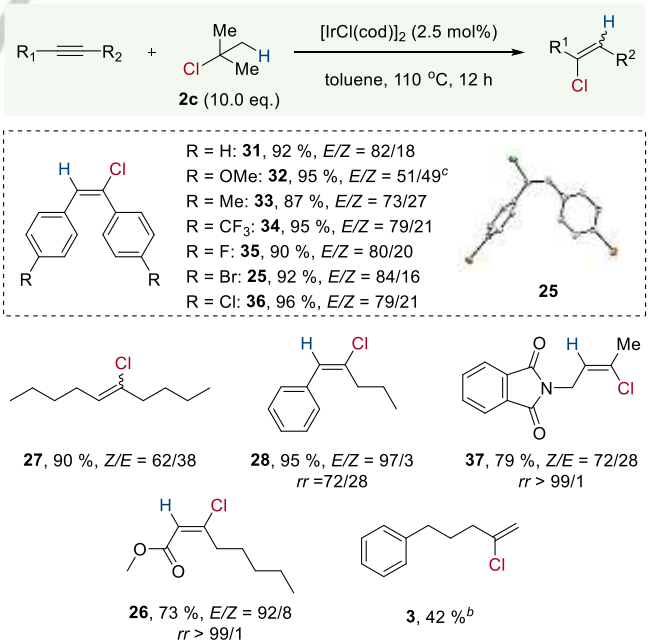
Table 2: Scope of iridium-catalyzed transfer hydrochlorination of alkynes with 4-chlorobutan-2-one.[a]



[a] alkyne (0.2 mol), **2d** (0.4 mmol, 2.0 eq.), $[IrCl(cod)]_2$ (2.5 mol%), CPhos (7.5 mol%), toluene (0.5 mL) at 80 °C, 5 h, given as isolated yields. [b] **2d** (4.0 eq.). [c] CPhos (15 mol%). [d] $[IrCl(cod)]_2$ (5 mol%), *t*-Bu-Xantphos (20 mol%), 12h. [e] Ruphos (7.5 mol%), 12h. [f] 110 °C, 12h.

Hydrochlorination using *tert*-butyl chloride. Although the method using 4-chlorobutan-2-one showed broad applicability and enabled the hydrochlorination without the use of corrosive reagent, its high price and the generation of highly reactive methyl vinyl ketone as a by-product can possibly limit its synthetic applicability. Thus, the discovery of more sustainable donors of HCl still remains highly significant. As shown in table 1, the use of *tert*-butyl chloride as a donor of HCl can produce the vinyl chloride product in trace amount under the conditions with more equivalents of the reagent, higher temperature and longer reaction time (table 1, entry 3). Encouraged by this result, we moved to explore the reactivity of *tert*-butyl chloride in the hydrochlorination of alkynes due to its higher availability and lower price than 4-chlorobutan-2-one. Furthermore, the use of *tert*-butyl chloride as a donor of HCl produces a non-toxic and benign by-product, isobutene. After screening of reaction's conditions (see details in SI), we found the optimal system for hydrochlorination reaction of internal alkynes using *tert*-butyl chloride under ligand-free conditions with $[IrCl(cod)]_2$ as a catalyst at 110 °C. A range of internal alkynes, either symmetric or asymmetric, aliphatic or aromatic, activated or unactivated, were successfully converted to the corresponding vinyl chlorides in good to excellent yields even without using any external ligands (Table 3, **26**, **27**, **31**-**37**). Regarding the symmetric internal alkynes, diarylethynes bearing either electron-donating (**32**, **33**) or electron-withdrawing groups (**25**, **34**, **35, 36**) were well tolerated, reacting with *tert*-butyl chloride to give vinyl chlorides in excellent yields with good *E/Z* selectivity. The symmetric aliphatic internal alkyne also reacted to afford the corresponding vinyl chlorides with high efficiency and moderate *Z/E* ratio (**27**). Besides, some asymmetric internal alkynes also showed good reactivity in the transformation, being converted to the vinyl chlorides in good yields and selectivity (**26**, **28**, **37**). Terminal alkynes, 5-phenyl-1-pentyne could also undergo hydrochlorination to give the vinyl chloride in 42% yield (table 3, **3**), albeit tris(pentafluorophenyl)phosphine is required to successfully promote this transformation.

Table 3: Scope of iridium-catalyzed transfer hydrochlorination of alkynes with *tert*-butyl chloride.[a]

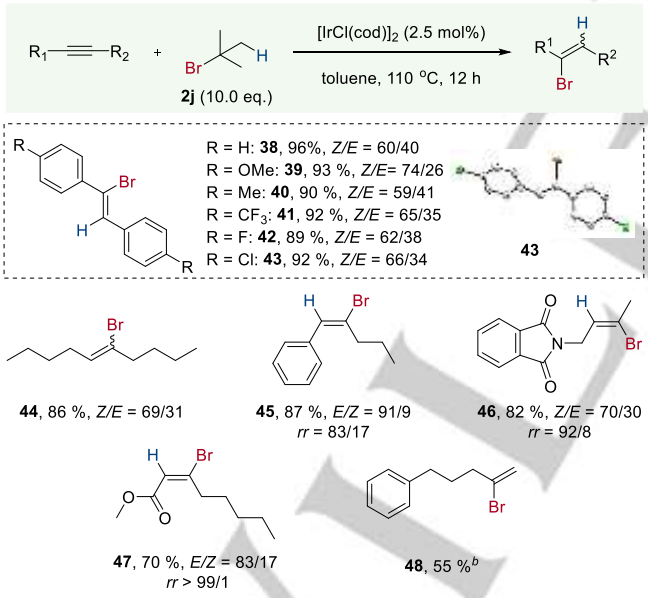


[a] alkyne (0.2 mol), **2c** (2.0 mmol, 10.0 eq.), $[IrCl(cod)]_2$ (2.5

mol%), toluene (1.0 mL) at 110 °C, 12 h, given as isolated yields. [b] tris(pentafluorophenyl)phosphine (7.5 mol%). [c] 5 h.

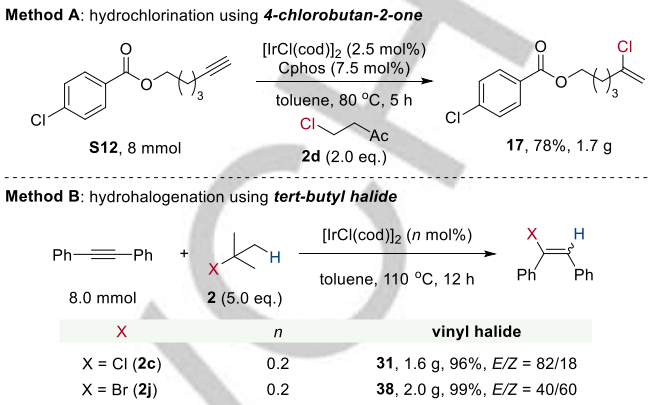
Hydrobromination using *tert*-butyl bromide. Catalytic hydrobromination of alkynes represents an efficient approach to synthesize vinyl bromides. However, current conditions for this process mainly rely on the use of corrosive and gaseous HBr or *in situ* generated HBr,[17] which is not ideal for laboratory-scale synthesis. Recently, an alternative method using a transfer hydrofunctionalization strategy was reported by Lautens[18] and Oestreich.[19] They achieved the hydrobromination of 1,6-enynes or alkynes through the transfer of HBr from $Et_3N{\cdot}HBr$ or 1-(2-bromoethyl)-1,4-dihydro-1,1'-biphenyl. In this context, we were delighted to see that our protocol for the transfer hydrochlorination using *tert*-butyl chloride could also be applied to the transfer hydrobromination using *tert*-butyl bromide as the source of HBr. We then decided to evaluate the scope and the potential of this transformation. As shown in table 4, an aliphatic terminal alkyne could successfully undergo hydrobromination reaction to give the branched vinyl bromide (**48**) in moderate yield. Internal alkynes, including symmetric diarylethynes and dialkylethynes and several asymmetric substrates, were also converted to the corresponding vinyl bromides (**38**-**47**) in good to excellent yield.

Table 4: Scope of iridium-catalyzed transfer hydrobromination of alkynes with *tert*-butyl bromide.[a]



[a] alkyne (0.2 mol), **2j** (2.0 mmol, 10.0 eq.), $[IrCl(cod)]_2$ (2.5 mol%), toluene (1.0 mL) at 110 °C, 12 h, given as isolated yields. [b] tris(pentafluorophenyl)phosphine (7.5 mol%).

Application on preparative scale. To demonstrate the robustness and applicability of those methodologies, we performed several scale-up experiments (Scheme 2). To our delight, both methods can be applied to a gram-scale synthesis with high efficiency. Furthermore, in the specific case of the methodology based on *tert*-butyl halide, we were able to reduce the amount of catalyst loading to 0.2 mol% with a TON of at least 480. This demonstrates the simplicity, efficiency and the synthetic value of this protocol.



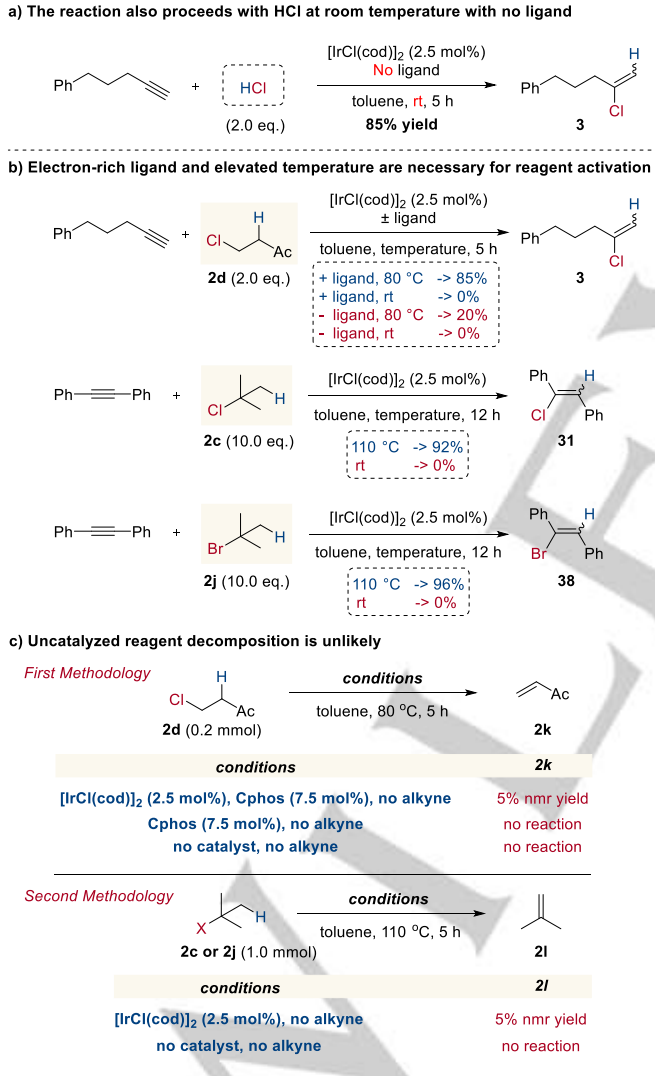
Scheme 2. Gram-scale experiments.

Mechanistic study

The lack of previously reported examples of iridium-catalyzed hydrohalogenation reactions raises questions regarding the mechanism of our processes. Thus, we became interested in investigating the mechanism of our novel methodologies performing both stoichiometric and catalytic experiments. We started evaluating the reactivity of the iridium catalyst, the phosphine ligand and the first reagent, 4-chlorobutan-2-one (**2d**). After forming the Ir-phospine *in situ*, which was confirmed by NMR spectroscopy, we added a stoichiometric amount of 4-chlorobutan-2-one and monitored the reaction over time and at different temperatures (see SI). Upon heating at 80 °C, trace amount of methyl vinyl ketone was observed together with formation of a new phosphorous compound which became the major product after 24 hours. Unfortunately, despite our efforts, this product could not be isolated. Interestingly, after 3 hours, trace amount of an Ir–H species was observed (see SI) which, however, subsequently disappeared upon further heating. Next, we investigated whether a different behavior was taking place with the other class of reagents, *tert*-butyl chloride and bromide. Reacting these species at 80 °C with $[IrCODCl]_2$ led, this time, to a significant formation of isobutene (see SI). In all the cases, no significant amounts of Ir–H species were observed, raising questions about the possible intermediacy and stability of such species under our reaction conditions.

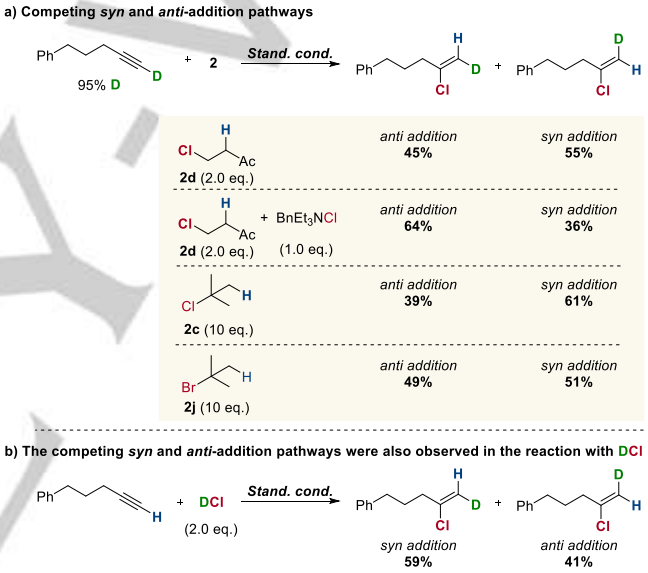
As we could not gather further information from the stoichiometric experiments, we wondered whether the reagent could just serve as a donor of HCl which then could be oxidatively added to the iridium and generate the active intermediate. Replacing our reagents, 4-chlorobutan-2-one or *tert*-butyl chloride, with an HCl solution in ether, led to product formation with similar conversion and yield (Scheme 3a). Besides being a new synthetic method on its own, this result suggests that both reactions could proceed through a similar Cl–Ir–H intermediate. Interestingly, and in contrast to the normal

reaction conditions, the reaction with HCl could even be run at room temperature in the absence of the phosphine ligand. These results suggest that the most challenging (and slower) part of the catalytic cycle in the shuttle process, the one which requires higher temperature and an electron-rich phosphine ligand or only higher temperature, is the activation of 4-chlorobutan-2-one or *tert*-butyl halide by the iridium catalyst (Scheme 3b). In order to test the thermal stability of those halide reagents and any possible *in situ* formation of HCl, we performed the reaction in the absence of the catalyst which showed no significant conversion of either chlorobutan-2-one or the *tert*-butyl halide as well as no formation of the desired vinyl halide product. This result, combined with the high tolerance of the reaction to acid-sensitive groups, makes the *in situ* generation of significant amounts of free HCl highly unlikely (Scheme 3c).



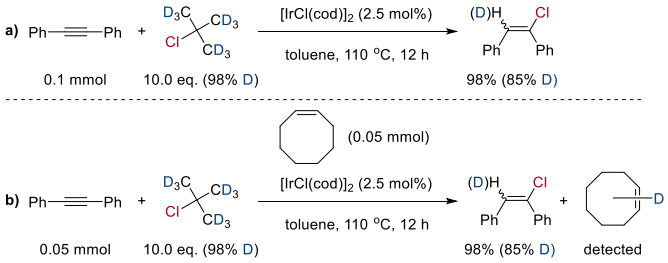
Scheme 3. Control experiments.

In order to gain more information regarding the actual alkyne addition step, a deuterium-labelled alkyne substrate was synthesized and subjected to the reaction conditions (Scheme 4a). Interestingly, a nearly equimolar mixture of the two possible isomers was obtained with both methodologies. This result was later confirmed by another labelling experiment wherein DCl was employed with a non-labelled alkyne substrate, which led to the formation of a similar ratio of both isomers. However, as expected, the other isomer was formed as the major product (Scheme 4b). While an initial Ir–H migratory insertion cannot be excluded at this stage, the results obtained, combined with the known propensity of Rh(III)–Cl and Ir(III)–Cl species to undergo rapid M–Cl insertion into unsaturated substrates,[6t] support a mechanism where an initial chloroiridation step occurs through competing *syn* and *anti*-addition pathways. In further support of this rationale, we treated the reaction with an exogenous source of Cl anion (Scheme 4a). As expected, a significant change in the observed ratio in favor of the *anti*-addition product was observed.



Scheme 4. Deuterium-labelling experiments.

Finally, we performed an experiment using a fully deuterated *tert*-butyl chloride (98% D) as the reagent to determine the level of deuterium incorporation in the product (scheme 5a). Interestingly, only 85% incorporation of deuterium in the product was observed, probably as a result of a side reaction with the COD ligand on the iridium catalyst. This side reaction might proceed through rapid and reversible Cl–Ir–D insertion into the alkene groups of COD, a process that could result in the loss of deuterium. To get evidence for the side reaction, an experiment using an equimolar mixture of diphenylacetylene and cyclooctene as the substrate was performed (scheme 5b). As expected, the deuterated cyclooctene was detected by deuterium NMR, a result which suggests the presence of a short lived Ir–D species under the catalytic reaction conditions.



Scheme 5. Deuterium-labelling experiments.

Conclusion

In conclusion, we have presented an iridium-catalyzed transfer hydrohalogenation reaction which proceeds through a shuttle catalysis strategy. The method uses chlorobutan-2-one as an HCl surrogate, enabling this milder protocol to tolerate the widest range of functional groups reported to date in a hydrochlorination reaction. Alternatively, a protocol using inexpensive *tert*-butyl chloride can be used with decreased catalyst loadings. The latter transformation can also be efficiently extended to hydrobromination reactions. In a broader context, this work highlights both the possibility to use the shuttle catalysis concept to elude the use of mineral acids, and the previously untapped potential of iridium complexes to catalyze hydrohalogenation reactions. Despite our extensive efforts, the isolation of relevant catalytic intermediates was hampered by the short life of those iridium species. Thus, further studies will be necessary to unravel the mechanism of these novel catalytic reactions.

Experimental Section

Experimental details and compound characterization are provided in the supporting information.

Acknowledgements

We thank the ERC (ShuttleCat, Project ID : 757608). Generous funding from the Max-Planck-Society and the Max-Planck-Institut für Kohlenforschung is acknowledged. We thank Prof. Dr. Benjamin List for sharing analytical equipment and X-ray departments of ETH Zürich (Dr. Nils Trapp) for technical assistance. We also thank Dr. Sayanti Chatterjee for fruitful discussion. P.Y. thanks the China Scholarship Council for a scholarship.

Keywords: Iridium • Hydrochlorination • Hydrobromination • Vinyl chloride • Shuttle catalysis

[1] a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem*. **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442; b) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054; c) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev*. **2011**, *111*, 1417; d) A. B. Dounay, L. E. Overman, *Chem. Rev*. **2003**, *103*, 2945

[2] a) K. C. Engvild, *Phytochemistry* **1986**, *25*, 781; b) G. W. Gribble, *Acc. Chem. Res.* **1998**, *31*, 141; c) J. Kim, Y. Zhang, C. Ran, L. M. Sayre, *Bioorg. Med. Chem*. **2006**, *14*, 1444.

[3] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) A.Thakur, K. Zhang, J. Louie, *Chem. Commun*. **2012**, *48*, 203; c) L. M. Geary, P. G. Hultin, *J. Org. Chem*. **2010**, *75*, 6354; d) A. B. Lemay, K. S. Vulic, W. W. Ogilvie, *J. Org. Chem.* **2006**, *71*, 3615; e) J. Choi, G. C. Fu, *Science* **2017**, *356*, DOI: 10.1126/science.aaf7230.

[4] a) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534; b) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev*. **2016**, *116*, 12564.

[5] a) S. Hirsl-Starcevic, Z. Majerski, *J. Org. Chem.* **1982**, *47*, 2520; b) J. Kagan, S. K. Arora, M. Bryzgis, S. N. Dhawan, K. Reid, S. P. Singh, L. Tow, *J. Org. Chem.* **1983**, *48*, 703; c) K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc*. **1986**, *108*, 7408; d) R. S. Al-awar, S. P. Joseph, D. L. Comins, *J. Org. Chem.* **1993**, *58*, 7732; e) C. Muthiah, K. P. Kumar, S. Kumaraswamy, K. C. Kumara Swamy, *Tetrahedron* **1998**, *54*, 14315; f) K. Kamei, N. Maeda, T. Tatsuoka, *Tetrahedron Lett.* **2005**, *46*, 229; g) A. Spaggiari, D. Vaccari, P. Davoli, G. Torre, F. Prati, *J. Org. Chem.* **2007**, *72*, 2216; h) W. Su, C. Jin, *Org. Lett.* **2007**, *9*, 993.

[6] a) H. Brown, T. Hamaoka, N. Ravindran, C. Subrahmanyam, V. Somayaji, N. G. Bhat, *J. Org. Chem*. **1989**, *54*, 6075; b) S. Ma, X. Lu, Z. Li, *J. Org. Chem*. **1992**, *57*, 709; c) K. Kokubo, K. Matsumasa, M. Miura, M. Nomura, *J. Org. Chem.* **1996**, *61*, 6941; d) Z. Wang, X. Lu, *Chem. Commun*. **1996**, 535; e) R. Hua, S. Shimada, M. Tanaka, *J. Am. Chem. Soc*. **1998**, *120*, 12365; f) A. Sun, X. Huang, *Synthesis* **2000**, *2000*, 1819; g) W. Yu, Z. Jin, *J. Am. Chem. Soc.* **2000**, *122*, 9840; h) M. Su, W. Yu, Z. Jin, *Tetrahedron Lett.* **2001**, *42*, 3771; i) J. A. Mulder, K. C. M. Kurtz, R. P. Hsung, H. Coverdale, M. O. Frederick, L. Shen, C. A. Zificsak, *Org. Lett.* **2003**, *5*, 1547; j) A. Coelho, H. Novoa, O. M. Peeters, N. Blaton, M. Alvarado, E. Sotelo, *Tetrahedron* **2005**, *61*, 4785; k) R. Hua, S.-Y. Onozawa, M. Tanaka, *Chem. Eur. J.* **2005**, *11*, 3621; l) J.-H. Li, S. Tang, Y.-X. Xie, *J. Org. Chem.* **2005**, *70*, 477; m) T. Kashiwabara, K. Fuse, R. Hua, M. Tanaka, *Org. Lett.* **2008**, *10*, 5469; n) L. Feray, P. Perfetti, M. P. Bertrand, *Synlett* **2009**, *01*, 89; o) T. Iwai, T. Fujihara, J. Terao, Y. Tsuji, *J. Am. Chem. Soc.* **2009**, *131*, 6668; p) T. Wada, M. Iwasaki, A. Kondoh, H. Yorimitsu, K. Oshima, *Chem. Eur. J.* **2010**, *16*, 10671; q) B. Wang, S. Wang, P. Li, L. Wang, *Chem. Commun*. **2010**, *46*, 5891; r) T. Kashiwabara, M. Tanaka, *Adv. Synth. Cat.* **2011**, *353*, 1485; s) Z. Lu, W. Kong, Z. Yuan, X. Zhao, G. Zhu, *J. Org. Chem*. **2011**, 76, 8524; t) T. Iwai, T. Fujihara, J. Terao, Y. Tsuji, *J. Am. Chem. Soc.* **2012**, *134*, 1268; u) G. Zhu, D. Chen, Y. Wang, R. Zheng, *Chem. Commun.* **2012**, *48*, 5796.

[7] For a review on catalytic C–halogen formation, see: D. A. Petrone, J. Ye, M. Lautens, *Chem. Rev*. **2016**, *116*, 8003.

[8] For an example of HCl-free alkene hydrochlorination, see: B. Gaspar, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 5842; *Angew. Chem. Int. Ed.* **2008**, *47*, 5758.

[9] S. Dérien, H. Klein, C. Bruneau, *Angew. Chem.* **2015**, *127*, 12280; *Angew. Chem. Int. Ed.* **2015**, *54*, 12112.

[10] R. Ebule, S. Liang, G. B. Hammond, B. Xu, *ACS Catalysis* **2017**, *7*, 6798.

[11] J. Derosa, A. L. Cantu, M. N. Boulous, M. L. O'Duill, J. L. Turnbull, Z. Liu, D. M. De La Torre, K. M. Engle, *J. Am. Chem. Soc.* **2017**, *139*, 5183.

[12] X. Fang, P. Yu, B. Morandi, *Science* **2016**, *351*, 832.

[13] P. Yu, B. Morandi, *Angew. Chem.* **2017**, *129*, 15899; *Angew. Chem. Int. Ed*. **2017**, *56*, 15693.

[14] X. Fang, B. Cacherat, B. Morandi, *Nat. Chem*. **2017**, *9*, 1105.

[15] a) B. N. Bhawal, B. Morandi, *ACS Catalysis* **2016**, *6*, 7528; b) B. N. Bhawal, B. Morandi, *Chem. Eur. J.* **2017**, *23*, 12004; c) D. A. Petrone, I. Franzoni, Y. Ye, J. F. Rodriguez, A. I. Poblador-Bahamonde, M. Lautens, *J. Am. Chem. Soc.* **2017**, *139*, 3546; d) S. K. Murphy, J.-W. Park, F. A. Cruz, V. M. Dong, *Science* **2015**, *347*, 56; e) X. Wang, M. Nakajima, E. Serrano, R. Martin, *J. Am. Chem. Soc.* **2016**, *138*, 15531;

f) M. D. Greenhalgh, S. P. Thomas, *J. Am. Chem. Soc.* **2012**, *134*, 11900; g) L. Ilies T. Yoshida; E. Nakamura, *J. Am. Chem. Soc.* **2012**, *134*, 16951.

[16] a) F. Cusmano Priolo, V. Marsala, G. Rizzardi, P. Vitarelli, *Inorg. Chim. Acta* **1983**, *76*, L193; b) M. A. Bennett, G. T. Crisp, *Aust. J. Chem.* **1986**, *39*, 1363.

[17] a) F. Gao, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10961; b) R. J. Van Hoveln, S. C. Schmid, M. Tretbar, C. T. Buttke, J. M. Schomaker, *Chem. Sci.* **2014**, *5*, 4763; c) M. R. Uehling, R. P. Rucker, G. Lalic, *J. Am. Chem. Soc*. **2014**, *136*, 8799; d) X. Ma, S. B. Herzon, *Chem. Sci.* **2015**, *6*, 6250; e) M. Das, T. Kaicharla, J. F. Teichert, *Org. Lett*. **2018**, *20*, 4926; f) S. Hara, H. Dojo, S. Takinami, A. Suzuki, *Tetrahedron Lett*. **1983**, *24*, 731; g) A. Bunrit, S. Ruchirawat, C. Thongsornkleeb, *Tetrahedron Lett.* **2011**, *52*, 3124; h) X. Chen, T. Chen, Y. Xiang, Y. Zhou, D. Han, L.-B. Han, S.-F. Yin, *Tetrahedron Lett.* **2014**, *55*, 4572; i) Y. Nishio, R. Mifune, T. Sato, S. Ishikawa, H. Matsubara, *Tetrahedron Lett.* **2017**, *58*, 1190; j) Z. Li, R. Ebule, J. Kostyo, G. B. Hammond, B. Xu, *Chem. - Eur. J.* **2017**, *23*, 12739.

[18] D. A. Petrone, I. Franzoni, J. Ye, J. F. Rodríguez, A. I. Poblador-Bahamonde, M. Lautens, *J. Am. Chem. Soc.* **2017**, *139*, 3546.

[19] a) W. Chen, M. Oestreich, *Org. Lett.* **2019**, *21*, 4531; b) P. Orecchia, W. Yuan, M. Oestreich, *Angew. Chem. Int. Ed.* **2019**, *58*, 3579; *Angew. Chem*. **2019**, *131*, 3617; c) W. Chen, J. C. L. Walker, M. Oestreich, *J. Am. Chem. Soc*. **2019**, *141*, 1135; d) J. C. L. Walker, M. Oestreich 10.1002/anie.201909852; e) S. Keess, M. Oestreich, *Org. Lett.* **2017**, *19*, 1898.

10.1002/anie.201912803

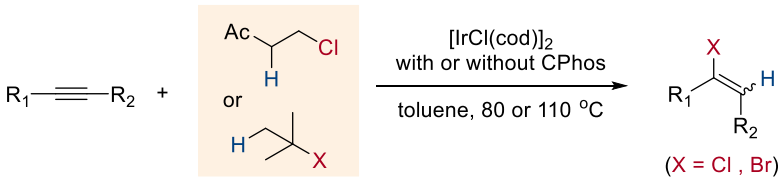
WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 2:

RESEARCH ARTICLE

Iridium-catalyzed hydrochlorination and Hydrobromination of alkynes



• easy-to-handle reagents
• broad functional group tolerance

*Peng Yu, Alessandro Bismuto and Bill Morandi**

Page No. – Page No.

Iridium-Catalyzed Hydrochlorination and Hydrobromination of Alkynes *via* Shuttle Catalysis