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Au(I)-catalyzed hydration of 1-iodoalkynes leading to α-iodoketones

Alberto Gómez-Herrera,[a] Ishfaq Ibni Hashim,[b] Marre Porré,[b] Fady Nahra[b,c] and Catherine S. J. Cazin*[b]

Dedication ((optional))

[a] dr. A. Gómez-Herrera
EaStCHEM School of Chemistry
University of St Andrews
St Andrews, KY16 9ST, UK
[b] I. Ibni Hashim, M. Porré, Prof. dr. F. Nahra, Prof. dr. C. S. J. Cazin
Department of Chemistry and Center for Sustainable Chemistry
Ghent University
Krijgslaan 281 - S3, 9000 Gent, Belgium
E-mail: Catherine.Cazin@UGent.be
[c] Prof. dr. F. Nahra
Separation and Conversion Technology Unit
VITO (Flemish Institute for Technological Research)
Boeretang 200, B-2400 Mol, Belgium

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Abstract: A catalytic protocol for the Au(I)-catalyzed hydration of 1-iodoalkynes is disclosed. The use of a Au(I)-NHC catalyst enabled the straightforward synthesis of a variety of α-iodomethyl ketones in good to excellent yields. The utility of this simple method is further highlighted by showcasing iodination/hydration and hydration/oxidation sequential protocols leading to the construction of molecular complexity.

Organoiodide compounds[1] are undoubtedly amongst the most synthetically useful building blocks in chemistry due to the highly reactive nature of the carbon-iodine bond. Their use as organic building blocks, additives or catalysts, as well as their presence in medicinal chemistry in drugs, radioactive tracers and contrast reagents,[2] highlights the need for better tools for efficient, sustainable, atom-economical and scalable syntheses of iodinated molecules.

Among the plethora of iodine-containing compounds, iodoketones, and more particularly α-iodomethyl ketones, represent an important family of halogenated molecules. These act effectively as substrates in the synthesis of carbon-carbon, carbon-oxygen and carbon-nitrogen bonds. These compounds are excellent substrates for the synthesis of heterocycles[3] or as reactive precursors for α-functionalization of ketones.[4] As a result of this versatility, the use of α-iodomethyl ketones in total synthesis is nowadays a valuable approach to increase molecular complexity. For example, the preparation of certain pharmacological substances, such as (-)-trachelanthamidine,[5] dendrobine[6] or cylindricine C,[7] among others,[8] has benefited from the use of iodoketones as key intermediates (Figure 1). These molecules can be prepared in various ways, with the direct iodination of methyl ketones being the most common approach[9] due to the availability of the corresponding substrates and the high atom economy of this reaction. However, direct iodination procedures present a number of drawbacks that have only been partially assessed over the last decades, such as undesirable polyhalogenation side-products and complex solvent/additive combinations required for high efficiency. The use of silyl enol ethers or acetates has been explored as a suitable alternative;[10] however, the difficult preparation and purification of the related substrates has precluded a more extensive use of the method.

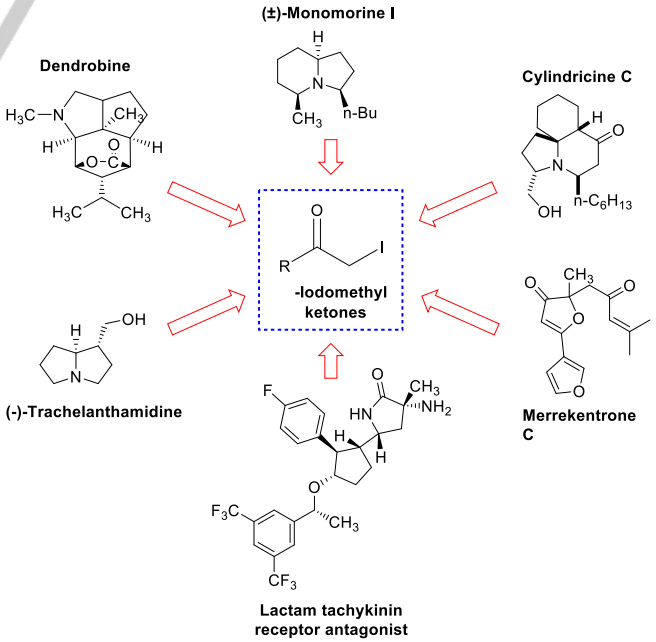
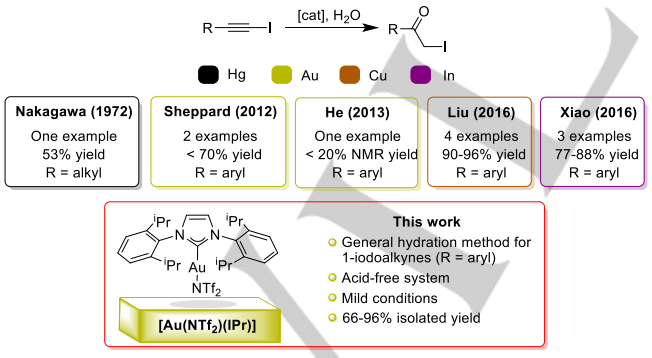


Figure 1. Examples of *Blockbuster* pharmacological compounds prepared *via* α-iodomethyl ketone intermediates.

Other protocols have taken advantage of the chemistry of different functional groups, such as the oxidation/iodination of alkenes,[11] the oxidation of iodoalcohols[12] or the electrophilic iodination of α-substituted methyl ketone precursors,[10b,13] resulting in a range of synthetic possibilities available for the preparation of these species. The use of oxidants and/or the need for α-substituents as directing groups significantly limit the application of these methodologies.

An alternative method involves the hydration of 1-iodoalkynes, presenting advantages such as the use of water as the only reagent and a broad scope of suitable substrates. Surprisingly, this strategy has been scarcely discussed in the literature (Scheme 1). A report by Nakagawa and co-workers in 1972 described the first attempt to hydrate 1-iodoalkynes by successfully converting iodopropargyl alcohol to its corresponding ketone.[14] However, the use of toxic mercuric oxide as catalyst significantly restricted the interest in this method. Later on, and in conjunction with the growing success of catalytic hydration of alkynes[15] mainly using gold catalysis,[16] a renewed interest in this reaction emerged. In 2012, Sheppard and co-workers reported, using the gold bistriflimide complex [Au(NTf$_2$)(PPh$_3$)], a mild catalytic system for the hydration of aromatic 1-iodoalkynes affording two examples of α-iodomethyl ketones in moderate yields.[17] However, limited experimental data were provided for this system. Encouraged by the performance of Au(I)-phosphine systems, He and co-workers later reported a more general hydration system for 1-haloalkynes;[18] despite its optimal application to bromo- and chloroalkyne substrates, very low catalytic activity was observed with the corresponding iodo derivatives.[19] Recently, two new alternatives to gold catalysis have expanded the available protocols for hydration chemistry. While these approaches report the use of simple Ag(I)[20] and Cu(II)[21] salts, important drawbacks still remain, such as the use of a non-innocent and strongly-acidic solvent (trifluoroacetic acid).[22] More recently, the use of 10 mol% In(OTf)$_3$ in AcOH at 100 ºC has also proven useful for the hydration of 1-iodoalkynes,[23] although displaying similar drawbacks to those reported in previous protocols.

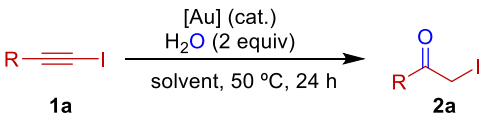


Scheme 1. Previous work and present approach to the catalytic hydration of 1-iodoalkynes.

Our interest in the preparation and application of transition metal-NHC complexes (NHC = *N*-heterocyclic carbene) led us to explore an alternative to the more sensitive phosphine-based systems used thus far. Considering the aforementioned success of gold catalysts, and with the wide range of complexes available for efficient hydration of alkynes in general,[16] the use of Au(I)-NHC catalysts in this reaction seemed a well-worth effort. We herein report the use of well-defined Au-NHC based systems in the hydration of 1-iodoalkynes to access α-iodomethyl ketones. The use of mild and green conditions was targeted and the possibility of sequential reactions leading to molecular complexity was also tested.

First, the optimization of a hydration protocol, using (iodoethynyl)benzene (**1a**) as model substrate, was tackled. This compound can be easily prepared using our recent methodology starting from the commercially available phenylacetylene.[24] The initial blank reaction revealed that stirring **1a** in the presence of two equivalents of water in MeOH at 50 ºC affords, as anticipated, no conversion towards the expected 2-iodo-1-phenylethanone (**2a**) (Table 1, Entry 1). However, when 5 mol% of the digold hydroxide complex [{Au(IPr)}$_2$(μ-OH)][BF$_4$] was introduced, quantitative NMR yield of **2a** was observed (Table 1, Entry 2). This complex was first selected due to its reported high reactivity in general alkyne hydration.[25] Further optimization revealed that a decrease in catalyst loading to 1 mol% afforded an acceptable 59% yield of **2a** (Table 1, Entry 3). A series Au(I)-NHC species were next screened for their activity (Table 1, Entries 3-7). An increase in the yield of **2a** was observed when using 1 mol% of [Au(NTf$_2$)(IPr)] (Table 1, Entry 7). This complex, first prepared by Gagosz in 2007,[26] provided 69% NMR yield for **2a**, surpassing all the screened catalysts, even the digold sulfate which is known to be highly active in this reaction (Table 1, Entry 5).[27] With these results in hand, [Au(NTf$_2$)(IPr)] was selected for further investigation, and the effect of solvent on catalyst performance was examined.

Table 1. Optimization of the Au(I)-catalysed hydration of (iodoethynyl)benzene (**2a**).



1a **2a**

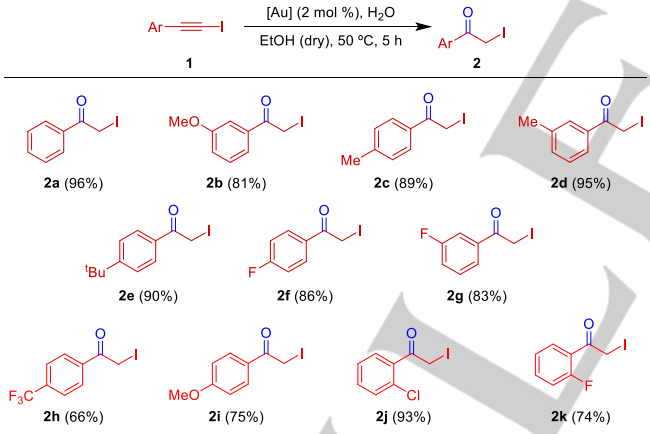
Entry[a]	[Au] (mol %)	Solvent	2a (%)[b]
1	---	MeOH	0
2	**[{Au(IPr)}$_2$(μ-OH)][BF$_4$] (5)**	**MeOH**	**>99**
3	[{Au(IPr)}$_2$(μ-OH)][BF$_4$] (1)	MeOH	59
4	[Au(OH)(IPr)] (1)	MeOH	0
5	[{Au(IPr)}$_2$(SO$_4$)] (1)	MeOH	44
6	[Au(IPr)(NEt$_3$)][HF$_2$] (1)	MeOH	0
7	**[Au(NTf$_2$)(IPr)] (1)**	**MeOH**	**69**
8	[Au(NTf$_2$)(IPr)] (1)	EtOH	76
9	**[Au(NTf$_2$)(IPr)] (1)**	**EtOH (dry)**	**86**
10[c]	[Au(NTf$_2$)(IPr)] (1)	EtOH	68
11[d]	[Au(NTf$_2$)(IPr)] (1)	EtOH	50
12[e]	[Au(NTf$_2$)(IPr)] (1)	EtOH	68

13[f]	[Au(NTf$_2$)(IPr)] (1)	EtOH	68
14	[Au(NTf$_2$)(IPr)] (2)	EtOH	99 (88)[g]
15[h]	**[Au(NTf$_2$)(IPr)] (2)**	**EtOH**	**99 (96)[g]**

[a] Reaction conditions: iodoalkyne (0.10 mmol), [Au] (cat.), H_2O (0.20 mmol), solvent (0.30 mL). [b] ^1H NMR yields using 1-bromo-3-fluorobenzene as NMR standard ($CDCl_3$ as solvent). [c] 40 ºC. [d] 60 ºC. [e] 1 equiv. H_2O. [f] 3 equiv. H_2O. [g] Isolated yields in parenthesis. [h] 5 h.

Alcohols as solvents were clearly superior to polar aprotic solvents and non-polar solvents. (See ESI, Table S1 for complete screening results). While the performance of commercial absolute EtOH was high (Table 1, Entry 8), the use of dried absolute EtOH[28] proved optimal for this reaction, leading to an 86% NMR yield of **2a** (Table 1, Entry 9). The system proved unaffected by increasing the temperature (Table 1, Entries 10-11). However, by increasing the catalyst loading to 2 mol%, complete conversion to **2a** was achieved, leading to an isolated yield of 88% (Table 1, Entry 14). Upon decreasing the reaction time to 5 h, full conversion of the starting material towards the desired product was maintained with an isolated yield of 96% (Table 1, Entry 15).

With the optimal conditions in hand, the reaction scope was investigated (Scheme 2). Electron-donating and withdrawing substituents at the *para*, *meta* as well as *ortho* positions were well tolerated, providing good to excellent isolated yields for the hydration reaction. Note here that the *ortho* substituted products **2j** and **2k** are noteworthy as they originate from substrates **1j** and **1k**, notoriously difficult to obtain substitution patterns in alkyne iodination.

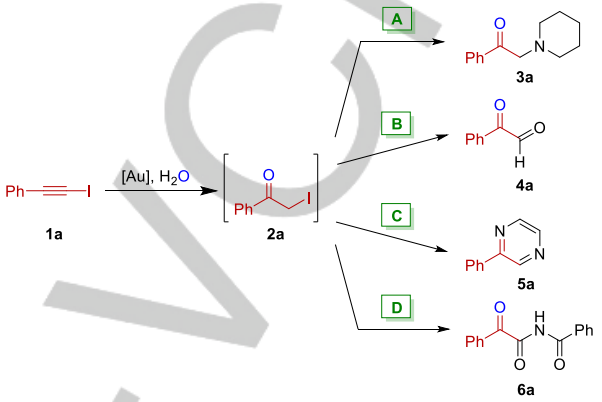


Reaction conditions: iodoalkyne (0.50 mmol), H_2O (1.00 mmol), [Au(NTf$_2$)(IPr)] (2 mol%), EtOH (dry), 50 ºC, 5 h. Isolated yields.

Scheme 2. Scope of the Au(I)-catalyzed hydration of 1-iodoalkynes.

Since α-iodoketones constitute an ideal platform for further functionalization, we reasoned that sequential reactions with substrates **2a-k** would constitute a great opportunity for proof-of-concept. The inertness of gold complexes and the sequential nature of our next strategy would eliminate the isolation of reaction intermediates and thus accelerate access to arylketone derivatives. In that context, a number of reactions using α-iodomethyl ketones as substrates, were selected (Table 2). The tested reactions include simple substitution chemistry (Table 2, **A**),[29] the Kornblum oxidation (**B**)[30-32] and diketone functionalization, including formation of heterocycles (**C**)[3d] or amides (**D**).[33] After some testing, simple removal of EtOH under reduced pressure from the initial hydration reaction provided **2a** in suitable purity for further functionalization. All prepared compounds were isolated in pure form and their spectroscopic data are in agreement with those found in the literature.

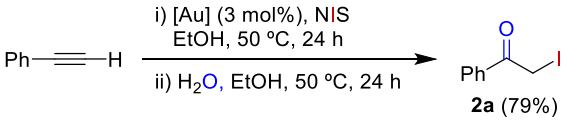
Table 2. Applications of α-iodomethyl ketones: sequential hydration/functionalization.



Route[a]	Conditions	Yield (%)
A	Piperidine, r.t., 16 h	88
B	DMSO, 110 ºC, 0.5 h	90
C	$H_2NCH_2CH_2NH_2$ (1 equiv.) K_2CO_3 (1.2 equiv.) DMSO, 100 ºC, 16 h	70
D	PhC(NH)NH_2·HCl (1 equiv.) DMSO, 130 ºC, 16 h	77

[a] Reaction conditions: iodoalkyne (0.50 mmol), [Au] (2 mol%), H_2O (1.00 mmol), EtOH (dry) (1.50 mL), 50 ºC, 5 h; then, removal of solvent followed by listed conditions.

Au(I) catalysis permitted "post-hydration" functionalization of terminal alkynes and integration with our previously reported Au-catalyzed iodination of terminal alkynes[24] for a sequential iodination/hydration procedure, converting terminal alkynes into α-iodomethyl ketones (Scheme 3). This direct transformation has only been achieved by means of oxidative iodination to date,[3d,11] and the reduced tolerance towards more sensitive functional groups has precluded wider investigation of these methods. However, the proposed sequential method employs much milder reagents and reaction conditions, thus representing an excellent functionalization tool for synthesis. Simple stirring a reaction mixture containing phenylacetylene, 3 mol% of [Au(NTf$_2$)(IPr)] and 1.1 equiv. of NIS in dry EtOH at 50 ºC for 24 h, followed by addition of water and stirring for additional 5 h, **2a** could be isolated in 79% yield after simple purification by column chromatography. This further highlights the robustness of Au-NHC species for fast access to α-iodomethyl ketones starting from terminal alkynes. Mechanistic studies relevant to this one-pot transformation are ongoing in our laboratories.



Reaction conditions: **1a** (0.50 mmol), [Au(NTf$_2$)(IPr)] (3 mol%) NIS (0.55 mmol), EtOH, 50 ºC, 24 h; then, H_2O (1 mmol), EtOH, 50 ºC, 5 h. Isolated yield.

Scheme 3. Sequential iodination/hydration of terminal alkynes.

Interestingly, during the optimization studies, the use of acetone as solvent showed an intriguing outcome. While no conversion towards the desired species **2a** could be detected using acetone as solvent, a clear new species was obtained in 32% yield. Full conversion towards this species was achieved by using an acetone/EtOH (1:1) mixture, and the compound was identified as the hydration/de-iodination product **2'a** (Scheme 4). Such type of reactivity has been observed when using other reactive systems, which include thiols or selenols as additives,[34] or the combination of acetone and Lewis acids.[35] To the best of our knowledge, this gold/acetone system has never been reported. This strategy is presently being further investigated in our laboratories.

In summary, a general methodology for the synthesis of α-iodomethyl ketones has been developed *via* NHC-based Au-catalyzed hydration of 1-iodoalkynes. By using a low loading of a well-defined Au(I)-NHC catalyst under mild conditions, the protocol presents good selectivity and provides good to excellent isolated yields for a variety of aromatic substrates. These compounds can also be prepared from terminal alkynes by means of a sequential Au-catalyzed iodination/hydration protocol. The versatility of this approach is highlighted in the easy access to arylketone derivatives by simply performing sequential hydration/functionalization reactions, owing to the robustness of the catalytic system. Several examples have been presented, broadening the applicability of Au-NHC catalysts in modern synthesis involving alkynes and 1-iodoalkynes. These results are an important step towards milder, faster and more efficient/sustainable synthetic routes.

Acknowledgements

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Keywords: Gold • N-heterocyclic carbenes • Iodination • Hydration • Sequential

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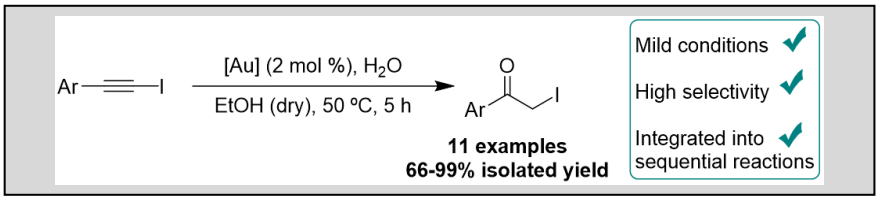
Entry for the Table of Contents



The Au(I)-catalyzed hydration of 1-iodoalkynes is reported, using a gold(I)-NHC catalyst. A variety of α-iodomethyl ketones are thus accessed in good to excellent yields. Several sequential protocols were also developed, leading to the construction of molecular complexity.

Institute and/or researcher Twitter usernames: ((optional))