Access to azetidines *via* gold mediated energy transfer photocatalysis

Sébastien G. Guillet,a Aleksei A. Logvinov,a Vladislav A. Voloshkin,a Ekaterina A. Martynovaa and Steven P. Nolana\*

aDepartment of Chemistry and Centre for Sustainable Chemistry, Ghent University, Campus Sterre, Building S-3, Krijgslaan 281, 9000 Ghent, Belgium.

\*Email: steven.nolan@ugent.be

KEYWORDS: Azetidines – Cycloaddition – Gold – N-Heterocyclic Carbenes – Photocatalysis.



ABSTRACT: The area of energy transfer photocatalysis to generate four-membered rings is experiencing an unprecedented level of activity. Here, we report an operationally simple method towards azetidines from 2-isoxasoline-3-carboxylates and alkenes, using [Au(cbz)(NHC)] complexes as photocatalysts. The procedure enables the reaction for a wide range of substrates. Mechanistic studies confirm the energy transfer pathway. This contribution adds to the earlier reported use of these gold catalysts as potentially versatile tool in energy transfer chemistry and catalysis.

Synthesis requires an ever-increasing number and variety of building blocks, and facile access to these. Four membered rings, and amongst them azetidines, hold great value,1 but have for long been tedious to access.2 However, recent progress in [2+2] photocycloadditions has created new methods toward four-membered ring construction.3 Facing a very rapid development as a common synthetic tool,4 photocatalysis has for long focused mainly on photo-redox pathways through Single Electron Transfer (SET),5 but in the past few years, Energy Transfer (EnT) has also emerged as a promising mechanism for photocatalysis and for molecular assembly construction.6

Energy transfer photocatalysis relies on energizing a photocatalyst to an excited singlet state that can then undergo intersystem crossing to a triplet state. With this, it is possible to sensitize substrates to their own excited triplet state through Dexter energy transfer, excitation that would have been inaccessible otherwise at a given wavelength of irradiation. The limitation of this strategy lies in the triplet energy (ET) of the photocatalyst (sensitizer). Indeed, substrates with a lower or similar ET can be activated efficiently.7 Therefore, significant efforts have been directed towards the design of sensitizers with the highest possible ET values to enable transformations that have been, up to now, impossible because of the ET values of existing state-of-the-art photocatalysts.

For years, the most popular sensitizers were organic molecules,8 ruthenium9 and iridium complexes.10 The latter, especially, have recently been modified to provide very high ET values (up to 73 kcal/mol) and promisingly, long lifetimes.10b However, iridium catalysts possess numerous drawbacks. Due to their ionic nature, the scope of (greener) solvents in which the photoreactions can be conducted is limited.11 Moreover, this traditionally employed metal in photocatalysis, oftentimes the metal/complex of first choice, are amongst the most expensive.12 Alternatives are needed to address the sustainability aspects of photocatalysis. We have recently reported a very promising family of NHC-gold-amido complexes (NHC = N-heterocyclic carbene), with high ET values (~66 kcal/mol), lifetimes in the range of several hundred microseconds enabling photocatalyzed cycloadditions.13

Recently, Schindler and co-workers have disclosed an efficient process leading to nitrogen bearing 4-membered rings, using an iridium photocatalyst.14 Here, we report the synthesis of azetidines using a simply accesses gold photocatalyst (Scheme 1).

Scheme 1. State-of-the-art and the gold-mediated method.



Initially, we wished to confirm the activity of our novel gold-based systems in the [2+2] cycloaddition between alkenes and cyclic oximes. We selected conditions closely mimicking the ones employed by Schindler in this transformation using an Ir-based photosensitizer.14 We also selected a green solvent, ethyl acetate, as the operating solvent as it had already proven successful in photocatalysis with our gold complexes.13 Under these initial conditions, some conversion was achieved and the different product isomers (diastereomers and regioisomers of **1**) were observed by 1H NMR spectroscopy (Table 1, entry 1). Increasing the catalyst loading to 3 mol% leads to improved conversion, but still the reaction did not reach completion (Table 1, entry 2). A solvent screen revealed that the green solvent, 2-methyltetrahydrofuran (MeTHF), was also an option but led to lower conversion (Table 1, entry 3). Interestingly, the use of acetonitrile as reaction solvent leads to no conversion (Table 1, entry 4). In our previous study dealing with indoles and diallyl ethers,13b solvent effects proved minor when our gold photocatalysts were used. The Schindler group did mention the existence of a solvent effect when using iridium photocatalysts.14 Similarly, it appears that moving away from the use of ethyl acetate to other solvent that have already proven themselves in EnT reactions, leads to poorer results or even substrate degradation (Table 1, entries 2-4).

Table 1. Conditions screening for the [2+2]-cycloaddition of oxime O1 and 1-octene (A1).



|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Entry | NHC | Catalyst loading (mol%) | Alkene (eq.) | Solvent | GC conversion (%) |
| 1 | SIPr | 1 | 1.5 | EtOAc | 38 |
| 2 | SIPr | 3 | 1.5 | EtOAc | 67 |
| 3 | SIPr | 3 | 1.5 | MeTHF | 20 |
| 4 | SIPr | 3 | 1.5 | MeCN | 0 |
| 5 | SIMes | 3 | 1.5 | EtOAc | 57 |
| 6 | IPr | 3 | 1.5 | EtOAc | 54 |
| 7 | IMes | 3 | 1.5 | EtOAc | 64 |
| 8 | IPr\* | 3 | 1.5 | EtOAc | 55 |
| 9 | IAd | 3 | 1.5 | EtOAc | 23 |
| 10 | SIPr | 3 | 1 | EtOAc | 76 |
| 11 | SIPr | 3 | 2 | EtOAc | >99 |
| 12 | SIPr | 3 | 3 | EtOAc | >99 |
| 13 | SIPr | 1 | 3 | EtOAc | 90 |
| 14 | IPr | 1 | 3 | EtOAc | 90 |
| 15 | SIPr | 1 | 5 | EtOAc | >99 |
| 16 | SIPr | 0.3 | 10 | EtOAc | 91 |
| 17a | SIPr | 1 | 5 | EtOAc | >99 |

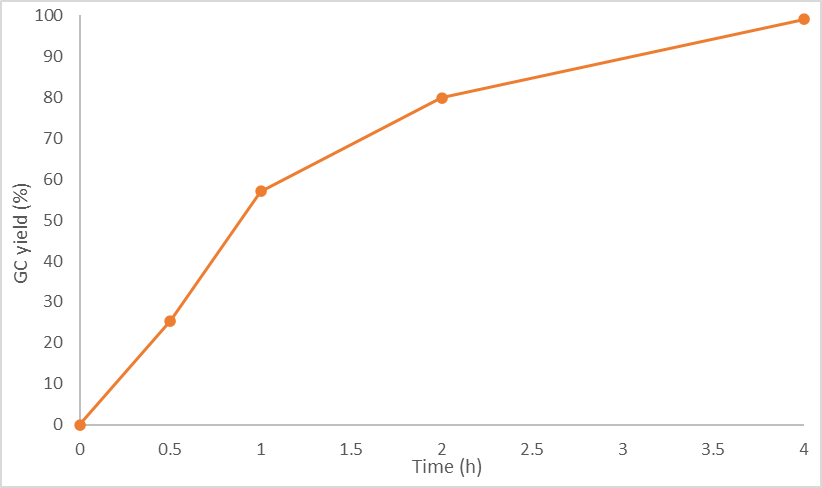
aReaction was conducted for 4h. GC conversions are determined using a previously established calibration curve for **O1**, with dodecane as internal standard.

Ethyl acetate being inexpensive and eco-friendly, a further optimization was carried out with this solvent. A next step was to compare the activity of different gold N-carbazolyl complexes within this family. By screening the most common NHCs, it was shown that aromatic substituted NHCs all lead to good conversions (Table 1, entries 2 and 5-8), with SIPr initially leading to the highest conversion (entry 2). On the other hand, the alkyl substituted IAd complex leads to significantly lower conversions (entry 9).

Since the Schindler group was able to sensitize oxime **O1** with an iridium photocatalyst with a lower ET value (60 kcal/mol compared with the 66 kcal/mol of [Au(cbz)(SIPr)]),14 the possibility of the energy transfer being the limiting step was rapidly ruled out. This left the diffusion of reactants as the main working axis for optimization. To confirm this working hypothesis, the effects of the use of excess alkene were examined. Satisfyingly moving to 2 or 3 equivalents of alkene lead to an immediate increase in conversion (Table 1, entries 11-12). The importance of an excess of alkene allowed us to reconsider the catalyst loading. Employing 1 mol% of gold catalyst and 3 equivalents of alkene leads to an excellent conversion (entry 13), and full conversion is rapidly reached with 5 equivalents of the alkene (entry 14). Further decrease of the catalyst loading to 0.3 mol% permitted to reach a 91% conversion by increasing the alkene amount to 10 equivalents (entry 16). This translates into the [Au(cbz)(SIPr)] photocatalyst being able to reach turnover numbers of at least 300 under these early conditions. To proceed with the optimization, the conversion as a function of time was examined. Reaction profiling was conducted and showed that reaction completion was reached after 4 h (Figure 1). All reactions from this point on were carried out with a reaction time of 4 hours.

**Figure 1.** Product formation for the photocyclization of oxime **O1** and 1-octene.a





aReaction conditions: **O1** (0.1 mmol), 1-octene (0.5 mmol), [Au(cbz)(SIPr)] (0.001 mmol), EtOAc (1 mL), LED (365 nm), room temperature. GC Yield determined using a calibration curve for **1**, with dodecane as internal standard.

We initially selected 365 nm as the operating wavelength that proved the most effective in our previous work with [Au(cbz)(NHC)] complexes.13, To show that this wavelength remains optimal for oximes sensitization, we tested reactions with other LED lamps. With the conditions presented in Figure 1, 380 nm irradiation only led to 15% GC yield, while irradiation at 405 nm led to no product. This is in line with the spectroscopic behaviour of the gold photocatalysts. With optimized conditions in hand, the versatility of the procedure towards various alkenes and oximes leading to a wide range of azetidines was next explored (Scheme 2).

Scheme 2. Scope of synthesized azetidines. GC conversions are given with isolated yields in parentheses. The structures within frames are previously unreported products.



The reaction outcome proved to be greatly influenced by the oxime substituents. Especially, the presence of an ethoxide group instead of the dimethyl substituent dramatically affects the conversion (products **2** and **14**). On the other hand, almost all alkenes lead to results close to near full conversion with excellent isolated yields when combined with oxime **O1**. Clearly, the procedure is very tolerant towards functions on the alkyl chain (products **7** and **8**), ethers (product **10**), and substituted alkenes (product **11**). In addition, this method also allows access to spirocyclic compounds (products **13** to **15**). Gratifyingly, the procedure is also compatible with the intramolecular version of the transformation (products **16** and **17**).

In parallel to the optimization, control experiments were performed to confirm the role of several elements of the procedure (Scheme 3). As expected, no reaction occurs without photocatalyst or in the absence of light (Scheme 2, reaction **a** and **b**), which highlights that the substrate cannot be directly sensitized by 365 nm irradiation (confirmed by the absorption spectra of the different oximes, ESI Figure S2); and the need for light to power the reaction.

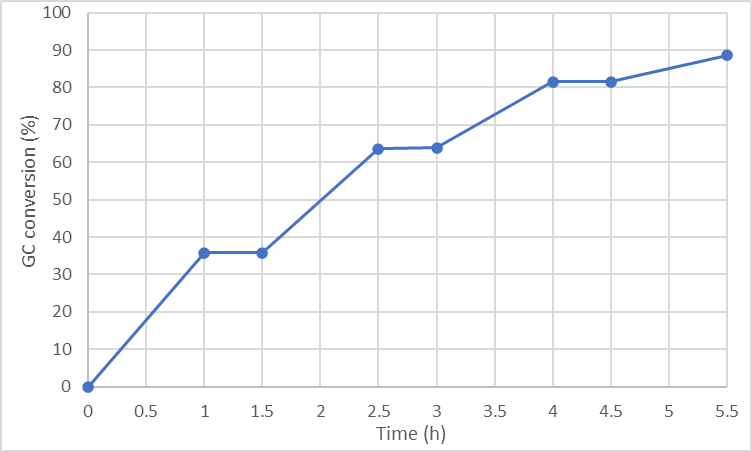
Reaction **c** of Scheme 3 shows that a conjugated unsaturation to the C=N double bond is necessary to lower the triplet state for the oxime to be sensitized. Finally, reaction **d** highlights how an acyclic oxime preferentially undergoes *Z*-*E* isomerization when activated to its triplet state, which is why cyclic analogues are needed to produce selective [2+2]-cycloaddition.

Scheme 3. Control experiments for the [2+2]-cycloaddition of oximes and alkenes: a) without photocatalyst; b) without light; c) without a conjugated group and d) with an acyclic oxime.



To rule out the possibility that light only serves in an activation step, and that the reaction might operate via a self-propagated chain mechanism without further need for light, an ON-OFF experiment was carried out (Figure 2). Stoppage of the reaction is observed when the light source is turned off and the reaction restarts when the light source is turned on again. Light is therefore clearly an integral part of the catalytic cycle.

**Figure 2.** GC conversion of the cycloaddition of oxime **O1** and 1-octene as a function of time. Conditions: **O1** (0.3 mmol), **A1** (0.9 mmol), [Au(cbz)(SIPr)] (0.009 mmol), EtOAc (3 mL), 365 nm, room temperature. Light is off between 1-1.5 h, 2.5-3 h, and 4-4.5 h. GC conversions are determined using a previously established calibration curve for **O1**, with dodecane as internal standard.



To support an operating triplet-triplet energy transfer (TTEnT) mechanism, several mechanistic experiments were performed. As previously reported,13b the cyclic voltammogram of [Au(cbz)(SIPr)] contains only irreversible redox events, which rule out the possibility of electron transfer mechanism under catalytic conditions. As previously mentioned, only the gold sensitizer absorbs light at the irradiation wavelength and the reaction requires light to proceed. These observations support the involvement of energy transfer. Next, we performed quenching studies with both oxime **O1** and octene **A1** (ESI figures S3 and S4). The photocatalyst phosphorescence was significantly quenched in the presence of oxime **O1** and proved dependent on the concentration of the latter. In contrast, the presence of octene did not affect the intensity of the phosphorescence. The Stern-Volmer plot for quenching sensitizer by **O1** is linear with large Stern-Volmer constant KV = 3.15•105 L•mol-1 (ESI figure S5). Having in hand this result and previously reported lifetime of the excited state of [Au(cbz)(SIPr)],13a the quenching rate constant was determined to be Kq = 1.18•109 M-1•s-1. Such a large value confirms that the triplet-triplet energy transfer between the excited sensitizer and oxime proceed near the diffusion limit, which is an indicator of the highly exergonic nature of the EnT. As was previously mentioned by Cismesia and Yoon, the ON-OFF experiment is often unreliable for probing a reaction chain mechanism.15 Therefore, to rule out this possibility, we determined the quantum yield of the reaction, which is a much more reliable method. The quantum yield of the reaction was determined to be 0.21 (see ESI), which is in-line with other studies.15 Based on our mechanistic experiments, we propose that a triplet-triplet energy transfer mechanism is at play in the present transformation and is mediated by gold. The same reaction mechanism has previously been proposed by Schindler *et al.* using an iridium-based sensitizer.14

The gold photocatalysts offer access to a wide range of functionalized azetidines and are compatible with a variety of substrates. The tolerance towards a wide scope of alkenes is especially noteworthy. The use of a green solvent is clearly an advantage for future syntheses of azetidines building blocks. The outcome of the present study clearly suggests the significant potential of gold complexes as surrogates for state-of-the-art iridium-based systems. As the gold complexes among which [Au(cbz)(IPr)] (**PhotAucat 1**) and [Au(cbz)(SIPr)](**PhotAucat 2**)12 perform in an outstanding manner in this [2+2] reaction, we feel these should be considered as alternatives to iridium for energy transfer mediated transformations. Studies along these lines are presently being explored in our laboratories.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information, containing additional experiments, procedure for the synthesis of substrates and product, and characterization of non-commercial chemicals, is available free of charge at

AUTHOR INFORMATION

Corresponding Author

\* Steven P. Nolan: Department of Chemistry and Centre for Sustainable Chemistry, Ghent University, Campus Sterre, Building S-3, Krijgslaan 281, 9000 Ghent, Belgium.

E-mail: steven.nolan@ugent.be.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

We gratefully acknowledge support from the Special Research Fund (BOF) of Ghent University (project grants to SPN), the iBOF project C3 and The Research Foundation – Flanders (FWO)(G0A6823N).

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ACKNOWLEDGMENT

Dr. Adrian Gomez-Suarez and his group (Universität Wuppertal) are gratefully acknowledged for initial testing of our gold catalysts. We thank Nikolaos Tzouras (UGent) for the synthesis of gold complexes. Ms. Emily Wearing and Prof. Corinna Schindler (University of Michigan) are thanked for helpful discussions.

ABBREVIATIONS

SET, Single Electron Transfer; EnT, Energy Transfer; ET, triplet state Energy; NHC, N-Heterocyclic Carbene; NMR, Nuclear Magnetic Resonance; cbz, carbazolyl; SIPr, N,N-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene; SIMes, N,N-bis(2,4,6-trimethyl)imidazolin-2-ylidene; IPr, N,N-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; IMes, N,N-bis(2,4,6-trimethyl)imidazol-2-ylidene; IPr\*, N,N-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazolidin-2-ylidene; IAd, N,N-bis(adamantyl)imidazol-2-ylidene.

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