Letter

Concurrent Biocatalytic Oxidation and C–C Bond Formation via Gold Catalysis: One-Pot Alkynylation of N-Alkyl Tetrahydroisoquinolines

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Concurrent Biocatalytic Oxidation and C–C Bond Formation via Gold Catalysis: One-Pot Alkynylation of *N*-Alkyl Tetrahydroisoquinolines

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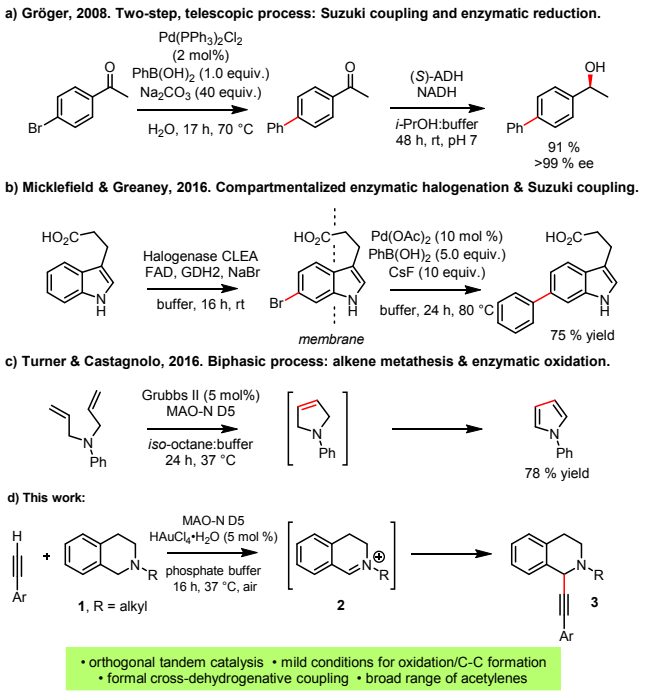
ABSTRACT: A cross-dehydrogenative coupling process has been developed involving the enzymatic oxidation of tetrahydroisoquinolines (THIQ) together with gold-catalyzed C–C bond-formation. The transformation demonstrates the compatibility of gold mediated chemocatalysis and monoamine oxidase biocatalysis which act co-operatively in one vessel. A range of *N*-alkyl THIQs were functionalized in this manner at C-(1) position in high yields.

KEYWORDS biocatalysis, gold catalysis, concurrent catalysis, chemobiocatalytic, one-pot process, cross-dehydrogenative coupling, green chemistry, process intensification

The development of one-pot chemoenzymatic processes is a very active area of research, creating new vistas to safer, shorter and more efficient routes[1–3]. The combination of chemo- and biocatalysis has great potential for advances in process intensification under Green Chemistry principles, taking inspiration from Nature[4] where chemical components can fulfil their tasks sequentially with enzymes as in a natural biosynthetic cascade.[5] In this way, not only reduction of production costs, waste generation and improvement of overall efficiency is achieved but also implementation of new technologies relying on clean reactions and fewer purification steps becomes feasible (*e.g.* flow chemistry).[6,7] Biocatalysts have proven extremely valuable in chemical production due to the exquisite efficiency and selectivity with which they catalyze reactions. The tolerance of biocatalysts to organic solvents and high substrate concentrations has been significantly improved through protein engineering,[8] setting the stage for new co-operative syntheses using concurrent chemobiocatalytic processes.

One of the strengths of chemocatalysis that is particularly attractive to combine with biocatalysis is the ability of chemocatalysts to catalyze carbon–carbon bond formation. For example, Suzuki cross-coupling of an aryl halide has been used by Gröger and-co-workers in a one-pot, two-step process in conjunction with ketoreductase. [Scheme 1., a)].[9] The Suzuki reaction has also been coupled with regioselective, enzymatic halogenation as shown by Micklefield and Greaney [Scheme 1., b)],[10] who used membrane compartmentalization to effect an efficient halogenation-coupling cascade of heteroarenes under aqueous conditions. Interestingly, Grubbs catalyst could be engaged in the alkene metathesis reaction leading to an intermediate pyrroline in a biphasic system where MAO-N oxidative activity allowed for the synthesis of *N*-phenyl pyrroles [Scheme 1., c)].[11,12] We were interested in expanding the scope of transition metals (TMs) that could be harnessed in chemobiocatalytic synthesis to catalyze the formation of carbon–carbon bonds under biological conditions (*i.e.* buffered aqueous system, aerobic atmosphere). Gold catalysis has witnessed extensive growth in recent years, particularly in respect to alkyne functionalization under mild conditions, creating new transformations for base chemical building blocks.[13,14] One of the main features of gold catalysis is that the oxidation state of the metal during the catalytic cycle often remains unchanged.[15] We reasoned that such redox neutrality of gold catalysts could be harnessed to address the issue of incompatibility of a metal catalyst and the enzymatic co-factor (*e.g.* FAD) which impacts on the design of concurrent chemobiocatalytic processes.

Scheme 1. Current State-of-the-Art Methods for One-Pot, Chemoenzymatic Processes Involving C-C Bond Formation.



a)-c) Chronological state-of-the-art examples combining chemo- and biocatalysis in one pot. d) Integrated chemobiocatalytic process without compartmentalization.

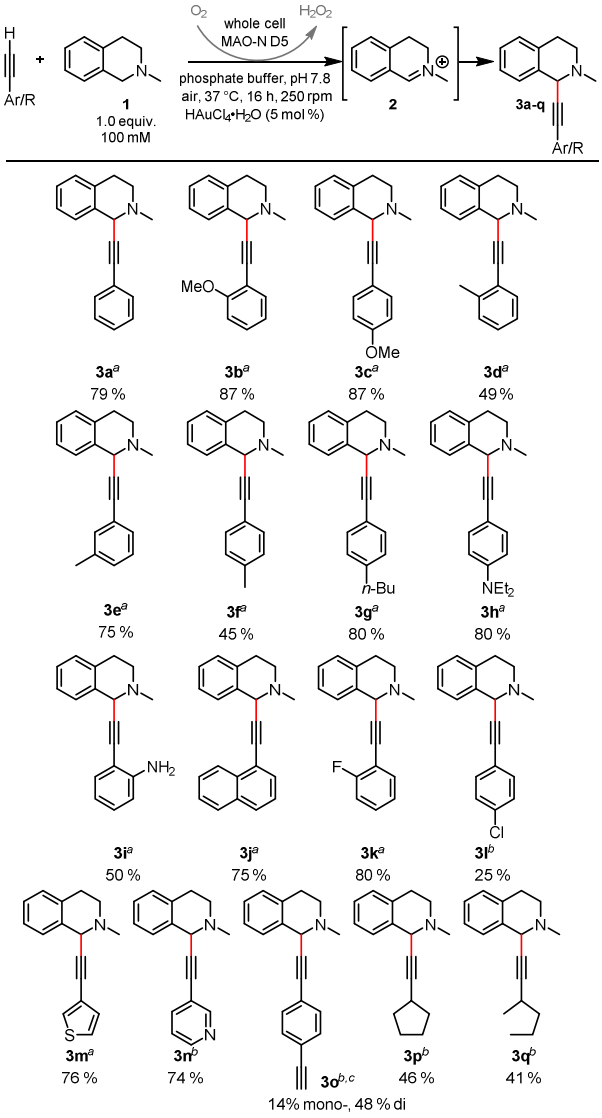
Pioneering work from the Toste and Raymond groups demonstrated combined gold catalysis for C–O bond formation triggered by an enzymatic hydrolysis step,[16] and the groups of González-Sabín and Mihovilovic have recently demonstrated gold-catalyzed alkyne hydration in conjugation with subsequent enzymatic reduction of a carbonyl group.[17,18] Sieber and co-workers have described a compartmentalized system for heterogeneous gold-catalyzed oxidation followed by enzymatic dehydration.[19] The combination of Au-catalyzed C–C bond formation, however, has yet to be explored in chemobiocatalytic transformations.[20]

Our proposed reaction system is shown in Scheme 1., d), and is inspired by the A^3 reaction from Li and co-workers who demonstrated gold-catalyzed addition of alkynes to iminium species in water at reflux.[21, 22] Oxidation of the isoquinoline **1** using the MAO-N class of oxygen-dependent enzymes[23-25] would form an iminium ion **2** that could potentially undergo electrophilic addition with a gold acetylide. While merging TM catalysis with biocatalysis in water is frequently challenging, some features of the proposed chemistry provided grounds for optimism, namely: i) the hydration of unfunctionalized alkynes does not occur where water is a dominant solvent,[26] ii) C-C bond formation through the A^3 reaction manifold is known to take place at room temperature[22] and iii) late stage TMs are reported to have diminished susceptibility to oxygen in aqueous medium in contrast to organic solvents.[27] We discovered that gold acetylide addition to iminium ions occurred with quantitative yield at room temperature in potassium phosphate buffered solution (0.2 M substrate concentration (see SI, Section 5, for discussion and optimization). With a view to achieving concurrent catalysis with a biocatalyst, it is critical to consider that enzymes often operate at lower substrate concentration. Therefore, we carefully optimized conditions for two separate processes: i) enzymatic oxidation of **1** and ii) organometallic addition to **2** and identified 0.1 M as optimum substrate concentration (see SI, Table S1.). Pleasingly, we were able to integrate these two transformations into a one-pot process where both catalysts operate in aqueous phase without mutual deactivation delivering product **3a** in excellent 79 % yield (Table 1.). To the best of our knowledge, this is the first example where gold catalysis is working simultaneously with an operational biocatalyst.

Having developed a simple procedure for the chemobiocatalytic, one-pot assembly of α-disubstituted *N*-Me-THIQ we next explored the substrate scope of this transformation. As illustrated in Table 1, substitution around the phenyl ring of arylacetylenes was well tolerated. In this fashion, electron-rich alkoxy- and alkylethynylbenzenes were coupled with excellent yields giving products 3a-g. Similarly, arylacetylenes decorated with an amino substituent (3h and 3i) coupled with good yields, including the unprotected *ortho*-aniline (3i) which coupled with 50 % yield without any formation of indole in the presence of gold catalyst. 1-Naphthyl- (3j) as well as heteroaromatic thiophenylacetylene (3m) coupled with good yields too. Typically, *para*- substitution with electron-withdrawing group was not well tolerated resulting in a low yield for *para*-chloroethynylbenzene (3l) and *para*-bromoethynylbenzene (not shown). At this point, we decided to develop two complementary methods A & B (see annotation under Table 1). Although most products were obtained under Method A, some exceptions, such as 3l was only achieved by performing the reaction in a sequential process whereby enzymatic oxidation occurred at 37 °C with the organogold addition step at 60 °C (Method B). In such case, formation of 2 was confirmed by NMR and TLC, suggesting the attenuated nucleophilicity of gold acetylides with *para*-EWGs on the aryl moiety. Interestingly, some electron-deficient ethynylbenzenes reacted with good yields. 2-fluoroethynylbenzene participated in a one-step reaction giving product 3k in 80 % yield. Simultaneously, 3-pyridylethynylbenzene afforded 3n in 74 % yield, whereas 2-pyridylethynyl-benzene resulted in traces of product (not shown). 1,4-Diethynylbenzene added effectively to the THIQ nucleus with 48 % obtained from addition at either end of diacetylene and 14 % of mono addition with facile separation of two products through flash chromatography. Alkylacetylenes led to 3p and 3q in moderate yields. Having established that a range of acetylenes can participate in

the reaction we progressed to probing the scope of the enzymatic oxidation of various *N*-substituted THIQs.

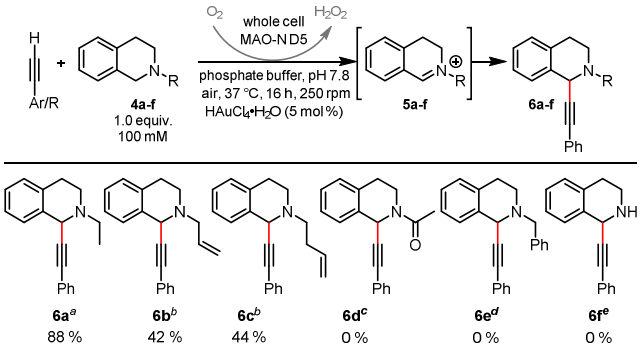
Table 1. Chemoenzymatic alkynylation of *N*-Methyl Tetrahydroisoquinolines.



[a]*Method A*: MAO-N (0.2 g, w/w), 1a (1 equiv., 0.2 mmol), acetylene (2 equiv., 0.4 mmol), $H[AuCl]_4 \cdot H_2O$ (0.05 equiv, 0.01 mmol), KPi, 16 h, 37 °C, air. [b]*Method B*: MAO-N (0.2 g, w/w), 1a (1 equiv., 0.2 mmol), KPi, 16 h, 37 °C, air, then: acetylene (2 equiv., 0.4 mmol), $H[AuCl]_4 \cdot H_2O$ (0.05 equiv, 0.01 mmol), KPi, 16 h, 60 °C, air. [c]mono- and diaddition products isolated separately.

Although MAO-N has been subjected to extensive protein engineering and the chemical space of its active site has been largely explored,[28] the current project served as a useful tool to identify new substrates for the D5 variant. A panel of THIQs was prepared with varied substitution on nitrogen (Table 2.). We were encouraged to see that *N*-Et-THIQ could be functionalized by the addition of phenylacetylene to furnish 6a in excellent 88 % yield. Nevertheless, allyl and homoallyl substituents resulted in moderate yields of 6b and 6c. Acyl- and benzyl-protected THIQs did not undergo biocatalytic oxidation due to electronic (6d) and steric effects (6e) affecting the oxidation. Furthermore, unprotected THIQ did not yield any addition product, even after the adjustment of pH with hydrochloric acid (adjusted to pH = 5) for the protonation of imine. However, this remains in accordance with literature precedence which suggests that only iminium ions arising from oxidation α- to tertiary amines are electrophilic enough for gold acetylide addition in the A^3 reaction.[22]

Table 2. Exploration of Nitrogen Substitution in Chemoenzymatic alkynylation of *N*-Substituted Tetrahydroisoquinolines.



[a]*Method A*: MAO-N (0.2 g, w/w), **1a** (1 equiv., 0.2 mmol), acetylene (2 equiv., 0.4 mmol), $H[AuCl]_4 \cdot H_2O$ (0.05 equiv, 0.01 mmol), KPi, 16 h, 37 °C, air. [b]*Method B*: MAO-N (0.2 g, w/w), **1a** (1 equiv., 0.2 mmol), KPi, 16 h, 37 °C, air, then: acetylene (2 equiv., 0.4 mmol), $H[AuCl]_4 \cdot H_2O$ (0.05 equiv, 0.01 mmol), KPi, 16 h, 60 °C, air. [c]recovered starting material in 83 %. [d]recovered starting material in 64 % [e]pH adjusted to 5 after enzymatic oxidation.

In conclusion, we have developed a chemobiocatalytic cross-dehydrogenative coupling process which combines benign biocatalytic oxidation of *N*-substituted THIQs and a gold-catalyzed alkynylation. This process exemplifies the complementarity of TM-catalysis for C–C bond formation integrated with biological catalysts for functional group manipulation. The process proceeds under mild conditions in aqueous media, and has been exemplified across a range of acetylene and THIQ coupling partners. Further investigations into Au / biocatalysis cascade chemistry are ongoing in our laboratories.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures and methods, substrate synthesis and isolated product characterization, and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS

TM, transition metal; MAO-N, monoamine oxidase type N; THIQ, tetrahydroisoquinoline; TLC, thin layer chromatography.

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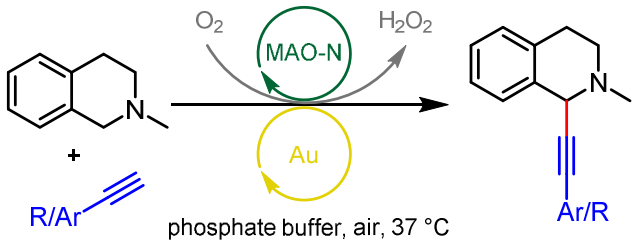

- *orthogonal tandem catalysis*
- *no compartmentalization*
- *mild conditions for oxidation/C-C formation*