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DOI:

[10.1021/acscatal.8b03169](https://doi.org/10.1021/acscatal.8b03169)

Document Version

Accepted author manuscript

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Citation for published version (APA):

Odachowski, M., Greaney, M. F., & Turner, N. J. (2018). Concurrent Biocatalytic Oxidation and C–C Bond Formation via Gold Catalysis: One-Pot Alkynylation of N-Alkyl Tetrahydroisoquinolines. *ACS Catalysis*, 8(11), 10032-10035. <https://doi.org/10.1021/acscatal.8b03169>

Published in:

ACS Catalysis

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

Marcin Odachowski^{†,‡}, Michael F. Greaney^{*,†} & Nicholas J. Turner^{*,‡}

[†]School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, United Kingdom.

[‡]School of Chemistry, University of Manchester, Manchester Institute of Biotechnology, 131 Princess Street, Manchester, M1 7DN, United Kingdom.

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

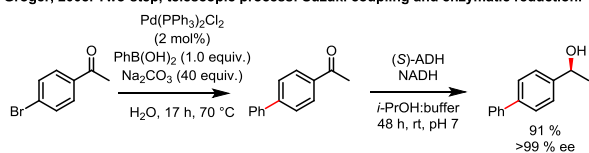
The development of one-pot chemoenzymatic processes is a very active area of research, creating new vistas to safer, shorter and more efficient routes^{1–3}. The combination of chemo- and biocatalysis has great potential for advances in process intensification under Green Chemistry principles, taking inspiration from Nature⁴ 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

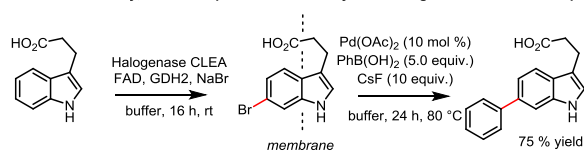
used membrane compartmentalization to effect an efficient halogenation-coupling cascade of heteroarenes under aqueous conditions. Interestingly, Grubbs catalyst could be engaged in the alkene metathesis reaction leading to an intermediate pyrroline in a biphasic system where MAO-N oxidative activity 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.

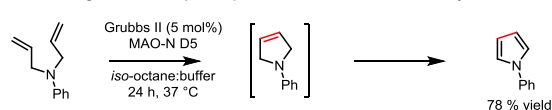
a) Gröger, 2008. Two-step, telescopic process: Suzuki coupling and enzymatic reduction.



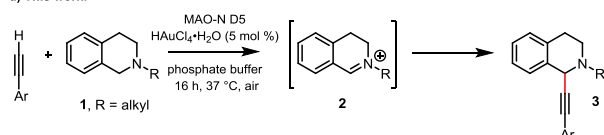
b) Micklefield & Greaney, 2016. Compartmentalized enzymatic halogenation & Suzuki coupling.



c) Turner & Castagnolo, 2016. Biphasic process: alkene metathesis & enzymatic oxidation.



d) This work:



- orthogonal tandem catalysis
- mild conditions for oxidation/C-C formation
- formal cross-dehydrogenative coupling
- broad range of acetylenes

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

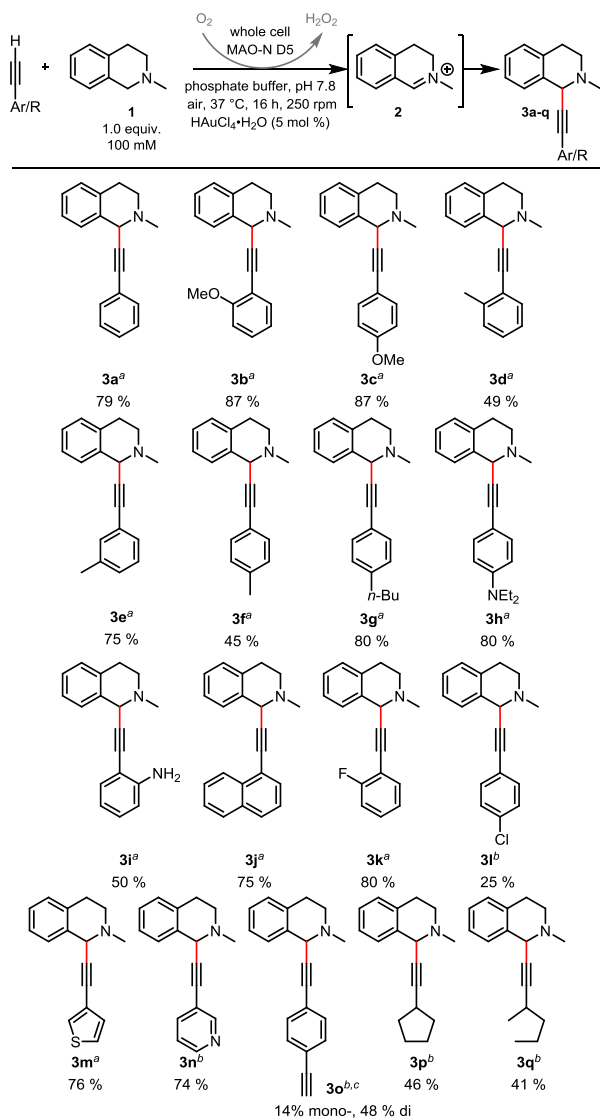
Our proposed reaction system is shown in Scheme 1, d), and is inspired by the A³ reaction from Li and co-workers who demonstrated gold-catalyzed addition of alkynes to iminium species in water at reflux.^{21, 22} Oxidation of the isoquinoline **1** using the MAO-N class of oxygen-dependent enzymes²³⁻²⁵ 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 A³ reaction manifold is known to take place at room temperature²² 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-pyridylethynylbenzene 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.

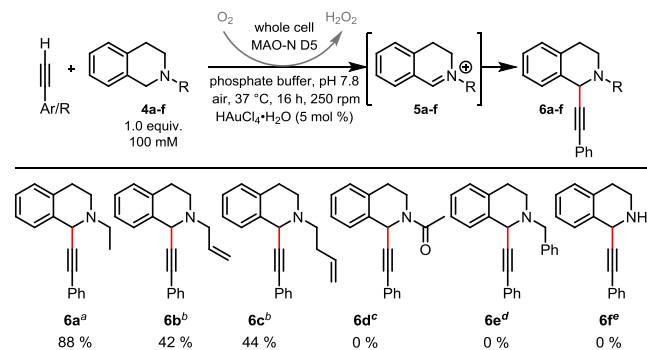


^aMethod A: MAO-N (0.2 g, w/w), **1a** (1 equiv., 0.2 mmol), acetylene (2 equiv., 0.4 mmol), H[AuCl₄·H₂O] (0.05 equiv, 0.01 mmol), KPi, 16 h, 37 °C, air. ^bMethod B: MAO-N (0.2 g, w/w), **1a** (1 equiv., 0.2 mmol), KPi, 16 h, 37 °C, air, then: acetylene (2 equiv., 0.4 mmol), H[AuCl₄·H₂O] (0.05 equiv, 0.01 mmol), KPi, 16 h, 60 °C, air. ^cmono- 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 A³ reaction.²²

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



^aMethod A: MAO-N (0.2 g, w/w), **1a** (1 equiv., 0.2 mmol), acetylene (2 equiv., 0.4 mmol), H[AuCl₄·H₂O] (0.05 equiv, 0.01 mmol), KPi, 16 h, 37 °C, air. ^bMethod 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[AuCl₄·H₂O] (0.05 equiv, 0.01 mmol), KPi, 16 h, 60 °C, air. ^crecovered starting material in 83 %. ^drecovered starting material in 64 % ^epH 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>.

AUTHOR INFORMATION

Corresponding Author

*E-mail for N.J.T.: Nicholas.Turner@manchester.ac.uk

*E-mail for M.F.G.: Michael.Greaney@manchester.ac.uk

ABBREVIATIONS

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

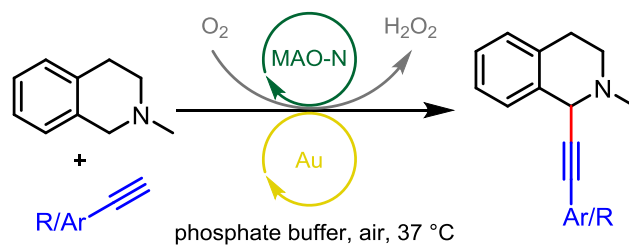
ACKNOWLEDGMENT

This work was supported by the Engineering and Physical Sciences Research Council (EPSRC) through grant EP/M013219/1.

REFERENCES

- Gröger, H.; Hummel, W. Combining the “Two Worlds” of Chemocatalysis and Biocatalysis towards Multi-Step One-Pot Processes in Aqueous Media. *Curr. Opin. Chem. Biol.* **2014**, *19*, 171–179.
- Wang, Y.; Zhao, H. Tandem Reactions Combining Biocatalysts and Chemical Catalysts for Asymmetric Synthesis. *Catalysts* **2016**, *6*, 194.
- Rudroff, F.; Mihovilovic, M. D.; Gröger, H.; Snajdrova, R.; Iding, H.; Bornscheuer, U. T. Opportunities and Challenges for combining chemo- and biocatalysis. *Nat. Catal.* **2018**, *1*, 12–22.
- Anastas, P.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010**, *39*, 301–312.
- Bruggink, A.; Schoevaart, R.; Kieboom, T. Concepts of Nature in Organic Synthesis: Cascade Catalysis and Multistep Conversions in Concert. *Org. Process Res. Dev.* **2003**, *7*, 622–640.
- Koenig, S. G.; Sneddon, H. F. Recent Advances in Flow Chemistry in the Pharmaceutical Industry. *Green Chem.* **2017**, *19*, 1418–1419.
- Planchestainer, M.; Contente, M. L.; Cassidy, J.; Molinari, F.; Tamborini, L.; Paradisi, F. Continuous Flow Biocatalysis: Production and in-Line Purification of Amines by Immobilised Transaminase from *Halomonas Elongata*. *Green Chem.* **2017**, *19*, 372–375.
- Bornscheuer, U. T.; Huisman, G. W.; Kazlauskas, R. J.; Lutz, S.; Moore, J. C.; Robins, K. Engineering the Third Wave of Biocatalysis. *Nature* **2012**, *485*, 185–194.
- Burda, E.; Hummel, W.; Gröger, H. Modular Chemoenzymatic One-Pot Syntheses in Aqueous Media: Combination of a Palladium-Catalyzed Cross-Coupling with an Asymmetric Biotransformation. *Angew. Chem. Int. Ed.* **2008**, *47*, 9551–9554.
- Latham, J.; Henry, J. M.; Sharif, H. H.; Menon, B. R. K.; Shepherd, S. A.; Greaney, M. F.; Micklefield, J. Integrated Catalysis Opens New Arylation Pathways via Regiodivergent Enzymatic C-H Activation. *Nat. Commun.* **2016**, *7*, 11873.
- Scalacci, N.; Black, G. W.; Mattedi, G.; Brown, N. L.; Turner, N. J.; Castagnolo, D. Unveiling the Biocatalytic Aromatizing Activity of Monoamine Oxidases MAO-N and 6-HDNO: Development of Chemoenzymatic Cascades for the Synthesis of Pyrroles. *ACS Catal.* **2017**, *7*, 1295–1300.
- (a) Tenbrink, K.; Seßler, M.; Schatz, J.; Gröger, H. Combination of Olefin Metathesis and Enzymatic Ester Hydrolysis in Aqueous Media in a One-Pot Synthesis. *Adv. Synth. Catal.* **2011**, *353*, 2363–2367. (b) Denard, C. A.; Huang, H.; Bartlett, M. J.; Lu, L.; Tan, Y.; Zhao, H.; Hartwig, J. F. Cooperative Tandem Catalysis by an Organometallic Complex and a Metalloenzyme. *Angew. Chem. Int. Ed.* **2014**, *53*, 465–469.
- Hashmi, A. S. K. Gold-Catalyzed Organic Reactions. *Top. Organomet. Chem.* **2013**, *44*, 143–164.
- Dorel, R.; Echavarren, A. M. Gold(I)-Catalyzed Activation of Alkynes for the Construction of Molecular Complexity. *Chem. Rev.* **2015**, *115*, 9028–9072.
- Boorman, T. C.; Larrosa, I. Gold-Mediated C–H Bond Functionalisation. *Chem. Soc. Rev.* **2011**, *40*, 1910–1925.
- Wang, Z. J.; Clary, K. N.; Bergman, R. G.; Raymond, K. N.; Toste, F. D. Enzymatic and Transition Metal Catalysis. *Nat. Chem.* **2013**, *5*, 100–103.
- Schaaf, P.; Gojic, V.; Bayer, T.; Rudroff, F.; Schnürch, M.; Mihovilovic, M. D. Easy Access to Enantiopure (*S*)- and (*R*)-Aryl Alkyl Alcohols by a Combination of Gold(III)-Catalyzed Alkyne Hydration and Enzymatic Reduction. *ChemCatChem* **2018**, *10*, 920–924.
- Rodríguez-Álvarez, M. J.; Ríos-Lombardía, N.; Schumacher, S.; Pérez-Iglesias, D.; Morís, F.; Cadierno, V.; García-Álvarez, J.; González-Sabín, J. Combination of Metal-Catalyzed Cycloisomerizations and Biocatalysis in Aqueous Media: Asymmetric Construction of Chiral Alcohols, Lactones, and γ -Hydroxy-Carbonyl Compounds. *ACS Catal.* **2017**, *7*, 7753–7759.
- Sperl, J. M.; Carsten, J. M.; Guterl, J. -K.; Lommes, P.; Sieber, V. Reaction Design for the Compartmented Combination of Heterogeneous and Enzyme Catalysis. *ACS Catal.* **2016**, *6*, 6329–6334.
- Gold catalyzed C–C bond formation has been carried out in cells for in situ formation of fluorescent probes: (a) Do, J. H.; Kim, H. N.; Yoon, J.; Kim, J. S.; Kim, H.-J. A Rationally Designed Fluorescence Turn-On Probe for the Gold(III) Ion. *Org. Lett.* **2010**, *12*, 932–934. (b) Tsubokura, K.; Vong, K. K. H.; Pradipta, A. R.; Ogura, A.; Urano, S.; Tahara, T.; Nozaki, S.; Onoe, H.; Nakao, Y.; Sibgatullina, R.; Kurbangalieva, A.; Watanabe, Y.; Tanaka, K. In Vivo Gold Complex Catalysis within Live Mice. *Angew. Chem. Int. Ed.* **2017**, *56*, 3579–3584. (c) Pérez-López, A. M.; Rubio-Ruiz, B.; Sebastián, V.; Hamilton, L.; Adam, C.; Bray, T. L.; Irusta, S.; Brennan, P. M.; Lloyd-Jones, G. C.; Sieger, D.; Santamaria, J.; Unciti-Broceta, A. Gold-Triggered Uncaging Chemistry in Living Systems. *Angew. Chem. Int. Ed.* **2017**, *56*, 12548–12552. (d) Vidal, C.; Tomás-Gamasa, M.; Destito, P.; López, F.; Mascareñas, J. L. Concurrent and Orthogonal Gold(I) and Ruthenium(II) Catalysis inside Living Cells. *Nat. Commun.* **2018**, *9*, 1913.
- For cross dehydrogenative coupling of THIQ and alkynes using copper catalysis and tBuOOH, see: Li, Z.; Li, C. J. Catalytic Enantioselective Alkynylation of Prochiral sp³ C–H Bonds Adjacent to a Nitrogen Atom. *Org. Lett.* **2004**, *6*, 4997–4999.
- Wei, C.; Li, C. J. A Highly Efficient Three-Component Coupling of Aldehyde, Alkyne, and Amines via C–H Activation Catalyzed by Gold in Water. *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585.
- Alexeeva, M.; Enright, A.; Dawson, M. J.; Mahmoudian, M.; Turner, N. J. Deracemization of α -Methylbenzylamine Using an Enzyme Obtained by in Vitro Evolution. *Angew. Chem. Int. Ed.* **2002**, *41*, 3177–3180.
- Carr, R.; Alexeeva, M.; Dawson, M. J.; Gotor-Fernández, V.; Humphrey, C. E.; Turner, N. J. Directed Evolution of an Amine Oxidase for the Preparative Deracemisation of Cyclic Secondary Amines. *ChemBioChem* **2005**, *6*, 637–639.
- Dunsmore, C.; Carr, R.; Fleming, T.; Turner, N. A Chemo-Enzymatic Route to Enantiomerically Pure Cyclic Tertiary Amines. *J. Am. Chem. Soc.* **2006**, *128*, 2224–2225.
- Das, A. K.; Park, S.; Muthaiah, S.; Hong, S. H. Ligand- and Acid-Free Gold(I) Chloride Catalyzed Hydration of Terminal Alkynes. *Synlett* **2015**, *26*, 2517–2520.
- Li, C. J. Quasi-Nature Catalysis: Developing C–C Bond Formations Catalyzed by Late Transition Metals in Air and Water. *Acc. Chem. Res.* **2002**, *35*, 533–538.
- Ghislieri, D.; Green, A. P.; Pontini, M.; Willies, S. C.; Rowles, I.; Frank, A.; Grogan, G.; Turner, N. J. Engineering

an Enantioselective Amine Oxidase for the Synthesis of
Pharmaceutical Building Blocks and Alkaloid Natural
Products. *J. Am. Chem. Soc.* **2013**, *135*, 10863–10869.



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

