

Orthogonal Photo-Click Reactions for Multimaterial Fabrication: Selectivity, Kinetics, Crosstalk and Network Compatibility

Chemical orthogonality as an evidence problem in sequential and multimaterial photofabrication

Juan Segurola

3Dresyns by Resyner Technologies S.L.

© 2026 Juan Segurola. All Rights Reserved.

Correspondence: info@3Dresyns.com · www.3Dresyns.com

ER-419 · Engineering Review · Version 0.1 · 7 October 2026

Abstract

Orthogonal photo-click chemistry can assign different reactions to different chemical handles or optical triggers, creating routes to sequential functionalisation and multimaterial fabrication. The key engineering claim is selectivity: activating one reaction must not consume, deactivate or substantially perturb the handles reserved for another step. λ -Orthogonal photochemistry has enabled sequence-defined macromolecular synthesis, and tetrazole photoclick reactions have been used for spatial functionalisation of porous polymer networks. [1,2] Thiol-ene photochemistry additionally offers rapid, robust network formation and has demonstrated multimaterial printability across very broad mechanical-property ranges. [3] ER-419 focuses on chemical compatibility of orthogonal reaction pairs. In accordance with the corpus boundary, it does not take ownership of wavelength-addressed multimaterial patterning architecture itself. Qualification requires a selectivity matrix, kinetic separation, residual-handle analysis and proof that one reaction does not compromise the network state needed by the next.

Keywords: photoclick; orthogonal chemistry; tetrazole; thiol-ene; multimaterial fabrication; wavelength selectivity; crosstalk; network compatibility

1. Scope and ownership boundary

ER-419 addresses whether two or more photo-click chemistries can coexist in one fabrication workflow without destructive crosstalk. It excludes the broader architecture of wavelength-addressed multimaterial patterning owned by ER-197. The evidence question is chemical: which handles react, under what stimulus, with what selectivity, and what remains available for subsequent reaction.

2. Orthogonality is conditional, not absolute

Two reactions can be orthogonal under one solvent, wavelength and concentration but interfere under another. Photoinitiator absorption tails, radical transfer, oxygen, sensitizer triplets and reactive intermediates can create crosstalk. A credible orthogonality claim therefore includes negative controls in which each stimulus is applied while the non-target handle is present.

3. λ -Orthogonal photochemistry

Sequence-defined macromolecules have been synthesised using wavelength-selective photochemical reactions that can be addressed independently, providing a strong molecular demonstration of λ -orthogonality. [1] In fabrication, however, optical penetration and spectral overlap add new constraints. A reaction that is molecularly orthogonal may still be spatially non-orthogonal if one wavelength penetrates or scatters differently.

Table 1. Orthogonality evidence matrix

Stimulus sequence	Target reaction	Off-target requirement
Stimulus A	High conversion of handle A	Handle B retained within declared loss
Stimulus B	High conversion of handle B	Previously formed A-network remains stable
A then B	Both functions achieved	No unacceptable interface or bulk drift
B then A	Order robustness assessed	Order dependence explicitly bounded

4. Tetrazole photoclick chemistry

Tetrazole-based photoclick reactions generate reactive nitrile-imine intermediates that can add to suitable dipolarophiles. Hooker et al. used tetrazole photoclick chemistry for spatial functionalisation of emulsion-templated porous polymers, demonstrating post-network photopatterning of functionality. [2] This supports the concept of reserving chemical handles for a later photochemical step, but the porosity and diffusion environment differ from dense VPP networks.

5. Thiol-ene and compatible network formation

Thiol-ene reactions are widely used as rapid step-growth photoclick processes. Recent multimaterial 3D-printing work showed a thiol-ene platform spanning a broad mechanical range and compatible with several printing methods. [3] For an orthogonal workflow, thiol-ene cure must be tested for consumption or poisoning of the second reaction's handles, and vice versa.

6. Selectivity matrix and kinetic separation

The most useful representation is a matrix with reaction handles as rows and stimuli as columns. Each cell records target conversion, off-target conversion and uncertainty. Selectivity should be measured at the conversion relevant to manufacturing, not only at initial rate. A small off-target reaction repeated across many layers can accumulate into material drift.

7. Network compatibility after the first reaction

The first network-forming step changes diffusion, free volume and local polarity. A second click reaction that is efficient in solution may become transport-limited in a crosslinked network. The post-first-step concentration and accessibility of remaining handles should therefore be measured, especially for post-functionalisation or interfacial bonding.

8. Interfaces between differently reacted regions

Multimaterial fabrication creates interfaces where chemistries meet. Even when each bulk reaction is selective, the interface can contain unbalanced functionality, different shrinkage or incomplete interpenetration. Interfacial strength, chemical mapping and ageing are needed to show that orthogonality does not create a weak boundary.

Table 2. Crosstalk mechanisms

Mechanism	Observable	Discriminator
Spectral overlap	Off-target conversion under wrong wavelength	Action spectrum / conversion measurement
Radical or intermediate transfer	Reaction without optical overlap	Chemical controls and scavengers
Thermal/post-cure effect	First network changes during second exposure	Temperature and conversion tracking

9. Optical and thermal crosstalk

A second exposure can heat or further cure the first network even if the chemical handles are spectrally separated. Conversely, photoproducts from the first step can absorb the second wavelength. Temperature monitoring, spectral measurements before/after each step and conversion controls are therefore part of the selectivity evidence.

10. Qualification decision boundary

An orthogonal photo-click pair is qualified only when each intended reaction reaches its target conversion while off-target conversion remains below a declared limit, residual handles remain available where required, and interfaces retain function after ageing. Successful sequential exposure is not sufficient if the second step merely proceeds despite partial destruction of the first.

11. Evidence gaps

Many elegant orthogonal photochemistry demonstrations are molecular, thin-film or porous-material studies, and tetrazole photoclick chemistry itself has known side-reactivity that must be considered when orthogonality is claimed. [4] Dense, high-conversion VPP networks introduce stronger diffusion and optical constraints. Quantitative selectivity matrices, interfacial durability and accumulated crosstalk over many layers are rarely reported together.

12. Research priorities

Future work should report full spectral action data, off-target conversion, residual functionality and interfacial properties. Matched two-reaction systems should be tested in both exposure orders. For multimaterial printing, the same pair should be evaluated across realistic layer counts so small crosstalk terms can be accumulated and bounded.

13. Measurement architecture for chemical orthogonality

Orthogonality should be measured as a conversion matrix rather than inferred from reaction names. Spectroscopy can quantify each handle before and after stimulus A, stimulus B and both exposure orders. Chromatography or model reactions can identify side products when overlapping bands make network spectroscopy ambiguous. For printed specimens, the chemical matrix is paired with spatial mapping so a low average off-target conversion does not hide severe crosstalk at an interface or surface.

14. Cumulative crosstalk in layerwise fabrication

A reaction that consumes only a small fraction of the wrong handle per exposure can still create a large error after hundreds of layers or repeated functionalisation steps. Qualification should therefore consider cumulative dose and the number of exposures seen by each region. Accelerated crosstalk tests can deliberately overexpose a representative volume to the maximum expected history and then measure remaining functionality. This is more informative than a single-pulse selectivity demonstration.

15. Discriminating experiment set

The core experiment has four arms: A-only, B-only, A-then-B and B-then-A. Each arm uses the same initial formulation and reports target conversion, off-target conversion, residual handle concentration and final mechanical/interface properties. A fifth dark control captures spontaneous reaction. If the intended manufacturing sequence uses different materials on each side of an interface, the same matrix is repeated with the actual two-material contact geometry.

16. Engineering conclusion

Orthogonal photo-click chemistry is a powerful tool for sequential and multimaterial fabrication, but orthogonality is an experimentally bounded property of a particular pair of reactions, stimuli and network states. A convincing system demonstrates not only that both reactions can occur, but that each remains selective after the other has changed the material environment. Chemical selectivity, optical selectivity and interface integrity should therefore be reported as separate gates.

References

1. Konrad W, Fengler C, Putwa S, Barner-Kowollik C. Protection-Group-Free Synthesis of Sequence-Defined Macromolecules via Precision λ -Orthogonal Photochemistry. *Angewandte Chemie International Edition*. 2019;58(21):7133-7137. doi:10.1002/anie.201901933.

2. Hooker JP, Parker B, Wright E, Junkers T, Cameron NR. Photoresponsive Emulsion-Templated Porous Materials via Orthogonal Photoclick Chemistry. *ACS Applied Materials & Interfaces*. 2023;15(8):11141-11149. doi:10.1021/acsami.2c22546.
3. Li Z, Xu Z, Propst S, Page ZA, Chen Y, Majidi C, Mueller J. Ultrawide Property Range Thiol-Ene Photopolymers for 3D Printing. *Advanced Materials Technologies*. 2025;10(17):e00422. doi:10.1002/admt.202500422.
4. Li Z, Qian L, Li L, Bernhammer JC, Huynh HV, Lee JS, Yao SQ. Tetrazole Photoclick Chemistry: Reinvestigating Its Suitability as a Bioorthogonal Reaction and Potential Applications. *Angewandte Chemie International Edition*. 2016;55(6):2002-2006. doi:10.1002/anie.201508104.

Competing interests

The author is Founder, CEO and CTO of 3Dresyns by Resyner Technologies S.L.; ER-419 contains no comparative product recommendation.

Data availability

ER-419 is a literature-based engineering review; no new experimental dataset was generated.