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Chemical Engineering of Artificial Transcription Factors

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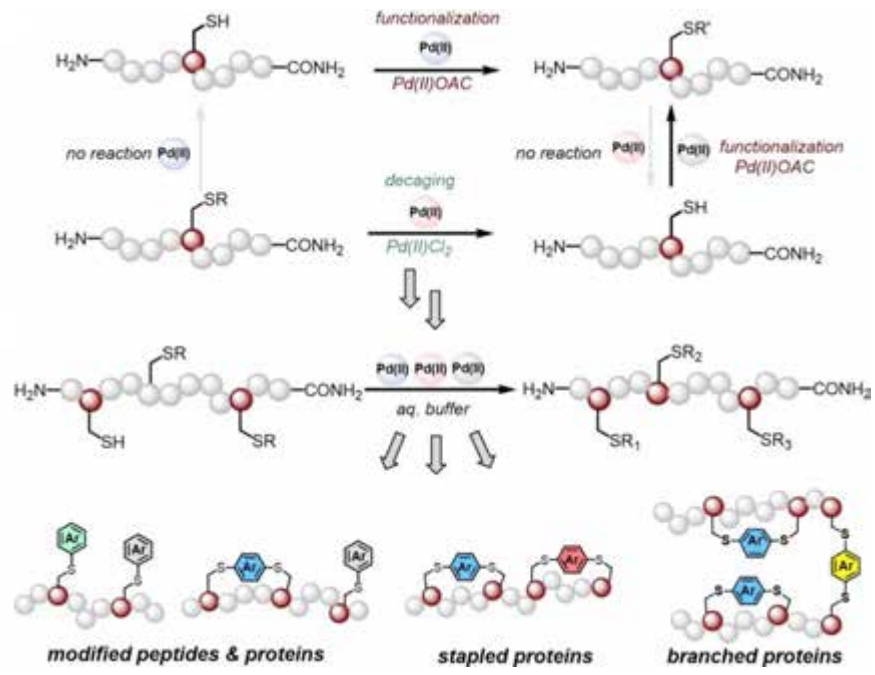
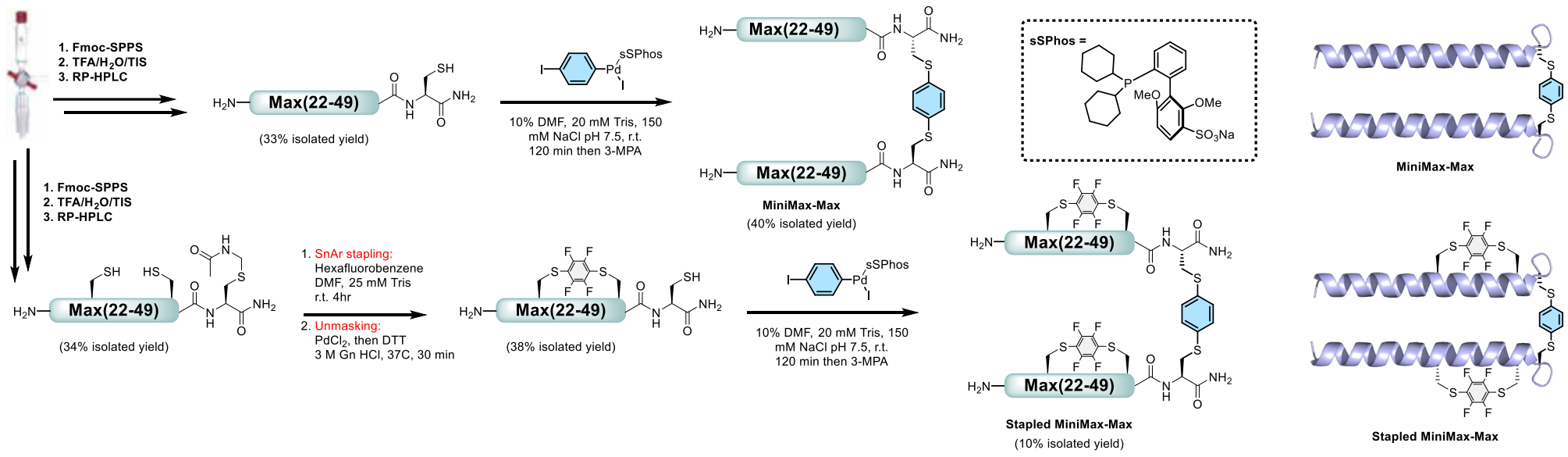
Abstract

The demand for site-selective functionalization strategies is crucial for generating precisely defined proteins and for advancing basic research and biomedical applications.[1,2] Cysteine-based reactions facilitate diverse transformations for modified proteins[3], yet achieving site selectivity or multiple transformations remains challenging. This study presents a site-selectivity methodology by manipulating C-S bond properties using palladium(II) complexes, enabling selective cysteine site editing in complex proteins.[4] Our orthogonal palladium(II) strategy allows rapid diversification of multiple cysteine sites, producing six covalently bound dimeric transcription factors (TFs) and six stapled linear analogs, on a milligram scale, with enhanced stability and potent DNA binding activity. This methodology facilitates protein editing and holds promise for engineering novel biomolecules, advancing biological understanding, and developing innovative therapeutics.

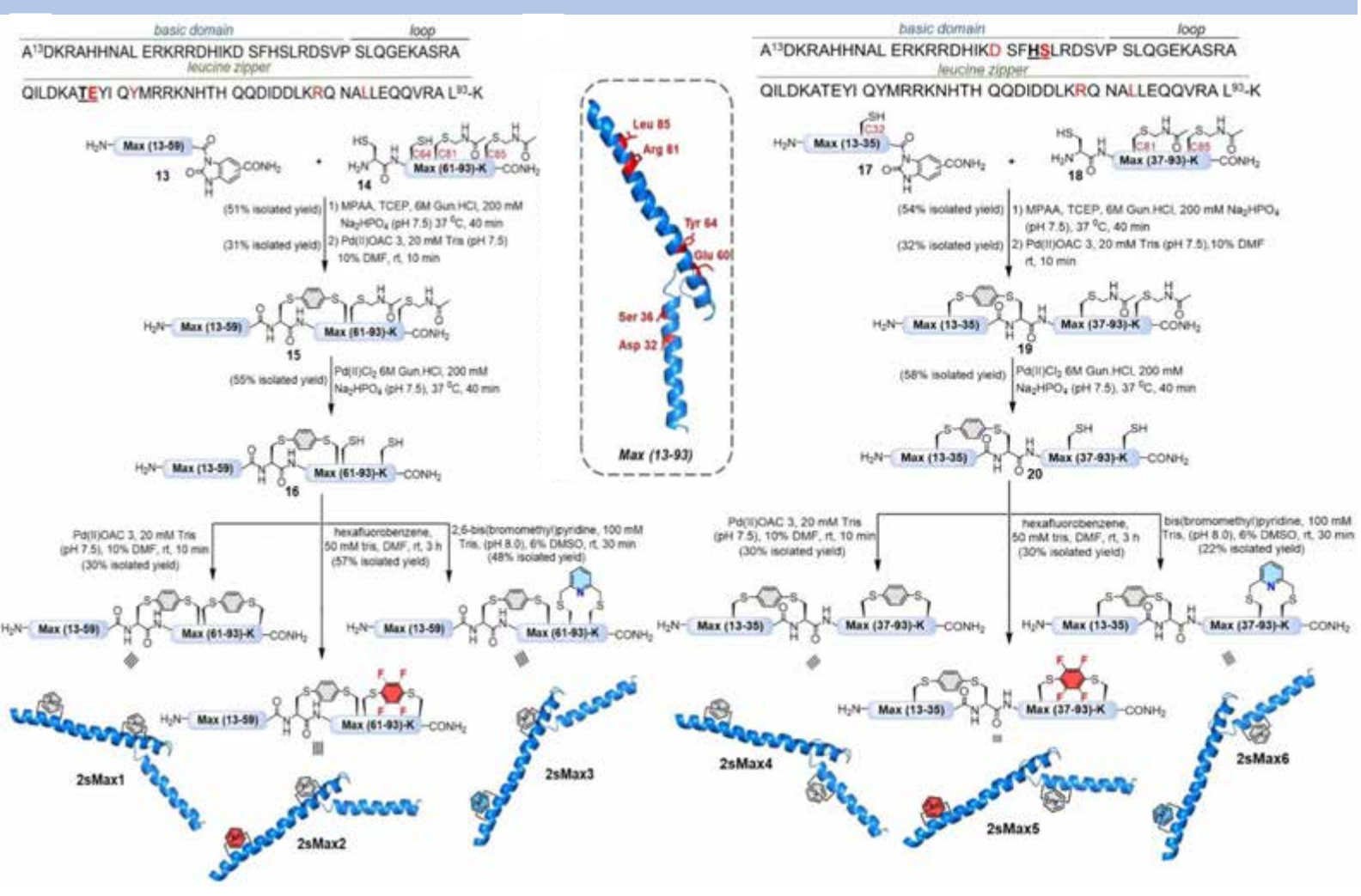
Selective Cys Modification via an Orthogonal Palladium(II) Strategy



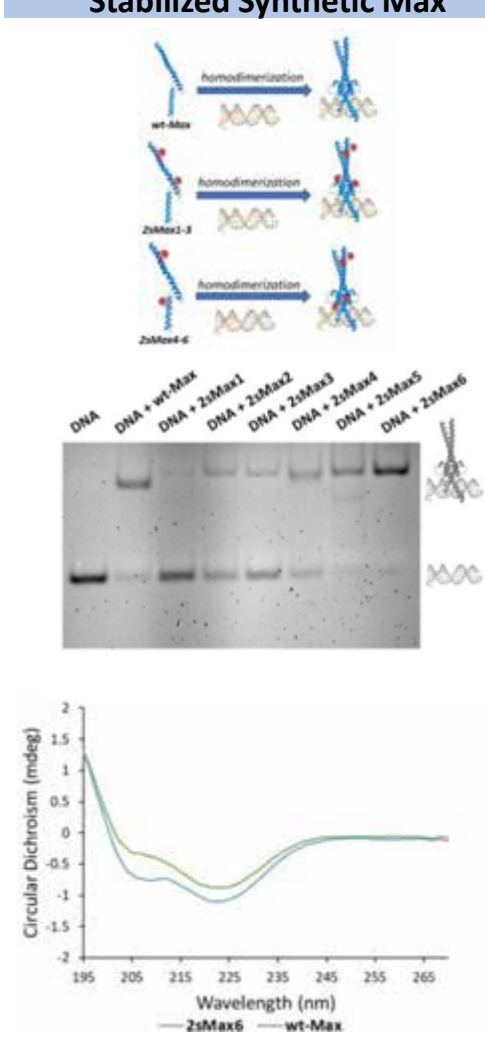
Late-Stage Dimerization and Editing of Minimized Transcription Factors Using Palladium(II) Strategy



Chemical Synthesis of Stabilized Transcription Factors via Orthogonal Palladium(II) Strategy



DNA Binding Activity of Stabilized Synthetic Max



- *Chemical synthesis of a focused library of dimeric and stabilized TFs by using orthogonal palladium(II) chemistry and native chemical ligation.*
- *The stapled monomeric TFs exhibit enhanced stability and retain potent DNA binding activity with the canonical E-box sequence.*

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References:

1. Harel, O. & Jbara, M. *Angew. Chem. Int. Ed. 62, e202217716* ***(2023)***
2. Harel, O. & Jbara, M. *Molecules 27(14), 4389* ***(2022)***
3. Lin, X., Nithun, R. V., Samanta, R., Harel, O., and Jbara, M. *Org. Lett. 25, 4715* ***(2023)***
4. Lin, X., Harel, O. & Jbara, M. *Angew. Chem. Int. Ed. 63, e202317511* ***(2024)***