Nickel-Catalysed Enantioselective Hydrosulfenation of Alkynes

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Chiral sulfur compounds – such as sulfoxides and sulfoximines – have broad applications in various areas of chemistry, especially at the interfaces with biology, drug discovery and materials science. Often, molecules with different stereochemistry at the sulfur atom exhibit dramatically different chemical and biological properties, which renders critically important the capacity of synthesizing these molecules in a stereocontrolled and stereospecific manner. "As a continuation of our research on the catalytic asymmetric synthesis of P-stereogenic compounds, we have expanded our synthetic strategy to include the synthesis of other coordinating elements, in collaboration with the Gang Lu group from Shandong University,"[1] explained Professor Qing-Wei Zhang from the University of Science and Technology of China (Hefei, P. R. of China). He continued: "Given the significant applications of sulfur-containing chiral compounds in pharmaceuticals and materials sciences, we aimed to develop a more efficient and convenient approach for synthesizing S-stereogenic compounds.[2] Among the various strategies available, transition-metal-catalyzed asymmetric hydrofunctionalization emerges as the most promising method in terms of atom-economy and efficiency. Building upon our previous research, we have established that the asymmetric hydrophosphinylation reaction of conjugated enynes, under the catalysis of a nickel complex, proceeds through a protonation mechanism.[3] Inspired by this mechanistic pathway, we postulated that sulfoxides, which can be considered analogous to phosphine oxides, can also be constructed using similar methodologies."

It has been reported that alkynes or alkenes can undergo a concerted reaction with in situ generated sulfenic acid, resulting in the formation of the corresponding racemic sulfoxides.[4] However, for over half a century, the chiral version of this method has not been achieved. Professor Zhang said: "Our research focuses on addressing several key challenges associated with this approach: 1) identifying a suitable catalytic system to prevent the occurrence of concerted background reaction; 2) mitigating the poisoning effect of sulfenic acid on the transition-metal catalyst; and 3) attaining high enantioselectivity and regioselectivity of the reaction. Leveraging our extensive investigations in nickel catalysis, we have successfully achieved the regio- and enantioselective hydrosulfenation of alkynes under mild reaction conditions, providing a reliable method for the preparation of structurally diverse chiral alkenyl sulfoxides (Figure 1)."[1]

Professor Zhang revealed that during their initial explorations, it was found that the ligand was critical to the success of the reaction, both in terms of reactivity and enantioselectivity. "Among the ligands investigated, the electron-rich Ph-BPE [1,2-bis((2*R*,5*R*)-2,5-diphenylphospholano)ethane] demonstrated superior performance, likely due to its ability to effectively stabilize the nickel catalyst through strong coordination, thereby minimizing its susceptibility to poisoning effects," explained Professor Zhang, who continued: "Remarkably, the reaction exhibited a broad functional group tolerance, enabling the late-stage modification of several specific drugs. The resulting alkenyl sulfoxide product also exhibited utility as a versatile Michael acceptor, displaying high reactivity towards a diverse range of nucleophiles."

The reaction mechanism was investigated using a combination of experimental and computational methods in collaboration with Prof. Gang Lu, which confirmed the group's initial expectations, aligning with their previous discoveries. Specifically, it was observed that the nickel catalyst coordinated with the alkyne following the Dewar–Chatt–Duncanson model.[5] "Through π-back donation, this coordination led to an enhancement in both the electron density and basicity of the alkyne, resulting in a greater negative charge on the terminal carbon," said Professor Zhang. He went on: "Simultaneously, the sulfenic acid coordinated with the nickel catalyst via its sulfur atom, further augmenting the basicity of the alkyne. Additionally, the electron transfer to the Ni-alkyne moiety increased the acidity of the sulfenic acid. This enhanced acidity of the sulfenic acid – in addition to the enhanced basicity of the alkyne – collectively facilitated the subsequent protonation step. Importantly, due to the electron-rich nature of the terminal carbon, the proton transfer occurred selectively from the sulfenic acid to the terminal carbon, thereby dictating the regioselectivity of the reaction. The investigation of these mechanisms holds significant implications for the design of additional nickel-catalyzed asymmetric hydrofunctionalization reactions aimed at synthesizing chiral compounds with heteroatom-stereogenic centers." Professor Zhang concluded: "By understanding the intricate details of these reaction mechanisms, researchers can make informed choices when designing catalytic systems and ligands, ultimately leading to the efficient and selective synthesis of a wide range of chiral compounds with heteroatom-stereogenic centers."

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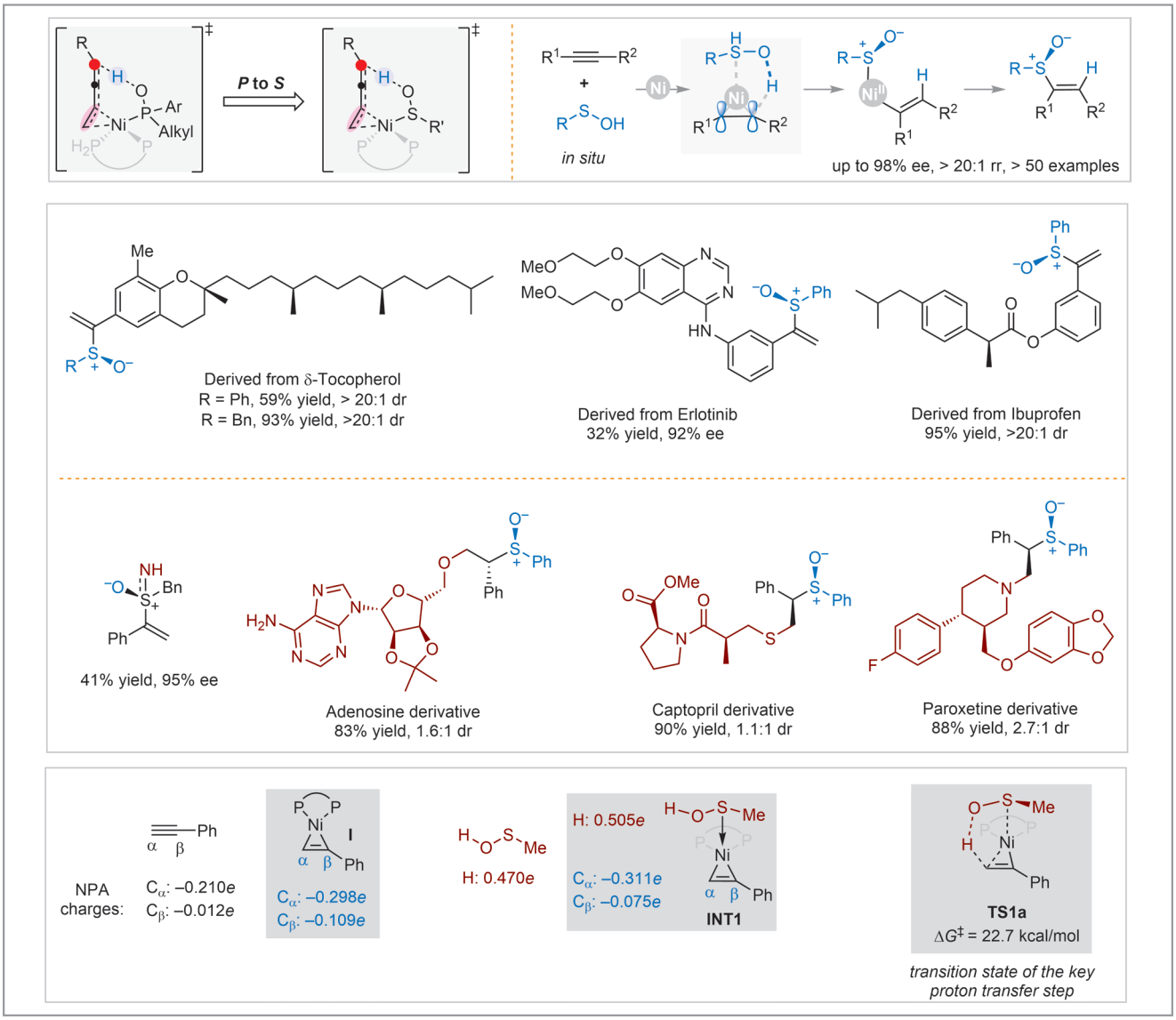

Figure 1 Hydrosulfenation of alkynes

REFERENCES

(1) Y.-Q. Zhang, L. Hu, L. Yuwen, G. Lu, Q.-W. Zhang *Nat. Catal.* **2023**, *6*, 487–494.
(2) I. Fernández, N. Khiar *Chem. Rev.* **2003**, *103*, 3651–3706.
(3) Y.-Q. Zhang, X.-Y. Han, Y. Wu, P.-J. Qi, Q. Zhang, Q.-W. Zhang *Chem. Sci.* **2022**, *13*, 4095–4102.
(4) J. R. Shelton, K. E. Davis *J. Am. Chem. Soc.* **1967**, *89*, 718–719.
(5) (a) M. J. S. Dewar *Bull. Soc. Chim. Fr.* **1951**, *18*, C79.
(b) J. Chatt, L. A. Duncanson *J. Chem. Soc.* **1953**, 2939–2947.
(c) J. Chatt, L. A. Duncanson, L. M. Venanzi *J. Chem. Soc.* **1955**, 4456–4460.

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