Wuhan University
Journal of Natural Sciences

2024, Vol.29 No.3, 195-197

Article ID 1007-1202(2024)03-0195-03 DOI https://doi.org/10.1051/wujns/2024293195

Cite this article: PAN Qi, KONG Wangqing. Ligand Controlled Stereodivergent Construction of 1,3-Nonadjacent Stereocenters via Nickel-Catalyzed Reductive Cyclization/Cross-Couplings[J]. *Wuhan Univ J of Nat Sci*, 2024, 29(3): 195-197.

Correspondence

Ligand Controlled Stereodivergent Construction of 1,3-Nonadjacent Stereocenters via Nickel-Catalyzed Reductive Cyclization/Cross-Couplings

PAN Qi, KONG Wangqing†

The Institute for Advanced Studies, Wuhan University, Wuhan 430072, Hubei, China

Molecules with multiple stereocenters are widely present in biologically active natural products and pharmaceuticals. These molecules exhibit great three-dimensional structural diversity, which can affect the strength and selectivity of protein-ligand interactions[1]. Therefore, the precise synthesis of each stereoisomer is very important in medicinal chemistry. In the past 40 years, asymmetric catalysis has developed rapidly, and a variety of methods has been developed to construct chiral compounds containing single or adjacent stereocenters[2]. However, there are few reports on the simultaneous construction of 1, 3-nonadjacent stereocenters in a highly stereoselective manner, especially in acyclic compounds[3] (Fig. 1(a)). In addition, for the stereodivergent synthesis of all possible stereoisomers of the product, most of the studies to date has focused on dual-catalyst systems, while it reamins extremely challenging to achieve such transformations using a single catalyst by adjusting the chiral ligand[4].

The Kong group has been focusing on nickel-catalyzed reductive cyclization and difunctionalization of alkenes to efficiently construct heterocycles containing all-carbon quaternary stereocenters. This transformation has attracted widespread attention due to its advantages in cases where C(sp^3) electrophiles are unstable or require multiple steps to prepare[5]. Although a variety of electrophiles have been explored, methods for constructing 1,3-nonadjacent stereocenters using secondary alkyl electrophiles have not been developed and remain a formidable challenge.

Received date: 2024-06-08

Foundation item: Supported by the National Natural Science Foundation of China (22171215 and 22301225), the Hubei Provincial Outstanding Youth Fund (2022CFA092), and Hubei Provincial Natural Science Foundation (2023AFB034)

Biography: PAN Qi, female, Ph.D., research direction: the efficient construction of functionalized heterocycles with quaternary stereocenters and their applications in the synthesis of biologically active natural products and drugs. E-mail: qi.pan@su.se

† Corresponding author. E-mail: wqkong@whu.edu.cn

Zhang *et al* developed a novel class of chiral Sadphos ligands that show unique potential in asymmetric catalysis[6]. This joint effort of the Kong and Zhang groups enabled the enantio- and diastereoselective reductive cyclization/cross-coupling of olefin-tethered aryl bromides with racemic α-bromoamides. This reaction was successfully applied to the production of a variety of oxindoles containing 1, 3-nonadjacent stereocenters[7] (*J. Am. Chem. Soc.* 2024, 146, 15453). A variety of aryl bromides and α-bromoamides are compatible with this trasnformation (Fig. 1(b)). Strikingly, using Ming-Phos and Ph-Phox, four stereoisomers were prepared from the same substrate with synthetically useful yields and high enantioselectivities, confirming the feasibility of stereodivergent synthesis using a single-catalyst system by adjusting the chiral ligands (Fig. 1(c)).

The authors also conducted a systematic mechanistic study. In the presence of $MgCl_2$, the reaction of racemic alkyl iodide with α-bromoamides afforded the desired product with excellent diastereoselectivity (> 20:1 d.r.). However, in the absence of $MgCl_2$, the diastereoselectivity of the product was significantly reduced to 1.3:1 (Fig. 1(d)). To further elucidate the role of $MgCl_2$, the collaborators in Wang's group conducted detailed DFT calculations, demonstrating that the Mg salt fixed the alkyl radical by coordination, enabling it to attack the nickel center through a nine-membered ring intermediate, thereby facilitating stereocontrol of the second chiral center (Fig. 1(e)).

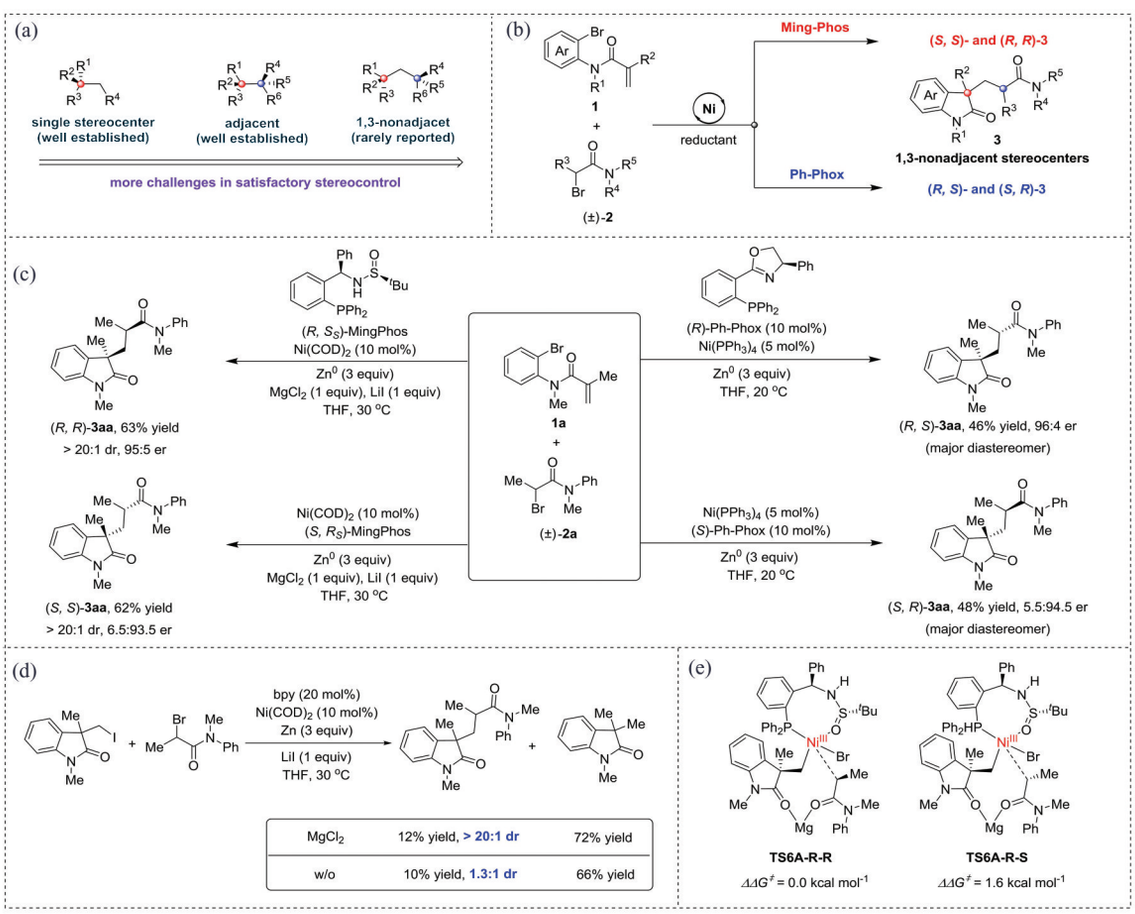

Fig.1 Ligand-Controlled, Nickel-Catalyzed Stereodivergent Construction of 1,3-Nonadjacent Stereocenters

(a) The difficulty of asymmetric induction. (b) Kong and his collaborators successfully achieved the stereodivergent construction of oxindoles containing 1, 3-nonadjacent stereocenters. (c) Four stereoisomers were prepared from the same substrate using four different chiral ligands. (d) Mechanistic study with or without $MgCl_2$. (e) DFT calculations for the origin of diastereoselectivity in the presence of $MgCl_2$ (1 kcal = 4.18 kJ)

In summary, Professor Kong's group and their collaborators successfully achieved the stereodivergent construction of 1,3-nonadjacent stereocenters, and also delved into the mechanism through experiments and DFT calculations. This study is of high synthetic value because it provides a practical and effective method to slove the major remaining stereochemical challenges in olefin reductive cyclization/cross-coupling reactions, and also provides insights into the

relationship between ligands and stereocontrol. However, when Ph-Phox ligand was used, the diastereoselectivity of products is still less than ideal. Therefore, future studies are required to focus on designing novel Phox-type chiral ligands to further improve the diastereoselectivity of this transformation.

References

[1] Prosser K E, Stokes R W, Cohen S M. Evaluation of 3-dimensionality in approved and experimental drug space[J]. *ACS Medicinal Chemistry Letters*, 2020, **11**(6): 1292-1298.

[2] Zhou Q L. *Privileged Chiral Ligands and Catalysts*[M]. Hoboken: Wiley-VCH, 2011.

[3] Jiang X M, Ji C L, Ge J F, *et al*. Asymmetric synthesis of chiral 1, 2-bis(boronic) esters featuring acyclic, non-adjacent 1, 3-stereocenters[J]. *Angewandte Chemie International Edition*, 2024, **63**(5): 2318441.

[4] Huo X H, Li G L, Wang X, *et al*. Bimetallic catalysis in stereodivergent synthesis[J]. *Angewandte Chemie International Edition*, 2022, **61**(45): 2210086.

[5] Pan Q, Ping Y Y, Kong W Q. Nickel-catalyzed ligand-controlled selective reductive cyclization/cross-couplings[J]. *Accounts of Chemical Research*, 2023, **56**(5): 515-535.

[6] Zhang Z M, Chen P, Li W B, *et al*. A new type of chiral sulfinamide monophosphine ligands: Stereodivergent synthesis and application in enantioselective gold(I)-catalyzed cycloaddition reactions[J]. *Angewandte Chemie International Edition*, 2014, **53**(17): 4350-4354.

[7] Pan Q, Wang K, Xu W P, *et al*. Ligand-controlled, nickel-catalyzed stereodivergent construction of 1, 3-nonadjacent stereocenters[J]. *Journal of the American Chemical Society*, 2024, **146**(22): 15453-15463.

□