PREPRINT VERSION

Chem Catalysis

CellPress

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Weak interactions crucial for better enantioselections

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In this issue of *Chem Catalysis*, Schomaker, Liu and co-workers describe the enantioselective intramolecular silver-catalyzed nitrene transfer (NT) leading to chiral six-member rings via C-H amidation. Initial experimental data were modeled with DFT calculations that returned crucial information about the relevance of non-covalent interactions on enantioselection. Novel ligands prepared on those bases led to ee enhancement for the asymmetric amidation of diverse C-H bonds.

With no doubt, one of the most developed transformations in this first quarter of century is the formation of carbon-nitrogen bonds from parent C-H bonds, mainly due to the array of applications of the former.[1] The generation of highly reactive L_nM=NR species from azides, iminoiodinanes or amines (NR = nitrene ligand) and the subsequent transfer of the NR unit in a catalytic manner to C-H bonds has become quite popular as a strategy to generate C-NHR compounds.[2,3] This nitrene transfer (NT) reaction is known for inter- and intramolecular fashions (Fig 1a). In the context of the intramolecular approach, sulfamate (DuBois, [4] Blakey)[5]or carbamate (Davies,[6] Meggers)[7] nitrene precursors containing a -NH_2 group have been employed in cyclization reactions with dirhodium- or ruthenium-based catalysts bearing chiral ligands to induce the generation of five- or six-membered rings displaying a stereocenter with moderate to high enantioselection (Fig 1b). It is of note that such cyclic amines are excellent precursors for chiral aminoalcohols upon ring-opening reactions.

Schomaker, Liu and co-workers describe [8] the use of silver-based catalysts containing bis(oxazoline) ligands for the site- and enantioselective intramolecular NT into C-H bonds of carbamate esters leading first to exclusive formation of six-member rings which can further be converted into chiral 1,3-aminoalcohols. Remarkably, the procedure followed for these achievements also reinforces the potential of experimental and computational studies and the feedback between both worlds.

The authors first investigated the use of a $AgClO_4$/(S,S)-Min-BOX system for the NT reaction with several carbamates, where the targeted C-H bond appeared in benzyl, allylic or alkylic positions. The results were good in terms of yields and ees, but not excellent when compared with the use of the above-mentioned Rh- or Ru-based catalysts. At this point, authors might have decided to prepare a full family of similar ligands to check, in an empirical manner, whether or not the different ligands affect the yields and ees. However, given that the intimate catalyst-substrate interaction influencing the development of ees in these transformations are not fully understood, DFT studies were run in advance to the generation of a ligand library (Fig 1c).

Calculations revealed that the reaction occurs via a singlet silver nitrene with undergoes the electrophilic attack onto the C-H bond in a concerted manner. The TS associated with this step displays a square-planar geometry, the donor atoms being the BOX-nitrogen donors, the N-nitrene and the O-carbonyl carbamate. An in-depth analysis of the different TSs leading to both enantiomers showed that (a) certain steric repulsions between substrate and BOX ligand were crucial, and (b) with the appropriate substituent at the latter, beneficial non-covalent C-H/π interactions help increasing the ee values.

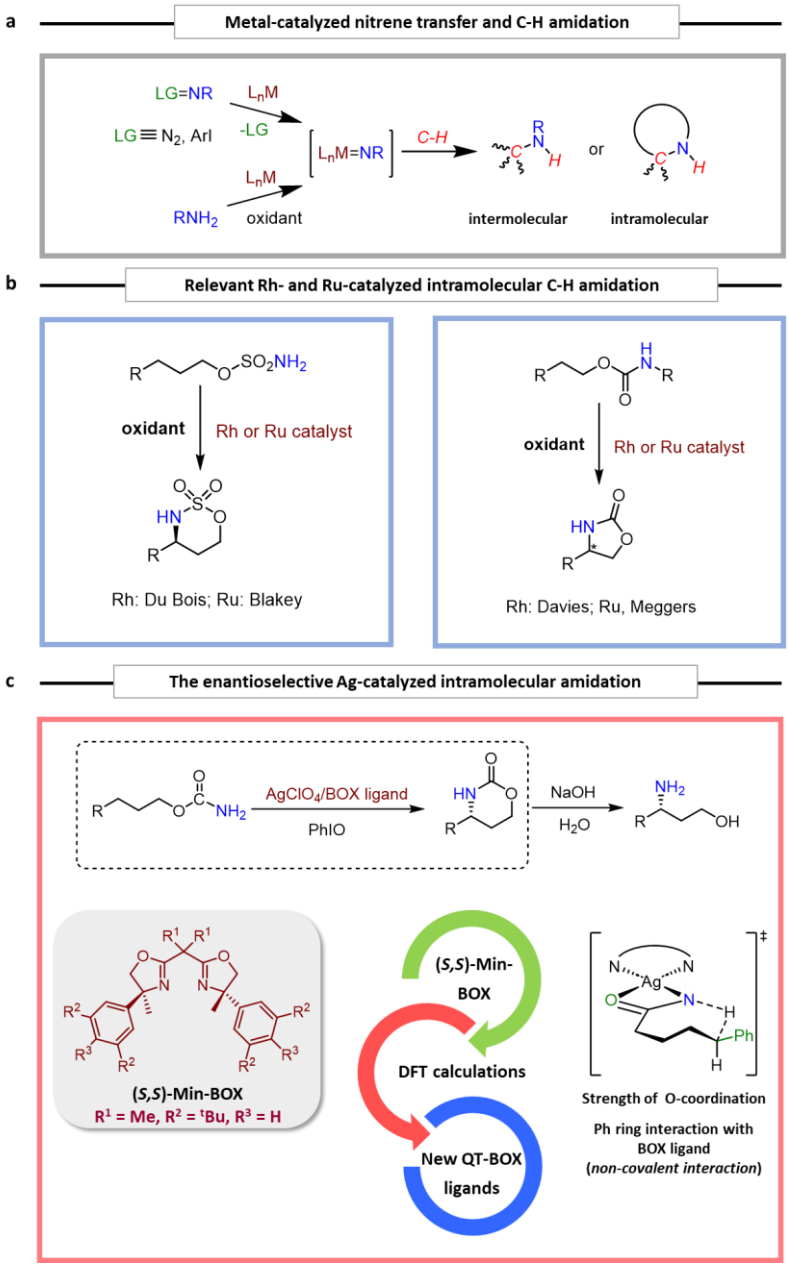

Figure 1. The Ag-catalyzed intramolecular C-H amidation by nitrene transfer.

With this information in hand, a set of new BOX ligands were prepared following a new modular route that allowed the incorporation of several substituents onto the ancillary ligand. Once they were available, the catalytic study was performed and yields and ees were significantly increased, not only for the somewhat activated allylic and benzylic positions, but also for the more challenging unactivated alkylic position, for which moderate but noticeable improvements were found. To validate this NT strategy with an application, the authors have targeted an alternative synthesis of dapoxetine, in two steps after the six-member ring is obtained via C-H amidation.

In conclusion, this contribution not only provides a catalytic system for the intramolecular asymmetric C-H amidation via nitrene transfer but also gives insights into the nature of the

catalyst-substrate interaction that governs the development of enantioselection. Of note the prevalent role of non-covalent interaction between the two actors, which can be amplified with the appropriate design of the BOX ancillary ligand. From calculations insights, expansion of the BOX family led to the enhancement of reaction yields and enantioselectivies.

ACKNOWLEDGMENTS

We thank to Ministerio de Ciencia e Innovación for Grant PID2023-146946NB-I00.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Trowbridge, A., Walton, S. M., Gaunt, M. J. (2020). New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. Chem. Rev. *120*, 2613 – 2692. https://doi.org/10.1021/acs.chemrev.9b00462.
2. Müller, P., and Fruit, C. (2003). Enantioselective Catalytic Aziridinations and Asymmetric Nitrene Insertions into CH Bonds. Chem. Rev. *103*, 2905-2920. https://doi.org/10.1021/cr020043t.
3. Buendia, J., Grelier, G., and Dauban, P. (2015). Dirhodium(II)-Catalyzed C(sp(3))-H Amination Using Iodine(III) Oxidants. Adv. Organomet. Chem. *64*, 77-118. https://doi.org/10.1016/bs.adomc.2015.08.001.
4. Zalatan, D.N., and Du Bois, J. (2008). A chiral rhodium carboxamidate catalyst for enantioselective C-H amination. J. Am. Chem. Soc. *130*, 9220–9221. https://doi.org/10.1021/ja8031955.
5. Milczek, E., Boudet, N., and Blakey, S. (2008). Enantioselective C-H Amination Using Cationic Ruthenium(II)-Pybox Catalysts. Angew. Chem. Int. Ed. *47*, 6825–6828. https://doi.org/10.1002/anie.200801445.
6. Reddy, R.P., and Davies, H.M.L. (2006). Dirhodium tetracarboxylates derived from adamantylglycine as chiral catalysts for enantioselective C-H aminations. Org. Lett. *8*, 5013–5016. https://doi.org/10.1021/ol061742l.
7. Zhou, Z., Tan, Y., Shen, X., Ivlev, S., and Meggers, E. (2021). Catalytic

Enantioselective Synthesis of β-Amino Alcohols by Nitrene Insertion. Sci. China Chem. *64*, 452–458. https://doi.org/10.1007/s11426-020-9906-x.

8. Schroeder, E. Z.; Kim, J. H., Fue, Y., Liu, W., Liu, P. and Schomaker, J. M. (2025). Modular silver catalysts to elucidate the role of noncovalent interactions in asymmetric C–H amidation reactions. Chem. Catalysis *XX*, XXXX-XXXX. https://doi.org/10.1016/j.checat.2025.101388.