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Chem Catalysis

Preview

Tuning catalyst performance in asymmetric carbene-transfer toward CF₃-cyclopropenes

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In this issue of *Chem Catalysis*, Zhang, Ma, Marek et al report a highly enantioselective carbene-transfer reaction of 2,2,2-trifluorodiazethane (CF₃CHN₂) and challenging disubstituted alkynes. Key to the success of this approach is the fine tuning of chiral dirhodium(II) carboxylate paddlewheel complexes featuring a molecule of dioxane as achiral axial ligand.

At the heart of this work is the cyclopropene motif, this small strained ring featuring a C=C double bond has fascinated chemists from all walks of life from drug discovery to materials science. As final components of target molecules or as versatile building blocks for further chemical transformations, the cyclopropene motif has long been considered a curiosity rather difficult to access because of its unique structural and electronic properties. However, recent progress in transition metal-catalyzed chemistry has triggered a revival of interest for these molecular scaffolds, in particular through the cyclopropenation of alkynes using diazo compounds acting as carbenoid precursors.¹

Similarly, fluorine chemistry became a mature area of research that spread out in all fields of chemistry. This is particularly true in medicinal chemistry with circa 25% of all marketed drugs containing at least one fluorine atom and an even higher ratio of 50% in agrochemical chemistry.² It is well known that the presence of fluorine or fluorinated functional groups in bioactive compounds profoundly alter physicochemical and biological properties together with alteration of steric, electronic, lipophilic, and metabolic properties. In modern organofluorine chemistry, the construction of enantiopure fluorinated molecules has stimulated tremendous interest and is at the forefront of innovation. Of the most encountered fluorinated motifs, the trifluoromethyl group is ubiquitous in pharmaceuticals and agrochemicals often as a (het)aryl substituent but also frequently as component of stereogenic sp³-hybridized carbon centers.

In this context, the work of Zhang, Ma, Marek and co-workers in this issue of *Chem Catalysis* represents a remarkable example connecting fluorine chemistry,

asymmetric synthesis and organometallic chemistry in a powerful approach for the enantioselective synthesis of highly substituted CF₃-cyclopropenes.³

As a preamble, we can note that alkynes are much less studied than alkenes in carbene transfer reactions to afford cyclopropenes and cyclopropanes, respectively. The same trend applies to the asymmetric versions. Pioneering works from Katsuki,⁴ Koenings⁵ and Bi⁶ groups focused on enantioselective cyclopropenation of donor/acceptor (Ar/CF₃) substituted carbenes with terminal alkynes using iridium or rhodium catalysts. Extension of these works to the more challenging internal alkynes was worth investigating as well as the use of single acceptor (H/CF₃) trifluoromethyl carbenes that would lead to tertiary CF₃-bearing stereogenic carbon centers. In 2010, Morandi and Carreira reported the non-asymmetric rhodium-catalyzed cyclopropenation reaction of 2,2,2-trifluorodiazaoethane with two internal alkynes that paved the way to the asymmetric version.⁷ Building on this literature precedence, Zhang, Ma, Marek and co-workers first described in 2019 an efficient Rh(II)-catalyzed enantioselective cyclopropenation reaction of internal alkynes by means of a masked difluorodiazaoethane reagent (PhSO₂CF₂CHN₂)⁸ and now have succeeded in the [2+1] cyclopropenation with the aid of 2,2,2-trifluorodiazaoethane (CF₃CHN₂) as carbenoid precursor.

The authors explored diversely decorated chiral dirhodium(II) carboxylates to promote the [2+1] cyclization of 2,2,2-trifluorodiazaoethane with various internal alkynes (Figure 1A). This class of catalysts proved to be highly efficient in a wide range of metal-carbene transformations.⁹ Specifically, in the present study, the tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinato] dirhodium Rh₂(*S*-TCPTTL)₄ was found optimal in a large screening of rhodium ligands and reaction conditions. A combination of 1,4-dioxane as solvent of the reaction and THF as solvent for the preparation of solutions of 2,2,2-trifluorodiazaoethane allowed to obtain the desired CF₃-cyclopropenes within one to twelve hours at room temperature in high yields and with excellent enantioselectivities. The optimization phase revealed the importance of the solvent that plays a decisive role in obtaining very high enantioselectivities up to 99%. Steric and electronic effects of the alkyne substituents were examined and a great tolerance was demonstrated. The reaction was further extended to diazo compounds featuring higher perfluorinated chains (pentafluoroethyl and heptafluoropropyl) with equal success in terms of yields and enantiomeric ratios (Figure 1A). Notably, the substrate scope was enriched with drug-like and agro-like products that are mimics of phenylalanine, Probenecid and Fenfluthrin to cite but a few (Figure 1A). The crystallization of one CF₃-cyclopropene and its X-ray crystallography analysis allowed to assign the absolute configuration of the CF₃-containing stereogenic carbon center for this compound and others by analogy.

Not only the optically enriched CF₃-cyclopropenes are important final products for biological evaluation but also substrates for further elaboration of even more functionalized derivatives taking advantage of the first stereogenic center to control the new generated ones. Indeed, a number of post-functionalizations were carried out that include hydrogenation and hydroboration of the C=C double bond to yield the corresponding cyclopropanes, Diels-Alder cycloaddition reactions with different dienes to end up with cyclohexene-fused CF₃-cyclopropanes in high yields without erosion of the ee values, and Pauson–Khand reactions to afford cyclopentenone-

fused CF₃-cyclopropanes in good yields with excellent regio- and diastereoselectivities (Figure 1B).

Lastly, the free energy profile of the reaction and the enantiomeric selectivity were investigated by density functional theory (DFT) calculations. By dint of halogen-bonding interactions between the four tetrachlorophthalimido groups, the catalyst adopts a C₄-symmetry “all-up” conformation. In such a system, the two rhodium atoms offer vacant axial sites (top face or bottom face) available for metal carbene formation; these sites are considerably different in space. The calculated structure showed that the entire carbene resides within a long narrow pocket formed by the four *N*-phthalimido groups of Rh₂(S-TCPTTL)₄ (Figure 1C). The authors demonstrated that exploring the axial modification with appropriate coordinating additive resulted in shape alteration of the catalyst and subsequently had a significant influence on the enantioselective induction. Indeed, additives that coordinate to the axial position of the dirhodium have been shown to influence the general outcome of carbene reactions, but the influence on enantioselectivity has not been extensively explored.¹⁰ In the present work, 1,4-dioxane as Lewis basic solvent stabilized the resulting Rh-dioxane complex by 6.9 kcal/mol and contributed to enhance its reactivity and to improve the stereoselectivity of metallocarbene towards internal alkynes. Specifically, transition states leading to both enantiomers of cyclopropene were compared and it revealed that *S*-selectivity is favorable with and without 1,4-dioxane coordination, but the trend is clearly dominant in the dioxane-ligation pathway in line with experimental results. The catalyst conformation, axial ligation, intermediate metal carbene, alkyne approach, stereoinduction and absolute configuration of the final cyclopropene are depicted in Figure 1C.

In summary, trifluoromethyl cyclopropenes being fully substituted at the C=C double bond, a challenging scaffold to construct, were obtained in highly enantioenriched form. The synthetic approach consists of a dirhodium(II)-catalyzed [2+1] cycloaddition reaction of internal alkynes with trifluoromethyl carbene of 2,2,2-trifluorodiazaoethane. A fine-tuning of the catalyst structure, which included the investigation of additives for axial ligation, triggered an enhanced enantiomer selectivity. Not only the new molecules are important building blocks but also this study laid a solid foundation for all future developments of chiral dirhodium(II) carboxylate catalysts.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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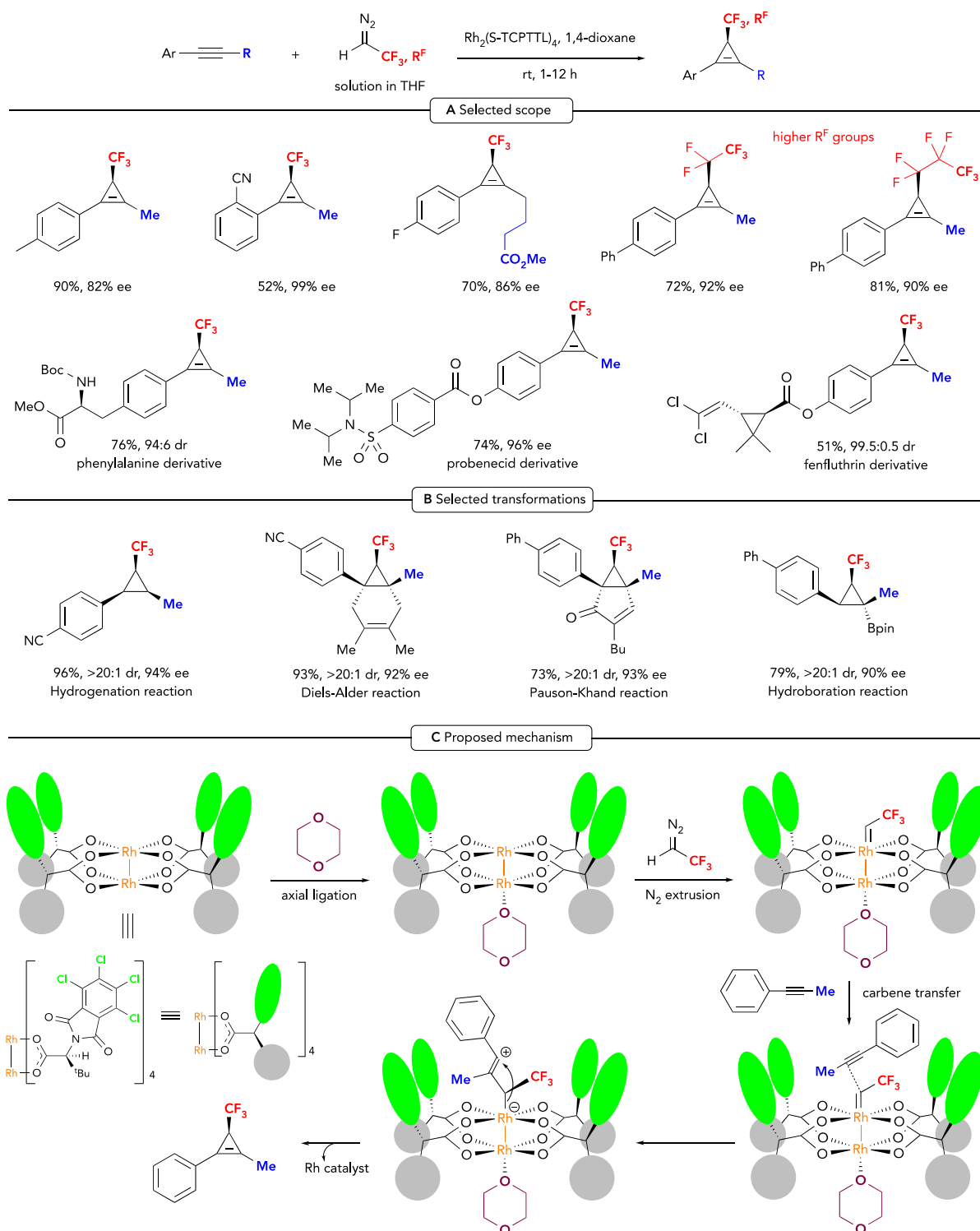


Figure 1. Dirhodium(II) carboxylate-catalyzed enantioselective cyclopropanation of internal alkynes by means of 2,2,2-trifluorodiazooethane