Copper-catalyzed enantioselective trifluoromethylation of benzylic radicals developed

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Scientists from the Shanghai Institute of Organic Chemistry of the Chinese Academy of Sciences (CAS) have developed the first copper-catalyzed enantioselective trifluoromethylation of benzylic radicals via a copper-catalyzed radical relay strategy.

The incorporation of trifluoromethyl (CF_3) groups into biologically active molecules has a significant effect on their physical and biological properties, and optically pure CF_3-containing organic molecules broadly exist in pharmaceuticals and agrochemicals. Thus, exploration of efficient asymmetric trifluoromethylation methods is highly demand. Recently, radical trifluoromethylation coupling presents one of most efficient method for their synthesis. However, so far, there are no reports of asymmetric radical trifluoromethylations to date.

As their ongoing research interest in asymmetric radical transformations, Lio Guosheng and his colleagues have recently developed a copper-catalyzed radical relay strategy for the enantioselective cyanation and arylation of sp^3 C-H bonds, including benzylic and allylic C-H bonds, which provide efficient method for later-stage modification of drugs and bioactive molecules. They devoted large efforts to mechanism studies, and found that the benzylic radical was enantioselectively trapped by $(Box)Cu(CN)_2$ or (Box)Cu-Ar species.

Inspired by the recent progress on the radical trifluoromethylation, they envisioned that the asymmetric trifluoromethylation of secondary alkyl radicals forging chiral $C\text{-}CF_3$ bonds might be possible by introducing chiral ligands.

The copper-catalyzed asymmetric trifluoromethylation of cyclopropanols successfully afforded the optically pure β-CF_3 ketones in good yields and excellent enantioselectivities under very mild conditions. Critical to the success of this reaction is that a benzylic radical intermediate can be enantioselectively trapped by reactive $(L^*)Cu^{II}CF_3$.

n addition, a novel quinolinyl-containing bisoxazoline ligand ($Bn\text{-}Box^{Qu}$)

plays a significant role in the asymmetric trifluoromethylation.

This study enables to synthesize diverse optically pure β-CF_3 ketones efficiently, which can serve as versatile building blocks for the synthesis of a (*R*)-CF_3-modified analog of drug Cinacalcet.

The research result was published in the journal *Chem*.

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