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Exploring the factors which control enantioselectivity in copper mediated C–H insertion reactions of α-diazocarbonyl compounds.

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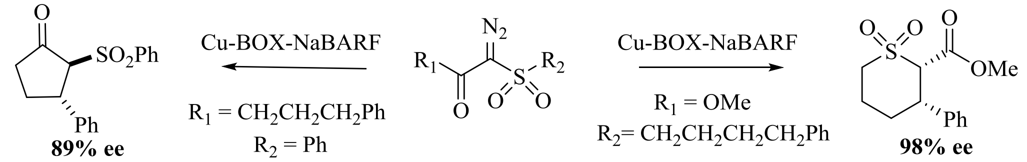
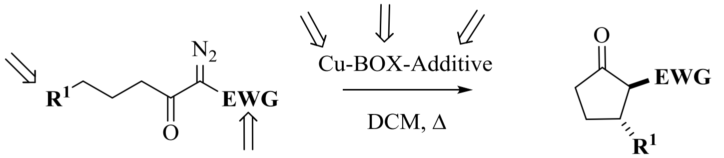
The transition-metal catalysed C–H insertion reaction of α-diazocarbonyl compounds provide a powerful synthetic tool in organic chemistry.[1] The enantioselective cyclisation of α-diazo-β-keto sulfones through asymmetric C–H insertion to form 2-sulfonylcyclopentanones, first reported by McKervey using rhodium catalysts,[2] has been extensively explored in recent years by the Maguire group using copper based catalysts with up to 89%ee.[3]



In related work, enantioselectivities of up to 98% ee have been achieved for the synthesis of *cis*-thiopyrans from α-diazo-β-oxosulfones[4] while up to 82% ee was reported for the synthesis of γ-lactams from α-diazoacetamides.[5] Key to success in the enantioselective C-H insertion is use of the Copper-NaBARF-bisoxazoline catalyst system.[4,6] While the optimal copper source and additive has been identified, the chemo-, regio- and stereo outcomes of the reaction are found to be strongly dependent on the structure of the substrate and the bisoxazoline ligand employed. Our continuing research is focused on investigating the fundamental aspects of the ligand-substrate relationship and how these affect enantiocontrol, with a view to developing new catalysts with broad applicability.

We report herein the outcome of systematic investigation of the impact of variation of each of the structural elements present, namely the substituent R^1 at the site of insertion, the substituent on the carbene carbon (EWG), the nature of the linking chain, the bisoxaline ligand, the counter ion and the additive. Both steric and electronic effects have been investigated to determine the impact of each element on the outcome of the insertion in terms of both degree and direction of enantiocontrol. It is clear from this work that the presence of a sulfonyl substituent on the carbene carbon is particularly effective in leading to high enantiocontrol in these systems.



EWG = SO_2R, $PO(OR)_n$, CO_2R
$\mathbf{R^1}$ = Aryl, Alkyl
⟹ Variation of these components will be discussed

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