DEVELOPMENT OF THE ASYMMETRIC KINUGASA REACTION

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INTRODUCTION

Since the discovery of the potent antibiotic activity of *Penicillium notatum* cultures against many strains of bacteria[1], the importance of the β-lactam moiety has grown significantly in both medicinal and synthetic chemistry. In addition to their antibacterial properties,[2] molecules containing a 2-azetidinone ring exhibit a broad variety of other useful biological activity.[3,4] β-Lactams are also useful as building blocks in the synthesis of more complex molecules.[5] Consequently, numerous methods have been developed for the synthesis of β-lactam rings.[3] A particularly mild, atom-economical route to β-lactams is the [3+2] cycloaddition of copper(I) acetylides and nitrones, a process known as the Kinugasa reaction.[6] Originally discovered in 1972 by Kinugasa and coworkers, the use of this reaction remained relatively dormant for many years. The Kinugasa reaction has lately seen a resurgence of interest, and effort has been made to broaden its utility, namely through the development of stereoselective, catalytic versions of the Kinugasa reaction.

THE ASYMMETRIC KINUGASA REACTION

Diastereoselective Variants

The current understanding of the mechanism of the Kinugasa reaction suggests that the stereoisomer of product formed is determined by the facial approach of the nitrone to the copper acetylide (Scheme 1).[7] This mechanism provides an opportunity for asymmetric induction by the introduction of stereogenic centers adjacent to the alkyne in the substrate. Chmielewski and coworkers have capitalized upon this opportunity by using chiral propargylic alcohols (Figure 1a).[4] These chiral substrates afford good dr's with cyclic nitrones (dr up to 95:5, yield 42-94%) and stoichiometric amounts of CuI. An alternative strategy is the use ynamides derived from oxazolidinones as the coupling partners to form chiral α-amino β-lactams (Figure 1b). Using these chiral auxiliaries, Hsung produced α-amino-β-lactams in moderate to good yields (28-80%) and with dr's up to 95:5, in the presence of 20 mol % of CuI.[8]

Scheme 1. Proposed mechanism of the Kinugasa reaction

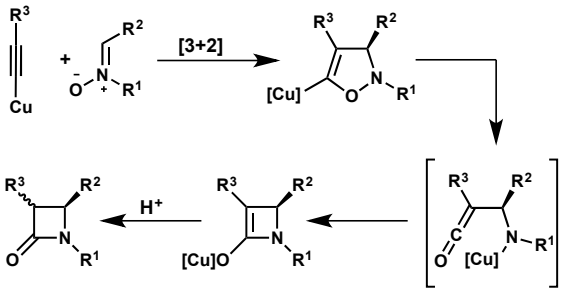
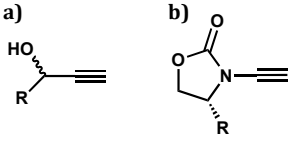


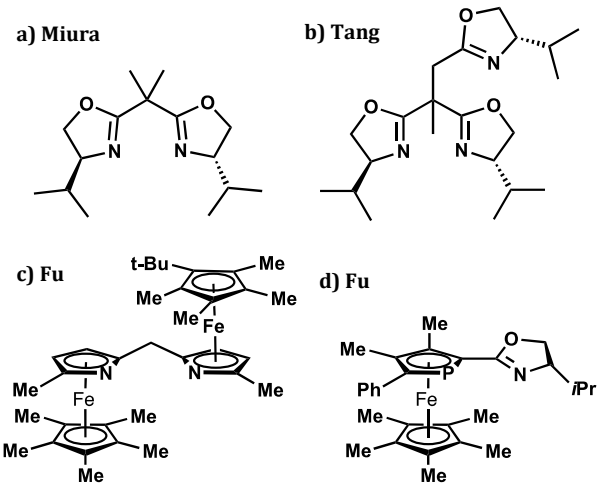
Figure 1. Chiral substrates



Enantioselective Variants

In 1995, Miura and coworkers reported a catalytic version of the Kinugasa reaction using bidentate, nitrogen-based ligands.[9] The use of copper(I) and a bisoxazoline ligand (Figure 2a) resulted in an er of 84:16 for the reaction between a C,N-diphenyl nitrone and phenylacetylene.[9] Inspired by this initial report, Fu et al. employed a copper(I)-bis(azaferrocene) (Figure 2c) catalyst for the construction of *cis*-, aryl substituted β-lactams with er's up to 92.5:7.5 (yields from 43% to 91%).[10] In 2003, Fu et al. reported the enantioselective, intramolecular Kinugasa reaction for the construction of polycyclic β-lactams using a phosphaferrocene-oxazoline ligand (Figure 2d), with er's up to 95:5 (yields 46-68%).[7] Finally, in 2006, Tang and coworkers achieved the catalytic, enantioselective formation of *cis*-β-lactams utilizing an air- and water-stable copper(II)-TOX catalyst system (Figure 2b), furnishing products in 25-98% yield with er's up to 91:9.[11]

Figure 2. Ligands for enantioselective Kinugasa Reaction



FUTURE DIRECTIONS

Although significant progress has been made since the report of Miura and coworkers,[5] there is still room for improvement. In the past decade, a few reports of catalytic systems have emerged using chiral amines,[4] indaBOX, indaTOX, or HETPHOX ligands,[12] but these systems have not represented great advances since the Fu and Tang systems. In addition, broadening of the substrate scope of non-aromatic substrates is necessary to increase the utility of this reaction. There is, therefore, still more to do for the Kinugasa reaction to reach its full potential.

References

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