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Journal Name

COMMUNICATION

Catalytic Asymmetric Synthesis of Tetrahydropyridazines via Inverse Electron-Demand aza-Diels-Alder Reaction of Enol Ethers with Azoalkenes

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Abstract: A highly efficient Cu(II)-catalyzed enantioselective inverse-electron-demand aza-Diels-Alder reaction of in situ formed azoalkenes with enol ethers is reported. This methodology provides a facile entry to biologically important and enantioenriched tetrahydropyridazine derivatives in generally good yield (up to 95% yield) with good to excellent enantioselectivity (up to 94% ee).

The catalytic asymmetric inverse-electron-demand Diels-Alder (IEDDA) reaction has been demonstrated to be one of the most efficient and atom-economic methods for the synthesis of optical pure six-membered functionalized carbocyclic and heterocyclic frameworks.1 Its versatility and importance in the synthesis of numerous nature products led to an ever-increasing interest to discover new catalytic strategies and substrates for this reaction. In particular, since the pioneering studies2 of Kobayashi and co-workers, who reported the first catalytic asymmetric IEDDA reactions using vinyl ethers as 2π-participation and cyclopentadiene as 4π-participation, considerable advances have been achieved by several research groups. Both Lewis acid catalysis3 and organocatalysis4 have been successfully applied to promote asymmetric IEDDA reactions. Variant chiral pepridine-, pyran- and cyclohexane derivatives were achieved through those well-established strategies. However, examples of asymmetric IEDDA reaction to afford multi-heteroatom containing and biologically important heterocycles are still scarce to date5. Undoubtedly, development of catalytic asymmetric IEDDA reaction that utilized novel diene-dienophile combinations is particularly an appealing and challenging task.

Tetrahydropyridazines6, as an important member of heterocycles family, constitutes the key structure of multitudinous nature products and pharmaceuticals. In decades, the ever-growing interests in tetrahydropyridazines motifs led to impressive advances in the field of synthesis. Lots of efficient methods to synthesize these privileged structure have been developed. Among them, the newly discovered inverse electron-demand aza-Diels-Alder reaction of in situ formed azoalkenes with dienophiles is arguably one of the most powerful and atom/step-economic approaches. Azoalkenes (1,2-diaza-1,3-dienes)7 can be mildly generated by base-treatment of α-halogeno hydrozone, which have attracted great attentions as to be efficient intermediates to construct plenty of multi-nitrogen-containing heterocycles. In recent years, a range of transformations have been established using azoalkenes as suitable chemical handles. However, this field has still met with some tough issues. In particular, catalytic asymmetric annulation for the synthesis of enantioenriched heterocycles represents the most formidable challenging.8 Very recently, our research group developed the first catalytic asymmetric IEDDA reaction between azoalkenes and indoles using Cu(II)/Bu-Phosferrox complex which delivers [2,3]-fused indoline-tetrahydropyridazine heterocycles with high chemical yield, exclusive regioselectivity and excellent enantioselectivity (Scheme 1).8a We envisioned that this chiral Cu(II)/Phosferrox complex could be applied to promote IEDDA reaction of azoalkenes with enol ethers as efficient dienophiles to afford biologically useful enantioenriched tetrahydro-pyrazadines bearing an N, O-acetal stereocenter.7 We report these results in this communication.

Scheme 1. Catalytic Asymmetric Inverse Electron-Demand aza-Diels-Alder Reaction (IEDDA) of Azoalkene with Indoles (Previous work) and Enol Ethers (This work).
The initial investigation was performed on an uncatalyzed IEDDA reaction of α-chloro N-benzoyl hydrazone 1a and 5 equivalents of tert-buty vinyl ether 2a in 2.0 mL of solvent. CuF₂ = Cu(MeCN)₂BF₄. Isolated yield. *Ee* was determined by HPLC analysis. †5 mol % catalyst was used.

With optimized reaction conditions in hand, we set out to extend this methodology with respect both to α-chloro N-benzoyl hydrazone (1) and enol ethers (2). Firstly, we investigated a series of α-chloro N-benzoyl hydrazones bearing different substitutes at the benzene rings. As shown in Table 2, under the optimized conditions, the reaction shows good tolerance towards substitution pattern (para-, meta-, ortho-) and electronic property (electron-rich, -deficient, and -neutral) of aromatic substitutes, and various chiral tetrahydropyrrolidines were synthesized in generally high yields (entry 1-9, 71-94% yield) with good to excellent enantioselectivities (72-94% ee). Additionally, 1- and 2-naphthyl-substituted N-benzoyl hydrazone 1j and 1k also proceeded well, affording the corresponding cycloadducts 3ja and 3ka in good yields with high enantioselectivities (entry 10-11). Remarkably, when the α,α-dichlorohydrazone 1l were employed as the precursor of azoalkene, the IEDDA reaction was completed in 18 h at -40 °C, delivering the corresponding 3la bearing two discontinuous...
stereogenic centers in slightly lower yield with exclusive
diastereoselectivity (20:1) and 83% ee (entry 12). The relative
configuration of 3la was determined through NOESY (see ESI for
more details).

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{Ph} & \quad \text{Cl} \\
\text{NH} & \quad \text{Ph} \\
\text{N} & \quad \text{C} \quad \text{N} \\
1a & \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

Cu(II)/L4 (10 mol%) Na2CO3 (2 equiv) DCM, -20°C

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{Ph} & \quad \text{Cl} \\
\text{NH} & \quad \text{Ph} \\
\text{N} & \quad \text{C} \quad \text{N} \\
1a & \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

Scheme 2: Scope of enol ethers for the Cu(II)/L4-catalyzed asymmetric IEDDA reaction of hydrazones 1a.

Encouraged by the results of α-chloro N-benzoyl hydrazones with bulky and branched tert-butyl vinyl ether 2a,
we then investigated the IEDDA reactions with an array of enol ethers bearing linear alkyl groups as the
dienophiles (Scheme 2). The tested enol ethers proved to be efficient reaction partners
delivering the desired cycloadducts in high yields (88-95%) with excellent enantioselectivities (88-90% ee).
The absolute configuration of the adduct 3fb was unequivocally determined to be R by the X-ray crystal structure analysis.

A plausible mechanism for this annulation was shown in
Scheme 3. We postulate that the reaction proceeds by
formation of azoalkene in situ under base condition, which coordinates with chiral catalyst I to generate intermediate A, then undergoes a stereo-controlled IEDDA reaction with enol ether 2b to form the species B via transition state shown in
Scheme 3. The back side of azoalkene is occupied by the bulky tert-butyl group of the chiral ligand, which forces the enol ether to approach from the front side. Subsequently, species B releases the desired product 3ab and then regenerates the catalyst.

To probe this synthetic potential, we carried out the reaction of α-chloro N-benzoyl hydrazone 1a with enol ether 2b on a gram scale, the tetrapyridazine 3ae was isolated in high yield without any loss in enantioselectivity (Scheme 4).

Reduction of C=N bond in optically active 3ae by direct hydrogenation with catalytic amount of Pd/C furnishes compound 4ae in good yield with excellent diastereoselectivity.

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{Ph} & \quad \text{Cl} \\
\text{NH} & \quad \text{Ph} \\
\text{N} & \quad \text{C} \quad \text{N} \\
1a & \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

Cu(II)/L4 (10 mol%) Na2CO3 (2 equiv) DCM, -20°C

Scheme 4. Scale-up of Catalytic Asymmetric azo-Diels-Alder Reaction and Synthetic Transformations of the Cycloadduct 3ae.

In summary, we have successfully disclosed a highly
efficient Cu(II)/Bu-Phosferrox complex catalyzed enantio-
selective IEDDA reaction of enol ethers with in situ formed
azoalkenes. This newly developed methodology provides an
alternative access to chiral tetrapyridazines bearing a N,N-acetal stereocenter in high yields with good to excellent
enantioselectivities. Further applications of this protocol in
synthetic chemistry are ongoing in this laboratory.

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Notes and references
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