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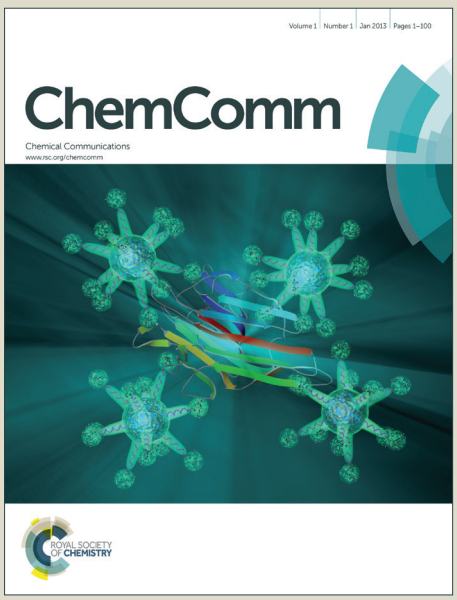

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Catalytic Asymmetric Synthesis of Tetrahydropyridazines *via* Inverse Electron-Demand aza-Diels-Alder Reaction of Enol Ethers with Azoalkenes

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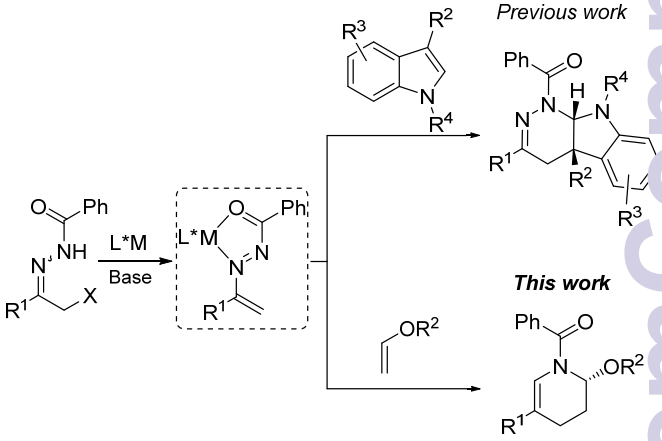
Abstract: A highly efficient Cu(II)-catalyzed enantioselective inverse-electron-demand aza-Diels-Alder reaction of *in situ* formed azoalkenes with enol ethers is reported. This methodology provides a facile entry to biologically important and enantioenriched tetrahydropyridazine derivates in generally 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 studies[2] of Kobayashi and co-works, 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 catalysis[3] and organocatalysis[4] have been successfully applied to promote asymmetric IEDDA reactions. Variant chiral pepiridine-, pyran- and cyclohexane derivates 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 date[5]. Undoubtedly, development of catalytic asymmetric IEDDA reaction that utilized novel diene-dienophile combinations is particularly an appealing and challenging task.

Tetrahydropyridazine[6], 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 hetercycles. In recent years, a range of transformations have been established using azoalkenes as suitable chemical handles. However, this field is 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(I)/^{t}Bu-Phosferrox complex which delivers [2,3]-fused indoline-tetrahydropyidazine heterocycles with high chemical yield, exclusive regioselectivity and excellent enantioselectivity (Scheme 1).[8a] We envisioned that this chiral Cu(I)/Phosferrox complex could be applied to promote IEDDA reaction of azoalkenes with enol ethers as efficient dienophiles to afford biologically useful enantioenriched tetrahydro-pyradazines bearing an *N, O*-acetal stereocenter.[9] 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).

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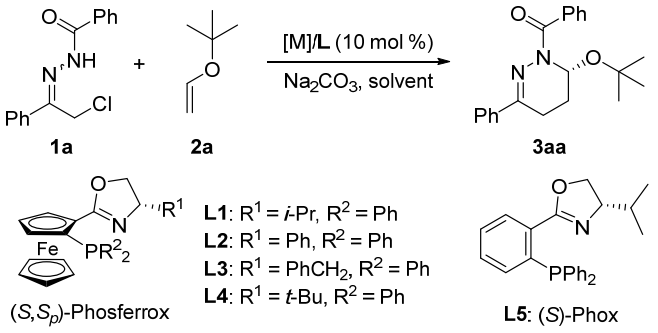
Table 1. Optimization of the Reaction Condition[a]

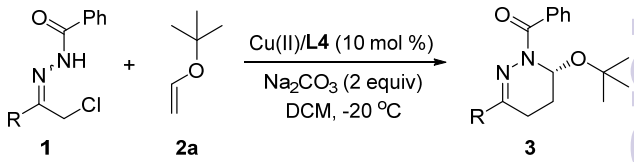


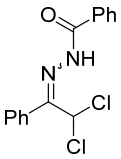
Entry	[M]	L	Solvent	*T* (°C)	Time (h)	yield (%)[b]	ee (%)[c]
1	-	-	DCM	rt	24	85	-
2	$CuBF_4$	**L1**	DCM	rt	12	58	56
3	$Cu(OTf)_2$	**L1**	DCM	rt	12	54	60
4	$Cu(OTf)_2$	**L2**	DCM	rt	12	78	5
5	$Cu(OTf)_2$	**L3**	DCM	rt	12	71	67
6	$Cu(OTf)_2$	**L4**	DCM	rt	12	92	80
7	$Cu(OTf)_2$	**L5**	DCM	rt	12	66	17
8	$Cu(OTf)_2$	**L4**	Ether	rt	18	trace	n.d
9	$Cu(OTf)_2$	**L4**	PhMe	rt	18	23	8
10	$Cu(OTf)_2$	**L4**	MeCN	rt	12	58	51
11	$Cu(OTf)_2$	**L4**	THF	rt	18	28	41
12	$Cu(OTf)_2$	**L4**	DCM	-20	18	83	94
13[f]	$Cu(OTf)_2$	**L4**	DCM	-20	30	77	82

[a] All reactions were carried out with 0.2 mmol of **1a** and 0.5 mmol of **2a** in 2.0 mL of solvent. $CuBF_4$ = $Cu(MeCN)_4BF_4$. [b] Isolated yield. [c] Ee was determined by HPLC analysis. [f] 5 mol % catalyst was used.

The initial investigation was performed on an uncatalyzed IEDDA reaction of α-chloro N-benzoyl hydrazone **1a** and 5 eqiuvalents of *tert*-butyl vinyl ether **2a** in the present of 2 eqiuvalents of Na_2CO_3. The transformation proceeded readily affording tetrahydropyridazines **3aa** in 85% yield (Table 1, entry1). The existence of strong background reaction has been the obstacle for developing asymmetric version of this transformation. Our previous work have demonstrated that the Cu(I)/Phosferrox complex effectively promoted catalytic aza-Diels-Alder and cross 1,3-dipolar cycloaddition reaction with high catalytic activity and excellent stereoselectivity control. Encouraged by those results and further examine the performance of this catalytic system, the model reaction was carried out with 10% mol of $Cu(MeCN)_4BF_4$/**L1** (1:1 ratio) as the catalyst in DCM at room temperature, which affording the desired product **3aa** in 58% yield and 56% ee (Table 1, entry 2). Switching the copper salts from Cu(I) to Cu(II) slightly improved the enatioselectivity (Table 1, entry 3). Inspired by this preliminary study, we further tested other commonly-used chiral P, N-ligands (Table 1, entry 4-7). To our delight, (S,S_p)-^{t}Bu-Phosferrox (**L4**) exhibited the highest asymmetric induction among them, delivering the compound **3aa** in 92% yield with 80% ee. Subsequent studies on solvent in the presence of $Cu(OTf)_2$/**L4** revealed dicloromethan to be optimal (Table 1, entry 5 versus entry 6-10), which disclosed a significant solvent effect for the cycloaddition both in reaction activity and stereoselectivity control. Reduce the reaction temperature from room temperature to -20 °C led to an improvement in the enantioselectivity without noticeable decrease in the chemical yield (entry 12). The catalyst Cu(II)/**L4** is quite efficient. When 5 mol % of the catalyst loading was employed, the desired cycloadduct could be isolated in 77% yield with 82% ee, albeit required a longer reaction time (entry13).

Table 2. Substrate Scope of Catalytic Asymmetric IEDDA Reaction of Various Hydrazones **1** with *tert*-Butyl Vinyl Ether **2a**[a]



Entry	**1**	R	**3**	yield (%)[b]	ee (%)[c]
1	**1a**	Ph	**3aa**	83	94
2	**1b**	*p*-MeO-C_6H_4	**3ba**	83	92
3	**1c**	*p*-Me-C_6H_4	**3ca**	90	94
4	**1d**	*m*-Me-C_6H_4	**3da**	71	87
5	**1e**	*o*-Me-C_6H_4	**3ea**	82	90
6	**1f**	*p*-Br-C_6H_4	**3fa**	92	92
7	**1g**	*p*-Cl-C_6H_4	**3ga**	92	93
8	**1h**	*m*-Cl-C_6H_4	**3ha**	78	72
9	**1i**	*o*-Cl-C_6H_4	**3ia**	90	94
10	**1j**	1-Nap	**3ja**	85	86
11	**1k**	2-Nap	**3ka**	88	84
12	**1l**		**3la**	62	83[d,e]

[a] All reactions were carried out with 0.2 mmol of **1** and 0.5 mmol of **2a** in 2.0 mL CH_2Cl_2. [b] Isolated yield. [c] Determined by HPLC analysis. [d] >20:1 dr was determined by the crude ^{1}H NMR. [e] The reaction was performed at -40 °C.

With optimized reaction conditions in hand, we set out to extend this methodology with respect both to α-chloro N-benzoyl hydrozone (**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 tetrahydropyridazines were synthesized in generally high yields (entry 1-9, 71-92% yield) with good to excellent enantioselectivities (72-94% ee). Additionally, 1- and 2-naphthyl-subsituted 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

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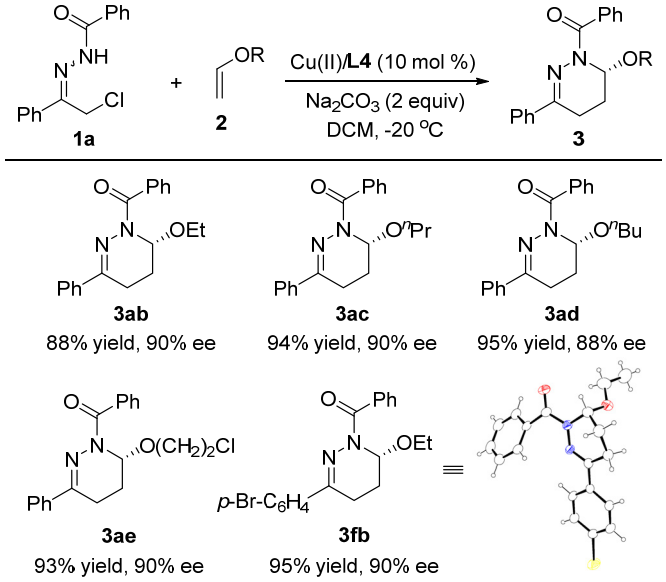
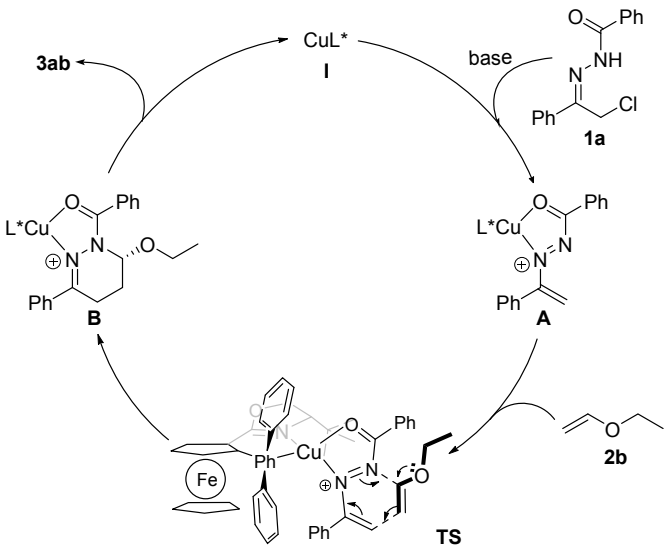
stereogenic centers in slightly lower yield with exclusive diastereoselectivity (>20:1) and 83% ee (entry 12). The relative configuration of **3la** was determined through NOESY (see ESI for more details).



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

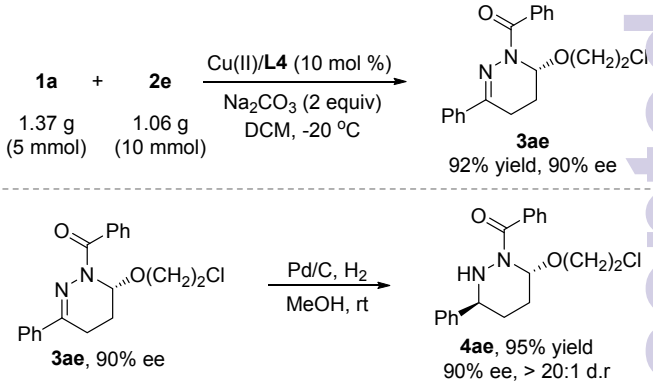
Encouraged by the results of α-chloro N-benzoyl hydrazones with bulky and branched *tert*-butyl vinyl ether **2a**, we then investigated the IEDDA reactions with an array of enol ethers bearing linear alkyl groups as the dienophiles (Scheme 2). The tested enol ethers proved to be efficient reaction partners delivering the desired cycloadducts in high yields (88-95% yield) 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.



Scheme 3. Proposed mechanism and transition state for Cu(II)-catalyzed asymmetric IEDDA reaction of azoalkenes with enols.

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**. **A** then undergoes a stereo-controlled IEDDA reaction with enol ether **2b** to form the species **B** via tranisiton 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 **2e** 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 furnished compound **4ae** in good yield with excellent diastereoselective manner.



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)/^{t}Bu-Phosferrox complex catalyzed enantioselective IEDDA reaction of enol ethers with *in situ* formed azoalkenes . This newly developed methodology provides an alternative access to chiral tetrapyridazines bearing a N,O-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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† Electronic supplementary information (ESI) available: Experimental section. CCDC 1416442. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc00000x

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