Metal-Containing Carbonyl Ylides: Versatile Reactants in Catalytic Enantioselective Cascade Reactions**

Jia-Rong Chen, Xiao-Qiang Hu, and Wen-Jing Xiao*

asymmetric catalysis · cyclizations · heterocycles · synthetic methods · ylides

Catalytic asymmetric cascade reactions represent one of the most powerful and efficient methods for the rapid assembly of biologically active and complex chiral molecules from simple substrates.[1] In this context, the discovery of new strategies through exploration of new reagents, reactive intermediates, and catalytic modes is extremely important in the search for more efficient and stereoselective cascade processes. In particular, the identification of highly reactive intermediates and reaction design provide a fruitful platform for the development of new cascade reactions. In situ generated transition-metal-containing carbonyl ylides have recently emerged as a unique type of versatile agent having a range of applications in various cascade reactions.[2]

Typically, these highly reactive ylide intermediates are generated in situ by the intramolecular cyclization of enynal or enyone substrates which are electrophilically activated by transition metals such as W^0, Cu^{II}, Pt^{II}, $Au^{I/III}$, Ag^I, Rh^I, and Pd^{II} (Scheme 1). By using these intermediates, many synthetically useful chemical reactions have been developed, reactions such as nucleophilic addition, [3+2] annulation, and [4+2] cycloaddition.[2] Because of their highly reactive properties and unique planar structure, however, the catalytic enantioselective variants of these transition-metal-containing carbonyl ylides remain largely unexploited and are a significant opportunity for organic chemists. Recent advances in the development of mechanistic approaches and chiral ligand/catalyst design have provided a new powerful platform for reaction engineering and stereocontrol.[3] Currently, this scenario seems to change rapidly and several conceptually new and catalytic asymmetric reactions with these intermediates have been elegantly devised. Herein we highlight the recent advances in this regard and hope to encourage chemists to think about such transition-metal-containing carbonyl ylides from different points of view, thereby identifying new enantioselective transformations with this species.

An inspiring breakthrough in this field was reported by Tanaka and colleagues in 2009.[4a] By employing a cooperative catalysis strategy, they developed the first example of chiral cationic rhodium(I) complexes for catalyzing the asymmetric cascade reaction of 2-alkynylbenzaldehydes (**1**) with the carbonyl compounds **2**, thus providing an efficient entry to highly functionalized and enantioenriched tetrasubstituted alkenes (Scheme 2a). The reaction was proposed to proceed through the initial formation of the key transition-metal-containing carbonyl ylide, rhodiumbenzopyrilium **A1**. The cycloaddition of this intermediate with **2** and a subsequent ring-opening/intramolecular enantioselective ketone hydroacylation sequence leads to the ketoaldehyde **C**, which afforded the desired products **3**. Notably, the Rh^I and additive Ag^I might work in a synergistic catalytic mode, though the exact role of silver salt remains elusive. By using a similar strategy, the group of Iwasawa developed an asymmetric [3+2] cycloaddition between the platinum-containing carbonyl ylides **A2**, derived in situ from the γ,δ-ynones **5**, and the vinyl ethers **6** (Scheme 2b).[4b] A wide range of synthetically valuable 8-oxabicyclo[3.2.1]octane derivatives (**7**) were obtained in a highly enantioselective fashion.

The development of novel catalytic systems and underlying modes of activation have played an important role in the identification of new enantioselective cascade reactions. In this regard, the group of Slaughter disclosed an alternative reaction mode for transition-metal-containing carbonyl ylides through the design of a new type of acyclic diaminocarbene
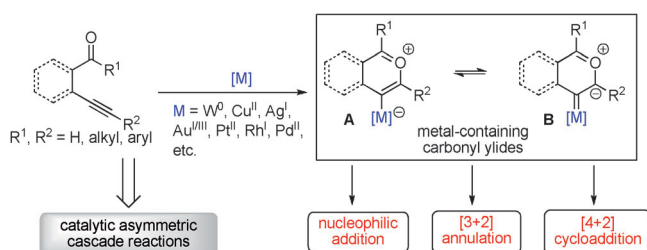
Scheme 1. Reactivity modes of transition-metal-containing carbonyl ylides.
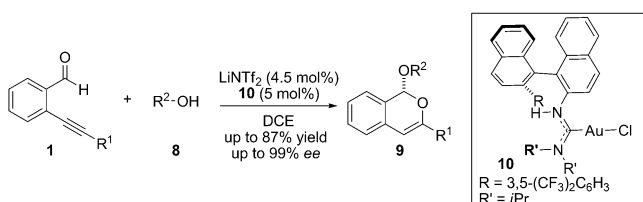
[*] Prof. Dr. J.-R. Chen, X.-Q. Hu, Prof. Dr. W.-J. Xiao
CCNU-OttawaU Joint Research Centre, Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University
152 Luoyu Road, Wuhan, Hubei 430079 (China)
and
Collaborative Innovation Center of Chemical Science and Engineering, Tianjin (China)
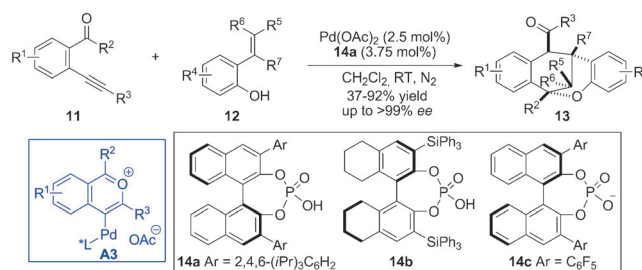E-mail: chenjiarong@mail.ccnu.edu.cn
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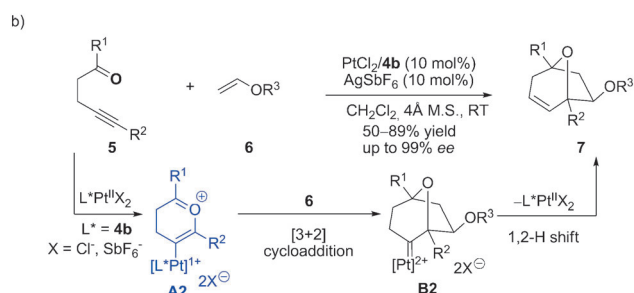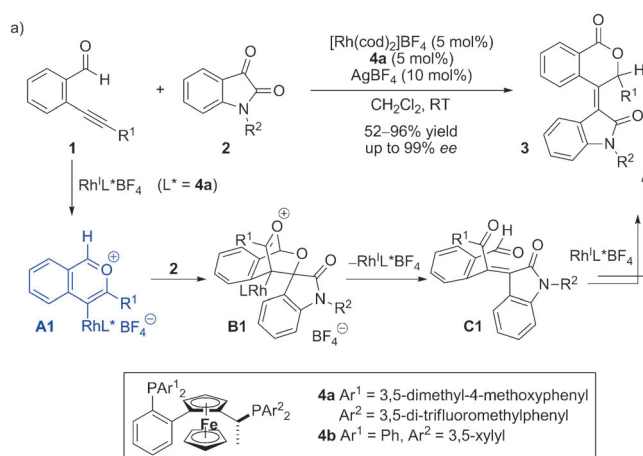
Scheme 2. Rhodium(I)- or platinum(II)-catalyzed asymmetric reactions through metal-containing carbonyl ylide intermediates.

Scheme 4. Palladium(II)/phosphoric-acid-catalyzed cascade annulations involving palladium-containing isochromenylium intermediates.

to the work of Tanaka et al.,[4a] the key chiral palladium-containing isochromenylium intermediate formed through intramolecular cyclization and anionic exchange underwent an oxa-Diels–Alder reaction/intramolecular nucleophilic substitution cascade. Control experiments with masked o-hydroxy groups on styrene substrates also confirmed the important role of the hydroxy moiety on the reaction pathway and stereochemical induction.

The strategy of Yao has also served as a good proof of concept for asymmetric counteranion-directed catalysis (ACDC),[3] and opened a new path for the application of transition-metal-containing carbonyl ylides in asymmetric synthesis. Quite recently, the ACDC strategy was successfully applied by the group of Akiyama to a copper(II) phosphate catalyzed intramolecular cyclization/asymmetric transfer-hydrogenation cascade of o-alkynylacetophenones (11; Scheme 5).[7a] The reaction worked efficiently to give the corre-

ligand (Scheme 3).[5] In this case, the chiral gold(I)/acyclic diaminocarbene complex 10 could efficiently catalyze the enantioselective cyclization/acetalization cascade of the alkynylbenzaldehydes 1 with aliphatic alcohols (8). A key aspect of the reaction relies on the successful formation of a gold-containing carbonyl ylide. Although the scope of alcohols is limited, this methodology has lent credence to the design of other new enantioselective reactions of metal-containing carbonyl ylides.

Scheme 5. Copper(II) or silver(I) phosphate catalyzed intramolecular cyclization/asymmetric transfer-hydrogenation cascade reactions.

sponding isochromenes 16 in fine yields and enantiomeric excesses of up to 97%. At the same time, a similar methodology with broader substrate scope was developed by Terada et al., wherein a chiral silver(I) phosphate complex served as an efficient catalytic system (Scheme 5).[7b] Notably, the control experiments with possible intermediates suggested that an ionic pair comprising a silver-containing isobenzopyrylium species and a chiral phosphate could be the key reactive intermediate for this cascade reaction.

In summary, recent advances on the use of transition-metal-containing carbonyl ylides in catalytic asymmetric cascade reactions have been highlighted with a focus on the reaction design and catalytic modes. However, the full exploration of these reactive intermediates in asymmetric synthesis requires additional research. We hope that this paper will encourage the development of more enantioselec-

Scheme 3. Gold(I)-catalyzed asymmetric cyclization/acetalization cascade of alkynylbenzaldehydes with alcohols.
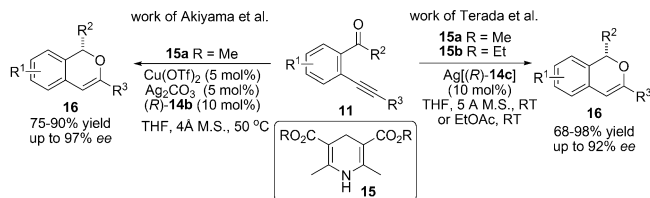
Quite recently, the group of Yao group reported an elegant enantioselective cascade annulation of 2-alkylbenzaldehydes or 1-(2-alkynylphenyl)ketones (11; Scheme 4).[6] The use of the cooperative catalytic system of Pd(OAc)$_2$ and the chiral binaphthyl phosphoric acid 14a afforded good yields of densely substituted and structurally complex bridged-ring systems (13) with excellent stereoselectivities. However, in sharp contrast

tive chemical transformations involving these reactive intermediates.

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