Relay Catalysis

DOI: 10.1002/anie.201204234

Relay Catalysis Enables Hydrogen Gas to Participate in Asymmetric Organocatalytic Hydrogenation

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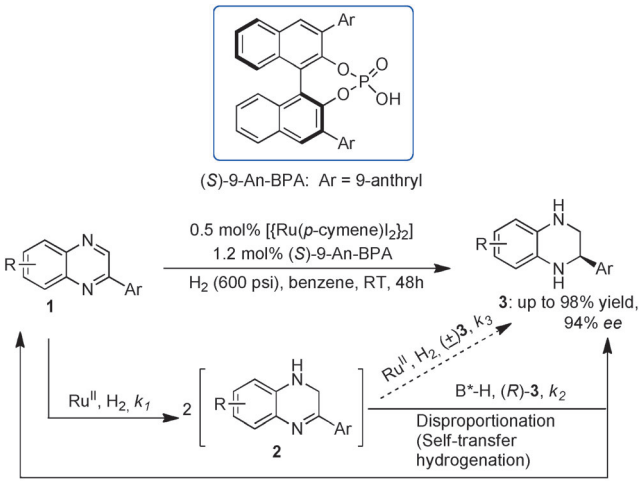
enantioselectivity · hydrogenation · organocatalysis · relay catalysis

Asymmetric hydrogenation using clean hydrogen gas provides an almost waste-free protocol for the preparation of a vast range of chiral molecules and thereby plays an important role in synthetic organic chemistry. The enantioselectivity of this transformation depends on the chiral ligands in the transition-metal complexes that activate both hydrogen gas and unsaturated chemical bonds.[1] The transition-metal-catalyzed reaction is the established and most reliable strategy to realize asymmetric hydrogenation. On the other hand, highly active hydride donors, such as Hantzsch esters (HEH), are exploited as external reductants in organocatalytic enantioselective reductions,[2] but hydrogen gas is considered to be an inert substrate in such processes.

However, these traditional concepts have been refuted by recent reports by Zhou and co-workers on the elegant asymmetric hydrogenation of N heterocycles.[3–5] These newer procedures take advantage of ruthenium complex/chiral phosphoric acid relay catalysis,[6,7] in which the hydrogen gas participates in the chiral phosphoric acid catalyzed hydrogenation of the aryl heterocycle and replaces the active hydride donor as the terminal reductant.

Rueping and co-workers reported that 2-arylquinoxalines and other heterocycles could undergo a highly enantioselective transfer hydrogenation with HEH catalyzed by a chiral phosphoric acid.[8] Xiao et al. demonstrated that the combination of chiral Ir^{III} catalysts and Brønsted acids afforded a highly enantioselective hydrogenation of acyclic ketimines, in which hydrogen gas was exploited as the reductant.[9] Inspired by these findings, Zhou et al. proposed the asymmetric hydrogenation of quinoxalines **1** to give chiral tetrahydroquinoxalines **3** through the relay catalysis of [{Ru(*p*-cymene)I_2}$_2$] and binol-based phosphoric acid derivatives (BPA; binol = 1,1′-bi-2-naphthol).[3] The hydrogenation of quinoxalines **1** with hydrogen gas in the presence of ruthenium(II) efficiently generated intermediate dihydroquinoxalines **2**, which then underwent self-transfer hydrogenation catalyzed either by a Brønsted acid (B*–H) or the ruthenium complex to deliver the starting compounds **1** along with tetrahydroquinoxalines **3** (Scheme 1). The first ruthenium(II)-catalyzed hydrogenation process is the rate-determining step. The enantioselective reduction of **2** was found to proceed much faster than the nonselective process catalyzed by the ruthenium complex, such that the entire relay catalytic reduction of **1** proceeded in excellent yields and with high enantioselectivity. More importantly, quinoxalines **1** actually function as a hydride shuttle by converting hydrogen gas into the active hydride source **2**.



Scheme 1. Disproportionation of dihydroquinoxalines.

This finding indicated that the use of a catalytic amount of the hydride source or the precursor, in combination with the ruthenium complex and the chiral phosphoric acid, could initiate the real organocatalytic enantioselective hydrogenation of N heterocycles using hydrogen gas as the terminal reductant. The hydride source, HEH and its analogues, could be catalytically regenerated by the partial hydrogenation of the corresponding N heterocycles in the presence of the ruthenium complex under hydrogen gas [Eq. (1)].

On the other hand, it has been well-established that aryl heterocycles are capable of undergoing enantioselective transfer hydrogenation using HEH-type hydride donors as

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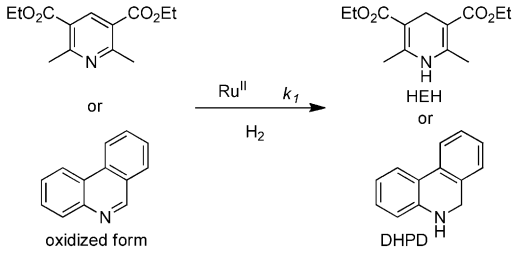
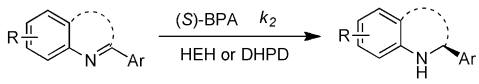


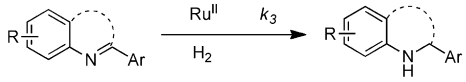
(1)

reductants in the presence of chiral BPA [Eq. (2)].[8] However, an undesired non-stereoselective hydrogenation of aryl heterocycles catalyzed by the Ru^{II} complex may also occur



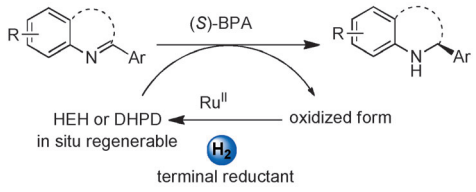
(2)

with hydrogen gas that competes with the chiral phosphoric acid catalyzed asymmetric transfer hydrogenation [Eq. (3)].



(3)

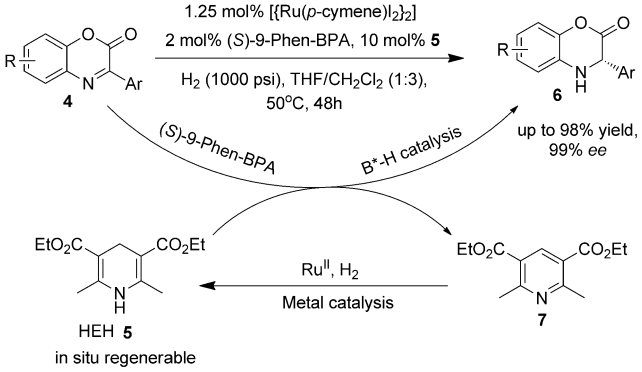
Despite this, excellent enantioselectivity could still be achieved as long as the rate of BPA-catalyzed transfer hydrogenation (k_2) is much greater than that of the undesired side reaction (k_3). As such, the relay catalysis using the combined Ru, chiral BPA, and a catalytic amount of catalytically regenerable hydride donor would afford the asymmetric hydrogenation in which the chiral BPA controls the stereochemistry [Eq. (4)].



(4)

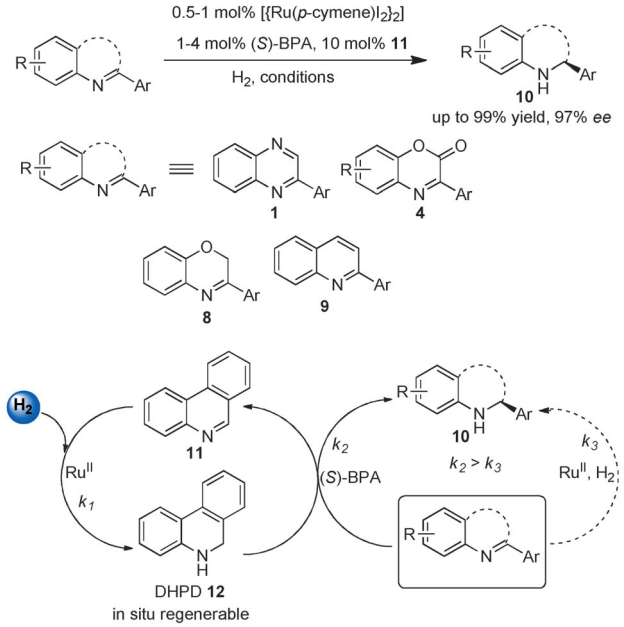
Indeed, Zhou and co-workers successfully exploited such a strategy for the asymmetric hydrogenation of benzoxazinones **4** in the presence of (*S*)-9-Phen-BPA and a catalytic amount of HEH (**5**). After participating in the enantioselective transfer hydrogenation of benzoxazinones **4** catalyzed by phosphoric acid, HEH could be regenerated in situ from the hydrogenation of its oxidized form, diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**7**), in the presence of the [{Ru(*p*-cymene)I_2}$_2$] catalyst under hydrogen gas (Scheme 2).[4]

In an extension of this work, this same group very recently found that 9,10-dihydrophenanthridine (DHPD, **12**) can act as a new and easily regenerable hydrogen source instead of the commonly used HEH. DHPD was capable of facilitating smooth transfer hydrogenation of a wide scope of aromatic



Scheme 2. Asymmetric hydrogenation of benzoxazinones using a catalytic amount of HEH. 9-Phen = 9-phenanthryl.

N heterocycles including quinoxalines (**1**), benzoxazinones (**4**), benzoxazines (**8**), and quinolines (**9**) (Scheme 3).[5] More importantly, this reagent could be generated readily from the



Scheme 3. Asymmetric hydrogenation of aromatic compounds using a catalytic amount of DHPD.

hydrogenation of phenanthridine (**11**) catalyzed by the ruthenium complex under mild conditions. Similar to the previous strategy of Ru^{II}/BPA relay catalysis, the asymmetric transfer hydrogenation of aromatic compounds with DHPD catalyzed by (*S*)-BPA gave enantiomerically enriched products **10** along with phenanthridine (**11**), which was then reduced by hydrogen gas in the presence of the ruthenium complex to regenerate DHPD for the next catalytic cycle. The excellent enantioselectivities observed in these transformations are explained by the fact that the rate of the BPA-catalyzed transfer hydrogenation (k_2) is faster than that of the undesired side reaction (k_3). Therefore, the multiple catalyst system consisting of the ruthenium complex, phenanthridine,

and phosphoric acid allows hydrogen gas to be the terminal reductant for the asymmetric hydrogenation of heterocyclic compounds in excellent enantioselectivities.

The process described herein is distinct from the classical chiral-ligand-controlled asymmetric hydrogenation and therefore represents a completely new strategy in asymmetric hydrogenation. This approach with hydrogen gas as the terminal reductant and a catalytic amount of HEH is more atom-economical than classical transfer hydrogenation with HEH or other hydride reagents alone.[2] Notably, these successful reactions actually confirm that the combination of metals with organocatalysts is indeed a robust concept for the creation of new reactions, in particular asymmetric catalytic reactions.[7,10]

Received: May 31, 2012
Published online: October 8, 2012

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