Tandem Reactions

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Asymmetric Hydrogenation of In Situ Generated Isochromenylium Intermediates by Copper/Ruthenium Tandem Catalysis

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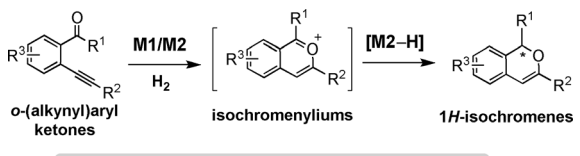
Abstract: *The first asymmetric hydrogenation of in situ generated isochromenylium derivatives is enabled by tandem catalysis with a binary system consisting of $Cu(OTf)_2$ and a chiral cationic ruthenium–diamine complex. A range of chiral 1H-isochromenes were obtained in high yields with good to excellent enantioselectivity. These chiral 1H-isochromenes could be easily transformed into isochromanes, which represent an important structural motif in natural products and biologically active compounds. The chiral induction was rationalized by density functional theory calculations.*

Optically active, saturated or partially saturated heterocycles are important structural motifs of many biologically active compounds, natural products, and chiral ligands.[1] While a huge number of methods have been developed for the synthesis of such chiral compounds, asymmetric hydrogenation (AH) of often readily available heteroaromatic compounds represents one of the most straightforward and efficient approaches.[2] Since Murata and co-workers reported the first homogeneous AH of 2-methylquinoxaline in 1987,[3] a variety of bicyclic and monocyclic N-heteroaromatic compounds have been hydrogenated with very good reactivity and excellent enantioselectivity.[4,5] However, significantly fewer effective AHs of oxygen- and sulfur-containing heteroaromatic compounds have been reported.[6]

Isochromenyliums are highly reactive intermediates that are often generated in situ for various transformations, and have found wide applications in synthetic chemistry.[7–9] Over the last decade, a range of catalytic cascade reactions based on isochromenyliums, such as [3+2] annulations, [4+2] cycloadditions, and nucleophilic addition reactions, have been realized by transition-metal catalysis and/or organocatalysis.[8] Despite this great progress, asymmetric variants of these transformations were developed only recently, mainly because of the lack of coordination sites within their planar structure (Hückel aromatic compounds), which is often crucial for achieving high reactivity and/or stereoselectivity.[9] Most recently, the groups of Akiyama[9g] and Terada[9h] independently reported notable examples of asymmetric transfer hydrogenation (ATH) reactions of in situ generated isochromenyliums by chiral-counteranion-directed catalysis. These methods, however, still suffer from some drawbacks, such as high catalyst loadings and lack of substrate generality (only one dialkyl-substituted substrate with 22% *ee*). To the best of our knowledge, catalytic AHs of isochromenylium derivatives, which would provide a facile and environmentally friendly approach to important enantiopure O-containing heterocycles, have not been reported thus far.[9g,h,10]

Most recently, we found that the cationic ruthenium complexes of chiral monosulfonated diamines are very efficient catalysts for the AH of various N-heteroaromatic compounds with excellent reactivity and enantioselectivity.[5] Encouraged by these results, we attempted to use these catalyst systems for the AH of the highly reactive isochromenyliums. According to reported methods,[9a] isochromenyliums can be generated in situ by treatment of *ortho*-(alkynyl)aryl ketones with various metal catalysts. It was thus important to find two compatible catalysts for the overall reaction that also control the chemoselectivity and enantioselectivity (Scheme 1). Herein, we report the first AH of a range of in situ generated O-heteroaromatic isochromenylium derivatives by bimetallic tandem catalysis that provides the corresponding 1*H*-isochromenes in high yields and enantioselectivities.

For our initial investigations, *ortho*-(alkynyl)aryl ketone **1a** was chosen as the model substrate as a precursor of the corresponding isochromenylium ion.[9g,h] Several chiral transition-metal complexes that had previously been proven to be



- Finding a compatible M1/M2 bimetallic catalyst system
- Controlling chemoselectivity (ketone vs. oxonium ion)
- Controlling the enantioselectivity (planar structure)

Scheme 1. Enantioselective hydrogenation of the in situ generated isochromenyliums.

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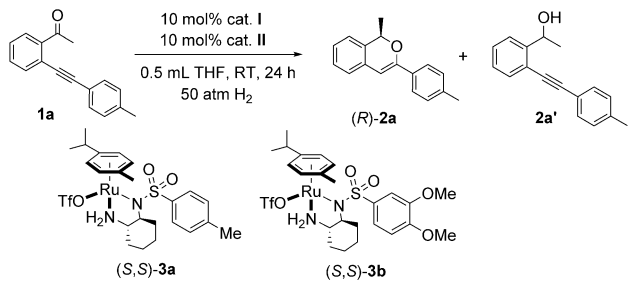
efficient AH catalysts were examined in combination with $Cu(OTf)_2$ as the second catalyst (Table 1; see also the Supporting Information, Table S1). However, the desired product was obtained in rather low yields and enantioselectivities when frequently used complexes based on a chiral diphosphine ligand, such as BINAP/Ru^{II}, BINAP/Rh^{I}, and BINAP/Ir^{I}, were used. Gratifyingly, the tandem reaction with ruthenium–diamine catalyst (*S*,*S*)-**3a** proceeded smoothly in THF, affording exclusively chiral 1*H*-isochromene **2a** in >95% yield and 88% *ee* (Table 1, entry 1). Several other π-Lewis acidic metal complexes, such as AgOTf, $Zn(OTf)_2$, $Pd(OAc)_2$, and $W(CO)_6$, were also tested; however, only AgOTf gave the desired product with similar enantioselectivity but in lower yield (Table 1, entry 2). Subsequently, several chiral ruthenium–diamine catalysts were screened with $Cu(OTf)_2$ as the optimal catalyst **I**. The catalytic performance was clearly affected by the *N*-sulfonate substituents, and catalyst (*S*,*S*)-**3b** turned out to be optimal in terms of both catalytic activity and enantioselectivity (Table S1). Interestingly, the ratio of the Cu and Ru catalysts significantly influenced the outcome of this tandem reaction. Rather low yields and enantioselectivities were observed with 5 mol% $Cu(OTf)_2$ and 10 mol% (*S*,*S*)-**3a** under otherwise identical reaction conditions (Table S5). Most importantly, excellent yields and similar enantioselectivities were also achieved with a much lower catalyst loading (Table 1, entry 6).[11]

Table 1: Catalyst screening.[a]

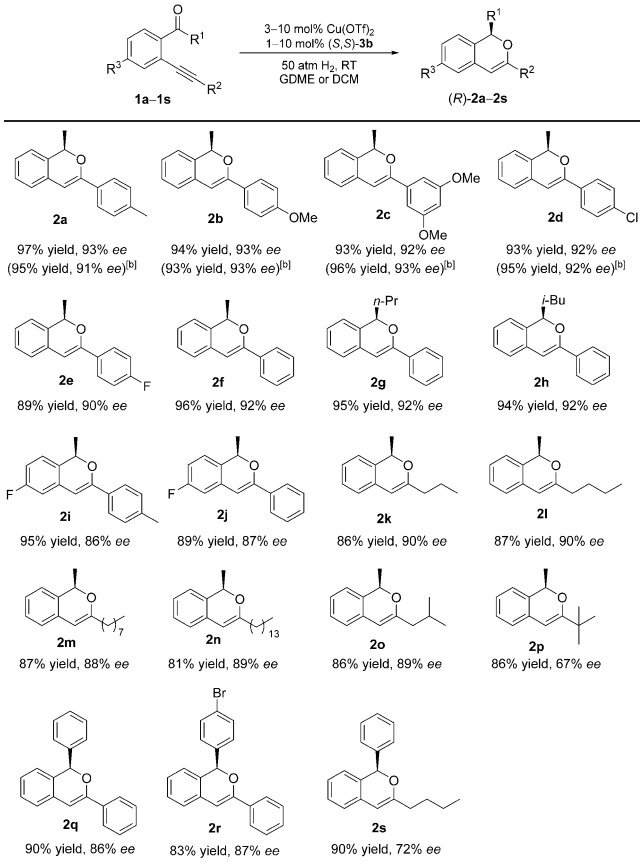


Entry	Catalyst I	Catalyst II	Conv. [%][b]	Yield [%][b] 2a	2a′	*ee* of 2a [%][c]
1	$Cu(OTf)_2$	(*S*,*S*)-**3a**	>95	>95	–[d]	88
2	AgOTf	(*S*,*S*)-**3a**	>95[e]	70	–[d]	88
3	–	(*S*,*S*)-**3a**	24	–[d]	21	5[f]
4	$Cu(OTf)_2$	(*S*,*S*)-**3b**	>95	92	–[d]	91
5[g]	$Cu(OTf)_2$	(*S*,*S*)-**3b**	>95	>95	–[d]	93
6[g,h]	$Cu(OTf)_2$	(*S*,*S*)-**3b**	>95	>95	–[d]	91

[a] Reaction conditions: **1a** (0.1 mmol) in 0.5 mL THF, **I** (10 mol%), **II** (10 mol%), H_2 (50 atm), stirred at room temperature for 24 h. [b] Determined by ^{1}H NMR analysis of the crude product mixture with 1,3,5-trimethoxybenzene as the internal standard. [c] Determined by HPLC analysis with a chiral OD-H column. [d] Compound **2a** or **2a′** not observed. [e] A complex mixture was obtained. [f] The *ee* value of **2a′**. [g] Ethylene glycol dimethyl ether (GDME) as the solvent, 4 h. [h] $Cu(OTf)_2$ (3 mol%) and (*S*,*S*)-**3b** (1 mol%), 24 h. Tf = trifluoromethanesulfonyl.

Under the optimized reaction conditions, a variety of *ortho*-(alkynyl)aryl ketones were subjected to the tandem reaction, affording the desired *R*-configured 1*H*-isochromenes **2a**–**2s** in excellent yields and enantioselectivities (Table 2). Introducing electron-donating or electron-withdrawing substituents at the *para* position of the aryl group at the alkyne terminus did not affect the reaction outcome, and high yields and excellent enantioselectivities were still observed (**2a**–**2f**). The high yields and enantioselectivities were also maintained when the catalyst loadings were reduced. Substrates bearing linear or branched alkyl chains at the R^1 position also reacted smoothly without a decrease in yield or enantioselectivity (**2g** and **2h**). The introduction of a fluorine substituent on the tethered aryl ring slightly decreased the *ee* (**2i** and **2j**). Gratifyingly, tandem reactions of substrates with alkyl substituents at both the R^1 and R^2 position afforded the desired products with slightly lower but still good reactivities and enantioselectivities (**2k**–**2o**), which are much better than the 22% *ee* achieved when **2l** was obtained by transfer hydrogenation.[9h] Interestingly, substrate **1p**, bearing a sterically demanding *tert*-butyl group at the R^2 position, gave the corresponding product in good yield, albeit

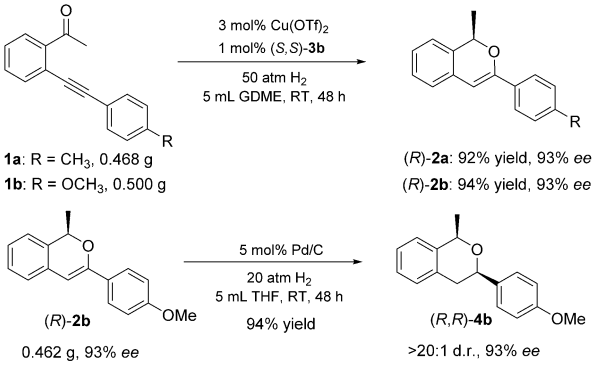
Table 2: Scope of the tandem reaction.[a]



[a] Reaction conditions: **1a**–**1s** (0.1 mmol), $Cu(OTf)_2$ (10 mol%), (*S*,*S*)-**3b** (10 mol%), H_2 (50 atm), stirred at room temperature for a certain period of time (**2a**–**2j**, **2q**, **2r**: 4 h; **2k**–**2o**, **2s**: 16 h; **2p**: 24 h). For **2a**–**2p**, the hydrogenation was done in GDME. For **2q**–**2s**, the hydrogenation was done in DCM. The absolute configurations of the products were determined by comparison with literature data.[9g,h] [b] $Cu(OTf)_2$ (3 mol%), (*S*,*S*)-**3b** (1 mol%), 24 h.

with much lower enantioselectivity. For substrates with an aryl substituent at the R^1 position, the reactions proceeded smoothly irrespective of whether R^2 was an aryl or alkyl group when dichloromethane (DCM) was used as the solvent (**2q**–**2s**).

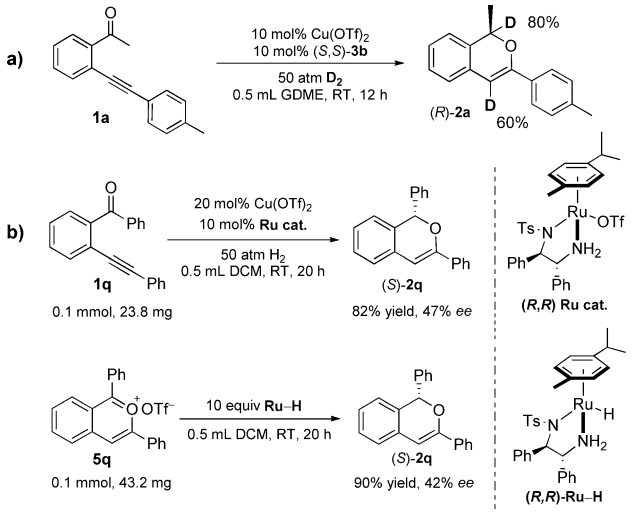
The usefulness of this catalytic asymmetric tandem reaction was exemplified by the scale-up synthesis of a few *R*-configured 1*H*-isochromenes (Scheme 2). With $Cu(OTf)_2$ (3 mol%) and (*S*,*S*)-**3b** (1 mol%), the 1*H*-isochromenes (*R*)-**2a** and (*R*)-**2b** were isolated in greater than 90% yield and with the same enantiopurity as for the small-scale reactions. Heterogeneous hydrogenation of (*R*)-**2b** provided the corresponding chiral isochromane with excellent diastereoselectivity.



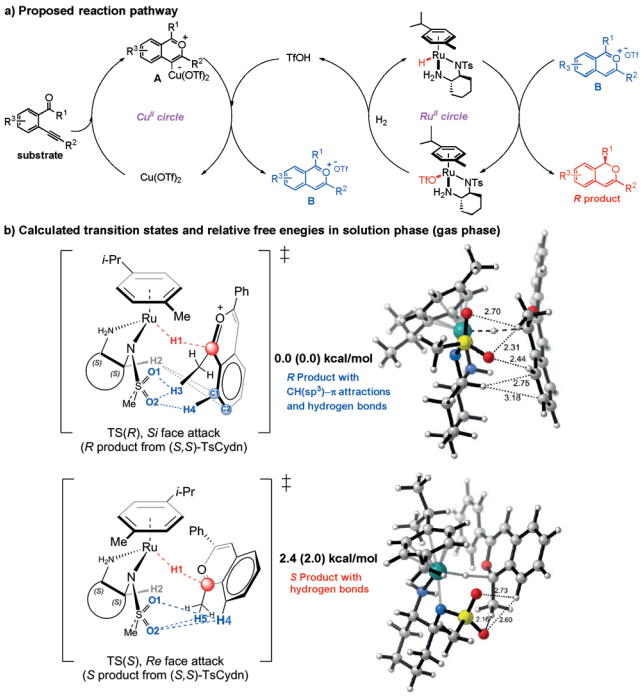
Scheme 2. Scale-up reactions and product transformation.

To understand the mechanistic details of this tandem reaction, several control experiments were carried out. First, we checked whether side product **2a′** undergoes intramolecular cyclization under the reaction conditions. As expected, no conversion was observed, and **2a′** was recovered. In a deuterium labeling study (Scheme 3a), 80% and 60% deuterium incorporation was observed at the C1 and C4 position, respectively.[12] In addition, the stable isochromenylium salt **5q** was successfully synthesized and reacted with an excess amount of a Ru–H complex. The yield and enantiopurity of the product were similar to those achieved in the standard tandem reaction starting from *ortho*-(alkynyl)aryl ketone **1q** (Scheme 3b). These results indicate that isochromenyliums are intermediates of these tandem reactions.

Based on the results obtained above, a plausible reaction mechanism was proposed for the cooperative catalysis process (Scheme 4). First, the *ortho*-(alkynyl)aryl ketone reacts with $Cu(OTf)_2$ to generate isobenzopyrylium salt **A**.[8b] Meanwhile, the ruthenium–diamine catalyst reacts with dihydrogen to produce a Ru–H complex and TfOH. Then, protonolysis of the C–Cu bond of **A** by TfOH regenerates $Cu(OTf)_2$ and gives the isobenzopyrylium intermediate **B**.[8b] Finally, hydride transfer from the Ru–H complex to isobenzopyrylium intermediate **B** affords the desired product and regenerates the ruthenium–diamine catalyst.



Scheme 3. Control experiments to confirm the involvement of isochromenylium intermediates.



Scheme 4. Proposed catalytic cycle and the transition states computed for the hydride transfer.

Density functional theory (DFT) calculations at the B3LYP/6-31G(d,p)(LANL2DZ for Ru) level of theory[13] were carried out to gain further insight into the origin of the enantioselectivity. Two hydride transfer transition states **TS(*R*)** and **TS(*S*)**, which lead to the *R*- and *S*-configured products, respectively, were located (Scheme 4 and Scheme S4). It was found that **TS(*R*)** is favored over **TS(*S*)** by 2.4 kcal mol^{-1} in terms of the Gibbs free energy in DCM solution (the energy difference in the gas phase is 2.0 kcal mol^{-1}), suggesting that the *R*-configured product is the kinetically favored product of the reaction. This is consistent with our experimental observations (Table 2, **2f**). It was

found that the most favorable transition state **TS(*R*)** was stabilized by three hydrogen bonding interactions between the O atoms of the tosyl group of the catalyst and two different H atoms (one from the methyl group and one on the fused arene ring) of the substrate. The fused arene ring of the substrate is almost perpendicular to the C–H2 bond that is adjacent to the *N*-tosyl group of the catalyst, affording a CH(sp^3)–π interaction that is similar to that found in Noyori's ketone ATH system.[14] These stabilization interactions by hydrogen bonding and CH(sp^3)–π attractions in **TS(*R*)** were supported by AIM calculations.[15] Such CH(sp^3)–π stabilizing interactions are absent in the competing transition state **TS(*S*)** even though **TS(*S*)** features three C–H–O interactions between hydrogen atoms on the fused arene ring of the substrate and the tosylate oxygen atoms. These interactions could be weaker than the hydrogen bonding and CH(sp^3)–π interactions in **TS(*R*)**, and consequently, **TS(*S*)** is not favored in the reduction process.

In conclusion, we have demonstrated that in situ generated isochromenyliums can be enantioselectively hydrogenated by Cu^{II}/Ru^{II} tandem catalysis. A broad range of *ortho*-(alkynyl)aryl ketones were transformed into chiral isochromenes in high yields with good to excellent enantioselectivity. This method thus provides a practical and green approach for the construction of optically pure isochromenes and other O-containing heterocycles. We believe that this strategy will stimulate further work on the asymmetric hydrogenation of other challenging reactive heteroaromatic compounds.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · heterocycles · hydrogenation · ruthenium · tandem reactions

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[11] Both the yield and the enantioselectivity of the tandem reaction were affected by the solvent (Table S3), and the enantioselectivity was insensitive to the reaction temperature and hydrogen pressure (Table S4).

[12] This deuterium distribution is discussed in Scheme S7.

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Communications

Tandem Reactions

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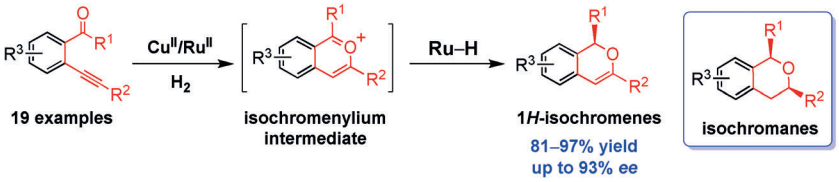
Asymmetric Hydrogenation of In Situ Generated Isochromenylium Intermediates by Copper/Ruthenium Tandem Catalysis



Two metal catalysts: The title reaction is catalyzed by a binary system based on $Cu(OTf)_2$ and a chiral ruthenium–diamine complex. A range of chiral 1*H*-isochromenes were obtained in high yields with good to excellent enantioselectivities, and were easily transformed into isochromanes.

