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Ruthenium–NHC–Diamine Catalyzed Enantioselective Hydrogenation of Isocoumarins

Wei Li, Mario P. Wiesenfeldt, and Frank Glorius*

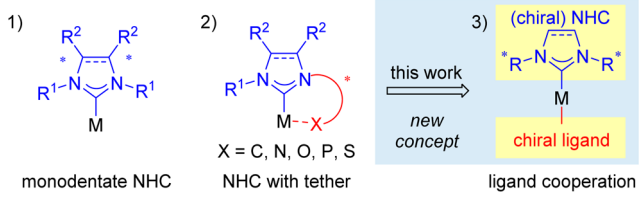
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, 48149 Münster, Germany

Supporting Information

ABSTRACT: A novel and practical chiral ruthenium–NHC–diamine system is disclosed for the enantioselective hydrogenation of isocoumarins, which provides a new concept to apply (chiral) NHC ligands in asymmetric catalysis. A variety of optically active 3-substituted 3,4-dihydroisocoumarins were obtained in excellent enantioselectivities (up to 99% *ee*). Moreover, this methodology was utilized in the synthesis of *O*-methylmellein, mellein, and ochratoxin A.

The N-heterocyclic carbenes (NHCs), with their strong σ-donor ability, are recognized as one of the most powerful ligand classes in transition-metal catalysis.[1] Since the pioneering work reported by Herrmann,[2] asymmetric catalysis involving NHC ligands has received considerable attention.[3] Two general strategies are employed for the design of chiral NHC-based catalysts. The chiral environment can be optimized by tuning the electronic and steric properties of the nitrogen substituents, as well as the backbone substituents (Scheme 1, 1)).[4]

Scheme 1. Strategies for the Design of Chiral NHC-Based Catalysts

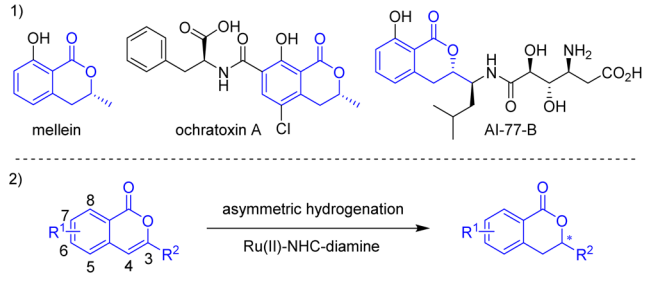


Alternatively, since the report of Burgess' efficient chiral NHC–metal complex,[5] tethering an additional intramolecular chiral coordinating moiety to NHC ligands has become a common way to chelate the metal center and further fix the chiral environment (Scheme 1, 2)).[6] Nevertheless, compared to the diverse applications of achiral NHC ligands in catalysis, the use of chiral NHCs is still much less explored.[1]

Undoubtedly, the development of new strategies and concepts for the design of chiral NHC catalysts holds great promise, and may be the key to achieve new reactivity in organic synthesis. In continuation of our efforts in this field,[3e,4g,7] we envisioned that a suitable combination of a chiral NHC with another chiral ligand might allow a new modular and systematic way to fine-tune the chiral environment of a catalyst (Scheme 1, 3)). Inspired by Noyori's elegant Ru(II)–diphosphine–diamine catalyst,[8] we identified chiral diamine ligands as promising candidates.[9] Usually, olefin hydrogenation does not proceed well with Noyori's ternary catalytic system,[9b,10] although efficient hydrogenation of alkenyl esters has been reported using Ru(II)–diphosphine catalysts.[11] Herein we describe an unprecedented strategy employing a chiral NHC ligand, in cooperation with a chiral diamine ligand, for the enantioselective hydrogenation of isocoumarins.

The 3,4-dihydroisocoumarin backbone, in particular the chiral 3-substituted system, represents a key structural motif in a wide range of natural products, many of which exhibit biological activities (Scheme 2, 1)). To name three such natural

Scheme 2. Natural Products Possessing a Chiral 3-Substituted 3,4-Dihydroisocoumarin Backbone



products: mellein, a trail pheromone, has been isolated from fungi and insects and possesses antibacterial, fungicidal and HCV protease-inhibitory activities.[12] Ochratoxin A is a well-known fungal toxin, and one of the most-abundant food-contaminating mycotoxins.[13] AI-77-B, isolated from a culture broth of *Bacillus pumilus*, exhibits gastroprotective and antiulcerogenic properties.[14] Conventional methods to access this important building block usually employ chiral starting materials that can be converted into the desired compounds by multistep synthetic sequences.[15] Only recently, a limited number of enantioselective catalytic methods have been reported.[16] Hence, the exploration of new catalytic strategies to construct diverse enantio-enriched 3-substituted 3,4-dihydroisocoumarin derivatives is of high importance as it would enable studies of their biological activity and facilitate drug discovery. Notably, the asymmetric hydrogenation of unsaturated heterocycles has been one of the most powerful methods to produce optically active cyclic molecules.[17] On the basis of our previous studies in this field,[7] we expected that the enantioselective hydrogenation of 3-substituted isocoumarins

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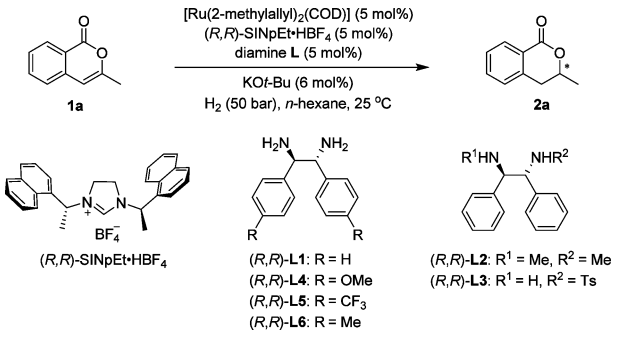
might be a direct way to form chiral 3-substituted 3,4-dihydroisocoumarins (Scheme 2, 2)).

Initially, a novel Ru(II)−NHC−diamine catalyst system was prepared by reacting [Ru(2-methylallyl)$_2$(COD)], NHC precursor (*R*,*R*)-SINpEt·HBF$_4$, diamine ligand (*R*,*R*)-**L1** (DPEN) and KO*t*-Bu in *n*-hexane at 50 °C for 16 h, giving a major ruthenium species (*m*/*z* 691.2373) corresponding to the complex [Ru^{2+} + (*R*,*R*)-SINpEt + (*R*,*R*)-**L1** − H^+]$^+$ (calc. *m*/*z* 691.2369) detected by ESI (see SI). In the presence of the prepared catalyst solution, 3-methylisocoumarin **1a** was smoothly reduced to 3-methyl-3,4-dihydroisocoumarin **2a** with 50 bar H_2 in 92% *ee* and 79% yield (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



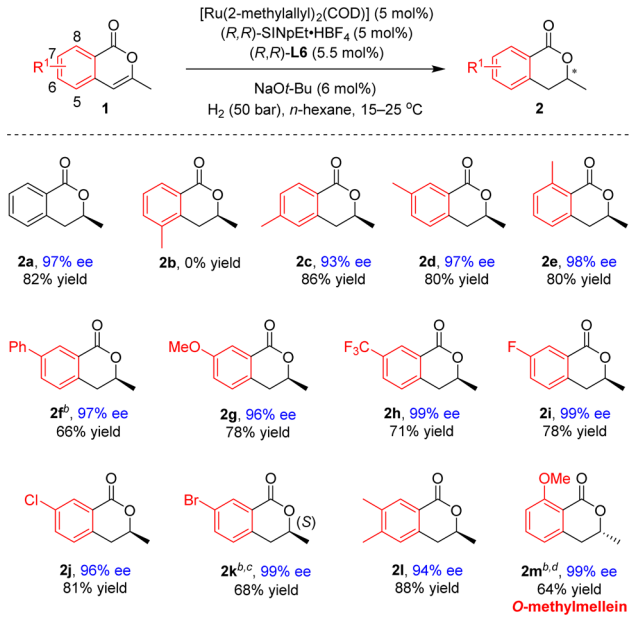
entry	NHC	diamine	time (h)	yield (%)[b]	*ee* (%)[c]
1	(*R*,*R*)-SINpEt	(*R*,*R*)-**L1**	10	79	92
2	(*R*,*R*)-SINpEt	–	10	69	−21
3	–	(*R*,*R*)-**L1**	10	trace	28
4	(*R*,*R*)-SINpEt	(*S*,*S*)-**L1**	10	trace	−20
5	(*S*,*S*)-SINpEt	(*S*,*S*)-**L1**	10	78	−92
6[d]	(*R*,*R*)-SINpEt	(*R*,*R*)-**L1**	10	18	−14
7	(*R*,*R*)-SINpEt	(*R*,*R*)-**L2**	10	trace	−18
8	(*R*,*R*)-SINpEt	(*R*,*R*)-**L3**	10	0	–
9	(*R*,*R*)-SINpEt	(*R*,*R*)-**L4**	8	80	92
10	(*R*,*R*)-SINpEt	(*R*,*R*)-**L5**	19	51	89
11	(*R*,*R*)-SINpEt	(*R*,*R*)-**L6**	10	78	94
12[e]	(*R*,*R*)-SINpEt	(*R*,*R*)-**L6**	8	80	95
13[f]	(*R*,*R*)-SINpEt	(*R*,*R*)-**L6**	21	82	97

[a]General conditions: [Ru(2-methylallyl)$_2$(COD)] (0.005 mmol, 5 mol %), (*R*,*R*)-SINpEt (0.005 mmol, 5 mol %), diamine **L** (0.005 mmol, 5 mol %) and KO*t*-Bu (0.006 mmol, 6 mol %) were stirred at 50 °C in *n*-hexane (0.5 mL) for 16 h, after which it was added to **1a** (0.10 mmol) in *n*-hexane (1.5 mL), and the hydrogenation was performed with 50 bar H_2 at 25 °C for the indicated time. [b]Isolated yields. [c]Determined by HPLC analysis using a chiral stationary phase. [d]Using isolated Ru(II)−NHC complex (5 mol %) and (*R*,*R*)-**L1** (5 mol %) without catalyst preformation. [e]Using NaO*t*-Bu (6 mol %) instead of KO*t*-Bu. [f]The reaction was performed at 15 °C.

Several control experiments were conducted to understand this cooperative system. In the absence of chiral diamine (*R*,*R*)-**L1**, the hydrogenation of **1a** proceeded, but gave the opposite enantiomer with a low *ee* value (entry 2). The reaction was sluggish without the NHC ligand (entry 3). Moreover, a strong matched/mismatched effect was observed, with the combination of (*R*,*R*)-SINpEt and (*S*,*S*)-**L1** giving a trace amount of product in −20% *ee* (entry 4 vs entry 1). On the basis of these results, we conclude that the high degree of enantioselectivity is a result of the synergistic effects of the chiral NHC and diamine. As expected, switching to (*S*,*S*)-SINpEt and (*S*,*S*)-**L1**, the opposite enantiomer was obtained with the same *ee* value (entry 5). The combination of isolated Ru(II)−NHC complex[18] and (*R*,*R*)-**L1** only gave −14% *ee* and 18% yield (entry 6), which implied that it is vital to coordinate the diamine ligand to ruthenium by preformation and that the diamine does not serve as a simple additive. The free NH_2 group on the diamine was determined to be crucial for the reactivity. The use of *N*,*N*′-dimethyl protected diamine **L2** or *N*-Ts protected diamine **L3** strongly inhibited the reaction (entry 7 and 8). To improve further the reaction, systematic optimization of the diamine ligand was carried out (see SI, for details). Substituents in the *ortho*- or *meta*-position of the phenyl ring of the diamine hampered the enantioselectivity. Electron-donating substituent OMe in the *para*-position gave similar results to the standard diamine **L1**, whereas electron-withdrawing group CF_3 provided the product in lower yield and enantioselectivity (entry 9 and 10). To our delight, the use of *para*-methyl diamine (*R*,*R*)-**L6** promoted the reaction in 94% *ee* and good yield (entry 11). Replacing KO*t*-Bu with NaO*t*-Bu as the base slightly increased the enantioselectivity and, more importantly, impoved the reproducibility of the reaction, presumably due to the higher solubility of NaO*t*-Bu in *n*-hexane (entry 12).[19] Finally, lowering the temperature to 15 °C led to the formation of the 3-methyl 3,4-dihydroisocoumarin **2a** in 97% *ee* and 82% yield (entry 13).

With the optimized conditions in hand (Table 1, entry 13), we then explored the substrate scope of the reaction (Scheme 3). First, the effect of substituents in different positions on the phenyl ring was investigated. We observed that 6-, 7- and 8-methyl substituted isocoumarins smoothly underwent the hydrogenation in excellent enantioselectivities and good yields (**2c**−**e**), whereas a methyl group in the 5-position completely inhibited the reaction, possibly due to the increased steric hindrance adjacent to the C−C double bond. Aryl-substituted

Scheme 3. Substrate Scope of Arene Substitution[a]



[a]For detailed conditions, see SI. Isolated yields after column chromatography are reported. [b]Using a solvent mixture of *n*-hexane: toluene (3:1). [c]The absolute configuration of **2k** was determined to be (*S*) by X-ray crystallographic analysis. [d]The catalyst was prepared with (*S*,*S*)-SINpEt·HBF$_4$ (5 mol %), and (*S*,*S*)-**L6** (5.5 mol %).

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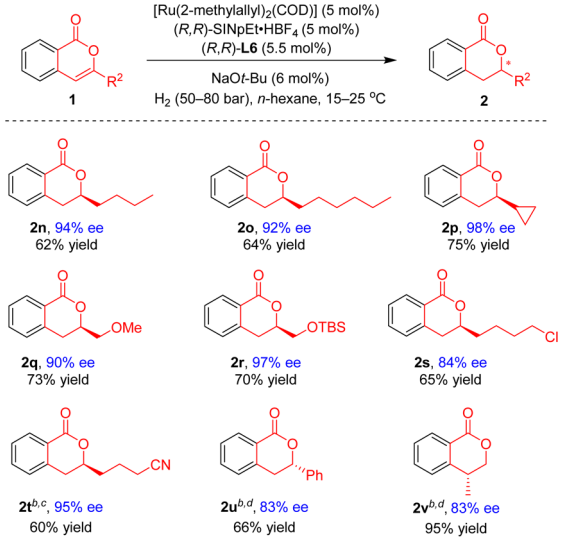
isocoumarin **1f** was converted into the corresponding product in 97% *ee* and 66% yield (**2f**). The electronic effect of substituents was also examined. Both, the electron-rich substrate **1g** and electron-deficient substrate **1h** were well-tolerated by the catalyst system (**2g** and 2**h**). Moreover, the halogenated substrates **1i**−**k** were transformed into the desired products **2i**−**k** in 96−99% *ee* and 68−81% yield, without formation of dehalogenated byproducts. The absolute configuration of **2k** was determined to be *S* by X-ray crystallographic analysis. The configurations of the other products were assigned by analogy. The disubstituted substrate **1l** was successfully reduced to give **2l** in 94% *ee* and 88% yield. Remarkably, the hydrogenation of 8-methoxy-3-methylisocoumarin **1m** using (*S*,*S*)-SINpEt and (*S*,*S*)-**L6** directly afforded the natural product *O*-methylmellein **2m** in 99% *ee* and reasonable yield (64%).[15a]

Next, we examined a variety of substituents at the 3-position of the isocoumarin as shown in Scheme 4. The use of long alkyl chain substrates **1n** and **1o** maintained high enantioselectivities with moderate yields. It is noteworthy that several functional groups such as cyclopropyl, ether, silyl ether, alkyl chloride and even alkyl nitrile were tolerated under the reaction conditions, giving the corresponding products **2p**−**t** in 84−98% *ee* and 60−75% yield. These functional groups provide a good opportunity for further modification of 3,4-dihydroisocoumarin products. The hydrogenation of 3-aryl substituted isocoumarin **1u** and 4-substituted isocoumarin **1v** with the cooperative Ru(II)−NHC−diamine catalyst was unsuccessful. However, the use of Ru(II)−NHC as catalyst gave the desired 3,4-dihydroisocoumarins **2u** and **2v** in good enantioselectivities with 66% and 95% yield, respectively.

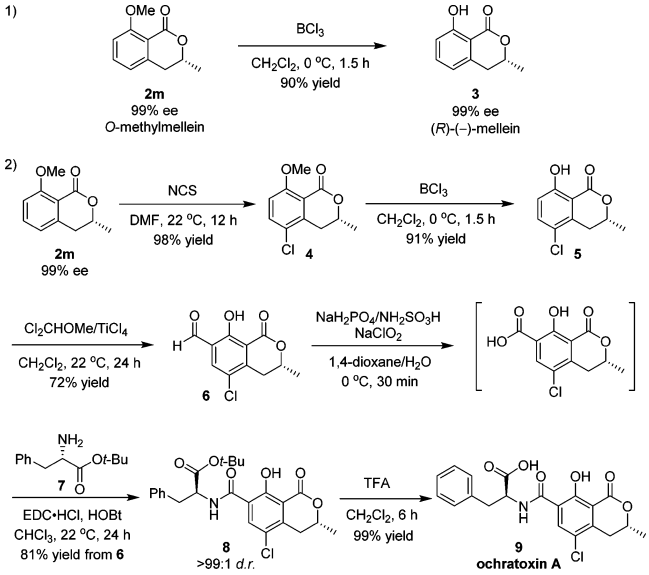
Scheme 4. Substrate Scope of Substitution on the C−C Double Bond[a]



[a]For detailed conditions, see SI. Isolated yields after column chromatography are reported. [b]Using a solvent mixture of *n*-hexane: toluene (3:1). [c]Using 10 mol % of the catalyst. [d]The catalyst was prepared with [Ru(2-methylallyl)$_2$(COD)] (5 mol %), (*R*,*R*)-SINpEt·HBF$_4$ (10 mol %) and NaO*t*-Bu (12 mol %).

To demonstrate the synthetic utility of this process, further transformations were carried out as shown in Scheme 5. Deprotection of optically pure *O*-methylmellein **2m** using BCl_3 readily gave the natural product (*R*)-(−)-mellein **3** in 90% yield

Scheme 5. Application to Natural Product Synthesis



and without loss of enantiomeric excess (Scheme 5, 1)). The absolute configuration of mellein **3** was confirmed by comparing the optical rotation with the known literature value.[15a] Starting from optically pure *O*-methylmellein **2m**, an efficient synthesis of the more complex natural product ochratoxin A was conducted (Scheme 5, 2)). First, chlorination of *O*-methylmellein **2m** using *N*-chlorosuccinimide (1.2 equiv) selectively gave the desired 5-chloro-*O*-methylmellein **4** in almost quantitative yield. Deprotection of the OMe group gave the 5-chloromellein **5** in 91% yield. Optimization of the reaction conditions allowed for the introduction of an aldehyde group at the 7-position of **5** using a Rieche formylation reaction, giving the aldehyde **6** in 72% yield.[20] A Pinnick oxidation of the aldehyde **6** afforded the corresponding acid, which was directly submitted to a peptide synthesis with optically pure L-phenylalanine derivative **7**, giving the amide **8** in >99:1 *d.r.* and 81% yield (for two steps from **6**).[21] Finally, deprotection of the *tert*-butyl ester of **8** gave ochratoxin A **9** in 99% yield.[22] To the best of our knowledge, this is the first asymmetric catalytic total synthesis of ochratoxin A.

In conclusion, we have developed a Ru(II)−NHC−diamine catalyst system for the enantioselective hydrogenation of isocoumarins, producing chiral 3,4-dihydroisocoumarins in excellent enantioselectivities (up to 99%) and good yields (up to 95%). Related natural products were readily synthesized based on this methodology. This work contributes the first use of a synergistic catalyst system based on a chiral NHC and a chiral diamine, thus demonstrating the possibility of this novel approach to the design of enantioselective NHC-based catalysis. Studies on the isolation of the catalyst, the reaction mechanism as well as further application of this strategy are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b13124.

Experimental procedures and spectroscopic data (PDF)

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AUTHOR INFORMATION

Corresponding Author

*glorius@uni-muenster.de

ORCID

Frank Glorius: 0000-0002-0648-956X

Notes

The authors declare no competing financial interest.

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