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# Enantioselective Synthesis of Isoflavanones by Catalytic Dynamic Kinetic Resolution

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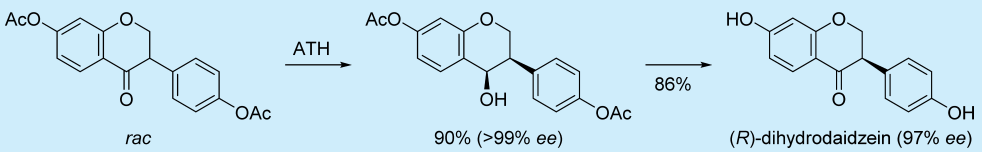
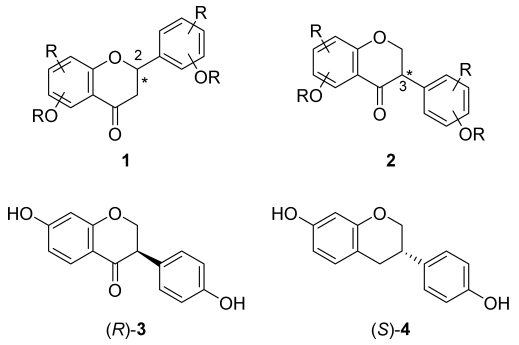
Supporting Information




**ABSTRACT:** A ruthenium-catalyzed asymmetric transfer hydrogenation of racemic isoflavanones with dynamic kinetic resolution yields virtually enantiopure isoflavanols as single diastereomers. Subsequent oxidation gives rise to isoflavanones in high enantiomeric purities.

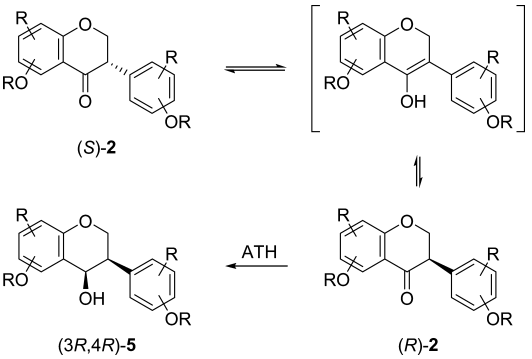
Flavanones **1** are an important subgroup of plant-derived flavonoids that have various beneficial health effects (Scheme 1).[1] Likewise, isoflavanones **2** and their reduced derivatives show a wide range of interesting bioactivities.[2] For example, (*R*)-dihydrodaidzein ((*R*)-**3**) acts as a cardioprotective agent,[3] and the heavily patented isoflavan derivative (*S*)-equol ((*S*)-**4**) is a selective estrogen receptor modulator (SERM) and a strong antioxidant.[4] In contrast to the enantioselective preparation of flavanones,[5] only a few appropriate procedures for the asymmetric synthesis of this group of natural products have been published so far.[6,7] These methods rely on a catalytic enantioselective arylation,[6a] decarboxylation/protonation,[6b,c] or an auxiliary-induced aldol addition[6d,e] to generate the stereogenic center.[8] We have recently discovered[9,10] a highly selective kinetic resolution of flavanones **1** by rhodium-catalyzed asymmetric transfer hydrogenation (ATH)[11] using a chiral rhodium diamine complex.[12] Herein, we communicate the evolution of a related ruthenium-catalyzed ATH of isoflavanones **2** that proceeds with dynamic kinetic resolution (DKR).[13]

**Scheme 1. Basic Structure of Flavanones (1) and Isoflavanones (2), (*R*)-Dihydrodaidzein ((*R*)-3), and (*S*)-Equol ((*S*)-4)**




Since isoflavanones **2** are $\alpha$-chiral ketones, an equilibrium between (*S*)-**2** and (*R*)-**2** might be established via an enol or enolate intermediate when the crucial ATH process is executed under acidic or basic conditions, respectively (Scheme 2). If the chiral catalyst clearly differentiates between the two enantiomers of substrates **2**, quantitative conversion of a racemic isoflavanone **2** to give an enantiopure isoflavanol **5** is within reach.

**Scheme 2. Dynamic Kinetic Resolution of Isoflavanones 2 by Asymmetric Transfer Hydrogenation**




In initial studies, the performance of the rhodium, ruthenium, and iridium catalysts **I**–**VI**[12,14] depicted in Scheme 3 for ATH of isoflavanone *rac*-**2a** with a mixture of formic acid and triethylamine was screened. Out of this set of chiral metal–diamine complexes, which were prepared in situ from the reported metal precursors and the monotosylated diamine

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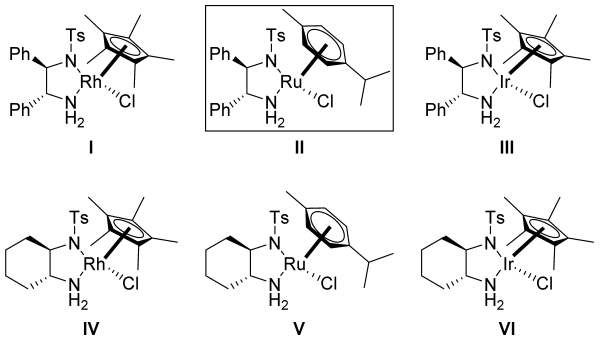
**Scheme 3. Chiral Metal–Diamine Complexes I–VI**




ligands, ruthenium complex **II**[14a,b] turned out to be optimal with respect to reactivity and stereoselectivity. While reactions with **II** at room temperature required several days for good conversions, heating the reaction mixture in ethyl acetate to 45 °C or reflux allowed an efficient transformation of the readily available racemic isoflavanones **2** to give isoflavanols (3*R*,4*R*)-**5** in ≥90% yield with >99% *ee* as single diastereomers in a few hours (Scheme 4).

Substrates **2** with *O*-acetyl substituents (*rac*-**2a**, *rac*-**2d**, *rac*-**2g**) are more reactive than the corresponding methyl ethers (*rac*-**2b**, *rac*-**2e**) or the unsubstituted isoflavanone *rac*-**2h**, whereas the analogous MOM acetals *rac*-**2c** and *rac*-**2f** require reflux in ethyl acetate for a practical reaction time without erosion of enantioselectivity. For substrates **2** with $R^2$ = OH no reduction was observed. Diacetate *rac*-**2d** was also subjected to ATH on a gram scale to give (3*R*,4*R*)-**5d** in 88% yield after 8 h.[15] The results compiled in Table 1 show that catalyst loadings as low as 0.5 mol % can be applied with only minimal effects on enantioselectivity but lead to significantly longer reaction times. Next to formic acid/triethylamine, ammonium formate and sodium formate can be successfully used as hydride donors, too.[15]

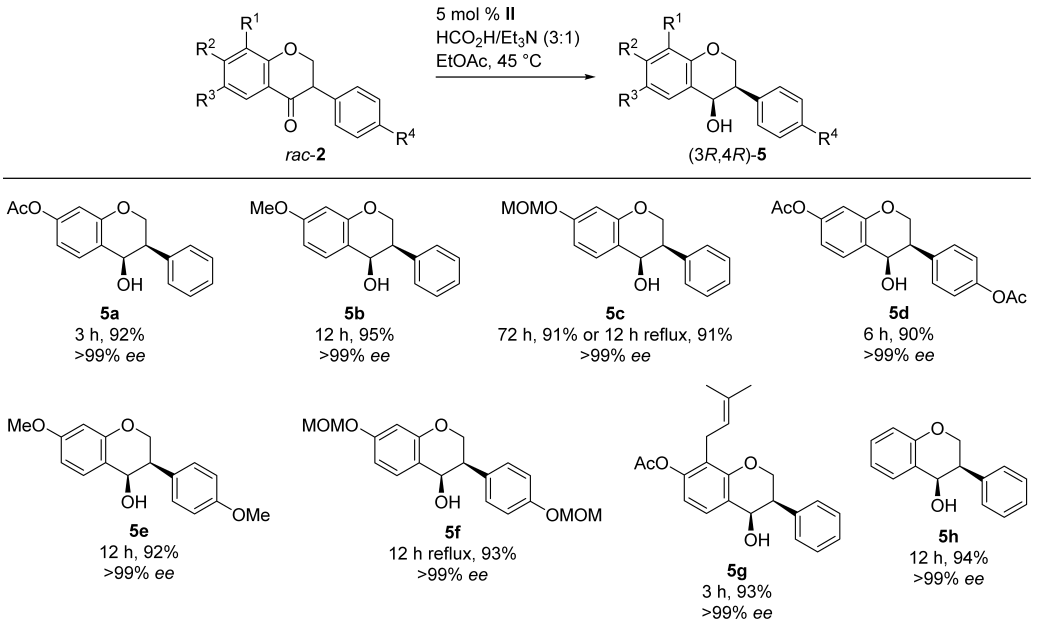
**Table 1. Asymmetric Transfer Hydrogenation of Isoflavanone Derivatives *rac*-2d,f with Various Loadings of Catalyst II**[a]

| | | | | (3*R*,4*R*)-**5** | |
|---|---|---|---|---|---|
| *rac*-**2** | **II** (mol %) | temp (°C) | time (h) | yield[b] (%) | *ee*[c] (%) |
| **d** | 5 | 45 | 6 | 90 | >99 |
| **d** | 1 | 45 | 14 | 83 | 99 |
| **d** | 0.5 | 45 | 24 | 71 | 96 |
| **f** | 5 | reflux | 12 | 93 | >99 |
| **f** | 1 | reflux | 48 | 81 | 99 |
| **f** | 0.5 | reflux | 48 | 52 | 98 |

[a]Ruthenium(II) catalyst **II**, $HCO_2H/Et_3N$ (3:1), EtOAc. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase.

The relative configuration of isoflavanols **5a**,[16] **5b**,[17] **5d**,[16] **5e**,[17b,c] **5f**,[18] and **5h**[17a,b,19] was assigned by comparison with literature data for the known racemic compounds, whereas the *cis* stereochemistry of the novel compounds **5c** and **5g** was allocated in analogy to the latter products. Isoflavanol (+)-(3*R*,4*R*)-**5f** has been reported,[20] and this absolute configuration was further corroborated by conversion of the ATH product (+)-(3*R*,4*R*)-**5f** to acetate **6** (see Scheme 7), the enantiomer of which is known.[20] The absolute configuration of (+)-(3*R*,4*R*)- **5h** was elucidated by comparison of CD data with the literature[21] and its oxidation to give the known ketone (+)-(*R*)-**2h** (see Scheme 6),[6a,22] while assignment for (+)-(3*R*,4*R*)-**5d** rests on its transformation to (+)-(*R*)-**3** via isoflavanone (+)-(*R*)-**2d** (see Scheme 7).[23,24] In addition, the relative and absolute configuration of all ATH products **5** can be readily understood by application of the model depicted in Scheme 5, which already served to rationalize the stereochemical outcome of the corresponding ATH of racemic flavanones.[9a,25] Accordingly, the absolute configuration of (3*R*,4*R*)-**5a–c,e,g** was deduced from this model in line with the assignment for (3*R*,4*R*)-**5d,f,h**.

**Scheme 4. Asymmetric Transfer Hydrogenation of Isoflavanone Derivatives *rac*-2 with Ruthenium Catalyst II**[a]




[a]Yields of isolated products and *ee* values determined by HPLC on a chiral stationary phase are given.



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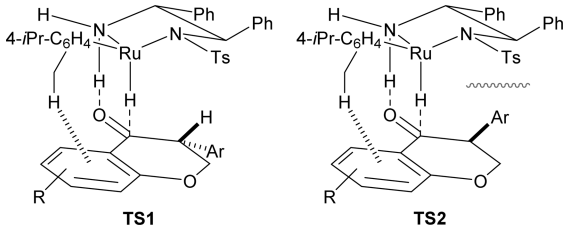
**Scheme 5. Unfavorable Steric Interaction in the Transition State TS2 of the Asymmetric Transfer Hydrogenation of the Less Reactive (*S*)-Isoflavanone Enantiomer with the Catalytically Active Species from II**

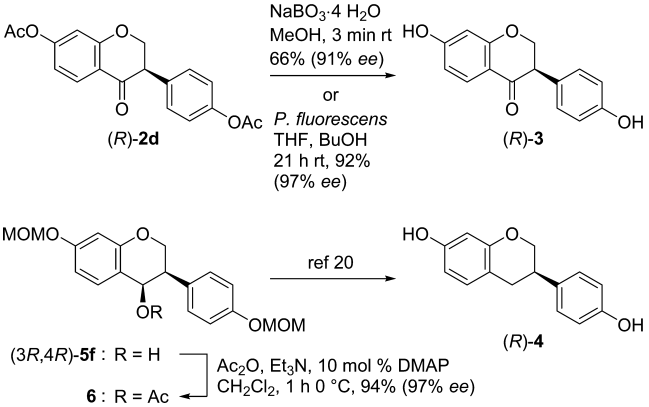



Oxidation of isoflavanols (3*R*,4*R*)-**5** with tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide[26] afforded isoflavanones (*R*)-**2** with high efficiency and only little racemization, if any (Scheme 6).

Scheme 7 exemplifies two synthetic applications of the crucial ATH process described above for the enantioselective synthesis of bioactive flavonoids. Deblocking of diacetate (*R*)-**2d** to give the isoflavanone (*R*)-dihydrodaidzein ((*R*)-**3**)[4a,23b,c] with sodium perborate[27] in methanol caused significant racemization of the α-chiral ketone. However, enzymatic deacylation of this substrate by transesterification catalyzed by a lipase from *Pseudomonas fluorescens* succeeded in high yield with no change in enantiomeric purity. Transformation of isoflavanol (3*R*,4*R*)-**5f** to diacetate **6** already constitutes a formal enantioselective synthesis of the isoflavan (*R*)-equol ((*R*)-**4**).[20] In contrast to the naturally occurring (*S*) enantiomer, (*R*)-**4** cannot be produced by biotechnological processes but is a highly interesting compound because it antagonizes the action of dihydrotestosterone and due to its exceptional bioavailability.[4c]

In summary, highly enantiomerically enriched isoflavanones can be prepared through ruthenium-catalyzed ATH with dynamic kinetic resolution of easily available racemic substrates followed by oxidation of the resulting isoflavanols. Utilization of this method enabled an efficient synthesis of the cardioprotective isoflavanone (*R*)-dihydrodaidzein and a formal synthesis of the bioactive isoflavan (*R*)-equol. Further applications are currently being explored and will be disclosed in due course.

**Scheme 7. Synthesis of (*R*)-Dihydrodaidzein ((*R*)-3) and Formal Synthesis of (*R*)-Equol ((*R*)-4)**




## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01218.

Experimental procedures, spectroscopic data, $^{1}H$ and $^{13}C$ NMR spectra, and HPLC traces (PDF)

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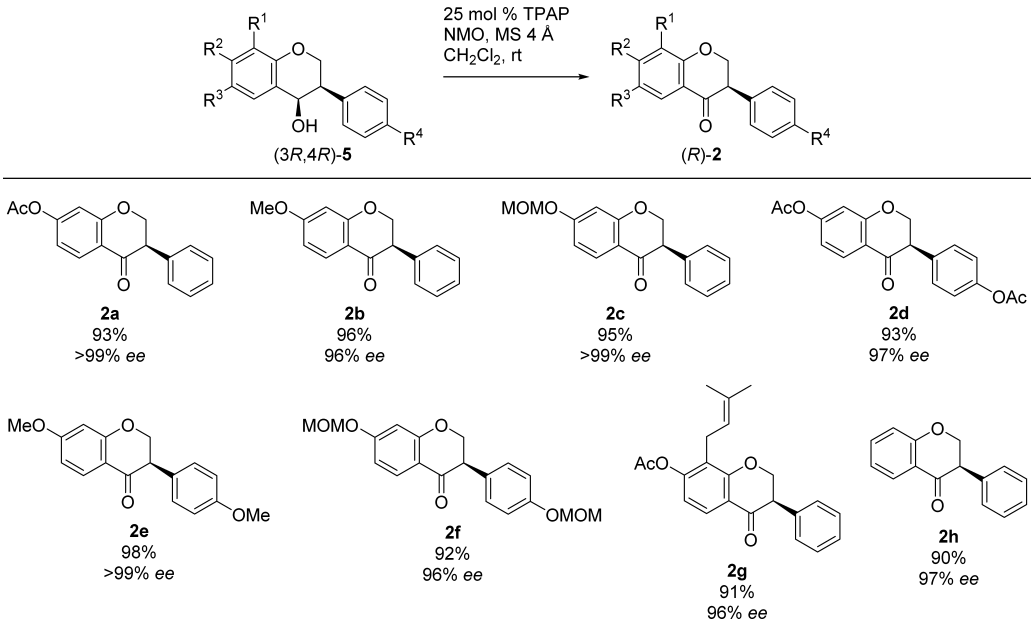
**Scheme 6. Oxidation of Isoflavanols (3*R*,4*R*)-5 To Give the Isoflavanone Derivatives (*R*)-2[a]**




[a]Yields of isolated products and *ee* values determined by HPLC on a chiral stationary phase are given.



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## Notes

The authors declare no competing financial interest.

## ■ DEDICATION

This paper is dedicated to Professor Hans J. Schäfer, Westfälische Wilhelms-Universität Münster, on the occasion of his 80th birthday.

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