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Deracemization of α-Aryl Hydrocoumarins via Catalytic Asymmetric Protonation of Ketene Dithioacetals

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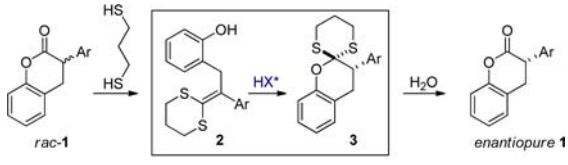
Supporting Information

ABSTRACT: An unprecedented catalytic asymmetric protonation of ketene dithioacetals is described. Various racemic α-aryl hydrocoumarin derivatives are transformed into enantioenriched dithioacetal-protected hydrocoumarins in the presence of a chiral Brønsted acid catalyst. A newly developed phosphoric acid, featuring the 3,5-bis(pentafluorothio)phenyl (3,5-$(SF_5)_2C_6H_3$) substituent, is introduced. The obtained products can be easily converted into either hydrocoumarins or the corresponding chromans via simple hydrolysis or hydrogenation, respectively.

Asymmetric protonations of enolate equivalents, at least in principle, offer a highly straightforward approach to enantioenriched α-tertiary carbonyl compounds. Since pioneering investigations by Duhamel and Yoshikawa,[1,2] such reactions have typically relied on a stoichiometric chiral proton source, although catalytic asymmetric versions have also been described.[3−5] In the context of a different project, we were in need of enantiomerically pure α-aryl hydrocoumarins (**1**). *Despite their high relevance as biologically active compounds, however, nonracemic α-aryl hydrocoumarins (**1**) have been entirely unknown.* Here we report a highly enantioselective, catalytic, asymmetric protonation-induced cyclization of ketene dithioacetals **2** to easily hydrolyzable ortho esters **3**. The overall sequence described here provides for an efficient entry toward enantiomerically pure α-aryl hydrocoumarins via an effective deracemization.



deracemization of hydrocoumarins via catalytic asymmetric protonative cyclization

In addition to their use in carbonyl protection and umpolung activation,[6] dithioacetals have been used by Corey et al. as protecting groups for lactones and esters.[7] Interestingly, it was found that dithioacetal protection of γ-valerolactone in chloroform led to an instantaneous and presumably acid-catalyzed cyclization of the ketene dithioacetal to the corresponding ortho ester. We envisioned that the reaction sequence of ketene dithioacetal formation, asymmetric Brønsted acid-catalyzed protonative cyclization, and hydrolysis may be an effective and general tool for the deracemization of enantiopure α-substituted cyclic esters.[8] In particular, we expected this reaction design to lead to an efficient approach to α-arylated hydrocoumarins[9,10] and related chroman derivatives (isoflavonoids),[11] as these compound classes include naturally abundant agents possessing antioxidant and various other biological activities (Figure 1).

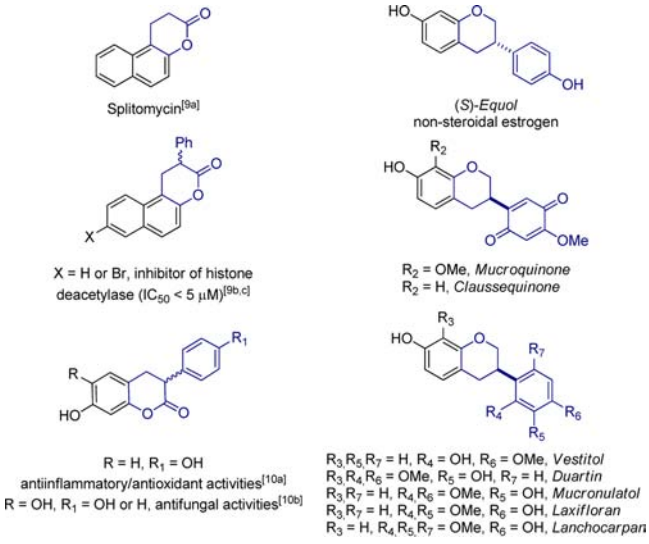


Figure 1. Selected examples of chiral α-aryl hydrocoumarins and chromans.

Syntheses of enantioenriched α-arylated hydrocoumarins have not been reported previously, and even relatively obvious approaches such as asymmetric α-arylations and hydrogenation reactions are completely unknown. Recently, an access to chromanones via a highly enantioselective NHC-catalyzed intramolecular Stetter reaction has been described.[12] Also, enantioselective Brønsted acid catalysis has been utilized in the synthesis of chroman derivatives from an activated allylic alcohol substrate via intramolecular allylic substitution.[13]

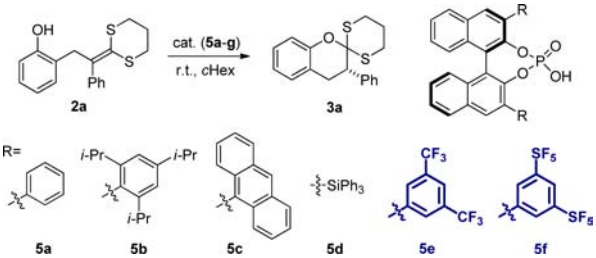
Our own studies commenced with the investigation of model substrate **2a**, which is obtained in quantitative yield by reacting 3-phenylhydrocoumarin with *in situ*-generated bis-(dimethylaluminum) 1,3-propanedithiolate (see Supporting Information). Encouraged by recent breakthroughs in asymmetric Brønsted acid catalysis,[14] we first tested catalytic

Received: September 28, 2012
Published: October 29, 2012

dx.doi.org/10.1021/ja3096202 | J. Am. Chem. Soc. 2012, 134, 18245−18248

amounts of chiral phosphoric acids **5**. These investigations revealed the facile catalyst **5a**-mediated cyclization of ketene dithioacetal **2a** to the protected hydrocoumarin derivative **3a** in excellent yield but disappointing enantioselectivity (Table 1,

Table 1. Establishing Suitable Reaction Conditions[a]



entry	catalyst	time	conv[b]	er[c]
1	**5a** (10 mol%)	8 h	90%	53:47
2	**5b** (10 mol%)	45 h	93%	65:35
3	**5c** (10 mol%)	8 h	91%	74:26
4	**5d** (10 mol%)	2 h	31%	54:46
5	**5e** (10 mol%)	2 h	95%	90:10
6[d]	**5e** (5 mol%)	18 h	98%	91:9
7[e]	**5e** (0.5 mol%)	2.5 d	93%[g]	93.5:6.5
8[d,f]	**5f** (5 mol%)	7 d	99%	95:5

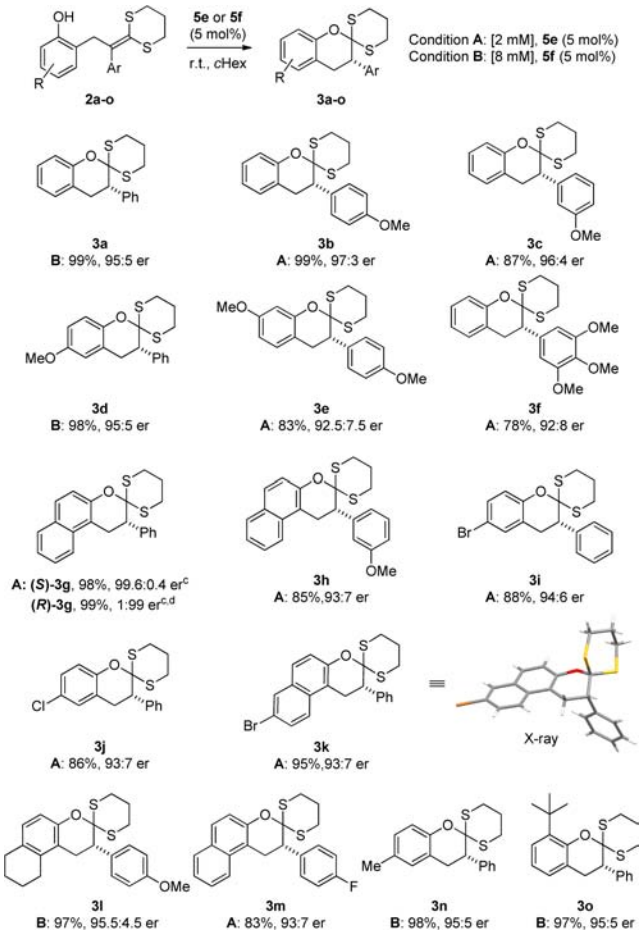
[a]Unless otherwise indicated, all reactions were carried out with substrate **2a** (0.016 mmol) and 5 mg of molecular sieves (4 Å) in cyclohexane (0.5 mL, 0.032 M). [b]Conversion determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Enantiomeric ratio determined by HPLC analysis. [d]Reaction carried out at 0.008 M. [e]Reaction carried out with 2 mmol of substrate **2a** (at 0.002 M). [f]Reaction carried out without molecular sieves. [g]Isolated yield.

entry 1, 53:47 er). Similarly, with sterically hindered phosphoric acids **5b–d**, only moderate enantioselectivities were observed (entries 2–4). Further screening of catalyst structures revealed that commercially available acid **5e**, featuring electron-withdrawing 3,5-bis(trifluoromethyl)phenyl substituents, was optimal in terms of reactivity and enantioselectivity (90:10 er, entry 5). By decreasing the catalyst loading to 5 mol% and diluting the reaction mixture, we could obtain orthoester **3a** with slightly higher enantioselectivity (91:9 er, entry 6). Moreover, the catalyst loading could be decreased to 0.5 mol% to afford product **3a** with similar enantioselectivity on a 2 mmol scale (entry 7). Gratifyingly, the enantioselectivity could be further improved by using a novel catalyst, acid **5f**, which displays the new 3,5-bis(pentafluorothio)phenyl substituent in its 3,3′-position.[15] The pentafluorothio group has recently been utilized in the context of medicinal chemistry as an alternative and larger substitute for the common trifluoromethyl group.[15c,d] Indeed, very high enantioselectivity was obtained with phosphoric acid **5f** (95:5 er), although this catalyst proved to be slightly less active (entry 8).

With the development of suitable reaction conditions and the identification of acids **5e** and **5f** as highly enantioselective catalysts, we next began investigating the substrate scope of this new asymmetric protonation-induced cyclization reaction (Chart 1).

The required racemic α-arylated hydrocoumarins can be easily obtained via condensation of salicylaldehyde derivatives and α-aryl acetyl chloride and subsequent reduction (see Supporting Information).[16] The corresponding ketene dithioacetals (**2b–o**) were then obtained in typically quantitative

Chart 1. Substrate Scope[a,b]



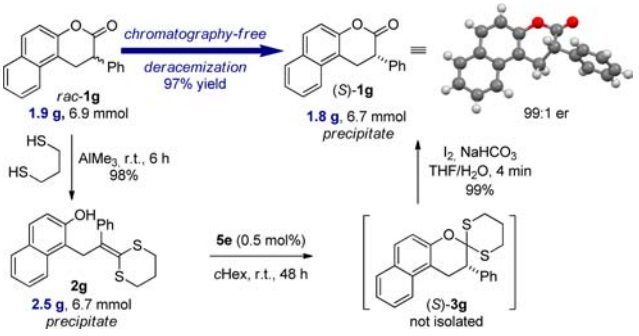
[a]Isolated yields (%) and enatiomeric ratios (er); see Supporting Information and Table S1 for the experimental details. [b]Enantiomeric ratio determined by HPLC analysis. [c]Reactions carried out with 1 mol % of catalyst at 25 mM **2g**. [d]Reaction carried out with the (*S*)-enantiomer of the catalyst to afford (*R*)-**3g**.

yields. As shown in Chart 1, various ketene dithioacetals were converted into the corresponding dithioacetal-protected hydrocoumarin derivatives with good to excellent enantioselectivity in the presence of catalytic amounts of a phosphoric acid **5e** or **5f**. The desired products **3b–o** were obtained with generally good to excellent yields and enantioselectivities and essentially unaffected by electronic or steric properties of the ketene dithioacetals. It is noteworthy that thioacetal **3g** was obtained with an outstanding yield and enantioselectivity (98% yield, >99:1 er) with only 1 mol% catalyst loading. In this case, the opposite enantiomer was also prepared with excellent enantioselectivity (1:99 er) by using the enantiomeric (*S*)-configured catalyst. The structures of a starting material (**2g**) and a product (**3k**), including its absolute configuration, were assigned unambiguously by X-ray crystallography (see Supporting Information).

To demonstrate the practical utility of our deracemization protocol, we examined the preparation of an optically enriched hydrocoumarin on a gram scale. As shown in Scheme 1, racemic hydrocoumarin **1g** could be transformed into the achiral ketene thioacetal intermediate **2g** and isolated by precipitation in cold diethyl ether. Thioacetal **2g** was then treated with a catalytic amount of phosphoric acid (0.5 mol%)

dx.doi.org/10.1021/ja3096202 | J. Am. Chem. Soc. 2012, 134, 18245–18248

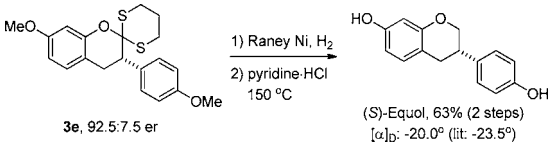
Scheme 1. Gram-Scale Deracemization of Hydrocoumarin 1g without Purification



in cyclohexane at room temperature to afford product **3g**, which could be hydrolyzed *in situ* with I_2/$NaHCO_3$ to provide enantiopure hydrocoumarin (*S*)-**1g** in quantitative yield (see Supporting Information).

Finally, the dithioacetal protecting group can also be removed reductively using Raney-Ni under a hydrogen atmosphere, affording valuable chroman or isoflavonoid derivatives. As illustrated in Scheme 2, dithioacetal-protected hydrocoumarin derivative **3e** was converted into the enantioenriched non-steroidal estrogen (*S*)-Equol via hydrogenation and demethylation.[17]

Scheme 2. Application to the Synthesis of (*S*)-Equol



In conclusion, we have developed a deracemization approach to enantiopure α-arylated hydrocoumarin derivatives that is based on an enantioselective protonation in the presence of commercially available phosphoric acid catalyst **5e** or the novel SF_5-substituted phosphoric acid catalyst **5f**. The operationally simple protocol allows facile catalysis at ambient reaction conditions. The obtained thioacetal-protected enantioenriched products can be easily transformed to hydrocoumarins and chromans via simple deprotection steps without loss of enantiopurity. Further application of our protocol to various lactones and biologically active target molecules is currently under investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous support by Max Planck Society and the European Research Council (Advanced Grant "High Performance Lewis Acid Organocatalysis, HIPOCAT" to B.L.) is gratefully acknowledged. We thank our analytical departments (mass spectroscopy and X-ray analysis) for their excellent support.

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