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Asymmetric Synthesis of Hydrobenzofuranones via Desymmetrization of Cyclohexadienones Using the Intramolecular Stetter Reaction

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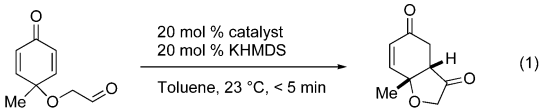
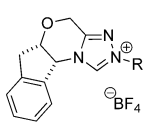
Dearomatization of aromatic compounds provides a useful alicyclic synthetic building block due to its high economy and simple elegance.[1] When coupled with a stereoselective process, it has the potential for affording enantioenriched material from commonly available precursors in rapid fashion.[2] Reactivity umpolung[3] affords an opportunity to take advantage of unobvious, complementary bond disconnections in the synthesis of complex molecules. One such reaction is the Stetter reaction, the nucleophile-catalyzed addition of an aldehyde to a Michael acceptor.[4] If the Michael acceptor involves a prochiral alkene, this reaction generates new stereocenters.[5] We have recently developed a family of catalysts capable of inducing highly enantioselective intramolecular Stetter reactions.[6] As part of an effort to extend the power of this transformation, we considered that cyclohexadienones, readily available from dearomatization of phenols,[7] could be suitable substrates for a desymmetrizing Stetter reaction. Herein we disclose that treatment of such substrates with chiral triazolium salts affords, in high yields and enantioselectivities, hydrobenzofurans, which are core skeletons found in many natural products.[8]

The requisite substrates are readily accessible from the corresponding phenols (Scheme 1). Hypervalent iodine reagents are used in conjunction with glycol to afford the dienone alcohols in good yield, whereupon Dess−Martin oxidation leads to the aldehydes and sets the stage for the asymmetric Stetter reaction. Upon cyclization, the desired product hydrobenzofuranones would contain at least two contiguous stereocenters.

The reactivity of a series of catalysts[6] was studied using substrate **1** (eq 1). The reactions were conducted in the presence of 20 mol % catalyst and 20 mol % KHMDS in toluene at 23 °C and proceeded to completion in less than 5 min, affording desired product **2**. Aminoindanol-derived triazolium salt **3** bearing an anisyl substituent was found to be the best catalyst precursor for this reaction, again reflecting the subtle impact of electronics arising from aryl substitution.[6]





R	catalyst	yield (%)	*ee* (%)
4-OMePh	**3**	90	88
Ph	**4**	75	80
C_6F_5	**5**	92	31

A range of substrates was synthesized following the general procedure (Scheme 1). Under optimized conditions,[9] the asymmetric intramolecular Stetter reaction proceeds very well (Table 1). The enantioselectivities are excellent (92−94% ee) when groups at the 4-position of the substrates are methyl, ethyl, isopropyl and *tert*-butyl (entries 1−4). Aromatic substituents result in slightly lower enantioselectivities (Table 1, entries 5 and 6). Similar effects are observed with more functionalized side chains at that position (entries 7−9). With all substrates, the reaction proceeds with very high diastereoselectivities (>95:5 by ^{1}H NMR).[10]

Scheme 1. Asymmetric Synthesis of Hydrobenzofuranones

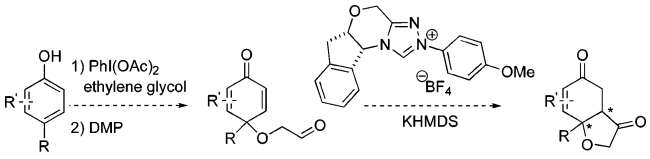
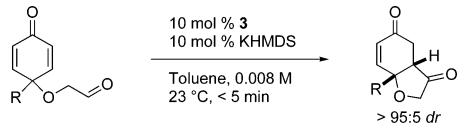


Table 1. Asymmetric Intramolecular Stetter Reaction of Monosubstituted Cyclohexadienones



entry[a]	R	substrate	product	yield (%)	ee (%)[b]
1	Me	**1**	**2**	90	92
2	Et	**6**	**7**	86	94
3	^{i}Pr	**8**	**9**	87	94
4	^{i}Bu	**10**	**11**	86	94
5	Ph	**12**	**13**	87	88
6	4-BrPh	**14**	**15**	78	85
7	CH_2OAc	**16**	**17**	86	83
8	CH_2CH_2OMe	**18**	**19**	86	82
9	$CH_2CH_2CO_2Me$	**20**	**21**	94	87

[a] All reactions conducted in the presence of 10 mol % catalyst and 10 mol % KHMDS in toluene at 23 °C. [b] Determined by HPLC or GC using a chiral stationary phase.

We have previously documented the ability of the Stetter reaction to form contiguous stereocenters with trisubstituted alkene acceptors.[6d] The use of 2,4,6-trisubstituted phenols as precursors in this chemistry allows a rapid entry into suitably functionalized substrates to test whether the desymmetrization would proceed. In the event, the dienone derived from 2,4,6-trimethylphenol proved remarkably efficient. This reaction provides hexahydrobenzofuranone **23** possessing three contiguous stereocenters in excellent yield and enantiomeric excess (entry 1 in Table 2). The reaction is tolerant of alkoxymethyl groups at the 2-position, providing **25** in excellent enantiomeric excess and good yield (entry 2). No elimination of the methoxy group is observed under these conditions. Remarkably, this reaction is also tolerant of as many as three *tert*-butyl groups in the vicinity of the reaction center, and the substrates provide one (entry 3) or two (entry 4) neopentyl stereocenters in excellent selectivity. In each of the cases examined to date, a single diastereomer is formed.[10]

Commercially available 3,4,5-trimethylphenol provides an opportunity to test whether this approach is capable of forming quaternary stereocenters as per our previous report.[6c] In the event,

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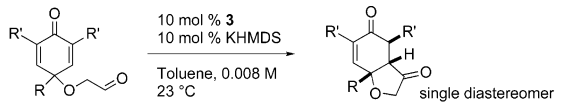
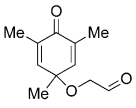
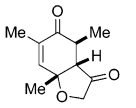
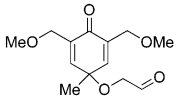
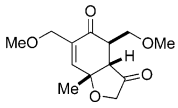
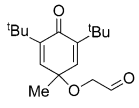
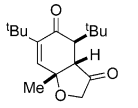
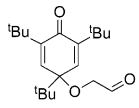
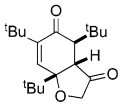
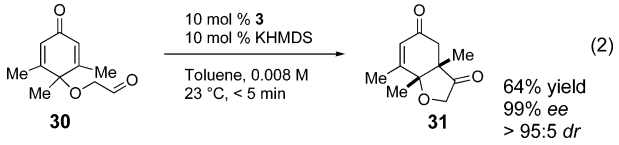
Table 2. Reaction of Trisubstituted Substrates



entry[a]	substrate	product	yield (%)	*ee* (%)[b]
1	 **22**	 **23**	86[c]	>99
2	 **24**	 **25**	71[c]	99
3	 **26**	 **27**	80[d]	>99
4	 **28**	 **29**	62[d]	>99

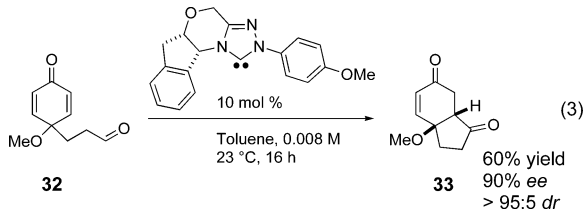
[a] See Table 1. [b] See Table 1. [c] Reaction time: 5 min. [d] Reaction time: 2 h.

cyclization of substrate **30** affords one quaternary stereocenter adjacent to a tertiary ether in excellent enantioselectivity and good yield (eq 2).



(2)

Although the bulk of our work focused on oxygen-tethered substrates due to their accessibility, the reaction is also capable of forming carbocycles. To that end, when **32** is subjected to the reaction conditions, hydrindane **33** is isolated in good yield and 90% ee (eq 3).



(3)

In conclusion, a family of phenol-derived substrates have been successfully synthesized and found to undergo asymmetric intramolecular Stetter reactions in very good yields. Quaternary stereocenters and up to three contiguous stereocenters may be formed in excellent enantioselectivities and diastereoselectivities.

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Lower catalyst loading or higher concentration results in comparable yields of product but lower enantioselectivity (2 mol % catalyst, 84% yield, 83% ee; 0.04 M, 90% yield, 88% ee).

(10) Relative and absolute configurations determined by nOe and X-ray for several compounds and the rest assigned by analogy (see Supporting Information for details). We have been unable to form the complementary diastereomers even by base-induced epimerization. A semiempirical calculation of **23**, **25**, **27**, and **29** suggests the minor diastereomers are as much as 9 kcal/mol less stable. Examination of GC traces suggests that this reaction is likely far more selective than 95% of a single diastereomer.

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