

Enantioselective Synthesis of Hydrobenzofuranones Using an Asymmetric Desymmetrizing Intramolecular Stetter Reaction of Cyclohexadienones

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Abstract:

A series of cyclohexadienones were synthesized by dearomatization of phenols followed by Dess–Martin oxidation. Asymmetric intramolecular Stetter reactions of these substrates provide hydrobenzofuranones in good to excellent yields and excellent stereoselectivities. Up to three stereocenters as well as a quaternary stereocenter are formed from polysubstituted substrates. A scale-up experiment demonstrates the utility of this transformation.

Introduction

Introduced by D. Seebach and E. J. Corey, reactivity umpolung¹ is a process in which the normal donor and acceptor reactivity of a functional group is inverted to provide non-obvious, complementary reactivity in organic synthesis. The Stetter reaction² is an umpolung process in which an acylanion equivalent, generated from an aldehyde in the presence of a nucleophilic catalyst, is added to a Michael acceptor to form a C–C bond. If the Michael acceptor involves a prochiral alkene, this reaction generates new stereocenters.³ Recently, our group developed a family of triazolium catalysts that promotes intramolecular Stetter reactions in excellent enantioselectivities and diastereoselectivities.⁴

As powerful as it may be, any strategy is inherently limited if the requisite substrates are esoteric or difficult to access. In an effort to expand the scope of the asymmetric intramolecular Stetter reaction in order to access more diverse product scaffolds amenable to complex molecule total synthesis, we initiated an effort at using aromatic feedstock starting materials to provide Stetter substrates. Dearomatization of aromatic compounds is a very useful strategy to synthesize alicyclic compounds due to the reaction's high

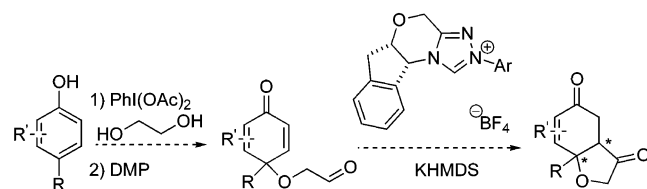
economy and simplicity.⁵ When this reaction is coupled with a stereoselective process, it has the potential to afford enantioenriched material from commonly available precursors.⁶ To contribute to efforts to extend this powerful transformation, we investigated cyclohexadienones, readily available from dearomatization of phenols,⁷ as substrates for an asymmetric desymmetrizing Stetter reaction (Scheme 1). In a preliminary communication, we reported the asymmetric intramolecular Stetter reaction of phenol-derived cyclohexadienones with chiral triazolium salt-based catalysts.⁸ This reaction allows for a rapid entry to hydrobenzofurans, which are core skeletons found in several natural products.⁹ Herein, we report our full investigation of this transformation, including the optimization of reaction conditions, expansion of the substrate scope, and scale-up of the reaction.

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Scheme 1. Intramolecular Stetter reaction of phenol-derived cyclohexadienones

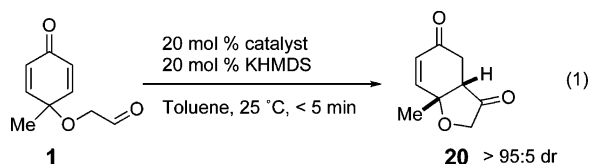


Results and Discussion

Our initial investigations were focused on substrate **1**, which was synthesized in two steps from cresol. (Table 1, entry 1). First, oxidation of cresol using iodobenzene diacetate in the presence of excess ethylene glycol as a trapping agent produces cyclohexadienone **1** in 49% yield. A large excess (30 equiv) of glycol is required to suppress formation of undesired byproducts in this reaction, which is rarely a problem given its cost and water solubility, the latter greatly facilitating workup. We have spent some effort at using fewer equivalents of alcohol with some success, but the above protocol is the most general. Alcohol thus generated is then converted to aldehyde **1** using Dess–Martin reagent (DMP) in 87% yield. Using this general procedure, a series of cyclohexadienones may be synthesized successfully (Table 1).

As can be seen from Table 1, this approach is remarkably tolerant of arene substitution. Although yields in the arene oxidation vary, most reactions were conducted only once and are thus unoptimized. The Dess–Martin oxidation was found to be the most appropriate for the second step, with fresh batches of reagent providing the highest and most reproducible yields.

Subjection of **1** to the standard Stetter reaction conditions using previously reported triazolium salts⁴ as catalyst precursors



	R	catalyst	yield (%)	ee (%)
	4-CF ₃ C ₆ H ₄	21	83	57
	Ph	22	84	49
	4-OMeC ₆ H ₄	23	79	34
	C ₆ F ₅	24	92	31
	Ph	25	75	80
	4-OMeC ₆ H ₄	26	90	88

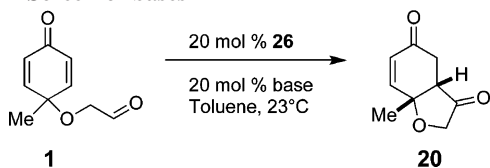
provides the desired benzohydrofuranone **20** in good yields. We found the best catalyst to be **26**, an aminoindanol-derived electron-rich triazolium salt, providing the product in 90% yield and 88% ee in 5 min. The diastereoselectivity of this transformation is excellent (>95:5 by ¹H NMR and GC), favoring formation of the *cis*-fused hydrobenzofuranone. Surprisingly, electron-tuning of the arene ring was required for optimal selectivities as the sterically identical phenyl and

Table 1. Syntheses of monosubstituted substrates

Entry	Phenol	B	Yield (%) A/B
1		1 R = Me	49/87
2		2 R = Et	42/78
3		3 R = ⁱ Pr	38/92
4		4 R = ^t Bu	31/78
5		5 R = Ph	56/64
6		6 R = 4-BrC ₆ H ₄	26/75
7		7 R = CH ₂ OAc	17/52
8		8 R = CH ₂ CH ₂ OMe	39/59
9		9 R = CH ₂ CH ₂ CO ₂ Me	20/47
10		10 R = CH ₂ CH ₂ NHBoc	22/26
11		11	93/56
12		12	25/54
13		13	31/89
14		14	70/74
15		15	56/62
16		16	93/56
17		17	25/54
18		18	70/74
19		19	31/89

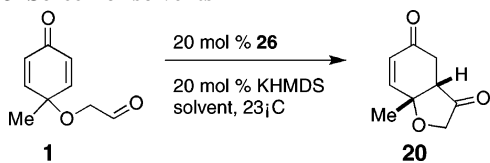
pentafluorophenyl catalysts provide lower selectivities. Although at this time we cannot account for these differences, the tunability of these azolium salts is a hallmark of their design.¹⁰

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Table 2. Screen of bases


entry ^a	base	reaction time	yield (%)	ee (%) ^b
1	KHMDS	5 min	90	88
2	KOt-Bu	30 min	83	88
3	KH	16 h	76	76
4	<i>i</i> -Pr ₂ NEt	21 h	62	70
5	Et ₃ N	32 h	68	66

^a [1] = 0.04 M. ^b Determined by GC using a chiral stationary phase.

Table 3. Screen of solvents


entry ^a	solvent	yield (%)	ee (%) ^b	entry ^a	solvent	yield (%)	ee (%) ^b
1	toluene	90	88	7	CH ₂ Cl ₂	16	67
2	xylenes	81	75	8	MeOH	29	-11
3	benzene	88	89	9	EtOH	63	-42
4	Et ₂ O	67	87	10	CF ₃ CH ₂ OH	0	N/A
5	DMF	71	73	11	<i>i</i> -PrOH	64	-63
6	THF	77	89	12	<i>t</i> -BuOH	30	-57

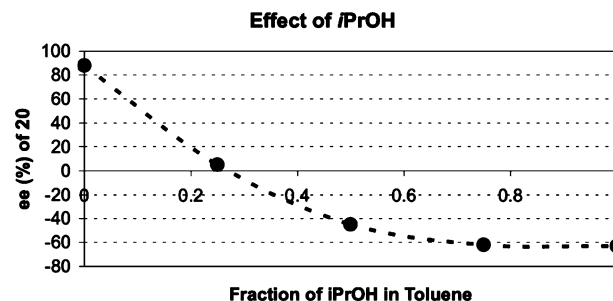
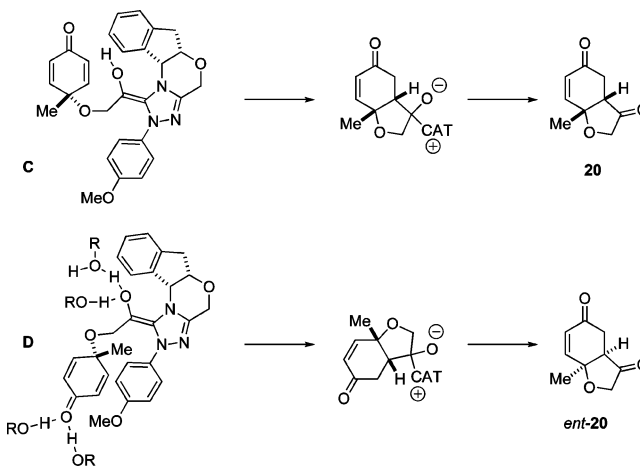
^a See Table 2. ^b See Table 2.

A screen of different bases revealed that KHMDS is the best base for this reaction (Table 2). KO-*t*-Bu is equally effective at inducing asymmetry but requires a longer reaction time. Amine bases also require longer reactions times, consistent with their reduced basicity, thereby leading to lower concentrations of active carbene catalyst. Somewhat surprising is the reduced selectivity evident when amine bases are used, a situation not generally encountered in other Stetter reactions developed in our laboratory.

When screening a variety of solvents (Table 3), we observed a large effect on both yield and ee. For example, the reaction results in 16% yield and 67% ee after 3 days when dichloromethane is used as solvent. Overall, toluene was found to be the best solvent for this reaction.

By far the most surprising aspect of this study was the effect of alcoholic solvents on the reaction, which invariably afford the opposite enantiomer using the same series of catalyst (Table 3). There is a clear effect of alcohol size on selectivity with isopropanol providing the highest ee's. Trifluoroethanol shuts down the reaction, presumably because of its increased acidity.

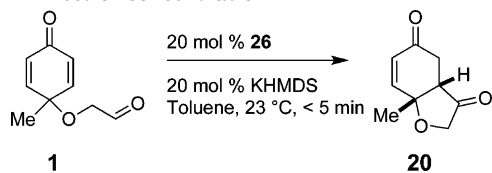
The profound difference between polar aprotic solvents such as DMF and the alcoholic solvents cannot be accounted for by polarity alone. In order to study the effect of the alcohol further, a mixture of toluene and isopropanol was


Figure 1. Effect of isopropanol as solvent.

Figure 2. Proposed model for turnover in selectivity in *i*-PrOH.

used as the solvent for the reaction. A gradual inversion in selectivity occurs as the volume fraction of isopropanol increases to a plateau of ~60% isopropanol in toluene (Figure 1). We suggest that these effects are most consistent with the involvement of the alcohol in the transition state likely via hydrogen bonding to either the nucleophilic enol or the carbonyl acceptor or both. This hydrogen bonding thus changes the chiral environment, ultimately affecting the stereochemical outcome of the reaction.

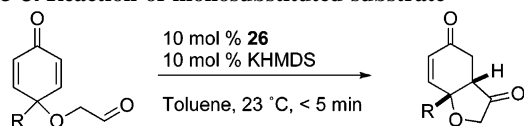
A stereochemical rationale to account for the turnover in selectivity is provided in Figure 2. The absolute stereochemistry of **20** is consistent with model **C** wherein minimization of charge separation is emphasized. We suggest that extensive hydrogen bonding in isopropanol destabilizes this transition state relative to **D** since the incipient enolate and alkoxide are each hydrogen-bonded to solvent. Solvation and electrostatic effects are likely also playing a role.

Having evaluated the effect of each component on the reaction, we were faced with a reaction that provided product in 88% ee. A preliminary screen of different substrates (not shown) revealed that the enantioselectivities were invariably <88%. We were particularly intrigued with the effect of alcoholic solvents on enantioselectivity and speculated whether hydrogen-bond donors present as intermediates in the reaction could be interfering. In an effort to minimize the contribution of bimolecular events to the stereoselectivity of the process, we evaluated the impact of reaction concentration. When the concentration of **2** decreased from 0.12 to 0.013 M, the ee increased from 79 to 90%. Selectivities were further improved by a serendipitous discovery that the use of an argon purge through the reaction leads to improved

Table 4. Effect of concentration


entry	concentration 1 (M)	yield (%)	ee (%) ^a
1	0.12	85	79
2	0.04	90	88
3	0.013	90	90
4	0.008	90	90
5 ^b	0.008	90	93
6	0.005	86	90
7 ^b	0.005	91	96

^a See Table 2. ^b Ar purge.

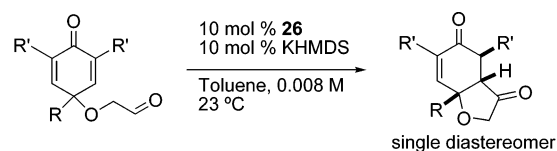
Table 5. Reaction of monosubstituted substrate


entry ^a	R	substrate	product	yield (%)	ee (%) ^b
1	Me	1	20	90	92
2	Et	2	27	86	94
3	<i>i</i> -Pr	3	28	87	94
4	<i>t</i> -Bu	4	29	86	94
5	Ph	5	30	87	88
6	4-BrC ₆ H ₄	6	31	78	85
7	CH ₂ OAc	7	32	86	83
8	CH ₂ CH ₂ OMe	8	33	86	82
9	CH ₂ CH ₂ CO ₂ Me	9	34	94	87
10	CH ₂ CH ₂ NHBoc	10	35	28	64

^a Argon purge, [substrate] = 0.008 M. ^b Determined by GC or HPLC using a chiral stationary phase.

ee's, entries 5 and 7 in Table 4. We suggest that these effects are a consequence of the availability of hydrogen-bond donors under conditions involving higher concentrations or adventitious oxygen-derived byproducts, and these lead to competitive transition states similar to **D** in Figure 2 above.

With the optimized reaction conditions in hand, we screened a series of monosubstituted dienone substrates. As the steric size of R group is increased from methyl to *tert*-butyl, the enantioselectivity of the transformation remained largely invariant (Table 5, entries 1–4). Aryl groups result in slightly lower selectivities (Table 5, entries 5–6). Single-crystal analysis of **31** (Table 5, entry 6) revealed the absolute configuration of this product, while the rest were assigned by analogy. More functionalized substitutions are also tolerated in the reaction, although with lower ee's (Table 5, entries 7–10). In light of the detrimental effect of groups capable of hydrogen bonding, it is tempting to invoke an intramolecular hydrogen bond that alters selectivities in the case of substrates **7**–**10**. However, this scenario clearly cannot account for depressed selectivities observed with aryl substituents in substrates **5** and **6**. Furthermore, it is difficult to envision an intramolecular hydrogen bonding affecting

Table 6. Reaction of polysubstituted substrates


Entry ^[a]	Substrate	Product	Yield (%)	ee (%) ^[b]
1			86 ^[c]	>99
2			71 ^[c]	99
3			80 ^[d]	>99
4			62 ^[d]	>99

^a See Table 5. ^b See Table 5. ^c Reaction time = 5 min. ^d Reaction time = 2 h.

the transition state when cyclization occurs trans to the R group at the 4-position of the dienone. We suggest, therefore, that this effect may best be rationalized as due to electronics. Every group in substrates **5**–**10** is sigma withdrawing, and this may have a subtle effect in altering the diastereomeric transition states. Of note is that all the substrates provide products in excellent diastereoselectivities (>95:5 by ¹H NMR and GC).

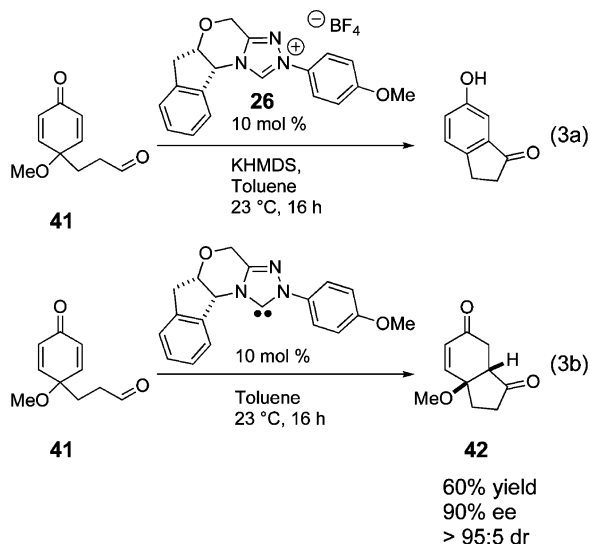
Given our previous success in cyclizing onto trisubstituted Michael acceptors,^{4d} we were intrigued to attempt cyclizations onto dienones derived from trisubstituted phenol starting materials. A number of 2,4,6-trisubstituted phenols are readily available. When the derived dienones are subjected to the optimized reaction conditions, hydrobenzofuranones with three contiguous stereocenters are formed in good yield and excellent selectivities (Table 6). No elimination of methoxy group is observed under the basic reaction conditions (Table 6, entry 2). The tolerance of this reaction to steric bulk is particularly noteworthy. Dienone **12**, derived from the ubiquitous and inexpensive antioxidant BHT, provides product **38** in good yield as largely a single enantiomer and diastereomer (Table 6, entry 3) possessing a neopentyl stereocenter. Substrate **13**, derived from 2,4,6-tri-*tert*-butyl phenol, provides product **39** in excellent ee, having three contiguous stereocenters, two of them being neopentyl. Significantly, for each reaction in Table 6, a single diastereomer is observed (>95:5 by ¹H NMR, GC, and HPLC).

Attempted epimerization experiments on products **36** and **38** (Et₃N in PhMe at 110 °C for 24 h) failed to provide noticeable evidence of epimeric products. Preliminary semi-empirical calculations suggest the major diastereomers are more thermodynamically stable products.¹¹ The relative configuration of the product was also confirmed by NOE experiments (see Supporting Information).

Analogously, in order to test whether this chemistry is able to generate quaternary stereocenters,^{4c,f} cyclohexadienone **15** was synthesized from commercially available 3,4,5-trimethylphenol. Cyclization of **15** provides the desired product **40** with a quaternary stereocenter adjacent to a tertiary ether in good yield and excellent stereoselectivity (eq 2).



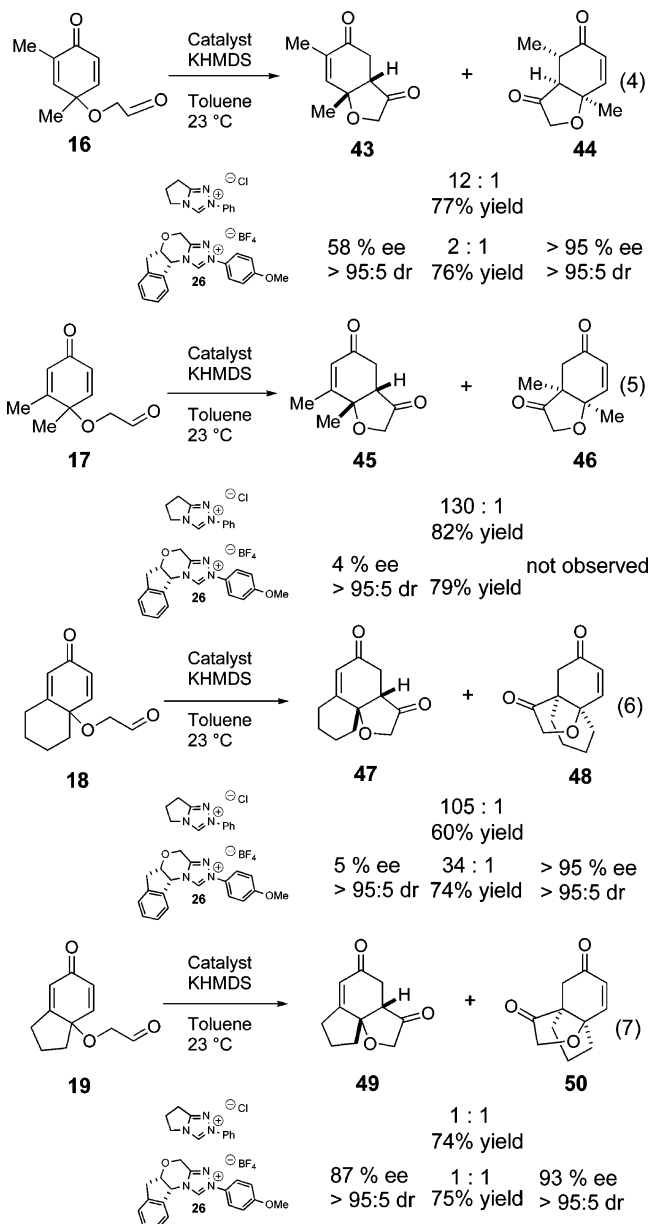
The above examples all involve the synthesis of hydrobenzofuranones, largely due to the accessibility of the substrate by the above route.¹² In order to test whether the oxygen tether was required, we synthesized substrate **41** starting from 4-(3-hydroxypropyl)phenol. However when **41** was subjected to the optimized conditions, the only isolated product was 6-hydroxy-1-indanone (eq 3a). We suggest this



product is derived from the elimination of the expected product under the reaction conditions. Fortunately, we found that the elimination may be avoided if the reaction of **41** is

(11) For example, **36** is ~9.9 kJ/mol more stable than the diastereomer having the methyl group on the endo face of the bicycle, while **38** is ~36 kJ/mol more stable than the diastereomer having the bulky *tert*-butyl in that position.

(12) The use of propylene glycol in the starting material synthesis affords homologous substrates. These substrates undergo efficient Stetter reactions using achiral catalysts, but are much more prone to base-induced Michael cyclization in the presence of our suite of chiral catalysts. Efforts to remedy this situation are currently underway.



conducted using the preformed free carbene,^{4d} providing the desired carbocycle **42** in 60% yield and 90% ee (eq 3b).

The use of several commercially available disubstituted phenols as starting materials in this chemistry would lead to chiral racemic dienones. Previous work in our laboratory has revealed that kinetic resolutions are not practical using this approach; rather, the catalysts override preexisting stereocenters unless they are alpha to the aldehyde.^{4e} However, we were intrigued by the opportunity to investigate the relative propensity of our catalysts to induce cyclization onto disubstituted versus trisubstituted Michael acceptors in an intramolecular competition. As such, chiral substrates **16**–**19** were assembled and subjected to optimized reaction conditions using catalyst **26** along with an achiral azolium salt. Substrates **16**, **17**, and **18** provided the products favoring cyclization onto the less-substituted olefin, consistent with expectations. The former provides **43** in 12:1 selectivity over **44** when using an achiral azolium salt. This selectivity is greatly degraded when the chiral catalyst is used, as it exerts its influence to provide only 2:1 selectivity, with the minor

adduct formed in high ee, (eq 4). Substrates **17** and **18** provide products **45** and **47**, respectively, in nearly exclusive selectivity regardless of catalyst, (eqs 5 and 6). However, when we subject substrate **19** to both catalysts, we observe both constitutional isomers formed in identical amounts, eq 7, illustrating no selectivity between cyclization onto a di- versus trisubstituted Michael acceptor. When this reaction is conducted using catalyst **26**, both isomers are formed in high ee's, as the chirality of the catalyst exerts its control.

The different behavior of substrates **17** and **18** versus **19** is not easy to rationalize. We speculated that the dichotomy lay in product stability. Semi-empirical calculations were carried out, and the results are consistent with our suggestion (Scheme 2). Products **45** and **47** are correspondingly more thermodynamically stable than **46** and **48** by ~15 kJ/mol. In contrast, **50** is actually very slightly more stable than **49** (but only ~1.5 kJ/mol), implying the fused five-membered ring has a profound effect on the outcome of the reaction. We suggest this is due to destabilization of **49** having the fused cyclopentane considerably twisted in the angular tricycle, a situation that is alleviated in **50**. We further suggest that this difference in ground-state energy is partially reflected in the transition states leading to each of these constitutional isomers, thereby negating the typical selectivities we observe between di- and trisubstituted Michael acceptors. This situation also allows the chiral catalyst to exert control over the newly formed, bond providing parallel kinetic resolution.

Finally, in order to test whether this chemistry could be used on scale, we conducted an experiment using one gram of **11** as the starting material. Although the catalyst loading was reduced to 3 mol % and the concentration (0.1 M) is much higher than that in small-scale experiments (0.008 M), the reaction proceeds efficiently, providing *ent*-**36** in 82% yield and 96% ee (eq 8).

In conclusion, a series of cyclohexadienones were synthesized in a rapid and efficient manner. The asymmetric intramolecular Stetter reactions of these substrates affords



* enantiomer of **26** was used as catalyst

hydrobenzofuranones in good yields and excellent selectivities. Up to three contiguous stereocenters as well as quaternary stereocenters can be formed using this transformation. A successful scale-up experiment demonstrates the utility of this methodology.

Experimental Section

General Procedure for Synthesis of the Substrates. A flame-dried 100-mL round-bottom flask was charged with cresol (1.08 g, 10 mmol); the flask was purged under vacuum for 5 min and then refilled with argon and 2 mL of CH₂Cl₂. Ethylene glycol (16.7 mL, 300 mmol) and then PhI(OAc)₂ (4.83 g, 15 mmol, dissolved in 40 mL of CH₂Cl₂) was added dropwise over 2 h. The solution was then allowed to stir at ambient temperature for further 30 min. The solution was concentrated in vacuo, and the residue was subjected to column chromatography (EtOAc/hexane = 1:1) to provide dienone alcohol (823 mg, 49%) as an orange oil.

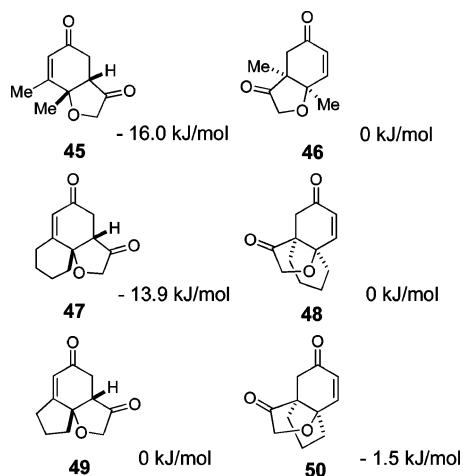
In a flame-dried 50-mL round-bottom flask, this alcohol (556 mg, 3.86 mmol) was dissolved in 36 mL CH₂Cl₂, Dess–Martin periodinane (1.80 g, 4.25 mmol) was added to the solution directly, and the solution was then allowed to stir at ambient temperature for 1 h. The solution was filtered through Celite 545 and then concentrated in vacuo, and the residue was subjected to column chromatography (EtOAc/hexane = 1:3) to provide **1** (556 mg, 87%) as yellow oil.

General Procedure for the Synthesis of Hydrobenzofuranones. A flame-dried, 25 mL round-bottom flask was charged with triazolium salt **26** (4.9 mg, 0.012 mmol). The flask was purged under vacuum for 5 min and then refilled with argon and 12 mL of toluene. Argon was bubbled through the solution for 5 min, then KHMDS (0.024 mL, 0.012 mmol) was added, and the solution was allowed to stir at ambient temperature for 15 min. The substrate (around 20 mg, 0.12 mmol) was dissolved in 3 mL of toluene and then was added via syringe; the reaction was allowed to stir at ambient temperature. After the reaction was complete (checked by TLC), usually in 5 min, the reaction mixture was directly purified by flash column chromatography.

Acknowledgment

We gratefully acknowledge the National Institute of General Medical Sciences (GM72586) and Johnson and

Scheme 2. Calculation of relative energies^a



^a Relative energies calculated using SPARTAN (PM3).

Johnson (Focused Funding) for partial support of this research. T.R. thanks Merck Research Laboratories, Eli Lilly, Amgen, and Boehringer Ingelheim for unrestricted support, and the Monfort Family Foundation for a Monfort Professorship. T.R. is a fellow of the Alfred P. Sloan Foundation.

Supporting Information Available

This information is available free of charge via the Internet at <http://pubs.acs.org>.

Received for review December 21, 2006.

OP600278F