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A Catalytic Asymmetric Bioorganic Route to Enantioenriched Tetrahydro- and Dihydropyranones

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Abstract: A conceptually novel approach to hetero Diels−Alder adducts of carbonyl compounds is described using as the key steps an antibody-mediated kinetic resolution of hydroxyenones followed by a ring-closure process. Various β-hydroxyenones proved to be very good substrates for antibodies 84G3- and 93F3-catalyzed retro-aldol reactions, allowing the preparation of highly enantiomerically enriched (up to 99% ee) precursors of pyranones. An attractive feature of this methodology is the possibility to convert these acyclic-enantioenriched β-hydroxyenones into tetrahydropyranones by a conventional Michael-type addition procedure or into the corresponding dihydropyranones using an alternative palladium-catalyzed oxidative ring closure. For the palladium-mediated cyclization, a biphasic system has been implemented that allows the direct preparation of enantiopure dihydropyranones from the corresponding racemic aldol precursors using a sequential antibody-resolution/palladium-cyclization strategy, without isolation of the intermediate enantioenriched hydroxyenones. This bioorganic route is best applied to the preparation of hetero Diels−Alder adducts otherwise derived from less nucleophilic dienes and unactivated dienophiles.

Introduction

The hetero Diels−Alder (HDA) reaction between carbodienes and carbonyl compounds has been the focus of extensive studies and has emerged as an important target for asymmetric catalysis. Successes reported in this area have mostly involved the reaction of electron-rich dienes such as 1-methoxy-3-(trimethylsilyloxy)-butadiene (Danishefsky's diene) with both activated and unactivated dienophiles, including ketones. The products resulting from these reactions are dihydropyranones, which are attractive substrates for the synthesis of carbohydrates and numerous other natural compounds.[1] Only more recently have Jacobsen et al. developed a metal-catalyzed enantioselective HDA reaction allowing the use of less nucleophilic dienes, bearing fewer than two oxygen substituents, combined with unactivated carbonyl compounds. These metal-catalyzed asymmetric HDA reactions allow ultimate access to structurally diverse tetrahydropyranones. Such transformations are successfully performed in the presence of chiral tridentate chromium(III) catalysts leading to enantioenriched all syn products possessing up to three stereocenters.[2] Nature also appears to have used the Diels−Alder reaction in the biosynthesis of several secondary metabolites,[3] and therefore it is not surprising that numerous biocatalysts have been prepared for the assembly of novel carbocyclic and heterocyclic products. The immune system has proven to be a rich source of unique Diels−Alderase antibodies as a result of ingenious approaches to elicit catalysts that are even able to promote disfavored reaction pathways preferentially over the other possible reaction outcomes.[4] More recently, modified RNA fragments have also been shown to be effective Diels−Alderase catalysts that seem to operate through Lewis acid-type catalysis, a different mechanistic mode to catalytic antibodies.[5] Surprisingly, none of these biopolymer catalysts were generated for hetero Diels−Alder reaction of carbonyl compounds, with the exception of a polyclonal antibody preparation that was shown to catalyze the cycloaddition of a carbodiene with ethyl glyoxylate with moderate rate acceleration.[6] In this article, we describe a conceptually novel approach to both enantioenriched dihydro-

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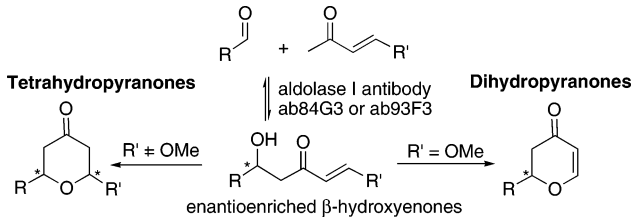
pyranones and tetrahydropyranones based on the use of aldolase I antibody 84G3 or antibody 93F3. These antibodies were raised by reactive immunization against a hapten featuring both a sulfone and a 1,3-diketone functionality.[7] The key step involves the kinetic resolution of structurally diverse enone-derived aldol products with aldolase antibody 84G3 or 93F3, followed by the cyclization of these various enantioenriched aldol products into one or the other class of hetero Diels−Alder adducts. This approach allows easy access to numerous adducts, including products otherwise derived from the combination of less nucleophilic dienes with unactivated aldehydes. We present herein full details of our studies, including an investigation of the scope and limitation of the aldolase I antibody route to various enantioenriched aldol products derived from enones and a discussion of how the ring-closure process controls the degree of oxidation of the cyclized product, leading either to enantioenriched tetrahydropyranones or dihydropyranones.

Results and Discussion

Two mechanistic pathways can operate for Lewis acid-mediated hetero Diels−Alder reactions of Danishefsky-type carbodienes with carbonyl compounds.[8] These two pathways are a concerted nonsynchronous mechanism by analogy with the catalyzed all-carbon Diels−Alder reaction or the formation of a Mukaiyama-aldol intermediate, followed by an intramolecular Michael-type addition. To a great extent, the mechanism that operates is a function of the catalyst and solvent system along with the structural features of the reactants.

Scheme 1. Aldolase Antibody Route to Hetero Diels−Alder Adducts



Specifically, we hypothesized that aldolase I antibodies are potential catalysts for the preparation of HDA adducts of carbonyl compounds, according to a stepwise pathway where an antibody-mediated aldol kinetic resolution will deliver enantioenriched aldol products and a ring closure on the β-carbon of the hydroxyenone would complete the cyclocondensation. This hypothesis is based on the mechanistic similarities between the first step of a stepwise hetero Diels−Alder reaction of carbonyl compounds and an aldolization process. In this strategy, the presence of a leaving group such as the methoxy group on the sp^2-hydridized carbon positioned β to the carbonyl in the aldol products will lead upon cyclization to the corresponding dihydropyranones. In the absence of this group, the enantioenriched tetrahydropyranones will be obtained instead (Scheme 1).

Preparation of Enantioenriched β-Hydroxyenones. To test this hypothesis, we investigated the capacity of aldolase I antibodies 84G3 and 93F3 to deliver enantioenriched aldol products derived from α,β-unsaturated methyl ketones and various aldehydes (Table 1). We first undertook preliminary work on selected synthetic forward aldol reactions in the presence of these aldolase I antibodies. These experiments revealed that only traces or no aldol products were formed following extended incubation with the antibody.[9] We therefore turned our attention to the antibody-catalyzed kinetic resolution of aldol product (±)-**1a**, and we found that the treatment of aldol (±)-**1a** with aldolase antibody 84G3 or antibody 93F3 resulted in the rapid formation of anisaldehyde. Gratifyingly, the retro-aldolization did not go beyond 50% conversion, auguring an efficient kinetic resolution process (entry 1). Given our encouraging results in the resolution of aldol (±)-**1a**, we set out to study the range of β-hydroxyenones that could be resolved using antibodies 84G3 and 93F3. We focused our study on aldol products derived from the combination of seven representative enones and six aldehydes. In total, 12 racemic aldols were prepared in one step from the corresponding donor enones and acceptor aldehydes. Indeed, the direct aldol reaction between various aldehydes and lithium enolates was successful for the preparation of all racemic aldols (±)-**1a**−**l** with excellent chemical yields.[10] The racemic aldols (±)-**1a**−**l** were then subjected to kinetic resolution with antibody 84G3 and/or 93F3 in PBS at pH 7.4 and at room temperature. Analysis by high-performance liquid chromatography (HPLC) indicated that a reaction is taking place with most aldol products. Conversion

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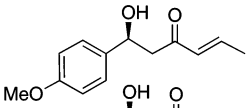
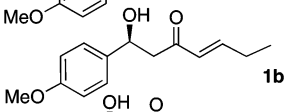
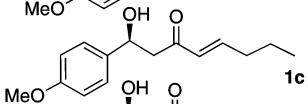
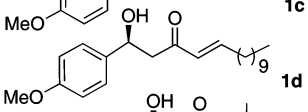
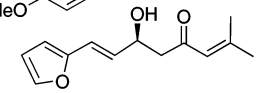
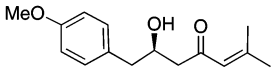
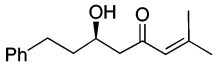
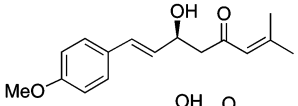
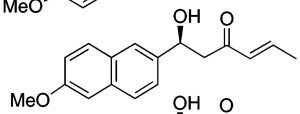
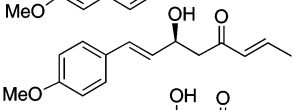
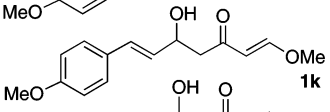
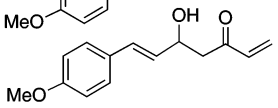
(9) A mixture of *para*-nitrobenzaldehyde and a large excess (700 equiv) of MVK, penten-3-one, or 4-methylbutanone was incubated in the presence of 10 mol % of ab38C2 or ab84G3. No trace of the desired aldol product was observed by HPLC upon extended reaction time when MVK or penten-3-one were used as donors. Only traces of aldol product could be detected for the reaction of *para*-nitrobenzaldehyde with 4-methylbutanone in the presence of ab84G3.

(10) See Supporting Information for full experimental details.

Table 1. β-Hydroxyenones Obtained via Kinetic Resolution with 84G3 or 93F3

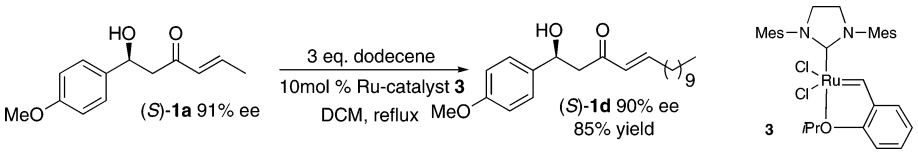
Entry	Product	Antibody	Time Conversion[a]	ee(%)[b]	Absolute configurations
1	 **1a**	84G3 93F3	0.25 h, 51% 1.25 h, 51%	99 98	(*S*)
2	 **1b**	84G3 93F3	12 h, 50% 12 h, 50%	40 --	(*S*)
3	 **1c**	84G3	77 h, 50%[c]	--	--
4	 **1d**	84G3	168 h, 0%	--	--
5	 **1e**	84G3 93F3	21 h, 50% 21 h, 50%	99 99	(*S*)
6	 **1f**	84G3 93F3	44 h, 47% 44 h, 49%	74 75	(*R*)
7	 **1g**	84G3 93F3	42h, 34% 42h, 46%	73 72	(*R*)
8	 **1h**	84G3 93F3	1h, 55% 1h, 51%	99 98	(*S*)
9	 **1i**	84G3 93F3	1h, 60% 1h, 57%	97[d] --	(*S*)
10	 **1j**	84G3 93F3	0.6h, 49% 0.6h, 55%	99 99	(*S*)
11	 **1k**	84G3	40h, 94%	0[e]	--
12	 **1l**	84G3 93F3	12h, 97% 12h, 98%	0[f] --	--

[a] 10 mol % antibody, room temperature, PBS/MeCN 9/1, pH 7.4. [b] 4 mol % antibody, room temperature, pH 7.4, all ee measured at about 50% conversion. [c] 20 mol % antibody for this experiment. [d] 1 mol % ab 84G3, PBS/toluene, room temperature. [e] ee measured at 60% conversion. [f] ee measured at 75% conversion.

slowed considerably at approximately 50% for most aldol products, suggesting that these reactions were highly enantioselective (entries 2−10), but went far beyond 50% for aldol products **1k** and **1l** (entries 11 and 12). It should be noted that, upon incubation of these two substrates **1k** and **1l** with antibodies 84G3 or 93F3, no aldehyde that should have resulted from a retro-aldol reaction or other products such as the target cyclized adducts were observed in the antibody crude mixture. The data also suggested that the antibodies do not accept aldol products derived from α,β-unsaturated ketones possessing long chain substituents β to the carbonyl group (entry 4). The presence of an ethyl or a propyl group in place of a methyl group on that position slowed the antibody-catalyzed retro-aldolization considerably (entries 1−3), and no reaction was observed with the aldol (±)-**1d** (entry 4). The aldol products derived from 4-methylbutenone were all accepted by antibodies 84G3 and 93F3 (entries 5−8). These experiments revealed that 84G3 and 93F3 tolerated more structural variations for the part of the molecule originally derived from the acceptor, although faster conversions were observed for aldols derived from the less electrophilic aldehydes as expected for a retro-aldolization process.

To ensure that catalysis proceeded as anticipated and to probe the synthetic scope of these reactions, the unconverted aldol products were recovered at approximately 50% conversion and studied using chiral phase HPLC. Comparison of the HPLC trace of the recovered aldol products with those of racemic standards indicated that the catalyst was highly enantioselective for most substrates, allowing the recovery of the (*R*)- or (*S*)-aldols with ee values ranging from 40 to 99%. For substrate **1b** recovered with an enantiomeric excess of only 40%, a control experiment revealed that this apparent lack of efficiency was not due to the inability of the antibody to discriminate between the two enantiomers but was the result of partial racemization of the substrate upon the extended reaction time required to reach 50% conversion. For substrates not prone to racemize under the

Scheme 2. Cross-Metathesis of β-Hydroxyenone **1a** with Dodecene



reaction conditions, the lower ee values were obtained for aldol products derived from nonconjugated aldehydes. In contrast, excellent levels of enantiocontrol were observed for aldol products derived from various conjugated aldehydes. We also found that the aldol products **1k** and **1l** recovered at 60 and 75% conversion, respectively, were racemic mixtures, suggesting that these antibody-mediated reactions were nonspecific. For these two substrates, we suggest that a Michael addition involving a reactive nucleophilic residue of the antibody competes with the desired retro-aldolization process. Indeed, observation that the aldol compound **1l** possessing the more exposed Michael-type acceptor could not be kinetically resolved supports this argument. For compound **1k**, we hypothesize that a Michael-type addition process followed by elimination of methanol also led to a covalently modified antibody, suggesting that this substrate acted as an irreversible inhibitor for antibody 84G3 and 93F3. Control experiments supported this hypothesis as the presence of aldol compounds **1k** or **1l** inhibited the antibody-catalyzed retro-aldolization of compound (±)-**1a**.

To assign the absolute configurations of the recovered aldol products, the enantiopure products **1f**, **1h**, and **1j** were synthesized by independent chemical asymmetric syntheses based on the use of Evans-type chiral oxazolidines.[10] Compound **1g** was prepared enantiopure from the corresponding hydroxyester obtained by Baker's yeast reduction of the ketoester.[10] The absolute configurations of all other compounds were assigned by analogy.

The data summarized in Table 1 demonstrated that the aldolase type I antibodies 84G3 and 93F3 were able to kinetically resolve various β-hydroxyenones but cannot mediate their cyclization.

Expanding the Repertoire of Enantioenriched β-Hydroxyenones. Because racemic aldol products derived from long chain enones are not accepted by antibodies 84G3 or 93F3, the need to overcome this limitation became apparent and led us to examine different possibilities to find a general solution to this problem. We discovered that subjecting the aldol product (*S*)-**1a** to a cross-metathesis reaction[11] was the most efficient way to elongate the alkenyl chain in a single-step process without epimerization or other undesirable side reactions (Scheme 2). We undertook the resolution of aldol product (±)-**1a**, and this procedure allowed us to prepare a sample of enantioenriched (*S*)-**1a** with an ee of 91% as verified by chiral HPLC.[10] This compound (*S*)-**1a** was used as a starting material for the preparation of aldol product **1d** that could not be resolved using antibody 84G3 or 93F3. Upon cross-metathesis with 3 equiv of dodecene in the presence of 10 mol % of the Ru-catalyst **3**, the desired aldol product (*S*)-**1d** was obtained with 85% yield and 90% ee. No detectable epimerization therefore occurred upon metathesis. The formation of compound **1d** also suggests that capping the double bond of **1a** with a methyl group does not prevent its reaction with dodecene. This sequential retro-aldolization/cross-metathesis process is extremely versatile and allows numerous structural variations, allowing the preparation of various enantioenriched aldol products that could be regarded as valuable precursors for the synthesis of many natural product targets.

Table 2. Kinetic Parameters for Selected Retro-Aldol Reactions

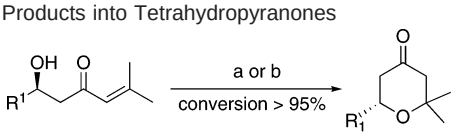
substrates	Ab	k_{cat} (min^{-1})	K_M (μM)
(±)-**1a**	84G3	0.45	46
(±)-**1a**	93F3	0.40	51
(±)-**1b**	84G3	0.03	116
(±)-**1g**	84G3	0.006	352
(±)-**1h**	84G3	2.7	59
(±)-**1h**	93F3	4.1	66
(±)-**1j**	84G3	2.2	40
(±)-**1j**	93F3	3.2	37

Kinetic Data. To gain more detailed information on the antibody-catalyzed transformations, kinetic studies were performed at room temperature on selected substrates (Table 2). For these reactions, the background retro-aldolization reaction was undetectable even after an extended period of time. Determination of k_{cat}/k_{uncat} was therefore not possible. The antibody-catalyzed transformations leading to enantioenriched aldol compounds follow Michaelis−Menten kinetics with some of these reactions rapidly catalyzed by the antibody as reflected with k_{cat} values up to 4.1 min^{-1}. As shown in Table 2, the efficiency with which the aldol compounds **1h** and **1j** derived from 4-methoxycinnamaldehyde are processed by antibodies 84G3 and 93F3 is remarkable, a highly desirable feature since both the allylic alcohol and the enone may be used for further functional manipulation. The antibody-catalyzed retro-aldol reactions were inhibited by the addition of an equimolar amount of 2,4-pentadione as expected for a covalent catalytic mechanism involving the reactive amine programmed in ab84G3 and ab93F3. The rate constants suggest that the best rate accelerations are obtained for aldol products derived from the less reactive aldehydes. These kinetic data suggest that this bioorganic approach will be the most efficient for the preparation of adducts derived from unactivated aldehydes that are more difficult to obtain using metal-catalyzed hetero Diels−Alder reactions.

Cyclization into Tetrahydropyranones. The enantioenriched aldol products **1f**−**h** obtained by kinetic resolution in the presence of antibody 84G3 or 93F3 were subsequently converted into the corresponding tetrahydropyranones (Table 3). A major concern for the cyclization step is the potential sensitivity of the aldol products **1f**−**h** to elimination or epimerization. Common reagents such as TFA or Amberlyst-15 failed to afford the cyclized compound or led to full or partial racemization. Direct cyclization of the recovered aldol products (*R*)-**1f** and (*R*)-**1g** was accomplished successfully in the presence of TMSOTf and iPr$_2$NEt, affording the desired HDA adducts (*R*)-

(11) For recent reviews on cross-metathesis, see: (a) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

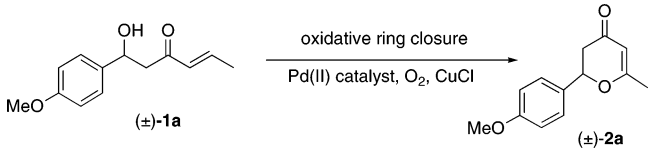
Table 3. Cyclization of Enantioenriched Aldol Products into Tetrahydropyranones



Conditions: (a) TMSOTf, *i*Pr_2NEt, DCM; (b) H_2, $RhCl(PPh_3)_3$ in toluene then TMSOTf, *i*Pr_2NEt, DCM

aldol	ee (%)	conditions	product	ee (%)
(*R*)-**1f** $R_1 = CH_2Ph$(*p*-OMe)	83[a]	a	(*R*)-**2f** $R_1 = CH_2Ph$(*p*-OMe)	83
(*R*)-**1g** $R_1 = CH_2CH_2Ph$	72	a	(*R*)-**2g** $R_1 = CH_2CH_2Ph$	72
(*S*)-**1h** $R_1 = CH{=}CHPh$(*p*-OMe)	>99	b	(*R*)-**2h** $R_1 = CH_2CH_2Ph$(*p*-OMe)	>99

Table 4. Ring Closure of (±)-**1a** in Different Solvent Systems



entry	solvent	reoxidant (mol %)	additive	*T*/°C	*t*/h	Pd cat (mol %)	conv. %[a] (yield %)
1	DME	CuCl (10)	Na_2HPO_4	50	20	$PdCl_2$ (10)	100(50)
2	PBS	CuCl (10)	−	50	21.5	$PdCl_2$ (10)	50
3	DMF/PBS (1/1)	CuCl (10)	−	50	17	$PdCl_2$ (10)	50
4	DMF/PBS (1/9)	CuCl (10)	−	50	21.5	$PdCl_2$ (10)	100
5	toluene/PBS (1/1)	CuCl (18)	−	50	18.5	$PdCl_2$ (10)	65
6	toluene/PBS (1/1)	CuCl (20)	−	50	72	$PdCl_2$ (10)	100(68)
7	toluene/H_2O (1/1)	CuCl (20)	−	50	21.5	$PdCl_2$ (10)	83

[a] Consumption of starting material by ^1H NMR; 10 mol % only. PBS = phosphate-buffered saline pH 7.4.

2f and (*R*)-**2g** with enantiomeric excesses of 72 and 83%, respectively, suggesting that no racemization had occurred under these conditions. However, the direct cyclization was not feasible for substrate (*S*)-**1h** because a competitive elimination occurred instead. For this substrate, a two-step sequence involving chemoselective hydrogenation of the allylic alcohol, followed by cyclization, afforded the hetero Diels−Alder adduct (*R*)-**2h** with an enantiomeric excess greater than 99%.

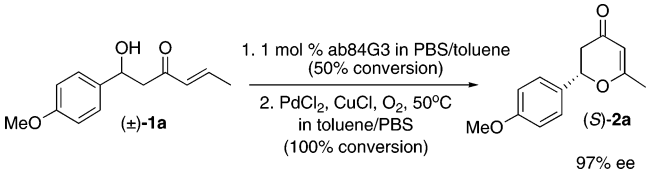
Cyclization into Dihydropyranones. The major issue clouding our initial strategy to access dihydropyranones in addition to tetrahydropyranones was the inability of antibodies 84G3 and 93F3 to kinetically resolve aldol products derived from 4-methoxybutenone. This limitation suggested the need to develop an alternative procedure for the ring-closure process if one wants to broaden the scope of this antibody route for the preparation of enantioenriched dihydropyranones. To restore the oxidation state of the sp^2-hybridized carbon positioned β to the ketone group, we reasoned that an oxidative ring closure can be used as an alternative to the intramolecular Michael-type addition reaction described above. We have recently reported that a palladium(II)-mediated oxidative cyclization was effective for the preparation of structurally diverse 2,3-dihydro-4*H*-pyran-4-ones from the corresponding β-hydroxyenones.[12] The best results were obtained using palladium(II) chloride/copper(I) chloride/oxygen in DME, which are the reaction conditions traditionally applied for a Wacker-type oxidation. Under these conditions, a series of β-hydroxyenones were converted into the corresponding dihydropyranones with good yields. The use of enantiopure aldol precursors also allowed the preparation of the corresponding dihydropyranones without any detectable racemization. To avoid, if at all possible, the isolation of the antibody-resolved aldol products before the cyclization, we adapted our original procedure using (±)-**1a** as model compound (Table 4). We discovered that the oxidative cyclization of aldol (±)-**1a** proceeded using PBS as the reaction solvent, albeit more slowly, auguring the possibility to establish a one-pot antibody/$PdCl_2$ process to access the desired enantioenriched dihydropyranones directly from the racemic aldol precursors (entry 2). We therefore investigated the compatibility of this reaction with various solvent systems, including solvent mixtures that could possibly tolerate the simultaneous presence of the two catalysts. This study revealed that the reaction is best performed in a mixture of DMF/PBS (1/9) (entry 4) or a biphasic mixture of toluene/PBS (1/1) (entry 6). Under biphasic conditions, the reaction is slower and requires up to 20 mol % CuCl and 20 mol % $PdCl_2$ as well as extended reaction time to reach completion. We were pleased to find that under these modified conditions, no racemization was observed if the starting aldol product is enantioenriched. For the biphasic solvent system, the use of PBS in place of water is advantageous as reflected by the higher conversion into the desired adduct (entries 6 and 7).

As an attempt to implement a one-pot retroaldolization/cyclization process, we studied the compatibility of the antibody with palladium dichloride. As matters transpired, it became apparent that although the antibody tolerated well the presence of $PdCl_2$ for the kinetic resolution process, the palladium-mediated oxidative cyclization did not proceed in the presence of the protein.[13] Inspired by the antibody-route to multigram

(12) Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* **2004**, *6*, 91.

(13) For another example of a palladium(II)-catalyzed Wacker reaction inhibited by an aldolase I antibody, see page 6 of the Supporting Information of: Finn, M. G.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2963.

Scheme 3. Direct Conversion of (±)-**1a** into Enantiopure Dihydropyranone (*S*)-**2a**



scale preparation of other enantioenriched aldol products,[14] we finally opted for a biphasic PBS/toluene or PBS/chlorobenzene system using the following procedure. In a typical reaction, a solution of the antibody in PBS was added to a solution of the racemic aldol in either toluene or chlorobenzene. The mixture was shaken, and when the desired ee was reached as monitored by HPLC, the reaction mixture was cooled, allowing separation of the organic layer containing the enantioenriched aldol product from the frozen aqueous antibody solution. To the organic layer was then added PBS, $PdCl_2$, and CuCl, and the reaction was heated at 50 °C and left stirring until complete conversion of the aldol product into the desired dihydropyranone. The cyclized product was easily recovered from the organic phase, and the ee was measured by HPLC. In this process, the antibody solution could be thawed for reuse. The procedure was successfully applied for the preparation of enantiopure adduct (*S*)-**2a** from the corresponding racemic aldol precursor. The best result was obtained by increasing the amount of both CuCl and $PdCl_2$ (up to 60% mol) relative to the substrate, allowing quantitative conversion of the enantioenriched aldol product into the desired dihydropyranone (*S*)-**2a** with no detectable epimerization (Scheme 3).

Conclusions

In summary, we have developed a bioorganic approach for the preparation of hetero Diels−Alder adducts of carbonyl compounds. This strategy represents the first aldolase I antibody route to enantioenriched HDA adducts of carbonyl compounds via a stepwise pathway with an aldol product as the key intermediate. The substrate limitation resulting from the inability of antibodies 84G3 and 93F3 to kinetically resolve racemic aldol products derived from long chain enones was solved using a cross-metathesis reaction with the appropriate olefinic partner. A remarkable feature of this approach is that it is particularly efficient for the preparation of adducts otherwise derived from less activated dienes and dienophiles for which only limited successes were obtained using the more traditional metal-catalyzed hetero Diels−Alder reaction. Another key feature of this antibody approach is the possibility to access both tetrahydropyranones and a representative dihydropyranone. This was achieved by modifying the reaction conditions for the ring-closure process. Applications of this route to hetero Diels−Alder adducts for the synthesis of natural products are now in progress.

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Supporting Information Available: Full Experimental Section (PDF) including procedures, spectroscopic data for all new compounds, full description of independent asymmetric syntheses for absolute configuration assignment including X-ray data, antibody screening, procedure for the determination of enantiomeric excesses, and detailed antibody kinetics. This material is available free of charge via the Internet at http://pubs.acs.org.

JA043925D

(14) (a) Sinha, S. C.; Barbas, C. F., III; Lerner, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, 14603. (b) Sinha, S. C.; Sun, J.; Miller, G. P.; Wartmann, M.; Lerner, R. A. *Chem.−Eur. J.* **2001**, *7*, 1692. (c) Turner, J. M.; Bui, T.; Lerner, R. A.; Barbas, C. F., III; List, B. *Chem.−Eur. J.* **2000**, *6*, 2772.