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Diametric Stereocontrol in Dynamic Catalytic Reduction of Racemic Acyl Phosphonates: Divergence from α-Keto Ester Congeners

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Supporting Information

ABSTRACT: An unexpected dichotomy was observed in the Ru-catalyzed asymmetric transfer hydrogenation of acyl phosphonates: reduction proceeded from the opposite face relative to that observed in the analogous reduction of α-keto esters. The first highly selective catalytic hydrogenation of acyl phosphonates was utilized in the dynamic kinetic resolution of α-aryl acyl phosphonates, providing β-stereogenic α-hydroxy phosphonic acid derivatives.

The asymmetric synthesis of small molecules has profited from the development of well-defined homogeneous catalysts.[1] Asymmetric catalysis relies on the fundamental paradigm that privileged catalysts generate well-defined chiral spaces that provide an environment capable of effectively directing similarly structured small molecules for enantiofacial discrimination.[2] This characteristic is practically useful insofar as a seminal advance can pave the way for useful extensions based on structurally related congeners. Deviations from this principle are rare and important in understanding substrate/catalyst interactions.[3] Herein we disclose an unusual diametric reversal in diastereofacial selection in the asymmetric transfer hydrogenation of acyl phosphonates compared to the related α-keto esters. The reactions described provide access to new β-stereogenic α-hydroxy phosphonic acid derivatives that have previously been inaccessible in stereoisomerically pure form.

Background/Rationale. α-Keto esters and acyl phosphonates **A** behave analogously in the bis(oxazoline)Cu(II)-catalyzed asymmetric hetero-Diels–Alder reaction with vinyl ethers to provide dihydropyrans **C** and **D**, respectively (Figure 1, paths a and b).[4] Activation of the dicarbonyl moiety via chelation is crucial in providing high levels of facial selectivity. We were interested in testing the notion that the α-keto ester/acyl phosphonate relationship could be exploited in the context of our laboratory's ongoing work involving dynamic kinetic resolution[5] by asymmetric transfer hydrogenation (DKR–ATH). We recently documented a new Ru(II)-catalyzed DKR–ATH of β-aryl α-keto esters **B**, providing hydride delivery from the *Si* face to afford α-hydroxy esters **E** with high levels of diastereo- and enantioselectivity (path c).[6] Extrapolating from precedent, we proposed that the dynamic reduction of racemic α-aryl acyl phosphonate **B** would proceed with an analogous facial preference; however, in the event, the reduction occurred from the *opposite* diastereotopic face, providing the quasidiastereomeric product **F** with excellent levels of selectivity (path d).[7]

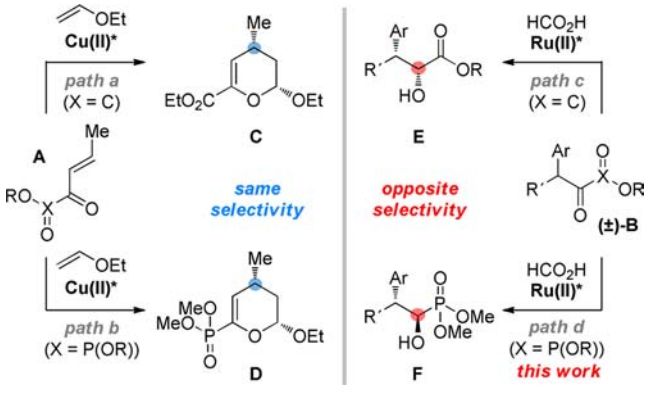

Figure 1. Reversal in enantiofacial selectivity.

Results. When α-aryl acyl phosphonate **1b** was employed as a test substrate, Noyori's RuCl[(*S*,*S*)-TsDPEN](*p*-cymene) complex[12] was found to provide hydroxy phosphonate **2b** with modest anti/syn selectivity but excellent levels of enantiocontrol for both diastereomers (Table 1, entry 1). On the basis of our group's recent success in tuning the diastereoselectivity of the DKR–ATH of β-chloro-α-keto esters through the application of a bulky *m*-terphenylsulfonamide ligand,[6b] aminosulfonamide **L2** was employed in the reduction of **1b** in *N*,*N*-dimethylformamide (DMF) and delivered a marked increase in diastereoselectivity (entry 2). Changing the solvent to dimethyl sulfoxide (DMSO) resulted in a boost in

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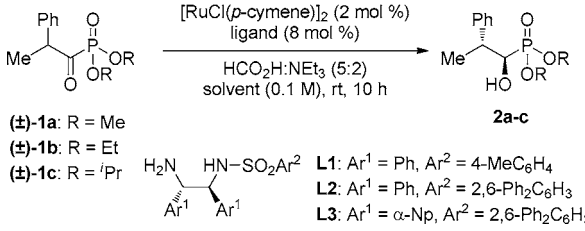
Table 1. Ligand/Substrate Optimization[a]



entry	1	L	solvent	conv. (%)[b]	anti:syn[b]	er[c]
1	**1b**	**L1**	DMSO	>95	3:1	>99.5:0.5 (98.5:1.5)[d]
2	**1b**	**L2**	DMF	>95	14:1	99:1
3	**1b**	**L2**	DMSO	>95	20:1	>99.5:0.5
4	**1b**	**L3**	DMF	>95	22:1	>99.5:0.5
5	**1b**	**L3**	DMSO	>95 (93)[e]	29:1	>99.5:0.5
6	**1a**	**L3**	DMSO	>95 (91)[e]	>30:1	>99.5:0.5
7	**1c**	**L3**	DMSO	19	–	–

[a]Reactions were performed on 0.155 mmol scale. [b]Determined by ^{31}P NMR analysis of the crude reaction mixture. [c]Determined by chiral HPLC analysis. [d]Syn isomer. [e]The value in parentheses is the isolated yield.

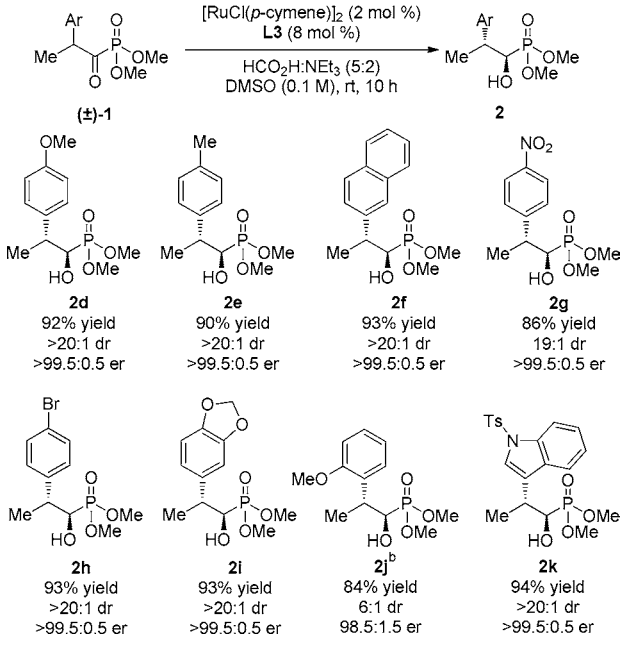
diastereoselection up to 20:1 (entry 3). α-Naphthyl ethylenediamine-derived **L3** was tested and found to engender even higher levels of diastereocontrol (entries 4 and 5). Both dimethyl and diethyl phosphonates were found to provide comparable levels of reactivity and selectivity (entries 5 and 6); however, the bulkier diisopropyl phosphonate **1c** suffered from reduced reactivity, presumably because of its increased steric requirements (entry 7).

The reaction scope was next examined (Table 2). A variety of electron-releasing and electron-withdrawing aryl groups were tolerated, providing products in uniformly high yield and selectivity. Heteroaromatic substituents were also amenable to the reaction, providing the *N*-Ts-indoyl product **2k** in 94% yield with excellent levels of diastereo- and enantiocontrol. Ortho substitutents resulted in reduced reactivity, necessitating elevated temperatures (45 °C) and longer reaction times to provide **2j** with 6:1 dr and 98.5:1.5 er.[13]

The identity of the α-aliphatic substituent was also investigated to probe the steric sensitivity of the system (Table 3). Linear aliphatic substituents were tolerated, providing products in equally high yield and selectivity and allowing for the incorporation of alkene and alkyne functional handles. The sterically demanding cyclopropyl acyl phosphonate reacted slower under the reaction conditions, requiring 36 h to provide **2p** with 5:1 dr and excellent enantiocontrol.

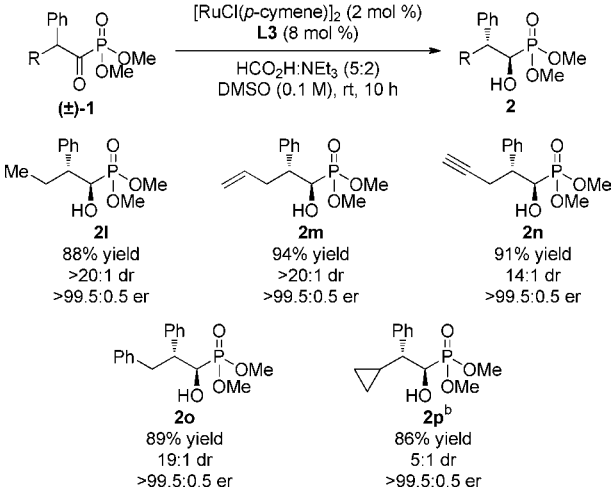
To probe the utility of this reaction further, bicyclic substrate **1q** was subjected to the reduction conditions and afforded **2q** in high yield with comparable levels of selectivity as for the acyclic examples (Scheme 1). In contrast to ortho-substituted **2j**, hydroxy phosphonate **2q** was obtained with excellent levels of diastereoselectivity, suggesting that the ortho substituent occupies a sterically encumbering conformation when uncon-

Table 2. Aromatic Substrate Scope[a]



[a]Reactions were performed on a 0.155 mmol scale employing 5 equiv of 5:2 HCO_2H:NEt_3. Isolated yields of analytically pure material are reported. Diastereomeric ratios were determined by ^{31}P NMR analysis of the crude reaction mixtures; enantiomeric ratios were determined by chiral HPLC analysis. [b]The reaction was performed at 45 °C for 20 h.

Table 3. Alkyl Substrate Scope[a]



[a]As in Table 2. [b]36 h.

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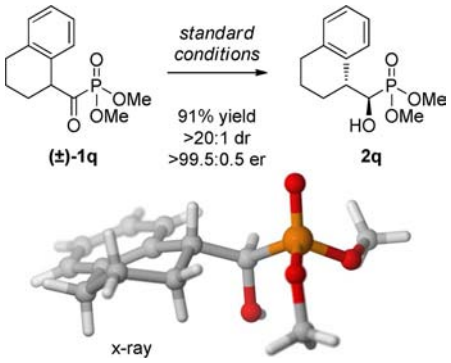
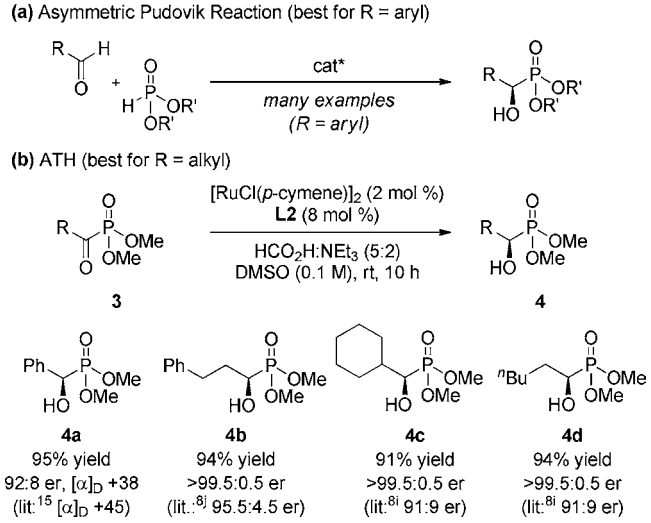
Scheme 1. DKR–ATH of Cyclic Substrate 1q



strained, causing nonideal substrate–catalyst interactions. The absolute stereochemistry of the products was established as (1*R*,2*R*) via X-ray crystallographic analysis of **2e** and **2q**, confirming the anti orientation of the alcohol and aryl groups.[14]

The presence of a β-substituent was found to be unnecessary for high levels of enantioselectivity (Scheme 2). Despite the

Scheme 2. ATH of Acyl Phosphonates



development of excellent catalysts for highly asymmetric Pudovik reactions involving aromatic aldehydes, simple aliphatic aldehydes typically provide lower levels of selectivity.[8] Although the reduction of aryl acyl phosphonate **3a** under the optimized reaction conditions provided (*R*)-**4a**[15] with only 92:8 er, the reduction of aliphatic acyl phosphonates proceeded to provide enantiopure products **4b–d** in high yield.[16] The excellent levels of enantiocontrol observed for **4b–d** are a marked improvement over those obtained using Pudovik-based methodologies, highlighting the potential utility and complementarity of this transfer hydrogenation in the preparation of enantiopure α-hydroxy phosphonic acids bearing one stereocenter.

Obtaining a full understanding of the turnover in stereoselectivity will require further investigation, but some initial observations that are relevant to the unusual effects we have uncovered can be offered (Figure 2). Despite being electronic congeners of α-keto esters, acyl phosphonates are tetrahedral rather than trigonal at the α-carbon, a circumstance that alters the steric environment at the ketone undergoing reduction. The impact of this geometric change is probably compounded

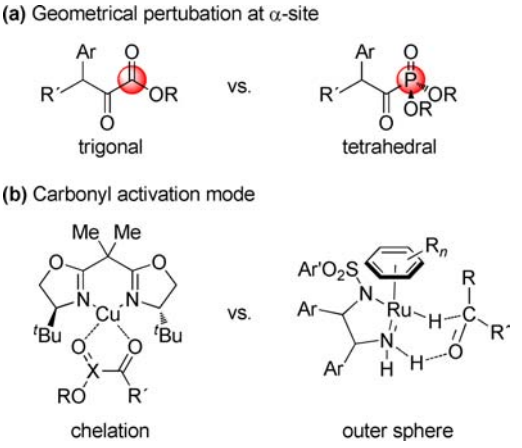


Figure 2. Variables that potentially account for the stereoselectivity inversion.

by the fact that the carbonyl activation mode in the (amido)Ru(II) complex is dramatically different (outer-sphere/bifunctional) than in the bis(oxazoline)Cu(II) systems (inner-sphere chelation control), where acyl phosphonates and α-keto esters experience identical influence from the chiral catalyst.

In summary, an unexpected reversal in facial selectivity was observed in the Ru-mediated asymmetric transfer hydrogenation of acyl phosphonates in comparison with their structural mimics, α-keto esters. This dichotomy in reactivity was exploited in the development of an extremely selective dynamic kinetic resolution of α-aryl acyl phosphonates to provide β-stereogenic α-hydroxy phosphonic acid derivatives. The first highly selective catalytic reduction of acyl phosphonates also provides complementary access to challenging Pudovik adducts. The precise identification of key catalyst/substrate interactions, reactant orientations, and activation modes will be important for understanding the divergence between α-keto esters and acyl phosphonates and exploiting this finding in future applications.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral and HPLC 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.

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(13) Under the standard reaction conditions (rt, 10 h), the reaction proceeded to 28% conversion with 11:1 dr.

(14) CCDC 908430 (**2q**), 908511 (**2e**), and 908431 (**S8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif. The structure in Scheme 1 was generated with CYLview: Legault, C. Y. *CYLview*, version 1.0b; Université de Sherbrooke: Sherbrooke, QC, 2009; http://www.cylview.org.

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(16) **L2** and **L3** provided identical enantioselectivity.