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Hammond Postulate Mirroring Enables Enantiomeric Enrichment of Phosphorus Compounds via Two Thermodynamically Interconnected Sequential Stereoselective Processes

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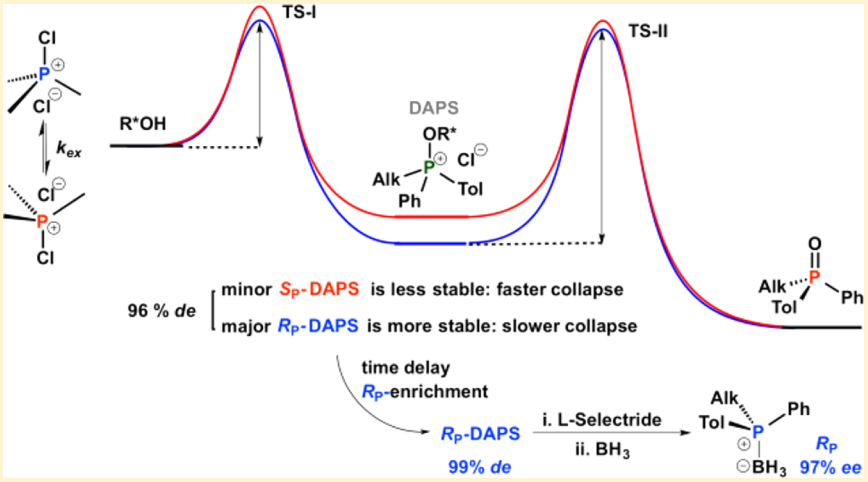
Supporting Information



ABSTRACT: The dynamic resolution of tertiary phosphines and phosphine oxides was monitored by NMR spectroscopy. It was found that the stereoselectivity is set during the formation of the diastereomeric alkoxyphosphonium salts (DAPS), such that their initial diastereomeric excess (de) limits the final enantiomeric excess (ee) of any phosphorus products derived from them. However, ^{31}P NMR monitoring of the spontaneous thermal decomposition of the DAPS shows consistent diastereomeric self-enrichment, indicating a higher rate constant for decomposition of the minor diastereomer. This crucial observation was confirmed by reductive trapping of the unreacted enriched DAPS with lithium tri-*sec*-butylborohydride (commercially distributed as L-Selectride reagent) at different time intervals after the start of reaction, which gives progressively higher ee of the phosphine product with time. It is proposed that the Hammond postulate operates for *both* formation and decomposition of DAPS intermediate so that the lower rate of formation and faster subsequent collapse of the minor isomer are thermodynamically linked. This *kinetic enhancement of kinetic resolution* furnishes up to 97% ee product.

INTRODUCTION

Commonly, asymmetric synthesis is achieved by the transfer of chirality from a chiral source to the required product.[1,2] Once a successful protocol has been established, there are a number of physical and chemical strategies to further enhance the outcome, including, e.g., variation of temperature, solvent, chirality source, and, especially, (re)crystallization.[3] Of particular interest is a superclass of approaches based on kinetic relationships between the starting material, intermediates, and products. In these, initially formed stereo-enriched material is further enriched by a subsequent chemical reaction. Preeminent among these approaches is classical kinetic amplification,[2] which is commonly applied by coupling an initial desymmetrization of a suitable starting material with kinetic resolution of the resulting scalemic mixture, often by the same chiral reagents.[4] Recent examples have shown the power of this type of methodology.[5] A typical kinetic resolution process starts with energy-equivalent enantiomers and furnishes two energy-inequivalent (diastereomeric) intermediates or products. Although this process follows kinetic control, its selectivity can often be rationalized by the Hammond postulate.[6] Thus, it is common that the more stable diastereomer is the one that is formed faster. Little is known, however, about the applicability of this principle in reverse: i.e., how selective is the transformation of two diastereomers to yield the corresponding energy-equivalent enantiomers?

The asymmetric synthesis of *P*-stereogenic phosphorus compounds has been a subject of interest for a long time[7] and for which many powerful methods have been developed,[8] often driven by their application in catalytic asymmetric synthesis.[9] However, despite great progress, successful synthesis

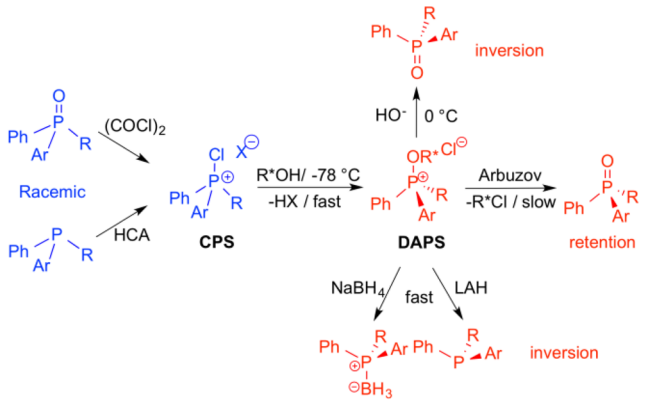
Received: April 28, 2015
Published: July 17, 2015

DOI: 10.1021/jacs.5b04415
J. Am. Chem. Soc. 2015, 137, 9375−9381

of a particular compound is not assured, so that only modest numbers of *P*-stereogenic catalysts have been studied, being difficult to synthesize in enantiomerically pure form. Notably, enrichment strategies such as kinetic amplification have rarely been applied.[10,11]

Our interest in this area arises from our recently developed dynamic kinetic resolution methodology, which allows the synthesis of a variety of *P*-stereogenic phosphines, their oxides, and their boranes (Scheme 1).[12] The heart of our process

Scheme 1. Asymmetric Synthesis of *P*-Stereogenic Phosphorus Compounds[a]



[a]HCA = hexachloroacetone; X = pentachloroacetonate or chloride; CPS = chlorophosphonium salt; DAPS = diastereomeric alkoxyphosphonium salt; blue indicates racemic, and red indicates stereoenriched.

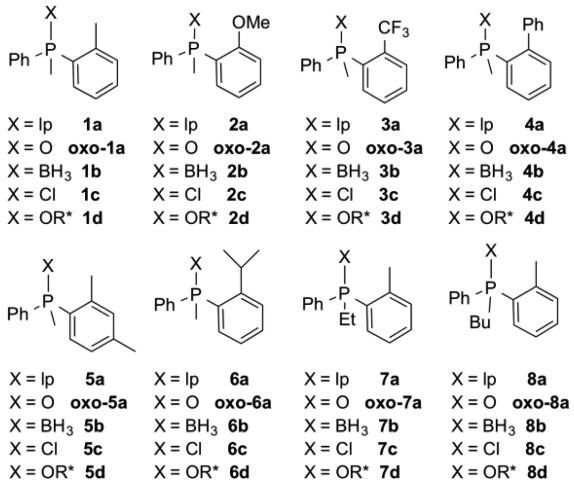
involves the generation of two rapidly interconverting enantiomeric chlorophosphonium salts (CPS),[13] which are then reacted with chiral non-racemic alcohol to generate *unequal* amounts of two diastereomeric alkoxyphosphonium salts (DAPS). In the absence of further intervention, as the temperature is increased, the two DAPS species undergo decomposition chiefly via Arbuzov collapse, to form enantioenriched *P*-stereogenic phosphine oxide.[12a,c] Alternatively the DAPS can be intercepted using hydride reagents to give either scalemic phosphines or phosphine boranes.[12d−f] Most recently we have shown that hydrolysis of the DAPS leads to the other enantiomer of the oxide, thus allowing both enantiomers to be generated from the same source of chirality.[14]

In Scheme 1, the selection outcome is set primarily in the DAPS formation stage, and we found that the *n*-alkylphenylaryl motif at phosphorus allowed very high selectivity (up to 97% de) in that step.[14,15] However, in other cases the selectivity is less, and its enhancement would be desirable. As the two DAPS in hand are, strictly speaking, two different compounds, it is not unreasonable to assume that the kinetics of their subsequent transformations should differ. Therefore, with three such subsequent reactions being applied to the DAPS, we were aware that we had good scope for some sort of kinetic enhancement; it cannot be termed "kinetic resolution" because of the diastereomeric nature of the DAPS. We now report that not only the *formation* but also the *decomposition* of these intermediates (the Arbuzov collapse) can be stereoselective and used to enhance the stereochemical purity of the product. We term this new phenomenon "kinetic resolution with subsequent kinetic enhancement" (KR/KE) to distinguish it from classical kinetic amplification by desymmetrization. It could be considered to fall into the category of divergent reactions on a racemic mixture (RRM),[4c] except, of course, that our mixture is not racemic. Whatever it is to be called, it enables the synthesis of chiral phosphines/boranes with surplus selectivity, based on timely intervention in the decomposition reaction.

RESULTS AND DISCUSSION

Identity of the Reaction Intermediates. Chart 1 shows the set of phosphorus substitution motifs investigated in this

Chart 1. Compounds Studied in This Work[a]



[a]R* = (−)-menthyl.

work. When mixtures of phosphines **1a**−**8a** and various chiral secondary alcohols were treated with hexachloroacetone, the only intermediates observed by ^{31}P NMR spectroscopy were the derived DAPS (shown in Figure 1 for the case of **1a** with (−)-menthol). The same intermediates were observed by sequential treatment of phosphine oxides **oxo-1a**−**oxo-8a** with oxalyl chloride followed by the chiral alcohol.

The identity of the intermediates in the reaction mixture from phosphine **1a** in toluene at 0 °C was fully confirmed by detailed NMR characterization (see Supporting Information for details). This showed it to be a clean combination of (R_P)-DAPS (***R*$_P$-1d**) and (S_P)-DAPS (***S*$_P$-1d**) in a ca. 4:1 diastereomeric ratio (62% de) with a small amount of (−)-menthol. Full assignment of all the peaks in both diastereomers was carried out with the assistance of 2D ^{1}H−^{1}H, ^{1}H−^{13}C, and ^{1}H−^{31}P correlation spectroscopy and NOE measurements. Characterization of the DAPS derived from **7a** was carried out in a similar fashion; however, full assignment of all signals attributable to the minor diastereomers was not possible owing to the very high diastereomeric excess (de) in those cases (details are given in the Supporting Information). As shown in Figure 1, the NMR data for the major diastereomer of **1d** was found to be consistent with its having the (*R*)- configuration in agreement with the known (*R*)- configuration of the **oxo-1a** product in this case.[12b,16] Careful analysis of 2D ^{31}P and ^{1}H NOE correlations revealed that no dynamic exchange between the two DAPS ***R*$_P$-1d** and ***S*$_P$-1d** takes place on the NMR time scale. This significant configurational stability of DAPS means that the net stereoselectivity of the reaction is set at the stage of DAPS formation. This was also consistent with our previous measurements of the enantiomeric excess (ee, by CSP-HPLC) of the oxide obtained at the end of the Arbusov collapse stage. These had suggested

DOI: 10.1021/jacs.5b04415
J. Am. Chem. Soc. 2015, 137, 9375−9381

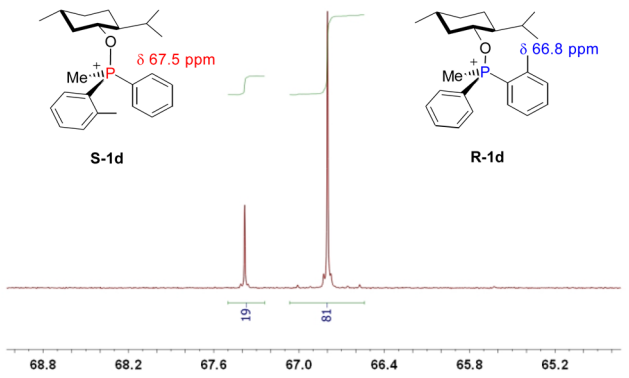


Figure 1. Configuration and ^{31}P NMR (242 MHz, $CDCl_3$) assignments of the diastereomeric R_P-**1d** and S_P-**1d** derived from (−)-menthol and the phosphine **1a** at 0 °C in toluene (de = 62%).

that the limit of selectivity of the reaction is set upon formation of DAPS and the final ee of the product is close to, but never exceeds, the initially attained DAPS de.[12e,f,14] However, these experiments do not address real-time changes that may occur during the decomposition, specifically whether it might be stereoselective.

NMR Monitoring of the Decomposition Process. The question of stereoselectivity in the conversion of DAPS intermediates R_P-**1d**/S_P-**1d**, to phosphine oxide was addressed by ^{31}P NMR monitoring of the process. The mixture used for the characterization above (62% de) was decomposed at 30 °C, with the results shown in Figure 2 (spectral data in Supporting Information, Figure S-i).

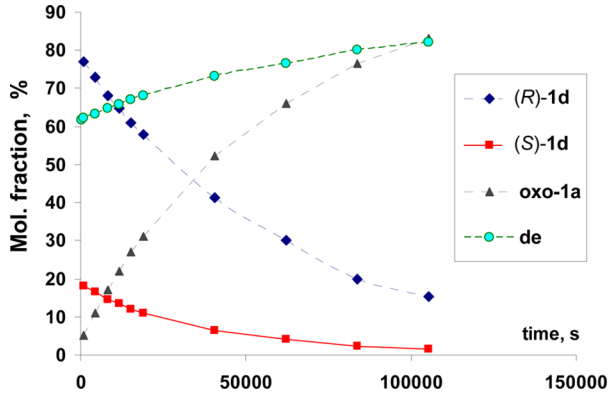


Figure 2. Kinetic plots of Arbusov collapse at 30 °C of DAPS R_P/S_P-**1d** and the production of product **oxo-1a** showing gradual enrichment of the de.

It can be seen clearly in Figure 2 that the rates of thermal collapse of the two salts are not the same. Effectively, there are two parallel first-order decomposition processes, with rate constants k_1(R_P-**1d**) = 1.5 × 10^{-5} s^{-1} and k_1(S_P-**1d**) = 2.4 × 10^{-5} s^{-1}, respectively. Significantly, as the rate constant of the minor diastereomer S_P-**1d** is higher than that of the major isomer R_P-**1d**, the remaining unreacted DAPS is gradually further enriched in the major component R_P-**1d**, so that the DAPS de rises to 82% at 80% conversion to oxide. Thus, the Arbusov step acts to kinetically enhance the de of the key DAPS intermediate, which itself was generated by dynamic resolution of racemic CPS.

To explore the generality of this DAPS de enrichment effect, we studied the Arbusov collapse of the DAPS derived from a variety of chiral non-racemic alcohol and phosphine combinations. For these experiments, the DAPS were formed at our normal reaction temperature of −78 °C, the reaction mixture was sampled under inert conditions for a ^{31}P NMR measurement 5 min after the start of the reaction and the mixtures were kept subsequently at room temperature and sampled at various time intervals. The overall outcomes of these experiments are shown in Table 1. (Full data and relevant spectra and chemical shifts are given in the Supporting Information.)

Table 1. Room-Temperature Arbusov Collapse of DAPS Generated at −78 °C from Various Phosphine/Alcohol Combinations[a]

Phos	Alcohol	DAPS de / PO conversion[b]		
		at 5 min:	after time:	
1a	(-)-menthol	80/14	92/74	72 hr
1a	(+)-isomenthol	62/17	82/93	48 hr
1a	(+)-neomenthol	63/76	---/99	3 hr
1a	(+)-8-Ph-menthol	76/0	88/75	24 hr
2a	(-)-menthol	50/0	70/63	96 hr
2a	(+)-isomenthol	60/7	68/41	48 hr
2a	(+)-neomenthol	68/55	---/99	3 hr
2a	(+)-8-Ph-menthol	70/10	86/98	14 hr
3a	(+)-menthol	68/19	87/65	1 hr
3a	(+)-isomenthol	66/25	80/82	1 hr
4a	(-)-menthol	68/6	96/75	48 hr
5a	(-)-menthol	76/14	84/75	48 hr
6a	(-)-menthol	80/10	94/75	72 hr

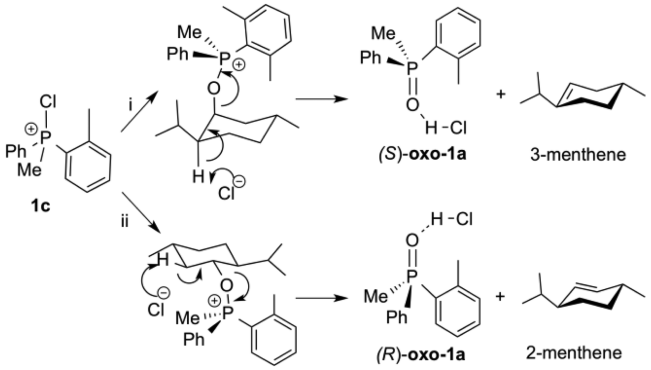
[a]To the solution of HCA and alcohol was added phosphine at −78 °C. After 5 min, the reaction was warmed to room temperature and its progress monitored by ^{31}P NMR at various elapsed times. Full data and spectra are given in the Supporting Information. [b]Extent of conversion (%) to phosphine oxide (PO).

The data in Table 1 confirm that the de enrichment process is a general phenomenon. In every case studied, the de of the DAPS mixture increases with time as the minor diastereomer converts to oxide more quickly. The values shown are the initial and maximum de achieved, occurring at the conversions and times shown. In several cases, >90% de is achieved at about 75% conversion. This data also shows that the overall rate of Arbusov collapse and the rate difference between the diastereomers varies widely depending on the phosphine and the alcohol. Thus, DAPS derived from *o*-tolyl-substituted phosphine **1a** decomposes about twice as fast as that with the more electron-donating *o*-methoxy (PAMP, **2a**) but >20 times more slowly than that with the electron-withdrawing *o*-trifluoromethyl substituent **3a**. Conversely, DAPS derived from 8-phenylmenthol or neomenthol decompose much faster than those from menthol.[17] The neomenthol cases are so fast that it was not possible to determine the degree of enrichment, their half-lives being less than 5 min. This, presumably, is due to their nearly perfect anti-periplanar geometry, which allows the DAPS to undergo rapid elimination reaction to form exclusively 3-menthene, as shown, for example, in Scheme 2(i) for the case of phosphine **1a**.

The case of neomenthol also highlights another related observation: the formation of the phosphine oxide is accompanied by a broadening and steady downfield drift of its ^{31}P NMR chemical shift (e.g., in the case of **oxo-1a** from δ 31.7 to approximately 47 ppm). We attribute this significant difference to the protonation of phosphine oxide by HCl[18] as it

DOI: 10.1021/jacs.5b04415
J. Am. Chem. Soc. 2015, 137, 9375−9381

Scheme 2. Different Elimination Behavior of DAPS: (i) From (+)-Neomenthol and (ii) from (−)-Menthol



is formed in the course of the elimination process, Scheme 2(i). This difference was also replicated by adding HCl to a pure sample of phosphine oxide. Similar but less dramatic downfield drift of the oxide signal occurs in other cases. For example, with menthol, the drift of the **oxo-1a** signal is from δ 31.7 ppm to ca. 37.5 ppm when the reaction is nearly complete. We attribute this to the much lower degree of elimination observed with menthol (about 25%) due to its less favorable elimination process, Scheme 2(ii).

Time-Delayed DAPS Reduction. Having found that the de of the DAPS *increases* as the reaction progresses, we were led to the idea to interrupt the reaction before its completion and thereby isolate a product of ee *higher* than the de of the DAPS intermediate formed initially. We have previously shown that scalemic phosphines and phosphine boranes can be synthesized directly by reduction of the DAPS, with $LiAlH_4$ or $NaBH_4$ respectively, at −78 °C before Arbuzov collapse to the corresponding oxide occurs (Scheme 1).[12d−f] Therefore, we realized that by delaying addition of the reducing agent we could potentially form a reduced product with enhanced ee. This time-delayed double kinetic resolution can colloquially be termed the "wait and attack" protocol, as the operator would simply wait before adding hydride reagent to attack the remaining DAPS.

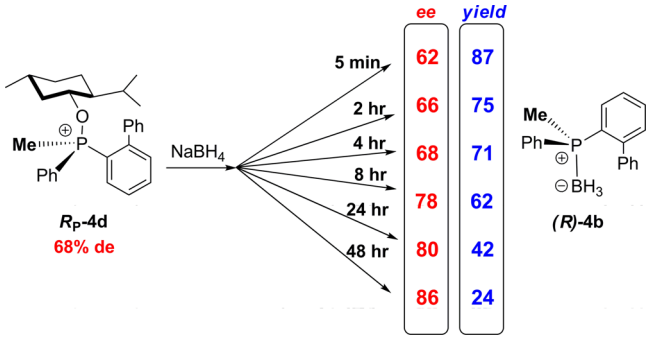
This concept has limitations: for instance, since $LiAlH_4$ is known to reduce *P*-stereogenic phosphine oxides with scrambling of the phosphorus stereocenter,[19] delaying the addition of $LiAlH_4$ until some phosphine oxide had formed would result in the formation of phosphine with a *lower* ee than is obtained when treating the DAPS immediately. However, phosphine oxides are unreactive toward $NaBH_4$ so only DAPS should be converted to phosphine borane with this reagent, leaving the phosphine oxide unaffected. This was achieved in practice for test reactions on DAPS derived from phosphines **1a**, **2a**, and **4a** by addition of a solution of $NaBH_4$ (in diglyme) after aging at room temperature for a certain period of time, Table 2. As expected, the ee of the phosphine borane[20] prepared by borohydride reduction of the aged DAPS increases progressively with time, up to the maxima shown in Table 2 and Scheme 3. This enhancement is happening, of course, at the expense of the reaction chemical yield. That the minor diastereomer of DAPS decomposes faster can clearly be seen in the switch of configuration of the oxide product with time, picked out in color in Table 2. This is particularly noticeable for phosphine **1a** in combination with menthol, where the first formed oxide is 72% ee of *S*-configuration, whereas near the end of the reaction it is 72% of *R*-configuration.

Table 2. Borohydride Reduction[a] of DAPS Derived from Menthol and Phosphines 1a, 2a, and 4a after Elapsed Times

Phos	1a		2a[b]		4a	
	5 min	48 hr	5 min	72 hr	5 min	48 hr
DAPS de[c]	80	92	50	60	68	96
PB ee[d]	76 (*R*)	89 (*R*)	51 (*S*)	60 (*S*)	62 (*R*)	86 (*R*)
PO ee[d]	72 (*S*)	72 (*R*)	32 (*R*)	36 (*S*)	17 (*S*)	40 (*R*)
PO/PB[e]	14/86	80/20	12/88	62/38	13/87	90/10

[a]To the solution of HCA and (−)-menthol (unless stated otherwise) was added phosphine solution at −78 °C, and the mixture was held at that temperature for 30 min. After warming to room temperature, samples of the mixture were treated at −78 °C with $NaBH_4$ solution at the time intervals noted (full details and spectra in Supporting Information). [b]With (+)-menthol. [c]Determined by ^{31}P NMR. [d]Determined by CSP HPLC; configuration assigned as noted in the Supporting Information. [e]Ratio of phosphine borane (PB) to phosphine oxide (PO) determined by ^{31}P NMR.

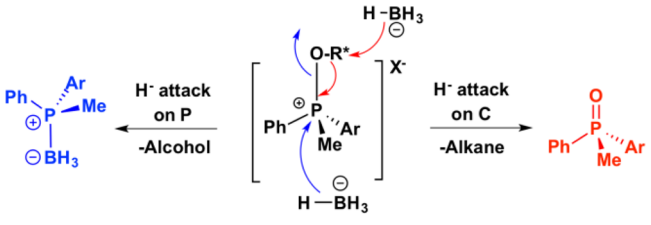
Scheme 3. Operation of "Wait and Attack" Protocol for Kinetic Enhancement of Kinetic Resolution[a]



[a]Increased time delay in borohydride reduction of DAPS **4d** leads to progressive increase of the ee at the expense of the yield of the derived phosphine borane **4b** (procedure as per Table 2, footnote *a*; full data and spectra in Table A in the Supporting Information).

Stereospecificity in DAPS Reduction—Preparation of Highly Enriched Phosphines and Phosphine Boranes. Although we had established proof of principle for the time-delayed reduction protocol, a particular issue remained to be solved. Careful examination of the results in Table 2 shows that, in several cases, the de of the DAPS and ee of the derived phosphine borane do not match fully, implying that there was stereochemical erosion during the reduction process. This is especially noticeable in the case of phosphines **1a** and **4a**. We have previously identified[12d,21] a likely source of this erosion: there can be an Arbusov-like side reaction with hydride attack at carbon, Scheme 4. This is reflected in the slightly higher amounts of oxide returned after reduction compared to that

Scheme 4. Potential Stereochemical Erosion in Hydride Reduction

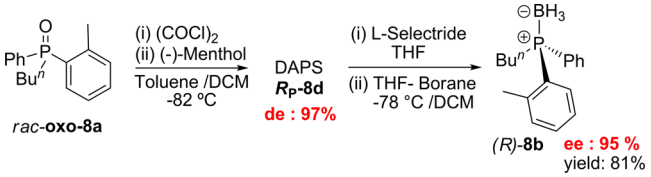


DOI: 10.1021/jacs.5b04415
J. Am. Chem. Soc. 2015, 137, 9375−9381

measured by NMR before reduction. If such reaction is slightly faster for the major diastereomer, the ee of the reduction product will be decreased.

We therefore embarked on a screening of hydride reducing agents (Supporting Information, Tables B and C) to see if we could minimize this erosion of stereoselectivity. To provide a stringent test, we used as substrates the ethylphenyl-o-tolylphosphine motif (**7a**/**oxo-7a**) because our recent studies showed that higher diastereoselectivity can be achieved at the DAPS formation stage by increasing the length of the *P*-alkyl chain.[14] Lithium tri-*sec*-butylborohydride (commercially distributed as L-Selectride reagent) emerged from the screen as a superior reagent for stereospecific reduction of DAPS. It allows the preservation of the configuration of 99% of *P*-stereogenic centers. The product is the corresponding phosphine, which was subsequently boronated for analysis purposes. The efficiency and robustness of this reduction method was then demonstrated at gram scale for the conversion of racemic **oxo-8a** to borane **8b** (Scheme 5). We used the protocol starting

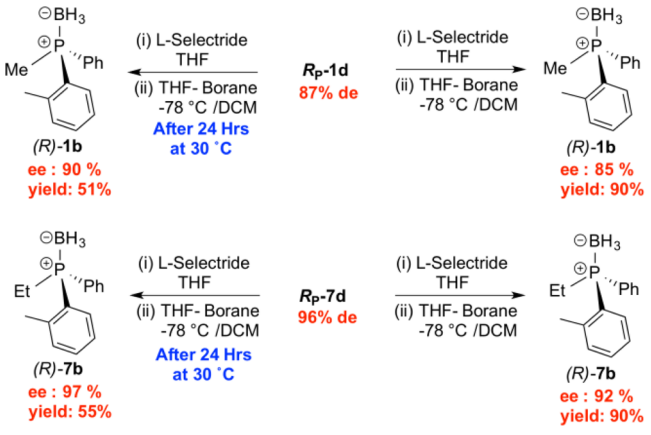
Scheme 5. Gram-Scale Synthesis of Scalemic Phosphine Borane 8b via DAPS 8d Derived from oxo-8a



from the oxide because it is more convenient to handle and because the rate of Arbusov collapse of the DAPS is somewhat slower,[22] allowing more leeway in its manipulation. More significantly, the high de[14] of the DAPS **8d** was satisfactorily translated in good yield to the borane.

These new optimized reduction reaction conditions were then applied in tandem with our "wait and attack" methodology, Scheme 6. Thus, treatment of 87% de R_P-**1d** with L-Selectride in dichloromethane at −78 °C immediately after its formation gives (*R*)-**1b** in 90% yield and 85% ee (Scheme 6, top). This can be compared to the time-delayed process

Scheme 6. Synthesis of Scalemic Phosphine Boranes 1b/7b from DAPS Prepared from Phosphine Oxides oxo-1a/oxo-7a, Applying the "Wait and Attack" Protocol To Achieve Kinetic Enhancement of Kinetic Resolution (Left), Compared to Direct Reduction (Right)



whereby the ee of (*R*)-**1b** has increased to 90% by carrying out the second reduction step after a 24 h delay. Similarly, time-delayed double kinetic resolution carried out on **oxo-7a** (Scheme 6, bottom) leads to phosphine borane (*R*)-**7b** in 97% ee as compared to 92% ee material obtained directly. It is noteworthy that the loss of the reduced material **1b**/**7b** associated with time-delayed double kinetic resolution is fully recoverable as the **oxo-1a**/**oxo-7a** formed during the delay.

SUMMARY AND CONCLUSIONS

Transient intermediates—diastereomeric alkoxyphosphonium salts (DAPS)—were generated and fully characterized by $^{1}H-^{13}C$ and $^{1}H-^{31}P$ 2D correlation NMR techniques at low temperature. The collapse of both diastereomeric forms was monitored by ^{31}P NMR at 30 °C. It was observed that the decomposition of the minor form is faster (e.g., ca. 1.6 times for S_P-**1d**), resulting in the remaining unreacted DAPS becoming gradually further enriched in the major component. Similar observations of spontaneous diastereomeric enrichment were made for a series of DAPS species at room temperature. Thus, the Arbusov step acts to kinetically enhance the diastereoselectivity of the key DAPS intermediate, which itself was generated by dynamic resolution of racemic CPS.

DAPS decomposition rates depend strongly on the alcohol and phosphine used. Our studies confirmed that the selectivity of this reaction is limited by the de of the DAPS at the starting point, since the initial de of the DAPS typically corresponds to the final ee of phosphine oxide. However, we found that, as the collapse of the minor diastereomer is faster than that of the major one, the de of the residual DAPS increases during the course of the reaction, leading to further diastereomeric enrichment. These observations were then utilized by employing hydride reduction of aged samples of DAPS (at different time intervals after the DAPS was formed). This time-delayed kinetic resolution with subsequent kinetic enhancement of the DAPS then yields high ee phosphine boranes.

A tentative explanation of the enhancement phenomenon is depicted in Figure 3. According to this schematic, the cold stage

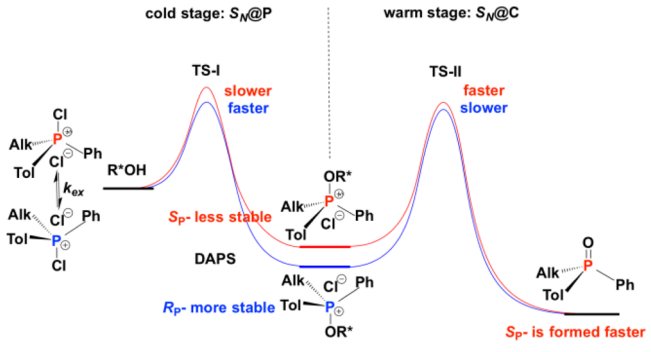


Figure 3. Proposed reaction energy profile for two sequential kinetic resolution steps: the major diastereomer (blue) is mainly formed at the cold stage but, being more stable, undergoes *slower* thermal collapse at the warm stage.

is an S_N@P irreversible dynamic kinetic resolution (DKR) process in which the formation of DAPS takes place and the more stable diastereomer, consistent with the Hammond postulate, is formed via a lower transition state, TS-I, i.e., faster. The thermal collapse of DAPS is an S_N2/E2 reaction at the carbon center of the auxiliary group R*, and, unlike TS-I, its respective diastereomeric transition states, TS-II, are less likely

DOI: 10.1021/jacs.5b04415
J. Am. Chem. Soc. 2015, 137, 9375−9381

to be affected by the stereochemistry of the phosphorus. Accordingly, it is the less stable, i.e., minor, diastereomer of DAPS that undergoes *faster* collapse because its ground state lies closer to TS-II. The net outcome is that the diastereoselectivity achieved at the cold-stage DKR process is further amplified in the course of the thermal decomposition of the minor diastereomer. We note that this kinetic enhancement is unlike classic kinetic amplification, which usually occurs in the course of the same reaction with the same chiral reagents.[4] In our system, the two selective processes, DKR run at −78 °C and the subsequent kinetic enhancement run at room temperature, are entirely different. The first is a stereoselective nucleophilic attack at tetracoordinate P, and the second is an Arbusov-type thermal collapse involving a carbon center. The relative selectivities of these two consecutive processes are, however, determined by the relative energies of the DAPS intermediates.

In summary, we have demonstrated an efficient general approach to synthesize various enantioenriched phosphorus compounds from racemic phosphine, which opens up a facile route for the synthesis of *P*-stereogenic compounds useful in asymmetric catalytic synthesis and in the emerging class of Protide drug candidates.[23]

Finally, we note that the concept of using the Hammond postulate to link the stability difference of two diastereomers generated in one process to their reactivity in a subsequent second process may be a general phenomenon. In Figure 3, the kinetic effect (i.e., relative rates R_P- vs S_P-) of the stability difference for the first selection is *mirrored* and *inverted* in the second selection, leading to the greater reactivity of the minor isomer. This occurs because the second TS is of closer energy for the two isomers. In general, this requires the second TS to be not subject to the same energetic factors as the first, achieved in our case by reaction at a site remote from phosphorus.[24]

■ ASSOCIATED CONTENT

Supporting Information

Full NMR characterization of the DAPS formed from **1a** and **7a** and (−)-menthol; DAPS thermal collapse data corresponding to Figure 2; ^{31}P NMR spectra and HPLC chromatograms corresponding to the results given in Tables 1 and 2; and the screen of hydride reductants and experimental details corresponding to Schemes 5 and 6. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04415.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We sincerely thank Science Foundation Ireland for funding this chemistry under Grants RFP/08/CHE1251 and 09/IN.1/B2627. We are also grateful to University College Dublin (UCD) Centre for Synthesis and Chemical Biology and the UCD School of Chemistry and Chemical Biology for access to their extensive analysis facilities. D.G.G. also thanks UC Dublin for a President's Research Fellowship.

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DOI: 10.1021/jacs.5b04415
J. Am. Chem. Soc. 2015, 137, 9375−9381