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Enantioselective reductive multicomponent coupling reactions between isatins and aldehydes

A highly stereoselective fully organic reductive coupling of two carbonyl electrophiles catalysed by a chiral iminophosphorane catalyst and mediated by an economical organic reductant.

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Received 16th June 2015

Accepted 23rd July 2015

DOI: 10.1039/c5sc02170g

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Enantioselective reductive multicomponent coupling reactions between isatins and aldehydes†

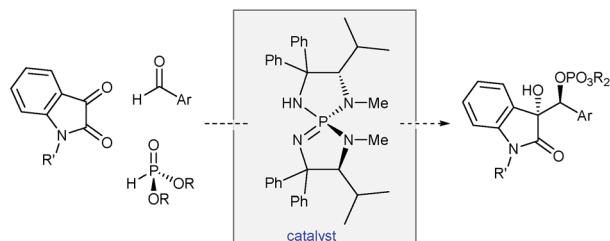
 Matthew A. Horwitz,^{‡a} Naoya Tanaka,^{‡b} Takuya Yokosaka,^a Daisuke Uraguchi,^b Jeffrey S. Johnson^{*a} and Takashi Ooi^{*bc}

A metal-free stereoselective reductive coupling reaction between isatins and aldehydes is reported. The reaction relies on commercial diethyl phosphite ($\sim 70 \text{ kg}^{-1}$) as the stoichiometric reductant. Base-catalyzed Pudovik addition and phosphonate/phosphate rearrangement achieved polarity inversion on the isatin, and the derived carbanions were trapped by aldehydes with subsequent dialkoxyphosphinyl migration. Chiral iminophosphoranones were used as basic catalysts to achieve high diastereo- and enantioselectivities with excellent yields.

The reductive coupling of π -unsaturation is a powerful method for the construction of carbon–carbon bonds. When the two coupling partners are prochiral, there exists the opportunity to establish multiple stereogenic centers concurrent with C–C bond formation. In the specific case of two carbonyl reactants, reductive coupling offers an attractive and straightforward method for the synthesis of vicinal diols, valuable building blocks in organic chemistry. A generic carbonyl reductive coupling manifold encompasses many mechanistic subtypes,¹ but the pinacol reaction is preeminent among them. The traditional pinacol coupling entails single-electron reduction of the carbonyl functionality to generate the corresponding ketyl radical and subsequent dimerization between two radical species. The reaction has been studied extensively using low-valent metals in this single-electron transfer manifold.^{2–6} Despite numerous advances, however, myriad challenges remain: a stoichiometric or superstoichiometric amount of metal agents is often required and there are sparse examples that use catalytic conditions.^{4*n–r*} Moreover, the nature of the mechanism can render it difficult to control both chemoselectivity (homo- versus cross-coupling) and stereoselectivity, and the lack of differentiation of the nascent alcohols can be nettlesome. These precedents collectively informed our interest in developing an

alternative, potentially generalizable reductive coupling strategy that utilizes a polar two-electron reaction mechanism for addressing the aforementioned issues. The purpose of this communication is to detail a new base-catalyzed cross coupling of carbonyls mediated by an economical organic reductant, diethyl phosphite; the stereochemical outcome of this multicomponent process is precisely controlled by a chiral triaminoiminophosphorane (Figure 1a).^{7,8}

a. Catalytic enantioselective three-component reductive coupling



b. Mechanistic proposal for asymmetric reductive coupling reaction

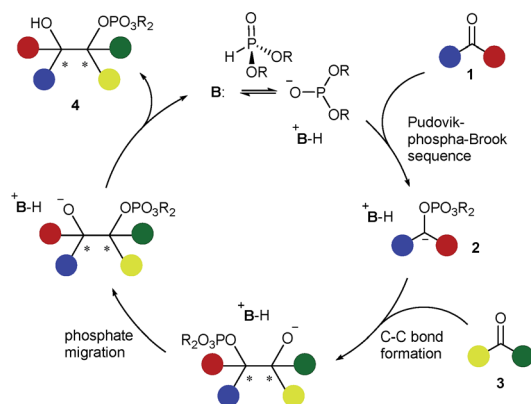


Fig. 1 Stereoselective reductive coupling reactions.

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† Electronic supplementary information (ESI) available: Experimental procedures and characterizations of compounds. CCDC 1055582. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5sc02170g

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At the outset, we envisaged the possibility of catalytic generation of an α -oxycarbanion from a carbonyl substrate and its rapid and selective trapping with another carbonyl compound to form 1,2-diols. For substantiating this hypothesis, polarity reversal of a particular carbonyl group is of critical importance and we sought to take advantage of the phosphonate–phosphate (phospha-Brook) rearrangement to achieve this requisite process. Thus, a base-catalyzed sequence of Pudovik addition and phosphonate–phosphate rearrangement between ketone **1** and dialkyl phosphite was projected to lead to carbanion **2**. The interception of this key intermediate by aldehyde **3** would afford mono-protected diol **4** through dialkoxylphosphinyl migration (Figure 1b).⁹ A crucial departure from prior art is the fully intermolecular nature of the coupling and the need for the phosphite to exhibit complete selectivity between the two carbonyl reactants. We reasoned that the crucial chemoselectivity issue underlying this mechanistic framework, *viz.* the selective generation of α -oxycarbanion **2** from ketone **1**, would be ensured by the inherent reversibility of Pudovik reaction and the reluctance of the aldehyde Pudovik product to undergo phospha-Brook rearrangement. In addition, absolute stereochemical guidance in the C–C bond-forming event could be provided by the conjugate acid of a suitable chiral base. In providing the conceptual blueprint for this scenario, we focused our attention on the exceptional electrophilicity and utility of α -dicarbonyls.^{9d–g,10}

Steps were initially taken to assess the feasibility of the proposed reaction in a racemic sense using achiral bases such as potassium *tert*-butoxide (KO^tBu). Initial trials with diethyl phosphite as the stoichiometric reductant indicated that the reaction proceeds most cleanly and efficiently when a protecting group is used on the isatin. Benzyl, allyl, and methyl protecting groups were examined using 20 mol% KO^tBu in THF at 0 °C (Table 1, (\pm)-**4a**–(\pm)-**4c**). Under these conditions, the reactions were complete in minutes with no observable intermediates (if the aldehyde is omitted from the reaction, the Pudovik-phospha-Brook product can be observed, however).^{9f} These experiments revealed that the benzyl protecting group provided the highest isolated yield and diastereoselectivity. We subsequently verified that *para*-tolualdehyde is not capable of phospha-Brook rearrangement when treated with diethyl phosphite and 20 mol% KO^tBu: only the Pudovik adduct was observed, implying that it is the isatin that is undergoing polarity reversal as we expected.

We then briefly studied the scope of the racemic reaction. The reaction gives consistently good yields for various aryl aldehydes incorporating substituents of different electronic properties (Table 1, (\pm)-**4d**–(\pm)-**4g**). At the current level of optimization, alkyl aldehydes and Boc-protected imine electrophiles were not well tolerated and only provided messy reactions.¹¹ The substitution pattern of the isatin was also examined; we found that the racemic reaction is reasonably flexible in terms of isatin electronics ((\pm)-**4h**–(\pm)-**4k**).

Efforts were next directed to the development of the enantioselective variant.¹² We were encouraged to find that when we used the chiral iminophosphorane (**C1**), we obtained the secondary phosphate **4a** with appreciable enantioenrichment

(er 89.5 : 10.5), although the diastereoselectivity was poor (Table 2, entry 1). Gratifyingly, we found that upon lowering the temperature to –78 °C, phosphate **4a** was obtained in 82% yield, 15 : 1 diastereoselectivity and an er of 96.5 : 3.5 (entry 2). Using the same temperature, we proceeded to evaluate the effect of the catalyst structure (entries 3 to 6), but ultimately concluded that α -branching in ligand substituent R is essential for promoting the desired transformations and the valine-derived iminophosphorane **C1** was optimal in terms of stereoselectivity and chemical yield.

The disparity between the stereoselectivities at 0 °C and –78 °C prompted us to investigate the reversibility of the carbon–carbon bond formation *via* crossover experiments in that temperature range (Table 3). When racemic phosphate (\pm)-**4a** was subjected to standard conditions in the presence of 4-fluorobenzaldehyde, significant incorporation of that component in the form of phosphate **4a–F** was observed at 0 °C and –40 °C, but no crossover was observed at –78 °C. These data support the hypothesis that the increase in enantioselectivity at –78 °C is not only a consequence of more rigorous facial discrimination of both substrates but also shutting down a stereoablative retro-aldol process that is operative at higher temperatures.

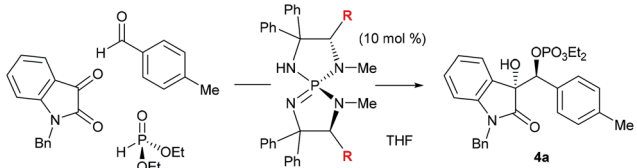
Using the optimized conditions, we evaluated the scope of the asymmetric reaction by initially looking at various isatins.

Table 1 Three component reductive coupling: racemic^a

Substituent	d.r.	Yield (%)
N-Protecting Groups (Ar = 4-tol, X = H):		
(\pm)- 4a (P = Bn)	4.3:1 d.r.	73% yield
(\pm)- 4b (P = allyl)	3.8:1 d.r.	68% yield
(\pm)- 4c (P = Me)	2.0:1 d.r.	95% yield ^b
Aldehydes (P = Bn, X = H):		
(\pm)- 4d (Y = 4-Br)	2.4:1 d.r.	84% yield
(\pm)- 4e (Y = 4-OMe)	2.3:1 d.r.	88% yield
(\pm)- 4f (Y = 3-Me)	3.3:1 d.r.	94% yield
(\pm)- 4g (Y = 2-Me)	7.0:1 d.r.	84% yield
Isatin Electronics (Ar = 4-tol, P = Bn):		
(\pm)- 4h (X = F)	3.9:1 d.r.	81% yield
(\pm)- 4i (X = Cl)	3.7:1 d.r.	74% yield
(\pm)- 4j (X = Br)	3.2:1 d.r.	76% yield
(\pm)- 4k (X = OMe)	2.5:1 d.r.	74% yield

^a All reactions were run on 0.2 mmol scale, using 1.1 equiv. of dialkylphosphite and 5.0 equiv. of aldehyde. % Yields refer to isolated yields. All d.r. and % yield values are the averages of two trials. Reactions were run until complete as adjudged by TLC. ^b % Yield determined by crude ¹H NMR using mesitylene as an internal standard. Products derived from apparent retro-reaction significantly diminished the isolated yield; therefore, this substrate was not selected for further study.



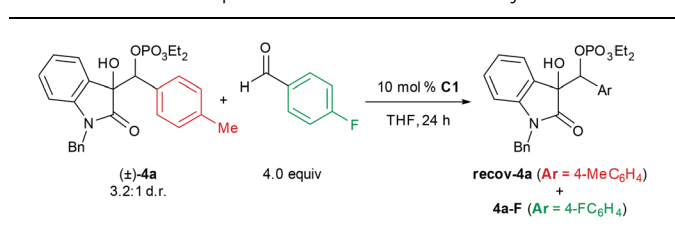
Table 2 Optimization of the asymmetric catalytic reductive coupling^a


Entry	T (°C)	Catalyst	d.r.	e.r.	% Conv.
1	0	C1	3.4 : 1	89.5 : 10.5	96
2	-78	C1	15 : 1	96.5 : 3.5	82
3	-78	C2	n.a.	n.a.	18
4	-78	C3	n.a.	n.a.	15
5	-78	C4	n.a.	n.a.	12
6	-78	C5	7.9 : 1	86 : 14	80

^a All reactions were conducted on a 0.1 mmol scale, using 1.1 equiv. of dialkylphosphite and 5.0 equiv. of 4-tolualdehyde. Argon was used to purge the reaction flasks. All d.r., e.r., and % conversion values are the average of two trials. n.a. = not analyzed.

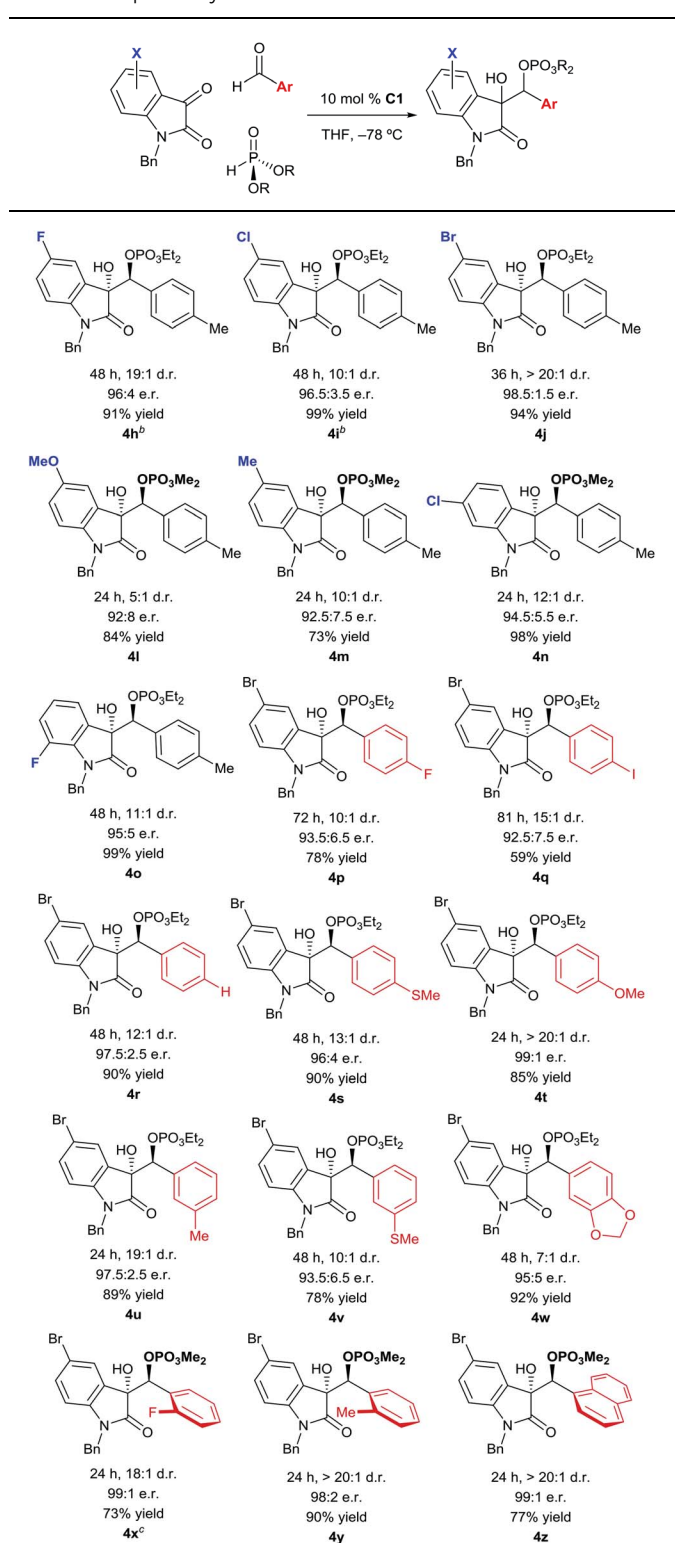
While electron-deficient 5-halogenated isatins were well accommodated under the optimized conditions, use of dimethyl phosphite was indispensable for completion of the reactions with 5-methyl and methoxy isatins probably because of the slow phospho-Brook rearrangement (Table 4, **4h–4m**).¹³ 6-Chloro and 7-fluoro isatins were also smoothly converted into the reductive coupling products of high stereochemical purity using appropriate phosphite (**4n** and **4o**). The absolute stereochemistry was determined at this stage by an X-ray diffraction study of phosphate **4j** (Fig. 2).¹⁴

For exploration of aldehyde generality, we selected 5-bromo isatin as a coupling partner in consideration of its high reactivity and advantage of having an additional functional handle at the aromatic nuclei. As included in Table 4, various *para*-

Table 3 Crossover experiments establish reversibility^a

Entry	T (°C)	4a : 4a-F
1	0	1.0 : 1.5
2	-40	1.0 : 1.1
3	-78	Only 4a

^a Product distributions were determined by ¹H NMR analysis (800 MHz) of the crude mixture.

Table 4 Scope of asymmetric reaction^a

^a All reactions were conducted on a 0.1 mmol scale, using 1.1 equiv. of dialkylphosphite and 5.0 equiv. of ArCHO. Argon was used to purge the reaction flasks. % Yields refer to isolated yields. All d.r., e.r., and % yield values are the average of two trials. ^b 15 mol% of catalyst was used. ^c 2.2 equiv. of dialkylphosphite was used.



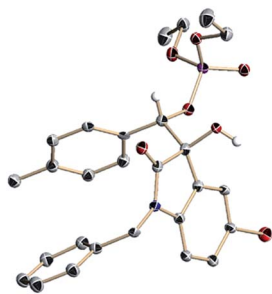


Fig. 2 ORTEP diagram of **4j** (ellipsoids displayed at 50% probability. Calculated hydrogen atoms except for that attached to the stereogenic carbon atom are omitted for clarity. Black: carbon, red: oxygen, purple: phosphorous, blue: nitrogen, vermilion: bromine, white: hydrogen).

substituted aromatic aldehydes were tolerated and relatively electron rich aldehydes exhibited higher reactivity and selectivity (**4p–4t**). Hetero-substituents at the *meta*-position slightly affected the stereochemical outcome (**4u–4w**). For sterically demanding *ortho*-substituted aldehydes, dimethyl phosphite was needed to accelerate the reaction and virtually complete stereocontrol could be achieved (**4x–4z**).

In summary, we have developed a highly stereoselective, fully organic multicomponent coupling reaction between isatins and aldehydes with dialkyl phosphite as an economical reductant. The advantages of extending the reductive coupling into a two-electron manifold are manifest, and the mechanistic framework established herein may be applicable to other stereoselective reductive carbon–carbon bond constructions. Efforts to exploit this reaction paradigm in other systems are ongoing in our laboratories.

Acknowledgements

Financial support to TO, DU, and NT was provided by CREST-JST, a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” from MEXT, Program for Leading Graduate Schools “Integrative Graduate Education and Research Program in Green Natural Sciences” in Nagoya University, and Grants of JSPS for Scientific Research. NT acknowledges JSPS for financial support. Financial support to JSJ, MH, and TY was provided by Award R01 GM103855 from the National Institute of General Medical Sciences and a JSPS Research Fellowship for Young Scientists (TY).

Notes and references

- For example: (a) F. Ramirez, N. B. Desai and N. Ramanathan, *Tetrahedron Lett.*, 1963, **4**, 323–328; (b) T. Mukaiyama, H. Sugimura, T. Ohno and S. Kobayashi, *Chem. Lett.*, 1989, **18**, 1401–1404; (c) S. N. Greszler and J. S. Johnson, *Org. Lett.*, 2009, **11**, 827–830.

- Reviews: (a) B. S. Terra and F. Macedo Jr, *Arkivoc*, 2012, 134–151; (b) A. Chatterjee and N. N. Joshi, *Tetrahedron*, 2006, **62**, 12137–12158.
- Seminal papers on cross pinacol reactions with low-valent metal reagents: (a) J. E. McMurry and L. R. Krepski, *J. Org. Chem.*, 1976, **41**, 3929–3930; (b) J. E. McMurry, *Chem. Rev.*, 1989, **89**, 1513–1524.
- Developments toward using aldehydes as coupling partners in stereoselective reductive coupling reactions: (a) P. M. Takahara, J. H. Freudenberger, A. W. Konradi and S. F. Pedersen, *Tetrahedron Lett.*, 1989, **30**, 7177–7180; (b) J. H. Freudenberger, A. W. Konradi and S. F. Pedersen, *J. Am. Chem. Soc.*, 1989, **111**, 8014–8016; (c) R. Annunziata, M. Cinquini, F. Cozzi and P. Giaroni, *Tetrahedron: Asymmetry*, 1990, **1**, 355–358; (d) R. Annunziata, M. Cinquini, F. Cozzi, P. Giaroni and M. Benaglia, *Tetrahedron*, 1991, **47**, 5737–5758; (e) R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi and P. Giaroni, *J. Org. Chem.*, 1992, **57**, 782–784; (f) A. W. Konradi and S. F. Pedersen, *J. Org. Chem.*, 1990, **55**, 4506–4508; (g) A. W. Konradi, S. J. Kemp and S. F. Pedersen, *J. Am. Chem. Soc.*, 1994, **116**, 1316–1323; (h) J. Park and S. F. Pedersen, *J. Org. Chem.*, 1990, **55**, 5924–5926; (i) F. R. Askham and K. M. Carroll, *J. Org. Chem.*, 1993, **58**, 7328–7329; (j) H. Yoda, K. Matsuda, H. Nomura and K. Takabe, *Tetrahedron Lett.*, 2000, **41**, 1775–1779; (k) K. Takai, K. Nitta and K. Utimoto, *Tetrahedron Lett.*, 1988, **29**, 5263–5266; (l) K. Takai, R. Morita and C. Toratsu, *Angew. Chem., Int. Ed.*, 2001, **40**, 1116–1119; (m) K. Takai, R. Morita, H. Matsushita and C. Toratsu, *Chirality*, 2003, **15**, 17–23; (n) R. K. Boeckman Jr and R. A. Hudack Jr, *J. Org. Chem.*, 1998, **63**, 3524–3525; (o) M. Jung and U. Groth, *Synlett*, 2002, 2015–2018; (p) U. Groth, M. Jung and T. Vogel, *Chem.–Eur. J.*, 2005, **11**, 3127–3135; (q) S. Fischer, U. Groth, M. Jung, M. Lindenmaier and T. Vogel, *Tetrahedron Lett.*, 2005, **46**, 6679–6682; (r) N. Miyoshi, T. Fukuma and M. Wada, *Chem. Lett.*, 1995, **24**, 999–1000; (s) H. Maekawa, Y. Yamamoto, H. Shimada, K. Yonemura and I. Nishiguchi, *Tetrahedron Lett.*, 2004, **45**, 3869–3872; (t) V. Nair, S. Ros, C. N. Jayan and N. P. Rath, *Tetrahedron Lett.*, 2002, **43**, 8967–8969; (u) Y.-S. Yang, Z.-L. Shen and T.-P. Loh, *Org. Lett.*, 2009, **11**, 2213–2215; (v) N. Kise, Y. Shiozawa and N. Ueda, *Tetrahedron*, 2007, **63**, 5415–5426; (w) N. Takenaka, G. Xia and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 13198–13199; (x) X.-F. Duan, J.-X. Feng, G.-F. Zi and Z.-B. Zhang, *Synthesis*, 2009, 277–282.
- R. Fittig, *Justus Liebigs Ann. Chem.*, 1859, **110**, 23–45.
- Recent developments in using ketones in pinacol reactions: (a) S. Matsukawa and Y. Hinakubo, *Org. Lett.*, 2003, **5**, 1221–1223; (b) L. Shi, C.-A. Fan, Y.-Q. Tu, M. Wang and F.-M. Zhang, *Tetrahedron*, 2004, **60**, 2851–2855; (c) H. C. Aspinall, N. Greeves and C. Valla, *Org. Lett.*, 2005, **7**, 1919–1922.
- (a) D. Uraguchi, T. Ito and T. Ooi, *J. Am. Chem. Soc.*, 2009, **131**, 3836–3837; (b) D. Uraguchi, T. Ito, S. Nakamura and T. Ooi, *Chem. Sci.*, 2010, **1**, 488–490.



- 8 (a) D. Uraguchi and T. Ooi, *J. Synth. Org. Chem., Jpn.*, 2010, **68**, 1185–1194; (b) D. Uraguchi, K. Yoshioka, Y. Ueki and T. Ooi, *J. Am. Chem. Soc.*, 2012, **134**, 19370–19373; (c) D. Uraguchi, R. Tsutsumi and T. Ooi, *J. Am. Chem. Soc.*, 2013, **135**, 8161–8164; (d) D. Uraguchi, S. Nakamura, H. Sasaki, Y. Konakade and T. Ooi, *Chem. Commun.*, 2014, **50**, 3491–3493; (e) H. Krawczyk, M. Dziegielewski, D. Deredas, A. Albrecht and Ł. Albrecht, *Chem.–Eur. J.*, 2015, **21**, 10268–10277.
- 9 Phosphonate–phosphate rearrangement from acyl phosphonates: (a) C. C. Bausch and J. S. Johnson, *Adv. Synth. Catal.*, 2005, **347**, 1207–1211; (b) A. S. Demir, Ö. Reis, A. Ç. İğdir, İ. Esiringü and S. Eymur, *J. Org. Chem.*, 2005, **70**, 10584–10587; Phosphonate–phosphate rearrangements from α -hydroxy trialkyl phosphonoacetates; (c) M. T. Corbett, D. Uraguchi, T. Ooi and J. S. Johnson, *Angew. Chem., Int. Ed.*, 2012, **51**, 4685–4689; Addition of phosphite to α -keto amides followed by phosphonate–phosphate rearrangement and intramolecular trapping; (d) A. Kondoh, T. Aoki and M. Terada, *Org. Lett.*, 2014, **16**, 3528–3531; Phosphite addition and rearrangement with protonation; (e) M. Hayashi and S. Nakamura, *Angew. Chem., Int. Ed.*, 2011, **50**, 2249–2252; (f) L. Wang, Z. Yao, F. Xu and Q. Shen, *Heteroat. Chem.*, 2012, **23**, 449–456; (g) W. Fang, G.-G. Liu, X.-F. Huang, J. Jia and X.-W. Wang, *Chin. J. Org. Chem.*, 2014, **34**, 1177–1182.
- 10 For example: (a) J. K. Whitesell, A. Bhattacharya, D. A. Aguilar and K. Henke, *J. Chem. Soc., Chem. Commun.*, 1982, 989–990; (b) D. A. Evans, C. S. Burgey, M. C. Kozlowski and S. W. Tregay, *J. Am. Chem. Soc.*, 1999, **121**, 686–699; (c) L. Peng, L.-L. Wang, J.-F. Bai, L.-N. Jia, Q.-C. Yang, Q.-C. Huang, X.-Y. Xu and L.-X. Wang, *Tetrahedron Lett.*, 2011, **52**, 1157–1160; (d) C. G. Goodman, M. M. Walker and J. S. Johnson, *J. Am. Chem. Soc.*, 2015, **137**, 122–125.
- 11 With respect to aldehyde electrophiles, we examined linear and alpha-branched alkyl aldehydes and observed slow conversion affording a mixture of unidentified products, together with a certain amount of the aldehyde Pudovik product and the desired mono-protected diol.
- 12 We studied a number of cinchona alkaloid-derived catalysts, as well as hydrogen-bonding catalysts of other types (ureas, thioureas, cyclopropyl imines) and found low levels of stereoselectivity and unacceptable isolated yields.
- 13 We were able to detect the formation of the Pudovik adduct with larger phosphites, implicating steric effects as being important in determining the rate of phosphonate–phosphate rearrangement.
- 14 Crystallographic data (excluding structure factors) for phosphate **4j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1055582†.

