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Catalytic Asymmetric Stetter Reaction Onto Vinylphosphine Oxides and Vinylphosphonates

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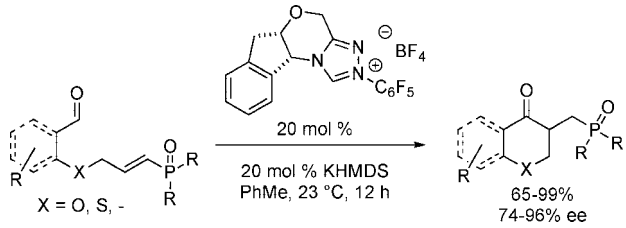
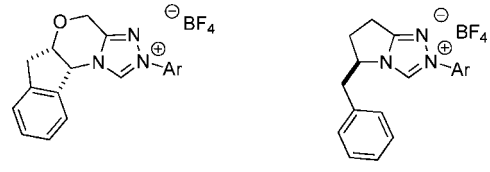
ABSTRACT



An intramolecular Stetter reaction of vinylphosphine oxides and vinylphosphonates has been developed. Treatment of an aldehyde with a nucleophilic N-heterocyclic carbene catalyst allows for addition of an acyl anion equivalent into a vinylphosphine oxide or vinylphosphonate Michael acceptor in yields up to 99% and ee values up to 96%.

Organophosphorus compounds are abundant in many facets of chemistry including agrochemistry[1] and medicinal chemistry.[2] They have also found much utility as ligands in asymmetric catalysis.[3] Owing to the multiple ways in which they can be employed, the synthesis of small molecules containing phosphorus has garnered significant attention.[4] More importantly, the ability to generate phosphorus compounds with chiral centers at or near phosphorus in an asymmetric fashion is particularly attractive.[5]

Since the first report of *N*-heterocyclic carbenes in 1991,[6] carbene catalysis has become a burgeoning field. NHCs have been used to propagate Umpolung reactivity of aldehydes to form new carbon−carbon bonds catalytically and enantioselectively.[7] Over the past several years, we have been engaged in developing a family of chiral nucleophilic carbenes (Figure 1)[8] and applying them to a variety of transformations. These catalysts, in particular **1a**−**d** and **2a**−**d**, have proven especially useful in the catalytic asym-



1a Ar = Ph
1b Ar = 4-OMe-C_6H_4
1c Ar = C_6F_5
1d Ar = 4-$CF_3C_6H_4$

2a Ar = Ph
2b Ar = 4-OMe-C_6H_4
2c Ar = C_6F_5
2d Ar = 4-$CF_3C_6H_4$

Figure 1. Chiral triazolium salts.

(1) (a) Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Wiley: New York, 2000. (b) Eto, M. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 1.

(2) (a) Krise, J. P.; Stella, V. J. *Adv. Drug Delivery Rev.* **1996**, *19*, 287. (b) Hwang, J. T.; Choi, J. R. *Drug Future* **2004**, *29*, 163–177.

(3) (a) Tang, W. J.; Zhang, X. M. *Chem. Rev.* **2003**, *103*, 3029–3069. (b) Zhou, Y. G. *Acc. Chem. Res.* **2007**, *40*, 1357–1366.

(4) (a) Mader, M. M.; Bartlett, P. A. *Chem. Rev.* **1997**, *97*, 1281. (b) Hanessian, S.; Rogel, O. *J. Org. Chem.* **2000**, *65*, 2667. (c) Bricklebank, N. *Organophosphorus Chem.* **2003**, *33*, 289. (d) McReynolds, M, D.; Dougherty, J. M.; Hanson, P. R *Chem. Rev.* **2004**, *104*, 2239. (e) Montchamp, J.-L. *J. Organomet. Chem.* **2005**, *690*, 2388. (f) Baumgartner, T.; Réau, R. *Chem. Rev.* **2006**, *106*, 4681.

(5) (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825.

(6) (a) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361. Also see: (b) Igau, A.; Grutzmacher, H.; Baceiredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, *110*, 6463.

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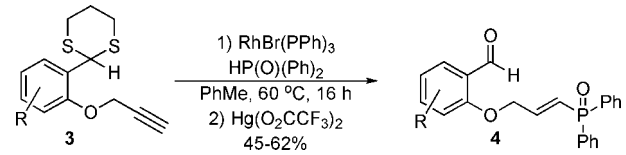
metric Stetter reaction providing ketoester products in typically high yield and enantioselectivity.[9]

Although there are numerous examples that exploit the nucleophilic nature of the acyl anion equivalent,[10] the α,β-unsaturated acceptors of the Stetter reaction[11] have been largely limited to simple enones and enoates. We envisaged that vinylphosphine oxides and vinylphosphonates would make excellent acceptors for the intramolecular Stetter reaction due to their highly electrophilic nature at the β-position.[12]

While many nucleophiles add readily to the β-position of vinylphosphines and vinylphosphine oxides, few examples have been shown to do so asymmetrically.[13] Recently, the first organocatalytic asymmetric transformation employing highly activated bis-phosphonates as electrophilic acceptors has been achieved by Alexakis and co-workers yielding chiral bis-phosphonates in good yields and enantioselectivities.[14] During the preparation of this manuscript, Jørgensen also reported a method complementary to Alexakis' work utilizing cinchona alkaloid derived catalysts in an asymmetric Michael-type addition affording high yields and enantioselectivities.[15]

We decided to employ a series of vinylphosphine oxides and vinylphosphonates as electrophilic acceptors in the intramolecular Stetter reaction. The vinylphosphine oxides of type **4** were prepared by using a modified procedure described by Tanaka and co-workers (Scheme 1).[16] The use

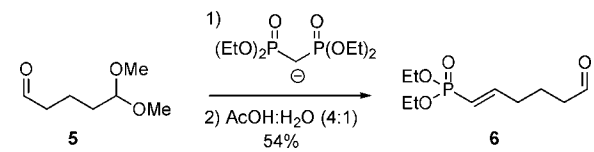
Scheme 1. Rhodium-Catalyzed Hydrophosphinylation



of the bromide salt of Wilkinson's catalyst[17] on alkynes **3** provides a smooth transformation to the desired vinylphosphine oxides in good yields. Deprotection of the 1,3-dithiane proved trivial and provided the desired aldehydes **4** in excellent yields.

The requisite vinylphosphonates of type **6** were prepared by treatment of the corresponding aldehyde **5** with a preformed bis-phosphonate complex, as demonstrated by Ojea and Ruiz (Scheme 2).[18]

Scheme 2. Aliphatic Vinylphosphonates



With a series of vinylphosphine oxides and vinylphosphonates prepared, we were able to test our hypothesis on the viability of these Michael acceptors for the intramolecular Stetter reaction.

Structures with an aromatic backbone employing a vinylphosphine oxide or vinylphosphonate as the electrophilic acceptor afford the Stetter product in typically high yields and enantioselectivities (Table 1). Vinylphosphine oxide **4a** provides higher yields than its vinylphosphonate congener **8** while enantioselectivities are increased as well (entries 1 and 9). The presence of halogen substituents on the aromatic ring (entries 2−4) is well tolerated as long as reaction time is limited to 30 min. When the reaction time is extended to 12 h, enantioselectivities drop significantly to 80% and 70% ee, respectively, due to epimerization. Electron-donating *p*-methoxy aldehyde **4e** shows only a slight increase in selectivity over σ withdrawing *m*-methoxy aldehyde **4d** and only a slight decrease in chemical yield.[19] The presence of sulfur in the tether (**4f**) leads to higher enantioselectivies, albeit in lower chemical yields than when an oxygen is used in the tether (e.g., **4a**). Five-membered carbocycle **7g** was also obtained in excellent yield and high enantioselectivity.[20,21]

Previously, we demonstrated that aliphatic aldehydes are competent substrates to undergo the intramolecular Stetter

(7) For recent reviews see: (a) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (c) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (d) Rovis, T. *Chem. Lett.* **2008**, *37*, 2.

(8) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725.

(9) (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (b) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934. (c) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (d) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (e) Moore, J. L.; Kerr, M. S.; Rovis, T. *Tetrahedron* **2006**, *62*, 11477. (f) Read de Alaniz, J.; Kerr, M. S.; Moore, J. L.; Rovis, T *J. Org. Chem.* **2008**, *73*, 2033. (g) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284.

(10) (a) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492. (b) Mattson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A. *J. Org. Chem.* **2006**, *71*, 5715. (c) See ref 9f.

(11) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407.

(12) For 1,4-additions with amines, see: (a) Collins, D. J.; Rowley, L. E.; Swan, J. M.; Rowley, L. E. *Aust. J. Chem.* **1974**, *27*, 841. (b) Pietrusiewicz, K. J.; Zablocka, M. *Tetrahedron Lett.* **1988**, *29*, 1991. (c) Cavalla, D.; Warren, S. *Tetrahedron Lett.* **1982**, *23*, 4505. For 1,4-additions with oxygen, see: (d) Johnson, C. R.; Imamoto, T. J. *J. Org. Chem.* **1987**, *52*, 2170. (e) Kawashima, T.; Nakamura, M.; Inamoto, N *Heterocycles* **1997**, *44*, 487. For 1,4-additions with sulfur, see: (f) Pietrusiewicz, K. M.; Wisniewski, W.; Zablocka, M. *Tetrahedron* **1989**, *45*, 337. For 1,4-additions with carbanions, see: (g) Berlan, J.; Battioni, J. P.; Koosha, K. *Tetrahedron Lett.* **1976**, 3351. (h) Pietrusiewicz, K. M.; Zablocka, M. *Tetrahedron Lett.* **1988**, *29*, 937.

(13) (a) Minowa, N.; Hirayama, M.; Fukatsu, S. *Tetrahedron Lett.* **1984**, *25*, 1147. (b) Ruiz, M.; Vicente, O.; Shapiro, G.; Weber, H. P. *Tetrahedron Lett.* **1994**, *35*, 4551. (c) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. (d) Fernández, M. C.; Diaz, A.; Guillin, J. J.; Blanco, O.; Ruiz, M.; Ojea, V. *J. Org. Chem.* **2006**, *71*, 6958. (e) Kondoh, A.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 6996. (f) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3410.

(14) Sulzer-Mossé, S.; Tissot, M.; Alexakis, A. *Org. Lett.* **2007**, *9*, 3749.

(15) Capuzzi, M.; Perdicchia, D.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 128.

(16) Han, L.-B.; Zhao, C.-Q.; Tanaka, M. *J. Org. Chem.* **2001**, *66*, 5929.

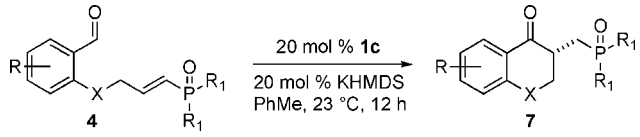
(17) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G *J. Chem. Soc. (A)* **1966**, 1711. Also see ref 16.

(18) Ruiz, M.; Fernandez, M. C.; Diaz, A.; Quintela, J. M.; Ojea, V. *J. Org. Chem.* **2003**, *68*, 7634.

(19) σ value for *p*-MeO = −0.27, σ value for *m*-MeO = 0.12: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanisms*, 5th ed.; Springer: New York, 2007; p 339.

(20) Substrate **4g** was also cyclized on 0.72 mmol scale with 20 mol % of **1c** to provide **7g** in 95% yield and 89% ee.

Table 1. Scope of Aromatic Aldehyde Substrates



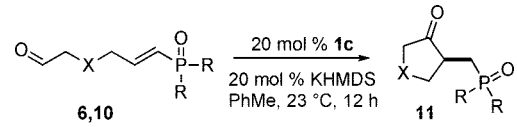
entry[a]	aldehyde	product	yield(%)	ee(%)[b]
1	4a	7a	90	86(74)
2	4b	7b	88	96[c]
3	4b	7b	80	93[d]
4	4c	7c	90	94(75)
5	4d	7d	75	87(91)
6	4e	7e	86	93
7	4f	7f	70	92
8	4g	7g	99	90
9	8	9	65	80

[a] All reactions conducted in the presence of 20 mol % of catalyst **1c**, 20 mol % of KHMDS (0.25 M in PhMe) in PhMe for 12 h at 23 °C. [b] Determined by HPLC, using a chiral stationary phase; ee values in parantheses were obtained with catalyst **2c**. [c] With catalyst **1a**, no reaction was observed. [d] 10 mol % of **1c** and 10 mol % of KHMDS.

reaction.[9a,f] By exchanging the acceptor to a vinylphosphonate or vinylphosphine oxide, the intramolecular Stetter reaction proceeds smoothly to give the desired products in high yields and enantioselectivities (Table 2).

(21) Absolute stereochemistry was unequivocally assigned for **7b** and **7g** by X-ray analysis; the rest were assigned by analogy to these products and those found in ref 9f. See the Supporting Information for details.

Table 2. Scope of Aliphatic Aldehyde Substrates



entry[a]	aldehyde	product	yield(%)	ee(%)[b]
1	6	11a	66	74
2	10b	11b	80	90
3	10c	11c	94	88
4	10d	11d	96	90

[a] See footnote *a* in Table 1. [b] See footnote *b* in Table 1.

Phosphonate **11a** was obtained in modest yield and enantioselectivity. Gratifyingly, when the diethyl vinylphosphonate was switched to the diphenyl phosphonate **10b**, the yield and enantioselectivity of the desired product **11b** were both improved substantially (entry 2). This increase in ee is most likely due to the increased steric demand of the diaryloxy group, but indicates that tuning of selectivities is possible with this approach.

Introduction of an oxygen in the aliphatic chain **10c** gives higher yields and enantioselectivities in the Stetter product **11c** compared to its alkyl congener **11a** (entry 3 vs entry 1). It is also possible to form a carbocycle bearing a phosphine oxide moiety **11d** that proceeds in good yield and enantioselectivity.[22]

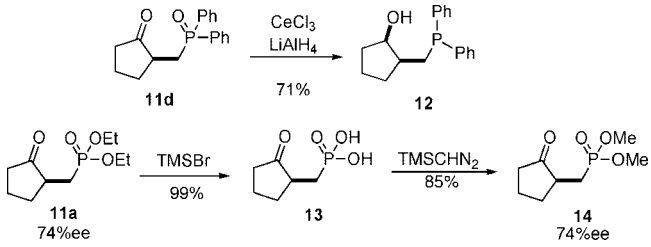
Treatment of **11d** under Luche-type conditions affords the global reduction product **12** (Scheme 3) bearing a syn relationship (>19:1), presumably due to the intervention of a Lewis acid chelation during the reduction step.[23,24] Hydrolysis of **11a** with bromotrimethylsilane in DCM overnight followed by a methanol quench affords phosphonic

(22) Six-membered aliphatic carbocycles bearing phosphonate Michael acceptors were not competent substrates in this reaction.

(23) (a) Constantino, M. G.; Matias, L. G. D.; da Silva, G. V. J.; Barbieri, E.; Gambardella, M. T. D. *Quim. Nova* **1998**, *21*, 719. (b) Dalpozzo, R.; Bartoli, G.; Bosco, M.; De Nino, A.; Procopio, A.; Sambri, L.; Tagarelli, A. *Eur. J. Org. Chem.* **2001**, 2971. (c) Kison, C.; Opatz, T. *Eur. J. Org. Chem.* **2008**, 2740.

(24) The use of $NaBH_4$ provides the hydroxy phosphine oxide in lower diastereoselectivity (6:1).

Scheme 3. Elaboration of Substrates



acid **13** in quantitative yield, which was then subjected to esterification with (trimethylsilyl)diazomethane[25] to generate methyl ester **14** with no loss of ee.

In summary, we have developed an intramolecular Stetter reaction employing vinylphosphine oxides and vinylphosphonates as electrophilic acceptors. Both aromatic and aliphatic substrates are tolerated providing keto phosphonates and phosphine oxides in good to excellent yields and enantioselectivities. This extension of the Stetter reaction leads to interesting new enantioenriched scaffolds of phosphorus-containing compounds not easily obtainable by other methods.

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Supporting Information Available: Experimental procedures, ^{1}H, ^{13}C, and ^{31}P spectra, and chiral separations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Joly, G. D.; Jacobsen, N. E. *J. Am. Chem. Soc.* **2004**, *126*, 4102.